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Treatment Decision for Locally Resected T1 Colorectal Carcinoma–Verification of the Japanese Guideline Criteria for Additional Surgery Based on Long-Term Clinical Outcomes

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INTRODUCTION: **To verify the value of the pathological criteria for additional treatment in locally resected pT1 colorectal carcinoma (CRC) which have been used in the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines since 2009.**

METHODS: **We enrolled 4,719 patients with pT1 CRC treated at 27 institutions between July 2009 and December 2016 (1,259 patients with local resection alone [group A], 1,508 patients with additional surgery after local resection [group B], and 1,952 patients with surgery alone [group C]). All 5 factors of the JSCCR guidelines (submucosal resection margin, tumor histologic grade, submucosal invasion depth, lymphovascular invasion, and tumor budding) for lymph node metastasis (LNM) had been diagnosed prospectively.**

RESULTS: **Any of the risk factors were present in 3,801 patients. The LNM incidence was 10.3% (95% confidence interval 9.3–11.4) in group B/C patients with risk factors, whereas it was 1.8% (95% confidence interval 0.4–5.2) in those without risk factors ($P < 0.01$). In group A, the incidence of recurrence was 3.4% in patients with risk factors, but it was only 0.1% in patients without risk factors ($P < 0.01$). The disease-free survival rate of group A patients classified as risk positive was significantly worse than those of groups B and C patients. However, the 5-year disease-free survival rate in group A patients with no risk was 99.2%.**

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DISCUSSION: **Our large-scale real-world multicenter study demonstrated the validity of the JSCCR criteria for pT1 CRC after local resection, especially regarding favorable outcomes in patients with low risk of LNM.**

KEYWORDS: colon; neoplasm recurrence; rectum; risk assessment; unnecessary procedures

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/D207

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INTRODUCTION

Colorectal carcinoma (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer death worldwide (1). Owing to recent advances in the field of gastrointestinal endoscopy, especially in diagnostic technology and therapeutic techniques, the incidence of T1 CRC initially treated with endoscopic resection has increased (2–5). Several standardized endoscopic resection procedures exist for colonic mucosal or submucosal lesions. Particularly, endoscopic submucosal dissection has increasingly been applied to relatively large-size lesions (6–8). Approximately 90% of patients with pathological T1 (pT1) CRC do not have lymph node metastasis (LNM) (9–13), although the principle for treatment of pT1 CRCs, which are invasive carcinoma with potential LNM, is bowel resection which can accomplish complete oncological curability. Given that currently no diagnostic method can infallibly predict LNM, appropriate risk assessment to minimize the incidence of tumor relapse in patients who are classified as low risk to select observation policies is essential.

At present, criteria for additional surgery in endoscopically resected pT1 CRC are not unified, although some clinical guidelines including the National Comprehensive Cancer Network (NCCN) guidelines in the United States, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines in Europe, and the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines in Japan have been published. In the NCCN guidelines (version 2, 2021 for colon cancer and version 1, 2021 for rectal cancer; see https://www.nccn.org), which is one of the most widely used guidelines worldwide, additional surgery is recommended for tumors with unfavorable histological features (grade 3/4), lymphovascular invasion, or resection margin involvement. According to the ESGE guidelines (14), additional surgery is recommended when positive lymphovascular invasion, submucosal infiltration deeper than sm1 (≥1,000 μm), positive/nonevaluable vertical margins, or poor tumor differentiation is diagnosed.

In the JSCCR guidelines published in July 2009, 5 pathological features were adopted as risk factors for LNM indicating the necessity of additional surgery, positive vertical (submucosal) margins, unfavorable histologic grade, submucosal invasion depth ≥1,000 μm, positive lymphovascular invasion, and tumor budding grade 2/3 (15–18); they are still used in the latest JSCCR guidelines. Since the present JSCCR criteria were based on retrospective studies that analyzed patients with pT1 CRC undergoing bowel resection with lymph node dissection, the validity of the JSCCR guidelines should be evaluated in cohort studies with prospective study design. To date, several reports about the prognosis of patients with pT1 CRC who underwent local resection (LR) or surgery have been published (19–25). However, these studies have some limitations such as limited numbers of patients analyzed, short surveillance periods after treatment, and the lack of prospective assessment according to JSCCR criteria. This study aimed to determine the validity of the JSCCR criteria based on clinical outcomes in a large-scale Japanese multicenter cohort of patients with pT1 CRC who were treated after July 2009.

METHODS

Study design, setting, and patients

In total, 6,212 patients with pT1 CRC treated between July 2009 and December 2016 at 27 high-volume institutions in Japan were enrolled. In all cases, the JSCCR criteria of additional surgery in endoscopically resected pT1 CRC were prospectively assessed in each institution (15–18). Patients with a previous history of CRC, synchronous CRC, familial adenomatous polyposis, inflammatory bowel disease, or unknown data were excluded from the study. Patients were classified into 3 groups according to treatment methods as follows: patients who underwent only LR by the endoscopic or surgical approach, those who underwent additional surgery (i.e., bowel resection with lymph node dissection) after LR, and those who underwent surgery alone. Endoscopic resection should not be applied for early CRC if *en bloc* resection is impossible or for clinical T1 CRC with deep submucosal invasion (≥1,000 μm) according to the JSCCR guidelines. Patients who underwent LR alone included those followed up without additional surgery despite their high risk for LNM because of their rejection of additional surgery or their physical conditions.

Patients with 1 or more JSCCR risk factors (i.e., positive vertical margin, unfavorable histologic grade, submucosal invasion depth ≥1,000 μm, positive lymphovascular invasion, and tumor budding grade 2/3) were defined as being at high risk of LNM, whereas those with none of these risk factors were defined as being at low risk. Among the 6,212 enrolled patients with pT1 CRC, 1,493 patients with insufficient information on clinicopathological features and follow-up data were excluded from the analysis. Finally, 4,719 patients with pT1 CRC were analyzed (Figure 1).

The study protocol was approved by the ethics committees of JSCCR (approval date: March 13, 2018) and each participating institution. This study was performed in accordance with the Declaration of Helsinki and its later amendments.

Indication of additional surgery after LR

All endoscopically resected specimens were fixed in 10% formalin and cut into 2-mm thick sections. The resection margin status, tumor histologic grade, depth of submucosal invasion, lymphatic invasion, venous invasion, and tumor budding were pathologically diagnosed in each participating institution. The resection margin was considered tumor-free when both horizontal (mucosal) and vertical (submucosal) margins of the resected specimen were negative for tumor cells. The tumor histologic grade was diagnosed based on predominant histological findings according to the Japanese Classification of Cancer of the Colon and Rectum (26). When it was possible

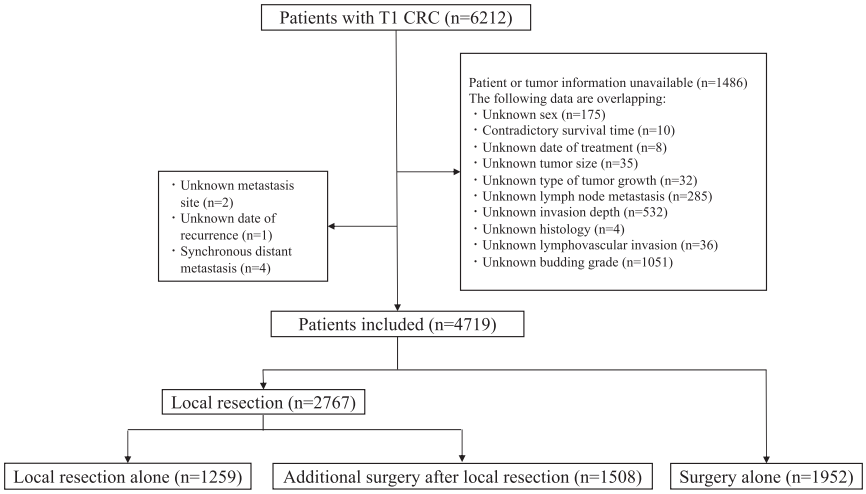


Figure 1. Flowchart for enrollment and stratification of patients in this study. CRC, colorectal carcinoma.

to sufficiently identify the muscularis mucosae, the depth of submucosal invasion was measured from the lower border of the muscularis mucosae. When it was impossible to identify the muscularis mucosae location, the depth of submucosal invasion was measured from the tumor surface, irrespective of macroscopic type. Especially for pedunculated lesions with tangled muscularis mucosae, the submucosal invasion depth was measured as the distance between the point of deepest invasion and the reference line, which was defined as the boundary between the tumor head and the stalk (Haggitt level 2 (27)). When the invasion was limited to the head (Haggitt level 1 (27)), the submucosal invasion depth was assessed as 0 μm. To confirm lymphovascular invasion, elastic fiber stainings (Victoria blue, Elastica van Gieson) and immunostainings (D2-40, etc.) were performed at the discretion of pathologists as necessary in each institution. Budding was defined as a single cancer cell or a cluster of <5 cells along the invasion margin. It was graded based on a 200× microscopic field (grade 1: 0–4 buds; grade 2: 5–9 buds; grade 3: ≥10 buds) (12). Budding grades 2 and 3 were defined as high grade and grade 1 as low grade in line with previous publications (12).

Since July 2009, the JSCCR guidelines specify that a positive vertical margin is an absolute indication for additional surgery after LR and additional surgery should be considered when at least one of the following findings is determined: (i) poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma; (ii) submucosal invasion depth ≥1,000 μm; (iii) positive lymphovascular invasion; and (iv) budding grade 2/3 at the deepest part of the submucosal invasion (15–18). Moreover, the JSCCR guidelines state that additional surgery should be performed only after systematically evaluating the predicted curability based on various LNM risk factors and the patient's condition (e.g., age, physical performance, and adverse events) after obtaining informed consent from the patient.

Surveillance schedule after T1 CRC treatment

In patients who underwent surgery, physical examinations and blood tests (including carcinoembryonic antigen level) were performed every 3 months postoperatively for the first 3 years and thereafter every 6 months. Contrast-enhanced computed tomography of the chest and abdomen was performed every 6 months postoperatively for the first 3 years and thereafter at least every 12 months, according to the JSCCR guidelines (15–18). In patients who underwent LR alone, surveillance was performed according to institutional procedures; however, most patients were followed up according to the above JSCCR guidelines (15–18). Recurrence was defined as the occurrence of metastasis in lymph nodes or distant organs during the follow-up period. The average follow-up duration after treatment was 41.2 ± 23.8 months (36.0 ± 25.9 months in the LR alone group, 43.3 ± 23.0 months in the additional surgery group, and 43.0 ± 22.5 months in the surgery alone group).

Investigated variables

The aim of the study was to validate the clinical value of JSCCR criteria for additional surgery in endoscopically resected pT1 CRC. The following clinicopathological characteristics and outcomes were evaluated and compared among patients of different groups: age, sex, tumor location, tumor size, macroscopic type, histologic grade, submucosal invasion depth, resection margin, lymphatic invasion, venous invasion, budding grade, and LNM incidence according to the treatment methods. Regarding the histologic grade, tumors were diagnosed as well-differentiated tubular adenocarcinoma, moderately differentiated adenocarcinoma, poorly differentiated adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma, according to the definition of the Japanese Classification of Colorectal Carcinoma (26). Tumors that contained more than 1 histologic grade were classified based on the predominant histologic grade. In patients who underwent surgery (bowel resection with lymph node dissection), we evaluated the incidence of LNM according to the JSCCR criteria for additional surgery in endoscopically resected pT1 CRC. The following clinical outcomes were also assessed in each group: disease-free survival (DFS) rate and overall survival (OS) rate as primary endpoints. DFS was defined as the time from the date of treatment to the date when recurrence was first confirmed, secondary cancer was diagnosed, or death from any cause occurred. OS was assessed up to the time of death from any cause. Furthermore, we aimed to identify predictive DFS factors, which we regarded as secondary endpoints in this study, based on an exploratory analysis using Cox regression models.

In this study, tumor locations were classified as follows: (i) the right colon, including the cecum, ascending colon, and transverse colon; (ii) the left colon, including the descending colon and

Table 1. Clinicopathological characteristics of 4,719 patients with pT1 colorectal carcinoma according to the treatment methods

Variables	Local resection alone (n = 1,259)	Additional surgery after local resection (n = 1,508)	Surgery alone (n = 1,952)	*P* value
Age (yr), mean ± SD	69.7 ± 10.8	64.7 ± 10.7	66.9 ± 11.0	<0.0001
Sex (male), n (%)	803 (63.8)	928 (61.5)	1,075 (55.1)	<0.0001
Location (colon), n (%)	918 (72.9)	968 (64.2)	1,231 (63.1)	<0.0001
Tumor size (mm), mean ± SD	22.6 ± 14.9	21.7 ± 15.6	21.8 ± 12.1	0.1897
Macroscopic type (protruded), n (%)	609 (48.4)	1,004 (66.6)	928 (47.5)	<0.0001
Histologic grade (por, sig, muc), n (%)	5 (0.4)	30 (2.0)	34 (1.7)	0.0002
Submucosal invasion depth ≥1,000 μm, n (%)	426 (33.8)	1,282 (85.0)	1,760 (90.2)	<0.0001
Lymphatic invasion, n (%)	104 (8.3)	539 (35.7)	553 (28.3)	<0.0001
Venous invasion, n (%)	81 (6.4)	469 (31.1)	713 (36.5)	<0.0001
Budding grade 2/3, n (%)	65 (5.2)	304 (20.2)	401 (20.5)	<0.0001
LNM, n (%)	—	147 (9.7)	197 (10.1)	0.7746
High risk of LNM, n (%)	506 (40.2)	1,471 (97.5)	1,824 (93.4)	<0.0001

A high risk of LNM indicates the presence of 1 or more risk factors of the JSCCR criteria (i.e., positive vertical margin, unfavorable histologic grade, submucosal invasion depth ≥1,000 μm, lymphovascular invasion, and tumor budding grade 2/3).
JSCCR, Japanese Society for Cancer of the Colon and Rectum; LNM, lymph node metastasis; muc, mucinous carcinoma; por, poorly differentiated adenocarcinoma; SD, standard deviation; sig, signet-ring cell carcinoma.

sigmoid colon; and (iii) the rectum. The macroscopic CRC type was classified as protruded or superficial, and pedunculated or nonpedunculated, as reported previously (6).

Statistical analyses

Data are presented as means (standard deviations). The Fisher exact test was used to compare categorical variables. Statistical analyses were performed using JMP statistical software, version 10.0.2 (SAS Institute, Cary, NC). Differences with $P < 0.05$ were considered statistically significant. DFS and OS rates were calculated using the Kaplan-Meier method. Cox regression analysis was used to calculate hazard ratios for DFS for the following variables: age, sex, tumor size, location, macroscopic type, histologic grade, submucosal invasion depth, lymphatic invasion, venous invasion, budding grade, and LNM.

RESULTS

Patient characteristics

The clinical characteristics of 4,719 patients divided into 3 groups based on the treatment methods are summarized in Table 1. The following procedures were performed for LR: endoscopic mucosal resection (n = 1,260), endoscopic submucosal dissection (n = 1,254), polypectomy (n = 187), and surgical excision (n = 66). *En bloc* resection and R0 resection rates in the LR group were 96.8% (2,678/2,767) and 77.6% (2,147/2,767), respectively. The incidence of LR failure (piecemeal resection) in the additional surgery after LR group was 3.8% (194/1,508). The number of patients at high risk of LNM was 3,801 (80.5%). Significant differences among the 3 groups were observed in age, sex, tumor location, macroscopic type, submucosal invasion depth, lymphatic invasion, venous invasion, budding grade, and high-risk LNM incidence.

Furthermore, the characteristics of clinicopathological findings were compared according to the treatment methods in patients with high risk of LNM (Table 2). Significant differences were observed in age, sex, location, macroscopic type, histology, submucosal invasion depth, lymphatic invasion, venous invasion, and budding grade.

Outcomes after treatment for pT1 CRC

LNM incidence. In patients who underwent additional surgery after LR or surgery alone, the overall incidence of LNM was 9.9% (344/3,460, 95% confidence interval [CI] 9.0–11.0). The LNM incidence was 10.3% (341/3,295, 95% CI 9.3–11.4) in patients at high risk of LNM, whereas it was only 1.8% (3/165, 95% CI 0.4–5.2) in those at low risk ($P < 0.01$).

Recurrence rate. Overall, recurrence was observed in 18 patients with LR alone (1.4%, 18/1,259, 95% CI, 0.9–2.3), 35 patients with additional surgery after LR (2.3%, 35/1,508, 95% CI 1.6–3.2), and 33 patients with surgery alone (1.7%, 33/1,952, 95% CI 1.2–2.4). The recurrence rate in patients with low LNM risk (0.5%, 5/918, 95% CI 0.2–1.3) was significantly lower than that in patients with high LNM risk (2.1%, 81/3,801, 95% CI 1.7–2.6; $P < 0.01$).

In patients with LR alone, the recurrence rate was 3.4% (17/506, 95% CI 2.0–5.3) in patients at high risk of LNM, whereas it was 0.1% (1/753, 95% CI 0.03–0.7) in patients at low risk of LNM ($P < 0.01$). In patients at low risk of LNM, no patient (0%, 0/37, 95% CI 0–7.8) treated with additional surgery after LR developed recurrence. In patients at high risk of LNM, recurrence was observed in 17 patients with LR alone (3.4%, 17/506, 95% CI 2.0–5.3), 35 patients with additional surgery after LR (2.4%, 35/1,471, 95% CI 1.7–3.3), and 29 patients with surgery alone (1.6%, 29/1,824, 95% CI 1.1–2.3). In total, 22 patients died of recurrent tumors. The details of the 86 patients with tumor recurrence are given in Supplementary Table 1 (see Supplementary Digital Content 1, http://links.lww.com/AJG/D207); only 1 patient at low risk of LNM died of recurrent tumor. The duration from treatment to recurrence was 23.9 ± 15.2 months.

Table 2. Comparison of clinicopathological characteristics of 3,801 pT1 colorectal carcinoma patients at high risk of lymph node metastasis according to the treatment methods

Variables	Local resection alone (n = 506)	Additional surgery after local resection (n = 1,471)	Surgery alone (n = 1,824)	*P* value
Age (yr), mean ± SD	71.7 ± 10.8	64.8 ± 10.7	66.8 ± 11.1	<0.0001
Sex (male), n (%)	316 (62.5)	900 (61.2)	1,004 (55.0)	<0.0001
Location (colon), n (%)	313 (61.9)	936 (63.6)	1,127 (61.8)	<0.0001
Tumor size (mm), mean ± SD	23.6 ± 16.5	21.7 ± 15.7	21.8 ± 12.2	0.1897
Macroscopic type (protruded), n (%)	298 (58.9)	983 (66.8)	868 (47.6)	<0.0001
Histologic grade (por, sig, muc), n (%)	5 (1.0)	30 (2.0)	34 (1.9)	0.0002
Submucosal invasion depth ≥1,000 μm, n (%)	426 (84.2)	1,282 (87.2)	1,760 (96.5)	<0.0001
Lymphatic invasion, n (%)	104 (20.6)	539 (36.6)	553 (30.3)	<0.0001
Venous invasion, n (%)	81 (16.0)	469 (31.9)	713 (39.1)	<0.0001
Budding grade 2/3, n (%)	65 (12.8)	304 (20.7)	401 (22.0)	<0.0001
LNM, n (%)	—	147 (10.0)	194 (10.6)	0.7746

LNM, lymph node metastasis; muc, mucinous carcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma.

DFS and OS rates. Among patients with low LNM risk, the 5-year DFS rate in patients with LR alone was 99.2%, which was significantly higher than that in patients with surgery alone (95.7%) (Figure 2). However, no significant difference in OS was found among the 3 groups. By contrast, among patients at high risk of LNM, the 5-year DFS rate in patients with LR alone (93.5%) was significantly worse than that of patients with additional surgery after LR (96.9%) or surgery alone (97.8%) (Figure 3). Similarly, the OS rate in patients with LR alone (90.6%) was significantly worse than that of patients with additional surgery after LR (96.7%) or surgery alone (96.6%).

Predicting factors of DFS after T1 CRC treatment. The results of Cox regression analysis for DFS in patients with pT1 CRC are summarized in Supplementary Table 2 (see Supplementary Digital Content 1, http://links.lww.com/AJG/D207). According to the multivariate analysis, positive LNM, tumor location in the rectum, and protruded type were significant predictors of DFS after T1 CRC treatment. The results of the multivariate analysis for DFS in patients at high risk of LNM are summarized in Table 3 in which LNM positivity and tumor location in the rectum were significant predictors of shorter DFS after T1 CRC treatment. On the other hand, the results of the multivariate analysis for DFS in patients at low risk of LNM are summarized in Table 4 in which protruded type was a significant predictor of shorter DFS after T1 CRC treatment.

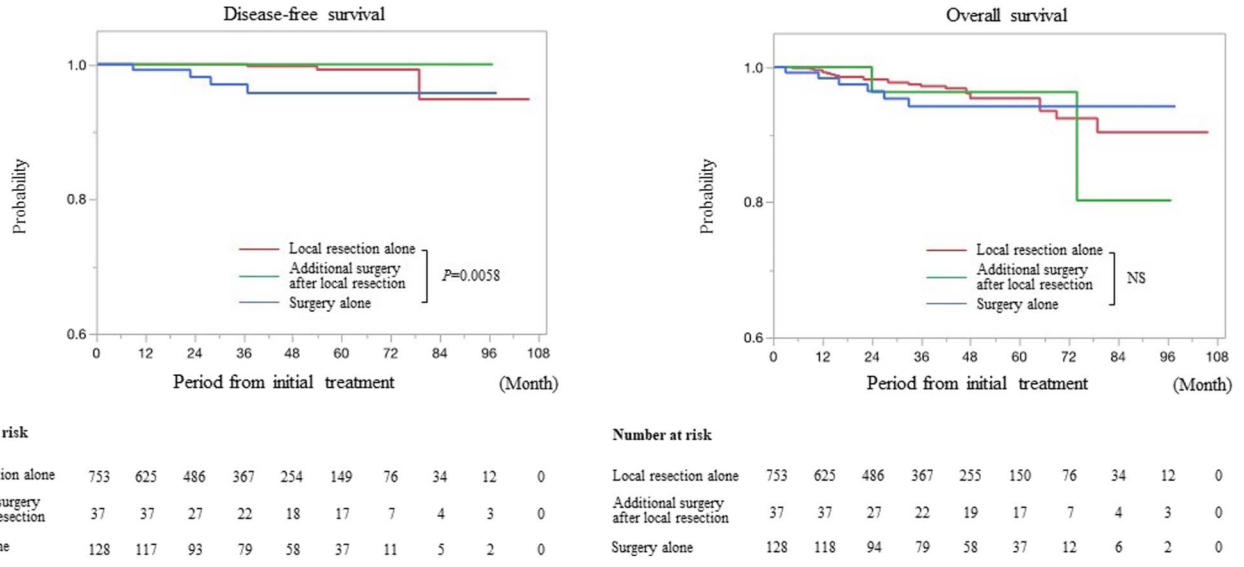
DISCUSSION

The findings of the present large-scale multicenter cohort study showed real-world clinical outcomes in patients with pT1 CRC when treated according to the JSCCR guidelines, which are unaltered since July 2009. Although the representative CRC treatment guidelines from Japan (JSCCR), the United States (NCCN), and Europe (ESGE) have the same basic principles, some details differ among regions. In the process of preparing the guidelines, not only the medical situation of the region but also the social background, such as the insurance system and culture, is taken into consideration; therefore, the guidelines from one country cannot simply be applied to other regions (28).

The JSCCR guidelines decisively differ from other guidelines in that the JSCCR criteria for additional surgery of T1 CRC after LR include submucosal invasion depth ≥1,000 μm and high-grade tumor budding, both of which were shown to be significant risk factors for LNM in patients with T1 CRC in some preceding studies, including a multicenter retrospective study conducted by the JSCCR guidelines (8,23,29,30).

Our study demonstrated that the recurrence risk was negligible in patients at low risk of LNM according to the JSCCR guidelines criteria as follows: 0.1% in patients with LR alone, 0% in patients with additional surgery after LR, and 3.1% in patients with surgery alone. It is noteworthy that recurrence was observed in only 1 patient (0.1%) with low LNM risk in the LR-alone group. Our results suggest that, practically, additional surgery after LR is unnecessary in patients at low risk of LNM after complete resection has been histologically confirmed. The validity of the JSCCR criteria of endoscopically resected pT1 CRC was proven for the first time by evaluating real-world data, including those of tumor budding assessed according to the International Tumor Budding Consensus Conference (ITBCC) methods. Previous studies reporting the outcomes after pT1 CRC treatment had nonnegligible limitations such as relatively small numbers of enrolled patients, lack of data regarding pathological findings, especially for tumor budding, and relatively short follow-up durations (19–22). An international evidence-based standardized definition and scoring system for tumor budding in CRC were established in the ITBCC (31).

Several studies support the consensus of gastroenterological endoscopists that preceding endoscopic resection does not adversely affect oncological outcomes in patients who underwent additional surgery for pT1 CRC (23–26,29,30,32,33). Surgical bowel resection with lymph node dissection can reduce the risk of recurrence of pT1 CRC by implementing *en bloc* resection of LNM and tumor deposits within lymphovascular vessels or those in regional soft tissues around primary lesions (20,22,23,25,34). Choi et al (34) reported that approximately 16% of pT1 CRC patients with deep submucosal invasion or unfavorable histology benefited from additional surgery in LNM and that recurrence inevitably occurred in patients who had chosen the observation



Number at risk

Local resection alone	753	625	486	367	254	149	76	34	12	0
Additional surgery after local resection	37	37	27	22	18	17	7	4	3	0
Surgery alone	128	117	93	79	58	37	11	5	2	0

Number at risk

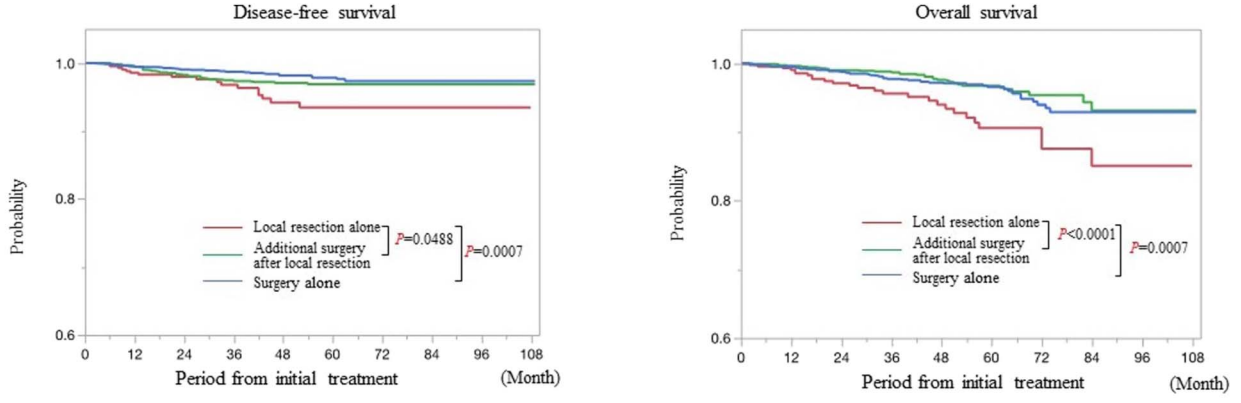
Local resection alone	753	625	486	367	255	150	76	34	12	0
Additional surgery after local resection	37	37	27	22	19	17	7	4	3	0
Surgery alone	128	118	94	79	58	37	12	6	2	0

Figure 2. Prognosis of 918 patients with pT1 colorectal carcinoma and low-risk lymph node metastasis, stratified by treatment methods. NS, not significant.

policy. Yoda et al (24) reported that among 302 pT1 CRC patients with risk factors of LNM including positive vertical margin, unfavorable histologic grade, submucosal invasion depth ≥1,000 μm, positive lymphovascular invasion, and tumor budding grade 2/3, the 5-year DFS rate for patients who underwent LR and additional surgery was 97%. They concluded that additional surgery after LR should be recommended in pT1 CRC patients with high risk of LNM.

The incidence of recurrence in patients with surgery is reportedly between 2.3% and 5.6% (1.1%–1.9% in low-risk patients and 3.8%–25.0% in high-risk patients) (20–23,27,28,30,35–37). Our results showed that the LNM incidence was 10.3% (341/3,295) in patients at high risk of LNM, indicating that approximately 9 of 10 patients are being recommended to receive unnecessary surgery based on pathological risk assessment. In clinical practice, physicians should consider the individual patient's age, concomitant diseases, wishes, life expectancy, performance status, and concrete LNM risk when deciding about additional surgery after endoscopic resection (38). Future research is warranted to develop more accurate risk assessment algorithms for patients with locally resected pT1 CRC, most probably by incorporating novel factors, for example, poorly differentiated clusters (39) or tumor grade based on the least differentiation policy with the 40× objective lens rule (40,41).

Our data showed that LNM positivity and CRC location in the rectum were important indicators for DFS in patients with T1 CRC. Kobayashi et al (19) reported T1 CRC recurrence rates of 4.2% in the rectum and 1.5% in the colon ($P = 0.02$). Ikematsu et al (22) also reported that the tumor location in the rectum was a significant indicator of recurrence after LR alone in patients with pT1 CRC and high risk of LNM. The underlying reasons for different recurrence rates between the colon and rectum might be differences in anatomical characteristics including lymphatic and vascular distributions or in biological tumor behaviors. The findings of our study suggest that LNM, tumor location in the rectum, and protruded type were significant predictors of DFS after pT1 CRC



Number at risk

Local resection alone	506	386	297	218	154	101	58	33	13	1
Additional surgery after local resection	1471	1366	1112	845	603	417	157	76	16	1
Surgery alone	1824	1729	1409	1078	777	516	198	92	24	2

Number at risk

Local resection alone	506	392	303	226	163	106	60	30	14	1
Additional surgery after local resection	1471	1372	1131	869	621	429	165	79	17	2
Surgery alone	1824	1738	1418	1087	788	527	202	94	25	2

Figure 3. Prognosis of 3,801 patients with pT1 colorectal carcinoma and high-risk lymph node metastasis, stratified by treatment methods.

Table 3. Cox regression analysis for disease-free survival in patients with pT1 colorectal carcinoma at high risk of lymph node metastasis (n = 3,801)

	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age (yr)						
<65	1	0.57–1.37	0.5799	1	0.68–1.66	0.7843
≥65	0.88			1.06		
Sex						
Male	1	0.57–1.40	0.6268	1	0.55–1.35	0.5200
Female	0.90			0.86		
Tumor size (mm)						
<20	1	1.04–2.55	0.0323	1	0.91–2.25	0.1194
≥20	1.63			1.43		
Location						
Colon	1	1.82–4.51	<0.0001	1	1.69–4.26	<0.0001
Rectum	2.86			2.68		
Macroscopic type						
Superficial	1	1.01–2.56	0.0459	1	0.99–2.54	0.0546
Protruded	1.61			1.59		
Histologic grade						
tub/pap	1	0.63–6.37	0.2353	1	0.53–5.48	0.3740
por/sig/muc	2.01			1.70		
Submucosal invasion depth						
T1a	1	0.52–2.75	0.6734	1	0.39–2.11	0.8114
T1b	1.20			0.90		
Lymphatic invasion						
Negative	1	1.24–2.97	0.0034	1	0.79–2.10	0.3030
Positive	1.92			1.29		
Venous invasion						
Negative	1	1.03–2.47	0.0371	1	0.80–1.97	0.3283
Positive	1.59			1.25		
Budding grade						
1	1	1.20–3.04	0.0068	1	0.73–2.03	0.4479
2/3	1.91			1.22		
LNM						
Negative	1	3.06–7.70	<0.0001	1	2.37–6.52	<0.0001
Positive	4.85			3.93		

CI, confidence interval; HR, hazard ratio; LNM, lymph node metastasis; muc, mucinous carcinoma; pap, papillary adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; tub, tubular adenocarcinoma.

treatment. It is reported that the significant predictors of recurrence after treatment for T1 CRC included protruded type (30,42). Compared with a superficial lesion, a protruded lesion has a protuberance, and there was a possibility that accurate pathological cutting had not been performed.

Our study has some limitations. First, this was a retrospective study based on clinical records, although each pathological risk factor was prospectively diagnosed according to the established criteria. Second, pathological diagnoses were conducted in each institution, and diagnostic precision was not evaluated. Third, the follow-up duration was relatively short. Currently, a large-scale Japanese multicenter prospective cohort study for pT1 CRC resections using LR, followed by surgery, and a follow-up period of more than 10 years is in progress (UMIN000024901). This prospective cohort study might validate our conclusions regarding the value of the JSCCR criteria for long-term survival.

In conclusion, the findings of our large-scale multicenter study revealed the validity of the JSCCR criteria for pT1 CRC after LR. Particularly, the frequency of recurrence was very low in patients pathologically diagnosed with low LNM risk according to the JSCCR criteria.

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Table 4. Cox regression analysis for disease-free survival in patients with pT1 colorectal carcinoma at low risk of lymph node metastasis (n = 918)

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	*P* value	HR	95% CI	*P* value
Age (yr)						
<65	1	0.51–33.8	0.1842	1	0.70–47.8	0.1021
≥65	4.14			5.80		
Sex						
Male	1	0.46–7.29	0.3961	1	0.46–7.97	0.3777
Female	1.82			1.90		
Tumor size (mm)						
<20	1	0.35–6.15	0.5985	1	0.38–7.00	0.5166
≥20	1.47			1.62		
Location						
Colon	1	0.28–7.00	0.6725	1	0.18–4.84	0.9404
Rectum	1.41			0.93		
Macroscopic type						
Superficial	1	1.19–78.9	0.0335	1	1.52–104	0.0189
Protruded	9.70			12.6		

CI, confidence interval; HR, hazard ratio.

CONFLICTS OF INTEREST

Guarantor of the article: Shiro Oka, MD, PhD

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Data availability statement: Data are available upon reasonable request.

Study Highlights

WHAT IS KNOWN

- ✓ Several guidelines describe additional surgery indications of endoscopically resected pT1 colorectal carcinoma.
- ✓ In Japan, the Japanese Society for Cancer of the Colon and Rectum criteria have been employed since 2009.
- ✓ Few real-world studies have validated their usefulness based on long-term clinical outcomes.

WHAT IS NEW HERE

- ✓ In the low-risk group, the recurrence rate was 0.1% in patients without additional surgery.
- ✓ In this group, the 5-year disease-free survival rate was satisfactory at 99.2%.
- ✓ Additional surgery was efficient in high-risk patients, improving the 5-year disease-free survival to 3%.

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