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ORIGINAL ARTICLE—ALIMENTARY TRACT

Evaluation of new subclassification of type V_I pit pattern for determining the depth and type of invasion of colorectal neoplasm

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Abstract

Background Colorectal neoplasms with a type V_I pit pattern include various lesions, such as adenomas, intramucosal cancers, and submucosal carcinomas.

Methods We analyzed 96 colorectal neoplasms with a type V_I pit pattern and identified six different variants: (1) unclear outline of the pit; (2) irregular margins of the pit; (3) narrowing of the pit; (4) ragged array of the pit; (5) high residual density of the pit; (6) abnormal branching of the pit. We examined the relationship between the appearance of each V_I pit pattern and histology, including the depth of invasion.

Results In univariate logistic regression analysis the unclear outline, irregular margins, and narrowing of the pit were significantly associated with a submucosal (SM) invasion ≥1000 μm ($P < 0.01$). In multivariate logistic regression analysis, unclear outline of the pit was shown to be the only significant predictor of highly invasive submucosal cancer (odds ratio = 24.20, $P < 0.0001$). Regarding tumor morphology, the following were significantly associated with an SM invasion ≥1000 μm: in protruded type, ragged array ($P = 0.022$), irregular margins of the pit ($P = 0.011$), and unclear outline of the pit ($P < 0.01$); in flat type, irregular margins of the pit ($P < 0.01$) and unclear outline of the pit ($P < 0.01$); and in the depressed type, narrowing of the pit ($P = 0.015$) and unclear outline of the pit ($P < 0.01$).

Conclusions Subclassification of the type V_I pit pattern is useful for determining the depth of invasion of colorectal neoplasms.

Keywords Magnifying chromoendoscopy · Colon cancer · Colonoscopy

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Introduction

Endoscopic mucosal resection (EMR) [1] is becoming more widely practiced worldwide, as are the techniques of high-magnification colonoscopy and chromoendoscopy [2]. Several studies have suggested that there is little risk of lymph node metastasis from an early colorectal carcinoma that involves the superficial layer of the submucosa only [3–7]. However, when there is massive submucosal infiltration, it appears that there are metastases to about 10% of lymph nodes [8–12]. Kitajima et al. reported a retrospective analysis of a total of 865 submucosal invasive colorectal carcinomas (SICC) from 865 patients who had undergone surgical resection at six institutions affiliated with the Japanese Society for Cancer of the Colon and Rectum [5]. They found that, with SICC, the rate of lymph node metastasis was also 0% if submucosal (SM) infiltration was <1000 μm. As a result of this study, the Japanese Society for Cancer of the Colon and Rectum proposed that complete EMR of submucosal carcinoma with curative intent should be limited to lesions meeting the following new histopathologic criteria: (1) SM invasion depth of <1000 μm, (2) well- to moderately differentiated adenocarcinoma including the invasive portion, and (3) no vessel involvement [5–7]. In accordance with these proposed criteria, it has become important to distinguish an SM invasion ≥1000 μm from an SM invasion <1000 μm prior to treatment of a submucosal carcinoma, in order to reduce the number of needless surgical resections.

Pit pattern (i.e., the shape of the opening of a colorectal crypt) classification of colorectal neoplasia based on stereomicroscopy, as proposed by Kudo et al. [13, 14] is reported to be useful for evaluating the histological features of a tumor for distinguishing neoplasms from non-neoplasms, as well as adenomas from cancer, and also for diagnosing the depth of early stage colon cancer [15, 16].

Recent advances in magnifying endoscopy have made it possible to examine pit patterns on the tumor surface even during routine colonoscopic examinations, and the results are as reliable as those obtained via stereoscopic observation of resected specimens [17–20]. Several studies have compared diagnoses based on histology with those based on pit patterns, and their results show a concordance of 90% or higher [14, 16, 21].

Currently, seven pit pattern classes are recognized: types I, II, III_s, III_L, IV, V_I, and V_N (Fig. 1) [14, 22]. Almost all lesions with a type V_N pit pattern are indicative of deep submucosal invading cancers [23]. Therefore, surgical resection is indicated for type V_N pit pattern lesions.

By contrast, type V_I pit pattern is associated with a variety of lesions, such as adenomas, intramucosal cancers, and submucosal carcinomas, with either an SM invasion <1000 or ≥1000 μm [24, 25]; thus, it is difficult to decide upon a therapeutic strategy on the basis of the current pit pattern classification system. Indeed, type V_I pit patterns encompass a wide spectrum of irregularities and the degree of irregularity varies from mild to severe. It is necessary to analyze the type V_I pit pattern in more detail in order to determine the appropriate therapeutic strategy for patients with tumors displaying this pattern.

In this study, we evaluated the clinical usefulness of the subclassification of type V_I pit patterns in determining the histology/invasion depth of colorectal neoplasms. In addition, we investigated if there was a correlation between the subcategories of type VI pit pattern and morphological classification.

Patients and methods

We retrospectively analyzed 247 colorectal neoplasm cases, diagnosed as having a type V pit pattern, and which were resected surgically or by EMR at Juntendo University Hospital from March 2002 to June 2006.

When a lesion was detected by standard colonoscopic observation, the surface mucus was washed away with lukewarm water, and indigo carmine dye was spread over the lesion. This dye enhances the colonoscopic appearance because it is retained within the pits and grooves of the mucosal surface. For more precise assessment, further staining was performed by using crystal violet (CV) 0.025%, which was applied with a nontraumatic steel-tipped catheter (Olympus Optical Co. Ltd., Tokyo, Japan), after a second water wash phase and mucolysis, using locally applied *N*-acetylcysteine (2 mg per ml). As CV is a reactive dye, actively taken up by the colonic crypts, a 2-min ‘fixing phase’ was allowed before obtaining further magnification views. The diameter of the lesions was estimated by using the width of standard fully opened biopsy forceps (4 mm, Olympus, Japan) with the vertical height estimated by placing the tip of the closed forceps next to the lesion (2 mm). A height/width ratio could thus be established for each lesion. Identified lesions were then classified according to the Japanese Research Society (JRS) guidelines (Fig. 2). To evaluate pit patterns, we used a magnifying videoendoscope system (CF240Z, PCF240Z, and H260AZI; Olympus, Optical Co. Ltd., Tokyo, Japan) with zoom functions ranging from ×17 to ×135 and a digital image filing system. Lesions which were suspected as cancerous were examined for invasion depth as follows: (1) by a standard colonoscopic view; (2) after staining with crystal violet, the pit pattern of the lesion was examined, and those lesions diagnosed with no massive SM invasion were resected endoscopically, while those diagnosed with massive SM invasion underwent surgical resection. After detailed observation, all lesions were resected surgically or by EMR. Specimens were pinned to a board and fixed in 10% buffered formalin for 12–48 h. These specimens were then cut into 2- to 3-mm blocks. Histologic diagnosis was based on the World Health Organization criteria [26]. The still images were downloaded from an endoscopic filing system, Scope Reader M1 (AZ Co. Ltd., Sendai, Japan) in JPEG format; file size of the downloaded image was about 100 kilobyte, with a pixel array of 640 × 480 and 24-bit color. When an unstructured area was observed in a lesion, it was subclassified into type V_N. Lesions with a type V_N pit pattern were excluded from further analysis. Thus, of the 247 cases diagnosed with a type V pattern, 96 cases (92 patients, males 67 and females 25; mean age 61.4 years) correctly diagnosed with a V_I pit pattern were examined further. In this study, massive submucosal invasion was defined as an invasion depth of at least 1000 μm by microscopic findings [5, 7, 22]. The depth of vertical invasion in the submucosal layer was measured in micrometers from the muscularis mucosae to the deepest cancer gland. However, in cases where the muscularis mucosae could not be identified owing to carcinomatous invasion, we measured from the superficial aspect to the deepest cancer gland [5, 23, 27].

We identified six different categories of the type V_I pit pattern with respect to the appearance of the shape of the

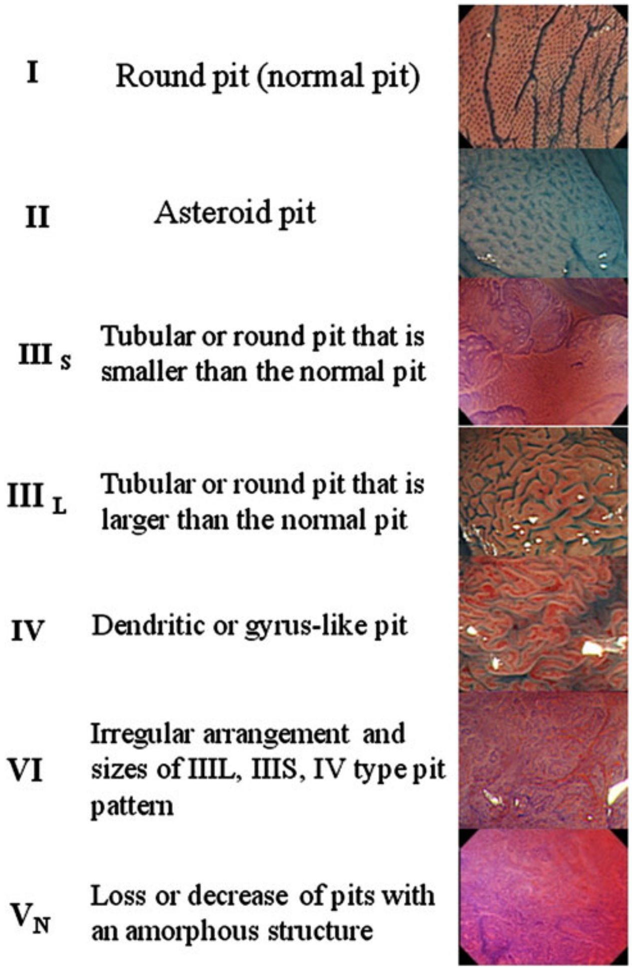

Fig. 1 Classification of pit patterns of colorectal lesions

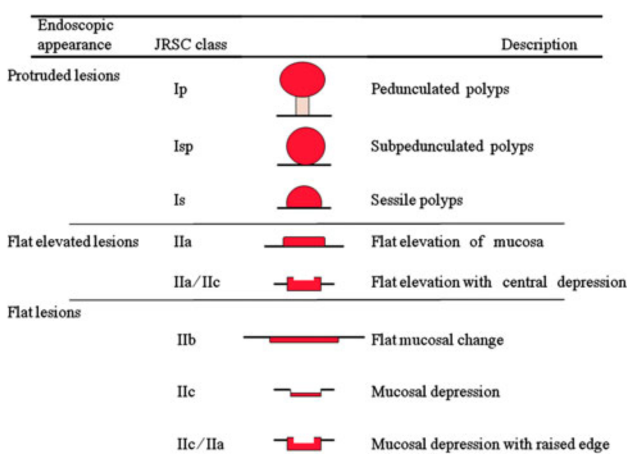

Fig. 2 The Japan Research Society (JRSC) guidelines for morphological classification of colorectal lesions

crypt opening (Fig. 3a–f). These comprised three types of mild irregular V_I pit pattern (ragged array, high residual pit density, abnormal branching of the pit) and three types of severe irregular V_I pit pattern (unclear outline, irregular margins, narrowing of the pit). All images were then placed in a random order according to a computer-generated random number sequence. Each image was analyzed by two endoscopists with more than 10 years of experience in the field of colonoscopy who were blinded to the depth of the tumors (and unaware of the histopathological diagnosis).

The lesions were divided into two groups: (1) group A: less invasive tumors ($n = 57$), comprising adenomas, intramucosal cancers, and shallow submucosal invasive cancers (depth of vertical invasion <1000 μm); and (2) group B: more invasive tumors ($n = 39$), comprising deep invading submucosal cancers (depth of vertical invasion 1000 μm). The relationship between each subtype and cancer depth was analyzed to evaluate the utility of the subtypes in establishing the extent of tumor invasion.

Firstly, we conducted a univariate logistic regression analysis between each subtype and cancer depth. Because more than one of these six subtypes of V_I pit pattern could appear in one lesion, a multivariate logistic regression analysis was subsequently conducted. In addition, we investigated the character of the subclassified pit pattern by categorizing according to a morphological classification. According to the JRSC classification, tumor morphology is classified into a protruded type, flat type, and depressed type (Fig. 2). Data were evaluated by the chi-square test and Fisher's exact test; $P < 0.05$ was taken to indicate significance. All statistical analyses were performed using ESUMI statistical software, version 1.0.

Results

Results of univariate logistic regression analysis of the six subtypes of V_I pit pattern with SM invasion ≥1000 μm

An unclear outline of the pit was identified in 17.5% (10/57) of cases in group A and 79.5% (31/39) in group B ($P < 0.01$) (Table 1). Irregular margins of the pit were identified in 17.5% (10/57) of cases in group A, and 46.2% (18/39) in group B ($P < 0.01$). Narrowing of the pit was identified in 14.0% (8/57) of cases in group A, and 48.7% (19/39) in group B ($P < 0.01$). Unclear outline of the pit, irregular margins of the pit, and narrowing of the pit (i.e., appearances classified with a severe irregular pit structure) were significantly associated with invasive cancers ($P < 0.01$). Ragged array was identified in 96.5% (55/57) of cases in group A, and 84.6% (33/39) in group B ($P = 0.059$). High residual pit density was identified in 71.9% (41/57) of cases in group A, and in 56.4% (22/39) in group B ($P = 0.131$). Abnormal branching was identified

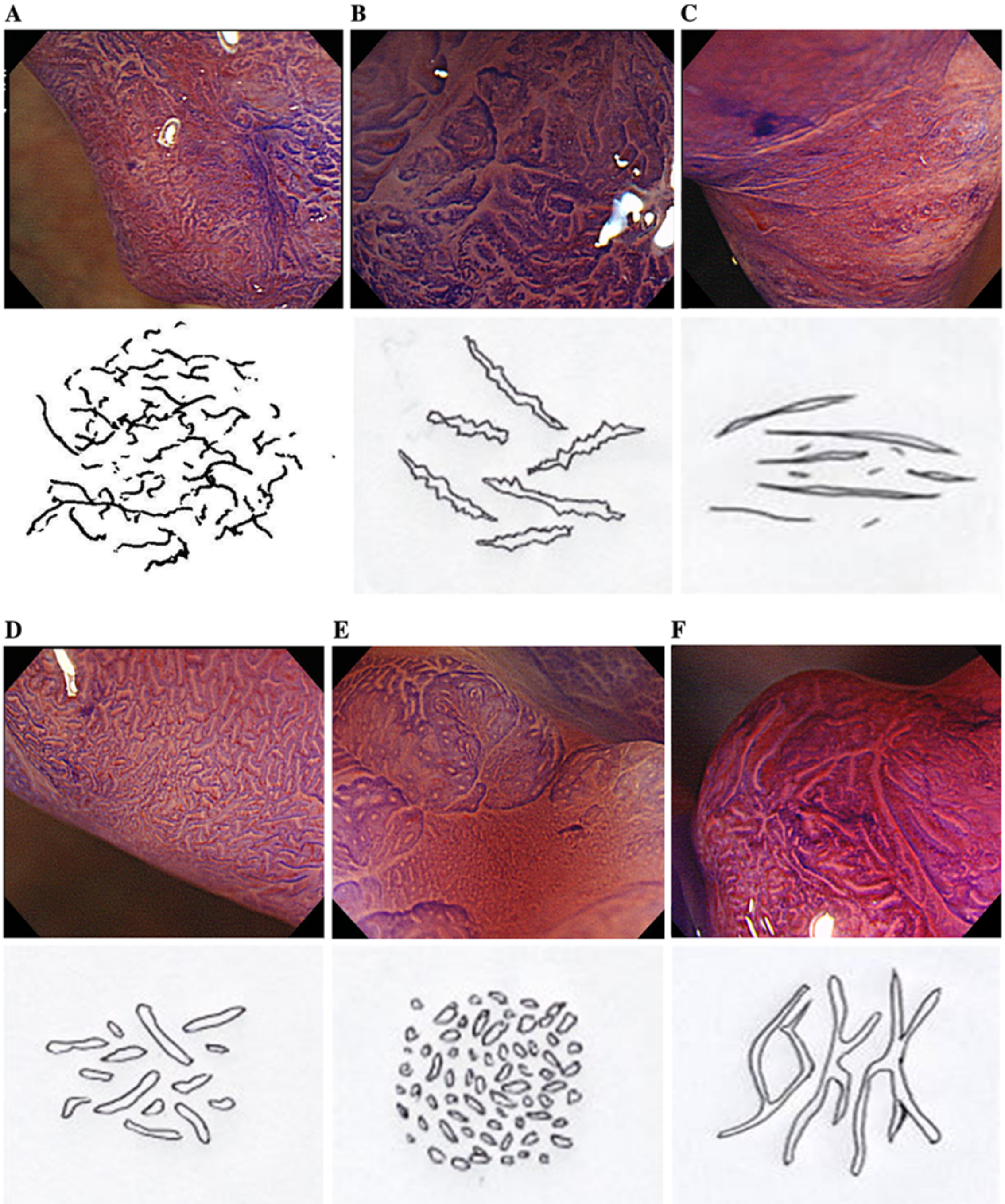

Fig. 3 **a** Unclear outline of the pit: the margin cannot be traced around the whole circumference of the gland duct. The starting point and end point cannot be followed. **b** Irregular margins of the pit: the margin of the gland duct is irregular and prominently rugged; the outline is clear. **c** Narrowing of the pit: the diameter of the gland duct orifice is uniform, and a narrowing of the duct can be observed. **d** Ragged array: there is an uneven appearance and lack of polarity to the direction of the pits. **e** High residual pit density: small irregular pits, which are densely gathered. **f** Abnormal branching: the pits have an abnormal branching appearance

in 19.3% (11/57) of cases in group A, and 20.5% (8/39) in group B ($P = 0.999$). Ragged array, high residual pit density, and abnormal branching (i.e., appearances classified as having a mild irregular pit structure) were not predictors of a more invasive submucosal cancers ($P > 0.05$).

Association between the six subtypes of V_I pit pattern and depth of invasion in the protruded type (Is, Isp, Ip) of colon neoplasms

The protruded type was identified in 47 cases (28 cases in group A; 19 cases group B) (Table 2). Unclear outline of the

Table 1 Results of univariate logistic regression analysis for predictors of SM invasion ≥1000 μm

	Group A (n = 57)	Group B (n = 39)	P value
Unclear outline of the pit	17.5% (10/57)	79.5% (31/39)	<0.01
Irregular margins of the pit	17.5% (10/57)	46.2% (18/39)	<0.01
Narrowing of the pit	14.0% (8/57)	48.7% (19/39)	<0.01
Ragged array	96.5% (55/57)	84.6% (33/39)	0.059
High residual pit density	71.9% (41/57)	56.4% (22/39)	0.131
Abnormal branching	19.3% (11/57)	20.5% (8/39)	0.999

Group A: adenoma, mucosal cancer, submucosal cancer invading <1000 μm

Group B: submucosal cancer invading deeper than 1000 μm

Table 2 Association between the six subtypes of V_I pit pattern and depth of invasion in the protruded type (Is, Isp, Ip) of colon neoplasms

	Group A (n = 28)	Group B (n = 19)	P value
Unclear outline of the pit	25% (7/28)	73.7% (14/19)	<0.01
Irregular margins of the pit	7.1% (2/28)	36.8% (7/19)	0.011
Narrowing of the pit	17.9% (5/28)	42.1% (8/19)	0.068
Ragged array	86.4% (27/28)	73.7% (14/19)	0.022
High residual pit density	50.0% (14/28)	31.6% (6/19)	0.210
Abnormal branching	21.4% (6/28)	42.1% (8/19)	0.128

Group A: adenoma, mucosal cancer, submucosal cancer invading <1000 μm

Group B: submucosal cancer invading deeper than 1000 μm

pit was identified in 25.0% (7/28) of cases in group A, and 73.7% (14/19) in group B. Irregular margins of the pit were identified in 7.1% (2/28) of cases in group A, and 36.8% (7/19) in group B. Narrowing of the pit was identified in 17.9% (5/28) of cases in group A, and 42.1% (8/19) in group B. Ragged array was identified in 86.4% (27/28) of cases in group A, and 73.7% (14/19) in group B. High residual pit density was identified in 50.0% (14/28) of cases in group A, and 31.6% (6/19) in group B. Abnormal branching was identified in 21.4% (6/28) of cases in group A, and 42.1% (8/19) in group B. In the protruded type, there was a significant association between unclear outline of the pit ($P < 0.01$), irregular margins of the pit ($P = 0.011$), and ragged array ($P = 0.022$) and SM invasion ≥1000 μm.

Association between the six subtypes of V_I pit pattern and depth of invasion in the flat type (IIa) of colon neoplasms

The flat type was identified in 28 cases (24 cases group A; 4 cases group B) (Table 3). Unclear outline of the pit was identified in 12.5% (3/24) of cases in group A, and 100% (4/4) in group B. Irregular margins of the pit were identified in 33.3% (8/24) of cases in group A, and 100% (4/4) in group B. Narrowing of the pit was identified in 12.5% (3/24) of cases in group A, and 25.0% (1/4) in group B. Ragged array was identified in 95.8% (23/24) of cases in group A, and 100% (4/4) in group B. High residual pit density was identified in 91.7% (22/24) of cases in group A, and 75.0% (3/4) in group B. Abnormal branching was identified in 20.8% (5/24) of cases in group A, and 0% (0/4) in group B. In the flat type, there was a significant association between unclear outline of the pit ($P < 0.01$) and irregular margins of the pit ($P < 0.01$) and SM invasion ≥1000 μm.

Association between the six subtypes of V_I pit pattern and depth of invasion in the depressed type (IIc, IIc + IIa, IIa + IIc) of colon neoplasms

The depressed type was identified in 21 cases (5 cases group A; 16 cases group B) (Table 4). Unclear outline of the pit was identified in 0% (0/5) of cases in group A, and 81.3% (13/16) in group B. Irregular margins of the pit were identified in 0% (0/5) of patients in group A, and 43.8% (7/16) in group B. Narrowing of the pit was identified in 0% (0/5) of cases in group A, and 62.5% (10/16) in group B. Ragged array was identified in 100% (5/5) of cases in group A, and 81.3% (13/16) in group B. High residual pit density was identified in 100% (5/5) of cases in group A, and 81.3% (13/16) in group B. No cases of abnormal branching were identified in either group. In the depressed type, there was a significant association between unclear outline of the pit ($P < 0.01$) and narrowing of the pit ($P = 0.015$) and SM invasion ≥1000 μm.

Results of multivariate logistic regression analysis for predictors of SM ≥1000 μm

In multivariate logistic regression analysis, unclear outline of the pit was shown to be the only significant predictor of SM invasion ≥1000 μm (odds ratio = 24.20, $P < 0.0001$) (Table 5).

Table 3 Association between the six subtypes of V_I pit pattern and depth of invasion in the flat type (IIa) of colon neoplasms

	Group A (n = 24)	Group B (n = 4)	P value
Unclear outline of the pit	12.5% (3/24)	100% (4/4)	<0.01
Irregular margins of the pit	33.3% (8/24)	100% (4/4)	<0.01
Narrowing of the pit	12.5% (3/24)	25% (1/4)	0.508
Ragged array	95.8% (23/24)	100% (4/4)	0.678
High residual pit density	91.7% (22/24)	75% (3/4)	0.318
Abnormal branching	20.8% (5/24)	0% (0/4)	0.313

Group A: adenoma, mucosal cancer, submucosal cancer invading <1000 μm

Group B: submucosal cancer invading deeper than 1000 μm

Table 4 Association between the six subtypes of V_I pit pattern and depth of invasion in the depressed type (IIc, IIc + IIa, IIa + IIc) of colon neoplasms

	Group A (n = 5)	Group B (n = 16)	P value
Unclear outline of the pit	0% (0/5)	81.3% (13/16)	<0.01
Irregular margins of the pit	0% (0/5)	43.8% (7/16)	0.070
Narrowing of the pit	0% (0/5)	62.5% (10/16)	0.015
Ragged array	100% (5/5)	81.3% (13/16)	0.296
High residual pit density	100% (5/5)	81.3% (13/16)	0.296
Abnormal branching	0% (0/5)	0% (0/16)	–

Group A: adenoma, mucosal cancer, submucosal cancer invading <1000 μm

Group B: submucosal cancer invading deeper than 1000 μm

Table 5 Results of multivariate logistic regression analysis for predictors of SM invasion ≥1000 μm

	Odds ratio	95% CI	P value
Unclear outline of the pit	24.20	5.59–97.78	<0.0001
Irregular margins of the pit	1.05	0.26–4.29	0.94
Narrowing of the pit	0.73	0.15–3.66	0.70
Ragged array	0.12	0.012–1.13	0.07
High residual pit density	0.80	0.19–3.36	0.76
Abnormal branching	0.86	0.18–4.18	0.85

Adjusted odds ratio for submucosal cancer with depth ≥1000 μm

Group A: adenoma, mucosal cancer, submucosal cancer invading <1000 μm

Group B: submucosal cancer invading deeper than 1000 μm

95% CI confidence intervals

Discussion

In December, 2005, the research group of the Ministry of Health, Labour and Welfare for the elucidation of the diagnostic meaning of pit structure in the large intestine neoplastic lesion classified severe irregular pit structure into the following five groups: (1) Unclear outline of the pit: the margin cannot be traced around the whole circumference of the pit. (2) Irregular margins of the pit: the margin of the pit is irregular and prominently rugged, but the outline is clear. (3) Narrowing of the pit: the diameter of the pit is uniform, and a narrowing of the pit is observed. (4) Unclear staining characteristics of the areas between pits: debasement of the stainability of the stromal area (surface covering the epithelium). (5) Scratch sign: the surfaces of the epithelium have a scratched appearance. Some studies have since been conducted using this classification. Onishi et al. classified V_I pit pattern into four types, as follows: (1) existing pits, (2) marginal irregularities in the gland duct, (3) narrowing of the gland duct lumen, and (4) unclear outline of the gland duct; they revealed that the probability of deep submucosal invading cancer was significantly higher in patterns negative for (1) and positive for (2)–(4). In that study, they developed a scoring system, which although is useful, is nevertheless complicated and makes it impossible to arrive at an on-site diagnosis [24]. Kanao et al. reported that irregular pit margins, and unclear staining characteristics of the areas between pits, are significant predictors for submucosal invasion of colorectal neoplasms of 1000 μm or more [25]. They reported that there may be a relationship between the expression of molecular markers and detailed magnifying colonoscopy features of the type V_I pit pattern. They estimated that the changes in the appearance of the pits are caused by the process of submucosal infiltration of the colorectal neoplasm, but the mechanism underlying this process is not clear and the relationship between pathology and pit pattern was not investigated [25]. In this current study, we selected unclear outline, irregular margins, and narrowing of the pit as being the most objective from the five classified severe irregular pit structures. In addition, we chose the definitions ragged array, high residual density, and abnormal branching, which are generally accepted as representing the mild form of irregular pattern.

The present study revealed that the lesions subclassified as severe irregular V_I pit pattern, namely unclear outline of the pit, irregular margins of the pit, and narrowing of the pit were mainly group B, and were therefore significant predictors for submucosal invasion of colorectal neoplasms ≥1000 μm. Multivariate logistic regression analysis also indicated that unclear outline is the only significant predictor for submucosal invasion of colorectal neoplasms ≥1000 μm. Although these results are similar to the previous report, the merit of our results is that the diagnosis was made by endoscopy. Furthermore, we included an examination of the type of V_I pit pattern that tended to be associated with morphological appearance. The protruded type was significantly associated with the presence of unclear outline, irregular margins of the pit, and ragged array; the flat type with an unclear outline, irregular margins of the pit; and the depressed type with unclear outline and narrowing of the pit. The relationship between these irregular patterns and morphological appearance could also be helpful for the diagnosis of deep invasive cancer.

In many cases, a submucosal deep invasive cancer is accompanied by a shallow invasive portion and an adenoma component. Because mild irregular patterns are associated with this shallow part of the lesion, mild irregularity also appeared in high frequency in cases of submucosal deep invasive cancer. Therefore, mild irregular patterns occurred with a similar high frequency in both group A and group B. In such situations, attention should be paid to the relative number of severe irregular patterns.

In addition, we found an overlap in the appearance of patterns in the various subclassification groups. Two or more of these six pattern subtypes were often observed together in the same lesion; therefore, we analyzed our data using multivariate logistic regression, and an unclear outline of the pit was shown to be the only a significant predictor of SM invasion $\geq$1000 μm. We believe that, if we can establish a correlation between the pit pattern and a morphological classification, the former could be valuable in establishing a diagnosis.

Some studies investigated the correlation between V type pit pattern and microscopic findings. Hamatani et al. [28] reported on the examination of V type pit pattern and the degrees of structural atypia. As a result, an irregular pit is considered to include both ductal structure disorder on the surface, as well as the advanced adhesive tubular duct bundles with structural atypia adjacent to the depths or surface part, which may or may not extend to include the surface. Karahara et al. reported that pathological changes associated with malignancy make the surface of cancers vulnerable. For example, the disappearance of the lamina muscularis mucosae due to deep infiltration by the growing tumor will lead to the destruction of the covering protective epithelium, with the result that the outline of the pit becomes unclear [29–32]. Another study suggested that the extent of the vulnerable condition can be related to the degree of surface epithelium erosion, which itself causes the irregularity and unclear outline of pit [33].

In conclusion, type V_I pit pattern subclassification is useful for determining the depth of invasion of colorectal neoplasms and can be applied to decisions about whether endoscopic treatment is indicated.

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