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The Modified eCura System for Identifying High-Risk Lymph Node Metastasis in Patients with Early Gastric Cancer Resected by Endoscopic Submucosal Dissection

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Abstract: Background: Endoscopic submucosal dissection (ESD) is widely used for early gastric cancer (EGC) in patients without lymph node metastasis (LNM). Prediction of LNM after ESD is important to determine prognosis in patients with EGC. In this regard, the eCura system was applied to predict LNM after noncurative ESD for EGC. This study aimed to identify risk factors for LNM and improve the accuracy of the eCura system for predicting the risk of LNM after ESD. Methods: A total of 150 patients who underwent noncurative resection of EGC by ESD were retrospectively enrolled at five institutions in Japan. All patients underwent additional surgery with lymph node resection after ESD. The risk factors for LNM among clinicopathological parameters were examined and receiver operating characteristic curve (ROC) analysis was used to determine the optimal cutoff point for predicting high LNM risk using the modified eCura system. Results: Of 150 patients, 19 (13%) had LNM. In the multivariate analysis, lymphatic invasion, and tumor size >30 mm were independent risk factors for LNM. Using a cutoff score of ≥4 for predicting high risk based on the eCura system, the rate of LNM was significantly higher in the high-risk group (4–7 points) than in the low-risk group (0–3 points) (odds ratio 12.0, 95% confidence interval 3.7–54.2, $p < 0.0001$). Conclusions: An eCura score ≥4 may improve the prediction of LNM risk after ESD in patients with EGC in the intermediate-risk group (2–4 points) of the eCura system, suggesting better treatment strategies for patients. Further prospective and long-term follow-up studies are needed to validate the efficacy of the modified system.

Keywords: gastric cancer; endoscopic submucosal dissection; risk factor; lymph node; metastasis

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1. Introduction

Early gastric cancer (EGC) without lymph node metastasis (LNM) can be resected by endoscopic resection [1–3]. Endoscopic submucosal dissection (ESD) for EGC is an effective treatment that was developed in Japan in the 1990s and is associated with a good long-term prognosis [4]. For lesions in which ESD is noncurative, radical gastrectomy with lymph node dissection is recommended [1–3]. However, LNM is seen in only 5–10% of such lesions [5–8]. Furthermore, preoperative staging of gastric cancer is difficult [9–11]. The accuracy rates of endoscopic ultrasonography in identifying T stage and N stage are 41% and 42.9%, respectively, and those of computed tomography (CT) are 4% and 56%, respectively [12].

In 2017, the eCura system to assess curability after ESD for EGC was reported to clarify the risk factors of LNM [12]. The rate of LNM after additional surgery in patients with noncurative resection is not very high [13]. Therefore, most patients do not actually require additional surgery. In the eCura system, lesions with noncurative resection are divided into three risk groups: high, intermediate, and low. The rate of LNM in the high-risk group is 22.7%, that in the intermediate-risk group is 6.7%, and that in the low-risk group is 2.5% [12]. In the high-risk group, cancer recurrence is significantly higher, and cancer-specific survival (CSS) tends to be lower in patients who did not receive additional treatment than in those who underwent radical surgery. In contrast, in the low-risk group, there was no significant difference in CSS between patients who did not receive additional treatment and those who underwent radical surgery after noncurative ESD of EGC (5-year CSS: 99.6% vs. 99.7%). A multivariate regression analysis also revealed that there was no significant difference in cancer recurrence and cancer-specific mortality between patients who did not receive additional treatment and those who underwent radical surgery [12].

Conversely, in the intermediate-risk group, patients who did not receive additional treatment have a high hazard ratio for cancer-specific mortality (1.66) and cancer recurrence (2.00); however, in multivariate regression analysis, there is no significant difference in cancer recurrence and cancer-specific mortality between patients who did not receive additional treatment after ESD and those who underwent radical surgery [14]. Therefore, in the intermediate-risk group, it is often difficult to decide the treatment policy. To address this, we examined the risk factors for LNM and modified the eCura system to stratify the risk of LNM by simplifying it into two groups, high-risk and low-risk, to avoid unnecessary radical surgery in patients with EGC who undergo ESD.

2. Materials and Methods

2.1. Study Design

The study was a retrospective, multicenter, hospital-based cohort study in Japan. We evaluated 2,434 patients with EGC who underwent ESD at five institutions in Japan between January 2004 and November 2018. Among these patients, 150 with noncurative resection who underwent additional surgery after ESD were included in this study. The study was approved by the Institutional Review Board of Aichi Medical University (No.2020-H149) and received ethical approval from each study center's local ethics committee. Written informed consent was obtained from all study participants.

2.2. ESD procedure

All the institutions that participated in the study were staffed by clinical staff from Aichi Medical University that perform treatment of EGC with the same protocol and procedures for ESD. A conventional gastroscope (GIF-H260, GIF-Q260J, GIF-HQ290, Olympus Corp., Tokyo, Japan) was used for ESD. A mixture of hyaluronic acid (MucoUp; Johnson & Johnson K.K. Medical Co., Tokyo, Japan) and saline solution with indigo carmine dye was injected into the perilesional submucosa. Mucosal incision and submucosal dissection were performed using a Dual Knife (Endoscopy Medical System, Olympus Corp., Tokyo, Japan), Flush Knife (Fujifilm Medical Co., Ltd., Tokyo, Japan), Insulation-Tipped diathermic (IT) Knife (Olympus Corp. Tokyo, Japan), IT Knife2 (Olympus Corp.), Clutch Cutter

(Fujifilm Medical Co., Ltd.), or SB Knife Jr. (Sumitomo Bakelite Co., Ltd., Tokyo, Japan), depending on the individual endoscopist's preference. Details of the ESD procedure have been described by Gotoda et al. previously [15].

2.3. Outcome Measures

The resected specimens were microscopically evaluated for tumor depth of invasion, lateral and vertical margin involvement, and lymphatic and venous invasion. En bloc resection was defined as the endoscopic removal of the tumor in a single piece. Endoscopic complete resection was defined as en bloc resection without tumor at the lateral or vertical margins of the resected specimen. All lesions were scored based on both the eCura system and modified eCura system. The eCura system was developed to predict LNM in patients undergoing definitive surgery after noncurative ESD and consisted of a 7-point risk scoring system with three risk groups based on five clinicopathological parameters [12]. The eCura system estimated the risk of LNM after calculating the total score of the patient, in which 1 point is given for tumor size >30 mm, positive vertical margin, venous invasion, and deep submucosal invasion $\geq$500 μm (SM2) and 3 points are given for lymphatic invasion. In this scoring system, patients are categorized into three LNM risk groups based on the scores, namely, low-risk (0–1 points), intermediate-risk (2–4 points), and high-risk (5–7 points) [12,14]. The modified eCura system has been simplified from the three risk groups of the eCura system to two groups by determining thresholds for predicting LNM. Histopathologically, hematoxylin-eosin staining and, if histopathological evaluation was difficult, immunohistochemical staining were used to determine lymphatic and venous invasion. Histopathological evaluation was based on the Japanese Classification of Gastric Carcinoma. Esophagogastroduodenoscopy and CT were performed annually for follow-up of all patients according to the guideline of the Japanese Gastric Cancer Association. Cancer recurrence was defined as histopathologically or radiologically confirmed recurrence in the lymph nodes and/or other organs of the patients treated with EGC.

2.4. Statistical Analysis

To identify risk factors for LNM, we collected data on sex, age, tumor location, tumor diameter, depth of invasion, degree of differentiation, lymphatic invasion, vascular invasion, ulceration, lateral margin positivity, vertical margin positivity, and LNM. The Mann–Whitney U-test and chi-square test with Bonferroni correction were used to compare continuous and categorical data among the low-risk, intermediate-risk, and high-risk groups. When the data followed a normal distribution based on the Shapiro–Wilks test, Student's t-test was used. Odds ratios and 95% confidence intervals (CIs) were calculated using univariate and multivariate logistic regression analyses adjusted for age and sex. A receiver operating characteristic (ROC) curve was applied to estimate the clinical suitability of the model for predicting LNM. The sensitivity and specificity were examined using optimal cutoff points based on the ROC curve and categorized into two groups to explore potential improvements in stratification of the eCura system. Statistical analyses were performed using EZR version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [16]. All statistical tests were two-sided, and a p-value of 0.05 was considered statistically significant.

3. Results

The enrolled patients were predominantly male (85%) and the median age (interquartile range, IQR) was 69 (65–76) (Table 1). One hundred and eleven patients (74%) had SM2 invasion. Eighteen lesions (12%) had undifferentiated histology, 70 (47%) had lymphatic invasion, and 32 (21%) had venous invasion. A positive horizontal margin was seen in seven lesions (5%), and a positive vertical margin was seen in 35 lesions (23%). There were 19 lesions (13%) with LNM. During a median follow-up of 5.0 years for all cases, two patients with no LNM experienced local recurrence and one patient with LNM experienced distant metastasis after the additional surgery.

Table 1. Patient characteristics.

Variables		*N* = 150
Sex, *n* (%)	Male	128 (85)
	Female	22 (15)
Age, years, median (IQR)		69 (65–76)
Invasion depth, *n* (%)	M	6 (4)
	SM1	33 (22)
	SM2	111 (74)
Histological type, *n* (%)	Differentiated	132 (88)
	Undifferentiated	18 (12)
Lymphatic invasion, *n* (%)	Positive	70 (47)
	Negative	80 (53)
Venous invasion, *n* (%)	Positive	32 (21)
	Negative	118 (79)
Ulceration, *n* (%)	Positive	28 (19)
	Negative	122 (81)
Horizontal margin, *n* (%)	Positive	7 (5)
	Negative	140 (93)
	Unclear	3 (2)
Vertical margin, *n* (%)	Positive	35 (23)
	Negative	109 (73)
	Unclear	6 (4)
Lymph node metastasis, *n* (%)	Positive	19 (13)
	Negative	131 (87)
Recurrence, *n* (%)	None	147 (98)
	Local	2 (1)
	Distant	1 (1)

IQR, interquartile range; M, mucosa; SM, submucosa.

Table 2 shows the results of univariate analysis of the risk factors for LNM. Patients with LNM were significantly older (median, 73 years, IQR, 69–78 years) than patients without LNM (median, 69 years, IQR, 63–75 years) ($p = 0.044$). Lymphatic invasion was significantly more common in patients with LNM (LNM vs. no LNM: 95% vs. 40%: $p < 0.0001$). Patients with LNM also had significantly larger tumors (median, 34 mm, IQR, 18–50 mm) than patients without LNM (median, 20 cm, IQR, 14–30 mm) ($p = 0.0019$). Venous invasion was also more common in patients with LNM (LNM vs. no LNM: 42% vs. 18%; $p = 0.032$). Lymphatic invasion and tumor size >30 mm were significant independent risk factors of LNM in multivariate analysis adjusted by age and sex (odds ratio, 22.9, 95% CI: 2.9–180.0, $p = 0.003$ and odds ratio, 2.9, 95% CI: 1.3–11.8, $p = 0.017$, respectively; Table 3).

The diagnostic efficacy of the modified eCura system for identifying the risk of LNM was assessed by ROC curve analysis (Figure 1). The cutoff for estimating the risk of LNM was 4 points based on the ROC curve analysis. The Youden index, sensitivity, and specificity were 0.563, 0.842, and 0.725, respectively, with a resulting area under the curve of 0.836 (95% CI, 0.702–0.970). Fifty-two patients with 4–7 points were defined as the high-risk group, and the rate of LNM in this group was 23.5%. Conversely, 98 patients with 0–3 points were defined as the low-risk group, and the rate of LNM in this group was 3.1% (4–7 points vs. 0–3 points: odds ratio 12.0, 95% CI: 3.7–54.2, $p < 0.0001$) (Table 4).

Table 2. Univariate analysis of the risk for lymph node metastasis.

Variables		Lymph Node Metastasis		*p*-Value
		Negative *N* = 131 (%)	Positive *N* = 19 (%)	
Age (years), median (IQR)		69 (63–75)	73 (69–78)	0.044
Sex	Male	111 (85)	17 (90)	0.741
	Female	20 (15)	2 (10)	
Location	U	32 (24)	3 (16)	0.773
	M	61 (47)	10 (52)	
	L	38 (29)	6 (32)	
Tumor size (mm), median (IQR)		20 (14–30)	34 (18–50)	0.0019
	>30	25	10	0.002
	≤30	106	9	
Invasion depth	M	6 (4)	0 (0)	0.717
	SM1	30 (23)	3 (16)	
	SM2	95 (73)	16 (84)	
Histological type	Differentiated	114 (87)	18 (95)	0.472
	Undifferentiated	17 (13)	1 (5)	
Lymphatic invasion	Positive	52 (40)	18 (95)	<0.0001
	Negative	79 (60)	1 (5)	
Venous invasion	Positive	24 (18)	8 (42)	0.032
	Negative	107 (82)	11 (58)	
Horizontal margin	Positive	7 (5)	0 (0)	0.597
	Negative	121 (92)	19 (100)	
	Unclear	3 (3)	0 (0)	
Vertical margin	Positive	29 (22)	6 (32)	
	Negative	96 (73)	13 (68)	0.389
	Unclear	6 (5)	0 (0)	
Ulceration	Positive	24 (18)	4 (21)	0.757
	Negative	107 (82)	15 (79)	
Recurrence	Local	2 (2)	0 (0)	
	Distant	0 (0)	1 (5)	0.140
	None	129 (98)	18 (95)	

IQR, interquartile range; U, upper; M, middle; L, lower.

Table 3. Multivariate analysis of the risk factors of lymph node metastasis.

Risk Factors	Odds Ratio [a]	95% CI	*p*-Value
Lymphatic invasion	22.9	2.9–180.0	0.003
Venous invasion	2.6	0.8–8.1	0.112
Tumor size >30 mm	2.9	1.3–11.8	0.017

CI, Confidence interval; [a] Adjusted by age and sex.

Table 4. Rate of lymph node metastasis based on the modified eCura system.

Risk Score Groups [b]	*n*	Lymph Node Metastasis (%)	Odd Ratio [a] (95% CI)	*p*-Value
High risk (4–7 points)	52	16 (23.5)	12.0 (3.7–54.2)	<0.0001
Low risk (0–3 points)	98	3 (3.1)	1	

CI, Confidence interval; [a] Adjusted by age and sex; [b] Based on the modified eCura system

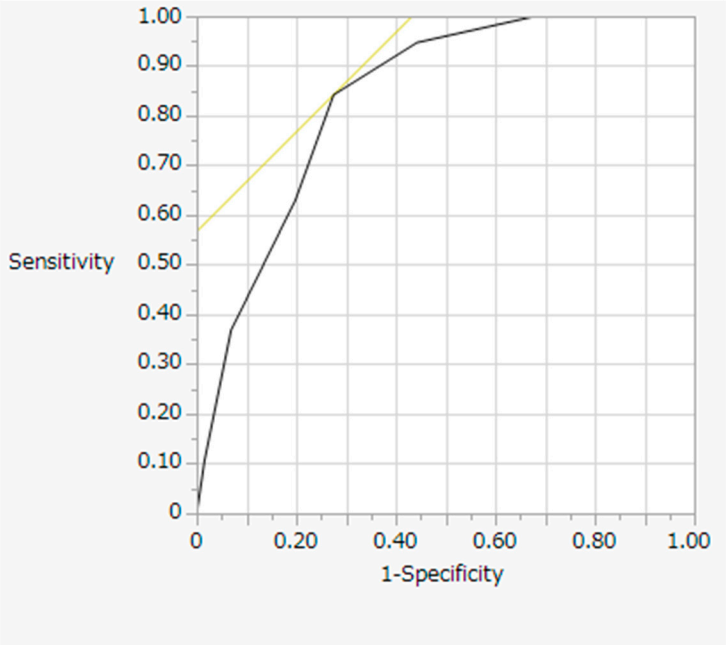

Figure 1. ROC curve analysis to determine the cutoff for predicting lymph node metastasis.

4. Discussion

Our results showed that lymphatic invasion and tumor size >30 mm were independent risk factors of LNM, as has been previously reported for the eCura system [9]. Hatta et al. established the eCura system to score the risk of LNM in EGC patients after ESD [12]. Based on this system, patients are divided into three risk groups, which may interfere with treatment policy decision-making [14]. Using this scoring system, the LNM risks are 2.5% in the low-risk group (0–1 points), 6.7% in the intermediate-risk group (2–4 points), and 22.7% in the high-risk group (5–7 points) [14]. In our study, ROC curve analysis indicated that the optimal cutoff point to determine LNM risk based on the eCura system was 4. Therefore, we divided the patients into two groups, namely, the low-risk group, with scores of 1–3 points, and the high-risk group, with scores of 4–7 points, which will contribute to better treatment policies for patients.

The risk of LNM is the most important factor when selecting a treatment strategy for EGC [17–19]. The curability of ESD and post-ESD treatment were factored into the gastric cancer treatment guidelines in 2018 [20]. According to the guidelines, EGCs resected by ESD are divided into three categories: absolute indication, expanded indication, and noncurative indication [5,21–24]. Absolute indication is defined as a risk of LNM <1% and good evidence of a long-term outcome. Expanded indication is defined as a risk of LNM <1% but little evidence of a long-term outcome. Jee et al. suggested that extending the indications for EMR and ESD according to the Japanese Gastric Cancer Association guidelines increased the risk of LNM because the long-term outcome of these lesions has not been discussed [25]. A systematic review indicated that expanding the indication for endoscopic resection of EGC to include lesions $\leq$3 cm suggests that T1b1 is associated with a 3% risk of LNM for EGC in Japan [2]. Additional surgery is recommended for lesions with noncurative resection; however, the rate of LNM among lesions with noncurative resection is only 2.6–10.6% [2]. Further, the risk of complications is statistically lower in ESD than in surgery [26–28]. With the aging of society, there is an increasing number of patients in whom surgery is difficult; therefore, less invasive treatment is needed.

With regard to tumor size, the result of our study indicated that tumor size >30 mm was a significant factor associated with LNM in EGC patients after noncurative ESD. Chu et al. reported that tumor size >30 mm was an independent risk factor for LNM (odds ratio, 1.900, p = 0.006) [17] and Feng et al. also reported an increase in the rate of LNM

among patients with larger tumors [19]. In this study, we reaffirmed the usefulness of the eCura system in stratifying the risk of LNM. The eCura system is an excellent mechanism for stratifying risk; however, our results make it easier to decide whether to perform additional surgery by proposing more appropriate cutoff values.

There are some limitations in this study. First, although this study was a multicenter study, it was retrospective and had a small sample size. Therefore, further prospective randomized control studies will be needed. Second, we cannot show the long-term outcomes at this time. In this regard, we are considering tracking the long-term outcome of this cohort in the future to confirm the effectiveness of the modified eCura system.

5. Conclusions

Lymphatic invasion and tumor size >30 mm were independent factors associated with LNM in EGC patients after noncurative ESD, and patients with 0–3 points in the eCura system had a low risk of LNM, whereas those with 4–7 points had a high risk. The modified system should be applied in the clinical setting to the intermediate-risk group (2–4 points) of the eCura system to suggest better treatment strategies for patients. This stratification could improve the outcome of EGC treatment.

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Informed Consent Statement: Written informed consent was obtained from all study participants.

Data Availability Statement: The data are available upon request from the corresponding author.

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