Clinical significance of type V\textsubscript{I} pit pattern subclassification in determining the depth of invasion of colorectal neoplasms

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Abstract

AIM: To clarify whether subclassification of the type V\textsubscript{I} pit pattern on the basis of magnifying colonoscopy findings is useful in determining the type and depth of invasion of colorectal neoplasms.

METHODS: We retrospectively analyzed 272 colorectal neoplasms (117 dysplasias and 155 submucosal invasive carcinomas; 228 patients) with a type V pit pattern (type V\textsubscript{I}, n = 202; type V\textsubscript{II}, n = 70 (Kudo and Tsuruta classification system)). We divided lesions with a type V pit pattern into two subclasses, mildly irregular lesions and severely irregular lesions, according to the prominent and detailed magnifying colonoscopy findings. We examined the relation between these two subclasses and histology/invasion depth.

RESULTS: One hundred and four lesions (51.5%) were judged to be mildly irregular, and 98 lesions (48.5%) were judged to be severely irregular. Ninety-seven (93.3%) mildly irregular lesions showed dysplasias or submucosal invasion of less than 1000 \( \mu \text{m} \) (SM < 1000 \( \mu \text{m} \)). Fifty-five (56.1%) severely irregular lesions showed submucosal invasion equal to or deeper than 1000 \( \mu \text{m} \) (SM \( \geq \) 1000 \( \mu \text{m} \)). Mild irregularity was found significantly more often in dysplasias or lesions with SM < 1000 \( \mu \text{m} \) than in lesions with SM \( \geq \) 1000 \( \mu \text{m} \) (\( P < 0.01 \)).

CONCLUSION: Subclassification of the type V\textsubscript{I} pit pattern is useful for identifying dysplasias or lesions with SM < 1000 \( \mu \text{m} \).

INTRODUCTION

Pit pattern classification (Figure 1) of colorectal lesions, initially proposed by Kudo\textsuperscript{[1]} and modified by Kudo and Tsuruta\textsuperscript{[2]}, is reported to be related to the histologic characteristics of the lesions.\textsuperscript{[3-9]} Magnifying colonoscopy is used for differential diagnosis between non-neoplastic and neoplastic lesions\textsuperscript{[7-14]} and for assessing the depth of invasion of early colorectal carcinomas\textsuperscript{[9,17-21]}.

Several studies have suggested that there is little risk of lymph node metastasis from early colorectal carcinoma that involves the superficial layer of the submucosa, less than 1000 \( \mu \text{m} \) from the muscularis mucosae.\textsuperscript{[9,17-22,24]} Recently, the Japanese Society for Cancer of the Colon and Rectum proposed the following new criteria for curative histopathologic conditions after complete endoscopic mucosal resection (EMR) of submucosal carcinoma:

1. a submucosal invasion depth of less than 1000 \( \mu \text{m} \) (SM < 1000 \( \mu \text{m} \)),
2. well to moderately differentiated adenocarcinoma including the invasive portion, and
3. no vessel involvement.\textsuperscript{[22,24]} In accordance with these proposed criteria, it has become important to distinguish submucosal invasion equal to or deeper than 1000 \( \mu \text{m} \) (SM \( \geq \) 1000 \( \mu \text{m} \)) from SM < 1000 \( \mu \text{m} \) prior to treatment of submucosal carcinoma, to reduce the number of needless surgical resections.

Many studies have shown that the type V\textsubscript{I} pit pattern is an indicator of massive submucosal invasion of colorectal neoplasm.\textsuperscript{[10]} However, colorectal neoplasms with a type V\textsubscript{I} pit pattern include various lesions, such as dysplasia and submucosal carcinoma, with either SM < 1000 \( \mu \text{m} \)}
or SM $\geq 1000 \mu m$. Thus, it is difficult to decide upon a therapeutic strategy for colorectal neoplasm on the basis of the current type V pit pattern classification. In this study, we assessed the clinical usefulness of type V pit pattern subclassification in determining the histology/invasion depth of colorectal neoplasms.

**MATERIALS AND METHODS**

We analyzed 272 colorectal neoplasms with a type V pit pattern (type V$_{I}, n = 202$; type V$_{S}, n = 70$). The colorectal neoplasms comprised 117 dysplasias and 155 submucosal invasive carcinomas, 129 of which were deeper than 1000 $\mu m$, resected endoscopically or surgically from 228 patients at Hiroshima University Hospital during the period January 1999 through March 2005. All lesions in this study were analyzed by five colonoscopists who were well trained in magnifying colonoscopy and blinded to the pathology findings, retrospectively.

To evaluate pit patterns, we used a magnifying colonoscope (EC-410CM, EC-450ZM, EC-450ZH or EC-450ZW, Fujinon Toshiba, Omiya, Japan; or CF-240Z or CF-H260AZI, Olympus, Tokyo, Japan) with zoom functions ranging from $\times 17$ to $\times 126$. 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, crystal violet stain was applied to the pits and grooves of the mucosal surface. For more precise assessment, crystal violet stain was applied to the margins of the pits, rendering each pit pattern clearly visible in all cases. The type V pit pattern was classified as one of two subtypes according to the Kudo and Tsuruta classification system$^{[1-2]}$ (Figure 1): type V$_{I}$, irregularly arranged and similar to type III$_{I}$, III$_{S}$, or IV patterns in size; and type V$_{S}$, an area of obvious non-structure (as per the Hakone consensus meeting in April 2004)$^{[9,23]}$.

Each resected neoplasm was fixed routinely with 10% buffered formalin and embedded in paraffin, after which the entire tumor was cut into serial 2- to 3-mm thick slices. Microscopic examination of hematoxylin and eosin-stained sections was performed by one pathologist unaware of other features of the case. Dysplasia was defined according to the Vienna criteria$^{[26]}$. According to previously proposed measuring methods$^{[22,24]}$, the depth of submucosal invasion was determined using a micrometer under a microscope, and taken as the distance from the muscularis mucosae to the point of the deepest invasion (tumor apex).

We first analyzed the relation between the type V pit pattern subtype (V$_{I}$ or V$_{S}$) and histology/invasion depth. We then examined the relation between SM $\geq 1000 \mu m$ and histology/invasion depth and the following five detailed magnifying colonoscopy findings: (1) irregularity of the pit margins, (2) staining characteristics of the areas between pits, (3) area diameter of the type V$_{I}$ pit pattern ($< 5 \, mm$ or $\geq 5 \, mm$), (4) density of the pits, and (5) width of the intervening membrane between the pits (Figure 2).

We divided the lesions with a type V$_{I}$ pit pattern into two subclasses (mildly irregular lesions and severely irregular lesions) according to the prominent and detailed magnifying colonoscopy findings of the first analysis. Mildly irregular lesions were defined as lesions with one or no significant magnifying colonoscopy findings, and severely irregular lesions were defined as lesions with two or more significant magnifying colonoscopy findings. This was done to diagnose SM $\geq 1000 \mu m$ on the basis of cluster analysis$^{[27,28]}$. Using these data, we examined the relation between the type V$_{I}$ pit pattern subclassifications and histology/invasion depth, the status of the muscularis mucosae, and the presence of desmoplastic reactions at the surface of the lesion (Figure 3). The muscularis mucosae were classified as detected, partially disappeared, or disappeared, as reported previously$^{[29]}$. Desmoplastic reaction of the submucosal layer was classified as absent (-), mild to moderate (+), or severe (++), as reported previously$^{[18,30]}$.

The associations of dysplasia, SM $< 1000 \mu m$, and SM $\geq 1000 \mu m$ with the type V$_{I}$ pit pattern subtypes, detailed magnifying colonoscopy findings, and the type V$_{I}$ lesion subcategories, were analyzed by chi-square test. $P < 0.05$ was accepted as statistically significant. In addition, to identify predictors of SM $\geq 1000 \mu m$, we performed multivariate logistic regression analysis. All statistical analyses were performed using JMP statistical software, version 5.0.1 J (SAS Institute Inc, Cary, NC).

**RESULTS**

**Histology/invasion depth of colorectal neoplasm in relation to type V pit pattern subtypes**

Dysplasia, SM $< 1000 \mu m$ and SM $\geq 1000 \mu m$ were found
in association with 57.9% (117/202), 11.4% (23/202), and 30.7% (62/202) of the neoplasms with type V pit patterns, respectively (Table 1). Dysplasia, SM < 1000 µm, and SM ≥ 1000 µm were found in association with 0% (0/70), 4.3% (3/70), and 95.7% (67/70) of the neoplasms with type Vn pit patterns, respectively. The type Vn pit pattern was found significantly more often in lesions with SM ≥ 1000 than in dysplasias or lesions with SM < 1000 µm (P < 0.01). Sensitivity and specificity of the type Vn pit pattern for a diagnosis of SM ≥ 1000 were 51.9% (67/129) and 97.9% (140/143), respectively.

**Histology/invasion depth of colorectal neoplasm with a type V pit pattern in relation to detailed magnifying colonoscopy findings**

SM ≥ 1000 µm was found in association with 58.2% (46/79) of the lesions with irregular pit margins, 57.5% (50/87) of the lesions with unclear staining characteristics of the areas between pits, 41.3% (57/138) of the lesions with a type Vi pit pattern area ≥ 5 mm in diameter, 26.6% (29/109) of the lesions with high residual pit density, and 31.9% (44/138) of the lesions with a wide intervening membrane between pits (Table 2). SM ≥ 1000 µm was
found significantly more often in association with irregular pit margins, unclear staining characteristics of the areas between pits, and a type Vi pit pattern area ≥ 5 mm in diameter than in association with regular pit margins, clear staining characteristics of the areas between pits, and a type Vi pit pattern area < 5 mm in diameter.

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

In multivariate logistic regression analysis, unclear staining characteristics of the areas between pits, irregular pit margins, and a Vi pit pattern area diameter of ≥ 5 mm were shown to be significant predictors of SM ≥ 1000 µm (Table 3). High residual pit density and a wide intervening membrane between pits were not significant.

**Histology/invasion depth of colorectal neoplasm in relation to type V pit pattern subclassifications**

One hundred and four lesions (51.5%) were judged to be mildly irregular, and 98 lesions (48.5%) were judged to be severely irregular (Table 4). Ninety-seven (93.3%) mildly irregular lesions showed dysplasias or SM < 1000 µm. Fifty-five (56.1%) severely irregular lesions showed SM ≥ 1000 µm. Mild irregularity was found significantly more often in dysplasias or in lesions with SM < 1000 µm than in lesions with SM ≥ 1000 (P < 0.01). Sensitivity and specificity of mild irregularity for dysplasias or SM < 1000 µm were 69.3% (97/140) and 88.7% (55/62), respectively.

**Status of the muscularis mucosae in relation to type V pit patterns**

The muscularis mucosae was detected in 97 (93.2%) mildly irregular lesions (Table 5). Partial disappearance or disappearance of the muscularis mucosae was seen in 60 (61.2%) severely irregular lesions and 67 (100%) lesions with a type Vn pit pattern. Severe irregularity was found significantly more often in association with partial disappearance or disappearance of the muscularis mucosae than in association with detection of the muscularis mucosae (P < 0.05). The type Vn pit pattern was found significantly more often in association with partial disappearance or disappearance of the muscularis mucosae than in association with detection of the muscularis mucosae (P < 0.01).

**Desmoplastic reactions at the surface of the lesion in relation to type V pit patterns**

No desmoplastic reaction of the superficial layer was observed in 100 (96.2%) mildly irregular lesions (Table 6). Desmoplastic reactions (+)/(++) were observed in 50

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Table 1 Histology/invasion depth of colorectal neoplasm in relation to type V pit pattern subtypes, n (%)  

| Type V pit pattern subtypes | Histology/invasion depth | Dysplasia | SM < 1000 µm | 1000 µm ≤ SM |
|----------------------------|--------------------------|-----------|--------------|--------------|
| Vi                         |                          | 202 (100) | 117 (57.9)   | 32 (15.4)    |
| Vn                          |                          | 70 (100)  | 0 (0)        | 4 (5.7)      |

1Dysplasia. SM < 1000 µm vs SM ≥ 1000 µm, P < 0.01. SM: Submucosa.

Table 2 Histology/invasion depth of colorectal neoplasm with type Vi pit pattern in relation to detailed magnifying colonoscopy findings, n (%)  

| Magnifying colonoscopy finding | Histology/invasion depth | Dysplasia | SM < 1000 µm | 1000 µm ≤ SM |
|-------------------------------|--------------------------|-----------|--------------|--------------|
| Irregular pit margins         |                          | 79 (100)  | 23 (29.1)    | 36 (46.2)    |
| Unclear staining characteristics of the area between pits | 87 (100) | 21 (24.1) | 36 (42.0) |
| Area diameter of type Vi pit pattern ≥ 5 mm | 138 (100) | 65 (47.1) | 57 (41.3) |
| High residual pit density | 109 (100) | 64 (58.7) | 29 (26.6) |
| Wide intervening membrane between pits | 138 (100) | 81 (60.7) | 44 (31.9) |

1Dysplasia. SM < 1000 µm vs SM ≥ 1000 µm, P < 0.01. SM: Submucosa.

Table 3 Results of multivariate logistic regression analysis for predictors of submucosal invasion deeper than 1000 µm (n = 202)  

| Magnifying colonoscopy finding | Odds ratio (P value) | Relevant finding |
|--------------------------------|----------------------|------------------|
| Unclear staining characteristics of the areas between pits | 6.24 (< 0.0001) | Clear staining characteristics of the areas between pits |
| Irregular pit margins | 4.89 (< 0.0001) | Regular pit margins |
| Area diameter of type Vi pit pattern ≥ 5 mm | 4.14 (0.0132) | Area diameter of type Vi pit pattern < 5 mm |
| High residual pit density | 1.51 (0.3335) | Low residual pit density |
| Wide intervening membrane between pits | 1.02 (0.9740) | Narrow intervening membrane between pits |

Table 4 Histology/invasion depth of colorectal neoplasm in relation to type V pit pattern subclassifications, n (%)  

| Type V pit pattern subclassification | Histology/invasion depth | Dysplasia | SM < 1000 µm | 1000 µm ≤ SM |
|-------------------------------------|--------------------------|-----------|--------------|--------------|
| Mildly irregular                     |                          | 104 (100) | 89 (85.6)    | 1 (0.1)      |
| Severely irregular                   |                          | 98 (100)  | 28 (28.6)    | 15 (15.3)    |

1Dysplasia. SM < 1000 µm vs SM ≥ 1000 µm, P < 0.01. SM: Submucosa.

Table 5 Status of muscularis mucosae in relation to type V pit patterns, n (%)  

| Type V pit pattern | Status of muscularis mucosae | Detected | Partially disappeared | Disappeared |
|--------------------|-------------------------------|----------|-----------------------|-------------|
| Vi                 |                               | 104 (100)| 57 (54.9)             | 1 (1.0)     |
| Vn                 |                               | 98 (100) | 31 (31.6)             | 29 (29.6)   |

1Detected vs partially disappeared, disappeared, *P < 0.01, *P < 0.05.
(51.0%) severely irregular lesions and 67 (100%) lesions with a type Vπ pit pattern. The type Vπ pit pattern was found significantly more often in lesions with a desmoplastic reaction (+)/(+ +) than in lesions with desmoplastic reaction (-) ($P < 0.01$).

**DISCUSSION**

Endoscopic treatment, such as EMR, is both a therapeutic technique and an important diagnostic technique. Therefore, it is important to be able to identify lesions for which endoscopic resection would be curative to avoid meaningless endoscopic resection for lesions that should be treated surgically. Pit pattern classification is used clinically to help determine the best treatment for colorectal tumors\(^9\). Type I and II pit patterns predict nonneoplastic lesions, whereas type III, IV, and V pit patterns predict neoplastic lesions. Lesions with a type III or IV pit pattern are almost always dysplasias and are thus indications for endoscopic resection. Almost all lesions with a type Vπ pit pattern show SM $\geq$ 1000 $\mu$m. The reported accuracy of detection of massive submucosal invasion on the basis of the type Vπ pit pattern is 97%\(^{23}\). In our study, SM $\geq$ 1000 $\mu$m was found in 95.7% of lesions with a type Vπ pit pattern. Therefore, surgical resection is indicated for such lesions. By contrast, lesions with a type Vι pit pattern include dysplasia and various submucosal carcinomas; thus, it is difficult to decide upon a therapeutic strategy on the basis of the current pit pattern classification system. It is necessary to analyze the type Vι pit pattern in detail to determine the appropriate therapeutic strategy. The present study revealed that irregular pit margins, unclear staining characteristics of the areas between pits, and a type Vι pit pattern area diameter $\geq$ 5 mm are significant predictors for submucosal invasion of colorectal neoplasms of 1000 $\mu$m or more.

Lesions that were subclassified as mildly irregular lesions were mainly dysplasias or lesions that showed SM $< 1000$ $\mu$m (93.3%). Therefore, endoscopic resection is indicated for mildly irregular lesions. On the contrary, lesions that were classified as severely irregular lesions included not only dysplasias or lesions with SM $< 1000$ $\mu$m (43.9%), but also lesions with SM $\geq$ 1000 $\mu$m (56.1%). For severely irregular lesions, the therapeutic strategy should be determined on the basis of standard endoscopic findings in conjunction with those of other modalities, such as contrast enema radiography or endoscopic ultrasonography\(^{29,32}\). New diagnostic modalities, such as narrow band imaging, are expected to provide more information about the invasion depth of colorectal carcinomas\(^{33,36}\).

Our results revealed that there is a significant histologic difference between mildly irregular and severely irregular lesions. The degree of disappearance of the muscularis mucosae increased as the pit patterns changed from Vι with mildly irregularity to Vπ with severely irregularity to Vσ. If we could determine the status of the muscularis mucosae by magnifying colonoscopy, the pit pattern would be helpful in determining the depth of submucosal invasion depth by endoscopic ultrasonography. The muscularis mucosae had disappeared in all lesions with a type Vσ pit pattern; thus, we can measure the invasion depth from the surface of a lesion of this type to the deepest portion\(^{29}\). It has been reported that desmoplastic reactions are related to massive submucosal invasion\(^9\). In the present study, the incidence of desmoplastic reactions increased as the pit patterns changed from Vι with mildly irregularity to Vπ with severely irregularity to Vσ. There were no desmoplastic reactions in mildly irregular lesions. These results indicate that changes in the appearance of the pits are caused by the process of submucosal infiltration of the colorectal neoplasm. Although the mechanism underlying this process is not clear, it is possible that irregular pit margins and unclear staining characteristics of the areas between pits may involve several molecular markers. We reported previously that the proliferation, infiltration and lymph node metastasis of submucosal colorectal carcinoma are significantly related to the expression of markers such as Ki-67, E-cadherin, MUC1, cathepsin D and MPP-7 at the deepest portion\(^{37,38}\). We also reported previously that MUC1 expression at the superficial layer may be related to colorectal tumors with a type V pit pattern\(^{39}\). However, there are few reports pertaining to the relationship between the expression of specific molecular markers and morphogenesis of the type Vι pit pattern. There may be a relation between the expression of molecular markers and detailed magnifying colonoscopy features of the type Vι pit pattern. Further investigation will clarify the relation between molecular morphogenesis at the lesion surface and type Vι pit pattern subclassifications.

We conclude that type Vι pit pattern subclassification is useful for identifying dysplasias or lesions with SM $< 1000$ $\mu$m. Subclassifications can be applied to decisions about whether endoscopic treatment is indicated for colorectal neoplasms. However, we cannot identify lesions with SM $\geq 1000$ $\mu$m on the basis of type Vι pit pattern subclassifications.

**COMMENTS**

**Background**

Colorectal neoplasms with a type Vι pit pattern include various lesions, such as dysplasias and submucosal carcinomas, with either SM $< 1000$ $\mu$m or SM $\geq 1000$ $\mu$m. Thus, it is difficult to decide upon a therapeutic strategy for colorectal neoplasm on the basis of the current type Vι pit pattern classification.

**Research frontiers**

In this study, we assessed the clinical usefulness of type Vι pit pattern subclassification in determining the histology/invasion depth of colorectal neoplasms. There has been little study on type Vι pit pattern subclassification.
Innovations and breakthroughs
Type V pit pattern subclassification is useful for identifying dysplasias or lesions with SM < 1000 μm.

Applications
Subclassification can be applied to deciding whether endoscopic treatment is indicated for colorectal neoplasms.

Terminology
Type V pit pattern subclassification: We divided the lesions with a Type V pit pattern into two subclasses (mildly irregular lesions and severely irregular lesions) according to the prominent detailed magnifying colonoscopy findings of the first analysis. Mildly irregular lesions were defined as lesions with one or no significant magnifying colonoscopy findings, and severely irregular lesions were defined as lesions with two or more significant magnifying colonoscopy findings.

Peer review
The authors retrospectively investigated whether subclassification of the type V pit pattern on the basis of magnifying colonoscopy findings was useful in determining the type and depth of invasion of colorectal neoplasm. They concluded that subclassification of the type V pit pattern is useful for identifying dysplasias or lesions with SM < 1000 μm.

REFERENCES
1. Kudo S, Hirotani S, Nakajima T, Hosobe S, Kusaka H, Kobayashi T, Himori M, Yagyuu A. Colorectal tumours and pit pattern. J Clin Pathol 1994; 47: 880-885
2. Imai Y, Kudo S, Tsunota O, Fujii T, Hayashi S, Tanaka S, Terai T. Problems and clinical significance of V type pit pattern diagnosis: report on round-table consensus meeting [in Japanese with English abstract]. Early Colorectal Cancer 2001; 5: 595-613
3. Kudo S, Tamura S, Nakajima T, Yamano H, Kusaka H, Watanabe H. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. Gastrointest Endosc 1996; 44: 8-14
4. Kudo S, Kashida H, Tamura T, Kogure E, Imai Y, Yamano H, Hart AR. Colonoscopic diagnosis and management of nonpolyoid early colorectal cancer. World J Surg 2000; 24: 1081-1090
5. Tanaka S, Haruna K, Ito M, Nagata S, Oh-e H, Hirota Y, Kunihito M, Kitadai Y, Yoshida M, Sumii K, Kajiyama G. Detailed colonoscopy for detecting early superficial carcinoma: recent developments. J Gastroenterol 2000; 35 Suppl 12: 125-132
6. Fujii T, Hasegawa RT, Saitoh Y, Fleischer D, Saito Y, Sano Y, Kato S. Colonoscopy during endoscopy. Endoscopy 2001; 33: 1036-1041
7. Hurlstone DP, Cross SS, Slater R, Sanders DS, Brown S. Detecting diminutive colorectal lesions at colonoscopy: a randomised controlled trial of pan-colonic versus targeted chromoscopy. Gut 2004; 53: 376-380
8. Hurlstone DP, Fuji T. Practical uses of chromoendoscopy and magnification at colonoscopy. Gastrointest Endosc Clin N Am 2005; 15: 687-702
9. Tanaka S, Kaltenbach T, Chayama K, Soetikno R. High-magnification colonoscopy (with videos). Gastrointest Endosc 2006; 64: 604-613
10. Togashi K, Konishi F, Iizuka T, Sato T, Senba S, Kanazawa K. Efficacy of magnifying endoscopy in the differential diagnosis of neoplastic and non-neoplastic polyps of the large bowel. Dis Colon Rectum 1999; 42: 1602-1608
11. Kiesslich R, von Bergh M, Hahn M, Herrmann G, Jung M. Chromoendoscopy with indigocarmine improves the detection of adenomatous and nonadenomatous lesions in the colon. Endoscopy 2001; 33: 1001-1006
12. Tung SY, Wu WS, Su MY. Magnifying colonoscopy in differentiating neoplastic from nonneoplastic colorectal lesions. Am J Gastroenterol 2001; 96: 2629-2632
13. Ko A, Fuji T, Koba I, Sano Y, Fu KJ, Parra-Blanco A, Tajiri H, Yoshida S, Rembacken B. Assessment of colorectal lesions using magnifying colonoscopy and mucosal dye spraying; can significant lesions be distinguished? Endoscopy 2001; 33: 306-310
14. Konishi K, Kaneko K, Kurashashi T, Yamamoto T, Kudoh M, Kanda A, Tajiri H, Mitamura K. A comparison of magnifying and nonmagnifying colonoscopy for diagnosis of colorectal polyps: A prospective study. Gastrointest Endosc 2003; 57: 48-53
15. Hurlstone DP, Cross SS, Adam I, Shorthouse AJ, Brown S, Sanders DS, Lobo AJ. Efficacy of high magnification chromoendoscopy for the diagnosis of neoplasia in flat and depressed lesions of the colorectum: a prospective analysis. Gut 2004; 53: 284-290
16. Fu KI, Sano Y, Kato S, Fujii T, Nagashima F, Yoshino T, Okuno T, Yoshida S, Fujimori T. Chromoendoscopy using indigo carmine dye spraying with magnifying observation is the most reliable method for differential diagnosis between non-neoplastic and neoplastic colorectal lesions: a prospective study. Endoscopy 2004; 36: 1089-1093
17. Yamamoto S, Watanabe M, Hasegawa H, Baba H, Yoshinare K, Shirasati J, Kitajima M. The risk of lymph node metastasis in T1 colorectal carcinoma. Hepatogastroenterology 2004; 51: 998-1000
18. Nagata S, Tanaka S, Haruma K, Yoshihara M, Sumii K, Kajiyama G, Shimamoto F. Pit pattern diagnosis of early colorectal carcinoma by magnifying colonoscopy: clinical and histological implications. Int J Oncol 2000; 16: 927-934
19. Tanaka S, Haruna K, Nagata S, Hirota Y, Furudoi A, Amioka T, Kitadai Y, Yoshihara M, Shimamoto F. Conditions of curability after endoscopic resection for colorectal carcinoma with submucosally massive invasion. Oncol Rep 2000; 7: 783-788
20. Tanaka S, Haruna K, Nagata S, Shiroyoka O, Kazuaki Chayama. Diagnosis of invasion depth in early colorectal carcinoma by pit pattern analysis with magnifying endoscopy. Dig Endosc 2001; 13S: s2-s5
21. Tanaka S, Nagata S, Oka S, Kawai T, Tamura T, Kitadai Y, Sumii M, Yoshihara M, Haruna K, Chayama K. Determining depth of invasion by VN pit pattern analysis in submucosal colorectal carcinoma. Oncol Rep 2002; 9: 1005-1008
22. Kitajima K, Fujimori T, Fujii S, Takeda J, Ohkura Y, Kawanaka H, Kumamoto T, Ishiguro S, Kato Y, Shimoda T, Iwashita A, Ajisaka Y, Watanabe H, Watanabe T, Muto T, Nagasako K, Kukita Y, Kato S, Ohnuma K, Bekku S. Risk factors for an adverse outcome in early colorectal cancer: a Japanese collaborative study. J Gastroenterol 2004; 39: 534-543
23. Oka S, Tanaka S, Kaneko I, Mouri R, Chayama K. Diagnosis of the invasion depth using magnifying videocolonoscopy in early colorectal carcinoma [in Japanese with English abstract]. Early Colorectal Cancer 2005; 9: 161-168
24. Ueno H, Murchizuki H, Hashiguchi Y, Shimazaki H, Aida S, Hase K, Matsukuma S, Kanai T, Kurihara H, Ozawa K, Yoshimura K, Bekku S. Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 2004; 127: 385-394
25. Kudo S, Kurashashi T, Kashida H, Ohtsuka T, Takeuchi T, Fukumi S, Tanaka T, Ishida F, Endou S, Kigure E, Kaga M, Sasashima K, Kudo Y, Sasaki H, Ohmae Y, Omori Y, Ohtani H, Fujisawa H. Diagnosis of invasion depth of colorectal lesions using magnifying colonoscopy [in Japanese with English abstract]. Stomach Intestine 2004; 9: 747-752
26. Schlimper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Flejou JF, Geboes K, Hattori T, Hirota T, Ihabashy M, Iwashita A, Kim YL, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Ohbergher G, Oppen F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Socolia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. Gut 2000; 47: 251-255
27. Hermens M, Postma C, Baak J, Weiss M, Rapallo A, Sciutto A, Roemen G, Arends JW, Williams R, Giaretti W, De Goeij JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, JF, Konishi K, Kurashashi T, Yamamoto T, Kudoh M, Kanda A, Tajiri H, Mitamura K. Problems and clinical significance of V type pit pattern subclassification is useful for identifying dysplasias or lesions with SM < 1000 μm.

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Selaru FM, Xu Y, Yin J, Zou T, Liu TC, Mori Y, Abraham JM, Sato F, Wang S, Twigg C, Olaru A, Shustova V, Leytin A, Hytrioglou P, Shibata D, Harpaz N, Meltzer SJ. Artificial neural networks distinguish among subtypes of neoplastic colorectal lesions. *Gastroenterology* 2002; 122: 606-613

Tanaka S, Yoshida S, Chayama K. Clinical usefulness of high-frequency ultrasound probes for new invasion depth diagnosis in submucosal colorectal carcinoma. *Dig Endosc* 2004; 16: 161-164

Oka S, Tanaka S, Nagata S, Masanori Ito, Yasuhiro Kitadai, Fumio Shimamoto, Masaharu Yoshihara, Kazuaki Chayama. Relationship between histopathological features and type V pit pattern determined by magnifying videocolonoscopy in early colorectal carcinoma. *Dig Endosc* 2005; 17: 117-122

Waxman I, Saitoh Y, Raju GS, Watari J, Yokota K, Reeves AL, Kohgo Y. High-frequency probe EUS-assisted endoscopic mucosal resection: a therapeutic strategy for submucosal tumors of the GI tract. *Gastrointest Endosc* 2002; 55: 44-49

Matsumoto T, Hizawa K, Esaki M, Kurahara K, Mizuno M, Hirakawa K, Yao T, Iida M. Comparison of EUS and magnifying colonoscopy for assessment of small colorectal cancers. *Gastrointest Endosc* 2002; 56: 354-360

Gono K, Obi T, Yamaguchi M, Ohyama N, Machida H, Sano Y, Yoshida S, Hamamoto Y, Endo T. Appearance of enhanced tissue features in narrow-band endoscopic imaging. *J Biomed Opt* 2004; 9: 568-577

Machida H, Sano Y, Hamamoto Y, Muto M, Kozu T, Tajiri H, Yoshida S. Narrow-band imaging in the diagnosis of colorectal mucosal lesions: a pilot study. *Endoscopy* 2004; 36: 1094-1098

Sano Y, Horimitsu T, Fu K, Katagiri A, Muto M, Ishikawa H. Magnifying observation of microvascular architecture of colorectal lesions using a narrow-band imaging system. 2006; 2: 168-179

Hirata M, Tanaka S, Oka S, Kaneko I, Yoshida S, Yoshihara M, Chayama K. Magnifying endoscopy with narrow band imaging for diagnosis of colorectal tumors. *Gastrointest Endosc* 2007; 65: 988-995

Tanaka S, Haruma K, Tatsuta S, Hiraga Y, Teixeira CR, Shimamoto F, Yoshihara M, Sumii K, Kajiyama G. Proliferating cell nuclear antigen expression correlates with the metastatic potential of submucosal invasive colorectal carcinoma. *Oncology* 1995; 52: 134-139

Aoki R, Tanaka S, Haruma K, Yoshihara M, Sumii K, Kajiyama G, Shimamoto F, Kohno N. MUC-1 expression as a predictor of the curative endoscopic treatment of submucosally invasive colorectal carcinoma. *Dis Colon Rectum* 1998; 41: 1262-1272

Hiraga Y, Tanaka S, Haruma K, Yoshihara M, Sumii K, Kajiyama G, Shimamoto F, Kohno N. Immunoreactive MUC1 expression at the deepest invasive portion correlates with prognosis of colorectal cancer. *Oncology* 1998; 55: 307-319

Kimura T, Tanaka S, Haruma K, Sumii K, Kajiyama G, Shimamoto F, Kohno N. Clinical significance of MUC1 and E-cadherin expression, cellular proliferation, and angiogenesis at the deepest invasive portion of colorectal cancer. *Int J Oncol* 2000; 16: 55-64

Oh-e H, Tanaka S, Kitadai Y, Shimamoto F, Yoshihara M, Haruma K. Cathepsin D expression as a possible predictor of lymph node metastasis in submucosal colorectal cancer. *Eur J Cancer* 2001; 37: 180-188

Nagata S, Tanaka S, Haruma K, Kitadai Y, Yoshihara M, Shimamoto F, Kohno N, Chayama K. MUC1 and cathepsin D expression in early colorectal carcinoma showing V type pit pattern. *Int J Oncol* 2003; 19: 665-672

Kaneko I, Tanaka S, Oka S, Kawamura T, Hiyama T, Ito M, Yoshihara M, Shimamoto F, Chayama K. Lymphatic vessel density at the site of deepest penetration as a predictor of lymph node metastasis in submucosal colorectal cancer. *Dis Colon Rectum* 2007; 50: 13-21