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Pathological Features of Colorectal Laterally Spreading Tumors
− Differences and Similarities between Granular and Non-Granular Type −

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Abstract：Five-hundred and two lesions of colorectal laterally spreading tumors（LSTs）from 502 patients were studied histopathologically to analyze differences and similarities between the four macroscopic subtypes. The colorectal LSTs were collected from 1999 through 2012 and were subclassified as follows: 373 lesions of granular type（140 homogenous type and 233 nodular mixed type）and 129 lesions of non-granular type（100 flat elevated type and 29 pseudo-depressed type）. The major anatomical sites of the granular type were the rectum and the proximal region of the ascending colon and cecum, whereas the non-granular type was commonly located in the transverse colon. Regardless of their maximum diameter, colorectal LSTs were low in height, and small-sized lesions（e.g., non-granular type）were also included. In 481（95.8%）lesions, the intramucosal spreading area contained adenomatous components. On histologic examination, non-granular types showed tubular adenoma with severe cytologic atypia（equivalent to high-grade adenoma）despite their relatively small size. In contrast, granular types showed tubular and/or tubulovillous adenoma with mild to moderate cytologic atypia（equivalent to low-grade adenoma）despite their relatively large size. Among the colorectal LSTs, both nodular mixed type, pseudo-depressed type, and flat elevated type contained a carcinomatous component with high frequency as compared with homogenous type. Different clinical management is needed to cope with these macroscopic subtypes. The conclusion from the standpoint of a pathologist is that it is worthwhile to subclassify colorectal LSTs into four distinct groups.

Key words：**Laterally spreading tumors, Granular type, Non-granular type, Adenoma, Adenocarcinoma, Macroscopic type**

Introduction

In the colon and rectum, epithelial neoplasia measuring less than 20 mm in diameter is generally an adenoma. However, a laterally spreading tumor（LST）is an exceptional lesion that extends widely in the mucosa in the macroscopic form of a sessile lesion.[1)] It comprises adenoma and/or adenocarcinoma. The existence of this type has been well known, and it has been called flower-bed-lesion,[2)] creeping tumor,[3)] carpet lesion,[4)] flat sessile elevated lesion composed of multiple aggregated granules,[5)] and IIa-aggregated lesion.[6)] With recent advances in colonoscopic examination, especially in Japan,

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the number of LSTs found clinically has been increasing.[7] Consequently, LST is known to be characteristically a large, intramucosally spreading neoplasia with or without submucosal invasion, macroscopically granular and/or granulonodular in appearance, and with a tubular to tubulovillous histology.[8),9)]

Furthermore, it has also been recognized that LSTs include a tumor type that even invades into the submucosal tissue despite the small tumor size with relatively high incidence of associated carcinoma. This type has a macroscopically flat and smooth surface and is classified as non-granular type, which is a subtype of colorectal LSTs.[10] Currently, treatment protocol for colorectal tumor with endoscopic mucosal resection or endoscopic submucosal dissection has become popular. Therefore, it is critical to understand pathological features of colorectal LSTs from the point of view of treatment strategy.[11),12),13)]

The purpose of our study was to clarify the correlations between anatomic distribution, macroscopic features, histologic features, and malignant potential in colorectal LSTs. We also aimed to elucidate differences and similarities between the macroscopic subtypes.

Materials and Methods

Patients

We reviewed 502 lesions of colorectal LSTs from 502 patients diagnosed between January 1999 and September 2012 at the Department of Pathology (Faculty of Medicine and Chikushi Hospital), Fukuoka University and Division of Pathology, Saiseikai Fukuoka General Hospital. Of 502 lesions, 344 lesions were endoscopically resected, and the remaining 158 lesions were surgically resected with regional lymph node dissection. Patients with familial adenomatous polyposis or colitis associated carcinoma were excluded from the study.

Macroscopic evaluation

Macroscopic types of the colorectal lesions more than

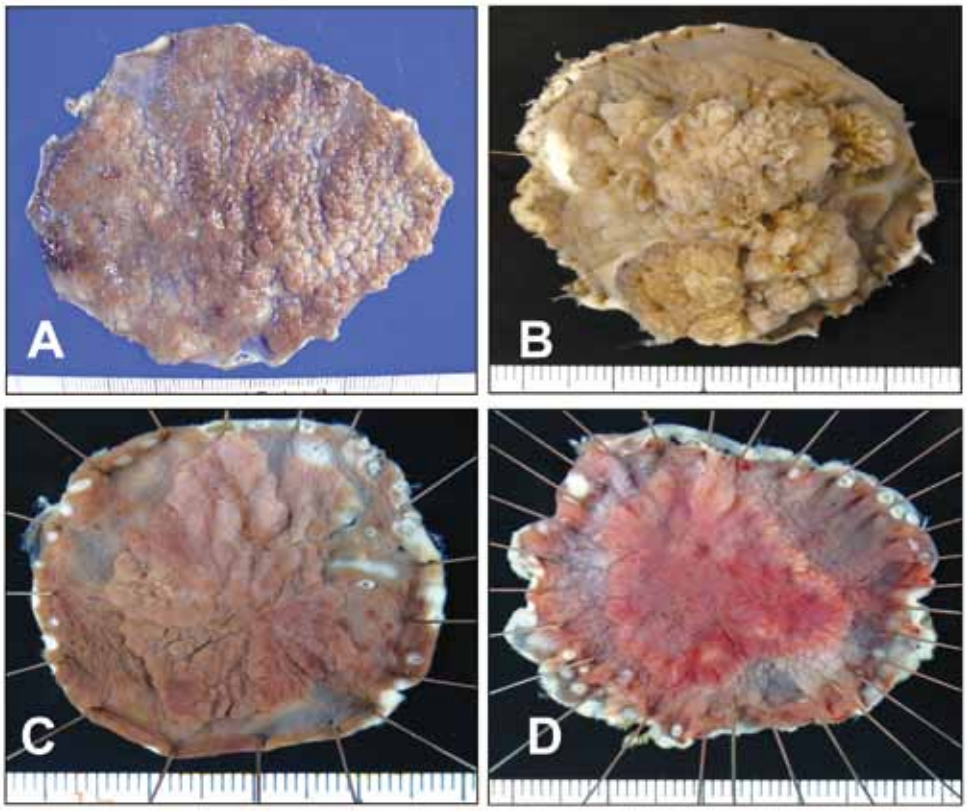

Figure 1. Macroscopic view of colorectal laterally spreading tumors. Homogenous type (A) : The mucosal surface appears uneven due to the conglomeration of small-sized nodules. Nodular mixed type (B) : Some large nodules show a nodular and villous-like appearance. Flat elevated type (C) : The slightly elevated lesion shows clear lateral margin and smooth surface. No definite depressed area is detected in the lesion. Pseudo-depressed type (D) : The slightly elevated lesion shows clear lateral margin and smooth surface. A shallow depressed area can be seen at its center.

larger than 10mm in diameter were classified into granular and non-granular type, according to the classification of Kudo *et al.*[1), 14), 15)] Macroscopically, granular types were recognized as broad-based lesions with conglomerated nodular surface and were further divided into two subtypes: homogenous type and nodular mixed type. Meanwhile, non-granular types were recognized as superficially spreading lesions with a flat and smooth surface and were divided into two subtypes: flat elevated type and pseudo-depressed type. Representative examples of these subtypes are shown in Figures 1 and 2. The maximum diameter of each colorectal lesion was measured by a ruler on macroscopic color photographs.

Histological evaluation

All specimens were fixed overnight in 20% neutral buffered formalin. The entire tumor tissue was sliced in serial fashion at approximately 3 to 5 mm in width, and tissue slices were routinely processed to paraffin blocks. The number of blocks prepared ranged from 4 to 32 (average, 10.3). All sections were cut at 3 μm and stained with hematoxylin and eosin (HE) for microscopic examination.

The histologic classification was based on the Japanese Classification of Colorectal Carcinoma.[16)] Adenomas were subclassified into low grade (equivalent to adenomas with mild and moderate atypia) and high grade (equivalent to adenomas with severe atypia) according to their degree of structural and/or cytological atypia. Adenocarcinoma, however, was subclassified into well-differentiated type, moderately differentiated type and a mixture of well and moderately differentiated

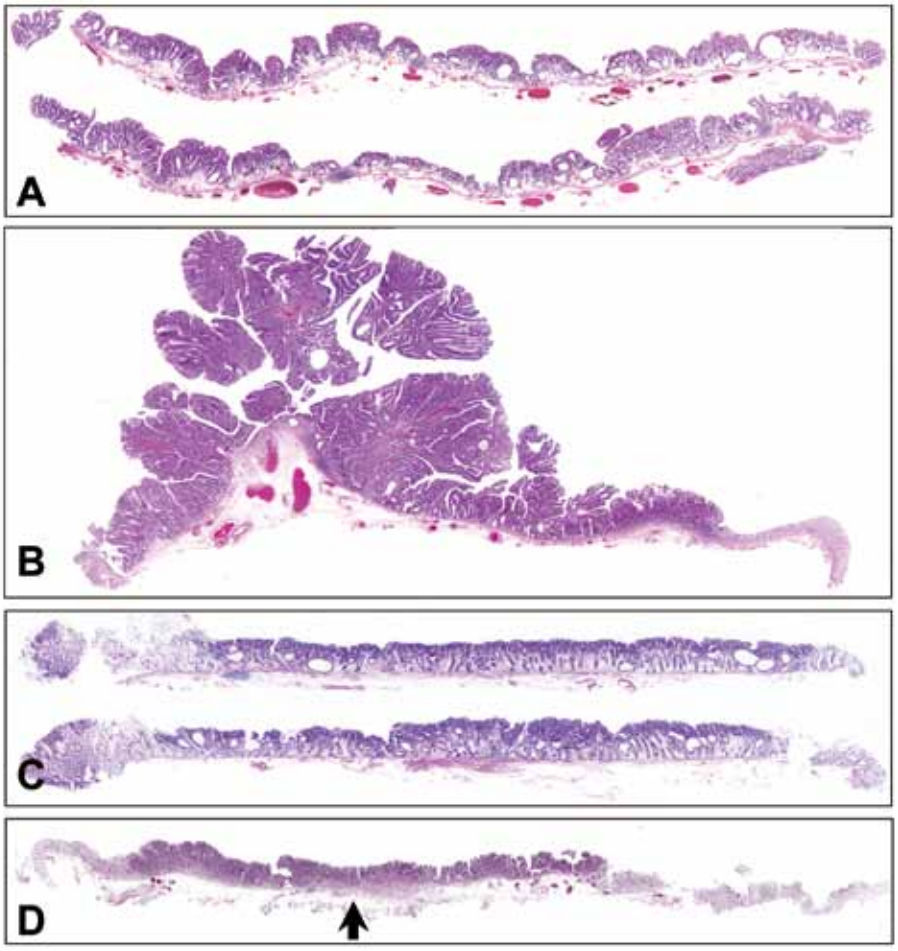

Figure 2. Whole-mount view of the cut section of colorectal laterally spreading tumors. Homogenous type (A): Tubular adenoma showing fine-granular surface. Nodular mixed type (B): Tubulovillous adenoma showing nodular surface. Flat elevated type (C) Tubular adenoma with replacing growth pattern in the mucosal area. Pseudo-depressed type (D): Depression is ill-defined and surrounded by a slightly elevated margin. Well-differentiated tubular adenocarcinoma with replacing growth pattern in the mucosal area. Minute focus of the submucosal invasion with stromal fibrosis (arrow) can be detected in the center of the lesion.

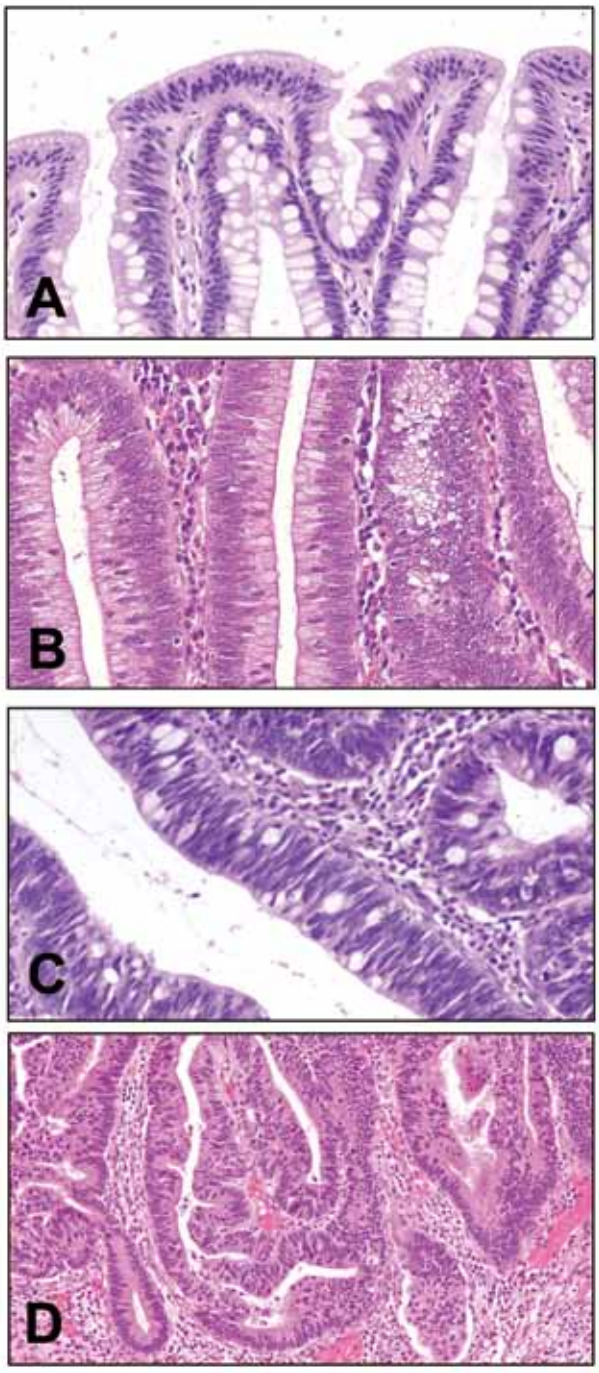

Figure 3. Histological appearance of adenoma and adenocarcinoma. Adenomas are defined by the presence of intraepithelial neoplasia, histologically characterized by hypercellularity, with enlarged, hyperchromatic nuclei and varying degrees of nuclear stratification. Nuclei may be spindle-shaped or ovoid. Adenomas are classified according to their degree of cytological atypia into low-grade adenomas (equivalent to adenomas with mild to moderate cytological atypia) (A, B) and high-grade adenomas (equivalent to adenomas with severe cytological atypia) (C). In contrast, a well-differentiated tubular adenocarcinoma shows obvious structural atypia and nuclear atypia (D).

type, according to their degree of architectural atypia. Representative examples of these adenomas and adenocarcinomas are shown in Figure 3.

Statistics

Statistical analysis was carried out with the Chi-squared test and Mann-Whitney's *U*-test. A *P* value of less than 0.05 was regarded as significant.

Results

Clinicopathological data

The clinical and pathologic features of patients are summarized in Table 1. Of 502 colorectal LSTs, 140 (27.9%) were classified as homogenous type, 233 (46.4%) as nodular mixed type, 100 (19.9%) as flat elevated type and 29 (5.8%) as pseudo-depressed type. The sex ratio of patients with granular-type lesions was male, 202 (51.2%) and female, 171 (45.8%), and with non-granular-type lesions was male, 104 (80.6%) and female, 25 (19.4%), indicating that although there was no significant difference in the ratio of males and females with granular-type lesions, the ratio of males with non-granular-type lesions was significantly higher than that of females.

As for tumor size, nodular mixed type lesions (average, 42.9±12.1 mm; range, 17 to 65 mm) were significantly larger than other macroscopic type lesions (P<0.0001). In contrast, incidence of homogenous type, flat elevated type and pseudo-depressed type gradually decreased in

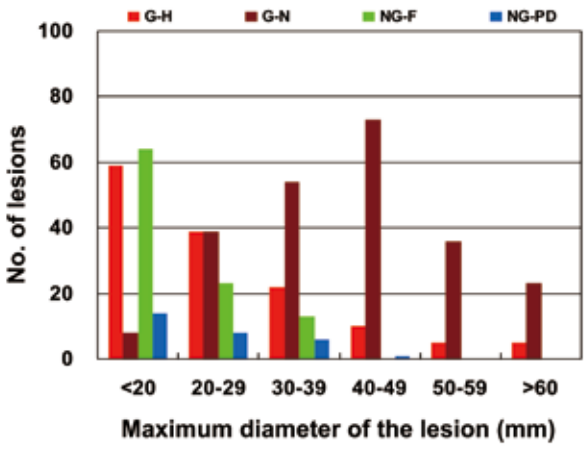

Figure 4. Incidence of macroscopic type by tumor size in colorectal laterally spreading tumors. G-H indicates granular homogenous type; G-N, granular nodular mixed type; NG-F, non-granular flat elevated type; and NG-PD, non-granular pseudo-depressed type.

accordance with increase in tumor size. Also, lesions of more than 50 mm in diameter were not found in the non-granular type (Figure 4).

Location of colorectal lateral spreading tumors

Among 502 colorectal LSTs (granular and non-granular type), 92 (18.3%) were located in the cecum, 105 (20.9%) were in the ascending colon, 90 (17.9%) were in the transverse colon, 30 (6.0%) were in the descending colon, 53 (10.6%) were in the sigmoid colon, and 132 (26.3%) were in the rectum (Table 2). The major anatomical sites of the colorectal LSTs were the cecum, the proximal region of the ascending colon, transverse colon, and rectum. As for anatomic distribution by macroscopic type, granular-type lesions were frequently located in the cecum (16.6%), proximal region of ascending colon (15.5%), and rectum (24.7%), whereas non-granular type lesions were commonly located in

Table 1 Clinical features and histology of 502 cases of colorectal laterally spreading tumors

	Granular type		Non-granular type	
	Homogenous type	Nodular mixed type	Flat elevated type	Pseudo-depressed type
	n=140	*n*=233	*n*=100	*n*=29
Age, y.o.*	66.7±13.4	65.4±12.1	65.7±11.6	66.3±10.8
Gender				
Male	82	120	79	25
Female	58	113	21	4
Tumor size, mm**	27.7±11.6	42.9±12.1§	20.9±7.0	21.5±10.0
Location				
Cecum	40	43	7	2
Ascending colon	36	52	24	3
Transverse colon	12	25	39	14
Descending colon	6	6	13	5
Sigmoid colon#	13	26	11	3
Rectum	33	91	6	2
Histologic type of adenoma				
Tubular adenoma	115	61	86	22
Tubulo-villous adenoma	25	172	0	0
Villous adenoma	0	0	0	0
Grade of cytologic atypia of adenoma				
Low grade	136	164	43	5
High grade	4	69	43	17
No. of lesions with carcinoma	17 (12.1)	145 (66.2)	28 (28.0)†	21 (72.4)‡
Frequency of submucosal invasion	4 (2.9)	67 (28.8)	5 (5.0)	8 (27.6)
Histologic type of carcinoma				
Tub1	15	111‖	28	21
Tub1 + Tub2	2	34¶	0	0
Poorly differentiated adenocarcinoma	0	0	0	0
Lymph node metastasis	0	11 (4.7)	1 (1.0)	2 (6.9)

**, *: Values are expressed as mean. Parentheses indicate percentage; *n*, number of lesions; Tub1, well-differentiated tubular adenocarcinoma; and Tub2, moderately differentiated tubular adenocarcinoma. #: including rectosigmoid, ‖: twelve lesions show mucinous adenocarinoma at the advancing margin, ¶: eight lesions show mucinous adenocarinoma at the advancing margin, †: including fourteen lesions of pure carcinoma, ‡: including seven lesions of pure carcinoma. Mann-Whitney's *U*-test was used for §$P<0.0001$ (*vs* other macroscopic types).

Table 2 Macroscopic type of colorectal laterally spreading tumors and their anatomic distribution

Macroscopic type	Cecum	Ascending colon	Transverse colon	Descending colon	Sigmoid colon*	Rectum	Total No. of lesions
Granular type	83 (16.6)	78 (15.5)	37 (7.4)	12 (2.4)	39 (7.8)	124 (24.7)	373 (74.3)
Homogenous type	40 (8.0)	36 (7.2)	12 (2.4)	6 (1.2)	13 (2.6)	33 (6.6)	140 (27.9)
Nodular mixed type	43 (8.6)	42 (8.4)	25 (5.0)	6 (1.2)	26 (5.2)	91 (18.1)	233 (46.4)
Non-granular type	9 (1.8)	27 (5.4)	53 (10.5)	18 (3.6)	14 (2.8)	8 (1.6)	129 (25.7)
Flat elevated type	7 (1.4)	24 (4.8)	39 (7.7)	13 (2.6)	11 (2.2)	6 (1.2)	100 (19.9)
Pseudo-depressed type	2 (0.4)	3 (0.6)	14 (2.8)	5 (1.0)	3 (0.6)	2 (0.4)	29 (5.8)

Parentheses indicate percentage. * : including rectosigmoid.

the transverse colon (10.5%). In addition, even when granular type and non-granular type were classified into subtypes, a similar trend was observed.

Histological characteristics of colorectal lateral spreading tumors

Of 502 colorectal LSTs, 481 (95.8%) contained adenomatous components of the intramucosal spreading area. The remaining 21 (4.2%) patients had a solitary lesion of pure adenocarcinoma. As for histologic type of adenoma, tubular adenoma was more common in the homogenous-type (115/140; 82.1%), flat elevated-type (86/100; 86%), and pseudo-depressed-type (22/29; 75.9%) than in the nodular mixed-type lesions (61/233; 46.4%). In contrast, tubulovillous adenoma was significantly more common in nodular mixed-type (172/233; 73.8%) than in the other macroscopic-type lesions (P<0.0001). In this study, villous adenoma was not found (Table 1).

As for the grade of cytologic atypia of adenomatous components, low-grade adenoma was more common in granular-type (300/373; 80.4%) than in non-granular-type lesions (48/129; 37.2%). In contrast, high-grade

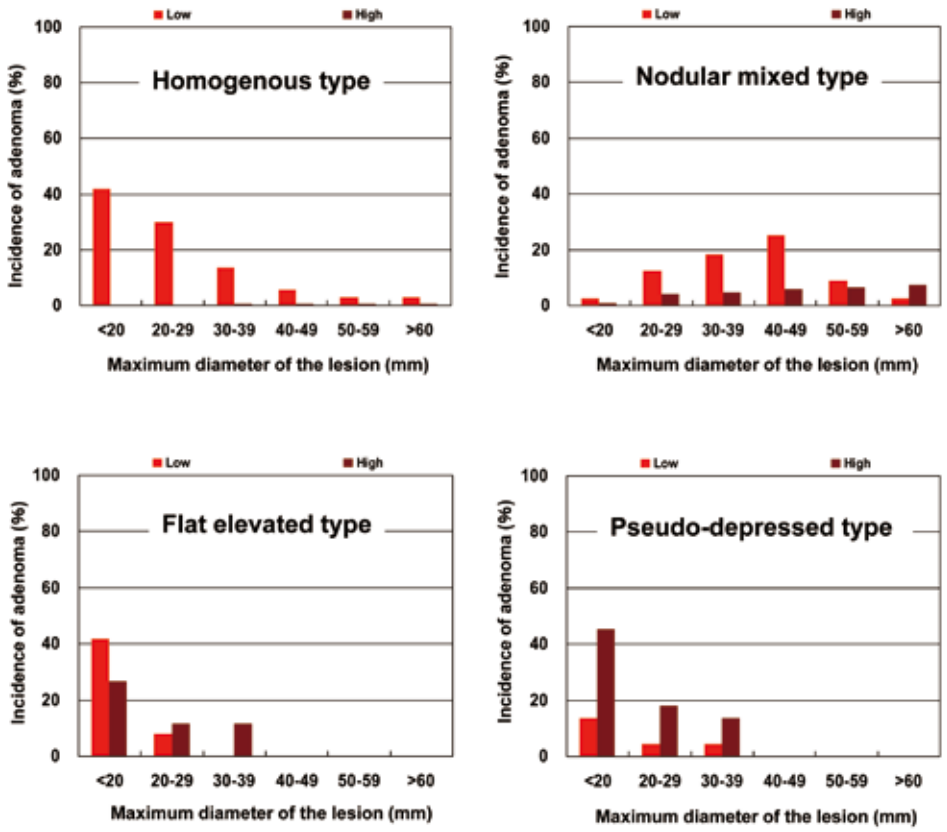

Figure 5.
Incidence of low-grade and high-grade adenoma by tumor size in colorectal laterally spreading tumors. Low indicates low-grade adenoma; and High, high-grade adenoma.

Table 3 The incidence of associated carcinoma and depth of the carcinoma invasion in colorectal laterally spreading tumors

Macroscopic type	Total No. of lesions	No. of lesions with carcinoma	Frequency of submucosal invasion	Depth of the carcinoma invasion			
				pTis	pT1/SM1	pT1/SM2	pT2 or pT3
Granular type	373	162 (43.4)[a]	71 (19.0)[d]	91 (24.4)	24 (6.4)	33 (8.9)	14 (3.8)
Homogenous type	140	17 (12.1)	4 (2.9)	13 (9.3)	2 (11.8)	2 (11.8)	0
Nodular mixed type	233	145 (66.2)[b]	67 (28.8)[e]	78 (33.5)	22 (16.8)	31 (23.7)	14 (10.7)
Non-granular type	129	49 (38.0)	13 (10.1)	36 (27.9)	10 (7.8)	3 (2.3)	0
Flat elevated type	100	28 (28.0)	5 (5.0)	23 (23.0)	4 (14.3)	1 (3.6)	0
Pseudo-depressed type	29	21 (72.4)[c]	8 (27.6)[f]	13 (44.8)	6 (28.6)	2 (9.5)	0

Parentheses indicate percentage, pTis, intramucosal carcinoma; pT1/SM1, carcinoma with a slightly submucosal invasion; pT1/SM2, carcinoma with a massively submucosal invasion; pT2, carcinoma invading into the muscularis propria; pT3, carcinoma invading through the muscularis propria into the subserosa, or into non-peritonealized perirectal tissues; and SM, submucosal tissue.

Chi-squared test was used for [a,d]NS (*vs* non-granular type); [b]$P<0.0001$ (*vs* homogenous type); [c]$P=0.0015$ (*vs* flat elevated type); [e]$P=0.0270$ (*vs* homogenous type); [f]$P=0.0273$ (*vs* flat elevated type). NS indicates not significant.

adenoma was more common in non-granular-type (60/129; 46.5%) than in granular-type lesions (73/373; 19.6%). Furthermore, non-granular-type lesions showed high-grade adenoma despite their relatively small size (Figure 5). In granular-type lesions, by contrast, low-grade adenoma was more common despite their relatively large size.

Incidence of associated carcinoma in colorectal laterally spreading tumors

Among 502 colorectal LSTs, 211 (42.0%) contained a carcinomatous component. Based on the incidence of associated carcinoma in each macroscopic subtype, of 373 granular-type lesions, 162 (43.4%) contained a carcinomatous component. Of 129 non-granular-type lesions, 49 (38.0%) contained a carcinomatous component. There was no significant difference in the incidence of associated carcinoma between the two types, whereas that of nodular mixed-type and pseudo-depressed-type lesions was significantly higher ($P<0.0001$ for the homogenous-type and $P=0.0015$ for flat elevated-type) than that of other macroscopic-type lesions (Table 3).

Any macroscopic type showed a tendency for gradual increase in the incidence of associated carcinoma in accordance with the increase in tumor size; however, homogenous type had a less than 40% incidence of associated carcinoma despite a tumor size of over 40 mm. In contrast, the pseudo-depressed type had a more than 50% incidence of associated carcinoma, even with a tumor size of less than 20 mm, reaching a plateau at a tumor size of 40 mm or more with 100% incidence of associated carcinoma (Figure 6A). The incidence of associated carcinoma in nodular mixed type was 50% with a tumor size of 30 mm or more and 100% at a plateau at a tumor size of 60 mm or more.

Frequency of submucosal invasion in colorectal laterally spreading tumors

The 162 granular-type lesions were composed of 91 (24.4%) intramucosal carcinomas and 71 (19.0%) invasive carcinomas, in which 57 had invaded into the submucosal tissue and 14 had invaded into the muscularis propria or beyond. The 49 non-granular-type lesions were composed of 36 (27.9%) intramucosal carcinomas and 13 (10.1%) carcinomas with submucosal invasion. Especially compared with the other macroscopic types, the nodular mixed-type and pseudo-depressed-type tumors invaded submucosal layers with significantly higher percentage. Based on the frequency of submucosal invasion for each tumor diameter, the pseudo-depressed type had a frequency of submucosal invasion of more than 50% at a tumor size of 30 mm or more and 100% at a plateau of tumor size of 40 mm or more (Figure 6B), whereas the frequency of submucosal invasion in nodular mixed type gradually increased to over 50% with tumor size of 50 mm or more. In contrast, the frequency of submucosal invasion of the homogenous type did not exceed 40% even at a tumor size of 60 mm or more.

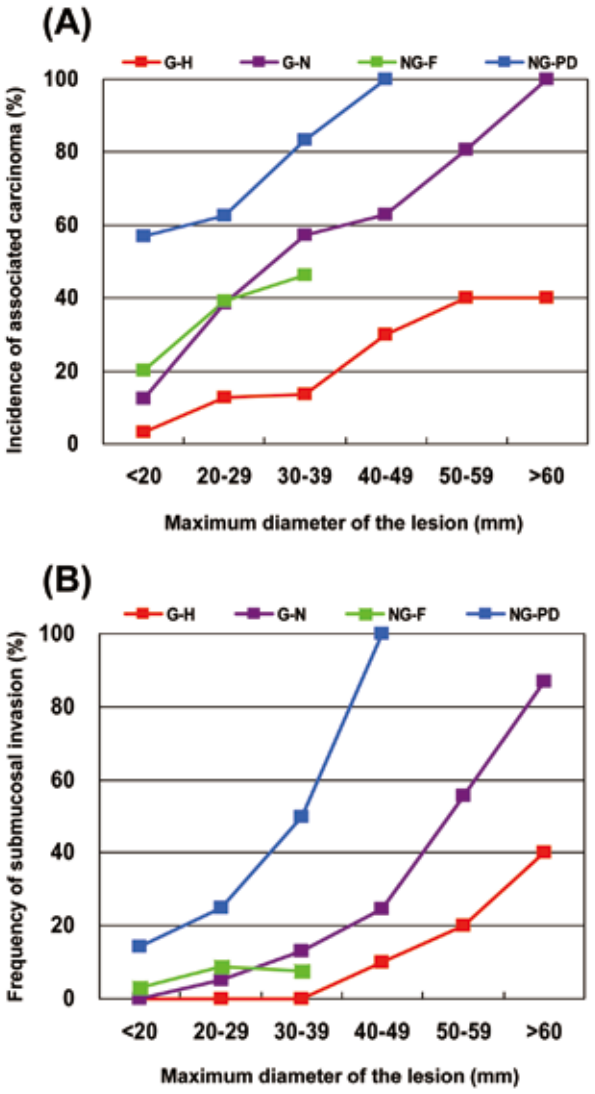

Figure 6. Incidence of associated carcinoma (A) and the frequency of submucosal invasion (B) by tumor size in colorectal laterally spreading tumors. Abbreviations are as defined in Figure 4.

Histological characteristics of associated carcinoma in colorectal laterally spreading tumors

All histologic types of associated carcinoma were that of adenocarcinoma. Regarding degree of tissue differentiation, 82.9% (175/211) was well-differentiated type and 17.1% (36/211) was well- to moderately differentiated type. Further, advancing margins of 20 lesions in nodular mixed type contained a component of mucinous adenocarcinoma. In this study, no poorly differentiated adenocarcinoma was found (Table 1).

Discussion

Kudo has defined large flat epithelial neoplasia that extends circumferentially along the colonic wall but is short in height compared with a large diameter of more than 10 mm as LST.[1] The colorectal LST has been recognized as an important precursor of colorectal carcinoma. Therefore, it is critical to understand the pathological features of the lesion when selecting treatment for colorectal LSTs. In our study, we analyzed 502 lesions of colorectal LSTs from 502 patients and classified them into granular and non-granular types by macroscopic findings, further dividing them into 4 subtypes (homogenous, nodular mixed, flat elevated, and pseudo-depressed type) based on detailed observation.

The observed incidence of macroscopic type lesions included 373 of the granular type (74.3%) and 129 of the non-granular type (25.7%), indicating that the incidence of the latter was obviously lower. In contrast, 318 lesions of the granular type (55.9%) and 251 lesions of the non-granular type (44.1%) were observed at the National Cancer Center Hospital, whereas in the Department of Gastroenterology, Juntendo University School of Medicine, 189 lesions of the granular type (43.2%) and 248 lesions of the non-granular type (56.8%) were observed.[17] The institutional difference in incidence may be attributed to the fact that some of the non-granular type lesions were classified into type IIa or type IIa + IIc. That is, whether clinicians use the exact wording of "non-granular type" was expected to generate an institutional difference in incidence.

Regarding average diameter of tumor size in each macroscopic type, nodular mixed type had the largest diameter, whereas non-granular type had a smaller size with no tumor size over 50 mm. LSTs were found to include small lesions of about 20 mm in tumor size.

Lesion height (i.e., vertical distance from the surface of the mucosa in non-tumor tissue to the apex of the mucosa in tumor tissue) in order of increasing height was 1.1±0.04 mm in non-granular type, 1.63±0.06 mm in homogenous type, and 7.06±0.39 mm in nodular mixed type (unpublished data). These results reflect the macroscopic features of non-granular type, which had lesions of smaller diameter and shorter height than those of the granular type.

Concerning the site of each macroscopic type, most of the granular-type lesions were located in the cecum, ascending colon, and rectum, whereas non-granular-

type lesions were located mostly in the transverse colon. The data showed obvious differences in distribution in the colon between granular-type and non-granular-type lesions. The results were consistent with reports from other institutions.[9), 11)] The exact reason for frequent occurrence of non-granular-type lesions in the transverse colon is unknown.

Based on the histology of the LSTs, among the 502 lesions, 481 (95.8%) contained a component of adenoma, and the remaining 21 lesions were composed of adenocarcinoma alone, both of which were of the macroscopic non-granular type. Based on the histology of the adenomas, nodular mixed type showed a high ratio of tubulovillous adenoma, reflecting its macroscopic image. However, the homogenous type was mainly comprised of tubular adenoma, and non-granular type was totally comprised of tubular adenoma. With respect to the grade of cytologic atypia of the adenoma, homogenous type showed an overwhelmingly high ratio of low-grade adenoma despite the increase in tumor size. Nodular mixed type generally showed a high ratio of low-grade adenoma; however, in this type, the ratio of high-grade adenoma increased in accordance with an increase in tumor size. When the tumor size was over 60 mm, the ratio of high-grade adenoma exceeded that of low-grade adenoma. Contrastingly, non-granular type showed a high ratio of high-grade adenoma even with small tumor size, indicating that non-granular type is considered to have a higher malignant potential than that of granular type.

Regarding the incidence of associated carcinoma of LSTs in each macroscopic type, the pseudo-depressed type had the highest incidence of associated carcinoma, at 72.4%, followed in decreasing order of incidence by nodular mixed type, flat elevated type, and homogenous type. Even when the incidence of associated carcinoma was assessed according to carcinoma size, the results showed a similar trend. Furthermore, with respect to the frequency of submucosal invasion, the pseudo-depressed and nodular mixed types had a significantly higher frequency than the other macroscopic types. This study revealed that among 84 lesions with submucosal invasion, in 36 (42.9%) lesions, intramucosal tumors remained immediately above the site of submucosal invasion (data not shown). It is likely to be difficult to identify the site of submucosal invasion in these lesions. Also, when assessing the distribution of sites of submucosal invasion in lesions, 72 (85.7%) were revealed to be located within the center of the lesion, and the distribution of the remaining 12 lesions (14.3%) was uneven (data not shown).

These results showed similarities between granular type and non-granular type in the high proportion of adenoma component and high proportion of intramucosal carcinoma in cases of associated carcinoma. In contrast, differences within types included difference in location, small tumor diameter along with high grade of cytologic atypia in the non-granular type, high proportion of tubulovillous adenoma in the nodular mixed type, and high incidence of associated carcinoma in both the pseudo-depressed and nodular mixed types. We conclude that clinically different treatment for colorectal LSTs is required based on their macroscopic types.

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Disclosure/Conflict of interests

There are no competing financial interests, and the authors have no conflicts of interest to declare.

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