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Should laterally spreading tumors granular type be resected en bloc in endoscopic resections?

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Abstract
Background Currently, granular-type laterally spreading tumors (LST-G) have been classified into uniform [LST-G (UNI)] and nodular mixed [LST-G (MIX)] subtypes. However, the progression pattern of each subtype has not been evaluated in detail. The present study was designed to assign adequate treatment strategies to each LST-G subtype, based on the progression pattern.
Methods This retrospective study included 457 consecutive patients with 482 LST-Gs that had been removed endoscopically or surgically in a tertiary cancer center between September 2002 and December 2011. We classified the tumors as LST-G (UNI) or LST-G (MIX) subtypes. We analyzed clinicopathological characteristics and submucosal invasion rates for both subtypes, and we determined the incidence of submucosal invasions associated with the largest nodules for each subtype.
Results We evaluated the histopathological data from 136 LST-G (UNI) and 316 LST-G (MIX) lesions with diameters of 10–19 mm (14 %), 20–29 mm (26 %), 30–39 mm (25 %), or >40 mm (35 %). Submucosal invasions were observed in 3 (1.8 %) LST-G (UNI) and 49 (15.5 %) LST-G (MIX) lesions. In LST-G (MIX) lesions, the submucosal invasion incidences (within a tumor-size category) were as follows: 5.8 % (10–19 mm), 11.1 % (20–29 mm), 14.7 % (30–39 mm), and 19.1 % (>40 mm), respectively. In LST-G (MIX) lesions that showed submucosal invasions, the invasive cancers were located under the largest nodule (69 %; 34/49), outside the largest nodule (25 %; 12/49), or in both sites (6 %; 3/49).
Conclusions Our results indicated that, for LST-G (UNI) lesions, piecemeal resections would be acceptable due to the low risk of submucosal invasion. For LST-G (MIX) lesions, particularly those with diameters ≥20 mm, en bloc removal in an endoscopic resection is preferable for sufficient histological evaluation.

Keywords Laterally spreading tumor · Laterally spreading tumor granular type · En bloc resection · Endoscopic submucosal dissection

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Colorectal cancer (CRC) is the third common cancer and the second leading cause of cancer-related deaths in the world [1]. Long-standing evidence has shown that early detection and removal of colorectal neoplasms has had a significant impact in reducing CRC mortality [2]. The term "laterally spreading tumor" (LST) was proposed by Kudo et al. to define specialized, flat neoplasms, >10 mm in diameter, which extend laterally and circumferentially, rather than vertically along the colonic wall [3, 4]. These superficial spreading neoplasms have been recognized as an important precursor of advanced CRC [3, 5]. Because LSTs run less risk of submucosal invasion than polypoid tumors in the same size category [6–9], LSTs are considered good

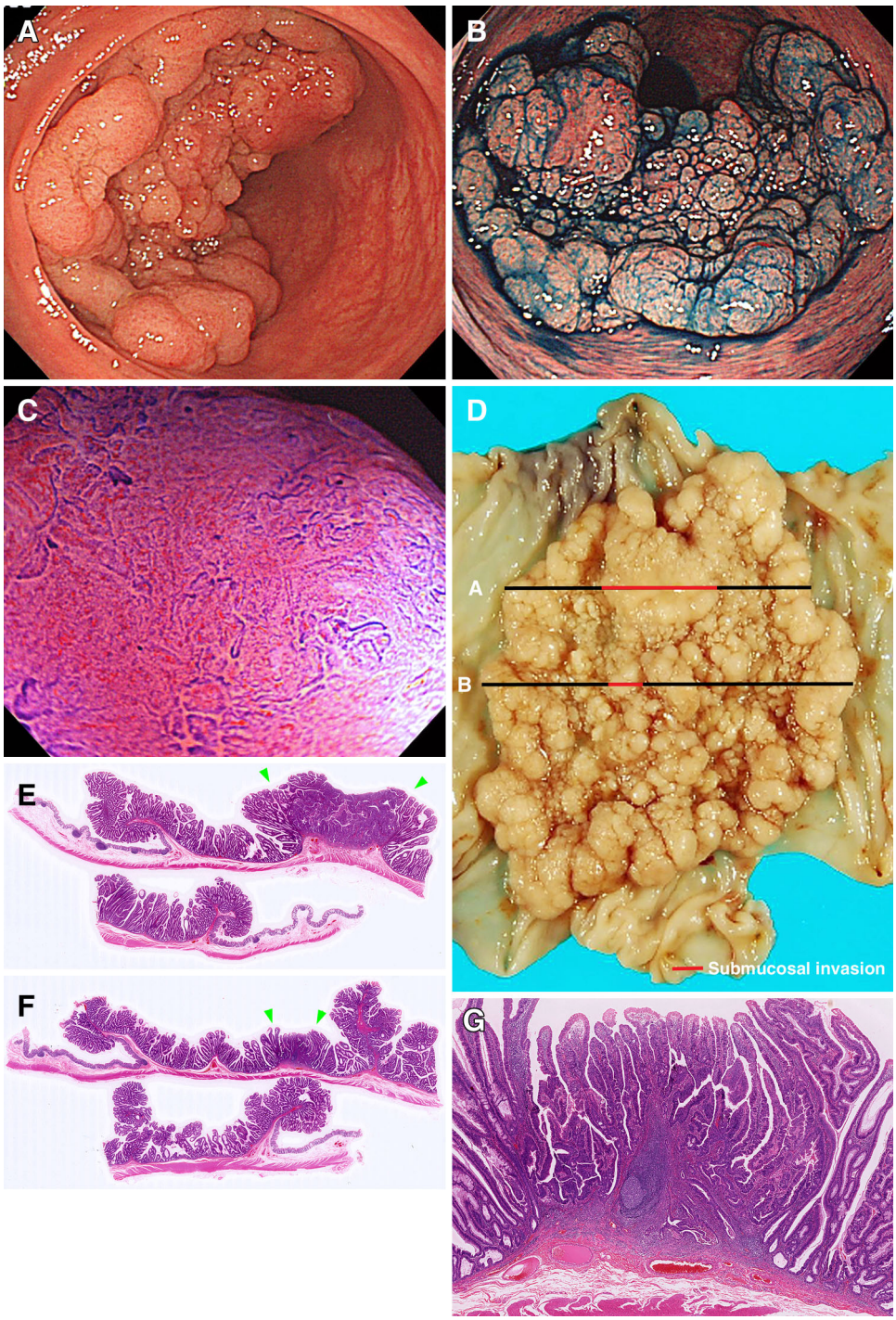


Fig. 1 Endoscopic images of a granular type laterally spreading tumor (nodular mixed type) with submucosal invasion, both under and outside the largest nodule. **A** White light endoscopy shows a granular type laterally spreading tumor (nodular mixed type) located in the rectum; it is 60 mm in diameter and characterized by a reddish nodule. **B** Chromoendoscopy shows the tumor sprayed with 0.4 % indigo carmine dye; this highlighted the depression area in the largest nodule. **C** Magnified chromoendoscopy with crystal violet staining of the depression area shows an irregular pit pattern (invasive pattern). **D** Resected specimen reveals the submucosal invasion (red lines), both within (**A**) and outside (**B**) the largest nodule. **E** Low-power view of tumor sections stained with hematoxylin-eosin. This shows a well-differentiated adenocarcinoma and a submucosal invasion that were located under the depression in the large nodule (*green arrows*), which corresponds to the lesion shown in **D** (*red area* on the line labeled '*A*'). **F** Low-power view of two sections from another specimen. A small nodule is visible at the center of the specimen (*green arrows*), which corresponds to the lesion shown in **D** (*red area* on the line labeled '*B*' in). **G** High-power view of the small nodule in **F** reveals a submucosal invasion

candidates for endoscopic resection. A clear description of the LST progression pattern is crucial for selecting an adequate treatment method. Recently, Kudo et al. subclassified granular type LSTs (LST-G) into uniform (LST-G (UNI)) and nodular mixed (LST-G (MIX)) subtypes [10]. The current treatment strategy for LST-Gs was based on previous reports that compared the progression patterns of granular and nongranular LSTs. However, subtypes of LST-Gs were not distinguished in that report. The purpose of the present study was to define adequate treatment strategies for LST-G subtypes based on progression patterns (Fig. 1).

Patients and methods

We used a prospectively designed clinical database for the present analysis. We identified 485 LST-Gs in 460 consecutive patients that were treated endoscopically or

surgically between September 2002 and December 2011. We excluded from the study two patients who were diagnosed with familial adenomatous polyposis and one who was diagnosed with a residual lesion from a previous endoscopic resection. Thus, we included a total of 457 patients with 482 lesions. For all patients, we analyzed clinicopathological variables, including age, sex, endoscopic findings, treatments, and histological results.

Written, informed consent was obtained from all patients. All patients were informed of the risks and benefits of the treatments before they underwent the procedure. Approval for this study was obtained from the Institutional Review Board of Shizuoka Cancer Center (Institutional No. 25-J10-25-1-3).

Endoscopic workup

Colonoscopies were performed with a high-resolution video endoscope equipped with a magnification function (PCF-Q240Z or CF-H260AZI or PCF-Q260AZI; Olympus, Tokyo, Japan). After the colonoscopy, all colonoscopy images and endoscopic diagnoses were reviewed and corrected by two supervisors (YY and KH), each with previous experience in performing more than 1,000 colonoscopies per year for more than 10 years. An LST was defined as a flat, elevated lesion, larger than 10 mm in diameter, which extended laterally, rather than vertically, along the interior luminal wall of the colorectum [4]. LST-Gs were defined as lesions of nodular aggregates with a granular surface. In addition, LST-Gs, which are composed of collecting nodules, were classified into LST-G (UNI) and LST-G (MIX) subtypes. The LST-G (UNI) and LST-G (MIX) subtypes corresponded to the Paris classification type 0–IIa, with an evenly granular surface, and type 0–Is + IIa, respectively.

LST-G treatment strategies included endoscopic mucosal resection (EMR), endoscopic piecemeal mucosal resection (EPMR), endoscopic submucosal dissection (ESD), and colectomy, based on decisions made at the weekly institutional conference among endoscopists, radiologists, oncologists, and colorectal surgeons. To assess the invasion depth, the endoscopists examined the morphology of the LST for the presence of large nodules and a depressed area. They also measured the fold convergence and fixed shape after air insufflations. In addition, they performed magnified endoscopy [11]. When the invasion depth was diagnosed as intramucosal or shallow submucosal, an endoscopic resection was performed. When the tumor was diagnosed as a deep submucosal invasive tumor, surgical resection was performed. Colectomy with lymph node dissection was performed as an additional treatment when, after endoscopic removal, the tumor histopathology indicated risk factors related to lymph node metastasis; these risk factors included a positive resection margin, a submucosal invasion deeper than 1,000 μm, a poorly differentiated type, tumor budding, or lymphovascular invasion [12].

Histological evaluation

Pathological diagnoses of all lesions were performed by experienced pathologists. The histological type of the adenoma or carcinoma was classified in terms of the World Health Organization classifications [13]. The depth of tumor invasion was classified, in terms of the Paris classifications, as intramucosal, submucosal shallow (invasion depth within 1,000 μm from the muscularis mucosa), or submucosal deep (invasion depth deeper than 1,000 μm from the muscularis mucosa) [14]. The association between the largest nodule and the submucosal invasion site was evaluated by comparing macroscopic images of the resected specimen to the histological images of the submucosal invasion site.

Statistical analysis

Analyses were performed with the Chi square test or Fisher's exact test. $P < 0.05$ was considered statistically significant. For descriptive statistics, the mean ± standard deviation (SD) was used when variables were normally distributed. Multivariate logistic regression analysis was performed to assess significant factors for submucosal invasion in LST-G lesions. Data management and statistical analyses were performed with JMP software (version 8.0; SAS Institute Inc., Cary, NC).

Results

Overall clinicopathological characteristics

A total of 457 eligible patients were studied with a mean age of 67 (range 34–94) years. The male-to-female ratio was 261:221. Lesion characteristics for the LST-Gs are shown in Table 1. The distribution of LST-G subtypes was 166 LST-G (UNI) and 316 LST-G (MIX). Among the entire group, histological types included 194 adenoma lesions (40.2 %), 236 intramucosal cancers (49 %), and 52 submucosal invasive cancer lesions (10.8 %). The initial treatment for LSTs was mainly endoscopic resection (91.7 %, 442/482). Pathological evaluation of an en bloc resected specimen was achieved for 367 lesions (76.1 %; 367/482).

Table 1 Comparison of clinicopathological characteristics of different LST subtypes

	Total LST-G $n = 482$	LST-G (UNI) $n = 166$	LST-G (MIX) $n = 316$	*P* value
Age, mean ± SD (range)	67 ± 10.5 (34–94)	70.6 ± 0.8 (39–90)	66.1 ± 0.58 (34–94)	<0.0001
Sex, male, *n* (%)	261 (54.2)	94 (56.6)	167 (52.9)	0.44
Tumor size, *n* (%)				<0.0001
10–19 mm	67 (13.9)	50 (30.1)	17 (5.4)	
20–29 mm	125 (25.9)	62 (37.3)	63 (19.9)	
30–39 mm	121 (25.1)	26 (15.7)	95 (30.1)	
≥40 mm	169 (35.1)	28 (16.9)	141 (44.6)	
Location, *n* (%)				<0.0001
Rectum	134 (27.8)	21 (12.7)	113 (35.8)	
Left colon	108 (22.4)	21 (12.7)	87 (27.5)	
Right colon	240 (49.8)	124 (74.6)	116 (36.7)	
Histology, *n* (%)				<0.0001
Adenoma	194 (40.2)	110 (66.3)	84 (26.6)	
Intramucosal cancer	236 (49.0)	53 (31.9)	183 (57.9)	
SM invasive cancer	52 (10.8)	3 (1.8)	49 (15.5)	
Initial treatment, n (%)				<0.0001
EMR	109 (22.6)	71 (42.8)	38 (12)	
EPMR	103 (21.4)	54 (32.5)	49 (15.5)	
ESD	230 (47.7)	29 (17.5)	201 (63.6)	
Colectomy	40 (8.3)	12 (7.2)	28 (8.9)	

LST laterally spreading tumor, *SD* standard deviation, *LST-G (UNI)* LST granular uniform type, *LST-G (MIX)* LST granular mixed nodular type, *Right colon* transverse colon proximal to the splenic flexure, ascending colon, and cecum, *Left colon* sigmoid, descending colon, *SM* submucosal, *EMR* endoscopic mucosal resection, *EPMR* endoscopic piecemeal mucosal resection, *ESD* endoscopic submucosal dissection

Clinicopathological characteristics of the different LST subtypes

LST-G (MIX) lesions were significantly larger than LST-G (UNI) lesions ($P < 0.0001$). The LST location varied according to tumor subtype ($P < 0.0001$). LST-G (UNI) lesions were found mainly in the right colon, and LST-G (MIX) lesions were frequently detected in the right colon and rectum. The incidence of malignancy was higher for LST-G (MIX) than for LST-G (UNI) lesions. Notably, among the LST-G (UNI) lesions, only three (1.8 %) had a submucosal invasion. In contrast, submucosal invasions were observed in 49 (15.5 %) LST-G (MIX) lesions.

Significant factors for submucosal invasion in LST-G lesions

Results of univariate and multivariate analysis for significant factors for submucosal invasion in LST-G lesions were shown in Table 2. In univariate analysis, significant differences were observed in each variable of tumor size, location, and LST-G subtype. In contrast, multivariate analysis demonstrated that LST-G subtype was only a significant factor for submucosal invasion in LST-G lesions.

Association between submucosal invasion and tumor size in LST-G (MIX)

The incidence of submucosal invasive cancer gradually increased with tumor size (Table 3). Submucosal invasive cancers were observed in 16.1 % (32/299) of LST-G (MIX) lesions that were larger than 20 mm in diameter. Submucosal invasive cancer was most frequently found under the largest nodule; however, 25 % (12/49) of submucosal invasive tumors were found outside the largest nodule (Fig. 2).

Discussion

This study demonstrated the progression pattern of two LST-G subtypes. Our results showed that: (1) LST-G (UNI) lesions were rarely associated with a submucosal invasion (1.8 %, 3/166); (2) LST-G (MIX) lesions larger than 20 mm in diameter frequently invaded the submucosal layer (16.1 %, 32/299); and (3) 25 % (12/49) of submucosal invasions in LST-G (MIX) lesions were found outside the largest nodule. Based on these results, we propose an updated treatment strategy for LST-Gs.

Currently, piecemeal resection is accepted for LST-Gs smaller than 30 mm in diameter, when the area that

Table 2 Significant factors for submucosal invasive cancer in LST-G lesions

	Total LST-G ($n = 482$)	SM invasive cancer ($n = 52$)			
	n (%)	Univariate analysis		Multivariate analysis	
		Prevalence, n (%)	P value	Odds ratio (95 % CI)	P value
Tumor size			0.005		0.1
<20 mm	67 (13.9)	1 (0.01)		1	
≥20 mm	415 (86.1)	51 (12.3)		4.00 (0.8–72.7)	
Location			0.012		0.34
Rectum	134 (27.8)	23 (17.2)		1	
Left colon	108 (22.4)	12 (11.1)		0.65 (0.29–1.36)	
Right colon	240 (49.8)	17 (7.1)		0.65 (0.31–1.24)	
LST-G subtype			< 0.001		<0.001
LST-G (UNI)	166 (34.4)	3 (1.8)		1	
LST-G (MIX)	316 (65.6)	49 (15.5)		7.22 (2.49–30.7)	

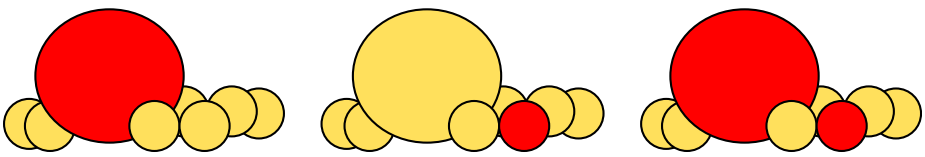
LST-G laterally spreading tumor granular type, *SM* submucosal, *CI* confidence interval, *Right colon* transverse colon proximal to the splenic flexure, ascending colon, and cecum, *Left colon* sigmoid, descending colon, *LST-G (UNI)* LST granular uniform type, *LST-G (MIX)* LST granular mixed nodular type

Table 3 Incidence of submucosal (SM) invasive cancer in different sized LST-G lesions

Tumor size (mm)	LST-G (UNI)	LST-G (MIX)
10–19	0/50 (0 %)	1/17 (5.8 %)
20–29	1/62 (1.6 %)	7/63 (11.1 %)
30–39	1/26 (3.8 %)	14/95 (14.7 %)
≥40	1/28 (3.6 %)	27/141 (19.1 %)
<20	0/50 (0 %)	1/17 (5.8 %)
≥20	3/116 (2.5 %)	48/299 (16.1 %)

The SM invasive cancer incidence (%) was calculated as the number of tumors with SM invasive cancer/total tumors in the indicated size group

includes the large nodule or depressed area being resected first. This practice was based on findings that submucosal invasions were associated with large nodules (>10 mm) or depressed areas within LST-Gs [5, 15, 16]. Uraoka et al. found that 84 % (16/19) of LST-G submucosal invasions was associated with nodules larger than 10 mm. Saito et al. reported that LST-Gs that lacked depressions and were smaller than 30 mm showed low risk of submucosal invasion (3.8 %, 3/82). However, those studies did not distinguish between LST-G (UNI) and LST-G (MIX) lesions. LST-G with a large nodule (>10 mm), which was reported as a predictor of submucosal invasion, corresponds to one which was defined as LST-G (MIX) in our study. Thus, those findings may be consistent with our finding that LST-G (MIX) lesions had significantly more frequent submucosal invasions than LST-G (UNI) lesions. Similar to previous results [10, 17], we found that LST-G (UNI) lesions were rarely associated with submucosal invasions, even when they were larger than 30 mm. The different progression patterns of these subtypes enhanced the significance of using this subtype classification in clinical practice. A recent study from Korea evaluated the progression of each LST-G subtype. However, that study could not provide conclusive guidance for treatment



Under the largest nodule	Outside of the largest nodule	Under and outside of the largest nodule
34/49 (69%)	12/49 (25%)	3/49 (6%)

Fig. 2 The frequencies of different submucosal invasion sites associated with the largest nodule within an LST-G (MIX) lesion

strategies, because the number of eligible LST-Gs with submucosal invasions was quite small ($N = 5$) [17]. Thus, the progression patterns of the different LST-G subtypes remained unclear in terms of submucosal invasions.

Endoscopic resection is generally accepted for lesions with a significantly low risk of lymph node metastasis [12]. A recent study demonstrated the feasibility of endoscopic resection for submucosal invasive carcinomas [18]. These significant advances would be applicable, once the disease is accurately stratified based on a precise histological evaluation. Conventional EMR with a snare was the standard treatment for early colorectal neoplasms, but this method had the disadvantage that piecemeal resection frequently occurred for large lesions (>2 cm in diameter) [8]. Piecemeal resections were significantly associated with local recurrences, and they required frequent endoscopic surveillance procedures [19–22]. ESD was introduced as an approach with improved efficacy; this approach provided high en bloc resection rates irrespective of tumor size [22–26]. Due to the widespread application of colorectal ESDs, particularly in Japan, changes in treatment strategies for large colorectal neoplasms improved the overall en bloc resection rate [27–29]. This study included a large series with a high proportion of en bloc resected specimens. This data contributed to the ability to define progression patterns. Based on our results, we propose that piecemeal resection is acceptable for LST-G (UNI) lesions, because they showed a low risk of submucosal invasion irrespective of tumor size, consistent with previous results [17, 27]. In contrast, LST-G (MIX) lesions larger than 20 mm in diameter should be resected in an en bloc fashion, due to the increased risk of submucosal invasion.

This study had some limitations. First, the design was retrospective, and it included only a single medical center. Second, we did not evaluate the effectiveness of magnified endoscopy for detecting submucosal invasions in LST-G (MIX) lesions. However, magnified endoscopy was demonstrated to be a powerful tool for evaluating the depth of tumor invasion [30]; thus, further study on this technique is necessary. Third, the cohort studied may represent a biased population, because our institution was a tertiary cancer center. However, the lesion characteristics were similar to those described in previous reports [5, 17, 28, 31, 32]. Therefore, our results are applicable to a clinical practice setting.

In conclusion, for LST-G (UNI) lesions, piecemeal resections are acceptable, because they showed a low risk of submucosal invasion. LST-G (MIX) lesions, particularly those 20 mm or larger in diameter, should be removed en bloc for accurate histological evaluations. When conditions make en bloc resection difficult to achieve with a conventional EMR, the ESD approach should be considered.

Disclosures Kenichiro Imai, Kinichi Hotta, Yuichiro Yamaguchi, Naomi Kakushima, Masaki Tanaka, Kohei Takizawa, Hiroyuki Matsubayashi, Noboru Kawata, Kimihiro Igarashi, Shinya Sugimoto, Masao Yoshida, Takuma Oishi, Keita Mori, and Hiroyuki Ono have no conflict of interest or financial ties to disclose.

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