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ORIGINAL ARTICLE

Long-term prognosis after treatment for T1 carcinoma of laterally spreading tumors: a multicenter retrospective study

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Abstract

Purpose Long-term prognosis of T1 laterally spreading tumors (LSTs) after treatment have not been clarified. This study compared clinicopathological characteristics and long-term prognosis of T1 LSTs.

Methods We retrospectively assessed 169 patients with 169 T1 LSTs between January 1992 and December 2008 by ten hospitals. Patients who did not meet the Japanese Society for Cancer of the Colon and Rectum (JSCCR) 2016 guidelines for the treatment of colorectal carcinoma (CRC) criteria were defined as non-endoscopically curable. The number of non-endoscopically curable patients with LST-granular/ nodular mixed (LST-G-M) was 61, that with LST-non-granular/ flat elevated (LST-NG-FE) was 23, and that with LST-non-granular/ pseudo depressed (LST-NG-PD) was 23. Clinicopathological variables and long-term prognosis were analyzed.

Results For overall patients, tumor size, number of non-endoscopically curable cases, and rate of submucosal invasion depth ≥ 1000 μm for the LST-G-M group were significantly higher than those in the other groups. For non-endoscopically curable patients, the tumor size for those with LST-G-M was significantly larger than those in the other groups. The rate of submucosal invasion width ≥ 4000 μm and type B/C muscularis mucosae with LST-G-M was higher than that with LST-NG-FE. All recurrences occurred in non-endoscopically curable patients with LST-G-M. Five-year overall and disease-free survivals for non-endoscopically curable patients with LST-G-M were significantly shorter than those for patients with non-endoscopically curable LST-NG-FE and PD.

Conclusions Our data supported adequacy of the JSCCR guidelines for the treatment of CRC criteria for endoscopically curable patients after T1 LSTs treatment. Patients with T1 LST-G-M should be followed up more carefully.

Keywords Laterally spreading tumor · T1 colorectal carcinoma · Treatment · Recurrence · Prognosis

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Introduction

A laterally spreading tumor (LST) is a colorectal tumor defined by a characteristic laterally spreading growth pattern ≥ 10 mm in diameter [1]. Moreover, LSTs are divided into four subtypes based on surface morphology: LST-granular/ homogeneous, LST-G-H; nodular mixed, LST-G-M; LST-non-granular/ flat elevated, LST-NG-FE; and pseudo depressed, LST-NG-PD [1, 2]. Recognition of LSTs was established by several reports concerning their clinicopathological features; therefore, the concept of LSTs has been accepted not only in Japan but also in Western countries [2]. It is clinically significant that each subclassification type of LST has different clinicopathological features [3–14]. The rates of submucosal invasion in LST-G-H, LST-G-M, LST-NG-FE, and LST-NG-PD were 0–9%, 5–16%, 0–8%, and 12–57%, respectively [3–5, 7–13].

Westernization in Japan has increased the occurrence of colorectal carcinoma (CRC) [9]; therefore, physicians are performing increasing numbers of colonoscopy procedures for patients with CRC [15]. Endoscopic submucosal dissection (ESD), which is a histologically complete en bloc resection, is also the standard treatment for early CRC [16, 17]. According to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) 2016 guidelines [18], endoscopically resected T1 CRC with positive vertical tumor margins, unfavorable histology, submucosal invasion depth ≥ 1000 μm, positive vessel invasion, and budding grade 2/3 should be considered for additional surgery with lymph node dissection.

Several studies of the prognosis of T1 CRC after treatment have been reported [19–24]; however, the prognosis of T1 LST has not been clarified. The aim of this study was to analyze the long-term prognosis of patients with T1 LST after treatment, including surgical resection alone. The following prognoses were analyzed: recurrence, 5-year overall survival, 5-year disease-free survival and 5-year disease-specific survival. We evaluated the pathological characteristics of T1 CRC according to the JSCCR 2016 guidelines [18].

Methods

Patients

At first, we retrospectively selected 970 consecutive patients with T1 CRC who underwent endoscopic resection (ER) alone, additional surgery after ER, or surgical resection alone between January 1992 and December 2008 by the Hiroshima Gastrointestinal Endoscopy Research Group (Hiroshima University Hospital and nine affiliated hospitals). A total of 801 patients were excluded for the following reasons: previous or synchronous advanced CRC, no follow-up period of at least 5 years, non-LSTs, and endoscopic piecemeal resection. The reason for excluding endoscopic piecemeal resection was that the significant factor associated with local recurrence for large colorectal neoplasia resected by ER [25], and accurate histological assessment was impossible for cases with piecemeal resection. Finally, 169 patients with T1 LST entered this study (Fig. 1). Patients with T1 CRC after en bloc ER who met the curative criteria of the JSCCR 2016 guidelines [18] were defined as endoscopically curable (e-curable) patients. However, those who did not meet the curative criteria were defined as non-endoscopically curable (non-e-curable) patients.

LSTs were defined as a lesion ≥ 10 mm in diameter that extended laterally rather than vertically along the colorectal wall. LSTs were divided into two subtypes based on their surface morphology: LST-G, which has even or uneven nodules on the surface, and LST-NG, which has a smooth surface. Furthermore, each type was divided into two subtypes: LST-G included LST-G-H and LST-G-M subtypes, and LST-NG included LST-NG-FE and LST-NG-PD subtypes [1, 2]. In this study, no patients were diagnosed with T1 LST-G-H. LSTs' classification was reevaluated at the University Hospital regardless of previous each institution's diagnosis.

The use of patient data for the purpose of this study was approved by the Institutional Review Board of Hiroshima University (no. 937). This study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments.

Indications of ER procedure

ER consists of polypectomy, endoscopic mucosal resection, and ESD. Indications for ER for CRC followed the latest JSCCR 2016 guidelines [18]. A low possibility of lymph node metastasis and the size and location of the tumor make en bloc resection possible. Indications for ER were as follows: intramucosal carcinoma or carcinoma with slight submucosal invasion; any size; and any macroscopic type.

Indications for additional surgery after ER

In the JSCCR 2016 guidelines [18], additional surgery after ER of pT1 was performed if surgical resection was preferable because the vertical margin was positive. If any of the following findings was observed during histological examination of the resected specimen, then intestinal resection with lymph node dissection was considered as an additional treatment: submucosal invasion depth ≥ 1000 μm; positive vascular invasion; poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma; and grade 2/3 budding at the site of the deepest invasion. In actual clinical practice, the patient's status (age, comorbidity, performance status, risk for surgery, quality of life after surgery, etc.) and wishes are also considered before finally deciding whether to perform additional surgery.

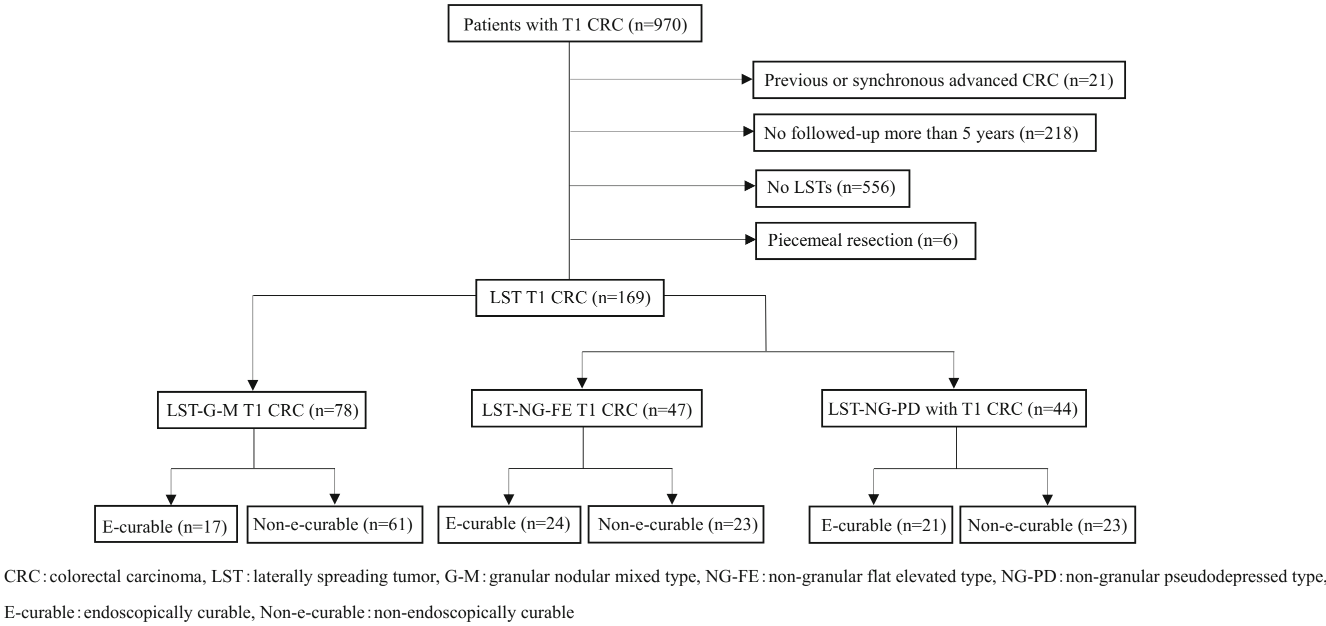


Fig. 1 Patient enrollment in this study. CRC, colorectal carcinoma; LST, laterally spreading tumor; G-M, granular nodular mixed type; NG-FE, non-granular flat elevated type; NG-PD, non-granular pseudodepressed type; E-curable, endoscopically curable; Non-e-curable, non-endoscopically curable

Histological examination

According to the JSCCR 2016 guidelines [18], the histologic diagnosis (histologic type, submucosal invasion depth, budding grade, vascular invasion) of CRC was performed after treatment. Budding grade was diagnosed using hematoxylin and eosin (HE) staining for all cases. In principle, vascular invasion was diagnosed using HE. However, if immunostaining (Victoria blue, Elastica van Gieson, D2-40) was performed at each of the institutions, then the results were consulted for the diagnosis. Moreover, submucosal invasion width, type of muscularis mucosae, type of deepest invasive tumor margin, and poorly differentiated cluster (PDC) grade were diagnosed during this study. Cases were classified into three groups according to the muscularis mucosae condition: type A, clearly identified; type B, incompletely disrupted with deformity; or type C, completely disrupted [26]. The submucosal invasion width was defined as the longest horizontal measurement of the submucosal invasive area [27]. In muscularis mucosae types B and C, the submucosal invasion width was defined as the length from both ends of muscularis mucosae incompletely disrupted with deformity or completely disrupted. Histologic subclassification was determined by the deepest invasive tumor margin and classified as well differentiated, moderately differentiated, or poorly differentiated. By assessing glandular configurations and cellular arrangements, the moderately differentiated type was further subdivided into the moderately well-differentiated group and moderately poorly differentiated group [28, 29]. PDC was defined as cancer cell clusters of ≥ 5 carcinoma cells that are lacking a glandular formation at the beginning of the invasion, and PDC was graded per microscopic field at × 200 magnification (grade 1, 0–4 PDCs; grade 2, 5–9 PDCs; grade 3, ≥ 10 PDCs). When evaluating the mucinous adenocarcinoma, cancer cell clusters within a large mucin pool were not classified as PDC; however, cancer cell clusters infiltrating the stroma with minimal extracellular mucin formation were classified as PDC [30]. Expert gastrointestinal pathologists (F.S. or K.K.) reevaluated all pathologic specimens regardless of the previous diagnosis that had been made at each of the institutions for all cases.

Surveillance schedule after treatment

Interviews, examinations, blood tests (including tumor markers), and chest and abdominal computed tomography (CT) were performed every 6 months postoperatively for 3 years; thereafter, they were performed every 12 months for 2 years. An annual colonoscopy was performed postoperatively for more than 5 years regardless of treatment. Recurrence was confirmed by endoscopy and/or other diagnostic imaging. Biopsy was performed as necessary. Local recurrence was defined as lesion or mass detected at the site of the resected CRC. When rectal CRC underwent surgery, recurrence within the pelvis was defined as local recurrence. A follow-up examination period of at least 5 years was set to detect recurrence after treatment. Patients who did not visit the hospital for a scheduled appointment were interviewed by telephone or letter and encouraged to visit.

Investigated variables

The following clinicopathological variables were investigated for each group: age, sex, tumor location, tumor size, treatment type, non-e-curable status, metastasis/recurrence, histology type, submucosal invasion depth, vertical positive margin, positive lymphatic invasion, positive venous invasion, budding grade 2/3, and lymph node metastasis. We compared these variables among the three groups of enrolled patients. For non-e-curable patients, we also compared submucosal invasion width, muscularis mucosae type, deepest invasive tumor margin type, and PDC grade 2/3. Long-term prognosis for each non-e-curable group was analyzed. The recurrence rate, 5-year overall survival, 5-year disease-free survival, and 5-year disease-specific survival rates were assessed. Overall survival was defined as the time from the date of initial treatment to the day of death from any cause. Disease-free survival was defined as the time from the date of initial treatment to the date of identification of local and/or distant recurrence. Disease-specific survival was defined as the time from the date of initial treatment to the day of death from CRC.

Statistical analysis

Quantitative data are shown as mean ± standard deviation or percentage. Differences in continuous values were analyzed by the chi-square test with the Yates correction or by the Fisher's exact test. A p value < 0.05 was considered significant. When comparing the three groups, the Bonferroni method was used. JMP statistical software version 12.2.0 (SAS Institute, Cary, NC) was used for all statistical analyses. The overall survival, disease-free survival, and disease-specific survival rates were calculated using the Kaplan-Meier method.

Results

Clinicopathological characteristics of T1 LSTs

T1 LSTs were divided into three groups: LST-G-M (e-curable, 17 patients; non-e-curable, 61 patients), LST-NG-FE (e-curable, 24 patients; non-e-curable, 23 patients), and LST-NG-PD (e-curable, 21 patients; non-e-curable, 23 patients) (Fig. 1). The clinicopathological characteristics of the enrolled patients are shown in Table 1. There were no significant differences among LST-G-M, LST-NG-FE, and LST-NG-PD in terms of age, sex, location, or treatment (ER or ER and surgery vs. surgery) distributions. The rate of non-e-curable patients was 78.2% (61/78) for LST-G-M, which was significantly higher than 48.9% (23/47) for LST-NG-FE and 52.3% (23/44) for LST-NG-PD ($p < 0.01$). The mean tumor size for the LST-G-M group (mean ± standard deviation [SD]: 35.1 ± 20.9 mm) was significantly larger than that for LST-NG-FE (mean ± SD: 22.2 ± 10.0 mm) and LST-NG-PD (mean ± SD: 22.9 ± 7.5 mm) ($p < 0.01$). The rate of submucosal invasion depth ≥ 1000 μm was 70.5% (55/78) for LST-G-M, which was significantly higher than 42.6% (20/47) for LST-NG-FE and 45.5% (20/44) for LST-NG-PD ($p < 0.01$). The positive vertical margin rates were 23.8% (10/42) for LST-G-M, 14.8% (4/27) for LST-NG-FE, and 0% (0/17) for LST-NG-PD; all these patients underwent surgery after ER. The budding grade 2/3 rate was 29.5% (23/78) for LST-G-M, which was higher than 11.4% (5/44) for LST-NG-PD ($p = 0.0255$). The rates of lymph node metastasis were 8.8% (5/57) for LST-G-M, 10.3% (3/29) for LST-NG-FE, and 3.5% (1/29) for LST-NG-PD. The clinicopathological characteristics of non-e-curable patients are shown in Table 2. The treatment rate (surgery alone) for LST-NG-PD was significantly higher than the rates for LST-G-M and LST-NG-FE ($p < 0.01$). The mean tumor size for LST-G-M (mean ± SD: 36.6 ± 22.6 mm) was significantly larger than that for LST-NG-FE (mean ± SD: 21.6 ± 7.2 mm) and LST-NG-PD (mean ± SD: 24.6 ± 7.6 mm) ($p < 0.01$). Although there was no significant difference among LST-G-M, LST-NG-FE, and LST-NG-PD in terms of the mean submucosal invasion width, the frequency of submucosal invasion width ≥ 4000 μm for LST-G-M was significantly higher than that for LST-NG-FE ($p < 0.01$). The rate of type B/C muscularis mucosae for LST-G-M was higher than that for LST-NG-FE ($p = 0.0228$), and the rate of moderately poorly differentiated/poorly differentiated at the deepest invasive tumor margin for LST-G-M was higher than that for LST-NG-PD ($p = 0.0429$). There was no significant difference in the rate of PDC grade 2/3 among the three groups. Five recurrences were found (local and distant recurrence, one patient; distant recurrence, four patients), and all of them occurred in non-e-curable LST-G-M patients.

Recurrence after treatment

There was no recurrence among the e-curable patients in the three groups, but five recurrences were found in non-e-curable patients with LST-G-M. In the non-e-curable patients, the recurrence rate in ER, ER and surgery, and surgery groups were 9.1% (2/22), 6.9% (2/29), and 1.8% (1/56), respectively. There was no significant difference in the recurrence rate among the three treatment groups. The details of the cases of recurrence are shown in Table 3. All patients had positive vessel invasion and/or a high budding grade. Two patients were treated with ER alone, two with additional surgery after ER, and one with surgery alone. There was no lymph node metastasis among three recurrent patients who underwent surgery. One patient had local recurrence and lung metastasis, and the other four had distant metastasis (bone, lung, or liver). All recurrences were found within 5 years after treatment. Three patients died of primary carcinoma. Among the non-e-curable patients with LST-G-M, 5-year overall survival, 5-year disease-free survival, and 5-year disease-specific survival rates were 91.3%, 90.5%, and 100%, respectively. Similarly, among the non-e-curable patients with LST-NG (LST-NG-FE + LST-NG-PD), 5-year overall survival, 5-year disease-free survival,

Table 1 Clinicopathological characteristics of enrolled patients (n=169)

Variables	LST-G-M[a], n=78	LST-NG		*P*-value
		FE[b], n=47	PD[c], n=44	
Age (years old, mean±SD)	66.9±10.4	65.8±9.5	66.7±11.3	0.8453
Sex				0.7003
Male	44 (56.4)	29 (61.7)	28 (63.6)	
Female	34 (43.6)	18 (38.3)	16 (36.4)	
Location				0.1750
Colon	54 (69.2)	39 (83.0)	35 (79.6)	
Rectum	24 (30.8)	8 (17.0)	9 (20.4)	
Tumor size (mm)				a vs. b*, a vs. c*
Mean±SD	35.1±20.9	22.2±10.0	22.9±7.5	
Median (range)	30 (10-120)	20 (10-60)	20 (10-40)	
Treatment				0.1553
ER	21 (27.0)	18 (38.3)	15 (34.0)	
ER and Surgery	21 (27.0)	9 (19.2)	2 (4.6)	
Surgery	36 (46.0)	20 (42.5)	27 (61.4)	
Non-e-curable	61 (78.2)	23 (48.9)	23 (52.3)	a vs. b*, a vs. c*
Metastasis/ Recurrence				0.0495
Local	1 (1.3)	0 (0)	0 (0)	
Distant	5 (6.4)	0 (0)	0 (0)	
Histology				0.5561
tub/ pap	78 (100)	47 (100)	44 (100)	
por/ sig/ muc	0 (0)	0 (0)	0 (0)	
SM depth (μm)				a vs. b*, a vs. c*
<1000	23 (29.5)	27 (57.4)	24 (54.5)	
≧1000	55 (70.5)	20 (42.6)	20 (45.5)	
Vertical margin positive	10 /42 (23.8)	4 /27 (14.8)	0 /17 (0)	a vs. c (p=0.0494)
Lymphatic invasion positive	25 (32.1)	6 (12.8)	12 (27.3)	a vs. b (p=0.0562)
Venous invasion positive	12 (15.4)	6 (12.8)	7 (15.9)	0.8966
Budding grade 2/3	23 (29.5)	9 (19.2)	5 (11.4)	a vs. c (p=0.0255)
Lymph node metastasis	5 /57 (8.8)	3 /29 (10.3)	1 /29 (3.5)	0.5780

LST, laterally spreading tumor; *G-M*, granular nodular mixed type; *NG*, non-granular; *FE*, flat elevated type; *PD*, pseudodepressed type; *SD*, standard deviation; *ER*, endoscopic resection; *Non-e-curable*, non-endoscopically curable; *tub*, tubular adenocarcinoma; *pap*, papillary adenocarcinoma; *por*, poorly differentiated adenocarcinoma; *sig*, signet-ring cell carcinoma; *muc*, mucinous adenocarcinoma; *SM*, submucosal invasion

*: p<0.01 (%)

and 5-year disease-specific survival rates were 95.5%, 100%, and 100%, respectively (Fig. 2). Overall and disease-free survivals for the non-e-curable patients with LST-G-M were significantly shorter than those for the non-e-curable LST-NG patients ($p < 0.05$).

Discussion

This is the retrospective, multicenter cohort study that evaluated the long-term prognosis of patients with T1 LST after treatment. Long-term prognosis of e-curable patients with T1 LST were satisfactory; however, a few recurrences in non-e-curable patients with T1 LST-G-M occurred. There have been several studies of the risk of LST with invasive carcinoma [3–12, 14, 25, 31–34]. We [3] reported that the frequency of submucosal invasion in LST lesions increases with size, that the frequencies of submucosal invasion in the LST-G-M (13.3%) and LST-NG-PD groups (42.1%) were significantly higher than those of the other types of LST, and that the frequency of submucosal invasion of LST-G-H was extremely low (0.9%) regardless of size. Uraoka et al. [32] reported that submucosal penetration determined histopathologically occurred under the largest nodules (84%; 16/19) and depressed areas (16%; 3/19) in 19 LST-G type with submucosal invasion. Deepest submucosal penetration in 32 LST-NG

Table 2 Clinicopathological characteristics of non-e-curable patients (n=107)

Variables	LST-G-M[a], n=61	LST-NG		*P*-value
		FE[b], n=23	PD[c], n=23	
Age (years old, mean±SD)	67.3±9.8	65.9±10.8	64.9±10.2	0.4325
Sex				0.4859
Male	30 (49.2)	12 (52.2)	15 (65.2)	
Female	31 (50.8)	11 (47.8)	8 (34.8)	
Location				0.5573
Colon	42 (68.9)	18 (78.3)	15 (65.2)	
Rectum	19 (31.1)	5 (21.7)	8 (34.8)	
Tumor size (mm)				a vs. b*, a vs. c*
Mean±SD	36.6±22.6	21.6±7.2	24.6±7.6	
Median (range)	30 (10-120)	20 (10-35)	30 (10-40)	
Treatment				b vs. c*, a vs. c*
ER	12 (19.7)	8 (34.8)	2 (8.7)	
ER and Surgery	21 (34.4)	6 (26.1)	2 (8.7)	
Surgery	28 (45.9)	9 (39.1)	19 (82.6)	
Metastasis/ Recurrence				0.1384
Local	1 (1.6)	0 (0)	0 (0)	
Distant	5 (8.2)	0 (0)	0 (0)	
Histology				-
tub/ pap	61 (100)	23 (100)	23 (100)	
por/ sig/ muc	0 (0)	0 (0)	0 (0)	
SM depth (μm)				0.8733
<1000	6 (9.8)	3 (13.0)	3 (13.0)	
≧1000	55 (90.2)	20 (87.0)	20 (87.0)	
Vertical margin positive	9 /33 (27.3)	3 /14 (21.4)	0 /4 (0)	0.4672
Lymphatic invasion positive	25 (41.0)	6 (26.1)	12 (52.2)	0.1860
Venous invasion positive	12 (19.7)	6 (26.1)	7 (30.4)	0.5483
Budding grade 2/3	23 (37.7)	9 (39.1)	5 (21.7)	0.3413
Lymph node metastasis	5 /49 (10.2)	3 /15 (20.0)	1 /21 (4.8)	0.2960
SM width (μm)				
Mean±SD	4412±581	3057±377	4119±488	0.3294
<4000	27 (44.3)	18 (78.3)	11 (47.8)	a vs. b*
≧4000	34 (55.7)	5 (21.7)	12 (52.2)	
Muscularis mucosae				a vs. b (*p*=0.0228)
Type A	7 (10.9)	8 (42.1)	4 (17.4)	
Type B/ C	54 (81.1)	15 (57.9)	19 (82.6)	
Deepest invasive tumor margin				a vs. c (*p*=0.0429)
W/ Mw	22 (36.1)	13 (56.5)	15 (65.2)	
Mp/ Por	32 (52.5)	9 (39.1)	7 (30.4)	
PDC grade 2/3	17 (27.9)	3 (13.0)	6 (24.3)	0.3594

LST, laterally spreading tumor; *G-M*, granular nodular mixed type; *NG*, non-granular; *FE*, flat elevated type; *PD*, pseudodepressed type; *SD*, standard deviation; *ER*, endoscopic resection; *Non-e-curable*, non-endoscopically curable; *tub*, tubular adenocarcinoma; *pap*, papillary adenocarcinoma; *por*, poorly differentiated adenocarcinoma; *sig*, signet-ring cell carcinoma; *muc*, mucinous adenocarcinoma; *SM*, submucosal invasion; *W*, well differentiated adenocarcinoma; *Mw*, moderately-well adenocarcinoma; *Mp*, moderately-poorly adenocarcinoma; *PDC*, poorly differentiated cluster

*: $p<0.01$ (%)

type was either under depressed areas (72%; 23/32) or lymph follicular or multifocal submucosal invasion (28%; 1/32 and 8/32, respectively). Yamada et al. [14] reported that the risk factors for deep submucosal invasion of LST-G according to

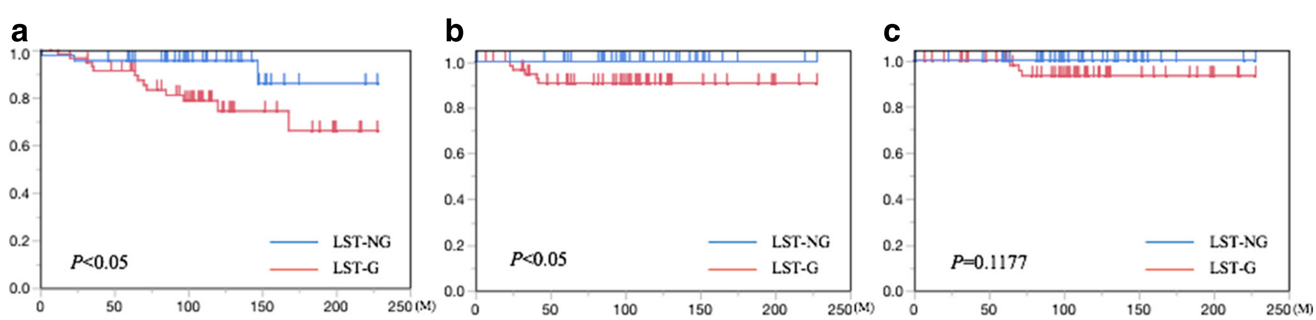
Table 3 Cases with recurrence after treatment for LST

Case	Age (years)	Sex	Location	Size (mm)	Growth type	SM depth (μm)	Ly/V	Histology	Budding grade	Treatment method	Recurrence	Interval of recurrence (month)	Prognosis
1	68	M	S	20	LST-G-M	250	+/+	Mod	1	EMR	L/ D	33	Alive
2	46	F	RS	50	LST-G-M	1800	−/−	Well	3	ESD	D	41	SD
3	62	M	RS	40	LST-G-M	2500	−/+	Mod	1	EMR→ Surgery	D	25	Alive
4	67	M	Rb	30	LST-G-M	2900	+/−	Well	2	EMR→ Surgery	D	4	SD
5	63	M	Ra	40	LST-G-M	1200	+/+	Well	1	Surgery	D	23	SD

S, sigmoid colon; *R*, rectum; *Rb*, rectum below the peritoneal reflection; *Ra*, rectum above the peritoneal reflection; *LST*, laterally spreading tumor; *G-M*, granular nodular mixed type; *SM*, submucosal invasion; *Ly*, lymphatic invasion; *V*, venous invasion; *Mod*, moderately differentiated tubular adenocarcinoma; *Well*, well differentiated tubular adenocarcinoma; *EMR*, endoscopic mucosal resection; *ESD*, endoscopic submucosal dissection; *L*, local recurrence; *D*, distant recurrence; *SD*, specific death

the multivariate analysis were the presence of a large nodule, depression, and invasive pit pattern; however, deep submucosal invasion of LST-NG according to the multivariate analysis was indicated by the presence of submucosal mass-like elevation, depression, and invasive pit pattern. Burgess et al. [33] reported that rectosigmoid 0-Is and 0-IIa + Is non-granular lesions present a high risk of malignancy, whereas proximally located 0-Is or 0-IIa granular lesions present a low risk. Each LST subtype had its own clinicopathological characteristics and corresponding treatment (ER or surgery). Furthermore, it was necessary to examine the pathology of the resected tissue in detail, decide on additional treatment according to the case, and determine the surveillance interval. This study showed that LST-NG-PD had the lowest rates in the positive vertical margin (0%, 0/17), in the budding grade 2/3 (11.4%, 5/44), and in the lymph node metastasis (3.5%, 1/29) among three subtypes of LST; however, the treatment rate (surgery alone) for LST-NG-PD was the highest among three subtypes of LST. Since cases in the early 1990s (before the introduction of ESD) were also included in this study, there was a possibility that surgery was selected as initial treatment in LST-NG-PD which looked like 0-IIa + IIc. There have been some studies of recurrence for LST. We [16] reported that long-term outcomes after ESD for 224 superficial colorectal tumors (LST-G, LST-NG, polypoid) and the local recurrence rate (1.5%) were significantly higher for patients who underwent piecemeal resection (9.1%) compared with en bloc resection (0.6%). Two of three recurrences were LST-G with piecemeal resection. We [25] also reported that significant factors associated with local recurrence for large colorectal neoplasia resected by ER were piecemeal resection, LST-G, tumor size ≥ 40 mm, no pretreatment magnification, ≤ 10 years of experience with conventional ER, and piecemeal resection only for ESD. Cong et al. [13] reported no significance for prognoses among LST subgroups (LST-G, 124 patients; LST-NG, 53 patients) with 44.4 ± 16.3 months of follow-up. These studies included not only CRC but also adenoma (mostly adenoma), but these were not recurrences that only involved carcinoma.

In the present study, all recurrences were LST-G-M; therefore, we analyzed whether there were pathological differences between LST-G-M and other subtypes. The incidence of submucosal invasion width ≥ 4000 μm (Ueno et al. [27] suggested that a submucosal invasion width ≥ 4000 μm could increase the probability of lymph node metastasis; therefore, we followed this suggestion) and the rate of type B/C muscularis mucosae for LST-G-M and LST-NG-PD was higher than that for LST-NG-



Non-e-curable: non-endoscopically curable, LST: laterally spreading tumor, NG: non-granular, G: granular

Fig. 2 Kaplan-Meier curves for **a** overall survival, **b** disease-free survival, and **c** disease-specific survival rates in the non-e-curable patients (n = 107). Key: blue line, LST-NG; red line, LST-G

FE, thus indicating that LST-G-M and LST-NG-PD extensively infiltrated the submucosal layer horizontally rather than vertically. Toh et al. [35] reported that the width and area of submucosal invasion are potential predictors of lymph node metastasis and are superior to the depth of invasion for making predictions. Smith et al. [36] reported that deep mucosal lymphatic vessels were significantly smaller than submucosal vessels. The submucosal layer was divided into three (sm1, sm2, and sm3) parts, and there were significantly more lymphatic vessels within sm1 than sm3. These studies suggested that the submucosal invasion width measurements, submucosal invasion area, and volume of the submucosal invasion area [37] might be more important for evaluating the risk of lymph node metastasis. Moreover, there was no statistical difference in the rate of moderately poorly differentiated/poorly differentiated status at the deepest invasive tumor margin for LST-G-M, which was higher than that for LST-NG-PD. The concept of the moderately poorly differentiated/poorly differentiated status at the deepest invasive tumor margin was inclusive of budding and PDC. Therefore, LST-G-M did not include high-grade budding and high-grade PDC; LST-G-M might have more lesions containing a small amount of poorly differentiated component (combination of low-grade budding and low-grade PDC) at the deepest invasive tumor margin than LST-NG-PD. Moreover, compared with LST-NG, which is a flat lesion, LST-G-M has a protuberance, and there was a possibility that accurate pathological cutting had not been performed. Therefore, the fact that the frequency of moderately poorly differentiated/poorly differentiated status at the deepest invasive tumor margin for LST-G-M was high meant that there might have been underestimation of budding and PDC for LST-G-M. We also reported that protruding gross type, lymphatic invasion, and high budding grade were significant predictors of recurrence after treatment for T1 CRC according to the multivariate analysis [20]. The sufficient study of relationship between growth type and recurrence has not yet been conducted; therefore, further studies are needed for clarification. The rate of T1 CRC recurrence was low (total, 2.3–4.9%; pathological low-risk, 0–1.1%; pathological high-risk, 3.3–25%) [19–23, 27, 38] but the risk varied [20–23, 38]. Kobayashi et al. [38] reported that the recurrence rate for patients with rectum T1 carcinoma resected by surgery and with lymph node metastasis was 25.0%, which was significantly higher than that without lymph node metastasis (1.1%). Lymph node metastasis and histological grade were independent risk factors for recurrence after curative resection for T1 CRC. Ikematsu et al. [22] reported that the risk for local recurrence was significantly higher for high-risk patients with submucosal rectal carcinoma than for patients with submucosal colon carcinoma when treated with ER alone. Therefore, the addition of surgery was recommended for patients with submucosal rectal carcinoma with pathologic features indicating a high risk of tumor progression. Our study showed that T1 LST-G-M is a risk factor for recurrence. Yoshii et al. [21] reported that patients with only deep submucosal invasion had a low cumulative risk of recurrence, even without surgery (2.3% for the ER plus surgery group and 3.4% for the ER-only groups; no significant difference). In contrast, patients with indications for surgery other than deep submucosal invasion had much better outcomes when they also underwent surgery. Yoda et al. [23] reported that among patients with low-risk pathological features (negative vertical margin, well or moderately differentiated adenocarcinoma, absence of lymphovascular invasion, and invasion depth < 1000 μm) treated by ER alone, the recurrence rate was 0.8%. In contrast, among the patients with high-risk pathological features (without low-risk pathological features), those who underwent additional surgery had a recurrence rate of 3.6%; however, for those who underwent ER alone, the recurrence rate was 6.6% ($p < 0.05$). The results of these studies agreed that ER alone was adequate for the management of T1 CRC patients with low-risk pathological factors. However, for T1 CRC patients with high-risk pathological factors, it may be necessary to suggest a strict surveillance program after treatment. Therefore, ESD as total excisional biopsy for clinical T1 CRC will become increasingly important [37]. It should be noted that recurrence occurred in some cases after curative surgical resection with lymph node dissection, even if it was the initial treatment (2.3–4.3%) [19, 20, 24, 38]. Our study showed that three of five recurrences were treated by surgical resection with lymph node dissection alone. Adjuvant chemotherapy or chemoradiotherapy might be necessary for patients with T1 LST-G-M. Four of five recurrences occurred within 3 years, but one recurrence occurred 41 months later. Interviews, examinations, blood tests (including tumor markers), and chest and abdominal CT might be performed every 6 months postoperatively for 5 years for those with LST-G-M.

Limitations of the present study were its retrospective nature and relatively low statistical power due to the small number of patients. A prospective study with a large number of cases should be conducted in the future. Next, this study might have been affected by selection bias because the indication for treatment of T1 CRC has been changing with the successive guidelines; therefore, a randomized study should be conducted.

In conclusion, this study supported the adequacy of the JSCCR 2016 guidelines for the treatment of CRC criteria for e-curable patients with T1 LSTs. However, non-e-curable patients with T1 LST-G-M should be followed up more carefully compared to those with T1 LST-NG.

Compliance with ethical standards

This study was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Kudo S (1993) Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. Endoscopy 25:455–461
2. Kudo S, Lambert R, Allen JI, Fujii H, Fujii T, Kashida H, Matsuda T, Mori M, Saito H, Shimoda T, Tanaka S, Watanabe H, Sung JJ, Feld AD, Inadomi JM, O'Brien MJ, Lieberman DA, Ransohoff DF, Soetikno RM, Triadafilopoulos G, Zauber A, Teixeira CR, Rey JF, Jaramillo E, Rubio CA, Van Gossum A, Jung M, Vieth M, Jass JR, Hurlstone PD (2008) Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc 68:S3–S47
3. Oka S, Tanaka S, Kanao H, Oba S, Chayama K (2009) Therapeutic strategy for colorectal laterally spreading tumor. Dig Endosc 21: S43–S46
4. Xu MD, Wang XY, Li QL, Zhou PH, Zhang YQ, Zhong YS, Chen WF, Ma LL, Qin WZ, Hu JW, Yao LQ (2013) Colorectal lateral spreading tumor subtypes: clinicopathology and outcome of endoscopic submucosal dissection. Int J Color Dis 28:63–72
5. Saito Y, Fujii T, Kondo H, Mukai H, Yokota T, Kozu T, Kozu T, Saito D (2001) Endoscopic treatment for laterally spreading tumors in the colon. Endoscopy 33:682–686
6. Shigita K, Oka S, Tanaka S, Sumimoto K, Hirano D, Tamaru Y, Tamaru Y, Ninomiya Y, Asayama N, Hayashi N, Nagata S, Arihiro K, Chayama K (2016) Clinical significance and validity of the subclassification for colorectal laterally spreading tumor granular type. J Gastroenterol Hepatol 31:973–979
7. Nishiyama H, Isomoto H, Yamaguchi N, Ishii H, Fukuda E, Machida H, Machida H, Nakamura T, Ohnita K, Shikuwa S, Kohno S, Nakao K (2010) Endoscopic submucosal dissection for laterally spreading tumors of the colorectum in 200 consecutive cases. Surg Endosc 24:2881–2887
8. Kim BC, Chang HJ, Han KS, Sohn DK, Hong CW, Park JW, Park JW, Park SC, Choi HS, Oh JH (2011) Clinicopathological difference of laterally spreading tumors of the colorectum according to gross appearance. Endoscopy 43:100–107
9. Rotondao G, Bianco MA, Buffoli F, Gizzi G, Tessari F, Cipolletta L (2011) The Cooperative Italian FLIN Study Group: prevalence and clinico-pathological features of colorectal laterally spreading tumors. Endoscopy 43:856–861
10. Lee YJ, Kim ES, Park KS, Cho KB, Lee MY, Kim SK, Kim SK, Jeon SW, Jung MK, Jang BI, Kim KO, Lee SH, Kim EY, Kwon JG, Jung JT, Yang CH, Kim WJ, Kim HJ, Seo HE (2014) Inter-observer agreement in the endoscopic classification of colorectal laterally spreading tumors: a multicenter study between experts and trainees. Dig Dis Sci 59:2550–2556
11. Zhao X, Zhan Q, Xiang L, Wang Y, Wang X, Li A, Liu S (2014) Clinicopathological characteristics of laterally spreading colorectal tumor. PLoS One 9:e94552
12. Myung DS, Kweon SS, Lee J, Shin IS, Kim SW, Seo GS, Kim HS, Joo YE (2017) Clinicopathological features of laterally spreading colorectal tumors and their association with advanced histology and invasiveness: an experience from Honam province of South Korea: a Honam Association for the Study of Intestinal Diseases (HASID). PLoS One 12:e0184205
13. Cong ZJ, Hu LH, Ji JT, Xing JJ, Shan YQ, Li ZS, Yu ED (2016) A long-term follow-up on the prognosis of endoscopic submucosal dissection for colorectal laterally spreading tumors. Gastrointest Endosc 83:800–807
14. Yamada M, Saito Y, Sakamoto T, Nakajima T, Kushima R, Parra-Blanco A, Matsuda T (2016) Endoscopic predictors of deep submucosal invasion in colorectal laterally spreading tumors. Endoscopy 48:456–464
15. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T (2012) Cancer incidence and incidence rates in Japan in 2006: based on data from 15 population-based cancer registries in the monitoring of cancer incidence in Japan (MCIJ) project. Jpn J Clin Oncol 42:139–147
16. Shigita K, Oka S, Tanaka S, Sumimoto K, Hirano D, Tamaru Y, Ninomiya Y, Asayama N, Hayashi N, Shimamoto F, Arihiro K, Chayama K (2017) Long-term outcomes after endoscopic submucosal dissection for superficial colorectal tumors. Gastrointest Endosc 85:546–553
17. Boda K, Oka S, Tanaka S, Nagata S, Kunihiro M, Kuwai T, Hiraga Y, Furudoi A, Terasaki M, Nakadoi K, Higashiyama M, Okanobu H, Akagi M, Chayama K (2018) Clinical outcome of endoscopic submucosal dissection for colorectal tumors. Gastrointest Endosc 87:714–722
18. Watanabe T, Muro K, Ajioka Y, Hashiguchi Y, Ito Y, Saito Y, Hamaguchi T, Ishida H, Ishiguro M, Ishihara S, Kanemitsu Y, Kawano H, Kinugasa Y, Kokudo N, Murofushi K, Nakajima T, Oka S, Sakai Y, Tsuji A, Uehara K, Ueno H, Yamazaki K, Yoshida M, Yoshino T, Boku N, Fujimori T, Itabashi M, Koinuma N, Morita T, Nishimura G, Sakata Y, Shimada Y, Takahashi K, Tanaka S, Tsuruta O, Yamaguchi T, Yamaguchi N, Tanaka T, Kotake K, Sugihara K (2018) Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2016 for the treatment of colorectal cancer. Int J Clin Oncol 23:1–34
19. Asayama N, Oka S, Tanaka S, Ninomiya Y, Tamaru Y, Shigita K, Hayashi N, Egi H, Hinoi T, Ohdan H, Arihiro K, Chayama K (2016) Long-term outcomes after treatment for T1 colorectal carcinoma. Int J Color Dis 31:571–578
20. Tamaru Y, Oka S, Tanaka S, Nagata S, Hiraga Y, Kuwai T, Furudoi A, Tamura T, Kunihiro M, Okanobu H, Nakadoi K, Kanao H, Higashiyama M, Arihiro K, Kuraoka K, Shimamoto F, Chayama K (2017) Long-term outcomes after treatment for T1 colorectal carcinoma: a multicenter retrospective cohort study of Hiroshima GI Endoscopy Research Group. J Gastroenterol 52:1169–1179
21. Yoshii S, Nojima M, Nosho K, Omori S, Kusumi T, Okuda H, Tsukagoshi H, Fujita M, Yamamoto H, Hosokawa M (2014) Factors associated with risk for colorectal cancer recurrence after endoscopic resection of T1 tumors. Clin Gastroenterol Hepatol 12(2):292–302
22. Ikematsu H, Yoda Y, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, Fujii T, Oono Y, Sakamoto T, Nakajima T, Takao M, Shinohara T, Murakami Y, Fujimori T, Kaneko K, Saito Y (2013) Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology 144:551–559
23. Yoda Y, Ikematsu H, Matsuda T, Yamaguchi Y, Hotta K, Kobayashi N, Fujii T, Oono Y, Sakamoto T, Nakajima T, Takao M, Shinohara T, Fujimori T, Kaneko K, Saito Y (2013) A large-scale multicenter study of long-term outcomes after endoscopic resection for submucosal invasive colorectal cancer. Endoscopy 45:718–724
24. Belderbos TD, van Erning FN, de Hingh IH, van Oijen MG, Lemmens VE, Siersema PD (2017) Long-term recurrence-free survival after standard endoscopic resection versus surgical resection of submucosal invasive colorectal cancer: a population-based study. Clin Gastroenterol Hepatol 15:403–411
25. Oka S, Tanaka S, Saito Y, Iishi H, Kudo SE, Ikematsu H, Igarashi M, Saitoh Y, Inoue Y, Kobayashi K, Hisabe T, Tsuruta O, Sano Y, Yamano H, Shimizu S, Yahagi N, Watanabe T, Nakamura H, Fujii T, Ishikawa H, Sugihara K (2015) Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol 110:697–707
26. Nakadoi K, Oka S, Tanaka S, Hayashi N, Terasaki M, Arihiro K, Shimamoto F, Chayama K (2014) Condition of muscularis mucosae is a risk factor for lymph node metastasis in T1 colorectal carcinoma. Surg Endosc 28:1269–1276
27. Ueno H, Mochizuki H, Hashiguchi Y, Shimazaki H, Aida S, Hase K, Matsukuma S, Kanai T, Kurihara H, Ozawa K, Yoshimura K, Bekku S (2004) Risk factors for an adverse outcome in early invasive colorectal carcinoma. Gastroenterology 127:385–394

28. Tanaka S, Haruma K, Teixeira CR, Tatsuta S, Ohtsu N, Hiraga Y, Yoshihara M, Sumii K, Kajiyama G, Shimamoto F (1995) Endoscopic treatment of submucosal invasive colorectal carcinoma with special reference. J Gastroenterol 30:710–717
29. Tanaka S, Haruma K, Oh-E H, Nagata S, Hirota Y, Furudoi AT, Kitadai Y, Yoshihara M, Shimamoto F (2000) Conditions of curability after endoscopic resection for colorectal carcinoma with submucosally massive invasion. Oncol Rep 7:783–788
30. Ueno H, Hase K, Hashiguchi Y, Shimazaki H, Yoshii S, Kudo SE, Tanaka M, Akagi Y, Suto T, Nagata S, Matsuda K, Komori K, Yoshimatsu K, Tomita Y, Yokoyama S, Shinto E, Nakamura T, Sugihara K (2014) Novel risk factors for lymph node metastasis in early invasive colorectal cancer: a multi-institution pathology review. J Gastroenterol 49:1314–1323
31. Miyamoto H, Ikematsu H, Fujii S, Osera S, Odagaki T, Oono Y, Yano T, Ochiai A, Sasaki Y, Kaneko K (2014) Clinicopathological differences of laterally spreading tumors arising in the colon and rectum. Int J Color Dis 29:1069–1075
32. Uraoka T, Saito Y, Matsuda T, Ikehara H, Gotoda T, Saito D, Fujii T (2006) Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. Gut 55:1592–1597
33. Burgess NG, Hourigan LF, Zanati SA, Brown GJ, Singh R, Williams SJ, Raftopoulos SC, Ormonde D, Moss A, Byth K, Mahajan H, McLeod D, Bourke MJ (2017) Risk stratification for covert invasive cancer among patients referred for colonic endoscopic mucosal resection: a large multicenter cohort. Gastroenterology 153:732–742
34. Goto SP, Sakamoto N, Mitomi H, Murakami T, Ritsuno H, Ueyama H, Matsumoto K, Shibuya T, Osada T, Nagahara A, Ogihara T, Yao T, Watanabe S (2014) Histological distinction between the granular and nongranular types of laterally spreading tumors of the colorectum. Gastroenterol Res Pract ID153935. https://doi.org/10.1155/2014/153935
35. Toh EW, Brown P, Morris E, Botterill I, Quirke P (2015) Area of submucosal invasion and width of invasion predicts lymph node metastasis in pT1 colorectal cancers. Dis Colon Rectum 58:393–400
36. Smith KJ, Jones PF, Burke DA, Treanor D, Finan PJ, Quirke P (2011) Lymphatic distribution in the mucosa and submucosa and potential implications of T1 colorectal tumors. Dis Colon Rectum 54:35–40
37. Asayama N, Oka S, Tanaka S, Hayashi N, Arihiro K, Chayama K (2015) Endoscopic submucosal dissection as total excisional biopsy for clinical T1 colorectal carcinoma. Digestion 91:64–69
38. Kobayashi H, Mochizuki H, Morita T, Kotake K, Teramoto T, Kameoka S, Saito Y, Takahashi K, Hase K, Oya M, Maeda K, Hirai T, Kameyama M, Shirouzu K, Sugihara K (2011) Characteristics of recurrence after curative resection for T1 colorectal cancer: Japanese multicenter study. J Gastroenterol 46:203–211