1991 and December 2012. The histological diagnosis was based on World Health Organization criteria. We measured the submucosal invasion depth according to the guidelines issued in 2014 by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) for the treatment of CRC.[13] Submucosal invasion was classified as <1000 μm (submucosal scanty invasion) or ≥1000 μm (submucosal deep invasion) according to the indication criteria for additional treatment after ER in the 2014 JSCCR guidelines.[13]

In the present study, gross type was classified as protruded (0-Ip, Isp, Is), flat elevated (0-IIa), and depressed (0-IIc, IIa+IIc, IIc+IIa).[14] Lesion size refers to its maximum diameter. The pit pattern diagnosis of colorectal lesions was conducted according to the Kudo and Tsuruta classification system.[3] Type V pit pattern was diagnosed by detailed magnifying observation using crystal violet. LN metastasis was evaluated by surgical resection with LN dissection. Statistical analyses were carried out using the chi-squared test.

RESULTS

Incidence of diminutive CRC per gross type and lesion size in colorectal tumors

THE INCIDENCE OF carcinoma was higher in proportion to tumor size regardless of gross type. In diminutive tumors, the overall carcinoma rate in colorectal tumors was 2.0% (157/7801). Among diminutive tumors, depressed lesions had a significantly higher frequency of carcinoma (21/114; 18.4%) than protruded (98/6479; 1.5%) or flat elevated lesions (38/1208; 3.1%) (Table 1).

Incidence of diminutive submucosal invasive CRC per gross type and lesion size in early CRC

The incidence of submucosal invasive carcinoma was higher in proportion to tumor size regardless of gross type. In diminutive tumors, the overall submucosal invasion rate in early CRC was 9.6% (15/157). Among diminutive tumors, depressed lesions had a significantly higher frequency of submucosal invasion (11/21; 52.4%) than protruded (3/98; 3.1%) or flat elevated lesions (1/38; 2.6%; Table 2).

The incidence of submucosal deep invasive CRC was higher in proportion to tumor size in the depressed type lesions. In diminutive tumors, the overall submucosal invasive CRC rate was 3.2% (5/157). Tumors 6–10 mm in size had a significantly higher frequency of submucosal deep invasion (54/593; 9.1%) than diminutive tumors (5/157; 3.2%). Among the diminutive tumors, depressed lesions had a significantly higher frequency of submucosal deep invasion (4/21; 19.0%) than protruded (1/98; 1.0%) or flat elevated lesions (0/38; 0%; Table 3).

Table 1 Incidence of carcinoma per gross type and lesion size in colorectal tumors ≤10 mm

Gross type	Initial ER method		Total
	<5 mm	6–10 mm	
Ip, Isp, Is	98/6479 (2)*	392/3527 (11)***	490/10 006 (5)*****
IIa	38/1208 (3)*	150/1034 (15)***	188/2242 (8)***
IIc, IIa+IIc	21/114 (18)**	51/159 (32)****	72/273 (26)******
Total	157/7801 (2)*******	593/4720 (13)********	750/12 521 (6)

* *vs* **, *** *vs* ****, ***** *vs* ******, ******* *vs* ********: $P < 0.01$.
Values are *n* (%).
ER, endoscopic resection.

Table 2 Incidence of submucosal invasive carcinoma per gross type and lesion size in early colorectal carcinoma ≤10 mm

Gross type	Initial ER method		Total
	<5 mm	6–10 mm	
Ip, Isp, Is	3/98 (3)*	47/392 (12)***	50/490 (10)*****
IIa	1/38 (3)*	9/150 (6)***	10/188 (5)*****
IIc, IIa+IIc	11/21 (52)**	40/51 (78)****	51/72 (71)******
Total	15/157 (10)*****	96/593 (16)******	111/750 (15)

* *vs* **, *** *vs* ****, ***** *vs* ******: $P < 0.01$; ***** *vs* ******: $P < 0.05$.
Values are *n* (%).
ER, endoscopic resection.

Table 3 Incidence of submucosal deep invasive carcinoma per gross type and lesion size in early colorectal carcinoma ≤10 mm

Gross type	Initial ER method		Total
	<5 mm	6–10 mm	
Ip, Isp, Is	1/98 (1)*	26/392 (7)***	27/490 (6)*****
IIa	0/38 (0)*	1/150 (1)***	1/188 (1)*****
IIc, IIa+IIc	4/21 (19)**	27/51 (53)****	31/72 (43)******
Total	5/157 (3)*******	54/593 (9)********	59/750 (8)

* *vs* **, *** *vs* ****, ***** *vs* ******: $P < 0.01$; ******* *vs* ********: $P < 0.05$.
Values are *n* (%).
ER, endoscopic resection.

Table 4 Location of submucosal invasive colorectal carcinoma ≤10 mm

Lesion size (mm)	No. cases	Location					
		C	A	T	D	S	R
<5	15 (100)		2 (13)	3 (20)	2 (13)	4 (27)	4 (27)
6–10	96 (100)	3 (3)	13 (14)	9 (9)	9 (9)	38 (40)	24 (25)
Total	111 (100)	3 (3)	15 (14)	12 (11)	11 (10)	42 (38)	28 (25)

Values are *n* (%).
A, *ascending colon*; C, *cecum*; D, *descending colon*; R, *rectum*; S, *sigmoid colon*; T, *transverse colon*.

Distribution of location in diminutive submucosal invasive CRC

A total of 63.1% (70/111) of the tumors were located in the sigmoid colon or rectum. Among the diminutive tumors, 53.3% (8/15) were also located in the sigmoid colon or rectum. There were no significant differences in the distribution of submucosal invasive CRC between the diminutive tumors and those 6–10 mm in size (Table 4).

Pit pattern diagnosis in diminutive submucosal invasive CRC

Only a few of the cases (19 total) that we evaluated for pit pattern diagnosis were ultimately submucosal invasive CRC, because the tumors that were not well magnified at observation or that were stained without the use of crystal violet were excluded from the present study. In all cases, diminutive submucosal invasive CRC had type V_I pit pattern. Submucosal invasive CRC that were 6–10 mm in size had the following patterns: type non-V pit pattern in two cases (12.5%); type V_I pit pattern in 11 cases (68.8%); and type V_N pit pattern in three cases (18.8%; Table 5).

Incidence of LN metastasis in diminutive submucosal invasive CRC

A total of 56 submucosal invasive CRC ≤10 mm underwent surgical resection with LN dissection. Occurrence of LN metastasis in relation to submucosal invasive CRC ≤10 mm is shown in Table 6. Diminutive submucosal CRC had undergone en bloc ER prior to eventual radical surgery in all cases, and there were no cases showing LN metastasis. The rate of overall LN metastasis in submucosal invasive CRC 6–10 mm was 12.2% (6/49). One case of submucosal invasion depth <1000 μm with lymphovascular invasion showed

Table 5 Pit pattern diagnosis in submucosal invasive colorectal carcinoma ≤10 mm†

Lesion size (mm)	No. cases	Pit pattern		
		Non-V	V_I	V_N
<5	3 (100)		3 (100)	
6–10	16 (100)	2 (13)	11 (68)	3 (19)

†Cases in which magnifying observation was carried out.
Values are *n* (%).

Table 6 Incidence of lymph node metastasis in submucosal invasive colorectal carcinoma ≤10 mm

Lesion size (mm)	No. cases	Lymph node metastasis	
		Positive	Negative
<5	7 (100)		7 (100)
6–10	49 (100)	6 (12)	43 (88)

Values are *n* (%).

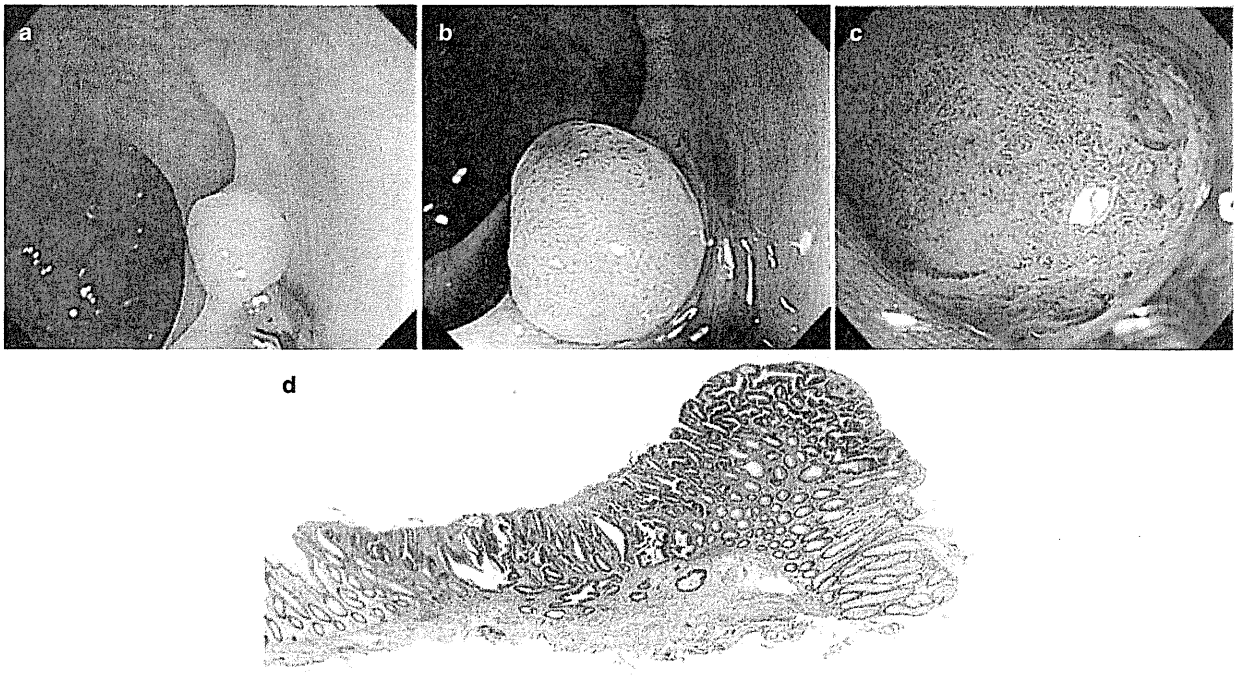

Figure 1 (a) Regular colonoscopic view of colorectal tumor. Type 0-Is, 4 mm in size. (b) Indigocarmine dye spraying view. A shallow depressed area can be seen in the center of the tumor. (c) Magnifying view with crystal violet dye showing type V_I pit pattern. (d) Cross-section of the resected specimen. Histopathological diagnosis was papillary > moderately differentiated adenocarcinoma with tubular adenoma, pT1a (SM200 μm), ly0, v0.

LN metastasis. Other cases 6–10 mm had a submucosal invasion depth ≥1000 μm with other non-curative factors proposed by the 2014 JSCCR guidelines.[13]

DISCUSSION

IN WESTERN COUNTRIES, diminutive polyps are resected and evaluated for histological examination to determine the timing of a patient's next surveillance colonoscopy.[15] Advances in endoscopic imaging using magnifying or image-enhanced endoscopy allow us to make a more precise diagnosis between non-neoplastic and neoplastic lesions or between non-invasive and invasive neoplastic lesions.[3–6] Based on the evidence of studies on pit pattern diagnosis or narrow-band imaging for the detailed diagnosis of colorectal lesions, the concept of the predict-resect-and-discard strategy was introduced for diminutive colorectal lesions to reduce the operation cost and time.[7–9] In fact, small diminutive colorectal adenomas rarely have advanced histological features, including submucosal invasion.

The American Society for Gastrointestinal Endoscopy recently developed a Prevention and Incorporation of Valuable endoscopic Innovations initiative (PIVI) statement that established thresholds for real-time endoscopic assessment for the histology of diminutive polyps.[16] The predict-resect-and-discard strategy for diminutive colorectal lesions appeared safe in earlier reports. However, application of the predict-resect-and-discard strategy for all diminutive colorectal lesions is unsatisfactory because the evidence from earlier reports was mainly based on sessile lesions.[1,2] In Japan, detailed endoscopic observation, including chromoendoscopy, magnifying endoscopy, or image-enhanced endoscopy has been standardized even for diminutive lesions. In fact, our data showed that 2.0% of cases of diminutive tumors were carcinoma, especially depressed tumor which has a significantly higher frequency of carcinoma and submucosal invasion regardless of tumor size.

Depressed colorectal tumors are generally difficult to detect compared with sessile lesions.[17,18] This is because most depressed tumors that show indications for ER are <10 mm and the clues to detection are faint mucosal changes characterized by reddened mucosa, localized disappearance or disruption of vascular network patterns, and a faint mucosal pattern. Chromoendoscopy using indigocarmine

dye spraying is clinically useful for confirming lesions with shallow depressed areas on the tumor surface of diminutive colorectal lesions. Therefore, even for sessile polyps, when we suspect an irregular tumor surface, we must confirm the presence or absence of shallow depression (Fig. 1).

It is important to be able to identify lesions for which ER would be curative to avoid incomplete ER for lesions that should be treated surgically. Pit pattern classification is used clinically to help determine the best treatment for CRC. Our data revealed that diminutive depressed colorectal tumors or lesions with type V pit pattern with magnifying endoscopy have indications for ER because they displayed a high incidence of carcinoma. Even in diminutive submucosal CRC, incomplete treatment makes it difficult to evaluate the resected specimen precisely. Therefore, when we find diminutive colorectal lesions during colonoscopy, it is important to consider the possibility of carcinoma from endoscopic findings to choose the appropriate treatment methods, such as endoscopic mucosal resection (EMR) instead of polypectomy or hot biopsy. Our data showed that all diminutive submucosal invasive CRC were resected completely by en bloc ER and there were no cases with LN metastasis. These results revealed that diminutive tumors, which carry the possibility of carcinoma, are an initial indication for ER, as a total excisional biopsy that provides a precise histological diagnosis may allow patients even with CRC to avoid meaningless surgical resection.[19]

Complete resection of tumors, including those with a negative vertical margin, is indispensable for curative conditions after ER for submucosal CRC. According to the 2014 JSCCR guidelines,[13] the curative conditions after ER for submucosal CRC state that 'if a tumor is completely resected by ER for cases of favorable histology with submucosal invasion of <1000 μm, absence of vascular invasion and grade 1 (low grade) tumor budding, the possibility of LN metastasis will be extremely low so that surveillance is allowed without additional surgical resection', a statement that has generated a certain consensus. ER is a therapeutic technique and an important diagnostic method that can be used as total excisional biopsy. Complete resection including a negative vertical margin is indispensable for curative conditions after ER for submucosal CRC. To achieve complete resection, hybrid endoscopic submucosal dissection (hybrid ESD) is also useful in the condition of insufficient elevation after injection, even for diminutive tumors.[20]

In conclusion, diminutive tumors with depressions have a high frequency of carcinoma and submucosal invasion, and can be an initial indication for EMR. It is important to carry out careful observation to prevent missing diminutive depressed tumors using indigocarmine dye spraying, if required, during colonoscopy.

CONFLICT OF INTERESTS

AUTHORS DECLARE NO conflicts of interest for this article.

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Condition of muscularis mucosae is a risk factor for lymph node metastasis in T1 colorectal carcinoma

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Abstract
Background The Japanese Society for Cancer of the Colon and Rectum Guidelines for the Treatment of Colorectal Cancer 2010 state that curable T1 colorectal carcinoma (CRC) after endoscopic resection shows favorable histologic grade, absence of vessel involvement, submucosal invasion depth of <1,000 μm, and low-grade tumor budding.
Methods We evaluated 322 consecutive T1 CRCs with LN dissection between January 1993 and March 2012. According to the muscularis mucosae condition, CRCs were classified into three groups: type A, clearly identified; type B, incompletely disrupted with deformity; or type C, completely disrupted. We examined the relationship between the muscularis mucosae condition, clinicopathological findings, and lymph node (LN) metastasis.
Results The overall incidence of LN metastasis was 11.8 % (38/322): 0 % (0/46) for the type A group, 7.2 % (7/97) for the type B group, and 17.3 % (31/179) for the type C group. In univariate analysis of type B and C groups, unfavorable histologic grade, submucosal invasion of ≥1,000 μm, positive lymphatic invasion, high-grade tumor budding, and the type C group were associated with a significantly higher incidence of LN metastasis. In multivariate analysis, high-grade tumor budding ($P < 0.001$, odds ratio [OR] = 4.86), unfavorable histologic grade ($P = 0.026$, OR = 4.83), positive lymphatic invasion ($P < 0.001$, OR = 4.17), and the type C group ($P = 0.012$, OR = 3.38) were significantly associated with LN metastasis. The type C group showed a high incidence of moderate/severe lymphatic invasion.
Conclusions The condition of the muscularis mucosae was an indicator of LN metastasis in T1 CRC.

Keywords Submucosal invasive colorectal carcinoma · T1 colorectal carcinoma · Muscularis mucosae · Lymph node metastasis

Colorectal carcinoma (CRC) is one of the most commonly diagnosed types of cancer in western countries. Similarly, CRC is ranked third among the causes of cancer-related deaths in Japan, and the associated morbidity and mortality rates have increased [1, 2]. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been established as standard therapies for early CRC, and complete en bloc resection is widely performed [3–5]. Recently, the frequency of pathological submucosal (T1) CRC detection after EMR/ESD has increased.

Lymph node (LN) metastasis is reported to occur in approximately 10 % of T1 CRCs [6–15]. According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for the Treatment of Colorectal Cancer, "if a T1 CRC is completely resected by endoscopic

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resection (ER), the depth of submucosal (SM) invasion is less than 1,000 μm, low-grade budding is noted, the histologic grade is favorable, and vessel involvement is absent, the possibility of LN metastasis is extremely low, and therefore, surveillance without additional surgical resection is applicable [16]." However, LN metastasis is absent in many patients who undergo additional surgeries, resulting in overtreatment. Moreover, the number of cases in which high risk is associated with surgical procedures under general anesthesia has increased due to the increased numbers of elderly cases and cases with concurrent diseases.

The muscularis mucosae is a thin smooth muscle layer that can be observed in the main parts of the alimentary canal. Unlike other gastrointestinal carcinomas, no metastasis is observed in CRCs when the tumors have not extended beyond the muscularis mucosae [17, 18]. This study examined the relationship between the condition of the muscularis mucosae and clinicopathological characteristics, as well as that between the condition of the muscularis mucosae and LN metastasis.

Materials and methods

Patients

Between January 1993 and March 2012, a total of 322 cases with T1 CRC underwent surgical resection with LN dissection at Hiroshima University Hospital, Japan. These cases represented a consecutive and unselected cohort. Of the 322 cases, 161 had undergone EMR or ESD before eventual radical surgery. Cases with synchronous CRC or positive vertical margin after ER were excluded. None of the cases had received preoperative radiotherapy or neoadjuvant chemotherapy. The study population included 196 men and 126 women, with a mean age of 63.8 (range 32–89) years. The mean tumor size was 20.5 (range 4–100) mm. Our treatment strategy for pT1 CRC was based on the 2010 guidelines for the treatment of colorectal cancer by JSCCR [16].

Pathologic evaluation

Resected specimens were pinned to a board and fixed in 10 % buffered formalin for 12–48 h. Surgical specimens were subsequently cut into parallel 3- to 4-mm–thick sections, whereas endoscopic specimens were cut into 2-mm–thick sections. The specimens were examined retrospectively by a single experienced pathologist. The pathologic features, including the depth of SM invasion, histologic characteristics, tumor budding grade, lymphatic and venous invasion, and the muscularis mucosae, were evaluated by hematoxylin-eosin (HE) staining. Histologic diagnoses were based on the World Health Organization criteria [19]. Tumor budding and the depth of SM invasion were graded according to the 2010 JSCCR guidelines [16]. Histologic grade was classified into two types: favorable type (tubular or papillary adenocarcinoma), and unfavorable type (poorly or mucinous adenocarcinoma). Tumor budding was defined as a single cancer cell or a cluster of fewer than five cells along the invasive margin, and budding was graded per microscopic field at 200× magnification: grade 1, 0–4 buds (low grade); grade 2, 5–9 buds; and grade 3, 10 or more buds (high grade) [20]. To determine the depth of SM invasion, if the level of the muscularis mucosae could be identified or presumed, we measured depth from the muscularis mucosae to the tumor apex. When the level of the muscularis mucosae could not be identified or presumed, we measured depth from the surface of the tumor to its apex. Lymphatic invasion (ly) and venous invasion (v) were defined as follows: ly(−)/v(−), no invasion; ly(+)/v(+), mild invasion; ly(++)/v(++), moderate-severe invasion.

Classification of the muscularis mucosae

The T1 CRCs were classified into three groups: types A, B, and C, according to the muscularis mucosae status (Fig. 1). The type A group was those for which it was possible to identify or estimate the location of the muscularis mucosae by HE staining. The type B group was those for which it was not possible to identify or estimate the location of the muscularis mucosae because of "deformity" (e.g., disarray, dissection, rupture, and fragmentation) of the muscularis mucosae as a result of SM invasion. Although determinations of the presence of a deformity are not always straightforward, if a desmoplastic reaction is noted around the muscularis mucosae, it is assumed to be deformed. The type C group was those for which the complete rupture of the muscularis mucosae was observed by HE staining. Desmin staining was performed for CRCs that could not be ascertained as the type B or C group by HE staining. Such CRCs were classified as the type C if a complete rupture of the muscularis mucosae was observed on desmin staining. Additionally, the SM invasion depth measurements were in conformity with the JSCCR 2010 criteria. The depth of SM invasion of the type A group was measured from the lower border of the muscularis mucosae of the lesion, regardless of the macroscopic type. The depth of SM invasion of the type B and C groups was measured from the surface of the lesion [16]. The muscularis mucosae status was classified in all cases by a single experienced pathologist (FS).

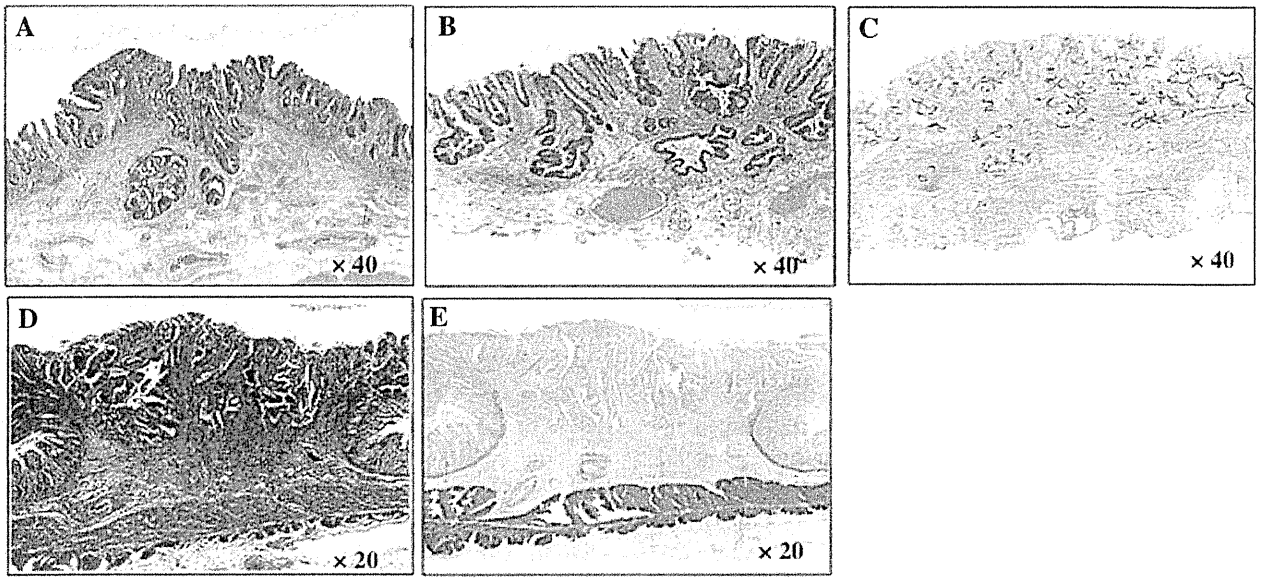

Fig. 1 Classification of the condition of muscularis mucosae in T1 CRC. **A** Image of the muscularis mucosae in type A by HE staining. It is possible to identify the location of the muscularis mucosae. **B**, **C** Image of the muscularis mucosae in type B (**B** HE staining, **C** desmin staining). It is not possible to estimate the location of the muscularis mucosae because of its deformity. Disordered direction and partial rupture in the muscularis mucosae were observed. **D**, **E** Image of the muscularis mucosae in type C (**D** HE staining, **E** desmin staining). The muscularis mucosae are completely ruptured

Outcome measurement

We examined the relationship between clinical characteristics (age, gender, region, size, macroscopic type, and therapy) and LN metastasis. Next, we examined the relationship between histopathological characteristics (histologic grade, SM invasion depth, lymphatic invasion, venous invasion, tumor budding, and the muscularis mucosae condition) and LN metastasis in T1 CRC. We also investigated the LN metastatic indicators for T1 CRC. We further investigated the relationships between the condition of the muscularis mucosae and the clinicopathological characteristics and between the condition of the muscularis mucosae and LN metastasis.

Statistical analysis

Data are presented as the mean ± standard deviation. Incidences of LN metastasis were examined in relation to various clinicopathological features, and the differences were analyzed by the χ^2 test or Fisher's exact test. Statistical significance was defined as $P < 0.05$. Multivariate analysis with logistic regression was used to identify risk factors for LN metastasis, with $P < 0.05$ being considered significant. Odds ratios were calculated to estimate the relative risk of LN metastasis when various factors were present. All statistical analyses were performed using PASW 18 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Relationship between clinicopathological features and LN metastasis

Table 1 shows the relationships between the clinicopathological characteristics and LN metastasis in T1 CRC. LN metastasis was observed in 38 of 322 cases (11.8 %). The number of cases in which LN metastasis was observed was significantly larger among those with initial surgical procedures than among those with additional surgery after ER. When the histopathological findings were analyzed, the frequency of cases with LN metastasis was significantly higher among those with unfavorable type, SM invasion depth ≥1,000 μm, positive lymphatic invasion, positive venous invasion, and grade 2/3 budding (high grade). When the condition of the muscularis mucosae was evaluated, the frequencies of LN metastasis were 0 % (0/46), 7.2 % (7/97), and 17.3 % (31/179) in the type A, B, and C groups, respectively, and these differences were found to be significant ($P = 0.003$). Additionally, the incidences of SM invasion depth ≥1,000 μm, positive vessel involvement, and high grade budding were significantly lower in the type A group than in the type B and C groups (data not shown).

Table 1 Relationship between clinicopathological features and LN metastasis ($n = 322$)

Clinicopathological features	No. of cases (%)	No. of LN + cases	*P* value
Age (mean ± SD)	63.8 ± 11.6	65.7 ± 12.1	0.28
Sex			
Male	196 (100)	18 (9.2)	0.069
Female	126 (100)	20 (15.9)	
Location			
Right colon	96 (100)	11 (11.5)	0.24
Left colon	148 (100)	16 (10.8)	
Ra	46 (100)	5 (10.9)	
Rb	32 (100)	6 (18.8)	
Size (mean ± SD)	20.5 ± 13.4	22.7 ± 15.8	0.3
Depression			
Positive	93 (100)	15 (16.1)	0.13
Negative	229 (100)	23 (10)	
Treatment method			
ER → ope	161 (100)	10 (6.2)	0.002
ope	161 (100)	28 (17.4)	
Histological grade			
Favorable	310 (100)	33 (10.6)	0.008
Unfavorable	12 (100)	5 (41.7)	
Invasion depth			
SM < 1,000 μm	45 (100)	1 (2.2)	0.026
SM ≥ 1,000 μm	277 (100)	37 (13.4)	
Lymphatic invasion			
ly(−)	190 (100)	10 (5.3)	<0.001
ly(+)	116 (100)	19 (16.4)	
ly(++)	16 (100)	9 (56.3)	
Venous invasion			
v(−)	264 (100)	26 (9.8)	0.02
v(+)	55 (100)	11 (20)	
v(++)	3 (100)	1 (33.3)	
Budding grade			
Low grade	271 (100)	21 (7.7)	<0.001
High grade	51 (100)	17 (33.3)	
Muscularis mucosae			
Type A	46 (100)	0 (0)	0.0035
Type B	97 (100)	7 (7.2)	
Type C	179 (100)	31 (17.3)	

LN lymph node, *ER* endoscopic resection

Risk factors for LN metastasis with type B and C tumors

Table 2 shows the relationships between the pathological characteristics and LN metastasis in T1 CRC with the type B and C groups ($n = 276$). Univariate analysis revealed that the number of cases in which LN metastasis was observed was significantly higher for the type C group with unfavorable type, positive lymphatic invasion, and high-grade budding than for the type B group with favorable type, negative lymphatic invasion, and low-grade budding. Multivariate analysis revealed that high grade budding ($P < 0.001$, odds ratio = 4.86), the unfavorable type ($P = 0.026$, odds ratio = 4.83), positive lymphatic invasion ($P < 0.001$, odds ratio = 4.17), and type C muscularis mucosae ($P \leq 0.012$, odds ratio = 3.38) were independent risk factors for LN metastasis.

Clinicopathological features of type B and C tumors

When the clinicopathological characteristics were compared between the type B and C groups, the SM invasion depth was found to be significantly larger for the type C group. However, the number of cases in which the SM invasion depth was <1,000 μm were seven (7.2 %) and five (2.8 %) among type B and C groups, respectively, and this difference was not significant (Table 3). Despite a lack of significant differences in histologic grade, the frequency of high grade budding was significantly higher in the type C group. Many positive lymphatic invasion cases were observed in the type B group. However, in the type C group, the number of positive lymphatic invasion cases with ly(++) was higher, and in this group, the frequency of LN metastasis of ly(++) was as high as 56.3 % (9/16). The number of cases in which LN metastasis was observed was significantly higher among cases of the type C group with unfavorable type, positive lymphatic invasion, positive venous invasion, and high-grade budding than among cases of the type B group with favorable type, negative lymphatic invasion, negative venous invasion, and low-grade budding (Table 4). In the type B group, the frequency of LN metastasis was significantly higher in cases of positive lymphatic invasion (+ or ++) than in cases of negative lymphatic invasion (−). However, no significant differences in LN metastasis were observed with regard to the histologic type, SM invasion depth, venous invasion, or budding.

Discussion

In this study of 322 T1 CRC patients who had undergone surgical resection with LN dissection, 46 (14.3 %) were classified as having the type A group, and no LN metastases were observed in this group. The incidence rates of LN metastasis in the types B and C groups were 7.2 and 17.3 %, respectively, and a significant difference was

Table 2 Risk factors for LN metastasis of T1 CRC with muscularis mucosae type B and C ($n = 276$)

Pathological features	Univariate analysis			Multivariate analysis	
	No. of cases (%)	No. of LN + cases (%)	*P* value	Odds ratio	*P* value
Histological grade					
Favorable	264 (100)	33 (12.5)	0.015	4.83	0.026
Unfavorable	12 (100)	5 (41.7)			
Invasion depth					
SM < 1,000 μm	12 (100)	1 (8.3)	0.9		
SM ≥ 1,000 μm	264 (100)	37 (14)			
Lymphatic invasion					
ly(−)	148 (100)	10 (6.8)	<0.001	4.17	0.001
ly(+)	112 (100)	19 (17.0)			
ly(++)	16 (100)	9 (56.2)			
Venous invasion					
v(−)	221 (100)	26 (11.4)	0.053	2.09	0.10
v(+)	52 (100)	11 (21.2)			
v(++)	3 (100)	1 (33.3)			
Budding grade					
Low grade	225 (100)	21 (9.3)	<0.001	4.86	<0.001
High grade	51 (100)	17 (33.3)			
Muscularis mucosae					
Type B	97 (100)	7 (7.2)	0.02	3.38	0.012
Type C	179 (100)	31 (17.3)			

LN lymph node, *CRC* colorectal carcinoma, *SM* submucosa

observed with regard to the condition of the muscularis mucosae. We consider that patients with type A group do not require additional surgery and those with type C group do require additional surgery after ER of T1 CRCs. As shown in Table 2, multivariate analysis revealed that high-grade tumor budding, unfavorable type, positive lymphatic invasion, and type C group were independent risk factors for LN in cases of type B and C. Accordingly, therapeutic methods should be decided after comprehensive consideration of various pathological factors in patients with type B group.

No previous studies of esophageal and gastric cancer cases have reported a relationship between the condition of the muscularis mucosae and LN metastasis. Tateishi et al. [21] reported that the condition of the muscularis mucosae should be examined during investigations of LN metastasis risk factors in cases of T1 CRC. In that report, tumors were classified into two groups—preserved/incompletely disrupted and completely disrupted—according to the condition of the muscularis mucosae. However, until now, no studies have classified T1 CRCs into three types according to the condition of the muscularis mucosae.

According to the JSCCR 2010 criteria [16], the SM invasion depth of type A tumors is measured from a virtual line that is drawn on the muscularis mucosae. No studies have investigated only T1 CRC in which such a virtual line could be drawn. However, Tateishi et al. [21] reported that the incidence of LN metastasis of T1 CRC in which the condition of muscularis mucosae was preserved/incompletely disrupted was 2 % (1/41). Therefore, the incidence of LN metastasis was considered to be very low in the type A group, regardless of other conditions. However, other risk factors of LN metastasis may affect the incidence of LN metastasis in the type A group.

According to the JSCCR 2010 criteria [16], the SM invasion depth of the type B and C groups should be measured from the surface of the lesion. In the present study, the type C was found to be an independent risk factor for LN metastasis. No significant differences in the incidence of LN metastasis were observed between tumors with SM invasion depths <1,000 μm and those with SM invasion depths >1,000 μm in the type B and C groups. This finding was likely due to the small number of cases in which the SM invasion depth was <1,000 μm in the overall type B and C group (4.3 %). Yoshida et al. [22] reported that the SM invasion depth of all lesions for which the condition of the muscularis mucosae could not be determined was deeper than 1,000 μm. In particular, the majority of lesions for which the SM invasion depth is measured from the surface do not satisfy the criteria for a radical-cure evaluation of T1

Table 3 Clinicopathological features of T1 CRC with muscularis mucosae type B and C ($n = 276$)

Clinicopathological features	Type B ($n = 97$)	Type C ($n = 179$)	*P* value
Age (mean ± SD)	64.3 ± 10.7	62.9 ± 12.5	0.35
Sex			
Male	55	106	0.69
Female	42	73	
Location			
Right Colon	29	48	0.99
Left Colon	44	85	
Ra	14	26	
Rb	10	20	
Size (mean ± SD)	18.2 ± 13.4	20.7 ± 12.8	0.11
Depression			
Positive	31	48	0.37
Negative	66	131	
Histological grade			
Favorable	93	171	1
Unfavorable	4	8	
Invasion depth			
SM < 1,000 μm	7	5	0.12
SM ≥ 1,000 μm	90	174	
Depth of SM invasion (mean ± SD)	2,687 ± 1,836	3,875 ± 1,998	<0.0001
Lymphatic invasion			
ly(−)	37	111	0.06
ly(+)	58	54	
ly(++)	2	14	
Venous invasion			
v(−)	75	146	1
v(+)	21	31	
v(++)	1	2	
Budding grade			
Low grade	87	138	0.01
High grade	10	41	
LN metastasis			
Negative	90	148	0.032
Positive	7	31	

CRC colorectal carcinoma, *SM* submucosa

CRC due to the SM invasion depth alone, leading to recommendations for additional surgery. Because the incidence of LN metastasis in our study was 13.8 % (38/276), an evaluation of the condition of the muscularis mucosae was considered useful in the identification of LN metastasis risk factors.

Interesting results were obtained from a comparison of the types B and C groups. Although the incidence of LN metastasis was significantly higher in the type C group, the number of cases with positive lymphatic invasion was significantly larger in the type B group. Because positive lymphatic invasion was an independent risk factor for LN metastasis, the above-mentioned results seemed to be inconsistent. This inconsistency was because the majority of the ly(++) tumors belonged to the type C group. Therefore, ly(++) was considered to be an important risk factor for LN metastasis.

It is important to identify low-risk groups according to various viewpoints in order to reduce the number of cases in which T1 CRC is treated with additional surgery after ER. According to the JSCCR 2010 criteria [16], cases of completely resected T1 CRC, a low-risk group for which postoperative surveillance is feasible after ER, satisfy all four conditions (favorable histologic grade, SM invasion depth <1,000 μm, negative vessel involvement, and low-grade budding). We reported previously that, when these four conditions were satisfied, no LN metastases and no recurrences or metastases were observed during the mid-term prognosis follow-up after ER for T1 CRC [23]. However, a meta-analysis showed that even if these four conditions were satisfied, the number of cases in which LN metastasis was observed was not 0 (1.9 %), and the qualitative formal data analysis was not strong [24]. We also reported that, when the three conditions of favorable histologic grade, negative vessel involvement, and low-grade budding were satisfied, the incidence of LN metastasis was as low as 1.2 %, regardless of the SM invasion depth [15]. Furthermore, the mortality rates related to surgical procedures were reported to be in the range of 0–2.46 % [25–27], and the mortality rates within 30 days after surgical procedures were reported to be in the range of 0.45–2.44 % [28–30]. The number of cases in which the risk of a surgical procedure under general anesthesia is high has increased due to the increased numbers of elderly patients and those with concurrent diseases. Therefore, stratification of surgical risk factors and LN metastasis risk factors was considered important.

The present study was performed at a single academic university hospital, and the number of cases used in the present study was limited. The results obtained in the present study should be verified at multiple facilities and with a larger number of cases in the near future.

In conclusion, the muscularis mucosae status correlated closely with LN metastasis in T1 CRC. Significant differences were observed in the degrees of lymphatic invasion and tumor budding grade, according to the condition of the muscularis mucosae. Thus, the condition of the muscularis mucosae was suggested to be a predictive factor for LN metastasis in T1 CRC.

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Table 4 Relationship between pathological features and LN metastasis with muscularis mucosae type B and C ($n = 276$)

Pathological features	Type B			Type C		
	No. of cases (%)	No. of LN + cases (%)	*P* value	No. of cases (%)	No. of LN + cases (%)	*P* value
Histological grade						
Favorable	93 (100)	7 (7.5)	1.00	171 (100)	26 (15.2)	0.004
Unfavorable	4 (100)	0 (0)		8 (100)	5 (62.5)	
Invasion depth						
SM < 1,000 μm	7 (100)	1 (14.3)	0.42	5 (100)	0 (0)	0.59
SM ≥ 1,000 μm	90 (100)	6 (6.7)		174 (100)	31 (17.8)	
Lymphatic invasion						
ly(−)	37 (100)	0 (0)	0.041	111 (100)	10 (9)	<0.001
ly(+)	58 (100)	7 (11.7)		54 (100)	12 (22.2)	
ly(++)	2 (100)	0 (0)		14 (100)	9 (64.3)	
Venous invasion						
v(−)	75 (100)	5 (6.7)	0.67	146 (100)	21 (14.4)	0.029
v(+)	21 (100)	2 (9.1)		31 (100)	9 (29)	
v(++)	1 (100)	0 (0)		2 (100)	1 (50)	
Budding grade						
Low grade	87 (100)	5 (5.7)		138 (100)	16 (11.6)	<0.001
High grade	10 (100)	2 (20)		41 (100)	15 (36.6)	

LN lymph node, *SM* submucosa

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Predictors of incomplete resection and perforation associated with endoscopic submucosal dissection for colorectal tumors

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Background and Objective: Colorectal endoscopic submucosal dissection (ESD) is technically challenging. Our aim was to identify predictors of incomplete resection and perforation in colorectal ESD.

Design: Retrospective study.

Setting: Academic Japanese endoscopy unit.

Patients and Main Outcome Measurements: A total of 267 consecutive cases of colorectal tumors treated by ESD from May 2010 to February 2013 were analyzed. Predictors of incomplete resection and perforation, including lesion size, growth type, pathological diagnosis, use of hemostatic forceps, degree of fibrosis, history of biopsy, history of local endoscopic treatment, and endoscopic operability.

Results: The incomplete resection rate was 4.1%. The perforation rate was 5.6%. Univariate analysis identified severe fibrosis ($P = .032$), submucosal (SM) deep (>1000 μm) invasion ($P = .033$) and poor endoscopic operability ($P = .030$) as predictors of incomplete resection, and severe fibrosis ($P = .038$), postendoscopic treatment ($P = .016$), and poor endoscopic operability ($P = .012$) as predictors of perforation. Multivariate analysis identified poor endoscopic operability and SM deep invasion as independent predictors of incomplete resection, and poor endoscopic operability and severe fibrosis as independent predictors of perforation. There was no adjustment of P values for multiple testing.

Limitation: A single-center study by a single colonoscopist. All statistical results should be taken as descriptive only.

Conclusions: Poor endoscopic operability and SM deep invasion were significant independent predictors of incomplete resections. Poor endoscopic operability and severe fibrosis were significant independent predictors of perforation. These features may provide helpful information when planning colorectal ESD. (Gastrointest Endosc 2014;79:427-35.)

With the development of various new tools and peripheral devices and the accumulation of experience and expertise in endoscopic submucosal dissection (ESD), colorectal ESD is gradually gaining widespread acceptance in Japan[1,2] and has been approved for health insurance coverage[3] since April 2012. According to a literature survey, colorectal ESD has been established as a procedure with reproducible safety and efficacy.[1] Technical difficulties associated with this procedure have been significantly reduced, and it is gaining popularity among experienced endoscopists.[4-9]

Colorectal ESD is more technically demanding than esophageal and gastric ESD because of the anatomic features of the large intestine, which is a long luminal organ with many folds and flexures that hinder the manipulation of the endoscope for some lesions, and an intestinal wall that is thin and easy to perforate. Moreover, operator skill can influence the outcomes, and the procedure has a learning curve that may hinder its widespread use by endoscopists. In fact, reports of the therapeutic outcomes of

Abbreviations: CI, confidence interval; ESD, endoscopic submucosal dissection; OR, odds ratio; SM, submucosal.

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TABLE 1. Baseline characteristics of colorectal tumors (N = 267)

Age, y [range]	66.4 (11.2) [22-91]
Sex, male/female, no.	176/91
Size of the tumor, mm [range]	35.6 (18.6) [10-100]
Growth type of lesion, no. (%)	
LST-G/polypoid	164 (61.4)
LST-NG	103 (38.6)
Location of the tumors, no. (%)	
Cecum or ascending	63 (23.6)
Transverse	46 (17.2)
Descending	5 (1.9)
Sigmoid	44 (16.5)
Rectum	109 (40.8)

LST-G, Lateral spreading tumor granular type; *LST-NG*, lateral spreading tumor nongranular type.

Take-home Message

- The incomplete resection rate was 4.1% and the perforation rate was 5.6%. Poor endoscopic operability and submucosal deep invasion were independent significant predictors of incomplete resections. Also, fibrosis based on previous endoscopic treatment was significantly associated with perforation.
- Poor endoscopic operability and severe fibrosis were independent significant predictors of perforation.

ESD in the literature suggest that the procedure currently has higher perforation rates than EMR. The aim of this study was to clarify the predictors of incomplete resection and perforation in colorectal ESD.

PATIENTS AND METHODS

Patients

Since May 2010, cases of colorectal ESD were prospectively registered in a multicenter listing in Japan, which included our hospital, as those requiring highly advanced medical treatment. A total of 267 consecutive colorectal tumors (adenoma/early carcinoma) treated by ESD at Hiroshima University Hospital in Hiroshima, Japan, from May 2010 to February 2013 were included in the analysis (Table 1). All patients had been informed about the risks and benefits of ESD and provided written informed consent for the procedure, which has been covered under health insurance since April 2012 in Japan. This study protocol was approved by the Institutional Review Board of Hiroshima University Hospital. In this study period, we had no patients who refused ESD. Age and coagulopathy are not limited for inclusion to this study.

The ESD procedures were performed by an endoscopic specialist (S.T.) who has performed about 550 colorectal ESD procedures from November 2002 to February 2013.

The indications for colorectal ESD at our center were based on the Criteria of Indications for Colorectal ESD proposed by the Colorectal ESD Standardization Implementation Working Group,[10,11] which specifically states that colorectal ESD is indicated for lesions requiring endoscopic en bloc excision that cannot be easily performed by using the snare technique, such as laterally spreading tumor nongranular type, especially the pseudodepressed type, tumors with a type V(I) pit pattern, shallow (submucosal [SM] $\leq$1000 μm) invasive SM carcinomas, large depressed tumors, and large elevated lesions that are probably malignant (ie, large nodular lesions such as the laterally spreading tumor granular type). Other lesions, such as intramucosal tumors accompanied by SM fibrosis, including those that occur as a result of chronic inflammation such as ulcerative colitis and local residual early carcinoma after endoscopic excision are also included in the indications. We included all cases that satisfied our inclusion criteria.

ESD procedure

The patients were sedated with intravenous diazepam 0.1 mg/kg, and cardiorespiratory function was monitored. We used a single endoscope attached to a transparent tip hood with carbon dioxide insufflation. We use a GIF-Q260J (Olympus, Tokyo, Japan), which is a gastroscope, for sigmoid colon or rectal lesions, and a PCF-Q260AZI (Olympus) for lesions from the descending colon and cecum. We usually use a standard tip hood (Olympus). A bell-shaped, small-caliber tip, transparent tip hood (ST hood; FTS, Omiya, Japan) was used in cases of severe fibrosis to make it easier to enter the SM layer. Hyaluronic acid-indigo carmine mixed with glycerol was injected to the SM layer using a 21-gauge injection needle. We mixed half and half 0.4% sodium hyaluronate (Muco Up; Johnson & Johnson, New Brunswick, NJ) and 10% glycerin solution, and added a small amount of indigo carmine (indigo carmine/Muco Up + glycerin: 0.2 mL/20 mL). Because the margin of colorectal tumors can be observed clearly, marking was not required. We never marked the borders of a lesion. A circumferential incision was made in the mucosa around the lesion. Because dissection of the entire circumference of the lesion causes the injection solution to flow from the lesion and results in poor observation of the SM layer, a partial dissection is performed first and then further local dissection is performed after the lesion is adequately located. The tissue was dissected along the SM layer with the DualKnife (Olympus), an SB knife Jr (Sumitomo Bakelite, Tokyo, Japan), or a HookKnife

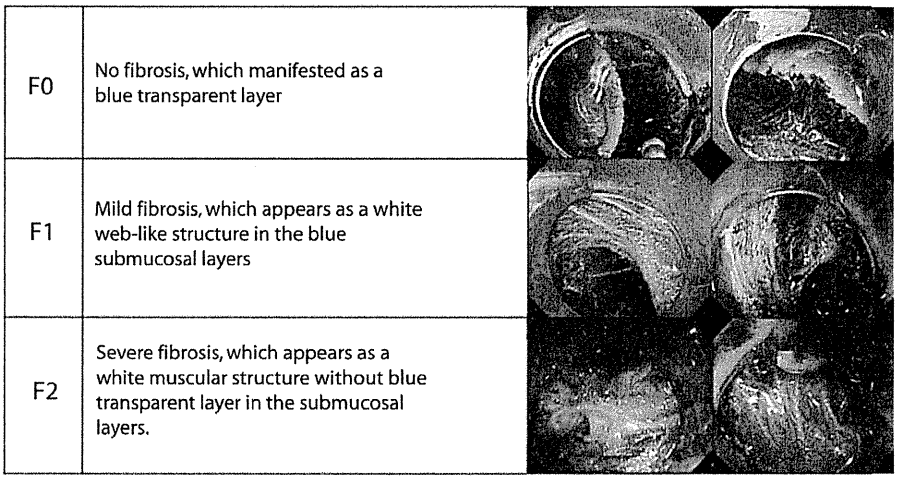

Figure 1. Degree of fibrosis of the submucosal layers in colorectal tumors. Degree of fibrosis of the submucosal layers was classified into the following 3 grades according to the appearance of the layers during the submucosal injection of a mixture of sodium hyaluronate and indigo carmine: F0, no fibrosis, which manifested as a blue transparent layer; F1, mild fibrosis, which appears as a white weblike structure in the blue submucosal layers; and F2, severe fibrosis, which appears as a white muscular structure without blue transparent layer in the submucosal layers.[12]

TABLE 2. Overall outcome of colorectal tumors (N = 267)

En bloc resection, no. (%)	256/267 (95.9%)
Perforation, no. (%)	15/267 (5.6)
Time of procedure, min [range]	79.6 (55.5) [10-340]
Pathological diagnosis, no. (%)	
Adenoma	115 (43.1)
Mucosal carcinoma	91 (34.1)
Submucosal carcinoma	
Scanty (SM ≤1000 μm) invasion	30 (11.2)
Deep (SM ≥1000 μm) invasion	31 (11.6)

SM, Submucosal.

(Olympus) depending on the situation. A DualKnife is a basic knife used for ESD procedures. If possible, we complete ESD with DualKnife alone. However, if the approach direction was positioned perpendicularly against the lesion, or if a rich vascular bed was found during SM dissection, the DualKnife was exchanged for an SB knife Jr or HookKnife. Basically we completed the ESD with 1 or 2 knives. Endoscopic hemostasis was achieved with hemostatic forceps (Coagrasper; Olympus) and the high-frequency generator was an ESG-100 (Olympus). The setting used was the pulse cut slow mode (25 W) for mucosal incision and forced coagulation mode (25 W) for SM dissection. With an SB knife Jr, we used the pulse cut fast mode setting (30 W) and soft coagulation (40 W). Further, we used a single overtube (Olympus) in 3 cases at the hepatic flexure.

We continued the procedure until the resection was accomplished.

Endoscopic and histopathological evaluations

Analysis of predictors of incomplete resection and perforation included the lesion size, growth pattern (lateral spreading tumor granular type/polypoid or lateral spreading tumor nongranular type), pathological diagnosis and depth of invasion (adenoma: SM shallow invasion or SM deep invasion), use of hemostatic forceps (low frequency or high frequency), degree of fibrosis, history of biopsy, history of local endoscopic treatment, and endoscopic operability. Complete resection is defined as histopathological complete en bloc resection with a negative tumor margin.

Endoscopically, the degree of SM fibrosis was classified as follows based on the findings obtained by using injection of indigo carmine solution under the SM layer (Fig. 1), as reported previously: no fibrosis (F0) (the layer appeared blue and transparent), mild fibrosis (F1) (the layer appeared as a white weblike structure in the blue SM layer), and F2, severe fibrosis (the layer appeared as a white muscle-like structure without a blue transparent component) as described previously.[12] Low frequency of bleeding during ESD was defined as no visible bleeding during the procedure or minor bleeding that stopped spontaneously or was easily controlled by a few applications of coagulation. High frequency of bleeding during ESD was defined as bleeding that required repeated coagulation by hemostatic forceps (>10 times). Poor endoscopic operability was characterized as paradoxical movement of the endoscope, poor control for adhesion,

TABLE 3. Summary of cases with incomplete resection

Case	Size, mm	Growth type	Location	Pathology depth	Histological type of deepest invasive site	Reason for incomplete resection
1	60	LST-G	R	M	–	Piecemeal mucosal resection because of bleeding
2	30	LST-NG	C	SM 1800 μm	por	Tumor cut end positive at the submucosal deepest margin
3	30	LST-G	A	Adenoma	–	Piecemeal mucosal resection because of poor operability
4	50	LST-G	T	SM 4500 μm	por	Tumor cut end positive at the submucosal deepest margin
5	80	LST-G	A	SM 2000 μm	tub	Tumor cut end positive at the submucosal deepest margin
6	20	LST-NG	A	Adenoma	–	Piecemeal mucosal resection because of fibrosis
7	40	LST-G	S	Adenoma	–	Piecemeal mucosal resection because of poor operability
8	20	LST-NG	R	Adenoma	–	Piecemeal mucosal resection because of fibrosis
9	25	LST-NG	S	Adenoma	–	Piecemeal mucosal resection because of poor operability
10	20	LST-NG	S	SM 3000 μm	por	Tumor cut end positive at the submucosal deepest margin
11	25	LST-NG	A	SM 3500 μm	muc	Tumor cut end positive at the submucosal deepest margin

LST-G, Lateral spreading tumor granular type; *R*, rectum; *M*, intramucosal carcinoma; *LST-NG*, lateral spreading tumor nongranular type; *C*, cecum; *SM*, submucosal invasive carcinoma; *por*, poorly differentiated adenocarcinoma; *A*, ascending colon; *T*, transverse colon; *tub*, tubular adenocarcinoma; *S*, sigmoid colon; *R*, rectum; *muc*, mucinous adenocarcinoma; –, not available.

and lesion motion with heart beat or breathing. Poor endoscopic operability was further analyzed according to age, sex, history of abdominal operation, location (colon or rectum), the presence of the lesion on a fold, the presence of the lesion on a flexure, and the presence of a perpendicular approach to the muscular layer.

Statistical analysis

Values are reported as mean (standard deviation). The Fisher exact test was used for comparison of categorical variables. Multivariate logistic regression analysis was performed to examine the effects of independent variables adjusted for the effects of all others. The method of selecting a variable is the stepwise method, and the Akaike Information Criterion used to determine the variable when the Akaike Information Criterion was the minimal. Analyses were performed with JMP Statistical software version 9.02 (SAS Institute, Cary, NC. P values $<.05$ were considered statistically significant. There was no adjustment of nominal P values to correct for multiple testing of outcome data arising from individual patients because the main focus of this research is exploratory in nature.

RESULTS

Overall outcome of ESD

The overall en bloc resection rate was 95.9% (256/267) (Table 2). There were 11 cases of incomplete resection. Three lesions were accompanied by severe fibrosis at the SM layer because of a previous EMR or ESD. Five lesions were tumor-cut end positive at the deepest SM margin because of SM deep invasion with poorly differentiated or mucinous carcinoma (Fig. 3), and 6 lesions were finally excised by piecemeal mucosal resection by using a snare instead of ESD because of poor endoscopic operability, fibrosis, or severe bleeding during ESD (Table 3). The perforation rate was 5.6% (15/267). One patient with perforation required emergent surgery because of peritonitis. This perforation was located on scar of intestinal tuberculosis. We performed clipping to close the perforation hole; however, complete closure was not possible, most likely because the severe fibrosis caused by tuberculosis was so hard that clipping was insufficient. The other 14 were successfully treated nonsurgically with endoscopic clipping, fasting, and intravenous antibiotic infusion.

TABLE 4. Univariate analysis of risk factors for incomplete resection

	Complete resections (n = 256)	Incomplete resections (n = 11)	P value
Size, mm	36.4 (17.9)	39.4 (20.4)	.670
Growth type, no. (%)			.871
LST-G/polypoid	158 (96.3)	6 (3.7)	
LST-NG	98 (95.2)	5 (4.8)	
Pathological diagnosis, no. (%)			.033
Adenoma/ M/SM-s	229 (97.0)	7 (3.0)	
SM-d	27 (87.1)	4 (12.9)	
Use of hemostatic forceps, no. (%)			.166
Low frequency	179 (97.8)	5 (2.2)	
High frequency	77 (89.6)	6 (10.5)	
Degree of fibrosis, no. (%)			.032
F0/F1	164 (98.2)	3 (1.8)	
F2	92 (92.0)	8 (8.0)	
History of biopsy, no. (%)			1.000
No	234 (95.5)	10 (4.5)	
Yes	22 (95.7%)	1 (4.3%)	
History of previous local endoscopic treatment, no. (%)			.050
No	239 (96.8)	8 (3.2)	
Yes	17 (85.0)	3 (15.0)	
Endoscopic operability, no. (%)			.030
Good/normal	144 (98.6)	2 (1.4)	
Poor	112 (95.6)	9 (4.4)	

LST-G, Lateral spreading tumor granular type; *LST-NG*, Lateral spreading tumor nongranular type; *M*, intramucosal invasion; *SM-s*, submucosal shallow invasion (SM ≤1000 μm); *SM-d*, submucosal deep invasion (SM >1000 μm); *F0*, no fibrosis; *F1*, mild fibrosis; *F2*, severe fibrosis.

TABLE 5. Multivariate analysis of risk factors for incomplete resection

Variable	OR (95% CI)	P value
Poor endoscopic operability	5.84 (1.18-28.8)	.030
SM deep invasion (SM ≥1000 μm)	4.96 (1.26-19.6)	.022
Degree of fibrosis F2 (severe)	3.73 (0.93-14.9)	.062

OR, Odds ratio; *CI*, confidence interval; *SM*, submucosal; *F2*, severe fibrosis.

Risk factors for incomplete resections

Severe fibrosis (F2), SM deep invasion, and poor endoscopic operability were significantly associated with a higher frequency of incomplete resections ($P = .032$, $P = .033$, and $P = .030$, respectively), whereas tumor size, growth type, location, and pathological diagnosis and depth of invasion, use of hemostatic forceps, and history of biopsy were not (Table 4).

On multivariate logistic regression analysis, poor endoscopic operability (odds ratio [OR] 5.84; 95% confidence interval [CI], 1.18-28.8) and SM deep invasion (OR 4.96; 95% CI, 1.26-19.6) were significant factors for predicting incomplete resections during the colorectal ESD procedure (Table 5).

Risk factors for perforation

Severe fibrosis, postendoscopic treatment, and poor endoscopic operability were significantly associated with perforation ($P = .038$, $P = .016$, and $P = .012$, respectively), but we did not detect an association among a higher frequency of perforation and tumor size, growth type, location, pathological diagnosis and depth of invasion, use of hemostatic forceps, and history of biopsy (Table 6).

On multivariate logistic regression analysis, poor endoscopic operability (odds ratio 4.58; 95% CI, 1.24-16.9) and severe fibrosis (OR 4.41; 95% CI, 1.35-14.5) were significant factors for predicting perforation during colorectal ESD procedures (Table 7).

The percentage of incomplete resection and perforation is shown in Figure 2. The ratio of incomplete resections (7.9%) in cases with either poor endoscopic operability or SM deep invasion were significantly higher than that (0.0%) in cases without both factors (Fig. 2, left; $P = .0009$). The ratio of perforation (8.3%) in cases with either poor endoscopic operability or severe fibrosis (F2) were significantly higher than that (1.0%) in cases without both of these factors (Fig. 2, right; $P = .0118$).

Furthermore, we analyzed the causes of poor endoscopic operability supplementally. We verified that location in colon ($P < .001$) and the presence of lesions on a flexure ($P < .001$) were significantly associated with poor endoscopic operability; however, our analysis did not indicate an association with age, sex, history of abdominal operation, the presence of a lesion on a fold, and the presence of a perpendicular approach to the muscular layer with poor endoscopic operability (Table 8).

TABLE 6. Univariate analysis of risk factors for perforations

	Perforations (−) (n = 252)	Perforations (+) (n = 15)	*P* value
Size, mm	36.5 ± 1.24	36.2 ± 4.98	.940
Growth type, no. (%)			.139
LST-G/polypoid	158 (96.3)	6 (3.7)	
LST-NG	72 (91.3)	9 (8.7)	
Pathological diagnosis, no. (%)			.052
Adenoma/M/SM-s	225 (95.3)	11 (4.7)	
SM-d	27 (87.1)	4 (12.9)	
Use of hemostatic forceps, no. (%)			1.000
Low frequency	174 (94.6)	10 (5.4)	
High frequency	78 (94.0)	5 (6.0)	
Degree of fibrosis, no. (%)			.038
F0/F1	163 (97.6)	4 (2.4)	
F2	89 (89.0)	11 (11.0)	
History of biopsy, no. (%)			1.000
No	230 (94.3)	14 (5.7)	
Yes	22 (95.7)	1 (4.7)	
History of local endoscopic treatment, no. (%)			.016
No	236 (95.6)	11 (4.4)	
Yes	16 (80.0)	4 (20.0)	
Endoscopic operability, no. (%)			.012
Good/normal	143 (98.0)	3 (2.0)	
Poor	109 (90.1)	12 (9.9)	

LST-G, Lateral spreading tumor granular type; *LST-NG*, Lateral spreading tumor nongranular type; *M*, intramucosal invasion; *SM-s*, submucosal shallow invasion (SM ≤1000 μm); *SM-d*, submucosal deep invasion (SM >1000 μm); *F0*, no fibrosis; *F1*, mild fibrosis; *F2*, severe fibrosis.

TABLE 7. Multivariate analysis of risk factors for perforations

Variable	OR (95% CI)	*P* value
Poor endoscopic operability	4.58 (1.24-16.9)	.022
Degree of fibrosis: F2	4.41 (1.35-14.5)	.014

OR, Odds ratio; *CI*, confidence interval.

DISCUSSION

Perforation is one of the most critical adverse events of ESD, particularly in colorectal cases. The anatomic characteristics of the colon and rectum present unique challenges, and it may be more difficult to perform ESD successfully and safely on colorectal lesions than on gastric lesions. However, with the increasing refinement of ESD and the improvement in the associated instruments and peripheral devices, both of which have enhanced the safety and clinical simplicity of ESD, the technique is being used more commonly for colorectal lesions.[1,13]

In this study, the overall en bloc resection rate and perforation rate were 95.9% and 5.6%, respectively. In previous reports from single-center studies, combined complete en bloc resection rates were 76.9% (range 58%-95.6%, 1385/1801),[12-29] and the combined perforation rate was 5.4% (range 1.3%-20.4%, 180/3339).[12-29] A summary of outcomes of colorectal ESD reported from previous multicenter studies included data from the early period of colorectal ESD to the more recent period without consideration for the learning curve, and complete en bloc resection rates were 62.4% to 83.8% with perforation rates of 3.3% to 14.0%.[11,13,30-34] Our study did not include data from the early period, and it was thought, therefore, that the en bloc resection rate was higher and the perforation rate was relatively low.

Until now, there have been no reports regarding the association between poor endoscopic operability and outcome of colorectal ESD. The current analysis showed that poor endoscopic operability could be a significant independent predictor of incomplete resection and perforation. Location in the colon and the presence of the lesion on a flexure were both significant predictors of poor endoscopic operability. Thus, when operators encounter these factors in ESD, it should be expected that the procedure will be more challenging, and this information can be useful in the selection of the device and operator and in maximizing operator vigilance.

In this study, there were 5 lesions with SM deep invasion that showed tumor-cut end positivity at the SM deepest invasive margin. All 5 of these lesions had poorly differentiated or mucinous carcinoma (unfavorable histology) at the SM deepest invasive margins, suggesting that unfavorable carcinoma cells at the SM deepest invasive margin may not be recognized during ESD because these types of cancer cells often invade diffusely without expansive growth.

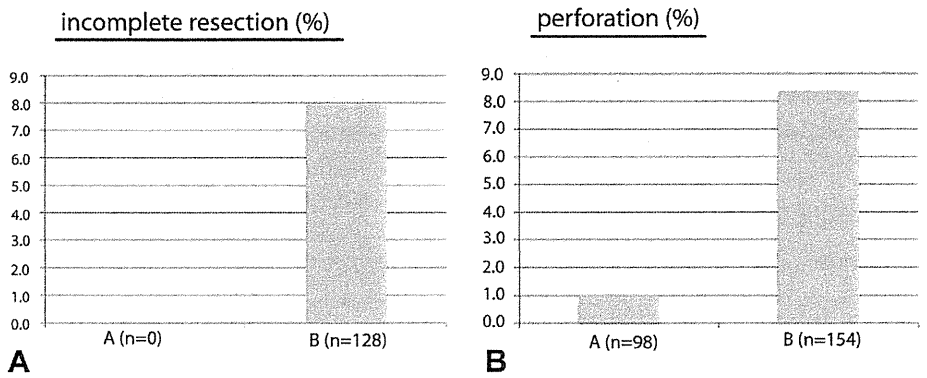

Figure 2. The prevalence (%) of incomplete resections and perforation. **A,** Cases with either poor endoscopic operability or submucosal deep invasion. **B,** Cases without both poor endoscopic operability and submucosal deep invasion.

TABLE 8. Univariate analysis of factors for poor endoscopic operability

Factor	Good/ normal (n = 146)	Poor (n = 121)	*P* value
Age, y	64.9 (0.92)	68.3 (1.00)	.054
Sex, no. (%)			.648
Male	98 (53.7)	78 (46.3)	
Female	48 (52.0)	43 (48.0)	
History of abdominal operation, no. (%)			.145
Yes	31 (46.3)	36 (53.7)	
No	115 (57.5)	85 (42.5)	
Location, no. (%)			<.001
Colon	54 (34.2)	104 (65.8)	
Rectum	92 (84.4)	17 (15.6)	
Lesion on a fold, no. (%)			.146
Yes	41 (47.7)	45 (52.3)	
No	105 (58.0)	76 (42.0)	
Lesion on a flexure, no. (%)			<.001
No	11 (17.5)	52 (82.5)	
Yes	135 (66.2)	69 (33.8)	
Perpendicular approach to the muscular layer, no. (%)			.297
No	19 (64.3)	10 (35.7)	
Yes	127 (53.4)	111 (48.7)	

We reported previously that risk factors for tumor-cut end positive at the deepest SM margin after ESD are severe SM fibrosis, unfavorable histology at the SM deepest invasive margin, and SM deep invasion. If a lesion is diagnosed as SM invasion by conventional and magnifying colonoscopy, we recommend additional EUS because an EUS-based assessment of invasion depth helps the operator to determine whether the lesion will be amenable to complete resection by ESD. However, even with EUS, it may be difficult to detect the diffuse spread of tumor cells at the SM deepest invasive margin.

Previous clinical studies focusing on the factors predicting perforation risk during colorectal ESD have shown that large lesions, fibrosis, tumor location, and operator experience are potential risk factors for perforation during ESD,[16,28,32,35,36] although another report on perforations indicated that there were no significant differences in terms of tumor location.[37] Isomoto et al[18] found that right-sided colon tumors and fibrosis had significant associations with incomplete resection and that perforation was associated with large tumor size (>30 mm) and the presence of fibrosis. These authors also reported that when the contributing factors for each element were combined, the risks of incomplete resection and perforation increased substantially. We previously[12] reported that in cases involving lesions with severe fibrosis, the rate of complete en bloc resection was low and the perforation rate was high, even when ESD was performed by a single experienced operator. However, it was impossible to know the presence and extent of fibrosis before the colorectal ESD.[12] Saito et al[32] reported that less experience performing ESDs (<50 cases) was an independent risk factor for adverse events.

Our study had the limitation of being a single-center study examining results from a single colonoscopist. Expertise is also reflected by a low rate of incomplete resection. Thus, the results may not apply to those experts with less experience. We would like to call attention to the studies of Western endoscopists in which the en bloc resection has been as low as 70%.[29] We anticipate that several other