A Scoring System to Stratify Curability after Endoscopic Submucosal Dissection for Early Gastric Cancer: "eCura system"

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OBJECTIVES: **Although radical surgery is recommended for patients not meeting the curative criteria for endoscopic submucosal dissection (ESD) of early gastric cancer (EGC) because of the potential risk of lymph node metastasis (LNM), this recommendation may be overestimated and excessive. We aimed to establish a simple scoring system for decision making after ESD.**

METHODS: **This multicenter retrospective study consisted of two stages. First, the risk-scoring system for LNM was developed using multivariate logistic regression analysis in 1,101 patients who underwent radical surgery after having failed to meet the curative criteria for ESD of EGC. Next, the system was internally validated by survival analysis in another 905 patients who also did not meet the criteria and did not receive additional treatment after ESD.**

RESULTS: **In the development stage, based on accordant regression coefficients, five risk factors for LNM were weighted with point values: three points for lymphatic invasion and 1 point each for tumor size >30 mm, positive vertical margin, venous invasion, and submucosal invasion ≥500 μm. Then, the patients were categorized into three LNM risk groups: low (0–1 point: 2.5% risk), intermediate (2–4 points: 6.7%), and high (5–7 points: 22.7%). In the validation stage, cancer-specific survival differed significantly among these groups (99.6, 96.0, and 90.1%, respectively, at 5 years; *P*<0.001). The C statistic of the system for cancer-specific mortality was 0.78.**

CONCLUSIONS: **This scoring system predicted cancer-specific survival in patients who did not meet the curative criteria after ESD for EGC. ESD without additional treatment may be an acceptable option for patients at low risk.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

Am J Gastroenterol 2017; 112:874–881; doi:10.1038/ajg.2017.95; published online 11 April 2017

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Received 19 September 2016; accepted 6 February 2017

INTRODUCTION

Recently, endoscopic submucosal dissection (ESD), which can achieve en bloc resection regardless of the tumor size (1–4), has been accepted in Eastern countries as it is a minimally invasive, curative treatment for early gastric cancer (EGC) with a negligible risk of lymph node metastasis (LNM) (5–9). This procedure is progressively gaining more attention in Western countries (10).

Currently, the European and Japanese guidelines (8–10) indicate the curability after endoscopic resection for EGC based on the curative criteria (6,11). According to these guidelines (8–10), a resection of a lesion that does not meet the curative criteria is considered a "non-curative resection," and radical gastrectomy with lymph node dissection is recommended. However, as LNM occurs in only 5–10% of patients who undergo radical surgery (12–17), this recommendation for all such patients may be overestimated and excessive. Our large-scale retrospective study with such patients demonstrated high cancer-specific survival (CSS) in patients who received no additional treatment after ESD as well as those who underwent radical surgery (97.5% and 98.7% 5-year CSS, respectively), although the difference was significant (18). Thus, this recommendation for all such patients may be overestimated and excessive. Furthermore, because of various factors, such as individual preferences (17,19), 29–68% of such patients did not undergo radical surgery (18–20).

Until now, the small number of cases in previous studies made it difficult to identify the patients who are actually at risk to develop LNM. However, if patients with a low risk of LNM are identified, no additional treatment after ESD may be an acceptable option. Thus, the aim of this study was to develop a risk-scoring system for LNM after ESD that does not meet the current curative criteria.

METHODS

Study populations

We conducted a multicenter retrospective study at 19 institutions in Japan; all institutions are members of the Establishment of Accommodation of Early Stomach Cancer Treatment (EAST) study group (18). Of the 15,785 consecutive patients who underwent ESD for EGC from January 2000 to August 2011, 2,208 patients who did not meet the guidelines' criteria for curative resection of ESD (9,10,21) (**Figure 1**) without merely positive for horizontal margin were initially evaluated for inclusion. Among them, we excluded those with (i) synchronous EGC that did not meet the curative criteria of ESD, (ii) ESD in the remnant stomach, (iii) additional treatment except for surgical resection (e.g., chemotherapy), (iv) invasion to the muscularis propria or deeper in the pathology of the surgically resected specimen, (v) synchronous or metachronous advanced cancer, and (vi) missing data. Regarding missing data, three patients were excluded because their tumor size could not be measured because of piecemeal resection. Despite the fact that radical surgery is indicated for all patients who do not meet the current curative criteria for ESD of EGC, this study included two cohorts: those who underwent radical surgery after ESD and those who did not receive additional treatment after ESD because of patients' refusal of surgery despite understanding the risk of LNM. The latter, with a follow-up period of <3 years, not including patients who died within that time, were excluded from this study because survival analysis was conducted for the latter, and according to previous studies (16,22,23), recurrence often appeared within 3 years after endoscopic or surgical resection, and such patients were considered inappropriate for evaluating the long-term prognosis in this study. As a result, 106

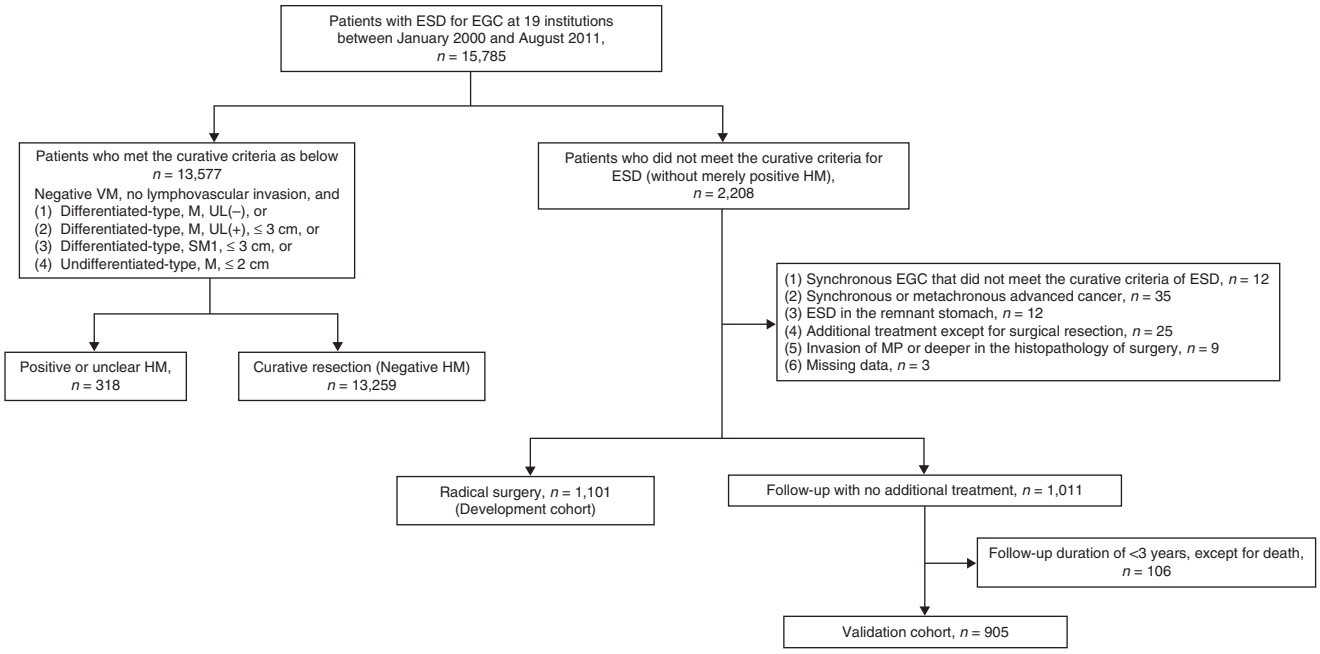

Figure 1. Flowchart of patients enrollment. EGC, early gastric cancer; ESD, endoscopic submucosal dissection; HM, horizontal margin; M, cancer confined to mucosa; MP, muscularis propria; SM1, cancer with depth of invasion from the muscularis mucosa <500 μm; UL, finding of ulceration (scar); VM, vertical margin.

patients were excluded due to a shorter follow-up period, mainly because of change in address. Finally, 2,006 patients, comprising 1,101 undergoing radical surgery and 905 with no additional treatment, were enrolled in this study (**Figure 1**).

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the institutional review board of each institution before the recruitment of patients. Written informed consent was obtained from all patients before ESD.

Clinicopathological data

The clinicopathological records of the enrolled patients with ESD and those of patients who underwent radical surgery after ESD for EGC were collected from each institution. All endoscopically and surgically resected specimens were processed according to the Japanese classification of gastric carcinoma (21) and evaluated by expert pathologists at each institution. Tumor histopathology was assessed according to the Japanese classification (21). The depth of submucosal invasion was classified as SM1 (tumor invasion into submucosa <500 μm from the muscularis mucosa) and SM2 (tumor invasion into submucosa ≥500 μm from the muscularis mucosa).

Two-stage study

This study consisted of two stages: the first stage for establishing the risk-scoring system for predicting LNM of EGC to stratify curability after ESD (eCura system) and the second stage for validating the scoring system.

In the first stage, we investigated the risk factors for LNM of EGC after ESD for establishing the risk-scoring system. The data of patients with radical surgery after ESD, referred to as the development cohort, were used in the first stage. For developing the clinical risk score, the factors with potential risk for LNM reported in the previous studies with surgery for EGC (6,11,24), including tumor size (>30 mm), tumor depth (SM2), histopathological type (undifferentiated-type), lymphatic invasion, venous invasion, and ulceration (scar), were evaluated in this study. In addition, positive vertical margin (VM) was also evaluated owing to the potential risk for LNM (25).

For internally validating the risk-scoring system, patients with no additional treatment, referred to as the validation cohort, were selected for enrollment in the second stage. It is difficult to capture LNM in these patients because gastrectomy with lymph node dissection was not performed. Meanwhile, previous reports revealed that LNM was the most important prognostic factor in gastric cancer (20,22,26,27). Thus, we regarded cancer-specific mortality and cancer recurrence as surrogates for LNM, and evaluated the validity of the established scoring system by evaluating these outcomes. In this study, cancer recurrence was defined as tumor relapse in the lymph nodes and/or other organs after ESD for EGC. The validation cohort underwent scheduled surveillance after ESD by esophagogastroduodenoscopy and computed tomography (usually with a follow-up interval of 6–12 months).

Statistical analysis

In the first stage, univariate and multivariate logistic regression analyses were performed for clarifying the risk factors for LNM. On multivariate analysis, odds ratio (OR) was adjusted for age, sex, and location (upper third compared with middle/lower third) in addition to all assessed factors because these factors have a potential risk of posing as confounders when evaluating LNM of cancer. According to a previous study (28), a *P*-value of <0.10 was predefined as the cut-off for inclusion of the assessed factors in the final risk model. For establishing the clinical risk score for predicting LNM, we assigned weighted points proportional to β regression coefficient values (rounded to the nearest integer) for the factors determined in the multivariate analysis. A risk score was then calculated for each patient, and the development cohort was classified into three categories according to the risk for LNM: low-, intermediate-, and high-risk groups. According to previous studies of gastrectomy with lymph node dissection for EGC and the guidelines (9,29,30), patients with a <3.0% risk of LNM in each total risk score were allocated to the low-risk group, those with ≥3.0 and <19.6% risk to the intermediate-risk group, and those with ≥19.6% risk to the high-risk group.

In the second stage, this risk-scoring system (eCura system) was applied to the validation cohort. On the basis of this system, patients with 0–1, 2–4, and 5–7 points were classified as low-risk group, intermediate-risk group, and high-risk group, respectively. As an internal validation analysis, CSS, cancer recurrence, and overall survival (OS) were estimated using the Kaplan-Meier method, and the differences in CSS, cancer recurrence, and OS among the three risk groups were assessed using the log-rank test. Furthermore, the Cox proportional hazards regression analysis was used to assess the performance of the scoring system in predicting cancer-specific mortality and cancer recurrence. Hazards ratios (HRs) were calculated.

For the development cohort, the trend of the risk for LNM between the three risk groups was evaluated using the Cochran-Armitage trend test. For both development and validation cohorts, the predictive accuracy of the scoring system was assessed by calculating the C statistic (31,32). In addition, for further internal validation of our risk model, bootstrapping with 1,000 replications was performed in the development cohort. Moreover, calibration of the model was evaluated using the Hosmer-Lemeshow goodness-of-fit test.

Data were analyzed using SPSS version 23.0 for Windows software (IBM Corp., Armonk, NY, USA) and R software version 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria). A *P*-value of <0.05 was considered statistically significant. Data processing and statistical analyses were conducted by an independent statistician. All authors had access to the study data and had reviewed and approved the final manuscript.

RESULTS

Baseline characteristics of the development and validation cohorts

The baseline characteristics of the development and validation cohorts are shown in **Table 1**. LNM was found in 94 patients (8.5%) in the development cohort. In the validation cohort, among 27 patients with cancer recurrence, 22 died of gastric cancer and 5 died of other diseases.

Table 1. Clinicopathological characteristics of the development (n=1,101) and validation (n=905) cohorts

	Development cohort (n=1,101)	Validation cohort (n=905)	P value
Age (y), median (IQR)	69 (61.5–75)	76 (69–81)	<0.001
Sex, n *(%)*			0.48
Male	863 (78.4)	697 (77.0)	
Female	238 (21.6)	208 (23.0)	
Location, n *(%)*			0.28
Upper third	302 (27.4)	274 (30.3)	
Middle third	468 (42.5)	357 (39.4)	
Lower third	331 (30.2)	274 (30.3)	
Tumor size (mm), median (IQR)	28 (19–40)	30 (20–40)	0.36
Invasion depth, n *(%)*			<0.001
M	180 (16.3)	246 (27.2)	
SM1	220 (20.0)	243 (26.9)	
SM2	701 (63.7)	416 (46.0)	
Histopathological type, n *(%)*			0.13
Differentiated	951 (86.4)	759 (83.9)	
Undifferentiated	150 (13.6)	146 (16.1)	
Lymphatic invasion, n *(%)*			<0.001
Negative	658 (59.8)	677 (74.8)	
Positive	443 (40.2)	228 (25.2)	
Venous invasion, n *(%)*			<0.001
Negative	852 (77.4)	785 (86.7)	
Positive	249 (22.6)	120 (13.3)	
Ulceration (scar), n *(%)*			0.004
Absence	816 (71.4)	617 (68.2)	
Presence	285 (25.9)	288 (31.8)	
Vertical margin, n (%)			<0.001
Negative	899 (81.7)	823 (90.9)	
Positive	199 (18.1)	80 (8.8)	
Unclear	3 (0.3)	2 (0.2)	
Lymph node metastasis, *n* (%)	94 (8.5)	—	

IQR, interquartile range; M, confined to mucosa; SM1, depth of invasion from the muscularis mucosa <500 μm; SM2, depth of invasion from the muscularis mucosa ≥500 μm; y, years.

Mann–Whitney *U*-test or χ^2-test (if appropriate, Fisher's exact test) was performed.

First stage (establishment of the risk-scoring system for predicting LNM)

In univariate analyses, tumor size >30 mm, SM2, lymphatic invasion, venous invasion, and positive VM were significantly associated with LNM (**Supplementary Table S1** online). Multivariate analysis demonstrated that independent risk factors for LNM were tumor size >30 mm, lymphatic invasion, venous invasion, and positive VM (**Table 2**). Furthermore, SM2 tended to be associated with LNM.

To calculate a risk score, we assigned points that were proportional to the regression coefficient for each of the five predictive variables: 1 point each for tumor size >30 mm, positive VM, venous invasion, and SM2 and 3 points for lymphatic invasion (**Table 2**). A total risk score, which ranged from 0 to 7 points, was calculated for each patient in the development cohort by adding together the points corresponding to his or her risk factors (**Table 3A**). Subsequently, according to the definition, this risk score was categorized as low (0–1 point), intermediate (2–4 points), and high risk (5–7 points) for LNM. As a result, the rates of LNM for each risk category were 2.5, 6.7, and 22.7%, respectively (**Table 3B**), with a significantly increasing trend of risk from low- to high-risk groups (P<0.001, Cochran-Armitage trend test). The predictive accuracy of the risk score for LNM, as measured by the C statistic, was 0.74 (95% confidence interval (CI), 0.62–0.87). The bootstrapping analysis result was similar to that obtained with the original samples (95% CI, 0.62–0.86). In addition, this model calibrated well with the Hosmer-Lemeshow goodness-of-fit test (χ^2=7.27, df=8, P=0.51).

Second stage (internal validation of the risk-scoring system by evaluating prognosis and cancer recurrence)

According to the risk category, 60.4%, 27.6%, and 11.9% of the patients in the validation cohort were assigned to the low-, intermediate-, and high-risk groups, respectively.

The CSS in the low-, intermediate-, and high-risk groups in the validation cohort differed significantly (P<0.001): 99.6%, 96.0%, and 90.1%, respectively, at 5 years (**Figure 2a** and **Supplementary Table S2**). In addition, Cox proportional hazards regression analysis adjusted for age, sex, location, histopathological type, and ulceration (scar) showed that the high-risk and intermediate-risk groups had significantly higher cancer-specific mortality compared with the low-risk group, with the risk significantly increasing from the low- to the high-risk group (P-trend<0.001) (**Table 4**). Receiver operating characteristic curve analysis of the Cox model revealed a C statistic of 0.78 (95% CI, 0.68–0.87) for cancer-specific mortality (**Supplementary Table S2**).

The analysis of cancer recurrence in the validation cohort showed similar results to that of CSS (**Figure 2b** and **Supplementary Table S2**). In addition, the analysis of OS in the validation cohort also showed similar results (**Supplementary Figure S1**), except for the low C statistic for all-cause mortality (0.59; 95% CI, 0.55–0.63).

DISCUSSION

This multicenter study of a large cohort established a novel, simple-to-use risk-scoring system (eCura system), which comprises five clinicopathological features, for LNM in patients who did not meet the current curative criteria for ESD of EGC and subsequently underwent radical surgery. This system accurately predicted cancer-specific mortality and cancer recurrence

Table 2. Multivariate logistic regression analysis[a] of risk factors for LNM in the development cohort and scoring system

	No. of patients	No. of LNMs	OR	95% CI	*P* value	β regression coefficient	Points[b]
Tumor size							
>30 mm	479	53	2.03	1.28–3.14	0.003	0.70	1
≤30 mm	622	41	1	Reference			
Tumor depth							
SM2	197	30	1.68	0.97–2.92	0.065	0.52	1
M/SM1	904	64	1	Reference			
Histopathological type							
Undifferentiated	701	73	1.22	0.62–2.41	0.56	0.20	—
Differentiated	400	21	1	Reference			
Lymphatic invasion							
Positive	443	69	3.99	2.43–6.55	<0.001	1.38	3
Negative	658	25	1	Reference			
Venous invasion							
Positive	249	35	1.65	1.01–2.70	0.046	0.50	1
Negative	852	59	1	Reference			
Ulceration (scar)							
Presence	285	21	0.98	0.57–1.69	0.95	–0.016	—
Absence	816	73	1	Reference			
Vertical margin							
Positive	198	30	1.81	1.10–3.00	0.020	0.60	1
Otherwise	903	64	1	Reference			

CI, confidence interval; LNM, lymph node metastasis; M, confined to mucosa; OR, odds ratio; SM1, depth of invasion from the muscularis mucosa <500 μm; SM2, depth of invasion from the muscularis mucosa ≥500 μm.

[a]For all factors in addition to age, sex, and location.

[b]The assignment of points to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by 0.50 (the lowest β value, corresponding to venous invasion) and rounded to the nearest integer.

of patients who did not receive additional treatment after ESD of EGC.

Our prior study revealed that, in addition to high CSS in patients who received no additional treatment after ESD, LNM was found in only approximately 8% of patients who underwent radical surgery after ESD for EGC (18). Hence, we considered that further risk stratification can be useful for deciding treatment strategy after ESD, and in this study, we established the "eCura system" by the detail statistical analysis of patients who underwent radical surgery after ESD, the number of whom is different from that or the cohort in our prior study because this study included those with a follow-up duration of <3 years for analyzing risk factors for LNM in the histopathology of surgery. Therefore, this system could predict the risk of LNM, which can be applied to clinical practice.

This scoring system has several advantages in the clinical and research settings. First, it is based on easily ascertainable clinicopathological features with fairly good predictive accuracy for cancer-specific mortality and cancer recurrence. A previous study reported an 11-point risk-scoring model for LNM in EGC (33). Meanwhile, we developed a 7-point risk-scoring system with three risk categories, defined according to the results of previous reports (9,29,30), for predicting LNM after ESD for EGC, which achieved a simpler scoring system and included important factors in patients with ESD (e.g., lymphatic and venous invasion, instead of lymphovascular invasion, and positive VM). Furthermore, in the present study, applying this system to the validation cohort revealed this risk-scoring system to be accurate and reliable, with the predicted risk for LNM correlating well with the observed risk for cancer-specific mortality and cancer recurrence. Therefore, this simple scoring system could have good applicability for clinical and research purposes.

Another advantage of this scoring system was that based on individual survival probabilities, it can provide guidance for a treatment strategy after ESD. The low-risk group showed a low rate of LNM (2.5%) in the development cohort and a high CSS (99.6% at 5 years) and low cancer recurrence (0.7% at 5 years) in the validation cohort. This high CSS in the validation cohort (i.e., patients with no additional treatment after ESD) was similar to that in patients who underwent radical surgery after ESD for EGC in this study (99.7% at 5 years) when the established risk-scoring system was

Table 3. Distribution of risk scores and risk classification for LNM in the development cohort

(A)

Total points	Patients (*n*=1,101)	LNM (*n*=94)	Rate of LNM (%)
0	62	1	1.6
1	341	9	2.6
2	185	9	4.9
3	148	11	7.4
4	132	11	8.3
5	141	28	19.9
6	77	21	27.3
7	15	4	26.7

(B)

Risk category	Total points	Patients (*n*=1,101)	LNM (*n*=94)	Rate of LNM (%)
Low	0–1	403	10	2.5
Intermediate	2–4	465	31	6.7
High	5–7	233	53	22.7

LNM, lymph node metastasis.

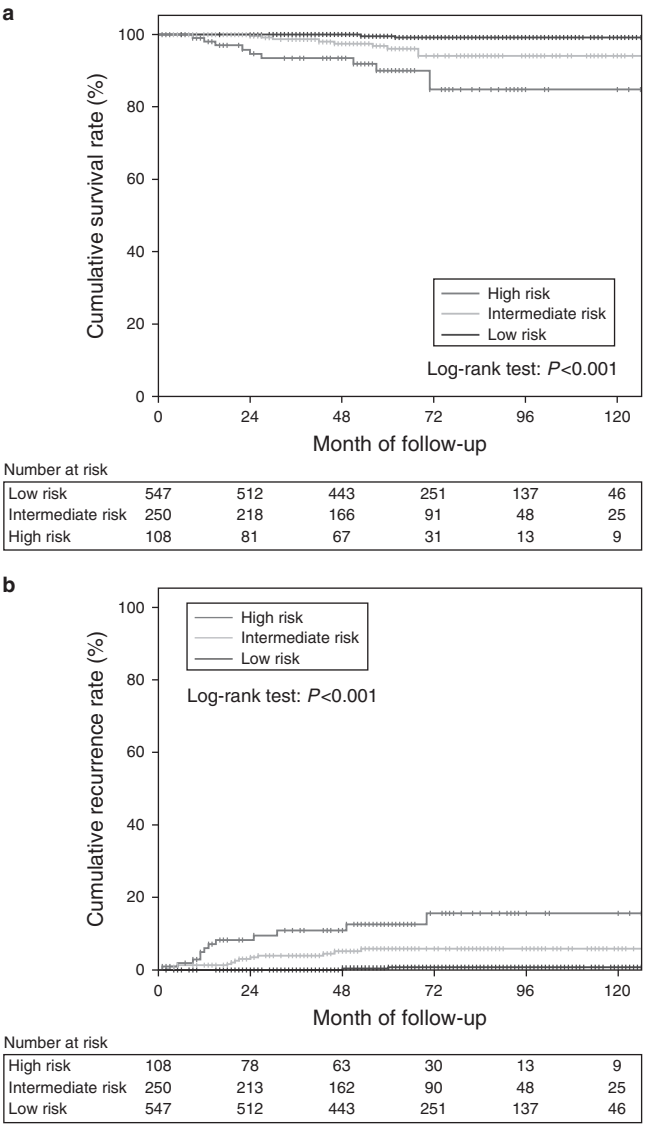

Figure 2. Cancer-specific survival and cancer recurrence according to the risk category in the validation cohort. (**a**) Cancer-specific survival. (**b**) Cancer recurrence. The cancer-specific survival and cancer recurrence differed among three risk groups in the validation cohort ($P<0.001$ and $P<0.001$, respectively; (**Supplementary Figure S1**). Overall survival according to the risk category in the validation cohort The overall survival differed among three risk groups in the validation cohort ($P<0.001$).

applied. Furthermore, a previous study of gastrectomy for EGC reported that 5-year CSS rates for intramucosal and submucosal cancers were 99.3% and 96.7%, respectively (30). Thus, ESD with no additional treatment may be an acceptable option for patients at low risk, although gastrectomy with lymph node dissection should be discussed with such patients. In contrast, the intermediate- and high-risk groups showed higher rates of LNM and showed higher HRs for cancer-specific mortality and cancer recurrence, compared with those in the low-risk group. Furthermore, 5-year CSS rate in the high-risk group was lower than that of surgery for EGCs (30), and was even lower in the intermediate-risk group. Clinicians should recognize that the detection of cancer recurrence at a stage that is eligible for curative treatment may be difficult in the majority of the patients who received no additional treatment after ESD for EGC (18). Therefore, for high-risk groups, no additional treatment after ESD is inappropriate and radical surgery should be recommended. Meanwhile, we cannot conclude whether radical surgery after ESD should be recommended for patients in the intermediate-risk group or not. However, it is significant to reveal that the rate of LNM was 6.7% in the intermediate-risk group. Although whether the rate of LNM in each risk category is high or low depends on the rate of surgery-related death, complications related to ESD, and patients' concept in various countries and ethnicities, this risk-prediction system can become a guide for clinical decision making after ESD worldwide.

There are certain limitations of this study. First, this study is retrospective, thus presenting an inherent potential for bias. However, we believe it is reliable because the number of excluded patients with missing data or a follow-up duration of <3 years was less than 10% of the study population. Second, there is a selection bias with respect to treatment strategy choices after ESD, a so-called "criteria issue" (34). Although we could develop and internally validate the risk-scoring system by making the best use of differences in treatment strategies, the selection bias by the "indication and criteria issue" (34) may give debates for the appropriateness of this method. In fact, this patient selection led to different baseline characteristics among the three risk groups (e.g., age, $P<0.001$), which may have resulted in significantly

Table 4. Cox proportional hazards model[a] for risk of cancer-specific mortality and cancer recurrence in the validation cohort, according to the risk category

Risk category	Cancer-specific mortality					Cancer recurrence				
	Person time at risk (months)	No. of cases	HR	95% CI	*P* value	Person time at risk (months)	No. of cases	HR	95% CI	*P* value
Low	39,923	3	1	Reference		39,910	3	1	Reference	
Intermediate	16,150	9	6.11	1.58–23.6	0.009	15,899	12	7.73	2.09–28.6	0.002
High	6,128	10	16.1	4.18–62.2	<0.001	5,917	12	18.1	4.82–68.2	<0.001
				P-trend	<0.001				*P*-trend	<0.001

CI, confidence interval; HR, hazards ratio.
[a]For age, sex, location, histopathological type, and ulceration (scar).

different OS among the three risk groups in the validation cohort and could affect the result of CSS and cancer recurrence. However, Cox analysis adjusted for factors such as age and sex showed that the risk for cancer-specific mortality and cancer recurrence significantly increased from the low- to the high-risk group, supporting the validity of the system. In the next stage, a large-scale prospective trial is warranted for external verification of this scoring system. Third, this scoring system did not consider the remnant cancer after ESD. Although ESD has a burning effect that sometimes leads to no remnant cancer after ESD even if there is a positive VM, caution regarding remnant cancer is required when R0 resection is not achieved. Lastly, events per variable value in this study were a little low for proper logistic regression analysis. In this study, the number of estimated variables in the logistic regression analysis was 10 and that of events corresponding to LNM was 94, resulting in an event per variable value of 9.4, which is a little lower than a preferable value of ≥10 (35). Thus, a type II error may occur in this analysis. However, this is the largest study to date, and it is important that we established the risk-scoring system based on the largest cohort.

In conclusion, this large-scale multicenter study allowed us to develop a clinically useful risk-scoring system (eCura system) based on five clinicopathological factors that predict LNM in patients who undergo radical surgery after ESD that does not meet the current curative criteria for EGC. This system may be helpful for clinicians to predict individual survival probabilities and cancer recurrence and determine a treatment strategy after ESD for EGC. However, a large-scale prospective trial is required for external verification of this scoring system.

ACKNOWLEDGMENTS

We thank Hiroyuki Ono (Shizuoka Cancer Center), Koki Nakamura (Hiroshima City Hospital), Naohiko Harada (National Hospital Organization Kyushu Medical Center), Yasumasa Hara (Toyama Prefectural Central Hospital), and Ryo Shimoda (Saga Medical School) for the enrollment of patients and data collection; and finally we thank Tomoyuki Koike (Tohoku University Graduate School of Medicine) and Katsunori Iijima (Akita University Graduate School of Medicine) for their insightful comments.

CONFLICT OF INTEREST

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Financial support: None.
Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Radical surgery is recommended for patients not meeting the curative criteria for endoscopic submucosal dissection (ESD) of early gastric cancer (EGC).
- ✓ Lymph node metastasis (LNM) occurs in only 5–10% of patients who undergo radical surgery after ESD that does not meet the curative criteria for EGC.

WHAT IS NEW HERE

- ✓ A 7-point risk-scoring system with three risk categories (eCura system) for predicting LNM after ESD for EGC was developed.
- ✓ The low-risk group showed a low rate of LNM in the development cohort and a high cancer-specific survival and low cancer recurrence in the validation cohort.
- ✓ ESD without additional treatment may be an acceptable option for patients with EGC at low risk.

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