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Factors Associated with Fibrosis during Colorectal Endoscopic Submucosal Dissection: Does Pretreatment Biopsy Potentially Elicit Submucosal Fibrosis and Affect Endoscopic Submucosal Dissection Outcomes?

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Keywords
Adenoma · Adenocarcinoma · Colorectal cancer · Endoscopic mucosal resection · Laterally spreading tumor

Abstract
Background: Submucosal fibrosis observed during colorectal endoscopic submucosal dissection (ESD) is an important factor related to incomplete resection. Biopsy is generally accepted as having the potential to elicit submucosal fibrosis, but few reports have presented definitive proof. This study investigated the relation between submucosal fibrosis and colorectal ESD outcomes and assessed factors related to fibrosis, including pretreatment biopsy. ***Methods:*** After reviewing 369 records of colorectal ESD performed between January 2011 and December 2016, we assessed the relation between fibrosis and ESD outcomes. Multiple logistic regression analysis revealed fibrosis risk factors. ***Results:*** Severe fibrosis was related significantly to ESD outcomes such as the mean procedure time ($p < 0.001$), en bloc resection rate ($p < 0.001$), and R0 resection rate ($p = 0.011$). Multivariate analyses indicated residual lesions (ORs 175.4, $p < 0.001$), pretreatment biopsy (ORs 8.30, $p = 0.002$), nongranular-type laterally spreading tumors (LST-NG; ORs 5.86, $p = 0.025$), and invasive carcinoma (ORs 5.83, $p = 0.03$) as independent risk factors of severe fibrosis. In each macroscopic type, LST-NG was more strongly related to fibrosis induced by pretreatment than granular-type laterally spreading tumors with adjust ORs of 50.8 and 4.69. ***Conclusions:*** Pretreatment biopsy causes submucosal fibrosis resulting in prolonged procedure times and incomplete resection. These findings suggest important benefits of avoiding biopsy before ESD.

Introduction

Colorectal endoscopic submucosal dissection (ESD) is gradually gaining widespread acceptance worldwide [1–3]. This technique permits en bloc removal of tumors of >2 cm in diameter, leading to precise histological assessment and a lower recurrence rate than that obtained using

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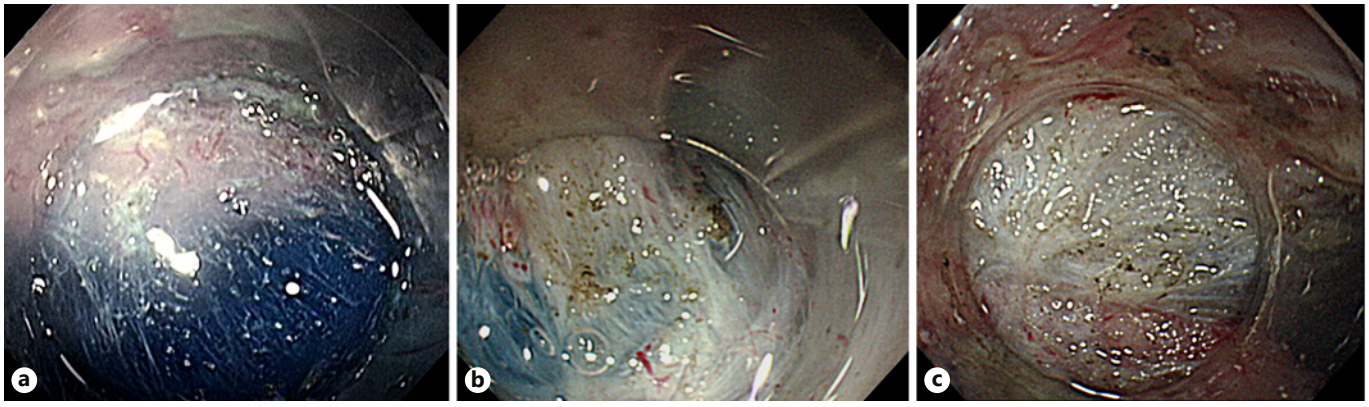


Fig. 1. Degree of fibrosis of the submucosal layers during colorectal ESD. No fibrosis: which manifested as a blue transparent layer. Mild fibrosis: which appears as a white web-like structure in the blue submucosal layers. Severe fibrosis: which appears as a white muscular structure without blue transparent layer in the submucosal layers.

endoscopic mucosal resection (EMR) [4]. Nevertheless, because of anatomical features of the organs such as a thin colonic wall and the presence of peristalsis leading to complications such as perforation during procedures and longer procedure times, colorectal ESD presents a higher degree of technical difficulty than gastric ESD [5, 6].

Reportedly, predictors of incomplete resection include the experience of endoscopists [7], paradoxical movement of the colonoscope [8], tumor size [6], tumor location [9], and submucosal fibrosis [6, 8, 10, 11]. Among them, submucosal fibrosis is an important factor related to incomplete resection. Japanese Society of Gastroenterological Endoscope (JSGE) guidelines state the indications of EMR and ESD for colorectal lesions [12]. The guidelines state that mucosal tumors with submucosal fibrosis caused by pretreatment biopsy indicate ESD because EMR is difficult as a result of nonlifting sign. The guideline also states that biopsy is not recommended at the lesion because biopsy potentially elicits submucosal fibrosis leading to a positive nonlifting sign, which makes subsequent endoscopic treatment difficult. Moreover, for large lesions such as granular laterally spreading tumor (LST-G), which is "carcinoma in adenoma" in many cases, biopsy might not support accurate diagnosis in many cases. These findings are widely accepted by gastroenterologists in Japan. Nevertheless, few studies have specifically examined the association between pretreatment biopsy and submucosal fibrosis observed during colorectal ESD. In the MINDS Grade of Recommendations [13], the evidence level related to pretreatment biopsies is rated as V (Descriptive study). The grade of recommendations is rated as C1. No scientific evidence exists, but therapy is recommended. In addition, biopsy capabilities for distinguishing adenocarcinoma from adenoma have been little reported.

This study evaluated the relation between submucosal fibrosis observed during colorectal ESD and colonic ESD outcomes. We evaluated factors associated with submucosal fibrosis and investigated whether pretreatment biopsy affected the fibrosis of the submucosal layer during ESD. We also examined whether adenocarcinoma is distinguishable from adenoma using pretreatment biopsy.

Methods

Patients

For this study, we reviewed ESD records of 369 colorectal lesions in 355 patients treated at Tohoku University Hospital between January 2011 and December 2016. This retrospective study was approved by the Ethics Committee of Tohoku University Hospital (No. 2016-1-003). All the patients provided written informed consent.

Indication Criteria for Colorectal ESD

We included colorectal lesions indicated by preoperative endoscopic findings as >20 mm in diameter. Indication criteria for colorectal ESD were based on JSGE guidelines as follows: (1) lesions for which endoscopic en bloc resection is required, that is, lesions for which en bloc resection with EMR is difficult such as nongranular-type laterally spreading tumor (LST-NG), lesions with a VI-type pit pattern, carcinoma with superficial invasion, large depressed-type tumors, and large protruded-type lesions suspected to be carcinoma; (2) mucosal tumors with submucosal fibrosis; (3) sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis; and (4) local residual or recurrent early carcinomas after endoscopic resection.

Colorectal ESD Procedures

Details of colorectal ESD procedures were presented in our earlier report [14]. Following is a brief description of the procedure.

Pediatric endoscopes were used (PCF-Q260JI and GIF-Q260J; Olympus Optical Co., Tokyo, Japan) with a disposable attachment. Into the submucosal layer, we injected a mixture of solution containing sodium hyaluronate with a small volume of epinephrine and indigocarmine. A tip-type knife (Dual Knife; Olympus Optical Co., Tokyo, Japan) was used for mucosal incision and submucosal dissection. We used an electrosurgical generator (ICC 200; ERBE Elektromedizin GmbH, Tubingen, Germany).

Procedures of colorectal ESD were performed by several endoscopists. All procedures were conducted by trainees under the supervision of experienced endoscopists. In cases of perforation induced by trainees, subsequent procedures were performed by experienced endoscopists.

Endoscopic and Histological Assessments

Tumor sites were divided into 3 groups: the rectum, left colon (sigmoid colon and descending colon), and right colon (transverse colon, ascending colon, and cecum). Macroscopic tumor types were classified as protruding tumor (Is), granular-type laterally spreading tumor (LST-G; Is + IIa, IIa), nongranular-type laterally spreading tumor (LST-NG; IIa, IIc), or residual lesions.

After colorectal ESD procedures, the case in which the tumor was resected in a single piece was judged as endoscopic en bloc resection. If the tumor was resected en bloc endoscopically and if the lateral and basal margins were free of tumor cells in histological analysis, the tumor was an intramucosal carcinoma or carcinoma with slight submucosal invasion (invasion depth <1,000 μm), and there was no lymphatic invasion and vascular involvement, then it was defined as R0 (complete) resection. Other cases were defined as R1 (incomplete) or Rx (not evaluable) resection.

Primary ESD outcomes were technical difficulty defined as procedure time and clinical success defined as en bloc resection and R0 resection. Secondary outcomes were complication rates such as delayed bleeding and perforation.

Based on findings obtained using injection of indigo carmine solution into the submucosal layer, the degree of submucosal fibrosis was classified as follows (Fig. 1): no fibrosis, mild fibrosis, and severe fibrosis [15]. Three experienced endoscopists independently reviewed the degree of submucosal fibrosis during ESD without information about the patients' background including the presence or absence of pretreatment biopsy, tumor histopathological types, or previous history of EMR. Sporadic localized lesions with inflammatory bowel disease such as ulcerative colitis are known to have a high rate of fibrosis in the submucosal layer [16]. Consequently, we exclude these conditions from this study.

Whether biopsy was performed and the number and location of biopsy in the lesion were decided before visiting our hospital by doctors who had no experience of colorectal ESD. For that reason, no standard criteria for pretreatment biopsy were found in our study. In many cases, biopsy was performed with 1 or 2 pieces from the central part of the lesion. We defined cases with biopsy within 3 months of colorectal ESD as pretreatment biopsy lesion.

Histopathological diagnoses were based on the Japanese classification of colorectal cancer [17]. Intramucosal carcinoma was defined as noninvasive carcinoma. Carcinoma that invades into the submucosal layer was defined as invasive carcinoma. Depth of tumor invasion was the distance between the deeper edge of the muscularis mucosae and the deepest invasion. Biopsy specimens were classified as follows: normal tissue lesion, material for which diagnosis of neoplastic or nonneoplastic lesion is difficult, adenoma, neoplastic lesion suspected of being carcinoma, and carcinoma. The pretreatment diagnosis from biopsy was regarded as carcinoma in cases with neoplastic lesion suspected of being carcinoma or carcinoma.

Table 1. Clinical characteristics of patients

	355 patients, 369 lesions
Age, years, mean (SD)	68.4 (10.6)
Sex, male/female, *n*	218/137
Mean tumor diameter, mm (SD)	44.1 (18.1)
<40 mm	203
≥40 mm	166
Location, *n* (%)	
Rectum	99 (26.8)
Left colon	59 (16.0)
Right colon	211 (57.2)
Macroscopic type, *n* (%)	
LST-G	181 (49.1)
LST-NG	102 (27.6)
Protruding	63 (17.1)
Depressed	9 (2.4)
Residual	14 (3.8)
Pretreatment biopsy[a], *n* (%)	63 (17.1)
Mean number of biopsies per lesion	1.8
Fibrosis, *n* (%)	
No fibrosis	276 (74.8)
Mild fibrosis	72 (19.5)
Severe fibrosis	21 (5.7)
Histological type, *n* (%)	
Adenoma	188 (51.0)
Noninvasive carcinoma	124 (33.6)
Invasive carcinoma	57 (15.4)

LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor nongranular type; SD, standard deviation.
[a] Lesion biopsied within 3 months of colorectal ESD.

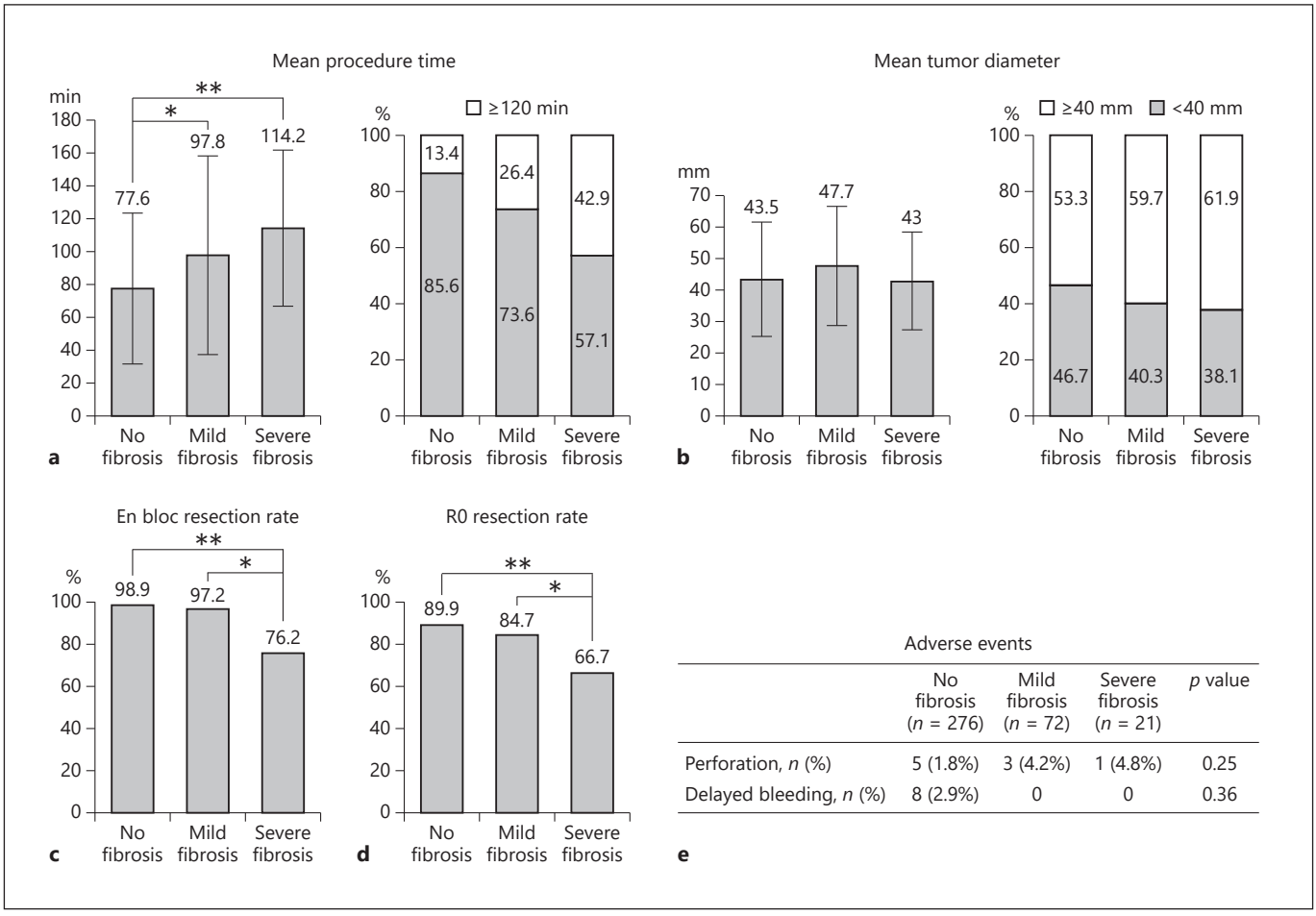
Statistical Analysis

Quantitative data are presented as mean with standard deviation (SD). All statistical analysis was done using software (JMP ver. 13; SAS Institute Inc., Cary, NC, USA). Differences among groups were evaluated using the χ^2 test or Fisher's exact probability test, as appropriate. Among the clinical characteristics, factors influencing the main outcome were identified using a multiple logistic regression method. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to assess the strength of the influence of each variable. Significance was inferred for $p < 0.05$.

Results

Patient and Lesion Characteristics

Three hundred seventy-two colorectal tumors were enrolled in this study. Three patients were excluded because



	No fibrosis (n = 276)	Mild fibrosis (n = 72)	Severe fibrosis (n = 21)	p value
Perforation, n (%)	5 (1.8%)	3 (4.2%)	1 (4.8%)	0.25
Delayed bleeding, n (%)	8 (2.9%)	0	0	0.36

Fig. 2. ESD outcomes. Left side: mean procedure times were 77.6 min in the nonfibrosis group, 97.8 min in the mild fibrosis group, and 114.2 min in the severe fibrosis group. Mean procedure times were significantly longer in the severe fibrosis group and mild fibrosis group than in the nonfibrosis group. *p = 0.01, **p < 0.001. Right side: proportion of ESD procedure times over 120 min. Left side: mean tumor diameter in each fibrosis group. No significant differences were found among the 3 groups. Right side: proportion of tumor diameter over 40 mm. En bloc resection rates were 98.9% in the nonfibrosis group, 97.2% in the mild fibrosis group, and 76.2% in the severe fibrosis group. The en bloc resection rate was significantly lower in the severe fibrosis group than in the mild fibrosis group or nonfibrosis group. *p = 0.004, **p < 0.001. R0 resection rates were 89.9% in the nonfibrosis group, 84.7% in the mild fibrosis group, and 66.7% in the severe fibrosis group. The R0 resection rate was significantly lower in the severe fibrosis group than in the mild fibrosis group and nonfibrosis group. *p = 0.047, **p < 0.003. If the tumor was resected en bloc endoscopically and if the lateral and basal margins were free of tumor cells, it was defined as R0 (complete) resection. Other cases were defined as R1 (incomplete) or Rx (not evaluable) resection. Adverse events in respective fibrosis groups. No significant difference was found among groups.

of sporadic localized lesions with ulcerative colitis. Clinicopathological characteristics of the enrolled 369 colorectal tumors are presented in Table 1. Three hundred sixty-nine lesions from 218 men and 137 women were reviewed. The mean age of the patients was 68.4 (±10.6) years. The mean colorectal tumor diameter was 44.1 mm. Locations of lesions were divided, respectively, into those of the rectum, the left colon, and the right colon in 99 (26.8%), 59 (16.0%), and 211 (57.2%) lesions. Macroscopic-type lesions were divided, respectively, into 181 (49.1%) LST-G, 102 (27.6%) LST-NG, 63 (17.1%) protruding, 9 (2.4%) depressed, and 14 (3.8%) residual lesions. Pretreatment biopsy was performed in 63 lesions (17.1%). In these cases, the mean number of biopsies taken from a lesion was 1.8. Additionally, 276 lesions (74.8%) were in the nonfibrosis group, 72 lesions (19.5%) were in the mild fibrosis group, and 21 lesions (5.7%) were in the severe fibrosis group. The histopathological diagnosis was adenoma in 188 lesions (51.0%), noninvasive carcinoma in 124 lesions (33.6%), and invasive carcinoma in 57 lesions (15.4%).

Table 2. Risk factors associated with mild fibrosis during ESD procedure

	Mild fibrosis	Univariate* *p* value	Multivariate**			
			ORs	*p* value	95% CI	
Location, *n* (%)						
Rectum	12/91 (13.2)	0.14	Reference			
Left colon	12/55 (21.8)		2.62	0.08	0.89	7.65
Right colon	48/202 (23.8)		4.03	0.002	1.70	9.57
Macroscopic type, *n* (%)						
LST-G	26/177 (14.7)	0.01	Reference			
LST-NG	25/97 (27.9)		2.18	0.03	1.08	4.39
Protruding	16/61 (26.2)		2.49	0.025	1.12	5.53
Depressed	1/7 (14.3)		0.47	0.52	0.05	4.65
Residual	4/6 (66.7)		14.4	0.008	2.04	101.3
Histological type, *n* (%)						
Adenoma	30/182 (16.5)	0.011	Reference			
Noninvasive carcinoma	24/116 (20.7)		1.69	0.14	0.84	3.38
Invasive carcinoma	18/50 (35.6)		3.51	0.03	1.55	7.93
Tumor size, *n* (%)						
<40 mm	29/158 (18.4)	0.33				
≥40 mm	43/190 (22.6)					
Pretreatment biopsy, *n* (%)						
Absent	46/294 (15.7)	<0.001	Reference			
Present	26/54 (48.2)		7.21	<0.001	3.51	14.8

CI, confidence interval; LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor nongranular type. * χ^2 test or Fisher's exact probability test was used. ** Variables with a *p* value of <0.2 in univariate analysis were included in a multiple logistic regression method.

Outcomes of ESD

The ESD outcomes are presented in Figure 2. The mean procedure times were 77.6 min in the nonfibrosis group, 97.8 min in the mild fibrosis group, and 114.2 min in the severe fibrosis group (Fig. 2a). The mean procedure time was significantly longer in either the severe fibrosis group or the mild fibrosis group than in the nonfibrosis group. Mean tumor diameter was 43.5 mm in the nonfibrosis group, 47.7 mm in the mild fibrosis group, and 43 mm in the severe fibrosis group (Fig. 2b). No significant difference was found among the 3 groups. Overall en bloc resection and R0 resection rates were 98.9 and 89.9% in the nonfibrosis group, 97.2 and 84.7% in the mild fibrosis group, and 76.2 and 66.7% in the severe fibrosis group (Fig. 2c, d). Rates of en bloc resection and R0 resection were significantly lower in the severe fibrosis group than in either the mild fibrosis group or the nonfibrosis group. The perforation and delayed bleeding rates were 1.8 and 2.9% in the nonfibrosis group, 4.2 and 0% in the mild fibrosis group, and 4.8 and 0% in the severe fibrosis group (Fig. 2e). No significant difference was found among the severe fibrosis, mild fibrosis, and nonfibrosis groups for perforation or delayed bleeding rates.

Risk Factors Associated with Submucosal Fibrosis Observed during Colorectal ESD

We analyzed possible risk factors of both mild and severe fibrosis. Regarding the mild fibrosis, univariate analyses revealed that macroscopic types, histological types, and pretreatment biopsy were associated significantly with mild fibrosis (Table 2). Multivariate analysis revealed that lesions at the right colon, macroscopic types (LST-NG, protruding, and residual lesions), invasive carcinoma, and pretreatment biopsy were significantly associated, respectively, with mild fibrosis with adjusted ORs of 4.03 (95% CI: 1.70–9.57), 2.18 (1.08–4.39), 2.49 (1.12–5.53), 14.4 (2.04–101.3), 3.51 (1.55–7.93), and 7.21 (3.51–14.8) (Table 2). Regarding the severe fibrosis, univariate analyses revealed that macroscopic types, histological types, and pretreatment biopsy were associated significantly with severe fibrosis (Table 3). Multivariate analysis revealed that macroscopic types (LST-NG and residual lesions), invasive carcinoma, and pretreatment biopsy were associated significantly with severe fibrosis with adjusted ORs of 5.86 (95% Cl: 1.25–27.4), 175.4 (22.2–1,382.7), 5.83 (11.5–29.6), and 8.30 (2.17–31.7) (Table 3).

Table 3. Risk factors associated with severe fibrosis during ESD procedure

	Severe fibrosis	Univariate* *p* value	Multivariate**			
			ORs	*p* value	95% CI	
Location, *n* (%)						
Rectum	8/87 (9.2)	0.51				
Left colon	4/47 (8.5)					
Right colon	9/163 (5.5)					
Macroscopic type, *n* (%)						
LST-G	4/155 (2.6)	<0.001	Reference			
LST-NG	4/77 (6.5)		5.86	0.025	1.25	27.4
Protruding	2/47 (4.3)		1.35	0.74	0.22	8.47
Depressed	2/8 (25.0)		5.86	0.22	0.41	45.7
Residual	8/10 (80.0)		175.4	<0.001	22.2	1,382.7
Histological type, *n* (%)						
Adenoma	6/158 (3.8)	0.007	Reference			
Noninvasive carcinoma	8/100 (8.0)		2.55	0.18	0.64	10.3
Invasive carcinoma	7/39 (18.0)		5.83	0.03	11.5	29.6
Tumor size, *n* (%)						
<40 mm	8/137 (5.8)	0.44				
≥40 mm	13/160 (8.1)					
Pretreatment biopsy, *n* (%)						
Absent	12/260 (4.6)	<0.001	Reference			
Present	9/37 (24.3)		8.30	0.002	2.17	31.7

CI, confidence interval; LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor nongranular type. * χ^2 test or Fisher's exact probability test was used. ** Variables with a *p* value of <0.2 in univariate analysis were included in a multiple logistic regression method.

Table 4. Association between pretreatment biopsy and fibrosis in respective macroscopic types

Pretreatment biopsy	LST-NG	*p* value	ORs	LST-G	*p* value	ORs	Protruding	*p* value	ORs
Fibrosis (mild and severe)									
Absent	18/88			21/144			15/51		
Present	14/15	<0.001	50.8	16/36	<0.001	4.69	4/9	0.37	1.92

LST-G, laterally spreading tumor granular type; LST-NG, laterally spreading tumor nongranular type.

To reveal the relation between fibrosis and pretreatment biopsy in each macroscopic type, subgroup analyses were conducted, respectively, for 3 major macroscopic types (LST-NG, LST-G, and protruding type) (Table 4). Depressed-type and residual lesions were excluded because of their few numbers. Because the severe fibrosis group was small and we specifically examined not the degree of fibrosis but the presence or absence of fibrosis, cases were divided into 2 groups as the no fibrosis and fibrosis groups (including mild fibrosis and severe fibrosis) in this subanalysis. Results of pretreatment biopsy revealed that LST-NG and LST-G were associated significantly with increased frequencies of fibrosis (mild and severe). The ORs of fibrosis induced by pretreatment biopsy were estimated, respectively, as 50.8 and 4.69 for LST-NG and LST-G.

Can Adenocarcinoma Be Distinguished from Adenoma by Pretreatment Biopsy?

Next, we examined whether adenocarcinoma is distinguishable from adenoma by histopathological assessment of biopsy specimens (Table 5). We compared the pretreatment diagnoses based on biopsy specimens and the histologic diagnoses of ESD specimens. Among the 17 lesions with biopsy sampling diagnoses of carcinoma, 15 (88.2%) were diagnosed as carcinoma. Among the 45 le-

Table 5. Comparison of diagnosis based on pretreatment biopsy specimens and histologic diagnosis of resected specimens

	Histological diagnosis of resected specimens	
	carcinoma	adenoma
Pretreatment diagnosis based on biopsy specimens		
Carcinoma	15	2
Adenoma	26	19

sions with biopsy diagnoses of adenoma, 26 (57.8%) were diagnosed as carcinomas. The biopsy sampling predicted final histologic diagnoses of carcinoma with a sensitivity of 36.6%, specificity of 90.5%, accuracy of 54.8%, positive predictive value of 88.2%, and negative predictive value of 42.2%.

Discussion

Results of our study demonstrated that the presence of severe fibrosis in submucosal is associated with a low en bloc resection rate and R0 resection rate. Moreover, the mean procedure time was significantly longer in both mild and severe fibrosis groups. Similarly to our result, earlier reports have described that the presence of submucosal fibrosis is associated with a low en bloc resection rate (63.1–77.4%) and extension of the mean resection time [6, 11, 18, 19].

In the present study, the most important risk factors of both severe fibrosis and mild fibrosis were residual lesions (severe fibrosis: ORs 175.4, mild fibrosis: ORs 14.4). The second important risk factor was pretreatment biopsy (severe fibrosis: ORs 8.30, mild fibrosis: ORs 7.21). Few studies have examined the association of submucosal fibrosis and pretreatment biopsy [20–22]. Kim et al. [18] reported a lack of association between pretreatment biopsy and submucosal fibrosis in 158 cases (91 cases of biopsy). Takeuchi et al. [23] reported pretreatment biopsy as not a risk factor for nonlifting sign at submucosal injection in 816 cases (446 cases of biopsy). Recently, Fukunaga et al. [24] reported pretreatment biopsy in a flat lesion such as LSTs may cause submucosal fibrosis. Results of the present study revealed that the effects of biopsy vary depending on the macroscopic type. Specifically, LST-NG was more strongly related to fibrosis (ORs 50.8). Moreover, LST-G (ORs 4.69) had less influence from biopsy than LST-NG had. Protruding type showed no biopsy effect. Because LST-NG is a flat lesion, one might infer that biopsy reaches a deeper layer of the submucosa than other macroscopic types, resulting in regenerative changes and subsequent submucosal fibrosis.

This study demonstrated LST-NG and protruding types as independent risk factors for mild fibrosis with adjusted ORs of 2.18 ($p = 0.03$) and 2.49 ($p = 0.025$). Moreover, LST-NG was associated significantly with severe fibrosis with adjusted ORs of 5.86 ($p = 0.025$). Although the depressed type is apparently a risk factor of fibrosis, we cannot assess the associations with fibrosis because few cases were examined in our study. Inada et al. [25] reported that macroscopic types such as LST-NG-pseudo-depressed and protruding type, which have >4 cm diameter, are risk factors for submucosal fibrosis. Takeuchi et al. [23] also reported the frequency of a nonlifting sign for LST-NG, protruding type, and LST-nodular mixed type (GM), respectively, as 38, 32, and 16%. A report has described a study demonstrating histologically verified submucosal fibrosis. Reportedly, microvessel density is higher in LST-NG than in LST-G; not only microvessel density but also the degree of fibrosis is higher in LST-NG than in LST-G, particularly in adenoma [26, 27]. These results are regarded as the same as those attained from our study.

This study examined whether biopsy is useful for distinguishing adenocarcinoma from adenoma. The biopsy sampling predicted final histologic diagnoses of carcinoma with a sensitivity of 36.6%, specificity of 90.5%, and accuracy of 54.8%. Several studies demonstrated narrow band imaging (NBI) and/or chromoendoscopy can distinguish neoplastic from nonneoplastic polyps. Kato et al. [28] have shown the accuracy of chromoendoscopy for diagnosing as carcinoma is 99.1%. Hayashi et al. [29] showed that NBI patterns can be used to predict submucosal invasion in colonic lesions, confirming magnifying chromoendoscopy and/or NBI as a highly effective method for predicting carcinoma in colorectal neoplasms.

Our study has several limitations. First, it is a retrospective study that enrolled few cases from a single center. Second, we evaluated the degree of fibrosis based on endoscopic findings but not on the histopathology. Lee et al. [19] reported the association between ESD outcomes and fibrosis using histopathological indicators. However, many reports have described diagnoses of fibrosis using endoscopic findings. Moreover, the frequency of fibrosis differs among reports (5.4–36.5% of cases in the studies). Third, because biopsy was performed before visiting our hospital, details of the biopsy site in the lesion were un-

clear in many cases. Therefore, it was impractical to verify that the biopsy site and the fibrosis site were truly matched in the lesion.

In conclusion, results of this study demonstrate that pretreatment biopsy causes submucosal fibrosis, thereby resulting in longer procedure times, lower en bloc resection rates, and lower R0 resection rates. Those findings were particularly noticeable in flat-type tumors such as LST-NG. The accuracy of pretreatment specimens for differentiating adenocarcinoma from adenoma is low. The evidence presented above suggests important benefits of avoiding biopsy before ESD.

Statement of Ethics

This study was approved by the Ethics Committee of Tohoku University Hospital (number: 2016–1-003). All the patients provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest, financial or otherwise, related to this article or the study it describes.

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Author Contributions

Masatake Kuroha designed the study and wrote the initial draft of the manuscript. Hisashi Siga and Yoshitake Kanazawa contributed to analysis and interpretation of data and assisted in the preparation of the manuscript. All other authors have contributed to data collection and interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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