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Clinicopathological features of T1 colorectal carcinomas with skip lymphovascular invasion

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Abstract. With recent advances in endoscopic treatment, many T1 colorectal carcinomas (CRCs) are resected endoscopically with a negative margin. However, some lesions exhibit skip lymphovascular invasion (SLVI), which is defined as the discontinuous foci of the tumor cells within the colon wall. The aim of the present study was to reveal the clinicopathological features of T1 CRCs with SLVI and validate the Japanese guidelines regarding SLVI. A total of 741 patients with T1 CRCs that were resected surgically between April 2001 and October 2016 in our hospital were divided into two groups: With SLVI and without SLVI. Clinicopathological features compared between the two groups were patient's gender, age, tumor size, location, morphology, lymphovascular invasion, tumor differentiation, tumor budding and lymph node metastasis. The incidence of T1 CRCs with SLVI was 0.9% (7/741). All cases with SLVI were found in the sigmoid colon or rectum. T1 CRCs with SLVI showed significantly higher rates of lymphovascular invasion than those without SLVI (P<0.01). In conclusion, lymphovascular invasion was a significant risk factor for SLVI in T1 CRCs, and for which surgical colectomy was necessary. The Japanese guidelines are appropriate regarding SLVI. Registered in the University Hospital Medical Network Clinical Trials Registry (UMIN000027097).

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Key words: colorectal carcinoma, endoscopic resection, lymphovascular invasion, skip metastasis, T1 carcinoma

Introduction

The incidence and mortality of colorectal carcinoma (CRC) have been increasing in Japan, where it accounts for the largest number of deaths from malignant neoplasms among women and the third largest number among men (1,2). Advanced methods of endoscopic treatment have been developed during recent decades, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) (3-8). Therefore, many T1 CRCs are resected endoscopically. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines for treatment of colorectal cancer indicate that the curative criteria for T1 CRCs after endoscopic resection are negative vertical margin, well/moderately differentiated tubular or papillary carcinoma, no vessel invasion, a submucosal invasion depth of less than 1,000 μm, and budding grade 1 because of the very low risk of lymph node metastasis (LNM) (1). When a lesion meets these criteria, endoscopic resection is considered to be an adequate cure, while additional surgery with lymph node dissection is recommended when these criteria are not met.

Recently, a Japanese study reported that there were some cases in T1 CRCs with 'skip lymphovascular invasion' (SLVI), which is defined as the discontinuous foci of the tumor cells within the colon wall (9). Lesions with SLVI cannot be diagnosed with specimens that have been endoscopically resected. However, lesions with SLVI require surgical colectomy to prevent recurrence or metastasis. Although detecting and managing such lesions are critical, the clinicopathological features of these lesions have not been fully elucidated. Because the number of colorectal ESD is increasing recently, these are urgent matters that need to be resolved. The aim of the present study was to reveal the incidence and the clinicopathological features of T1 CRCs with SLVI, and to validate the JSCCR guidelines regarding SLVI.

Materials and methods

Study patients. A total of 789 patients with T1 CRC surgically resected between April 2001 and October 2016 at

Showa University Northern Yokohama Hospital, Japan, were recruited. Patients who were diagnosed with familial adenomatous polyposis, Lynch syndrome, ulcerative colitis, and those who had synchronous invasive carcinoma or chemotherapy were excluded. Those who were unable to obtain clinicopathological features were also excluded. Initial or additional surgeries after endoscopic resection with lymph node dissection were performed based on the JSCCR guidelines. Patients were divided into two groups, with SLVI and without SLVI (Fig. 1). SLVI is a form of lymphovascular invasion or carcinoma within the colon wall, which is consistent with Okamoto *et al* (9) (Figs. 2 and 3). The following clinicopathological features were analyzed and compared between the two groups: Patient's gender, age, tumor size, location, morphology, lymphovascular invasion, tumor differentiation, tumor budding and the presence of LNM.

In a substudy, 560 patients with T2 CRCs resected surgically in our hospital between April 2001 and October 2016 were divided into two groups, with SLVI and without SLVI, and compared (Fig. 4). Features analyzed were patient's gender, age, tumor size, location, lymphovascular invasion, tumor differentiation and the presence of LNM.

Assessment of clinicopathological factors. Patients' gender, age, tumor size, location and morphology were reviewed from the electronic records system. Endoscopic morphology was classified as a depressed, flat, or protruded type according to Kudo's morphological classification (10).

All resected lesions were retrieved and immediately fixed in a 10% buffered formalin solution for 24-48 h. Each species was cut into 2- or 3-mm-wide longitudinal slices. The tissues were examined by one pathologist (SH) based on the World Health Organization criteria and the JSCCR guidelines, and assessed using hematoxylin and eosin (H&E) staining (Dako; Agilent Technologies, Inc., Santa Clara, CA, USA) (1,11). In addition, lymphovascular invasion was evaluated using Victoria blue (Muto Pure Chemicals Co., Ltd., Tokyo, Japan) or immunostaining with D2-40 (Dako; Agilent Technologies, Inc.). Histological grade was based on dominant differentiated tumor component and was classified according to World Health Organization criteria (11).

Statistical analysis. All statistical analyses were performed by using 'EZR' (Easy R) v.1.37 for Windows (12). Independent Student's t-tests were used to compare the groups of continuous, normally distributed variables. Fisher's exact test was used to determine the significance of differences between groups for dichotomous variables. All statistical tests were two-tailed, and $P<0.05$ was considered to indicate a statistically significant difference.

Ethical considerations. This study was approved by the Institutional Review Board of Showa Northern Yokohama Hospital (no. 1508-03), and was registered in the University Hospital Medical Network Clinical Trials Registry (UMIN000027097). Written informed consent was obtained from all patients before endoscopy.

Results

Patients' characteristics. A total of 741 T1 CRC patients were included in this study, 469 (63%) were men and 272 (37%) were women. The mean age was 65 years old (range 31-94). The mean tumor size was 21 mm (range 10-120). In total, 515 cases (69%) were located in the sigmoid colon or rectum, and 226 (31%) were located in other sites. Regarding morphology, 220 cases (29%) were diagnosed as depressed type and 521 cases (71%) were non-depressed type. Lymphovascular invasion appeared in 356 cases (48%). A total of 4 cases (0.5%) were poorly differentiated adenocarcinoma or mucinous adenocarcinoma (por/muc). LNM was found in 84 cases (11%). The incidence of T1 CRCs with SLVI was 0.9% (7/741).

A total of 501 patients with T2 CRCs were included, 253 (51%) of whom were men and 248 (49%) were women. The mean age was 66 years old (range 28-91). The mean tumor size was 31 mm (range 8-117). There were 357 cases located in the sigmoid colon or rectum. Lymphovascular invasion appeared in 348 cases (70%). LNM was found in 136 cases (27%). The incidence of T2 CRCs with SLVI was 1.6% (8/501).

Table I. Comparison of clinicopathological features between patients with and without skip lymphovascular invasion in T1 colorectal carcinomas.

Characteristics	With SLVI (n=7)	Without SLVI (n=734)	P-value
Sex			0.96
Male	5	464	
Female	2	270	
Age, years (range)	68 (42-79)	65 (31-94)	0.30
Tumor size, mm (range)	20 (13-33)	21 (10-120)	0.44
Location			0.11
Sigmoid or rectum	7	508	
Other site	0	226	
Morphology			0.03
Depressed	5	215	
Non-depressed	2	519	
Lymphovascular invasion			<0.01
Positive	7	349	
Negative	0	385	
Tumor differentiation			0.84
Por or Muc	0	4	
Well or Mod or Pap	7	730	
Tumor budding			0.11
Positive	2	472	
Negative	5	262	
Lymph node metastasis			0.18
Positive	2	82	
Negative	5	652	

SLVI, skip lymphovascular invasion; CRC, colorectal carcinoma; Por, poorly differentiated adenocarcinoma; Muc, mucinous carcinoma; Well, well differentiated adenocarcinoma; Mod, Moderately poorly differentiated adenocarcinoma; Pap, papillary adenocarcinoma.

Table II. Comparison of clinicopathological features between patients with and without skip lymphovascular invasion in T2 colorectal carcinomas.

Characteristics	With SLVI (n=8)	Without SLVI (n=493)	P-value
Sex			0.29
Male	6	247	
Female	2	246	
Age, years (range)	61 (44-84)	67 (28-91)	0.41
Tumor size, mm (range)	23 (10-37)	31 (8-117)	0.15
Location			0.11
Sigmoid or rectum	8	349	
Other site	0	144	
Lymphovascular invasion			0.11
Positive	8	348	
Negative	0	145	
Tumor differentiation			0.59
Por or Muc	0	15	
Well or Mod or Pap	8	478	
Lymph node metastasis			0.76
Positive	2	131	
Negative	6	362	

SLVI, skip lymphovascular invasion; CRC, colorectal carcinoma; Por, poorly differentiated adenocarcinoma; Muc, mucinous carcinoma; Well, well differentiated adenocarcinoma; Mod, Moderately poorly differentiated adenocarcinoma; Pap, papillary adenocarcinoma.

Table III. Comparison of clinicopathological features between patients with and without skip lymphovascular invasion in T1 and T2 colorectal carcinomas.

Characteristics	With SLVI (n=15)	Without SLVI (n=1227)	P-value
Sex			0.14
Male	11	711	
Female	4	516	
Age, years (range)	64 (42-84)	65 (25-94)	0.96
Tumor size, mm (range)	21 (10-37)	25 (8-120)	0.70
Location			<0.01
Sigmoid or rectum	15	857	
Other site	0	370	
Lymphovascular invasion			<0.01
Positive	15	697	
Negative	0	530	
Tumor differentiation			0.57
Por or Muc	0	19	
Well or Mod or Pap	15	1,208	
Lymph node metastasis			0.31
Positive	4	213	
Negative	11	1,014	

SLVI, skip lymphovascular invasion; CRC, colorectal carcinoma, Por, poorly differentiated adenocarcinoma; Muc, mucinous carcinoma; Well, well differentiated adenocarcinoma; Mod, Moderately poorly differentiated adenocarcinoma; Pap, papillary adenocarcinoma.

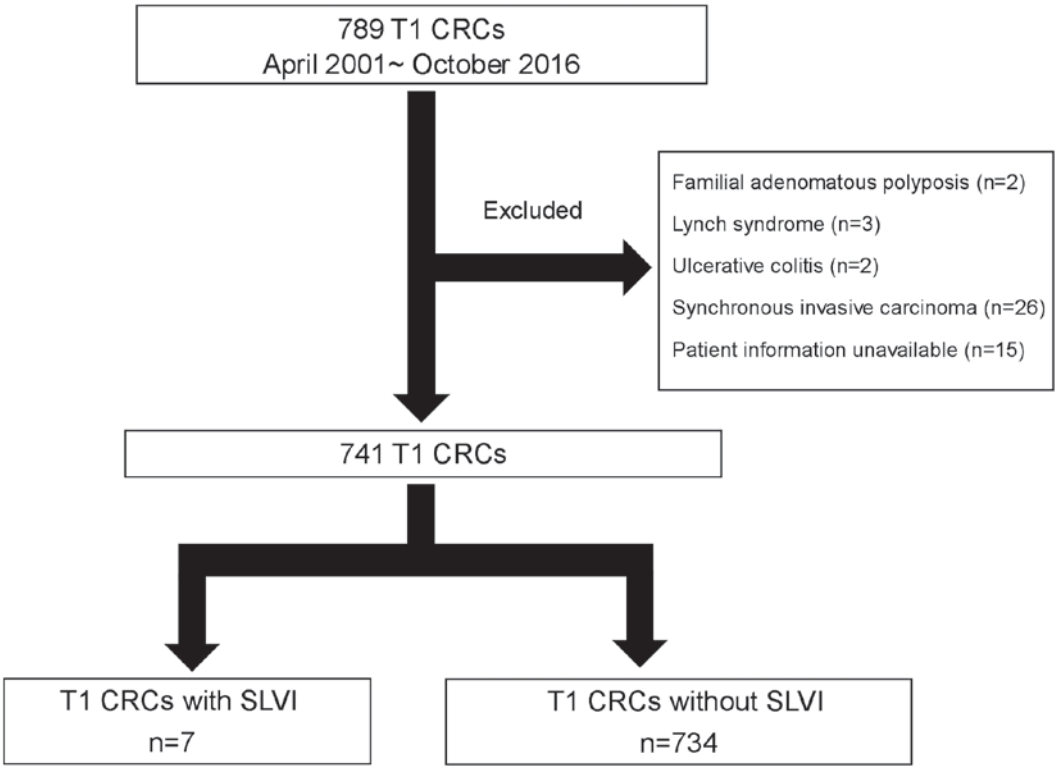

Figure 1. Patient flow chart in T1 colorectal carcinomas: CRC, colorectal carcinoma; SLVI, skip lymphovascular invasion.

Table IV. Details of the patients with SLVI in T1 and T2 colorectal carcinomas.

No.	Sex	Age	Tumor size (mm)	Location	Depth of direct invasion (μm)	Lympho-vascular invasion	Tumor differentiation	Morphology	LNM	Recurrence
1	F	42	33	R	T1 (3,800)	+	Mod	IIa+IIc	-	-
2	M	79	20	S	T1 (6,100)	+	Well	Is	-	-
3	M	76	16	S	T1 (1,000)	+	Well	LST-NG	-	-
4	M	78	22	S	T1 (6,750)	+	Mod	Is+IIc	+	-
5	M	66	17	S	T1 (5,300)	+	Well	IIa+IIc	-	-
6	M	70	13	S	T1 (5,900)	+	Mod	IIa+IIc	+	-
7	F	62	16	S	T1 (3,800)	+	Mod	IIa+IIc	-	-
8	M	57	37	R	T2	+	Well	Type2	-	-
9	M	64	21	S	T2	+	Mod	Type2	-	Liver
10	M	55	30	S	T2	+	Well	Type2	-	-
11	M	84	20	S	T2	+	Mod	Type2	+	-
12	M	59	27	S	T2	+	Well	Type2	+	Liver
13	F	60	20	R	T2	+	Mod	Type2	-	-
14	M	66	20	R	T2	+	Well	Type2	-	Liver, lung
15	F	44	10	S	T2	+	Mod	Type1	-	-

SLVI, skip lymphovascular invasion; R, rectum; S, sigmoid colon; v, vascular invasion; ly, lymphatic invasion; Mod, moderately differentiated carcinoma; Well, well differentiated carcinoma; LST-NG; laterally spreading tumor-non granular; LNM, lymph node metastasis; F, female; M, male.

Comparisons of pathological features between the patients with and without SLVI. The comparisons of clinicopathological features between patients with and without SLVI in T1 CRCs are shown in Table I. All T1 CRCs with SLVI showed lymphovascular invasion. In addition, cases with SLVI also showed a higher rate of lymphovascular invasion (P<0.01) and depressed type (P=0.03) than cases without SLVI. Although all cases with SLVI were in the sigmoid or rectum, there were no significant differences between occurrence at either site (P=0.11). There were no significant differences in other clinicopathological features between the two groups.

The comparisons of clinicopathological factors between cases with SLVI and cases without SLVI in T2 CRCs are shown in Table II. All T2 CRCs with SLVI were also in the sigmoid colon or rectum (P=0.11) and showed lymphovascular invasion (P=0.11). There were also no significant differences in other clinicopathological features.

We also examined T1 and T2 CRCs together (Table III). Significant differences were observed concerning location (P<0.01) and lymphovascular invasion (P<0.01). There were no significant differences in other clinicopathological features. Table IV shows the details of T1 and T2 CRCs with SLVI. All cases showed lymphovascular invasion and were located in the sigmoid colon or rectum.

Discussion

In the present study, we retrospectively investigated the incidence and clinicopathological features of T1 and T2 CRCs with SLVI. The incidence of SLVI in T1 and T2 CRCs was 0.9 and 1.6%, respectively. All cases with SLVI were located in the sigmoid colon or rectum and showed lymphovascular invasion.

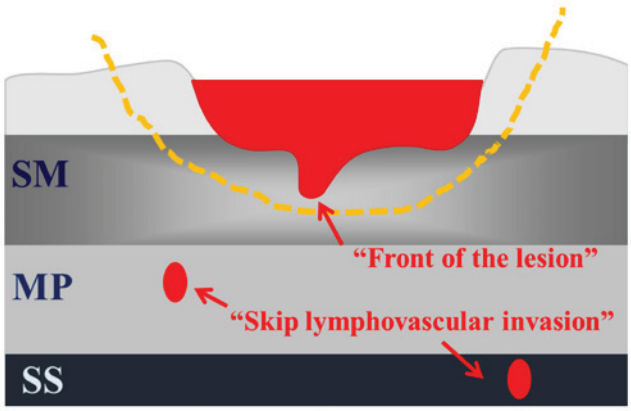

Figure 2. Scheme of skip lymphovascular invasion. SM, submucosa; MP, muscularis propria; SS, subserosa.

We focused on T1 CRCs with SLVI in the present study. With recent advances in endoscopic treatments, such as ESD, many T1 CRCs can be resected endoscopically with negative margin. Although endoscopic treatment is an attractive option for the patients, T1 CRCs show approximately 10% of LNM, which requires surgical colectomy with lymph node dissection to cure the cancer (13-20). Therefore, it is important to reveal the risk factors for LNM in the patients with T1 CRCs, and we should decide whether additional surgery after endoscopic resection is needed according to the presence of risk factors for LNM. Previously identified risk factors for LNM in T1 CRCs are lymphovascular invasion, tumor budding, histological grade, and the degree of submucosal invasion. These risk factors are listed in current guidelines such as the National Comprehensive Cancer

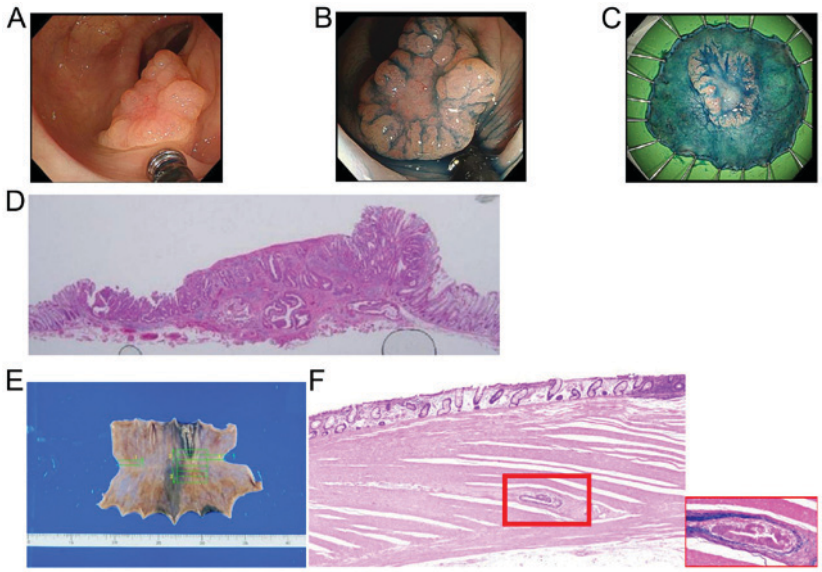

Figure 3. A typical case of T1 colorectal carcinoma with skip lymphovascular invasion: (A) A 16-mm-sized flat lesion located in the sigmoid colon (B) In indigocarmine-sprayed magnifying observation, morphology was diagnosed as a laterally spreading tumor (non-granular type). (C) With patient request, endoscopic submucosal dissection was performed. (D) Histology by hematoxylin and eosin staining. The diagnosis was T1 carcinoma (depth of submucosal invasion was 1,000 μm), 16 mm, well-differentiated adenocarcinoma, lymphovascular invasion positive, vertical margin negative. Magnification, x20. (E) Additional surgery was undergone. (F) Lymphovascular invasion was recognized in the muscularis propria by using Victoria blue staining. Magnification, x40 (left), x200 (right).

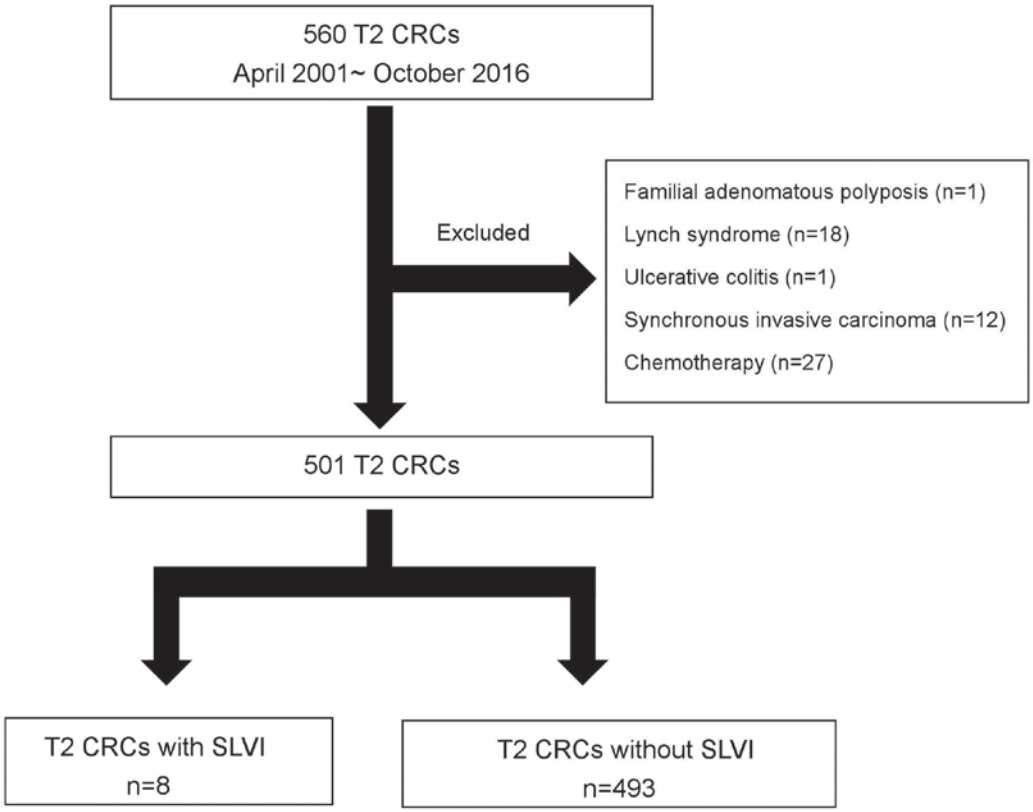

Figure 4. Patient flow chart in T2 colorectal carcinomas: CRC, colorectal carcinoma; SLVI, skip lymphovascular invasion.

Network (NCCN), European Society for Medical Oncology (ESMO) or JSCCR. Currently, these are the only indications for surgery after endoscopic resection in the patients with T1 CRCs (1,21-24). However, a recent report has investigated T1 CRCs with SLVI (9). These lesions also need to undergo surgical resection because they have the potential to recur or to develop metastasis when treated with endoscopic resection alone. Specifically, we should decide the indication for surgery in patients with T1 CRCs in terms of not only the risk of LNM but also the existence of SLVI. We therefore planned

this study, which investigated the risk factors for lesions with SLVI.

The incidence of T1 CRCs with SLVI was 0.9%, which were the same as previously reported (9). Our study revealed that lymphovascular invasion was a significant risk factor for SLVI in patients with T1 CRCs. Currently, the mechanism of SLVI remains unknown. All lesions with SLVI demonstrated lymphovascular invasion, and discontinuous foci were all lymphovascular invasion. Considering these results, lymphovascular invasion could be associated with the development of SLVI. There were no significant differences in other clinicopathological features. Thus, patients with T1 CRCs that show lymphovascular invasion are recommended for surgery after endoscopic resection. In addition, the JSCCR guidelines are appropriate regarding SLVI.

To reveal the features of CRCs with SLVI in more detail, we analyzed not only T1 CRCs but also T2 CRCs. The location, that is, the sigmoid colon or rectum, was a risk factor in T1 and T2 CRCs with SLVI accompanied by a significantly higher rate of lymphovascular invasion than CRCs without SLVI. This difference may have resulted from differences between anatomical features, such as blood vessel density, of the sigmoid colon/rectum and the other sites. Although all cases were located in the sigmoid colon or rectum, there were some cases with SLVI at locations other than the sigmoid colon or rectum in previous reports by Okamoto *et al* (9). Further research is needed.

There are some limitations to this study. First, this was a single center retrospective study. Although the sample size was larger than the previous report (9), there could be a regional or institutional selection bias. Second, we investigated only patients with surgically resected T1 CRCs because SLVI was not able to be diagnosed when treated by only endoscopic resection. Hence, the clinicopathological features identified in this study are not necessarily applicable to patients treated by endoscopic resection alone.

In conclusion, although the incidence is very low, there are some T1 CRCs with SLVI, and its risk factor is the presence of lymphovascular invasion. These lesions are likely to recur when treated by endoscopy alone. Therefore, T1 CRCs with lymphovascular invasion require surgical colectomy, which also follows the current JSCCR guidelines. To reveal the clinicopathological features of CRCs with SLVI in more detail, further research is needed.

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Availability of data and materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Authors' contributions

YSa contributed to the study concept and drafted the manuscript. YSa and KI contributed to statistical analysis and interpretation of data. SK, FI and HM contributed to administrative support and study supervision. YSa, SK, KI, SM, YK, KK, TB, KW, TH, TK, NO, YM, MM, NT, TI, YY, HK, TS, YSh, KS, YK, SH, FI and HM contributed to data collection at Showa University and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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