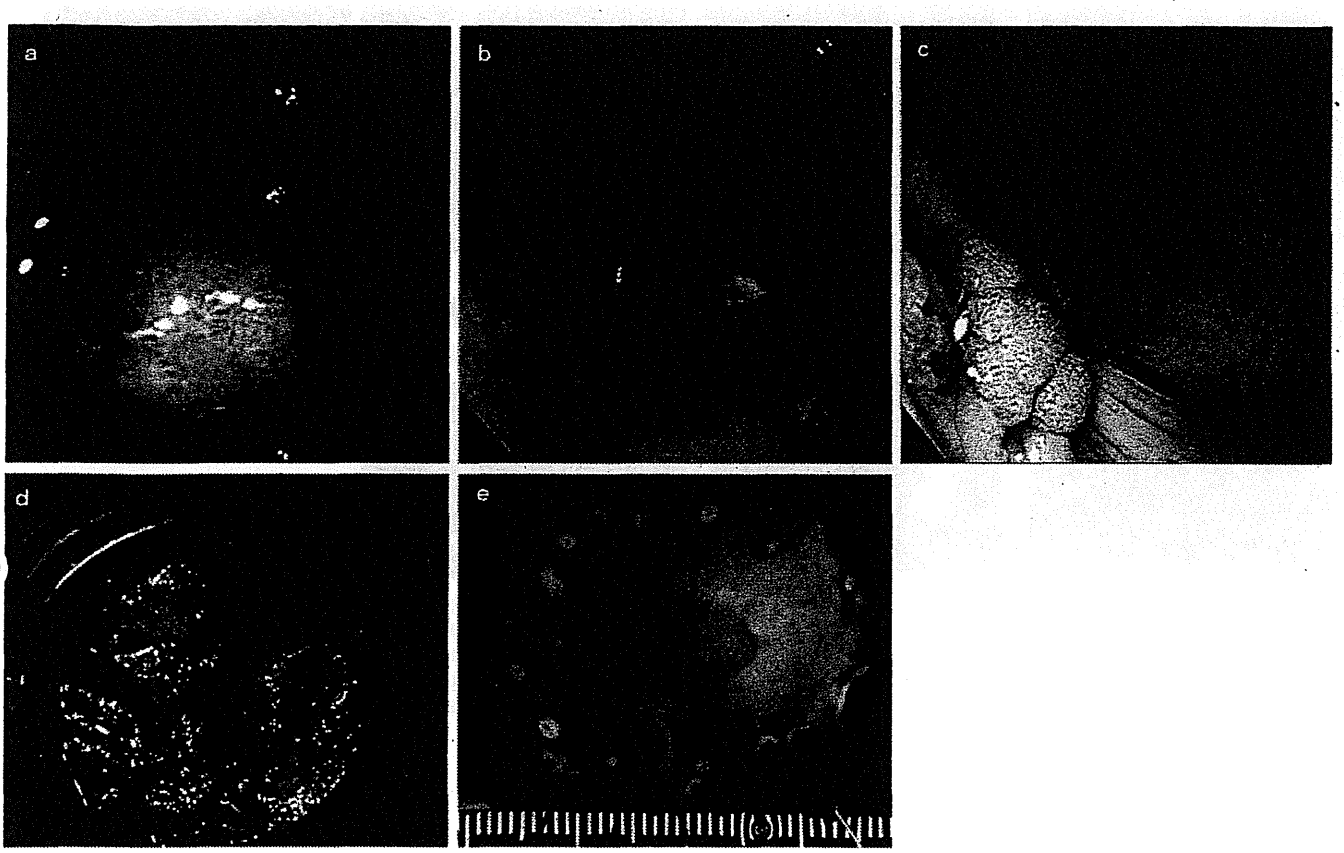

Fig. 2. A case of a local recurrence after endoscopic piecemeal mucosal resection (EPMR). (a) Conventional colonoscopy performed in the previous hospital showed a laterally spreading granular type (mixed nodular type) tumor, 30 mm in diameter, in the rectum. (b) Colonoscopy showed an artificial ulcer after EPMR. Pathological diagnosis was an intramucosal cancer and positive lateral margin. (c) Two months later a local recurrence (a residual lesion) was detected in our hospital as a protruding lesion with fold convergence. (d) The recurrence was treated with endoscopic submucosal dissection. During submucosal dissection severe fibrosis was seen. (e) The en bloc resected specimen revealed that the recurrence was 13 × 8 mm in diameter. Pathological diagnosis was tubulovillous adenoma.

Table 1. Previous reports of local recurrence after endoscopic mucosal resection of colorectal tumors (en bloc versus piecemeal)

Author	Design	Journal	Lesion size	*n*	Local recurrence rates	
					En bloc	Piecemeal
Tanaka S[2]	Retrospective	*Gastrointest Endosc* 2001	≧20 mm	81	4.9% (2/41)	10% (4/40)
Higaki S[17]	Prospective	*Endoscopy* 2003	≧20 mm	24	0% (0/5)	21.1% (4/19)
Hurlstone DP[18]	Prospective	*Gut* 2004	≧10 mm	58	9.1% (2/22)	22.2% (8/36)
Hotta K[19]	Retrospective	*Int J Colorectal Dis* 2009	≧10 mm	572	0.7% (3/440)	23.5% (31/132)
Saito Y[4]	Retrospective	*Surg Endosc* 2009	≧20 mm	228	2.7% (2/74)	20.1% (31/154)

used in clinical settings.[3] Recently, the ESD was developed and recognized for its effectiveness in large, complete, en bloc resections and precise pathological assessments (Fig. 3). ESD also showed lower local recurrence rates, ranging from 0 to 3% in previous, retrospective studies[23–28] (Table 2). Our retrospective controlled study suggested that local recurrence after an ESD (2%) was significantly lower than an EMR/EPMR (14%).[4] However, ESD showed a higher perforation rate and longer procedure times; thus, it is necessary to improve ESD.[4]

APPROPRIATE INTERVAL AFTER ENDOSCOPIC RESECTION

The National polyp study determined the appropriate interval after endoscopic resection for concluding complete removal of small colorectal adenomas.[29] They found that a 3-year interval after the removal of all adenomatous polyps was sufficient to detect newly adenomatous polyps.[29] In Japan, we also conducted a randomized controlled trial (the Japan polyp study) to determine an appropriate interval

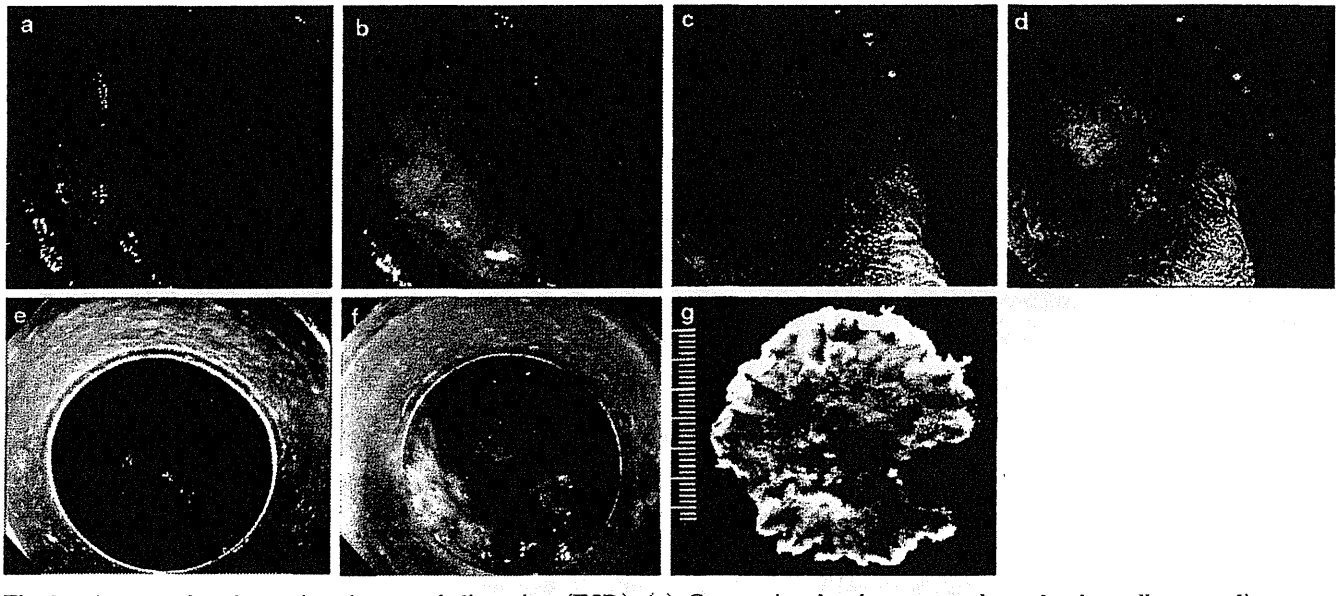

Fig. 3. A case of endoscopic submucosal dissection (ESD). (a) Conventional colonoscopy showed a laterally spreading non-granular type tumor, 30 mm in diameter, on the ileocecal valve. (b) Chromoendoscopy with indigo-carmine spray dying showed a demarcated line of the lesion. (c,d) Magnified chromoendoscopy with crystal violet staining showed a non-invasive pattern. (e,f) The lesion was treated with ESD and lipid deposit and severe fibrosis was seen during submucosal dissection. (g) The en bloc resected specimen revealed that the lesion was 28 × 20 mm in diameter. Pathological diagnosis was submucosal invasive cancer (2000 μm) and additional surgery was carried out later.

Table 2. Previous large-scale reports of colorectal endoscopic submucosal dissection

Author	Journal	*n*	En bloc resection	En bloc and R0 resection	Perforation	Local recurrence
Isomoto H[22]	*Endoscopy* 2009	292	90.1%	79.8%	8.2%	0.3%
Saito Y[23]	*Gastrointest Endosc* 2007	200	84%	83%	5%	0.5%
Fujishiro M[24]	*Clin Gastroenterol Hepatol* 2007	200	91.5%	71%	6%	1%
Zhou PH[25]	*Surg Endosc* 2009	74	93.2%	89.2%	8.1%	0%
Tamegai Y[26]	*Endoscopy* 2007	71	98.6%	95.6%	1.4%	2.8%
Tanaka S[27]	*Gastrointest Endosc* 2007	70	–	80%	10%	0%

after endoscopic resection of not only protruded but also flat and depressed type colorectal tumors.[30] The result of that study will be available in 2012. In the case of large colorectal tumors, the US multi-society task force on colorectal cancer and the American Cancer Society recommended that, after piecemeal removals of sessile adenomas, patients should be considered for follow-up colonoscopy at 2- to 6-month intervals to verify complete removal. Once complete removal has been established, subsequent surveillance should be individualized, based on the endoscopist's judgment. The completeness of removal should be based on endoscopic and pathological assessments.[31] On the other hand, based on the expert panel's opinions, the 2008 European Panel on the Appropriateness of Gastrointestinal Endoscopy (EPAGE II) also recommended that, after piecemeal removals of sessile adenomas, a follow-up colonoscopy was appropriate and necessary within the first 9 months following the index colonoscopy.[32] In our previous study, 572 colorectal tumors were followed up at 3 and 6 months after endoscopic resection. We found that 28 of the 34 lesions with local recurrences were detected at the first follow-up colonoscopy, and the remaining six lesions were detected at the second or a subsequent colonoscopy.[20] Four of the last six local recurrences were missed in the first colonoscopy performed at 3 months, due to the size limits of detection. Thus, we concluded that 6 months was an appropriate interval for assessing complete removal after EPMR to avoid missing local recurrences.[20] When a large colorectal tumor is removed with a complete en bloc resection by ESD, more than 12 months is considered necessary for the follow-up colonoscopy, due to the estimated risk of newly adenomatous polyps.

FUTURE PROSPECTS

No randomized controlled trial has studied surveillance intervals after an EPMR. We are currently conducting a prospective, randomized controlled trial to determine an appropriate interval after EPMR. We are considering follow ups at both 3 and 6 months versus only one at 6 months. Currently, the ESD requires a high level of skill; thus, the indication for

an ESD was proposed as a limited category. Once the problems associated with ESD are overcome, such as complications and procedure times, we will consider expanding the indication for the ESD category. One randomized controlled study revealed that an electrosurgical knife with a water-jet function (the FlushKnife) significantly shortened operation times of ESD for large colorectal tumors compared with a knife without a water-jet function.[33] In our retrospective analysis of a single colonoscopist result, 40 cases were necessary for reducing perforations.[34] Actually after the introduction of ESD, surgical treatments for non-granular type LST, which were adenoma and intramucosal or submucosal superficial cancers, were replaced by ESD.[35] In the near future, as ESD for large colorectal tumors becomes more common, the number of local recurrences after EPMR will be reduced.

CONCLUSION

Local recurrences frequently occur after EPMR of large colorectal tumors. To reduce recurrence, careful observation with magnification may be important. An appropriate interval after EPMR remains controversial, but ranges from 2 to 9 months. A randomized controlled study is necessary to determine the appropriate interval.

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ORIGINAL ARTICLE

Effectiveness of narrow-band imaging magnification for invasion depth in early colorectal cancer

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Abstract

AIM: To evaluate the surface microvascular patterns of early colorectal cancer (ECC) using narrow-band imaging (NBI) with magnification and its effectiveness for invasion depth diagnosis.

METHODS: We studied 112 ECC lesions [mucosal/submucosal superficial (m/sm-s), 69; sm-deep (sm-d), 43] ≥ 10 mm that subsequently underwent endoscopic or surgical treatment at our hospital. We compared microvascular architecture revealed by NBI with magnification to histological findings and then to magnification colonoscopy pit pattern diagnosis.

RESULTS: Univariate analysis indicated vessel density: non-dense ($P < 0.0001$); vessel regularity: negative ($P < 0.0001$); caliber regularity: negative ($P < 0.0001$); vessel length: short ($P < 0.0001$); and vessel meandering: positive ($P = 0.002$) occurred significantly more often with sm-d invasion than m/sm-s invasion. Multivariate analysis showed sm-d invasion was independently associated with vessel density: non-dense [odds ratio (OR) = 402.5, 95% confidence interval (CI): 12.4-13133.1] and vessel regularity: negative (OR = 15.9, 95% CI: 1.2-219.1). Both of these findings when combined were an indicator of sm-d invasion with sensitivity, specificity and accuracy of 81.4%, 100% and 92.9%, respectively. Pit pattern diagnosis sensitivity, specificity and accuracy, meanwhile, were 86.0%, 98.6% and 93.8%, respectively, thus, the NBI with magnification findings of non-dense vessel density and negative vessel regularity when combined together were comparable to pit pattern diagnosis.

CONCLUSION: Non-dense vessel density and/or negative vessel regularity observed by NBI with magnification could be indicators of ECC sm-d invasion.

Key words: Colorectal neoplasms; Narrow-band imaging; Microvasculature

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INTRODUCTION

Magnified colonoscopy and the development of pit pattern diagnosis[1] not only permits us to distinguish neoplastic from non-neoplastic colorectal lesions[2-5], but also helps to assess the invasion depth of early colorectal cancers (ECC)[6-9]. Similarly, vascular findings on the surface of gastric lesions have also been observed by

magnification endoscopy, and the usefulness in predicting the histological nature of such lesions and assessing their invasion depth has also been reported in the upper gastrointestinal (GI) tract[10-12].

The recently developed narrow-band imaging (NBI) system is a noninvasive optical technique that uses reflected light that provides clearer images of surface microvascular architecture than the conventional observation modality[13]. To date, the use of magnification endoscopy with the NBI system has been studied in the upper GI tract[14-20] and the suitability of this new modality for differentiating neoplastic from non-neoplastic lesions and its potential for pit pattern diagnosis have also been reported for the lower GI tract[21-30].

As previously indicated, colorectal lesions with mucosal (m) or submucosal (sm) superficial invasion < 1000 μm (sm-s) have an extremely low risk of lymph-node metastasis and are good candidates for endoscopic treatment[31]. It is helpful therefore, to differentiate endoscopically between m/sm-s and deeper sm invasion (sm-d ≥ 1000 μm) lesions. There have been only a few reports concerning invasion depth diagnosis using NBI with magnification in a large series of cases, however, a number of questions remain regarding the comparative effectiveness of a diagnosis based on NBI observation and one using pit pattern analysis by dye chromoendoscopy for determining invasion depth.

Using magnification colonoscopy with the NBI system, we evaluated the characteristics of the surface microvascular architecture of ECC and investigated the effectiveness of this new optical modality for the diagnosis of invasion depth. In addition, we evaluated the comparative relationship between NBI with magnification and pit pattern diagnoses.

MATERIALS AND METHODS

NBI system

NBI is a novel technique that uses spectral narrow-band optical filters instead of the full spectrum of white light. It is based on the phenomenon that the depth of light penetration depends on its wavelength, with a short wavelength penetrating only superficially and a longer wavelength penetrating into deeper layers. In the NBI mode, optical filters that allow narrow-band light to pass at wavelengths of 415 and 540 nm are mechanically inserted between a xenon arc lamp and a red/green/blue rotation filter. Thin blood vessels such as capillaries on the mucosal surface can be seen most clearly at 415 nm, which is the wavelength that corresponds to the hemoglobin absorption band, while thick vessels located in the deep layer of the mucosa can be observed at 540 nm. Current NBI technology limits mucosal surface light penetration, thereby enhancing visualization of the fine capillary vessel structure on the surface layer.

Patients and evaluation methods

We studied a total of 112 ECC lesions ≥ 10 mm analyzed with NBI with magnification colonoscopy examination, which then underwent endoscopic or surgical treatment at the National Cancer Center Hospital between January 2006 and February 2007. All colonoscopies were performed with a PCF-Q240ZI or CF-H260AZI endoscope (Olympus Optical Co. Ltd., Tokyo, Japan) by three experienced endoscopists (MF, YS, TM) each of whom had annually performed more than 1000 magnifying chromoendoscopy examinations and at least 500 NBI examinations per year. Endoscopic images of each lesion were taken in the following order: conventional colonoscopy, NBI with magnification, chromoendoscopy and magnification chromoendoscopy. When a lesion was detected by conventional colonoscopy, its surface was washed with proteinase to remove excess mucus. Magnification NBI views of the microvascular architecture concentrated on those portions of the lesion where invasion seemed to have permeated the deepest regions, such as depressed areas and large nodules[32,33].

After completion of NBI with magnification, the pit pattern of each lesion was assessed with magnification chromoendoscopy performed using 0.4% indigo-carmine (IC) dye spraying. When high magnification observation with IC dye did not permit us to determine adequately the surface structure for pit pattern analysis, 0.05% crystal violet was applied for staining[7]. The visible pit pattern was then assessed during the course of the examination by the endoscopist conducting the procedure. All lesions were resected subsequently endoscopically or surgically and histological diagnosis was performed by three experienced pathologists based on the Vienna classification[34,35]. The depth of sm invasion was determined as being either sm-s < 1000 μm or sm-d ≥ 1000 μm[31]. After pathological diagnosis was completed on all resected lesions, three endoscopists (Fukuzawa M, Saito Y and Matsuda T) who performed the examination individually reviewed the endoscopic images of the NBI findings that were taken prior to treatment. All endoscopic images were chosen by one of these endoscopists. Their evaluation of the NBI images of the m/sm-s and sm-d lesions focused on the suspected areas, respectively, of higher grade dysplasia and deepest suspected invasion. Each characteristic of microvascular architecture was finally determined based on the agreement of at least two of the three reviewing endoscopists. Microvascular findings with a high frequency of sm-d were assessed as to whether those were significant sm-d indicators by univariate and multivariate analysis. In addition, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy were calculated for each microvascular architectural feature observed during NBI, as well as every pit pattern diagnosis determined by magnification chromoendoscopy. We then compared the various types of microvascular architecture characteristics revealed by NBI with magnification to the chromoendoscopy pit pattern diagnoses.

The protocol for this study was approved by our institutional review board and all patients gave written informed consent.

Chromoendoscopy with magnification

Our pit pattern evaluation method relied on the clinical classification system proposed by Fujii *et al*[7] and Matsuda *et al*[8], with reference to the Kudo Classification System. Lesions were categorized into noninvasive and invasive

patterns. The noninvasive pattern included regular crypts with or without a demarcated area (e.g. depression, large nodule, or reddened area) and irregular pits without a demarcated area, and are usually observed in Kudo's types IIIs, IIIL, IV and VI without demarcated areas (e.g. adenomatous polyps, m and sm-s cancers), with endoscopic resection being the appropriate treatment. The invasive pattern was characterized by irregular and distorted crypts in a demarcated area, as observed in Kudo's type VN and VI with a demarcated area (e.g. sm-d), and should be treated by surgical resection. As indicated, Kudo's type VI can be observed in either noninvasive or invasive patterns. Those differences are dependent on the presence or absence of a demarcated area.

Microvascular architecture of ECC

Microvascular architectural images taken during magnification colonoscopy with NBI were reviewed retrospectively by three endoscopists who referenced the microvascular architectural features of superficial esophageal carcinoma[15], and included the following characteristics: (1) caliber, narrow or wide; (2) caliber regularity, positive or negative; (3) meandering, positive or negative; (4) vessel regularity, positive or negative; (5) vessel length, short or long; and (6) vessel density, non-dense or dense. These characteristics were evaluated by comparing the NBI with magnification images to representative photographs of model examples (Figure 1).

Statistical analysis

We compared microvascular architecture as revealed by NBI with magnification to histological findings using the χ^2 test of independence or Fisher's exact test for univariate analysis. Variables with a P value of < 0.05 in our univariate analysis were subsequently included in a logistic regression multivariate analysis. The StatView program, version 5.0 (SAS Institute, Cary, NC, USA), was used for data analysis and $P < 0.05$ was considered to be statistically significant.

RESULTS

Clinicopathological features of patients and lesions

The clinicopathological details of the patients and colorectal lesions involved in this study are shown in Table 1.

Univariate analysis

Univariate analysis indicated characteristics involving vessel density: non-dense ($P < 0.0001$); vessel regularity: negative ($P < 0.0001$); caliber regularity: negative ($P < 0.0001$); vessel length: short ($P < 0.0001$); and vessel meandering: positive ($P = 0.002$) occurred significantly more often with sm-d invasion than m/sm-s invasion (Table 2).

Multivariate analysis

Multivariate analysis demonstrated that sm-d invasion was independently associated with vessel density: non-dense [odds ratio (OR) = 402.5, 95% confidence interval (CI): 12.4-13 133.1]; and vessel regularity: negative (OR = 15.9, 95% CI: 1.2-219.1) (Table 2). The sensitivity, specificity, PPV, NPV and diagnostic accuracy rate for each characteristic are shown in Table 3. The two vascular findings that were confirmed by multivariate analysis had the highest values for specificity, PPV and accuracy (non-dense vessel density: specificity 0.99, PPV 0.95, accuracy 90.2%; negative vessel regularity: specificity 0.99, PPV 0.95, accuracy 90.2%).

Table 1 Clinicopathological features of evaluated colorectal lesions

	m/sm-s	sm-d
Lesions (n = 112)	69	43
Gender (male/female)	42/27	24/19
Age (range, yr)	63.2 (37-79)	62.5 (32-80)
Location		
Right colon	29	15
Left colon	18	12
Rectum	22	16
Morphology[1]		
Ip/Is/Isp	21	18
IIa/IIa + IIc/IIc	10	16
LST-G	20	5
LST-NG	18	4
Mean size (range, mm)	32.3 (10-100)	24.4 (10-90)

[1]Update on the Paris classification of superficial neoplastic lesion in the digestive tract[36]. LST-G: Laterally spreading tumor-granuler type; LST-NG: Laterally spreading tumour-non granular type; m/sm-s: Mucosal/submucosal superficial; sm-d: Submucosal-deep.

Pit pattern diagnosis

The pit patterns of 21 m/sm-s lesions were evaluated following IC dye spraying, whereas the pit patterns of the other 48 m/sm-s lesions and all 43 sm-d lesions were assessed after crystal violet staining. We subsequently calculated the sensitivity, specificity, PPV, NPV and accuracy in differentiating m/sm-s from sm-d for: (1) the pit patterns that were diagnosed as being invasive; and (2) the NBI with magnification characteristic findings of (a) non-dense vessel density and/or negative vessel regularity and (b) non-dense vessel density and negative vessel regularity, which were both considered to be indicators for sm-d invasion. Pit pattern analysis sensitivity, specificity, PPV, NPV and diagnostic accuracy were 0.86 (95% CI: 0.72-0.95), 0.99 (0.92-0.99), 0.97 (0.86-0.99), 0.92 (0.83-0.97) and 93.8%, respectively. The NBI with magnification characteristic findings of non-dense vessel density and negative vessel regularity were comparable to pit pattern diagnosis results [0.81 (0.67-0.92), 1.00 (0.95-1.00), 1.00 (0.90-1.00), 0.90 (0.81-0.95), 92.9%] (Table 4). Seven of the lesions in this study were incorrectly diagnosed using pit pattern analysis including six sm-d lesions mistakenly diagnosed as m/sm-s invasion depth. In two of these cases, however, both non-dense vessel density and negative vessel regularity had also been observed by magnification NBI, which suggests its potential use as a supplementary diagnostic tool to pit pattern diagnosis (Figures 2 and 3).

DISCUSSION

It has been reported previously that observation of intra-

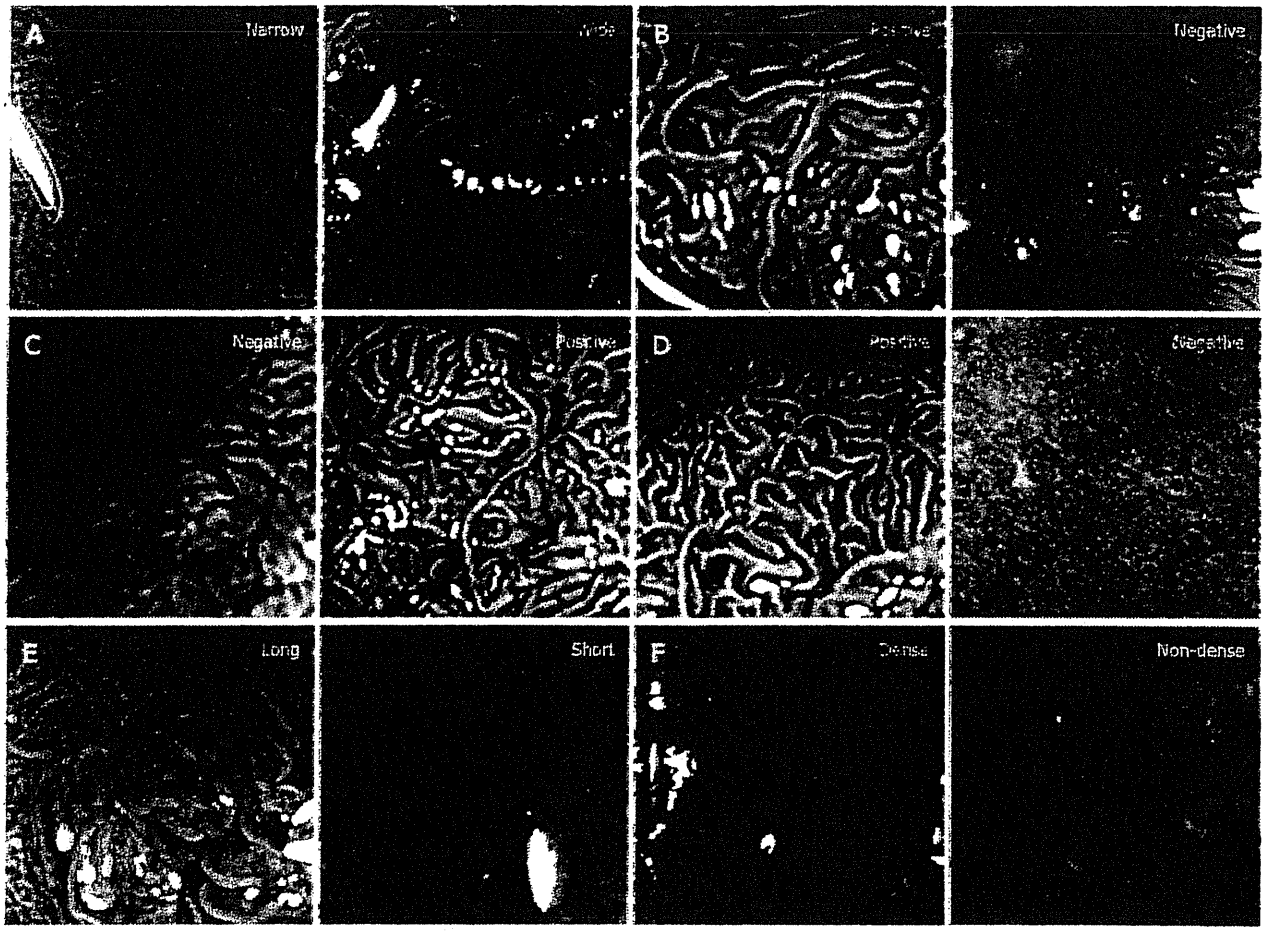

Figure 1 Microvascular architecture. A: Caliber, narrow: Capillaries are narrow diameter. Caliber, wide: Capillaries are wide diameter; B: Caliber regularity, positive: Capillaries are uniform thickness. Caliber regularity, negative: Capillaries are unequal thickness; C: Meandering, negative: Capillaries are linear. Meandering, positive: Capillaries are meandering; D: Vessel regularity, positive: Capillaries surround mucosal glands regularly. Vessel regularity, negative: Capillaries irregularly branching; E: Vessel length, long: Long capillaries. Vessel length, short: Short capillaries; F: Vessel density, dense: Dense capillaries. Vessel density, non-dense: Sparse capillaries.

Variables			Univariate analysis *P*-value[1]	Multivariate analysis		
				P-value[1]	Odds ratio	95% CI
		Non-dense/dense				
Vessel density	m/sm-s	1/68	< 0.001	0.001	402.5	12.4-13 133.1
	sm-d	33/10				
		Negative/positive				
Vessel regularity	m/sm-s	8/61	< 0.001	0.038	15.9	1.2-219.1
	sm-d	38/5				
		Negative/positive				
Caliber regularity	m/sm-s	44/25	< 0.001	0.056	17.3	0.9-323.4
	sm-d	42/1				
		Short/long				
Vessel length	m/sm-s	20/49	< 0.001	0.161	0.2	0.01-2.10
	sm-d	37/6				
		Positive/negative				
Meandering	m/sm-s	49/20	0.002	0.110	0.1	0.01-1.60
	sm-d	41/2				
		Wide/narrow				
Caliber	m/sm-s	62/7	NS			
	sm-d	41/2				

[1]χ^2 or Fisher's test. 95% CI: 95% confidence interval; NS: Not significant.

papillary capillary loops by magnification endoscopy is useful in the diagnosis of invasion depth of superficial esophageal cancer[10,11]. The intra-papillary capillary loops can be seen in the normal esophageal mucosa by mag-

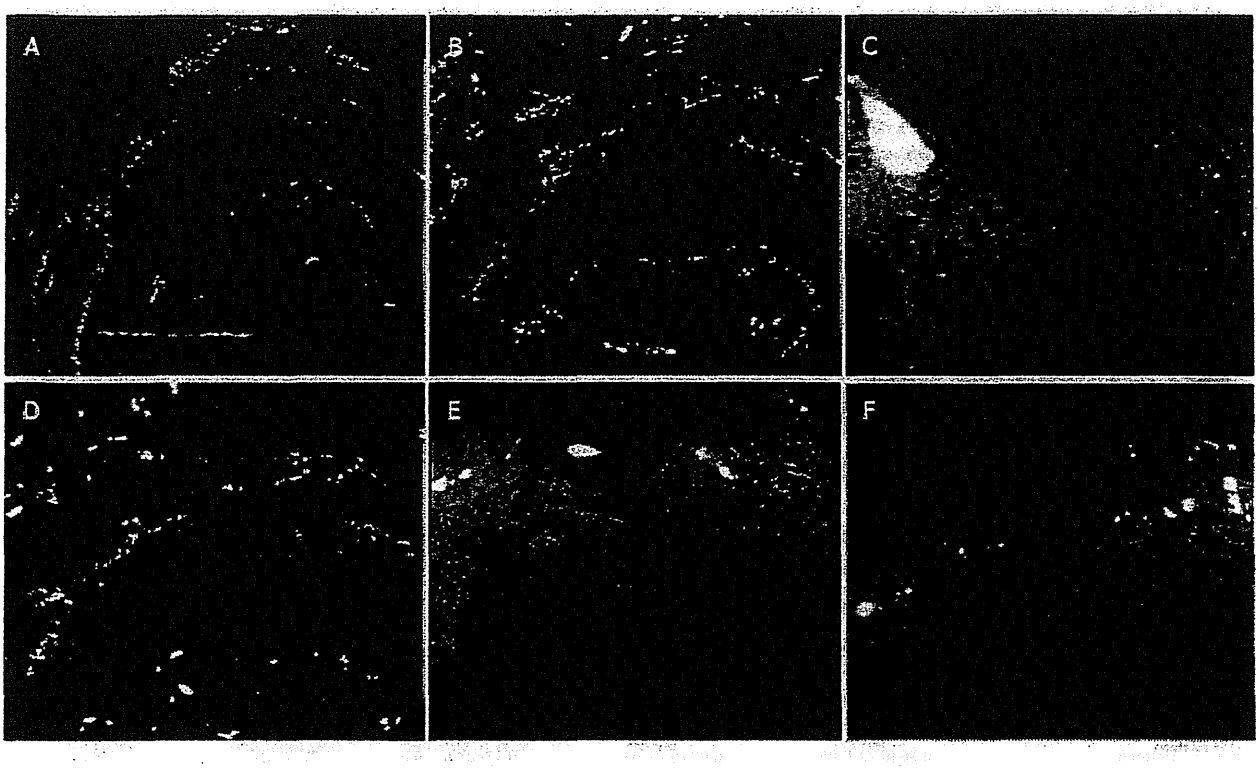

Figure 2 35 mm laterally spreading tumor, non-granular (LST-NG) type, located in the ascending colon. A: Conventional colonoscopy image; B: Conventional colonoscopy image following 0.4% IC dye spraying; C: Narrow-band imaging (NBI) with magnification image at center of the lesion enclosed by the red box in A. Microvascular architecture consisted of non-dense vessel density and negative vessel regularity; D: Crystal violet staining image; E: Magnification view of the portion enclosed by the red box in D revealed a noninvasive pattern; F: Magnification view of the portion enclosed by the yellow box in D also revealed a noninvasive pattern, such the estimated depth was intramucosal and this LST-NG lesion was treated by endoscopic submucosal dissection.

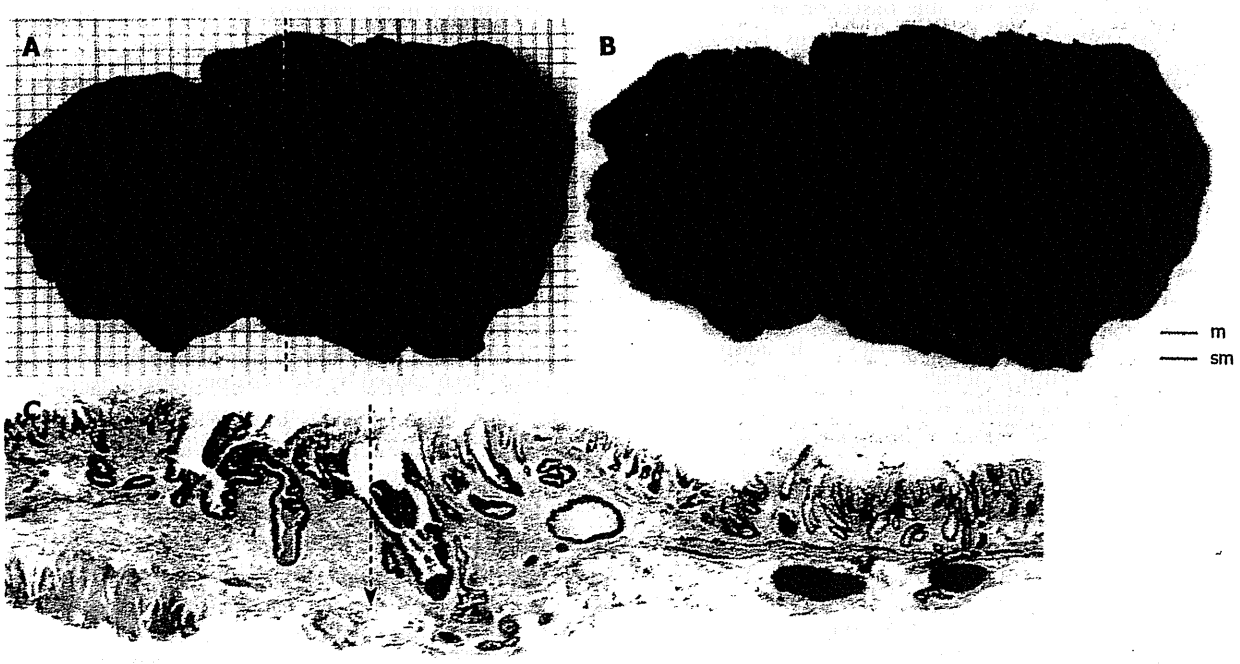

Figure 3 Stereomicroscopic view and histological images. A: Stereomicroscopic view; B: Red lines indicate submucosal penetration of the tumor; C: Histological diagnosis at dotted line in A was a well-differentiated adenocarcinoma and depth of invasion was sm (1300 mm) shown with the arrow. Invasion depth diagnosis using NBI with magnification was correct, based on findings of non-dense vessels and negative vessel regularity, but pit pattern diagnosis of this lesion was inaccurate.

nifying endoscopy. In cancerous lesions, characteristic changes of the intrapapillary capillary loops can be seen in the superficial mucosa according to the depth of tumor invasion. There have been few studies to assess invasion depth in cancerous lesions from microvascular architecture. However, the NBI system enabled observation of

Microvascular architecture	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (%)
Vessel density	33/43	68/69	0.97 (0.85-0.99)	0.87 (0.78-0.94)	90.2
Non-dense	0.77 (0.61-0.88)	0.99 (0.92-0.99)			
Vessel regularity	38/43	61/69	0.83 (0.69-0.92)	0.92 (0.83-0.97)	88.4
Negative	0.88 (0.75-0.96)	0.88 (0.78-0.95)			
Caliber regularity	42/43	25/69	0.49 (0.38-0.60)	0.96 (0.80-0.99)	59.8
Negative	0.98 (0.88-0.99)	0.36 (0.25-0.49)			
Vessel length	37/43	49/69	0.65 (0.51-0.77)	0.89 (0.78-0.96)	76.8
Short	0.86 (0.84-0.99)	0.71 (0.59-0.81)			
Meandering	41/43	20/69	0.46 (0.35-0.56)	0.91 (0.71-0.99)	54.5
Positive	0.95 (0.84-0.99)	0.29 (0.19-0.41)			
Caliber	41/43	7/69	0.40 (0.30-0.50)	0.78 (0.40-0.97)	42.9
Wide	0.95 (0.84-0.99)	0.10 (0.04-0.20)			

PPV: Positive predictive value; NPV: Negative predictive value.

Microvascular architecture	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (%)
Non-dense vessel density	38/43	60/69	0.81 (0.67-0.91)	0.92 (0.83-0.97)	87.5
and/or negative vessel regularity	0.88 (0.75-0.96)	0.87 (0.77-0.94)			
Non-dense vessel density	35/43	69/69	1.00 (0.90-1.00)	0.90 (0.81-0.95)	92.9
and negative vessel regularity	0.81 (0.67-0.92)	1.00 (0.95-1.00)			
Pit pattern	37/43	68/69	0.97 (0.86-0.99)	0.92 (0.83-0.97)	93.8
(Invasive pattern)	0.86 (0.72-0.95)	0.99 (0.92-0.99)			

microvascular architecture of the tumor surface in the GI tract. In a similar fashion, we used NBI with magnification to investigate whether or not quantitative ECC invasion depth diagnosis was possible based on analysis of capillary vessel patterns instead of pit patterns. Based on our results, it appeared that non-dense vessel density and negative vessel regularity, as observed by NBI with magnification, could be diagnostic indicators of sm-d invasion, as effectively as pit pattern analysis.

Regular hexagonal or honeycomb-like capillary patterns are formed around the crypts of normal colorectal mucosa. In contrast, it has been reported that these capillaries are larger in tumor adenomas, whereas vascular disruption, caliber irregularity and dense vessels have been observed in severe atypical cases[37]. In addition, vascular changes do not generally occur in non-neoplastic lesions such as hyperplastic polyps, with the exception of inflammatory polyps[38]. The NBI technique provides clearer observation of microvascular architectural characteristics, therefore, it has been reported that differentiation of neoplastic from non-neoplastic lesions on the basis of different vascular patterns is equally possible using NBI or chromoendoscopy[21-30], and pit pattern diagnosis has likewise been explored using NBI[21,24,27,28]. Previous studies have shown that the accuracy of pit pattern diagnosis of invasion depth by magnification endoscopy was 98.8%[8], whereas such diagnostic accuracy in this study was 93.8%.

The area surrounding crypts in the superficial layer of the mucosa is covered with capillaries and has previously been recognized as a pit using the NBI technique. Machida *et al*[21] have reported that NBI pit pattern diagnosis is significantly more useful ($P < 0.001$) than conventional observation, but inferior to chromoendoscopy ($P < 0.05$). Hirata *et al*[24] have reported that overall diagnostic consistency in pit patterns between magnification NBI and dye-spraying observations was 84%, but even higher for types Ⅱ, Ⅲ, Ⅳ and V_N pit patterns, although somewhat lower at 78%, for the type V_I pit pattern. In addition, Tischendorf *et al*[27] have reported that there is no significant difference in the PPV for neoplastic lesions as determined by pit pattern and vascular findings using NBI. There was a discrepancy, however, between two endoscopists in their NBI pit pattern diagnosis of types Ⅲ-Ⅴ neoplastic lesions[27]. This may have been because the actual pit structure was not observed using the NBI technique, unlike the results from the contrast and staining methods; or, it could have been caused by the NBI pit pattern diagnosis of types Ⅲ-Ⅴ lesions, which are considered particularly important in determining the most suitable method of treatment, not having been performed accurately.

More recently, Katagiri *et al*[30] have reported that capillary patterns observed by NBI with magnification are highly accurate in distinguishing between low-grade and high-grade dysplasia/invasive cancer, and thus could be used to predict the histopathological features of colorectal neoplasia. In addition, Hirata *et al*[25] have reported vascular findings of significant sm-d invasion based on their NBI observation of thick blood vessels with irregularity on the surface of tumors. This differs somewhat from the results of our investigation, but the difference could be caused by a number of factors, such as variations in our respective definitions of vascular findings, and the macroscopic types of lesions involved in the two studies.

Magnification observation with dye spraying and staining, in particular crystal violet staining, however, can be time-consuming. Patient symptoms including abdominal discomfort and peristalsis are more likely to appear in longer duration colonoscopy examinations, which may render detailed observation more problematic. In contrast, the press of a single button on the handle of the endoscope with the NBI system can almost immediately change from NBI to the conventional view and back again, thereby shorting examination times and reducing the burden on patients and endoscopists alike. A mucous attachment on the endoscope can also interfere with diagnosis, and washing the surface of a lesion with pronase solution takes additional time during pit pattern diagnosis by magnification colonoscopy with IC dye spraying or crystal violet staining. Hirata *et al*[24] have further reported that NBI observation results in more accurate pit pattern diagnosis than dye spraying observation in cases with mucous attachment.

Our study suffered from some limitations. First, the NBI assessments were made on still images by three endoscopists, whereas the pit pattern diagnosis was done in real time after initial inspection with NBI, which could account for some further bias. Second, the different NBI features of the microvasculature are not independent: the endoscopist is not blinded to one feature if he scores the other. In addition, lesions that were diagnosed histologically as cancer had a diameter of at least 10 mm, thus lesions < 10 mm in diameter were not assessed in this study. Accordingly, future prospective studies will require that relevant data be accumulated and analyzed on a more objective basis.

In conclusion, the results of this study indicated that two microvascular architectural characteristics, non-dense vessel density and negative vessel regularity, observed using NBI with magnification during colonoscopy examinations could be reliable indicators of ECC sm-d invasion.

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COMMENTS

Background

The intra-papillary capillary loops can be seen in the normal esophageal mucosa by magnifying endoscopy. In cancerous lesions, characteristic changes of the intrapapillary capillary loops can be seen in the superficial mucosa according to the depth of tumor invasion. Narrow-band imaging (NBI) enables detailed observation of microvascular architecture of the tumor surface.

Research frontiers

NBI provides clearer observation of microvascular architectural characteristics, and it has been reported that differentiation of neoplastic from non-neoplastic lesions on the basis of different vascular patterns is equally possible using NBI or chromoendoscopy. However, there have been only a few reports concerning invasion depth diagnosis using NBI with magnification in a large series of cases. This study clarifies the efficiency of NBI with magnification colonoscopy for invasion depth diagnosis of early colorectal cancer (ECC).

Innovations and breakthroughs

Some studies have already reported the clinical usefulness of pit pattern diagnosis using magnifying chromoendoscopy for predicting the depth of invasion of ECC. The authors' results indicate that NBI with magnification findings were comparable to pit pattern diagnosis results.

Applications

Magnification observation with dye spraying and staining, in particular crystal violet staining, however, can be time-consuming. In contrast, the press of a single button on the handle of the endoscope with the NBI system can almost immediately change from NBI to the conventional view and back again, thereby shortening examination times and reducing the burden on patients and endoscopists alike.

Peer review

The authors present a trial analyzing the impact of NBI colonoscopy on assessing the invasion depth in ECC. Overall, 112 patients were included; additionally pit pattern analysis was performed in 64 patients. The study investigated interesting questions.

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GASTROENTEROLOGY

Diagnosis of depth of invasion for early colorectal cancer using magnifying colonoscopy

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Key words
colon cancer, colorectal cancer, depth diagnosis, magnifying endoscopy, submucosal cancer.

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Abbreviations:
CRC, colorectal cancer; EMR, endoscopic mucosal resection; s.m., submucosal; s.m.-s., submucosal slight; s.m.-d., submucosal deep; LST-G, laterally spreading tumor granular type.

Abstract

Background and Aims: Early colorectal cancer (CRC) with submucosal deep (s.m.-d.) invasion should not be treated with endoscopic mucosal resection due to the higher incidence of lymph-node metastasis. It is, therefore, clinically important to accurately diagnose s.m.-d. lesions before treatment.

Methods: We analyzed the endoscopic features, including pit patterns, of early CRC with s.m.-d. invasion observed using magnifying colonoscopy. We retrospectively investigated 379 cases of early CRC. Lesions were divided into three macroscopic subtypes (pedunculated type, sessile type and superficial type) based on endoscopic findings. Eight endoscopic factors were evaluated retrospectively for association with s.m. invasion and then compared to histopathological findings.

Results: The superficial type had a significantly higher frequency of s.m.-d. invasion (52.4% [77/147] vs 24.6% [14/57] and 39.4% [69/175], P-value < 0.05, respectively, for pedunculated and sessile types). Based on multivariate analysis, an independent risk factor for s.m.-d. invasion was the existence of an invasive pit pattern in sessile and superficial types (odds ratios of 52.74 and 209.67, respectively). Fullness was also an independent risk factor for s.m.-d. invasion in the superficial type (odds ratio = 9.25). There were no independent risk factors for s.m.-d. invasion in the pedunculated type.

Conclusion: High magnification pit pattern diagnosis proved to be useful for predicting s.m.-d. invasion in sessile and superficial types although it was not as helpful with the pedunculated type.

Introduction

The incidence of colorectal cancer (CRC) has recently been increasing in Japan. Early CRC that consist of intramucosal cancers or submucosal (s.m.) cancers that only superficially invade the s.m. layer (s.m.-s.) can be removed by endoscopic mucosal resection (EMR).[1] Endoscopic treatment for early CRC is considered appropriate when the following conditions have been satisfied: a lesion is determined histopathologically to be well differentiated; invasion of the s.m. layer is < 1000 μm (s.m.-s.); and the lesion is negative for both lymphovascular invasion and sprouting.[2] Early CRC with s.m. deep (s.m.-d.) invasion should not be treated with EMR due to an increased risk of lymph-node (LN) metastasis, which has been reported to range from 6.9% to 22.2%.[2] Consequently, it is clinically important to accurately diagnose the depth of invasion before treatment.

A role for magnifying endoscopy in the colon has previously been indicated for the diagnosis of flat and depressed lesions, identification of dysplasia in ulcerative colitis, discrimination among polyp types and assessing the completeness of EMR.[3–5] Pit pattern classification for colonic lesions has also been well documented in the past. We have already reported that pit pattern analysis using magnification colonoscopy was useful in the diagnosis of invasive depth in early CRC, particularly flat and depressed lesions.[6–9] No studies have been reported as yet, however, that focused on the diagnosis of s.m. invasion in pedunculated and sessile type lesions.

The aim of this study was to analyze the endoscopic features (including pit patterns) of early CRC with s.m.-d. invasion from a large number of early CRC including pedunculated and sessile types using magnifying colonoscopy in order to determine the appropriate therapeutic strategy.

Methods

A total of 844 early CRC were resected endoscopically or surgically at the National Cancer Center Hospital in Tokyo between October 1998 and September 2005. In this series, 687 lesions were removed by endoscopic resection and 157 underwent surgical treatment. All lesions were examined using magnifying colonoscopy before treatment. Among them, 232 tumors were positive for s.m. invasion (612 intramucosal cancer lesions, 52 s.m.-s. lesions

and 180 s.m.-d. lesions). We also investigated the 256 consecutive intramucosal early CRC that were resected between January 2004 and September 2005 as our control group (EMR, 253 lesions; and surgery, three lesions) to help ascertain and evaluate differences between intramucosal and s.m. invasive cancers. From this total of 488 early colorectal lesions, 68 (13.9%) were excluded because the quality of their magnifying colonoscopy pictures was too poor for an accurate assessment either because of mucous or the pictures were out of focus leaving 420 (86.1%) lesions with suitable pictures for s.m. invasion diagnostic purposes. In addition, granular type laterally spreading tumors (LST-G) consist of several different shapes. For example, some LST-G have a flat elevated component surrounding a large nodule. It is therefore difficult to categorize such lesions as being either the protruded or flat type.[10,11] Accordingly, 41 LST-G were excluded from this study. Eventually, a total of 379 lesions were analyzed retrospectively (179 intramucosal lesions, 40 s.m.-s. lesions and 160 s.m.-d. lesions). These lesions were then divided into three subtypes according to the Paris classification: pedunculated type (type 0-Ip), sessile type (type 0-Is) and superficial type, which included slightly elevated (0-IIa), completely flat (0-IIb) and slightly depressed lesions without ulcer (0-IIc).[13]

Endoscopic examination

In our medical facility, all colonoscopies are performed with magnification. When a lesion was detected by conventional endoscopic examination, surface mucin was washed away with lukewarm water containing pronase (Pronase MS, Kaken Pharmaceutical, Tokyo, Japan) and then 0.4% indigo-carmine dye was sprayed over the lesion in order to enhance its surface detail. High magnification colonoscopes (CF-240ZI, PCF-240ZI and CF-200Z, Olympus Optical, Tokyo, Japan) were also used in this study. When a high magnification observation with indigo-carmine dye was not enough to determine the surface structure (pit pattern analysis), staining was added with 0.05% crystal violet.[14] The additional time usually needed to complete the magnification observation was less than 10 min including 30 s to one minute to wash the lesion, one minute for crystal violet staining and one to five minutes for the actual observation.

The depth of tumor invasion was classified as intramucosal, s.m.-s. (invasion < 1000 μm from the muscularis mucosa) and s.m.-d. (invasion ≥ 1000 μm from the muscularis mucosa). In order to elucidate the possible association between s.m.-d. invasion and various endoscopic findings, we selected eight endoscopic factors related to s.m. deep invasion from previously published literature[10–12] and then those eight endoscopic factors were investigated retrospectively.

1 Tumor Size—receiver operating characteristic (ROC) curves were used to determine the relationship between tumor size cut-offs and diagnostic accuracy. Based on these ROC curves, we chose tumor size cut-offs for pedunculated (20 mm), sessile (15 mm) and superficial (10 mm) tumors. The size for en bloc resected specimens was estimated by histopathological examination and for piecemeal resected specimens by reviewing endoscopic photographs.
2 Loss of Lobulation—with or without a loss of lobulation (Fig. 1).

Figure 1 Loss of lobulation.

Figure 2 Excavation.

3 Excavation—a crumbled, damaged area of the tumor that prevents observation of the surface structure (Fig. 2).
4 Demarcated Depressed Area—with or without such a demarcation (Fig. 3).
5 Stalk Swelling—a thickened and expanded stalk (Fig. 4).
6 Fullness—a bursting appearance due to expansive growth of the tumor (Fig. 5).
7 Fold Convergency—a fold convergency towards the tumor (Fig. 6).

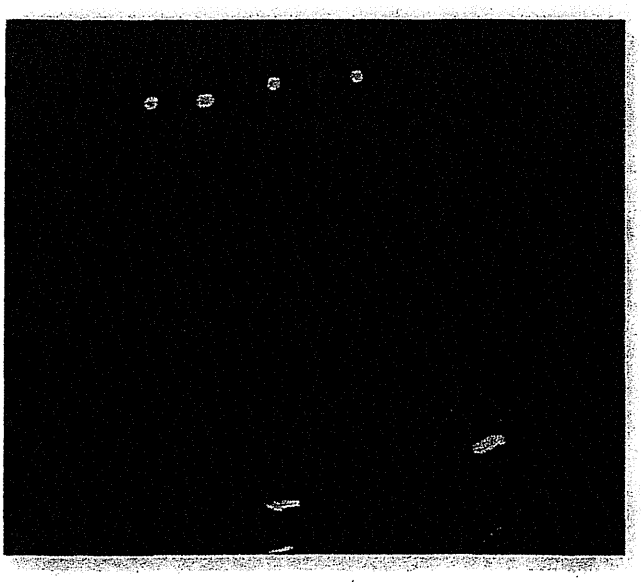

Figure 3 Demarcated depressed area.

Figure 5 Fullness.

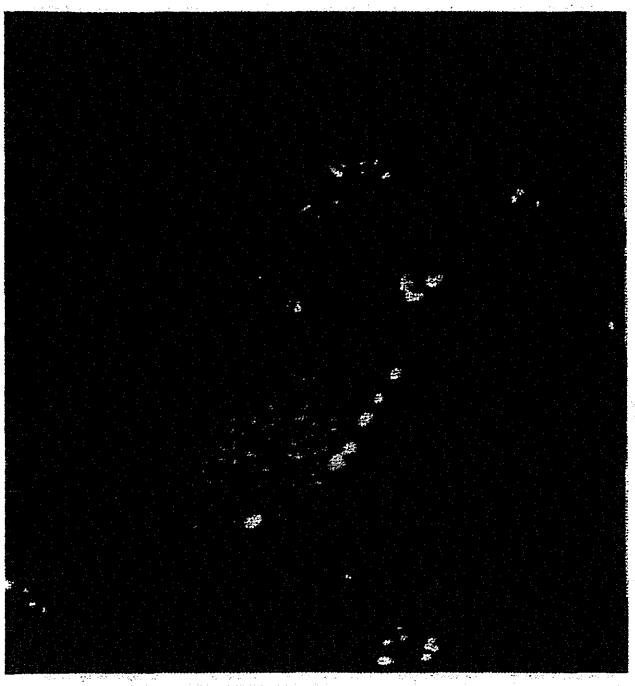

Figure 4 Stalk swelling.

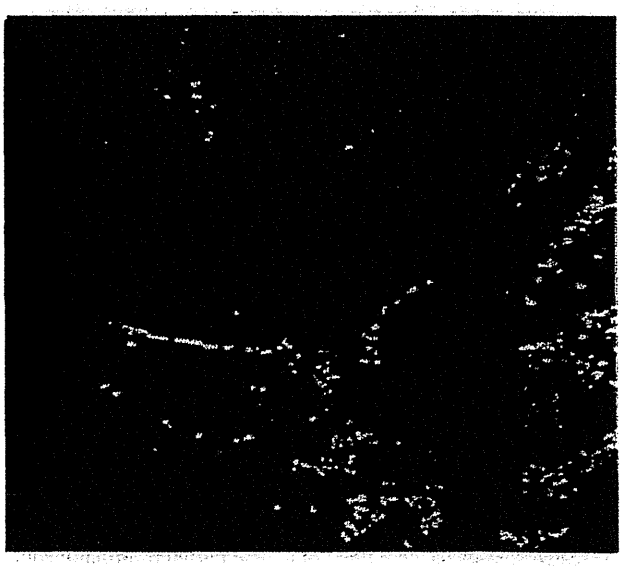

Figure 6 Fold convergency.

8 Pit Pattern—'Invasive pattern' or 'Non-invasive pattern' with the 'Invasive pattern' characterized by irregular and distorted epithelial crests observed in a demarcated area suggesting s.m.-d. invasion $\geq 1000\,\mu m$ while the 'Non-invasive pattern' did not have those two findings that suggested intramucosal neoplasia or s.m.-s. invasion $< 1000\,\mu m$ (Fig. 7a,b).[2,3,15]

Different endoscopic factors were assessed for each type. 'Stalk Swelling' was assessed for only the pedunculated type; 'Loss of Lobulation' and 'Excavation' were assessed for the pedunculated and sessile types; 'Fullness' and 'Fold Convergency' were assessed for the superficial type; and 'Size', 'Demarcated Depressed Area' and 'Pit Pattern' were assessed for all three types.

All endoscopic factors were determined retrospectively by three highly experienced endoscopists (H. I., Y. S. and T. M.) each of whom had previously performed over 1000 colonoscopies each year for more than five years. Final determination of endoscopic findings was decided by agreement of at least two of the three endoscopists. The relationships between the various endoscopic factors and the extent of s.m.-d. invasion were analyzed histopathologically in those lesions with s.m.-d. invasion.

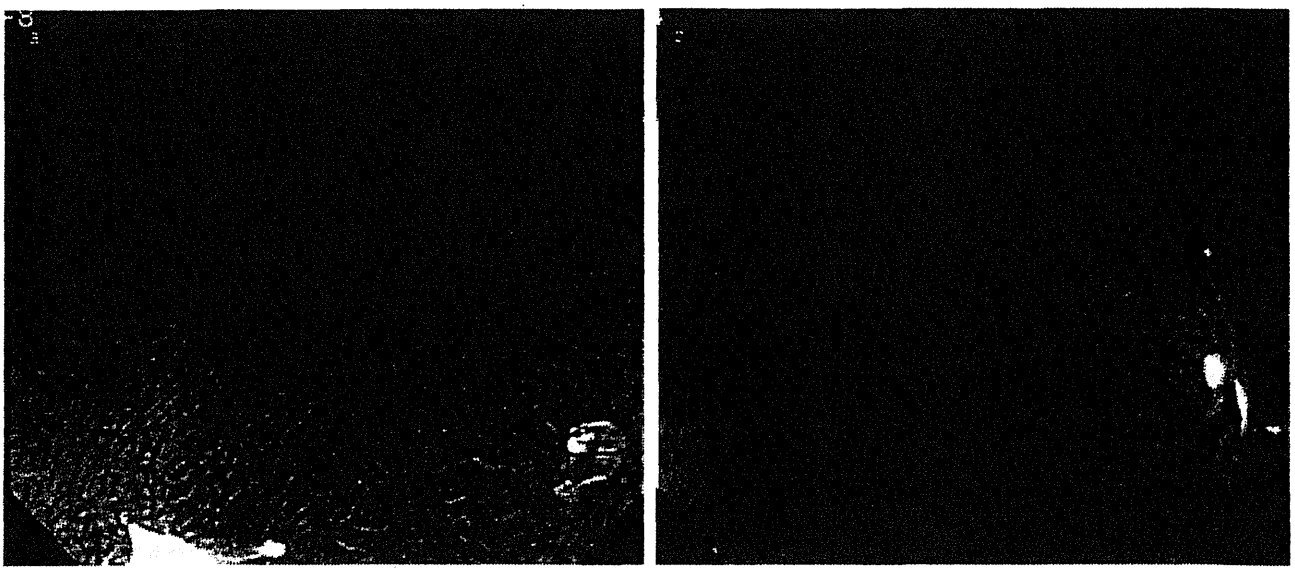

Figure 7 (a) Non-invasive pattern. (b) Invasive pattern.

Table 1 Clinicopathological characteristics of lesions

	Pedunculated type	Sessile type	Superficial type
Number of lesions	57	175	147
Tumor size (mean ± SD)	17.2 ± 6.5 mm	16.5 ± 8.5 mm	16.3 ± 8.6 mm
Histopathological diagnosis			
Intramucosal cancer	37	98	44
s.m.-s. (< 1000 μm)	6	8	26
s.m.-d. (≥ 1000 μm)	14 (24.6%)	69 (39.4%)	77 (52.4%)
Distribution			
Right colon	9 (15.8%)	43 (24.6%)	58 (39.5%)
Left colon	44 (77.2%)	60 (34.3%)	41 (27.9%)
Rectum	4 (7.0%)	72 (41.1%)	48 (32.6%)

SD, standard deviation; s.m.-d., submucosal deep invasion; s.m.-s., submucosal superficial invasion.

Histopathology

Resected specimens were fixed in a 10% buffered formalin solution, embedded on paraffin and then cut into 2–3 mm slices. Each section was stained with hematoxylin–eosin and then histopathologically diagnosed by a highly experienced pathologist. Histopathological diagnosis was based on the Vienna classification.[16] A microscope with a built-in ruler was used to determine the depth of s.m. invasion.

Statistical analysis

Among the three macroscopic subtypes, the proportion of s.m. invasion was compared using the χ^2-test. When characteristics showed a significant difference, we performed logistic regression including all such characteristics as part of the model. Statistical analyses were done with the SPSS 11.0 for Windows software package (SPSS, Chicago, IL, USA). Each test was two-sided and a P-value < 0.05 was defined as being statistically significant.

Results

Clinicopathological characteristics

Table 1 shows the clinicopathological characteristics of the early CRC examined in this study. The superficial type had a significantly higher frequency of s.m.-d. invasion compared to the pedunculated and sessile types (52.4% [77/147] vs 24.6% [14/57] and 39.4% [69/175], respectively). The pedunculated type was most commonly diagnosed in the left colon (77.2% [44/57]) in contrast to the sessile and superficial types, which were most commonly diagnosed in the rectum (41.1% [72/175]) and the right colon (39.5% [58/147]), respectively.

Endoscopic factors for submucosal deep invasion

In the pedunculated type, a larger tumor size (≥ 20 mm), loss of lobulation, excavation, the presence of an invasive pit pattern and

Table 2 Relationship between endoscopic factors and submucosal deep invasion in 57 pedunculated type lesions

		s.m.-d. ca./*n*	Univariate analysis	Multivariate analysis (includes pit pattern)		
			P-value	Odds ratio	95% CI	*P*-value
Size	≥ 20 mm	10/22	< 0.01	1.49	0.22–10.31	0.69
	< 20 mm	4/35				
Loss of lobulation	Present	12/28	< 0.01	3.15	0.47–21.01	0.24
	Absent	2/29				
Excavation	Present	7/11	< 0.001	2.52	0.36–17.47	0.35
	Absent	7/46				
Demarcated depressed area	Present	2/4	0.25	ND	ND	ND
	Absent	12/53				
Pit pattern	Invasive	7/9	< 0.0001	4.62	0.50–42.98	0.18
	Non-invasive	7/48				
Stalk swelling	Present	9/19	< 0.01	2.00	0.40–10.10	0.40
	Absent	5/38				

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

Table 3 Relationship between endoscopic factors and submucosal deep invasion in 175 sessile type lesions

		s.m.-d. ca./*n*	Univariate analysis	Multivariate analysis (includes pit pattern)		
			P-value	Odds ratio	95% CI	*P*-value
Size	≥ 15 mm	53/96	< 0.0001	1.86	0.61–5.66	0.28
	< 15 mm	16/79				
Loss of lobulation	Present	63/92	< 0.0001	5.99	1.76–20.42	< 0.01
	Absent	6/83				
Excavation	Present	42/57	< 0.0001	1.51	0.45–5.05	0.50
	Absent	27/118				
Demarcated depressed area	Present	19/29	< 0.01	0.20	0.03–1.44	0.11
	Absent	50/146				
Pit pattern	Invasive	55/61	< 0.0001	52.74	10.89–255.33	< 0.0001
	Non-invasive	14/114				

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

swelling of the stalk were each significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, however, there was no independent risk factor for s.m.-d. invasion (Table 2).

In the sessile type, the presence of a larger tumor size (≥ 1.5 mm), loss of lobulation, excavation, a demarcated depressed area and an invasive pit pattern were each significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, the independent risk factors for s.m.-d. invasion were loss of lobulation and the existence of an invasive pit pattern ($P < 0.01$, odds ratio = 5.99; and $P < 0.0001$, odds ratio = 52.74, respectively) (Table 3).

In the superficial type, fullness, fold convergency, a demarcated depressed area and an invasive pit pattern were significantly associated with an increased risk of s.m.-d. invasion according to univariate analysis. Based on multivariate analysis, the independent risk factors for s.m.-d. invasion were the existence of fullness and an invasive pit pattern ($P < 0.01$, odds ratio = 9.25; and $P < 0.0001$, odds ratio = 209.67, respectively) (Table 4).

Pit pattern analysis

The clinical classification of pit patterns has proven to be effective in differentiating intramucosal or s.m.-s. invasion < 1000 μm from s.m.-d. invasion (≥ 1000 μm). The calculated sensitivity, specificity, positive predictive value, negative predictive value and accuracy are shown in Table 5. The overall accuracy for differentiating intramucosal or s.m.-s. invasion from s.m.-d. invasion was 84.2% in the pedunculated type, 88.6% in the sessile type and 92.5% in the superficial type. The diagnostic accuracy of the invasive pit pattern was lower for pedunculated type lesions than for the other two macroscopic subtypes.

Number of endoscopic factors analysis

Diagnostic accuracy based on the number of positive endoscopic factors observed during conventional endoscopy performed without magnification is shown in Table 6. When a particular lesion included four or more such endoscopic factors, overall accuracy was highest for the pedunculated type (86.0%). As for both the sessile and superficial types, however, overall accuracies of 81.1% and 80.3%, respectively, were highest when a particular lesion included two or more of the endoscopic factors.

Table 4 Relationship between endoscopic factors and submucosal deep invasion in 147 superficial type lesions

		s.m.-d. ca./n	Univariate analysis	Multivariate analysis (includes pit pattern)		
			P-value	Odds ratio	95% CI	*P*-value
Size	≧ 10 mm	68/123	0.11	ND	ND	ND
	< 10 mm	9/24				
Fullness	Present	66/86	< 0.0001	9.25	2.14–40.00	< 0.01
	Absent	11/61				
Fold convergency	Present	38/50	< 0.0001	1.99	0.50–7.97	0.33
	Absent	39/97				
Demarcated depressed area	Present	52/68	< 0.0001	1.92	0.45–8.15	0.37
	Absent	25/79				
Pit pattern	Invasive	76/86	< 0.0001	209.67	23.05–1907.48	< 0.0001
	Non-invasive	1/61				

CI, confidence interval; *n*, total number; ND, no data; s.m.-d. ca., submucosal deep invasion cancer.

Table 5 Diagnostic analysis of invasive pit pattern by macroscopic type

	Macroscopic type		
	Pedunculated type	Sessile type	Superficial type
Sensitivity	50.0%	79.7%	98.7%
Specificity	95.3%	94.3%	85.7%
PPV	77.8%	90.2%	88.4%
NPV	85.4%	87.7%	98.4%
Overall Accuracy	84.2%	88.6%	92.5%

The χ^2-test evaluates differences in sensitivity and there were significant differences among all three groups ($P < 0.05$).
NPV, negative predictive value; PPV, positive predictive value.

Discussion

Diagnosis of submucosal deep invasive cancer

We investigated various endoscopic factors including high magnification diagnosis of pit patterns in order to evaluate the predictive factors for s.m.-d. invasion in three macroscopic subtypes of early CRC. A higher incidence of s.m.-d. invasion in the superficial type and a difference in the diagnostic accuracy for predicting s.m.-d. invasion between the pedunculated type and the other two macroscopic types were found in our study.

In the superficial type, fullness and existence of the invasive pit pattern were independent risk factors for s.m.-d. invasion. Yokota *et al.* reported that conventional endoscopic findings were subjective,[12] however, fullness may not be a universal factor for determining s.m.-d. deep invasion. In the sessile type, multivariate analysis showed that loss of lobulation and existence of the invasive pit pattern were each independent risk factors for s.m.-d. invasion. A total of 68 lesions were excluded because of the poor quality of their magnifying colonoscopy pictures, however, so there could very well be a bias towards better pit pattern diagnostic analysis results in this study for both the superficial and sessile types.

In the pedunculated type, we were unable to demonstrate any independent endoscopic factors despite using pit pattern analysis. In addition, a combination of factors in pedunculated type lesions examined without magnification indicated that size and stalk swelling together had the same degree of overall diagnostic accuracy as produced by an analysis of invasive pit pattern using magnification. These results indicated that it is difficult to estimate the depth of tumor invasion in pedunculated type lesions using current magnification methods.

Endoscopic diagnosis versus non-lifting sign

In previous studies, Uno *et al.* reported the clinical usefulness of the non-lifting sign to predict the depth of invasion prior to EMR for early CRC.[17] In addition, Ishiguro *et al.* classified s.m. extension of early colorectal cancer as s.m.1 (infiltration into the upper third of the s.m. layer), s.m.2 (middle third) or s.m.3 (lower third) according to the vertical level of s.m. invasion. They reported that the non-lifting sign indicated s.m.3 invasion had a sensitivity of 100% and a specificity of 83% although only 30.4% of s.m.2 cancers were non-lifting sign positive in their study.[18]

Our group reported that the sensitivity, specificity and accuracy of the non-lifting sign (61.5%, 98.4% and 94.8%, respectively) were insufficient in comparison with endoscopic diagnosis of invasion depth (84.6%, 98.8% and 97.4%, respectively).[19] Given these results, magnifying colonoscopy can be considered more effective than the non-lifting sign in distinguishing s.m.-d. invasive cancer based on the techniques and methods used in this study.

Magnifying colonoscopy versus endoscopic ultrasonography

We previously reported that high magnification colonoscopy was superior to endoscopic ultrasonography (EUS) for the determination of invasion depth in early CRC.[13] In contrast, Hurlstone *et al.* demonstrated the superiority of EUS mini-probe staging over magnification colonoscopy.[20] At the present time, it is unclear whether magnification colonoscopy or EUS is superior for staging purposes. There is a learning curve associated with both modalities so the results can be influenced by the skill and experience of the endoscopist performing the procedure.

Magnifying endoscopy

We routinely use magnifying colonoscopy because a magnifying endoscope enables standard conventional observations, but can

Table 6 Diagnostic analysis according to number of positive endoscopic factors

		Number of positive endoscopic factors				
		≧1	≧2	≧3	≧4	≧5
Pedunculated type	Sensitivity	92.7%	71.4%	64.3%	42.7%	14.3%
	Specificity	44.2%	67.4%	86.1%	100%	100%
	PPV	35.1%	41.7%	60.0%	100%	100%
	NPV	95.0%	87.9%	88.1%	84.3%	78.2%
	Overall accuracy	56.1%	68.4%	80.7%	86.0%	79.0%
Sessile type	Sensitivity	97.1%	87.0%	52.2%	13.0%	ND
	Specificity	46.2%	77.4%	90.6%	99.1%	ND
	PPV	54.0%	71.4%	78.3%	90.0%	ND
	NPV	96.1%	90.1%	74.4%	63.4%	ND
	Overall accuracy	66.3%	81.1%	75.4%	65.1%	ND
Superficial type	Sensitivity	100%	87.0%	45.5%	1.3%	ND
	Specificity	34.3%	72.9%	91.4%	100%	ND
	PPV	62.6%	77.9%	85.4%	100%	ND
	NPV	100%	83.6%	60.4%	48.0%	ND
	Overall accuracy	68.7%	80.3%	67.4%	48.3%	ND

ND, no data; NPV, negative predictive value; PPV, positive predictive value.

also provide images from low to high magnification using a one-touch operational system. It is possible to distinguish between non-neoplastic and neoplastic lesions and estimate depth of tumor invasion in less than 10 minutes. The insertion technique and manipulation of the magnifying endoscope also are similar to those of a conventional endoscope during colonoscopy.[21,22]

Treatment strategy

In considering therapeutic strategies, EMR should be the first-line treatment for intramucosal and s.m.-s. early CRC because it is less invasive. LN metastasis is more frequently present in s.m.-d. invasive cancer,[23,24] however, so we should avoid EMR for s.m.-d. invasive cancer because histopathological assessment is more difficult. In addition, incomplete EMR is thought to cause accelerated growth of any residual cancer and is also considered to be a positive risk factor for distant metastasis.[25,26] Recognizing the importance of reported endoscopic factors for predicting s.m.-d. invasion therefore is essential in determining the proper treatment choice in any given case.

For sessile and superficial type lesions endoscopically diagnosed as having an invasive pit pattern, a high percentage of cases revealed invasive cancer, particularly s.m.-d. cancer, so surgical resection is undoubtedly the appropriate treatment. Those lesions endoscopically diagnosed as having a non-invasive pattern, however, were mostly limited to the intramucosal layer, which makes EMR feasible. It is also technically possible now to remove large superficial lesions using the more recently developed endoscopic submucosal dissection procedure.[27–30]

In the pedunculated type, it is difficult to accurately estimate the depth of s.m.-d. invasion prior to endoscopic treatment, but the endoscopic resection of a pedunculated polyp is relatively easy from a technical point of view. It is recommended therefore that a pedunculated type lesion first be removed endoscopically followed by a histopathological determination of the depth of invasion. A surgical resection should then be performed when stalk invasion or lymph-vessel involvement has been revealed histopathologically.

Limitations

This was a retrospective study conducted in a single center so the results need to be confirmed in a prospective multi-center trial. In addition, only pedunculated, sessile and superficial lesion macroscopic subtypes were included in this study.

Conclusion

Pit pattern high magnification diagnosis proved to be useful for predicting s.m.-d. invasion in sessile and superficial type lesions, although it was not helpful with the pedunculated type. Consequently, diagnostic endoscopic treatment is advisable for pedunculated early CRC.

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