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ORIGINAL ARTICLE

Additional surgery for non-curative resection after endoscopic submucosal dissection for gastric cancer: a retrospective analysis of 200 cases

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Abstract

Purpose Endoscopic submucosal dissection is recommended for early gastric cancer with a low risk of lymph node metastasis. When the pathological findings do not meet the curative criteria; then, an additional gastrectomy with lymph node dissection is recommended. However, most cases have neither lymph node metastasis nor a local residual tumor during an additional surgery.

Methods This was a single-institutional retrospective cohort study, analyzing 200 patients who underwent an additional gastrectomy after non-curative endoscopic submucosal dissection from January 2005 to October 2015. We reviewed the patients' clinicopathological data and evaluated the predictors for the presence of a residual tumor.

Results Histopathology revealed lymph node metastasis in 15 patients (7.5 %) and a local residual tumor in 23 (11.5 %). A multivariable analysis revealed macroscopic findings (flat/elevated type) ($p = 0.011$, odds ratio = 4.63), lymphatic invasion ($p < 0.0001$, odds ratio = 14.2), and vascular invasion ($p = 0.04$, odds ratio = 4.00) to be predictors for lymph node metastasis. A positive vertical margin ($p = 0.0027$, odds ratio = 3.26) and horizontal margin ($p = 0.0008$, odds ratio = 5.74) were predictors for a local residual tumor. All cases with lymph node metastasis had lymphovascular invasion with at least one other non-curative factor.

Conclusions The risk of a residual tumor can, therefore, be estimated based on the histopathology of endoscopic submucosal dissection samples. Lymphovascular invasion appears to be a pivotal predictor of lymph node metastasis.

Keywords Gastric cancer · Additional gastrectomy · Endoscopic submucosal dissection · Lymph node metastasis

Introduction

Recent progress in diagnostic technology has increased the detection of early gastric cancer (EGC), especially in Japan and Korea, where nationwide screening systems have been established, and where EGC exceeds 50 % of all detected gastric cancer. EGC is defined as invasive cancer existing within the submucosa, regardless of the presence of lymph node (LN) metastasis. A large-scale analysis of surgical EGC revealed that the majority of EGC cases have no LN metastasis [1, 2]; therefore, endoscopic intervention, currently the performance of endoscopic submucosal dissection (ESD), has been recommended when patients are diagnosed with possible EGC with low risk of LN involvement.

According to the 2010 Japanese Gastric Cancer Association (JGCA) treatment guidelines [3], the absolute indications for endoscopic resection are the following

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tumor characteristics: differentiated-type in histology, T1a, ulceration (UL) (−), and ≤2 cm in diameter. The following are expanded indications: (a) differentiated-type, T1a, UL (−), but >2 cm; (b) differentiated-type, T1a, UL (+), and ≤3 cm; and (c) undifferentiated-type, T1a, UL (−), and ≤2 cm. The JGCA guidelines include the pathological criteria of curative resection after ESD, and patients not fulfilling the criteria are diagnosed as non-curative resection. For the non-curative resection patients, an additional gastrectomy with LN dissection is recommended because of the potential risk of LN metastasis or a local residual tumor. Although the JGCA guidelines recommend an additional surgery based on these criteria, many cases have neither LN metastasis nor a local residual tumor in surgical specimens obtained during an additional surgery. Therefore, avoiding unnecessary surgery is desirable regarding surgical invasiveness, medical costs, and expected effects on the patients' quality of life. However, clinically, it can be difficult to decide whether to perform additional surgery when a patient is elderly or in the poor general condition, even if the pathological findings do not satisfy the criteria. In addition, the indications for ESD have recently been expanded; therefore, it is even more important to clarify the predictive factors for the presence of residual cancer.

This retrospective cohort study aimed to analyze the clinicopathological features of patients who underwent additional gastrectomy after ESD in our institution as well as to determine the predictive factors for LN metastasis or a local residual tumor and to identify the optimal strategy or management of non-curative resection after ESD.

Methods

Study design

This was a retrospective single-institutional cohort study using a clinical database. The medical records of patients who underwent additional gastrectomy after ESD from January 2005 to October 2015 at our institution were retrospectively reviewed. The incidence of pathologically proven LN metastasis or local residual tumor was investigated. In addition, using clinicopathological variables, the predictive factors for these outcomes were estimated by the univariable and multivariable analyses. This study was approved by the Institutional Review Board of the National Cancer Center, Japan (IRB file No.: 2015-050, approval date: May. 27, 2015).

ESD procedure

All ESD procedures were performed by endoscopic instructors or skillful endoscopists using a single-channel upper gastrointestinal endoscope (GIF-Q260J; Olympus

Medical Systems, Tokyo, Japan) with a water-jet system (OFP; Olympus), and a high-frequency generator (ICC200 or VIO300D; Erbe Elektromedizin Ltd, Tuebingen, Germany). The transparent attachment (disposable distal attachment; Olympus) was fitted onto the tip of the endoscope.

The mucosa around the lesion was cut circumferentially with an insulation-tipped diathermic knife 2 (IT knife 2; Olympus) after injection into the submucosal layer of 0.4 % sodium hyaluronate (MucoUp®; Johnson & Johnson, Tokyo, Japan) diluted with normal saline solution to create a submucosal cushion. The swollen submucosal layer was subsequently dissected with the same devices after additional injections into the submucosal layer. All patients underwent ESD using carbon dioxide (CO_2) insufflation.

The patients were placed in the left lateral decubitus position and put under sedation with an intravenous injection of 2–3-mg midazolam and 35-mg pethidine hydrochloride. Sedative drugs were added as required to keep the patients calm, and the patients were monitored with pulse oximeters and administrated oxygen via a cannula when their saturation became low.

Criteria for non-curative resection of ESD

Pathological diagnoses were provided by two authorized pathologists. The pathological findings were evaluated according to the JGCA classification, the third English Edition [4]. In this study, non-curative resection of ESD was diagnosed when the pathological findings did not fulfill the criteria for curative resection as defined by the JGCA guidelines [3]. The JGCA guidelines have been amended several times during the study period. Until 2010, we followed the second edition algorithm and the third edition algorithm until 2014. Since 2014, we have followed the fourth edition algorithm. Following the latest guidelines, in this study, patients were diagnosed as non-curative resection when they satisfied at least one of the following conditions (Table 1): (1) undifferentiated dominant type, and (1-a) submucosal invasion, (1-b) ulceration (+), and (1-c) >2 cm; (2) differentiated dominant type, and (2-a) the existence of an undifferentiated component in the submucosal (sm) layer, (2-b) within mucosa but ulceration (+) and >3 cm, (2-c) sm1 invasion (<500 μm) and >3 cm, and (2-d) sm2 invasion (≥500 μm); (3) lymphatic invasion (+); (4) vascular invasion (+); (5) vertical margin (VM) (+) or could not be assessed; (6) horizontal margin (HM) (+) or could not be assessed; and (7) without *en-bloc* resection. Tubular adenocarcinoma and papillary adenocarcinoma were defined as differentiated. Poorly differentiated adenocarcinoma, signet-ring cell adenocarcinoma, and mucinous adenocarcinoma were defined as undifferentiated. The histological type was determined according to each quantitatively predominant component.

Table 1 Pathological determinants of a diagnosis of non-curative resection

Reasons for non-curative resection (with overlap)	n	%
1. Undifferentiated dominant type		
(a) Submucosal invasion	18	(9.0)
(b) Ulceration (+)	2	(1.0)
(c) >2 cm	16	(8.0)
2. Differentiated dominant type		
(a) Existence of undifferentiated component in the submucosal layer	17	(8.5)
(b) Within mucosa but ulceration (+) and >3 cm	5	(2.5)
(c) sm1 invasion (<500 μm), and >3 cm	15	(7.5)
(d) sm2 invasion (≥500 μm)	117	(58.5)
3. Lymphatic invasion (+)	73	(36.5)
4. Vascular invasion (+)	48	(24)
5. Vertical margin (+) or could not be assessed	35	(17.5)
6. Horizontal margin (+) or could not be assessed	34	(17.0)
7. Without *en-bloc* resection	9	(4.5)

Additional gastrectomy

The type of gastrectomy was determined based on the location of the ESD scar [3]. Regarding the extent of LN dissection, in principle, D1 + dissection was performed, but D2 was also done when an undifferentiated tumor massively invaded the submucosa in an ESD specimen. The surgical approach has changed over time with open surgery performed until 2009 and laparoscopic surgery the predominant choice since 2010. Robot-assisted surgery was introduced in 2014 as a clinical investigation. The grading of postoperative complications was done according to the Clavien-Dindo classification system [5].

Statistical analysis

All analyses were conducted by the Chi-square test using the JMP software version 12.0 for windows (SAS Inc., Cary, NC, USA). Univariable and multivariable analyses were performed using a logistic regression analysis. $p < 0.05$ was considered statistically significant. Odds ratios (OR) and 95 % confidence intervals (CI) were also calculated for the multivariable analyses.

Results

Patients' characteristics

A total of 1884 patients underwent ESD between January 2005 and October 2015 at our institution. Among these, 1349 (71.6 %) satisfied the criteria of curative resection.
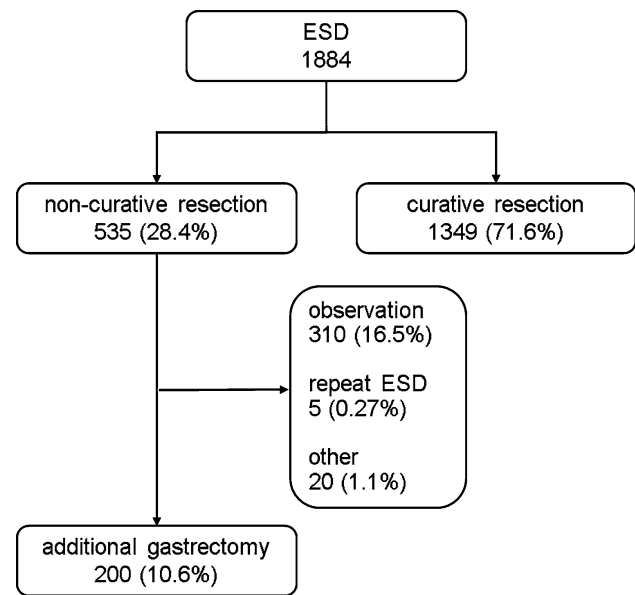
Fig. 1 Flowchart after ESD for clinically early gastric cancer. Among 1884 patients who underwent ESD, 1349 fulfilled the criteria of curative resection. In 535 patients diagnosed as non-curative resection. 310 were observed without treatment, five underwent repeat ESD, and the remaining 200 underwent additional gastrectomy. *ESD* endoscopic submucosal dissection

In 535 patients, (28.4 %) diagnosed as non-curative resection. 310 (16.5 %) were observed without further treatment, because the patients either declined treatment or had a poor general condition related to comorbidities, five (0.27 %) underwent repeat ESD, and the remaining 200 (10.6 %) underwent additional gastrectomy (Fig. 1). The clinicopathological features of these 200 patients are summarized in Table 2. Among them, 95 patients (47.5 %) underwent ESD as absolute indications of the JGCA guidelines, 98 patients (49 %) as expanded indications and 7 patients (3.5 %) beyond these indications, but with a diagnostic intent due to the patients' request or conditions. Regarding the macroscopic appearance of the primary tumor, a depressed type was the most common (72 %). Histologically, the undifferentiated dominant type was recorded in 15.0 % of patient specimens. The pathological statuses defining non-curative resection in these 200 patients are shown in Table 1. The most frequent factor for non-curative resection was sm2 invasion in the differentiated dominant type (58.5 %), and the second was lymphatic invasion (36.5 %). VM (+), and HM (+) were recognized in 17.5 and 17.0 % of the specimens, respectively.

Additional surgery

The most common procedure was distal gastrectomy (65.5 %). Proximal gastrectomy, a type of

Table 2 Patients' clinicopathological features before additional surgery

Variables		
Sex ratio (male:female)	158:42	
Age (years)[a]	68	(43–81)
Types of macroscopic appearance		
Depressed	144	(72.0)
Elevated	53	(26.5)
Flat	3	(1.5)
Maximum diameter (mm)[a]	25	(5–77)
Depth of tumor invasion		
m	35	(17.5)
sm1	37	(18.5)
≥sm2	128	(64.0)
Dominant histological type		
Differentiated	168	(84.0)
Undifferentiated	30	(15.0)
Special type	2	(1.0)
Tumor location		
Upper	55	(27.5)
Middle	77	(38.5)
Lower	68	(34.0)
Circumferential location of tumor		
Less	92	(46.0)
Post	44	(22.0)
Ant	22	(11.0)
Gre	42	(21.0)
Indication criteria for ESD		
Absolute indications	95	(47.5)
Expanded indications	98	(49)
Beyond indications	7	(3.5)

Values in parentheses are percentages unless indicated otherwise

Less lesser curvature, *Post* posterior wall, *Ant* anterior wall, *Gre* greater curvature, *ESD* endoscopic submucosal dissection

[a] Values are the median (range)

function-preserving surgery, was also commonly performed (21.0 %) (Table 3). Approximately half of the patients underwent laparoscopic surgery (46.5 %), no deaths were observed related to the surgery. Ten patients (5.0 %) developed grade III postoperative complications, including pancreatic fistula or anastomotic leakage. A pathological examination of the surgical specimens revealed LN metastasis in 15 patients (7.5 %) and local residual tumor in 23 patients (11.5 %). When these incidences were analyzed for each of the indication criteria of ESD, the incidence of LN metastasis was 4.2 % in absolute indications, 10.2 % in expanded indications, and 14.0 % beyond these indications. Likewise, the incidence of a local residual tumor was 9.5 % in absolute indications, 13.2 % in expanded indications, and 14 % beyond

Table 3 Clinical outcomes of additional surgery

Variables		
Type of gastrectomy		
Distal gastrectomy	131	(65.5)
Total gastrectomy	10	(5.0)
Proximal gastrectomy	42	(21.0)
Pylorus-preserving gastrectomy	13	(6.5)
Remnant gastrectomy	4	(2.0)
Approach		
Laparoscopic surgery	93	(46.5)
Open surgery	104	(52.0)
Robot-assisted surgery	3	(1.5)
Operating time (min)[a]	197.5	(97–371)
Operative blood loss (g)[a]	71.5	(0–1129)
Lymph node metastasis (+)	15	(7.5)
Local residual tumor (+)	23	(11.5)

Values in parentheses are percentages unless indicated otherwise

[a] Values are the median (range)

these indications. The median number of metastatic LNs was 1 (range 1–7). All patients exhibited LN metastasis within D1 + level LN stations for each type of gastrectomy; two patients at station 1, eight at station 3, one at station 4d, two at station 6, two at station 7, two at station 8a, and one at station 11p.

Relationship between the clinicopathological parameters and LN metastasis/a local residual tumor

Table 4 shows the association between the clinicopathological parameters and LN metastasis/local residual tumor. A univariable analysis verified that LN metastasis was associated with the macroscopic appearance (flat/elevated type) ($p = 0.004$), lymphatic invasion ($p < 0.0001$), and vascular invasion ($p = 0.007$). Likewise, a local residual tumor was associated with VM (+) ($p = 0.0005$) and HM (+) ($p < 0.0001$). A multivariable analysis also revealed the macroscopic appearance (flat/elevated type) (OR = 4.63, 95 % CI 1.41–16.8), lymphatic invasion (OR = 14.2, 95 % CI 3.55–97.4), and vascular invasion (OR = 4.00, 95 % CI 1.04–18.0) to be independent predictive factors for LN metastasis, and that VM (+) (OR = 3.26, 95 % CI 1.15–8.94) and HM (+) (OR = 5.74, 95 % CI 2.10–15.8) were independent predictive factors for local residual tumor (Table 5). We further examined the patients' characteristics of a flat/elevated appearance type. As one of the possible associated factors; histologically, a papillary type was also considered. A papillary type was more frequently found in patients with a flat/elevated type (11/56; 19.6 %) compared with those with a depressed type (10/144; 6.9 %), and the difference was statistically significant ($p = 0.0012$).

Table 4 Relationship between the clinicopathological data and LN metastasis or a residual tumor

	Total	LN metastasis (n = 15)	p value	Local residual tumor (n = 23)	p value
Macroscopic appearance			0.004		NS
Depressed	144	6 (4.2)		19 (13.2)	
Flat/elevated	56	9 (16.1)		4 (7.1)	
Depth of invasion			NS		NS
<sm1	72	3 (4.2)		5 (6.9)	
≥sm2	128	12 (9.4)		18 (14.1)	
Diameter			NS		NS
<3 cm	116	7 (6.0)		10 (8.6)	
≥3 cm	80	8 (10.0)		13 (16.3)	
Ulceration			NS		NS
Negative	182	15 (8.2)		21 (11.5)	
Positive	18	0 (0)		2 (11.1)	
Histological type			NS		NS
Differentiated	168	14 (8.3)		16 (9.5)	
Undifferentiated	30	1 (3.3)		7 (23.3)	
Special type	2	0 (0)		0 (0)	
Lymphatic invasion			<0.0001		NS
Negative	128	2 (1.6)		13 (10.2)	
Positive	72	13 (18.1)		10 (13.9)	
Vascular invasion			0.007		NS
Negative	151	7 (4.8)		13 (8.6)	
Positive	49	8 (17.0)		10 (20.4)	
Vertical margin			NS		0.0005
VM (−)	165	12 (7.3)		13 (7.9)	
VM (+)	35	3 (8.6)		10 (11.5)	
Horizontal margin			NS		<0.0001
HM (−)	166	15 (9.0)		12 (7.2)	
HM (+)	34	0 (0)		11 (32.4)	

Values in parentheses are percentages

VM vertical margin, *HM* horizontal margin, *NS* not significant

Table 5 Multivariable analysis of the relationship between the clinicopathological data and LN metastasis, or a local residual tumor

	OR	95 % CI	*p* value
LN metastasis			
Depth of invasion: ≥sm2	1.55	0.31–8.75	NS
Macroscopic appearance: flat/elevated	4.63	1.41–16.8	0.011
Lymphatic invasion positive	14.2	3.55–97.4	<0.0001
Vascular invasion positive	4.00	1.04–18.0	0.04
Local residual tumor			
Depth of invasion: ≥sm2	2.61	0.90–9.01	NS
Histological type: undifferentiated	2.23	0.69–6.68	NS
VM (+)	3.26	1.15–8.94	0.0027
HM (+)	5.74	2.10–15.8	0.0008

sm2 submucosal invasion ≥500 μm, *OR* odds ratio, *CI* confidence interval, *NS* not significant, *VM* vertical margin, *HM* horizontal margin

Table 6 A 2 × 2 contingency table showing the interactions between lymphovascular invasion plus at least one other non-curative factor, and the presence of lymph node metastasis

	Lymphovascular invasion plus at least one other non-curative factor		Total
	Yes	No	
LN metastasis (+)	15	0	15
LN metastasis (−)	67	118	185
Total	82	118	

LN lymph node

However, a papillary type was not identified as an independent predictor for LN metastasis.

The clinicopathological characteristics of 15 patients with LN metastasis were further examined, and all 15 patients were diagnosed histopathologically as either lymphatic or vascular invasion positive. In addition, at least one other non-curative factor was present in each patient. Regarding this finding, a 2 × 2 contingency table was created (Table 6) which shows that the sensitivity of this qualification was 100 % (95 % CI 80.5–100 %), specificity was 63.8 % (95 % CI 62.2–63.8 %), positive predictive value was 18.3 % (95 % CI 14.7–18.3 %), and negative predictive value (NPV) as 100 % (95 % CI 97.5–100 %).

Recurrence

The median follow-up period in the additional surgery group was 25.3 months (range 1–126 months). One patient experienced recurrence. This patient had a 0-IIc lesion (45 mm, tub2, cT1a) on the posterior wall of the prepyloric region. Primary ESD was employed as an expanded indication, but the pathological findings of the ESD specimen were sm1 (420 μm), tub2 > por/sig, ly2, v0, pHMX, and pVM0. As additional surgery, laparoscopic distal gastrectomy was performed. In the resected specimen, a residual tumor (poorly differentiated component) was recognized in the subserosal layer apart from the ESD scar. There were seven pathological metastatic LNs (LN stations of No.6, 7, and 8a); therefore, the patient was diagnosed as pT3Na3M0 StageIIIB. Adjuvant chemotherapy was done, but peritoneal recurrence was seen 10 months after the additional surgery.

Discussion

To the best of our knowledge, the present study had the largest number of cases compared with similar published studies. In our 200 cases of additional surgery, the rate of LN metastasis was 7.5 % and the rate of a local residual tumor was 11.5 %, which were similar to the outcomes in previous reports with smaller numbers of cases [6–10].

Regarding local residual tumor at the ESD scar, as expected, positive VM and positive HM were independent predictors in our study, as reported in previous studies [6, 8, 9, 11]. On the other hand, some authors reported only HM as risk factors for local residual tumor because of lower thermal injury caused by electrocoagulation devices [8, 12]. In the present study, actually 32.4 % of patients with positive HM had a local residual tumor. However, we believe that positive VM may suggest deep submucosal invasion of the primary tumor; therefore, careful clinical decision-making is necessary. In our series, 8.6 % of patients with positive VM had LN metastasis and 11.5 % had local residual tumor. The management of positive HM is debated, and there is no persuasive consensus. Several researchers have stated that LN metastasis is very low when positive HM is the only non-curative factor [13]. Numata et al. [14] reported that all local recurrences during follow-up in the positive HM cases that were intramucosal lesions and could be treated by repeat ESD. They concluded that for the positive HM cases, strict surveillance should be considered first; and repeat ESD can be employed when the recurrent lesion is a differentiated intramucosal lesion. Clinically, the decision should be specific for each patient. If there is an additional non-curative factor combined with the positive HM, then additional surgery should be considered.

In terms of ESD for remnant gastric cancer, some researchers have already reported its efficacy and favorable long-term outcomes [15–17], though for lesions involving an anastomotic ring or suture line, this procedure is technically demanding. In our center, ESD for remnant gastric cancer is basically applied with the same indications as

that for usual cases. However, given the difficulty of surgical resection, it is likely to be employed as for diagnostic purposes. The current study included four cases (2 %) of ESD for remnant gastric cancer, and these patients received remnant gastrectomy as additional surgery. Among them one local residual tumor was recognized, and actually this patient received ESD for diagnostic purposes in spite of a suspicion of cT1b.

Regarding the predictive factors for LN metastasis, previous reports identified several parameters, including submucosal invasion, tumor size (larger than 2–3 cm), lymphovascular invasion, or undifferentiated-type [6, 7, 11]. Among these factors, several authors emphasized lymphovascular invasion as a crucial prognostic factor [6, 7, 18]. Kim et al. [19] and Lee et al. [20] stated that there was no LN metastasis in patients with the differentiated-type without lymphovascular invasion in their series. Lymphovascular invasion is also a reported prognostic factor in such patients without additional surgery [21, 22]. The present study also revealed that lymphovascular invasion and flat/elevated type are independent risk factors, and we, therefore, made an index to more precisely estimate the risk of LN metastasis using these factors. Interestingly, the condition "lymphovascular invasion plus at least one other noncurative factor" was an indicated factor for estimating LN metastasis, with an NPV of 100 %. High NPV means that this qualification is useful to define a low-risk subpopulation. In other words, patients not meeting this qualification are unlikely to have LN metastasis. This qualification may be helpful when treating elderly patients or patients with severe comorbidities. However, it should be noted that this qualification is not useful for making definitive diagnoses because of its low positive predictive value of 18.3 %. It is unclear why the flat/elevated type was associated with LN metastasis, although Jung et al. [8] also reported similar results. They presumed that the estimation of the invasion depth during diagnostic endoscopy might have been difficult with the elevated type tumor. Sekiguchi et al. [23] reported that the EGC cases with a papillary adenocarcinoma (pap) component were at higher risk for lymphatic invasion and also showed a higher percentage of positive LN metastasis. Actually, in our study, a pap component was found more frequently in 11 (19.6 %) of 56 cases with a flat/elevated type than in 10 (6.9 %) of 144 cases with a depressed type ($p = 0.012$).

Regarding the optimal extent of LN dissection in the additional surgery, there is also no consensus or ideal recommendation. Performing D1 + dissection appears reasonable, because in principle, ESD-treated lesions are EGC. In the present study, extragastric LN metastasis was detected in four of 15 patients, but all were within D1 + level LN stations. Son et al. [7] also reported the status of LN metastasis after additional surgery, and stated that all except

one patient exhibited metastases within level D1+; however, the invasion depth of this exceptional case was T3. If LN metastasis is strongly suspected, for example, several predictive factors coexist, D2 dissection may be selected, because in the JGCA guidelines [4], D2 LN dissection is recommended for patients preoperatively diagnosed with LN involvement. When there is a probability of invasion to the muscle layer (T2) based on the pathological findings, D2 dissection should thus be applied.

There are several limitations associated with our study, including the retrospective design and single-institution setting, which may include some selection bias. To more precisely identify risk factors, studies using larger, multi-institutional databases are required. A prospective study comparing additional surgery and observation, evaluating recurrence rate as an endpoint, should be conducted in the low-risk subpopulation with residual cancer. It also remains necessary to determine the optimal surveillance strategy for patients without additional surgery.

In conclusion, positive HM and VM were found to be independent predictive factors for a local residual tumor, and lymphovascular invasion and a macroscopic flat/elevated type were identified to be predictors for LN metastasis in patients who underwent additional surgery after ESD. Patients without lymphovascular invasion appear to be a low-risk subpopulation for LN metastasis. To determine the indications for additional surgery, both surgeons and gastroenterologists should consider the balance of risk for LN metastasis and a local residual tumor on and individual basis, including the presence of comorbidities or the patient's life expectancy.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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