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ORIGINAL ARTICLE

Additional surgery after endoscopic submucosal dissection for colorectal cancer: a review of 53 cases

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Abstract

Background Endoscopic submucosal dissection (ESD) allows the en bloc resection of tumors and is particularly indicated for T1 colorectal cancer. The number of patients undergoing additional surgery after colorectal ESD is increasing. This study aimed to retrospectively evaluate the efficacy and long-term outcomes in patients with additional surgery.

Methods Of 1018 patients who underwent colorectal ESD in our hospital between February 2010 and July 2018, 53 patients who underwent additional surgery in our hospital were retrospectively analyzed and investigated for their clinicopathological characteristics. The need for additional surgery was determined by a pathological examination according to the guideline [1].

Results In total, 53 patients (24 men, 29 women; mean age, 68.2 years; mean tumor diameter, 30.5 mm) were included. Laparoscopic surgery was performed in 47 (88.7%) patients. Liver metastases were preoperatively observed in one patient, for whom hepatectomy was simultaneously performed. All procedures included pathological R0 resection. Postoperative complications occurred in 9 (17.0%) patients. There were no complications requiring reoperation. Fifteen (28.3%) patients had a positive vertical margin; of these patients, residual tumor was observed in the resected specimens of two (13.3%) patients. Eight patients (15.1%) had lymph node metastasis (LNM): four (25.0%) and four (10.8%) of 16 and 37 patients with and without vascular invasion, respectively. Eleven patients (20.8%) had grade 2 or 3 tumor budding, and four (36.4%) of these had LNM. Postoperative recurrence was observed in two (3.8%) patients.

Conclusion Additional surgery after ESD for T1 colorectal cancer was effective and had good long-term outcomes.

Keywords Endoscopic submucosal dissection · Lymph node metastasis · Submucosal colorectal carcinoma · Vascular invasion · Tumor budding

Introduction

Endoscopic resection has become the standard treatment for early colorectal cancer, and its indications currently range from mucosal cancers to submucosal (SM) invasive cancers. Endoscopic submucosal dissection (ESD) is a reliable method for en bloc resection regardless of the lesion size and may be useful for the total biopsy of suspected T1 colorectal carcinoma. The use of ESD has become increasingly widespread with the development of devices for T1 colorectal cancer treatment. However, the number of patients who require additional surgery after undergoing ESD is also increasing. Moreover, approximately 10–15% of colorectal submucosal cancers metastasize to the regional lymph nodes [1–5]. Thus, in this study, we investigated the efficacy and long-term outcomes in patients with additional surgery after colorectal ESD and the postoperative outcomes. We also evaluated various risk factors for lymph node metastasis (LNM).

Materials and methods

Patients and study design

ESD is primarily indicated for large tumors, especially for early cancers that cannot be resected by endoscopic mucosal resection (EMR). Between February 2010 and July 2018, 1018 patients underwent colorectal ESD in the Department

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of Gastroenterology of our hospital. Lesions were evaluated using magnifying chromoendoscopy and were assessed according to the Kudo classification and clinical classification [6, 7]. Most patients enrolled in the study had not undergone a pre-ESD biopsy. Meanwhile, 32 patients whose ESD was discontinued or caused perforation were excluded. Of the 986 patients with completed ESD, 274 had benign lesions and 5 had malignant lesions other than carcinoma. Of the 707 patients diagnosed with colorectal carcinoma, 608 had no indication for additional surgery and 21 opted to not undergo additional surgery. A total of 78 patients underwent additional surgery, 53 of whom underwent it in the Department of Surgery of our hospital (Fig. 1). We retrospectively analyzed the clinicopathological features of these 53 patients.

Pathological evaluation

Following resection, specimens were immediately fixed in 10% buffered formalin.

Each specimen was sliced into 2-mm-thick sections. These sections were stained using hematoxylin and eosin and then examined by a pathologist. Subsequently, a pathological diagnosis was made, and the depth of tumor invasion was measured according to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) guideline [1, 5].

Additional surgery

Each patient received an explanation regarding the risk of not undergoing additional surgery. The need for additional surgery was judged by referring to the JSCCR guideline [1, 5]. The criteria for additional surgery after ESD for T1 colorectal carcinoma are as follows: positive vertical margin, a depth of SM invasion ≥ 1000 μm, vascular invasion, poorly differentiated/signet-ring cell/mucinous adenocarcinoma, and grade 2 or 3 tumor budding (Fig. 2). Additional surgery was performed if any of these criteria was present, unless the patient refused surgery or had a severe comorbidity. Most of the additional surgical procedures were laparoscopically performed. D2 or D3 lymphadenectomies were performed in all patients.

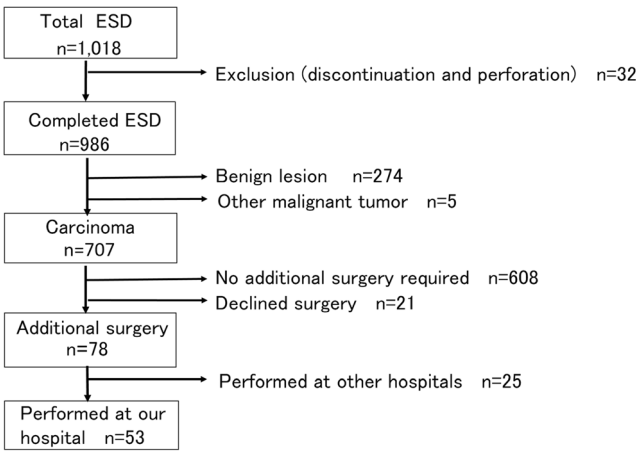

Fig. 1 Flow chart for selection of cases for analysis. ESD, endoscopic submucosal dissection

Outcome measures

Postoperative outcomes included the number of cases with LNM, residual tumor positive or negative, postoperative complications, postoperative stay, mortality within 3 months, and postoperative recurrence. We examined the association between clinicopathological features and LNM to identify the risk factors for LNM. According to the JSCCR guideline [1, 5], patients should receive adjuvant chemotherapy for 6 months, if necessary, on the basis of pathological results. In this study, we planned to follow up all patients for 5 years after the additional surgery. In an event of recurrence after the additional surgery, we decided to perform salvage surgery if an R0 resection was expected. Chemotherapy and radiotherapy were also considered.

Statistical analysis

Data are shown as the mean ± standard deviation. The incidence of LNM was examined in relation to various clinicopathological features, such as age, depth of SM invasion, vascular invasion, tumor budding, and the presence of muconodules. Differences were analyzed using Fisher's exact test. Mean age was compared using Student's *t* test. Survival was estimated using Kaplan-Meier method. p values < 0.05 were considered to be statistically significant. All statistical analyses were performed using R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 shows the demographic and tumor characteristics of the 53 patients with T1 colorectal cancer who underwent additional surgery. Among these patients, 24 (45.3%) were men and 29 (54.7%) were women. Mean age was 68.2 (range, 49–87) years. Furthermore, 22 patients (41.5%) had a tumor in the right colon, 11 (20.8%) in the left colon, and 20 (37.7%) in the rectum. The mean tumor diameter was 30.5 (range, 12–68) mm. Macroscopically, 23 (43.4%) patients had granular-type laterally spreading tumors (LST), 15 (28.3%) had polypoid type, and 13 (24.5%) had non-granular-type LST.

The pathological features of the patients are shown in Table 2. Histologically, 47 (88.7%), 4 (7.5%), and 2 (3.8%) patients had well-differentiated, moderately differentiated,

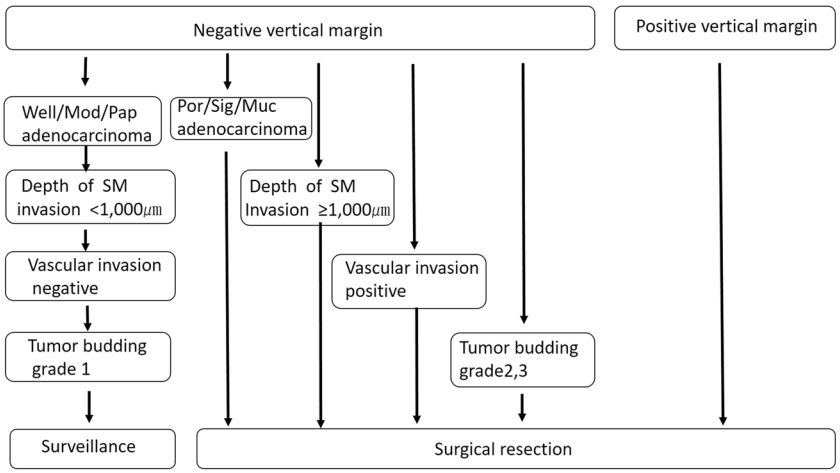

Fig. 2 Treatment strategies for colorectal submucosal (T1) carcinoma resected endoscopically according to Japanese Society for Cancer of the Colon and Rectum guidelines for the treatment of colorectal cancer 2016. Well, well differentiated; Mod, moderately differentiated; Pap, papillary; Por, poorly differentiated; Sig, signet-ring cell; Muc, mucinous; and SM, submucosal

and papillary adenocarcinoma, respectively. Additional surgery was performed for those who had a depth of SM invasion ≥ 1000 μm. However, three patients (5.7%) with a depth of SM invasion of < 1000 μm underwent surgery for other reasons. Meanwhile, 22 (41.5%) patients had a depth of SM invasion ranging from ≥ 1000 to < 2000 μm and 28 (52.8%) had a depth of SM invasion of ≥ 2000 μm. Sixteen (30.2%) of the 53 patients had vascular invasion, 14 (26.4%) had lymphatic invasion, 8 (15.1%) had venous invasion, and 6 (11.3%) had both venous and lymphatic invasion. Fifteen patients (28.3%) had a positive vertical margin and subsequently underwent additional surgery. Meanwhile, 11 (20.8%) patients had grade 2 or 3 (high grade) tumor budding at the site of the deepest invasion, and 42 (79.2%) patients had grade 1 tumor budding. Muconodules at the site of the deepest invasion were observed in only four patients (7.5%), and these patients were not diagnosed with mucinous adenocarcinoma.

Table 1 Demographic and tumor characteristics of patients. LST-G, granular-type laterally spreading tumor; LST-NG, non-granular-type laterally spreading tumor

	n = 53 (%)
Mean age (years)	68.2 (49–87)
Sex	
Male	24 (45.3%)
Female	29 (54.7%)
Location	
Right colon	22 (41.5%)
Left colon	11 (20.8%)
Rectum	20 (37.7%)
Mean tumor size (mm)	30.5 (12–68)
Tumor macroscopic type	
LST-G	23 (43.4%)
Polypoid	15 (28.3%)
LST-NG	13 (24.5%)
Depressed	2 (3.8%)

Laparoscopic colorectal surgery was performed in 47 (88.7%) patients. Open colorectal surgery was performed in the remaining 6 (11.3%) patients (Table 3). Four patients were converted from laparoscopic surgery to open surgery owing to severe adhesions, one patient underwent open surgery because of simultaneous hepatectomy, and one underwent gastric cancer surgery at the same time. Multiple liver metastases were preoperatively found in one patient, for whom hepatectomy

Table 2 Pathological features of patients who underwent additional surgery after endoscopic submucosal dissection. SM, submucosal; CD, Clavien-Dindo classification of postoperative complications

	n = 53 (%)
Pathology	
Well differentiated	47 (88.7%)
Moderately differentiated	4 (7.5%)
Papillary	2 (3.8%)
SM invasion depth (μm)	
< 1000	3 (5.7%)
1000–2000	22 (41.5%)
≥ 2000	28 (52.8%)
Vascular invasion	
Negative	37 (69.8%)
Positive	16 (30.2%)
Lymphatic invasion	14 (26.4%)
Venous invasion	8 (15.1%)
(Both)	6 (11.3%)
Vertical margin	
Negative	38 (71.7%)
Positive	15 (28.3%)
Tumor budding	
Grade 1	42 (79.2%)
Grade 2,3	11 (20.8%)
Muconodules	
Negative	49 (92.5%)
Positive	4 (7.5%)

Table 3 Additional surgery and postoperative outcomes. LNM, lymph node metastasis

	$n = 53$ (%)
Additional surgery	
Laparoscopic colorectal surgery	47 (88.7%)
Open colorectal surgery	6 (11.3%)
Number of cases with LNM	8 (15.1%)
Number of positive nodes	
1	4 (7.5%)
2	2 (3.8%)
6	2 (3.8%)
Vertical margin positive	15 (28.3%)
Residual tumor negative	13 (24.5%)
Residual tumor positive	2 (3.8%)
Postoperative complications(CD ≥ grade II)	9 (17.0%)
Intra-abdominal abscess	4 (7.5%)
Anastomotic leakage	1 (1.9%)
Surgical site infection	1 (1.9%)
Duodenal bleeding	1 (1.9%)
Arrhythmia	1 (1.9%)
Heart failure	1 (1.9%)
Postoperative stay (days), median (range)	11 (6–58)
Mortality within 3 months	0 (0%)
Postoperative recurrence	2 (3.8%)
Distant metastasis (lung and bone)	1 (1.9%)
Lymph node metastasis	1 (1.9%)

was simultaneously performed. All procedures included pathological R0 resection. LNM was confirmed in 8 (15.1%) patients, of which 4, 2, and 2 patients had one, two, and six positive nodes, respectively. Fifteen (28.3%) patients had a positive vertical margin and two (3.8%) had residual tumors in the resected specimens. Nonetheless, no LNM were found in these 15 patients. Postoperative complications occurred in 9 (17.0%) patients. There were no complications requiring re-operation. The median postoperative stay was 11 (range, 6–58) days. Mortality within 3 months was 0%. Postoperative recurrence was detected in two (3.8%) patients.

We then examined the risk factors for LNM (Table 4). All patients with LNM had well-differentiated adenocarcinoma; thus, no difference was noted in the risk of LNM according to the histological type. We investigated whether the depth of SM invasion was higher or lower than 2000 μm in patients with LNM; the findings were insignificant ($p = 1$). LNM was confirmed in 4 (25.0%) of 16 patients with vascular invasion and in 4 (10.9%) of 37 without vascular invasion ($p = 0.224$). Univariate analysis revealed that these factors were not significant. Furthermore, LNM was confirmed in 4 (36.4%) of 11 patients with grade 2 or 3 tumor budding and in 4 (9.5%) of 42 with grade 1 tumor budding ($p = 0.048$). These factors were significant in univariate analysis but not in multivariate analysis. Muconodules at the site of the deepest invasion were observed in four patients (7.5%); LNM was confirmed in one (25.0%) of four patients with muconodules and in 7 (14.3%) of 49 without muconodules ($p = 0.491$). According to univariate analysis, these factors were insignificant. The patients with LNM were significantly younger than those without LNM (57.6 ± 4.9 years vs 70.1 ± 7.2 years; $p < 0.0001$). These were also significant in the multivariate analysis ($p = 0.018$).

The clinicopathological features of the two patients (3.8%) with postoperative recurrence are shown in Table 5. One patient underwent hepatectomy and developed lung metastases 16 months later; subsequently, bone metastases were noted. Distant metastases were treated using chemoradiotherapy; however, the patient died 26 months after the additional surgery. For the other patient, six positive nodes were identified at the time of additional surgery. Moreover, LNM was noted

Table 4 Risk factors for lymph node metastasis. LNM, lymph node metastasis; SM, submucosal; SD, standard deviation; OR, odds ratio; and CI, confidence interval

	LNM(−)	LNM(+)	Univariate analysis p value	Multivariate analysis OR (95% CI) p value
SM invasion depth			1	
< 2000 μm	21	4		
≥ 2000 μm	24	4		
Vascular invasion			0.224	19.1 (0.546–671) 0.104
Negative	33	4		
Positive	12	4		
Tumor budding			0.048	
Grade 1	38	4		
Grade 2,3	7	4		
Muconodules			0.491	
Negative	42	7		
Positive	3	1		
Age (mean ± SD)	70.1 ± 7.2	57.6 ± 4.9	< 0.0001	0.468 (0.248–0.882) 0.018

Table 5 Clinical and pathological characteristics of patients with recurrence. LN, lymph node; LNM, lymph node metastasis: SM, submucosal; Rt, right; and Well, well differentiated

Age	Sex	Location	SM invasion depth μm	Vascular invasion	Tumor budding grade	Muconodules	Histologic type	Additional surgery	Surgical findings	Time to recurrence months	Location of recurrence	Outcome after surgery months
58	Female	Rt colon	3500	Positive	3	Negative	Well	Rt hemicolectomy hepatectomy	Liver meta 2 LNM	15	Lung, bone	Dead 26
49	Female	Rectum	2000	Negative	1	Positive	Well	Laparoscopic low anterior resection	6 LNM	54	LN	Alive 58

deep within the pelvic cavity 54 months postoperatively. Considering the patient's request, chemoradiotherapy was administered.

In the follow-up period, one patient without LNM died of other disease after additional surgery. Kaplan-Meier analysis showed no significant difference in survival between patients with and without LNM (Fig. 3).

Discussion

ESD is a procedure that allows en bloc resection in a minimally invasive manner. It is primarily indicated for large tumors, particularly early stage cancers that cannot be resected using EMR [1, 5, 8]. In the present study, patients underwent additional surgery in accordance with the JSCCR guidelines after undergoing ESD for T1 colorectal carcinoma [1, 5]. As the incidence of LNM is approximately 10–15%, D2 dissection is necessary for T1 colorectal cancer [1, 4, 5, 9]. In the present study, 15.1% of patients who underwent additional surgery after colorectal ESD had LNM. Of the patients with vascular invasion, 25.0% had LNM. In addition, LNM was noted in two (33.3%) of six patients with both lymphatic and venous invasion. Vascular invasion appeared as a possible risk factor of LNM but was not significant in univariate analysis.

We compared by the degree of depth of SM invasion. It was reported that the depth of SM invasion of ≥ 2000 μm led to an increased risk for LNM [10, 11]: however, we could not confirm this in our study. Tumor budding is a strong predictor of LNM in patients with SM invasive colorectal cancer [1, 5, 12, 13]. In the present study, this factor deemed significant by univariate analysis and tumor budding seemed to be an important risk factor for LNM in patients with colorectal cancer. However, multivariate analysis could not show significance

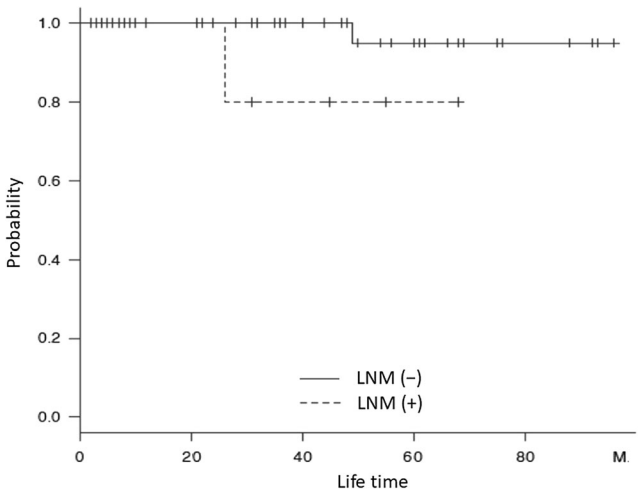

Fig. 3 Kaplan-Meier curves for the 53 patients who were treated with additional surgery after colorectal ESD. ESD, endoscopic submucosal dissection; LNM, lymph node metastasis; and M, month

of this factor. Muconodules at the site of the deepest invasion are a risk factor for regional LNM in T1 colorectal carcinoma [1, 5, 14]. In this study, muconodules appeared to be the only potential risk factor in one patient with recurrence. However, the number of patients was less and muconodules were not evaluated in this study. The risk of LNM could not be histologically determined because all patients with LNM had well-differentiated adenocarcinoma.

Additional surgery was performed for all patients with positive vertical margin, and none of these patients had LNM. However, residual tumor was observed in the resected specimens of 2 (13.3%) of 15 patients with positive vertical margin; moreover, the need for additional surgery was strongly suggested. There were no reports of younger patients being at risk for LNM of T1 colorectal cancer. Meanwhile, in this study, patients with LNM were significantly younger than those without LNM and were significant in multivariate analysis. Therefore, patient age may need to be considered in future research. Additional surgery is recommended for patients with a high risk of LNM after ESD for colorectal cancers [4, 15]. In this study, two patients with LNM had six positive nodes and two patients with LNM had two positive nodes. Moreover, the incidence of liver metastasis is markedly low (1.2%) in patients with T1 colorectal cancer [16]; however, multiple liver metastases were preoperatively noted in one of our patients. Appropriate lymph node dissection is required, and the possibility of distant metastasis should be considered when performing additional surgery.

Postoperative recurrence was detected in 2 (3.8%) patients in this study. Reportedly, local recurrences are mainly observed in patients with rectal cancer [4, 17]; consistent with this, in the present study, recurrence was also observed in one patient with rectal cancer. Particular care is needed when following up high-risk patients, and at least 5 years of follow-up appears to be necessary. The prognosis has been noted to be poor in patients with recurrence during follow-up after ESD [15, 18]. Nevertheless, if patients with non-R0 resection undergo appropriate additional surgical resection, long-term outcomes may be favorable [19, 20]. The 5-year recurrence-free survival rate of high-risk patients following endoscopic resection and additional surgery has been reported to be 97%, which is slightly higher than that of patients following endoscopic resection alone [4]. Furthermore, the mortality of standard colorectal cancer surgery is reported to be 1–3% [21, 22] and the outcomes of this study were considered safe and effective. Therefore, additional surgery should be conducted based on appropriate criteria.

This study has several limitations. First, it was a single-center retrospective study that included relatively few cases. Although surgery was indicated, many patients declined additional surgery because of their age and comorbidities and many underwent surgery at other hospitals. Second, a total of 53 patients were followed up for a median duration of 45 (range, 2–96) months; however, 17 (32.1%) were followed up for < 2 years. The findings of this study should be further verified using a larger sample. Prospective studies assessing the effect of additional surgery for preventing recurrence after ESD are also needed.

In conclusion, additional surgery after ESD for T1 colorectal cancer was effective and had good long-term outcomes. Additional surgery should be considered in patients who are at a high risk of LNM after undergoing colorectal ESD.

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Compliance and ethical standards

This study was approved by the institutional ethics committee of the Kishiwada Tokushukai Hospital. Written informed consent was obtained from all participating patients.

Conflict of interest The authors have no conflicts of interest.

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