

# The risk of lymph node metastasis makes it unsafe to expand the conventional indications for endoscopic treatment of T1 colorectal cancer

## A retrospective study of 428 patients

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### Abstract

Though endoscopic treatment is an option for T1 colorectal cancer (CRC), the optimal indications and long-term outcomes of this strategy need to be validated. Therefore, the aim of this study is to investigate long-term outcomes of endoscopy versus surgery and optimal indications for endoscopic treatment of T1 CRC.

This retrospective study included 428 T1 CRC patients treated with initial endoscopy (n=224) or surgery (n=204) at Severance Hospital between 2005 and 2012. Patients were subdivided into 4 groups according to conventional indications (CIs) for endoscopic treatment: negative lateral/vertical margins; submucosal invasion depth within 1000  $\mu\text{m}$ ; no lymphovascular invasion (LVI); well or moderately differentiated. For prognosis evaluation, short-term outcomes (resection margin and complications) and long-term outcomes (recurrence and cancer-specific mortality) were evaluated.

Endoscopic treatment achieved en bloc resection in 86.6% of 224 patients. Recurrence and mortality did not differ between the endoscopy and surgery groups with or without CIs. For patients with CIs, although 80 patients were treated endoscopically with 1 (1.3%) recurrence and 0 mortality, 75 patients were treated surgically with 2 (2.7%) recurrence and 1 (1.3%) mortality. Multivariate analysis revealed that LVI positivity and poorly differentiated histology were independently associated with lymph node metastasis (LNM;  $P < 0.001$  and  $P = 0.001$ , respectively).

To determine whether the depth of submucosal invasion among criteria of CIs could be extended for endoscopic treatment, LNM was analyzed by extending the depth of submucosal invasion. There was no LNM in 155 patients within conventional indication. When the depth of submucosal invasion was extended up to 1500  $\mu\text{m}$ , LNM was occurred (1/197 patient [0.5%]). In addition, when the depth of submucosal invasion was extended up to 2000  $\mu\text{m}$ , LNM was increased (4/271 patient [1.5%]).

Endoscopic treatment is safe, effective, and is associated with favorable long-term outcomes compared to surgery for initial treatment of T1 CRC patients with CIs. However, the risk of LNM makes it unsafe to extend the CIs for endoscopic therapy in these patients.

**Abbreviations:** CEA = carcinoembryonic antigen, CIs = conventional indications, CRC = colorectal cancer, ECC = early colorectal cancer, EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, ET-CI group = endoscopic therapy with conventional indications group, ET-NCI group = endoscopic therapy with nonconventional indications group, LNM = lymph node metastasis, LVI = lymphovascular invasion, OR = odds ratio, ST-CI group = surgical therapy with conventional indications group, ST-NCI group = surgical therapy with non-conventional indications group.

**Keywords:** colorectal cancer, endoscopic treatment, prognosis, submucosal cancer, surgery

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## 1. Introduction

Colorectal cancer (CRC) is one of the most common malignancies in both Asian and Western countries.<sup>[1,2]</sup> A vigorous CRC screening program and improvements in endoscopic techniques have led to an increase in the proportion of colorectal cancer cases that are diagnosed at early stages.<sup>[3–5]</sup> As a result, the incidence of T1 CRC has increased, and some T1 CRC patients are candidates for endoscopic treatment.<sup>[6,7]</sup> However, 6% to 12% of T1 CRC patients experience lymph node metastasis (LNM), which requires subsequent surgical resection.<sup>[8–10]</sup> Though the likelihood of LNM in T1 CRC patients is low, surgical resection and removal of regional lymph nodes is considered the definitive treatment for this disease.<sup>[11]</sup>

Many studies have been performed in recent decades to validate clinical and histological factors that predict LNM, as this knowledge is needed to establish the proper indications for endoscopic treatment of T1 CRC.<sup>[12–15]</sup> According to the Paris classification and Japanese clinical guidelines, CRC is considered to be low-risk for LNM and local recurrence if it is submucosal

invasive CRC with negative vertical margins, well or moderately differentiated adenocarcinoma, lacks evidence of vascular or lymphatic invasion, and has an invasion depth  $<1000\ \mu\text{m}$ .<sup>[16,17]</sup> Endoscopic resection is commonly performed for low-risk T1 CRC based on these guidelines, and these histologic factors are considered to be the conventional indications (CIs) for endoscopic treatment alone. Recent studies have reported the feasibility and favorable short-term outcomes of endoscopic treatment for T1 CRC.<sup>[18–20]</sup> However, the long-term outcomes of endoscopic treatment compared to surgery are not well-established. Furthermore, although the expanded indications have been applied to the endoscopic treatment of early gastric cancer,<sup>[21–23]</sup> there are no data about the expanded indications for endoscopic treatment of T1 CRC.

The present study focused on these points by evaluating long-term outcomes of T1 CRC patients treated endoscopically compared to patients treated surgically and determined the optimal indications for endoscopic treatment with respect to the risk of LNM.

## 2. Methods

### 2.1. Patients

The present study included 549 patients who were diagnosed with cT1N0 CRC at Severance Hospital between January 2005 and March 2012. A total of 121 patients were excluded because: they had other coexisting malignancies within 5 years before CRC diagnosis ( $n=32$ ); they had coexisting synchronous advanced CRC ( $n=5$ ); they were lost to follow-up ( $n=22$ ); there were insufficient pathology reports ( $n=46$ ); they received neoadjuvant therapy before surgery ( $n=15$ ); or they had familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, or inflammatory bowel disease ( $n=1$ ). Finally, 428 patients with T1 CRC who underwent endoscopic ( $n=224$ ) or

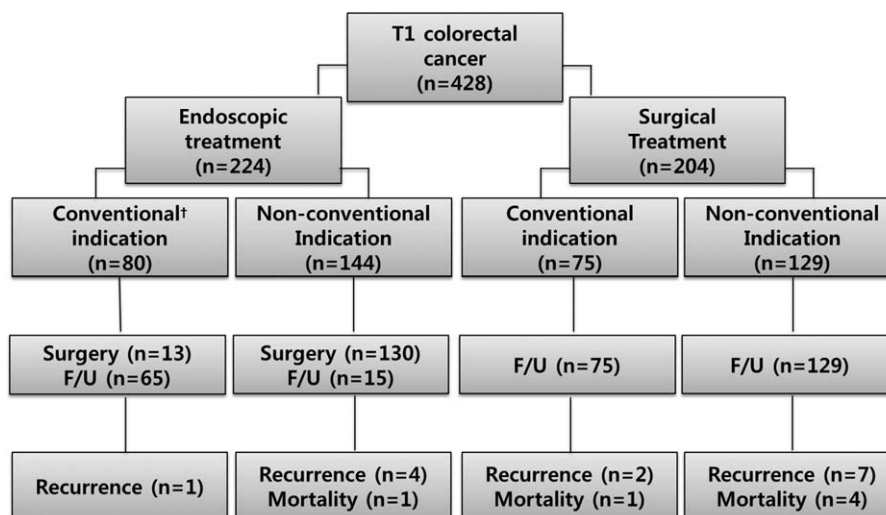
surgical ( $n=204$ ) initial treatment were included in the study. The patients were subdivided into 4 groups according to CIs: endoscopic therapy with CIs (ET-CI group), endoscopic therapy with non-conventional indications (ET-NCI group), surgical therapy with CIs (ST-CI group), and surgical therapy with non-conventional indications (ST-NCI group) (Fig. 1).

The CIs were: negative lateral/vertical margins; submucosal invasion depth  $<1000\ \mu\text{m}$ ; no lymphovascular invasion (LVI); well or moderately differentiated.

The institutional review board approved the study protocol. All study procedures were conducted in accordance with the International Conference on Harmonization Good Clinical Practices and the Declaration of Helsinki and its amendments.

### 2.2. Procedures

**2.2.1. Endoscopic treatment.** Endoscopic procedures were performed using a single-channel colonoscope (CF Q240L, CF Q240I, CF H260AI, CF Q260AI, or PCF Q260AI; Olympus Optical Co., Tokyo, Japan) and a high-frequency generator with an automatically controlled system (VIO300; ERBE Elektromedizin GmbH, Tübingen, Germany). All procedures were performed by 4 experienced gastroenterologists. Endoscopic treatments, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), were chosen based on the characteristics of the lesion and the preference of the operating physician. EMR was performed using a snare after injecting solution (normal saline, 0.04% indigo carmine, with or without 1:100,000 diluted epinephrine) into the submucosa. If tumors remained, sequential submucosal injection and snare polypectomies were performed. ESD was performed with a flex knife (Flex Knife; KD-630L, Olympus Optical Co.) or a dual knife (Dual Knife; KD-650L, Olympus Optical Co.). After spraying the lesion with 0.4% indigo carmine dye and injecting solution into the submucosa beneath the lesion, a knife was used



**Figure 1.** Clinical courses of 428 patients with T1 colorectal cancer treated by endoscopy ( $n=224$ ) or surgery ( $n=204$ ) as the initial treatment. The patients were subdivided into 4 groups based on whether or not their lesions satisfied the conventional indications. Among the 80 patients who satisfied the conventional indications and underwent initial endoscopic treatment, 13 patients (16.3%) underwent additional surgery and 1 patient (1.3%) experienced recurrence. Among 144 patients with nonconventional indications who underwent initial endoscopic treatment, 130 patients underwent additional surgery, 4 patients (2.8%) experienced recurrence, and there was 1 (0.7%) mortality. For the initial surgical treatment groups, there were 2 patients (2.7%) with recurrence and 1 (1.3%) mortality among the 75 conventional indication cases, and 7 patients (5.4%) with recurrence and 4 (3.1%) mortalities among the 129 nonconventional indication cases. ECC=early colorectal cancer, F/U=follow-up, LN=lymph node, LVI=lymphovascular invasion, MM=muscularis mucosa, PD=poorly differentiated, RM=resection margin. †Conventional indications: patients who underwent curative resection by endoscopy or surgery. The conventional indications were: negative lateral/vertical margins; submucosal invasion depth within  $1000\ \mu\text{m}$ ; no lymphovascular invasion; well- or moderately differentiated tumors.

to make an incision that was approximately 2-mm long. After an additional injection beneath the lesion to lift it up from the muscularis propria, a knife was used to directly dissect the submucosal layer. If a residual lesion was detected endoscopically, additional EMR was performed. Resections were classified as either en bloc resection (resection in a single piece) or piecemeal resection (resection in multiple pieces).

**2.2.2. Surgical treatment.** Laparoscopic and open surgeries were performed by experienced colorectal surgeons. The type of surgery (right hemi-colectomy, left hemi-colectomy, segmentectomy, anterior resection, low anterior resection, or abdominoperineal resection) was determined based on the tumor site and at the discretion of the surgeon. For patients with NCIs in the pathology analysis after endoscopic resection, an additional curative surgical resection with lymph node dissection was recommended.

### 2.3. Main outcome measurements

To evaluate adverse events, we analyzed perforations, intestinal obstructions, and pneumonia using simple chest and abdominal x-rays that were taken immediately after endoscopies or surgeries. Immediate bleeding was determined by endoscopic findings during the procedure (continued for over 60 seconds), and late bleeding was determined by clinical symptoms, vital signs, and laboratory tests after the procedure (within 30 days of the procedure and required hospitalization or treatment).

To check the resection status, all resected specimens were cut into 2-mm-wide longitudinal slices. Experienced gastrointestinal pathologists evaluated all pathologic specimens for resection margin status and tumor characteristics, including histologic type, depth of invasion, vascular invasion, and lymphatic invasion. Histologic diagnoses were determined and measurements of tumor invasion depth were obtained according to the guidelines of the Japanese Society for Cancer of the Colon and Rectum.<sup>[17]</sup>

For evaluation of long-term outcomes, we considered physical examinations, blood tests (including measurement of carcinoembryonic antigen [CEA] levels), chest radiography, and computed tomography scans of the abdomen and pelvis taken after endoscopic or surgical treatment during follow-up visits every 6 months for the first 2 years, and every year thereafter until 5 years. A colonoscopy was performed within a year after endoscopic or surgical treatment. Recurrence was diagnosed by radiologic images or positive biopsies. Mortality was confirmed using information from the national cancer registry of Korea.

### 2.4. Statistical analysis

Continuous variables are expressed as the mean  $\pm$  standard deviation and categorical variables are expressed as number (%). In the univariate analyses, baseline characteristics of each group (initial endoscopic treatment vs. initial surgical treatment and LNM negative vs. LNM positive) were compared using Student *t* test for continuous variables and  $\chi^2$  tests or Fisher exact tests for categorical variables. The Kaplan–Meier method was used to estimate the distribution of the time from diagnosis to recurrence or mortality according to independent variables. In the multivariate analysis, binomial logistic regression analysis was used to analyze the factors that affected LNM. Results were

considered to be statistically significant if  $P < 0.05$ . All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL).

## 3. Results

### 3.1. Baseline characteristics of included patients

The 428 T1 CRC patients in this study were divided into 4 groups based on their initial treatment modality and whether or not they satisfied the CIs: the ET-CI group ( $n=80$ ), the ST-CI group ( $n=75$ ), the ET-NCI group ( $n=144$ ), and the ST-NCI group ( $n=129$ ). The mean follow-up duration was  $>40$  months for all 4 groups and  $>3.5$  years for all patients (Table 1).

The baseline characteristics of included patients are described in Table 1. In patients with the CIs, there were no significant differences in baseline characteristics including age, sex, morphology, and histologic differentiation of T1 CRC between the endoscopy and surgery groups. Mean tumor size was significantly larger in the surgery group compared to the endoscopy group ( $23.7 \pm 14.4$  mm vs.  $18.1 \pm 9.2$  mm;  $P=0.005$ ). With regard to tumor location, rectal lesions tended to be more frequent in the surgery group compared to the endoscopy group (46.7% vs. 37.5%;  $P=0.071$ ).

Among the 80 ET-CI patients, 71 patients (88.7%) underwent EMR and 9 patients (11.3%) were treated with ESD. En bloc resection was achieved in 72 patients (90%), whereas 8 patients (10.0%) had piecemeal resections (Table 1). All 75 ST-CI patients had en bloc resections. The duration of follow-up was not different between the 2 groups.

### 3.2. Clinical outcomes of endoscopic treatment compared to surgery in T1 CRC

Adverse events in the endoscopy group included delayed bleeding in 1 patient (0.4%) and bowel perforations in 2 patients (0.9%), which were successfully treated endoscopically (Table 2). Among the 80 ET-CI patients, 14 patients (17.5%) underwent additional surgeries because of the willingness of the patients. Among the 144 ET-NCI patients, 130 patients (89.6%) underwent additional surgeries, whereas additional surgeries were not performed in 15 patients (10.4%) because of patient refusal or poor medical condition.

Eventually, 347 patients underwent surgery: there were 9 patients with anastomosis site leakage (2.6%), 3 patients with intestinal obstruction (0.9%), and 1 patient each with urinary dysfunction, pneumonia, and mortality (0.3% for each).

There were no differences in recurrence or mortality between the endoscopic and surgical therapy groups, with or without CIs (recurrence:  $P=0.611$  and  $P=0.192$ ; mortality:  $P=0.484$  and  $P=0.267$ , respectively). Among the 80 ET-CI patients, there was only 1 patient (1.3%) with recurrence and no mortalities. Among the 75 ST-CI patients, there were 2 patients (2.7%) with recurrence and 1 with (1.3%) mortality. In the NCI group, there were 4 patients (2.8%) and 7 patients (5.4%) with recurrence in the endoscopic and surgical therapy groups, respectively, and there were 1 (0.7%) and 4 (3.1%) mortalities in the endoscopic and surgical therapy groups, respectively. For the 4 mortalities in the ST-NCI group, 1 was because of a surgical adverse event, and the others were because of cancer recurrence and progression (Table 2).

**Table 1****Comparison of baseline characteristics between T1 colorectal cancer patients who underwent initial endoscopic treatment or initial surgery.**

Initial therapy	Conventional indications (n=155) <sup>*</sup>			Non-conventional indications (n=273)		
	Endoscopy (n=80)	Surgery (n=75)	P	Endoscopy (n=144)	Surgery (n=129)	P
Age (mean ± SD), y	62.9 ± 10.5	62.9 ± 9.9	0.998	62.3 ± 10.6	62.5 ± 10.1	0.845
Male, n (%)	52 (65.0)	45 (60.0)	0.520	86 (59.7)	79 (61.2)	0.798
Location, n (%) <sup>†</sup>			0.071			0.003
Right	17 (21.3)	22 (29.3)		26 (18.1)	24 (18.6)	
Left	33 (41.3)	18 (24.0)		66 (45.8)	35 (27.1)	
Rectum	30 (37.5)	35 (46.7)		52 (36.1)	70 (54.3)	
Size (mean ± SD), mm	18.1 ± 9.2	23.7 ± 14.4	0.005	18.6 ± 8.8	23.9 ± 11.5	<0.001
Morphology, n (%) <sup>‡</sup>			0.388			0.017
Is	51 (63.7)	42 (56.0)		100 (69.4)	69 (53.5)	
Ila	27 (33.8)	33 (44.0)		40 (27.8)	51 (39.5)	
Ila + Ilc	2 (2.5)	0 (0.0)		4 (2.8)	9 (7.0)	
Histologic dif., n (%) <sup>§</sup>	(n=79)	(n=74)	0.849	(n=143)	(n=129)	<0.001
G1	49 (62.0)	47 (63.5)		67 (46.9)	39 (30.2)	
G2	30 (38.0)	27 (36.5)		70 (49.0)	90 (69.8)	
G3				6 (4.2)	0 (0.0)	
LVI+, n (%)				(n=130) 24 (18.5)	(n=127) 13 (10.2)	0.060
Endoscopic therapy method, n (%)						
EMR	71 (88.7)			131 (91.0)		
ESD	9 (11.3)			13 (9.0)		
Resection type, n (%)						
En bloc	72 (90.0)			122 (84.7)		
Piecemeal	8 (10.0)			22 (15.3)		
F/U duration (mean ± SD), mo	40.4 ± 20.6	44.3 ± 22.6	0.264	43.4 ± 21.5	46.2 ± 19.3	0.267

Variables are expressed as mean ± SD or n (%). EMR = endoscopic mucosal resection, ESD = endoscopic submucosal dissection, F/U = follow-up, G = grade, histologic dif = histologic differentiation, LVI = lymphovascular invasion, SD = standard deviation, SM = submucosa.

<sup>\*</sup> Conventional indications: patients that underwent curative resection by endoscopic or surgical therapy. The conventional indications were: negative lateral/vertical margins; submucosal invasion depth within 1000 μm; no lymphovascular invasion; well or moderately differentiated tumors.

<sup>†</sup> Right-sided colon was defined as the region from the cecum to the transverse colon. Left-sided colon was defined as the region from the splenic flexure to the rectosigmoid junction. Rectum was defined as the region distal to the rectosigmoid junction to the anus.

<sup>‡</sup> Morphology was classified using the Paris classification.

<sup>§</sup> G1 tumors are defined as well differentiated, G2 tumors as moderately differentiated, G3 tumors as poorly differentiated.

**Table 2****Comparison of procedure- or surgery-related adverse events and prognosis among T1 colorectal cancer patients who underwent initial endoscopic treatment or surgery.**

	Endoscopy (n=224)		Surgery (n=204)		P
	Conventional indications (n=80) <sup>*</sup>	Nonconventional indications (n=144)	Conventional indications (n=75) <sup>*</sup>	Nonconventional indications (n=129)	
Endoscopy AE, n (%)					0.486
Immediate bleeding	13 (16.3)	16 (11.1)			
Delayed bleeding	0	1 (0.7)			
Bowel perforation	0	2 (1.4)			
Additional surgery, n (%)	14 (17.5)	129 (89.6)			
Surgery AE, n (%)	(n=14)	(n=129)			0.113 <sup>†</sup>
Anastomosis site leakage	0	2 (1.6)	3 (4.0)	4 (3.1)	
Intestinal obstruction	0	1 (0.8)	1 (1.3)	1 (0.8)	
Urinary dysfunction	0	0	0	1 (0.8)	
Pneumonia	0	0	0	1 (0.8)	
LN metastasis, n (%)		11 (7.6)		8 (6.2)	0.621 <sup>  </sup>
Recurrence, n (%)	1 (1.3)	4 (2.8)	2 (2.7)	7 (5.4)	0.611 <sup>§</sup>
Mortality, n (%)	0	1 (0.7)	1 (1.3)	4 (3.1)	0.484 <sup>§</sup>
Procedure-related mortality, n (%)	0	0	0	1 (0.8)	0.267 <sup>  </sup>

Variables are expressed as n (%). AE = adverse event, LN = lymph node.

<sup>\*</sup> Conventional indications: patients who underwent curative resection by endoscopy or surgery. The conventional indications were: negative lateral/vertical margin; submucosal invasion depth within 1000 μm; no lymphovascular invasion; well or moderately differentiated tumors.

<sup>†</sup> Value was compared between the surgical therapy with conventional indications group and the surgical therapy with nonconventional indications group.

<sup>§</sup> Value was compared between the endoscopic therapy with conventional indications group and the surgical therapy with conventional indications group.

<sup>||</sup> Value was compared between the endoscopic therapy with non-conventional indications group and the surgical therapy with non-conventional indications group.



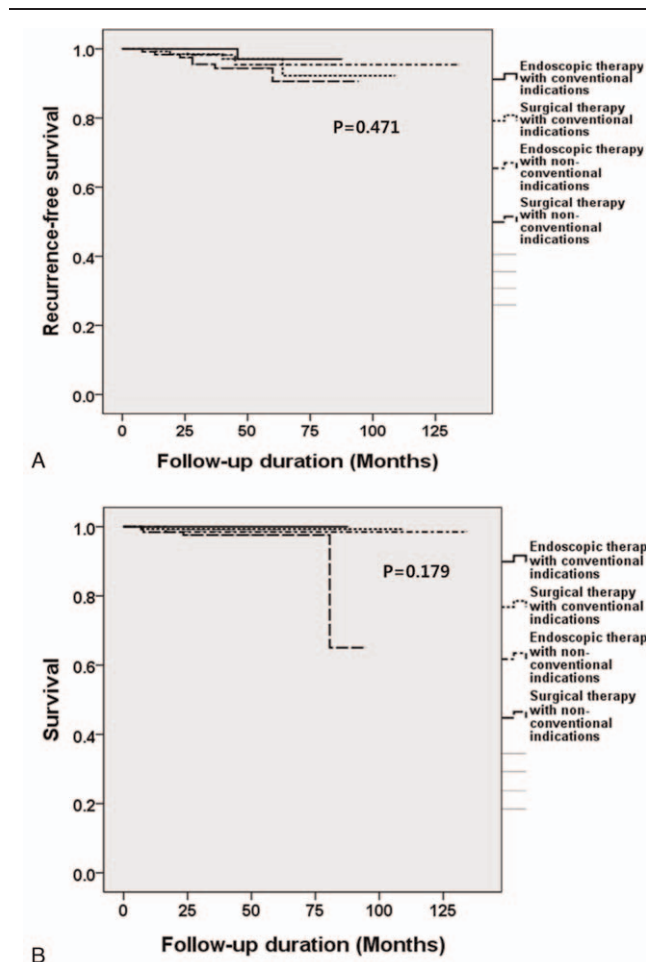
**Table 3**  
**Characteristics of colorectal cancer patients with recurrence.**

	Age	Sex	Initial size, mm	Initial location*	Morphology†	Initial treat. Method	Resection Resection	Resection margin	Histology	SM invasion depth, μm	LVI	Recurrence type	Months to recurrence
1	78	M	30	Rectum	Ila	EMR	Piecemeal	Positive	WD	2000	Positive	Distant (lung)	13
2	53	F	25	Rectum	Is	EMR	En bloc	Negative	MD	2000	Negative	Local	19
3	74	F	30	Rectum	Ila	ESD	En bloc	Positive	PD	500	Negative	Local	40
4	72	M	15	Rectum	Is	EMR	En bloc	Negative	MD	1000	Negative	Local	46
5	70	M	10	Right	Is	EMR	En bloc	Negative	WD	1000	Negative	Distant (lung)	64
6	68	M	30	Rectum	Ila	LAR		Negative	MD	1750	Positive	Local	8
7	63	F	20	Rectum	Is	LAR		Negative	MD	2000	Positive	Distant (liver)	13
8	62	M	8	Rectum	Is	LAR		Negative	WD	1000	Positive	Local	28
9	33	F	55	Rectum	Ila	LAR		Negative	WD	1000	Negative	Distant (Peritoneum)	26
10	61	M	20	Rectum	Is	LAR		Negative	WD	3000	Negative	Local	60
11	54	M	32	Left	Is	LHC		Negative	WD	2000	Negative	Distant (liver)	23
12	51	M	70	Rectum	Ila	LAR		Negative	WD	1000	Negative	Distant (lung)	45
13	60	M	20	Rectum	Is	LAR		Negative	MD	4000	Positive	Local	37
14	49	M	12	Rectum	Is	LAR		Negative	MD	1000	Positive	Distant (lung)	28

EMR=endoscopic mucosal resection, ESD=endoscopic submucosal dissection, F=female, LAR=lower anterior resection, LHC=left hemicolectomy, LVI=lymphovascular invasion, M=male, MD=moderately differentiated, PD=poorly differentiated, SM=submucosa, WD=well differentiated.

\* Right-sided colon was defined as the region from the cecum to the transverse colon. Left-sided colon was defined as the region from the splenic flexure to the rectosigmoid junction. Rectum was defined as the region distal to the rectosigmoid junction to the anus.

† Morphology was classified using the Paris classification.



**Figure 2.** Analysis of recurrence and mortality in T1 colorectal cancer (CRC) patients using Kaplan–Meier curves stratified by initial therapeutic modality. (A) The recurrence-free rate was not significantly different between patients who underwent initial endoscopic treatment and patients who underwent initial surgery ( $P=0.471$ ). (B) The survival rate was not significantly different between patients who underwent initial endoscopic treatment and patients who underwent initial surgery ( $P=0.179$ ).

In the total group of 428 patients, 14 patients (3.3%) experienced CRC recurrence. Details for the patients who experienced recurrence are reported in Table 3. For the 14 patients with recurrence, local recurrence was detected in 7 patients (50%) and distant metastasis was detected in 7 patients (50%). The mean time to recurrence was 32.1 months. Ten patients with recurrence were male, and 12 recurrence cases were located at the rectum. Seven patients had sessile type disease and 5 patients had flat type disease. Three patients developed recurrence even after curative resection during the first treatment (EMR), and 1 patient developed recurrence even though the initial endoscopic treatment met the CIs.

We used Kaplan–Meier curves stratified by initial therapeutic modality to identify associations between initial therapeutic modality and T1 CRC prognosis. The recurrence-free rate was not significantly different in patients treated with initial endoscopic therapy versus patients treated with initial surgical therapy ( $P=0.471$ ) (Fig. 2A). Also, the mortality-free rate was not significantly different in patients treated with initial endoscopic therapy versus patients treated with initial surgical therapy ( $P=0.179$ ) (Fig. 2B).

**3.3. Risk factors for LNM in T1 CRC treated surgically**

Among 347 patients who underwent surgery, 3 patients were excluded because of the lack of the information about lymph node metastasis. Among 344 patients who were analyzed, 89 patients belonged to the CI group and 258 patients belonged to the NCI group. To identify factors related to LNM, we compared clinical and pathological baseline characteristics. Clinical baseline characteristics including age, sex, and T1 CRC location, size, and morphology were not significantly different between the LNM-negative and LNM-positive groups. However, pathological baseline characteristics were significantly different. With regard to histologic differentiation, poor differentiation was more frequent in the LNM-positive group compared to the LNM-negative group (10.5% vs. 1.2%;  $P<0.001$ ). Additionally, LVI occurred more frequently in the LNM-positive group than the LNM-negative group (47.4% vs. 8.4%;  $P<0.001$ ). However, submucosal invasion depth  $>1000\mu\text{m}$  was not significantly

**Table 4****Univariate and multivariate analysis of factors related to lymph node metastasis in patients who underwent surgery because of submucosal invasive colorectal cancer.**

Characteristics	LNM-negative (n = 325)	LNM-positive (n = 19)	Univariate	Multivariate*	P
			P	Odds ratio (95% CI)	
Age, y (mean ± SD)	61.8 ± 10.2	66.0 ± 10.2	0.081	1.051 (0.994–1.113)	0.081
Male, n (%)	194 (59.7)	13 (68.4)	0.450	1.067 (0.329–3.464)	0.914
Location, n (%)			0.683		
Colon	185 (57.0)	9 (47.4)			
Rectum	140 (43.1)	10 (52.6)			
Size (mean ± SD), mm	21.5 ± 11.4	21.1 ± 8.8	0.880	0.987 (0.926–1.052)	0.684
Size, mm, n (%)			0.497		
<10	30 (9.2)	1 (5.3)			
10–19	107 (32.9)	3 (15.8)			
20–30	119 (36.6)	13 (68.4)			
>30	69 (21.2)	2 (10.5)			
Morphology, n (%) <sup>†</sup>			0.221		
Is	176 (54.1)	9 (47.4)			
Ip	24 (7.4)	4 (21.1)			
Ila	114 (35.1)	6 (31.6)			
Ila + IIc	11 (3.4)	0 (0.0)			
Histologic dif., n (%), (n = 323, n = 19) <sup>‡</sup>			<0.001		
G1	152 (47.1)	2 (10.5)		1	
G2	167 (51.7)	15 (78.9)		3.928 (0.826–18.691)	0.086
G3	4 (1.2)	2 (10.5)		45.945 (4.591–459.820)	0.001
LVI+, n (%), (n = 308, n = 19)	26 (8.4)	9 (47.4)	<0.001	11.654 (3.638–37.336)	<0.001
SM invasion >1000 μm	204 (62.8)	16 (84.2)	0.058		
SM invasion >1500 μm	159 (48.9)	14 (73.7)	0.036	2.156 (0.677–6.864)	0.193

Variables are expressed as mean ± SD or n (%). Histologic dif = histologic differentiation, LNM = lymph node metastasis, LVI = lymphovascular invasion, SD = standard deviation, SM = submucosa, WD = well differentiated.

\* Multivariate analysis used binomial logistic regression adjusted for age, sex, size of colorectal cancer, histologic differentiation, LVI, and SM invasion depth.

<sup>†</sup> Morphology was classified using the Paris classification.

<sup>‡</sup> G1 tumors are defined as well differentiated, G2 tumors as moderately differentiated, G3 tumors as poorly differentiated.

associated with LNM (84.2% vs. 62.8%;  $P=0.058$ ). Instead, submucosal invasion depth >1000 μm occurred significantly more frequently in the LNM-positive group compared to the LNM-negative group (73.7% vs. 48.9%,  $P=0.036$ ) (Table 4).

In our multivariate analysis, which was adjusted for age, sex, CRC size, histologic differentiation, LVI, and submucosal invasion depth, LNM was related to positivity for LVI (odds ratio [OR], 11.654; 95% confidence interval [CI], 3.638–37.336;  $P<0.001$ ) and poorly differentiated histology (OR, 45.945; 95% CI, 4.591–459.820;  $P=0.001$ ). However, submucosal invasion depth >1500 μm was not a significant

predictor of LNM (OR, 2.156; 95% CI, 0.677–6.864;  $P=0.193$ ) (Table 4).

### 3.4. The risk of LNM and recurrence rate according to the depth of submucosal invasion

There was no LNM in the patients within conventional indication. When the depth of submucosal invasion was extended up to 1500 μm, LNM was occurred (1 patient [0.5%]). In addition, when the depth of submucosal invasion was extended up to 2000 μm, LNM was increased even though recurrence rate was not increased (4 patients [1.5%]) (Table 5).

**Table 5****The risk of lymph node metastasis and recurrence rate according to the depth of submucosal invasion in the nonconventional indication.**

	Conventional indications	Nonconventional indication	
Inclusion indication			
Negative lateral/vertical margins	0	0	0
No lymphovascular invasion	0	0	0
G1 or G2 histologic dif.*	0	0	0
Submucosal invasion depth, μm	1000	1500	2000
Included patients	n = 155	n = 197	n = 271
Initial treatment modality	Endoscopy: 80 Surgery: 75	Endoscopy: 101 Surgery: 96	Endoscopy: 125 Surgery: 146
Lymph node metastasis, n (%)	0 (0.0)	1 (0.5)	4 (1.5)
Recurrence, n (%)	3 (1.9)	3 (1.5)	5 (1.8)

Histologic dif = histologic differentiation.

\* G1 tumors are defined as moderately differentiated, G2 tumors defined as moderately differentiated.

#### 4. Discussion

Advances in colonoscopy devices and techniques have made it possible to perform endoscopic resection of colorectal neoplasms, including mucosal and submucosal cancer.<sup>[24,25]</sup> We found no differences in the rate of surgical adverse events and outcomes between patients treated with initial endoscopic therapy versus patients treated with initial surgery. Therefore, clinicians have 2 options for the initial treatment of early CRC (ECC). Importantly, sequential surgery after an initial endoscopy does not increase surgical adverse events. Moreover, considering the high rate of en bloc resection and the less invasive nature of endoscopic approaches, it is reasonable to consider endoscopy as an option for T1 CRC.

In this study, LNM was found in 19 of 428 patients (4.4%), which is slightly lower than previous studies (6%–12%). Indeed, some studies have suggested that up to 16% of patients with localized submucosal invasive disease may already have LNM.<sup>[12–15,26,27]</sup> This study had a lower rate of LNM because it only included subjects with submucosal ECC that was clinical stage T1N0 disease. Lack of gross lymph node enlargement on computed tomography scans at the time of CRC diagnosis is a characteristic of T1N0 disease. Accordingly, only micrometastatic lymph node involvement was identified in this study.

Our findings that positive LVI and poorly differentiated histology were associated with LNM are consistent with previous studies of factors related to LNM. However, submucosal invasion depth was not statistically significantly related to LNM. This result could indicate that submucosal invasion depth is not the most effective predictor of LNM in patients with submucosal ECC that is clinical stage T1N0 disease. Among the 19 patients with LNM, 1 patient had a submucosal invasion depth of only 100  $\mu\text{m}$ . In contrast, 15 of the 144 ET-NCI group patients (10.4%) could not undergo sequential operations because of patient refusal or poor medical condition, and there were no patients with CRC recurrence during the follow-up period. Among these 15 patients, no patients had tumors with poorly differentiated histology, 1 patient was LVI-positive, and the other 14 had submucosal invasion depths  $>1000\mu\text{m}$  in pathology analysis. Supporting these results, a few studies have indicated that additional surgery and lymph node dissection are not absolutely required for endoscopically resected pT1b CRC (submucosal invasion depth  $\geq 1000\mu\text{m}$ ) in cases where vascular invasion, poorly differentiated adenocarcinoma, signet ring cell carcinoma, mucinous carcinoma, and grade 2/3 budding at the deepest part of the submucosal invasion are not detected, as these tumors have a very low rate of LNM (1%–2%).<sup>[28,29]</sup> However, the rate of LNM in these studies was not zero.

Considering these findings, we can see that the present CIs are not perfect when it comes to selecting the initial treatment for T1 CRC. Hopefully, in the near future, novel imaging technologies (e.g., confocal endomicroscopy) coupled with increased pathological recognition of high-risk markers for LNM will lead to improved staging and clinical care. For example, expert pathologists recently emphasized that tumor budding is an independent prognostic indicator for risk of lymph node involvement, especially in early stage CRC.<sup>[30]</sup> The description of tumor budding is attributed to Imai, who first postulated that this particular pathological feature of invasive colon cancer represented a sudden or rapid growth of the leading or invasive edge of the carcinoma and is partially related to interactions between epithelial and mesenchymal elements at the tumor margin.<sup>[30]</sup> Accumulated evidence indicates that tumor budding

as well as high tumor grade and LVI are independent risk factors for LNM in patients with submucosally invasive colon cancer.<sup>[31,32]</sup>

The strength of this study is that it is the first analysis to specifically examine patients with submucosal ECC that was initially clinical stage T1N0 disease to evaluate outcomes of endoscopic treatment versus surgery and to determine the optimal indications for endoscopic treatment. Additionally, the mean follow-up period was  $>3.5$  years, which is long enough to evaluate long-term prognosis.

A limitation of this study is its retrospective nature. Insufficient record-keeping could give rise to inaccurate information about medications. Therefore, a prospective study that includes a large number of patients is needed to evaluate the outcomes of endoscopic treatment and to determine the optimal indications for endoscopic treatment in T1 CRC patients.

In conclusion, T1 CRC patients treated by endoscopic resection, surgical resection, or both, depending on the CIs, had good long-term clinical outcomes. However, it might not be safe to extend the present CIs for endoscopic therapy in T1 CRC. For patients with T1 CRC lesions that do not satisfy the CIs, we strongly recommend adequate surgical resection with lymph node dissection.

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