Gut and Liver
https://doi.org/10.5009/gnl220333
pISSN 1976-2283 eISSN 2005-1212

Original Article

External Validation of the eCura System for Undifferentiated-Type Early Gastric Cancer with Noncurative Endoscopic Resection

Hyo-Joon Yang[1], Young-Il Kim[2], Ji Yong Ahn[3], Kee Don Choi[3], Sang Gyun Kim[4], Seong Woo Jeon[5], Jie-Hyun Kim[6], Sung Kwan Shin[7], Hyuk Lee[8], Wan Sik Lee[9], Gwang Ha Kim[10], Jae Myung Park[11], Woon Geon Shin[12], and Il Ju Choi[2]

[1]Division of Gastroenterology, Department of Internal Medicine and Gastrointestinal Cancer Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, [2]Center for Gastric Cancer, Research Institute and Hospital, National Cancer Center, Goyang, [3]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, [4]Division of Gastroenterology, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul, [5]Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, [6]Department of Internal Medicine, Institute of Gastroenterology, Gangnam Severance Hospital, Yonsei University College of Medicine, [7]Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, [8]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [9]Department of Internal Medicine, Chonnam National University Medical School, Gwangju, [10]Department of Internal Medicine, Pusan National University College of Medicine, and Biomedical Research Institute, Pusan National University Hospital, Busan, [11]Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, and [12]Department of Internal Medicine, Institute for Liver and Digestive Diseases, Hallym University College of Medicine, Chuncheon, Korea

Article Info

Received July 27, 2022
Revised November 6, 2022
Accepted December 20, 2022
Published online May 10, 2023

Corresponding Author

Il Ju Choi
ORCID https://orcid.org/0000-0002-8339-9824
E-mail cij1224@ncc.re.kr

Hyo-Joon Yang and Young-Il Kim contributed equally to this work as first authors.

Background/Aims: The eCura system, a scoring model for stratifying the lymph node metastasis risk after noncurative endoscopic resection for early gastric cancer (EGC), has been internally validated, primarily for differentiated-type EGC. We aimed to externally validate this model for undifferentiated-type EGC.

Methods: This multicenter, retrospective cohort study included 634 patients who underwent additional surgery (radical surgery group, n=270) or were followed up without additional treatment (no additional treatment group, n=364) after noncurative endoscopic resection for undifferentiated-type EGC between 2005 and 2015. The lymph node metastasis and survival rates were compared according to the risk categories.

Results: For the radical surgery group, the lymph node metastasis rates were 2.6%, 10.9%, and 14.8% for the low-, intermediate-, and high-risk eCura categories, respectively (p for trend=0.003). For the low-, intermediate-, and high-risk categories in the no additional treatment group, the overall survival (92.7%, 68.9%, and 80.0% at 5 years, respectively, p<0.001) and cancer-specific survival rates (99.7%, 94.7%, and 80.0% at 5 years, respectively, p<0.001) differed significantly. In the multivariate analysis, the hazard ratios (95% confidence interval) in the no additional treatment group relative to the radical surgery group were 3.18 (1.41 to 7.17; p=0.005) for overall mortality and 2.60 (0.46 to 14.66; p=0.280) for cancer-specific mortality in the intermediate-to-high risk category. No such differences were noted in the low-risk category.

Conclusions: The eCura system can be applied to undifferentiated-type EGC. Close follow-up without additional treatment might be considered for low-risk patients, while additional surgery is recommended for intermediate- and high-risk patients. **(Gut Liver 2023;17:537-546)**

Key Words: Stomach neoplasms; Undifferentiated-type histology; Endoscopic mucosal resection; Lymphatic metastasis; Validation study

INTRODUCTION

Endoscopic resection (ER) is recommended for the treatment of early gastric cancer (EGC) that has a very low risk of lymph node (LN) metastasis, not only by Korean and Japanese guidelines[1-4] but now also by U.S., European,

and British guidelines.[5-7] However, approximately 16.0% to 23.5% of patients who underwent ER for EGC did not meet the curative resection criteria; therefore, their procedures were considered to be noncurative resections.[8-12] Radical gastrectomy with LN dissection is recommended for noncurative ER cases because of the risk of LN metastasis. However, LN metastasis has only been found in 5.1% to 12.2% of patients during subsequent surgery.[8-12] In addition, in clinical practice, some patients refuse radical surgery because of patient choice, comorbidities, or old age.[9,13,14]

Recently, a risk scoring model called the eCura system was proposed to assist clinicians in the decision-making process after noncurative ER.[15] This model assigns a risk score for each risk factor for LN metastasis. According to the sum of scores, it categorizes patients into low-, intermediate-, and high-risk groups according to their LN metastasis risk.[15] For patients in the high-risk category, radical surgery was recommended because surgery was associated with lower cancer recurrence and cancer-specific mortality rates compared with no additional treatment.[16] In contrast, ER without additional treatment might be acceptable for patients in the low-risk category.[15] However, the eCura system is currently only recommended for use in patients with differentiated-type EGCs because patients with an undifferentiated-type (UD) EGC comprised only 14.8% of the cohort that was used for development of the model.

UD EGC has a higher risk of LN metastasis than differentiated-type EGC; therefore, it has the following stricter curative resection criteria: intramucosal tumor, absence of ulceration, and ≤2 cm in size.[3] The noncurative resection rate for UD EGC was 29.1% to 38.6%, which appears higher than the rate for differentiated-type EGC.[17-20] The risk factor criteria for the eCura system, including tumor size and submucosal invasion, were set for differentiated-type histology.[15] Thus, the applicability of the eCura system for selecting the appropriate treatment after noncurative ER for UD EGC remains unclear. Therefore, we performed an external validation study to evaluate whether the eCura system is useful for clinical decision-making process after noncurative ER for UD EGC.

MATERIALS AND METHODS

1. Patients

This multicenter retrospective cohort study used the same database as the previous study.[21] In brief, the study population included patients who underwent noncurative ER for UD EGC at 18 institutions in Korea. Noncurative ER was defined as a resection that did not meet the following curative resection criteria: *en bloc* resection, negative horizontal margin, negative vertical margin, mucosal cancer, tumor size ≤2 cm, absence of ulceration, and absence of lymphovascular invasion (LVI).[3,4] We did not include noncurative ER cases in which a positive horizontal margin was the only noncurative factor to match the inclusion criteria with those of the original eCura study.[15] Additional exclusion criteria were prior gastric cancer history, multiple initial gastric cancers, proper muscle invasion at additional surgery, additional endoscopic treatment after noncurative ER, and no follow-up after ER. The study protocol was approved by the Institutional Review Boards of Kangbuk Samsung Hospital (IRB number: 2017-09-035) and each of the other participating hospitals. The informed consent was waived.

2. Baseline clinicopathological data

The medical records of the patients were reviewed, and baseline clinical data, including age, sex, American Society of Anesthesiologists (ASA) physical status classification, and tumor location were collected. Pathological data were also collected from the pathology reports of the endoscopic and surgical resections. All pathological specimens were processed and evaluated according to the Japanese Gastric Cancer Association guidelines at each hospital without a central pathology review.[22] The UD histology was defined as signet ring cell carcinoma, poorly differentiated adenocarcinoma, or mucinous adenocarcinoma.[3,22] A tumor containing dominant UD histology mixed with a differentiated-type component was also defined as UD histology. Submucosal invasion was categorized as SM1 with depth of invasion <500 μm from the muscularis mucosa and SM2 with ≥500 μm.[3,22] Lymphatic and vascular invasion was assessed using hematoxylin and eosin staining, and D2-40 monoclonal antibody immunohistochemical (IHC) staining for lymphatic invasion was used at the pathologist's discretion at each institute. Elastic-Van Gieson staining or IHC staining using CD31 or CD34 for venous invasion was not performed.

3. Patient group definitions and follow-ups

Patients were divided into two groups according to the treatment they received after the noncurative ER. The radical surgery group included patients who underwent radical gastrectomy and LN dissection, and the no additional treatment group included patients who were followed without additional treatment. Patients in the radical surgery group underwent follow-up endoscopy and abdominal computed tomography every 6 to 12 months for the first 3 years and then annually for 5 years. Patients in the no additional treatment group were initially followed with endoscopy at 3 months after the noncurative ER, after which they followed the same schedule as the radical surgery group.[3,23]

4. eCura system and outcomes for validation

The eCura system is a risk score model that estimates the likelihood of LN metastasis for patients with EGC after noncurative ER.[15] For each patient, the risk score is calculated as the sum of the scores for five risk factors: tumor size >30 mm (1 point), SM2 (1 point), lymphatic invasion (3 points), venous invasion (1 point), and positive vertical margin (1 point). Patients are classified into three risk tiers based on their cumulative scores: low-risk (0–2), intermediate-risk (3–4), and high-risk (5–7). In the present study, however, we obtained lymphatic and venous invasion information in combination, rather than individually, because IHC staining was not performed routinely for these patients. Thus, we assigned 3 points to LVI; consequently, the maximum point total was 6, rather than 7. Therefore, the high-risk category was assigned 5 to 6 points.

In this study, we validated the eCura system for UD EGC in three steps. First, we assessed the rate of LN metastasis as diagnosed during the additional surgery for patients in the radical surgery group according to their risk scores and categories of the eCura system. Second, we evaluated the overall survival (OS), cancer-specific survival (CSS), and cancer recurrence rates in the no additional treatment group according to the risk categories of the eCura system. Third, we compared the OS, CSS, and cancer recurrence rates between the radical surgery and no additional treatment groups stratified by the risk categories of the eCura system. OS was defined as the time from the initial ER to death from any cause. We also used claims data to determine mortality, and the disqualification of health insurance before the screening date (March 31, 2019) was considered death from an unknown cause.[24] CSS was defined as the time from the initial ER to death from gastric cancer. Cancer recurrence was defined as LN or distant recurrence, as in the original eCura system study.[15]

5. Statistical analysis

The distribution of baseline characteristics according to the risk categories of the eCura system was summarized as numbers (percentage) for the categorical variables and medians (interquartile range) for the continuous variables, and comparison was performed using a linear-by-linear association for the categorical variables and an analysis of variance or Kruskal-Wallis test for the continuous variables. The LN metastasis rate according to the eCura system in the surgery group was also evaluated using the chi-square analysis or Fisher exact test, and the p for trend was obtained using the Cochran-Armitage trend test. Survival analyses were performed using the Kaplan-Meier method with a log-rank test and Cox regression analysis that was adjusted for age, sex, ASA physical status, tumor location, histology, and ulceration. The performance of the eCura system was evaluated by calculating the C statistics for the prediction of LN metastasis in the radical surgery group with bootstrapping of 1,000 replications and for the prediction of survival outcomes in the no additional treatment groups as in the original study.[15] A two-sided p-value <0.05 was considered significant. Statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) and R statistical package version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Patients

A total of 634 patients with noncurative ER for UD EGC were included into the radical surgery group (n=270) or the no additional treatment group (n=364) (Fig. 1). According to the eCura system, 151 (55.9%), 92 (34.1%), and 27 (10.0%) patients in the radical surgery group and 317

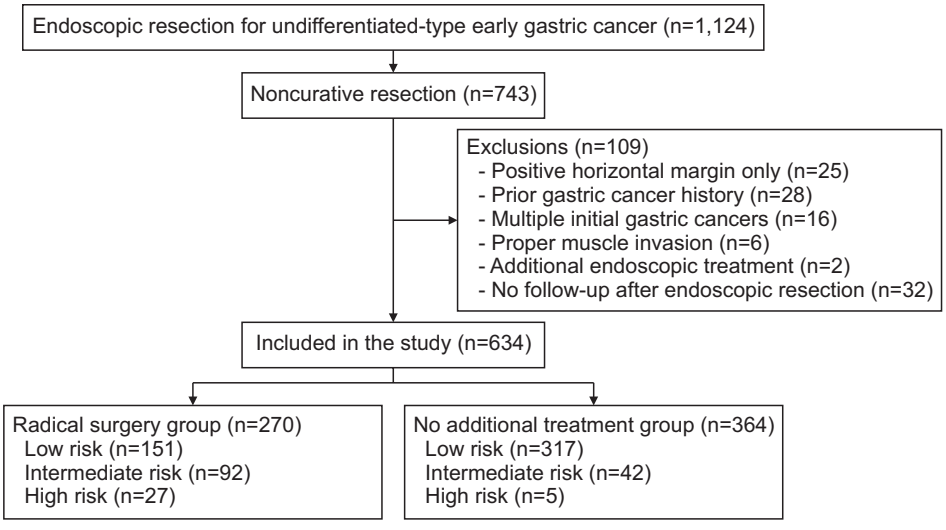

Fig. 1. The flowchart of the study cohort.

(87.1%), 42 (11.5%), and five (1.4%) patients in the no additional treatment group were assigned to the low-, intermediate-, and high-risk categories, respectively. The baseline characteristics are summarized in Table 1. The median follow-up durations were 84.0 months (interquartile range, 61.7 to 108.6 months) for survival and 58.9 months (interquartile range, 40.2 to 71.4 months) for cancer recurrence. The minimum follow-up durations without having any event were 40.6 months for survival and 0.6 months for cancer recurrence.

2. LN metastasis according to the eCura system during surgical resection

LN metastasis was present in 18 patients (6.7%) of the radical surgery group. The LN metastasis rate significantly increased with an increasing eCura risk score (p for trend=0.004) (Table 2). Accordingly, the LN metastasis rates for patients in the low-, intermediate-, and high-risk categories showed a significantly increasing trend of 2.6%, 10.9%, and 14.8%, respectively (p for trend=0.003). Patients in the intermediate- and high-risk categories showed

Table 2. Lymph Node Metastasis Rate According to the eCura System in the Radical Surgery Group

Score	Patients (n=270)	LNM (n=18)	Rate of LNM, % (95% CI)
Risk score			
0	51	2	3.9 (0.0–9.4)
1	100	2	2.0 (0.0–4.8)
2	36	4	11.1 (3.3–21.9)
3	26	2	7.7 (0.0–18.7)
4	30	4	13.3 (4.2–26.2)
5	19	2	10.5 (0.0–25.7)
6	8	2	25.0 (0.0–63.7)
p for trend			0.004
Risk category (score)			
Low (0-1)	151	4	2.6 (0.1–5.2)
Intermediate (2-4)	92	10	10.9 (4.4–17.6)*
High (5-6)	27	4	14.8 (4.9–29.1)*
p for trend			0.003

LNM, lymph node metastasis; CI, confidence interval.
*The intermediate- and high-risk category groups each showed a significantly higher lymph node metastasis rate than the low-risk category group (p=0.008 and p=0.019, respectively).

Table 1. Baseline Characteristics of Patients in the Radical Surgery and No Additional Treatment Groups According to the Risk Categories of the eCura System*

Characteristic	Radical surgery group (n=270)				No additional treatment group (n=364)			
	Low-risk (n=151)	Intermediate-risk (n=92)	High-risk (n=27)	p-value	Low-risk (n=317)	Intermediate-risk (n=42)	High-risk (n=5)	p-value
Age, yr	57.6 (51.1–66.7)	62.8 (55.6–70.4)	59.8 (52.4–71.8)	0.017	63.1 (53.0–72.5)	69.9 (54.8–78.4)	75.4 (72.2–79.6)	0.005
Male sex	93 (61.6)	57 (62.0)	22 (81.5)	0.132	185 (58.4)	27 (64.3)	1 (20.0)	0.695
ASA physical status				0.165				0.035
I	93 (61.6)	48 (52.2)	17 (63.0)		176 (55.5)	19 (45.2)	3 (60.0)	
II	57 (37.7)	38 (41.3)	8 (29.6)		125 (39.4)	15 (35.7)	1 (20.0)	
III-IV	1 (0.7)	6 (6.5)	2 (7.4)		16 (5.1)	8 (19.1)	1 (20.0)	
Tumor location				0.247				0.511
Upper third	61 (40.4)	43 (46.7)	13 (48.2)		119 (37.5)	16 (38.1)	2 (40.0)	
Middle third	71 (47.0)	42 (45.7)	11 (40.7)		173 (54.6)	20 (47.6)	2 (40.0)	
Lower third	19 (12.6)	7 (7.6)	3 (11.1)		25 (7.9)	6 (14.3)	1 (20.0)	
Tumor size, mm	26.0 (20.0–35.0)	23.0 (18.0–33.0)	35.0 (18.0–44.0)	0.014	26.0 (22.0–34.0)	25.5 (17.5–36.0)	24.0 (21.5–42.3)	0.872
Depth of invasion				<0.001				<0.001
Mucosa	85 (56.3)	13 (14.1)	0		233 (73.5)	8 (19.1)	0	
Submucosa <500 μm	27 (17.9)	20 (21.8)	0		45 (14.2)	5 (11.9)	0	
Submucosa ≥500 μm	39 (25.8)	59 (64.1)	27 (100.0)		39 (12.3)	29 (69.0)	5 (100.0)	
Histology				0.003†				0.019†
PD	112 (74.2)	74 (80.4)	24 (88.9)		195 (61.5)	30 (71.4)	4 (80.0)	
SRC	39 (25.8)	14 (15.2)	1 (3.7)		118 (37.2)	10 (23.8)	0	
Mucinous	0	4 (4.4)	2 (7.4)		4 (1.3)	2 (4.8)	1 (20.0)	
Lymphovascular invasion	0	49 (53.3)	27 (100.0)	<0.001	0	18 (42.9)	5 (100.0)	<0.001
Ulceration	15 (9.9)	10 (10.9)	2 (7.4)	0.856	32 (10.1)	4 (9.5)	1 (20.0)	0.749
Positive vertical margin	4 (2.6)	33 (35.9)	17 (63.0)	<0.001	5 (1.6)	17 (40.5)	4 (80.0)	<0.001

Data are presented as median (interquartile range) or number (%).
ASA, American Society of Anesthesiologists; PD, poorly differentiated adenocarcinoma; SRC, signet ring cell carcinoma.
*The low-, intermediate-, and high-risk categories of the eCura system are assigned 0–2, 3–4, and 5–6 points, respectively, according to the sum of the following risk scores: 1 point for tumor size >30 mm, 1 point for submucosal invasion ≥500 μm from the muscularis mucosa, 3 points for lymphovascular invasion, and 1 point for positive vertical margin; †The proportion of patients with signet ring cell carcinoma was compared against the proportion of patients with poorly differentiated or mucinous adenocarcinoma.

a significantly higher LN metastasis rate than those in the low-risk category (p=0.008 and p=0.019, respectively). The C statistic of the eCura score in the prediction of LN metastasis was 0.69 with 95% confidence intervals (CIs) of 0.55 to 0.82 for the original sample and 0.54 to 0.80 for the bootstrap sample.

3. Survival and recurrence outcomes according to the eCura system

The OS rates for patients in the low-, intermediate-, and high-risk categories in the no additional treatment group were 92.7%, 68.9%, and 80.0% at 5 years, respectively, and the differences were significant (p<0.001) (Fig. 2A). However, the OS rates were not significantly different in the radical surgery group (p=0.686) (Fig. 2B). The CSS rates also differed significantly between patients in the low-, intermediate-, and high-risk categories in the no additional treatment group, with 5-year rates of 99.7%, 94.7%, and 80.0%, respectively (p<0.001) (Fig. 3A). However, there were no such differences in the radical surgery group (p=0.052) (Fig. 3B).

In the Cox regression model that was adjusted for age, sex, ASA physical status, location, histology, and ulceration, overall mortality was significantly higher for patients in the intermediate-risk category (hazard ratio [HR], 2.80; 95% CI, 1.45 to 5.40; p=0.002) and in the high-risk category (HR, 4.61; 95% CI, 1.01 to 21.08; p=0.049) compared to those in the low-risk category in the no additional treatment group. In addition, cancer-specific mortality rate was significantly higher for patients in both the intermediate- and high-risk categories than those in the low-risk category (p=0.007 and p=0.005, respectively). The C statistics (95% CI) of the Cox models were 0.84 (0.79 to 0.89) for overall mortality, 0.93 (0.85 to 1.00) for cancer-specific mortality, and 0.87 (0.78 to 0.97) for cancer recurrence.

Cancer recurrence outcomes were similar to the CSS outcomes (Table 3, Supplementary Fig. 1). In the adjusted analysis, both the intermediate- and high-risk categories

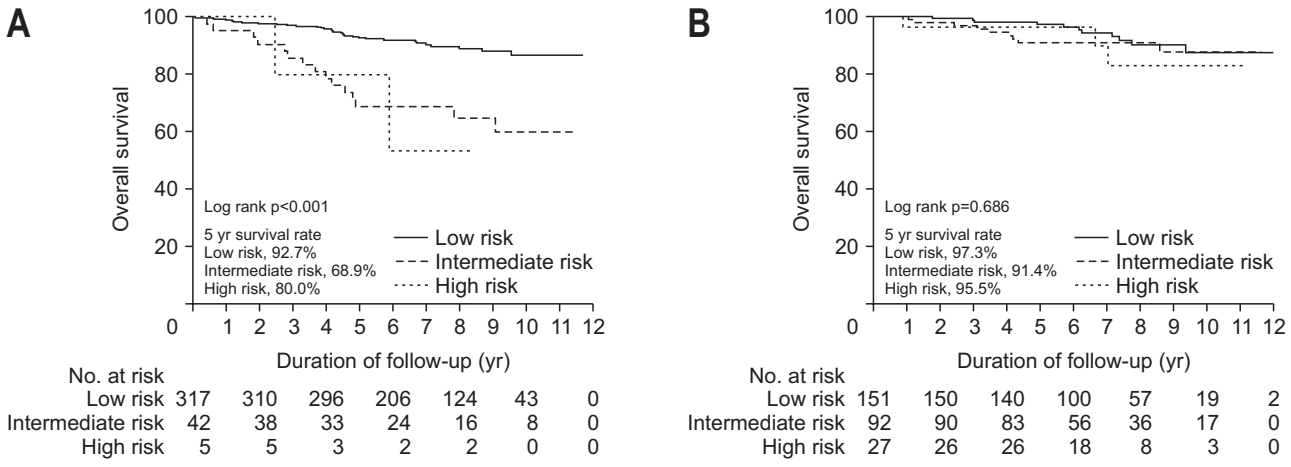

Fig. 2. Overall survival according to the risk categories of the eCura system. (A) No additional treatment group. (B) Radical surgery group.

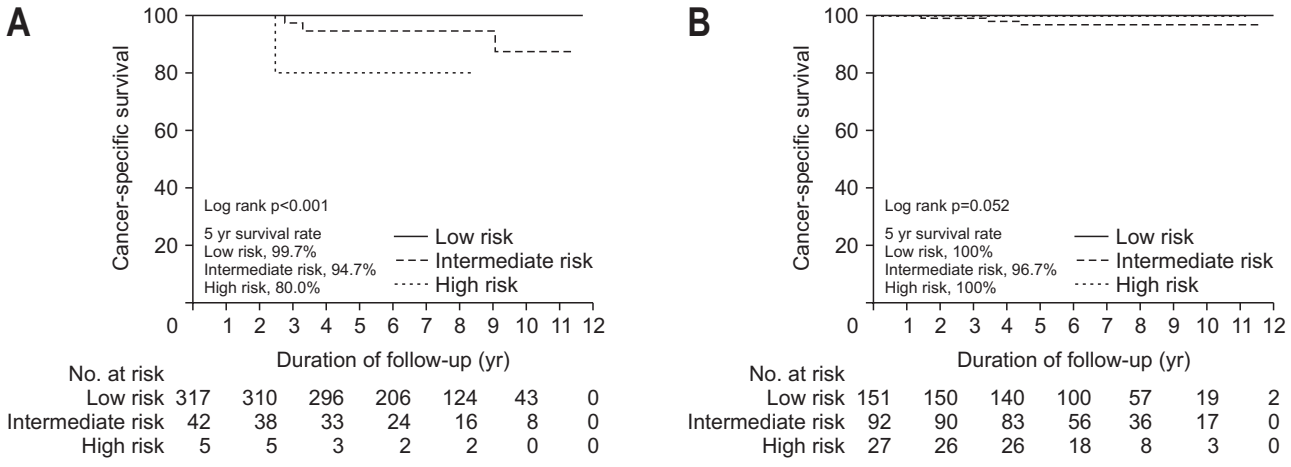

Fig. 3. Cancer-specific survival according to the risk categories of the eCura system. (A) No additional treatment group. (B) Radical surgery group.

Table 3. Adjusted Analysis* of Hazards for Mortality and Recurrence According to Risk Categories of the eCura System in the No Additional Treatment Group†

Risk category	Overall mortality				Cancer-specific mortality				Cancer recurrence			
	Person time at risk, mo	No. of cases	HR (95% CI)	p-value	Person time at risk, mo	No. of cases	HR (95% CI)	p-value	Person time at risk, mo	No. of cases	HR (95% CI)	p-value
Low-risk	27,165	31	1		27,165	1			18,563	3		
Intermediate-risk	3,342	15	2.80 (1.45–5.40)	0.002	3,342	3	49.39 (2.95–826.70)	0.007	2,004	3	12.63 (1.91–83.31)	0.008
High-risk	346	2	4.61 (1.01–21.08)	0.049	346	1	586.83 (6.81–50,574)	0.005	195	1	57.32 (2.37–1,384)	0.013
Overall p-value				0.004				0.011				0.011
p for trend			2.48 (1.46–4.21)	0.001			27.45 (3.27–230.26)	0.002			8.98 (2.16–37.32)	0.003

HR, hazard ratio; CI, confidence interval.
*HRs were adjusted for age, sex, American Society of Anesthesiologists physical status, location, histology, and ulceration; †The low-, intermediate-, and high-risk categories of the eCura system are assigned 0–2, 3–4, and 5–6 points, respectively, according to the sum of the following risk scores: 1 point for tumor size >30 mm, 1 point for submucosal invasion ≥500 μm from the muscularis mucosa, 3 points for lymphovascular invasion, and 1 point for positive vertical margin.

were associated with significantly higher cancer recurrence rates compared to the low-risk category in the no additional treatment group (p=0.008 and p=0.013, respectively).

4. Survival and recurrence outcomes according to the treatment after noncurative ER

We compared the OS, CSS, and cancer recurrence rates between patients in the radical surgery and no additional treatment groups stratified by the risk categories of the eCura system. Because the intermediate-risk category showed an increased rate of LN metastasis in the radical surgery group, we combined the intermediate- and high-risk categories in this analysis.

In the intermediate-to-high risk category, mortality was significantly higher for patients in the no additional treatment group than those in the radical surgery group (HR, 3.18; 95% CI, 1.41 to 7.17; p=0.005) (Table 4). In addition, HRs in the no additional treatment group compared to the radical surgery group were 2.60 (95% CI, 0.46 to 14.66; p=0.280) for the cancer-specific mortality and 2.23 (95% CI, 0.41 to 12.18; p=0.354) for the cancer recurrence in the intermediate-to-high risk category, respectively. However, no such differences were noted in the low-risk category.

DISCUSSION

In this study, we validated the usefulness of the eCura system for patients with UD EGC using a large independent multicenter cohort. This model discriminated the risk of LN metastasis for patients who underwent radical surgery, as well as the OS, CSS, and cancer recurrence rates for patients with no additional treatment after noncurative ER for UD EGC. Additionally, the effect of radical surgery compared to no additional treatment on mortality and recurrence outcomes differed between patients in the low-risk and intermediate-to-high risk categories. Our results indicate that the eCura system may be applicable for risk stratification after noncurative ER for UD EGC.

The eCura system was developed using a cohort that was dominated by patients with differentiated-type EGC.[15] Consequently, there were discrepancies between the criteria for the eCura system risk factors and the curative resection criteria for UD EGC from Japanese Gastric Cancer Association guidelines,[3] including tumor size, depth of invasion, and presence of ulceration. Because we aimed to validate whether this original model could predict LN metastasis and cancer-specific outcomes for patients with UD EGC, we used the model without modification. However, lymphatic and venous invasion were combined as a single risk factor for LVI because the data available did not sepa-

Table 4. Adjusted Analysis* of Hazards for Mortality and Recurrence in the No Additional Treatment Group Compared to the Radical Surgery Group Stratified by Risk Categories of the eCura System†

Risk category	Overall mortality				Cancer-specific mortality				Cancer recurrence			
	Person time at risk, mo	No. of cases	HR (95% CI)	p-value	Person time at risk, mo	No. of cases	HR (95% CI)	p-value	Person time at risk, mo	No. of cases	HR (95% CI)	p-value
Low												
Radical surgery	13,104	11	1		13,104	0	1		9,169	0	1	
No additional treatment	27,165	31	0.52 (0.24–1.13)	0.099	27,165	1	4,128.26 (not estimated)	0.983	18,563	3	3.70×10^{5} (not estimated)	0.978
Intermediate–high												
Radical surgery	1,003	12	1		1,003	3	1		6,651	4	1	
No additional treatment	3,688	17	3.18 (1.41–7.17)	0.005	3,688	4	2.60 (0.46–14.66)	0.280	2,199	4	2.23 (0.41–12.18)	0.354

HR, hazard ratio; CI, confidence interval.
*HRs were adjusted for age, sex, American Society of Anesthesiologists physical status, location, histology, and ulceration; †The low-, intermediate-, and high-risk categories of the eCura system are assigned 0–2, 3–4, and 5–6 points, respectively, according to the sum of the following risk scores: 1 point for tumor size >30 mm, 1 point for submucosal invasion ≥500 μm from the muscularis mucosa, 3 points for lymphovascular invasion, and 1 point for positive vertical margin.

rate the information. This might have caused patients to be misclassified by the risk model in our study compared with the original eCura system—the risk score would have been lower by one point in our model than in the original one in patients with both lymphatic and venous invasion, while being higher by 2 points in patients with venous invasion without lymphatic invasion. The LVI rate was 15.6% (99/634) in our study. In the original study, lymphatic and venous invasion were noted in 40.2% and 22.6% of patients who underwent radical surgery, respectively.[15] In previous studies, 12.0% to 23.6% of patients had both lymphatic and venous invasion among those with LVI, and 13.0% to 20.8% of patients had venous invasion without lymphatic invasion.[25,26] In a recent systematic review, the OR for LN metastasis associated with LVI (4.17; 95% CI, 2.90 to 5.99) was similar to that of lymphatic invasion (4.22; 95% CI, 2.88 to 6.19),[27] which may support the appropriateness of using this modified version of the eCura system.

In our study, patients in the low-risk category showed a 2.6% LN metastasis rate, which was very similar to the 2.5% rate for those in the original eCura study.[15] Patients with no additional treatment in the low-risk category also showed a high CSS rate (99.7% at 5 years) and low risk of cancer recurrence (0.8% at 5 years). In the adjusted analysis, there were no differences in the OS, CSS, and cancer recurrence rates between patients who underwent radical surgery and those with no additional treatment. These results are consistent with those of previous eCura studies that were performed primarily with patients with differentiated-type EGC.[15,16] Notably, however, even an eCura score of 0, which indicates curative resection for a patient with differentiated-type EGC, represented a noncurative resection with a tumor size of 2 to 3 cm, SM1, or ulceration in patients with UD EGC. Nevertheless, it appears that patients in the low-risk category experienced favorable outcomes because most patients in this category underwent noncurative resections due to tumor size >2 cm. We previously showed that patients with UD EGC whose only noncurative factor was a tumor size >2 cm might have a low risk of LN metastasis.[28] Thus, close follow-up without additional treatment after noncurative ER may be considered for patients with UD EGC who are in the low-risk category of the eCura system, as suggested in the original study.[15]

Patients in the high-risk category showed a 14.8% LN metastasis rate in our study; although this rate is high, it still appeared to be lower than the 22.7% rate that was reported in the original Japanese study.[15] This category was also associated with significantly higher risks of overall mortality, cancer-specific mortality and cancer recurrence than the low-risk category, which is consistent with the results of a previous study of patients with differentiated-type

EGC.[15] However, the high-risk category comprised only 5.0% (32/634) of the patients in our cohort, which is less than one-third of the 17.0% (341/2,006) reported in the original study; this suggests that there was a possible selection bias in our study. This discrepancy may be owing to the difference in the curative resection criteria between the differentiated-type and UD EGC. As the rate of LN metastasis in the radical surgery group was similar to that from previous reports, it suggests that the LN metastasis risk has been underestimated for some patients. Despite these discrepancies and wide CIs for cancer-specific outcome estimates, our results may further support the need for additional surgery in these patients. Therefore, radical surgery is still strongly recommended for patients in the high-risk category of the eCura system after noncurative ER for UD EGC, as it is for patients with differentiated-type EGC.

For patients in the intermediate-risk category of the eCura system, conclusive recommendations were not provided in previous studies because the LN metastasis rate was 6.7%, and radical surgery was not significantly associated with a higher CSS rate and lower cancer recurrence rate.[15,16] In contrast, the 10.9% LN metastasis rate for patients in the intermediate-risk category in our study seemed higher than the 6.7% rate in the previous study. In addition, the overall mortality, cancer-specific mortality, and cancer recurrence rates were significantly higher for patients in the intermediate-risk category than those in the low-risk category in the no additional treatment group. Furthermore, in a combined intermediate-to-high risk category, radical surgery was significantly associated with a better OS rate compared with no additional treatment. Therefore, additional surgery should be recommended for patients in the intermediate-risk category of UD EGC. In terms of risk stratification, the intermediate- and high-risk categories may be combined for UD EGC. If surgery is not advisable due to old age or poor physical status, clinicians need to discuss sufficiently with the patient based on the assessed risk of residual disease and recurrence.[3] It should be noted that distant recurrence usually leads to gastric cancer death.

One of the advantages of our study was that we collected large-scale multicenter data in Korea for patients with UD EGC. The number of patients enrolled in our study was more than two times that of the largest study (n=292).[15] Another advantage was that our LN metastasis risk factor evaluation after radical surgery was based on the noncuratively resected ER specimens that were evaluated with a 2-mm section interval. In the recent Japanese guidelines, the LN metastasis rate after noncurative ER was presented based on surgically resected specimens evaluated in 5 to 7 mm section intervals.[3] Our data from 2-mm section interval are expected to be more accurate because risk factor evaluation in wider section interval might significantly miss minute submucosal invasion or LVI.[29]

Our study has several limitations. First, the study had a retrospective design. This resulted in incomplete mortality and recurrence outcome data, as the cause of death was unknown for some of the patients. Second, selection bias inevitably affects our results on two levels. The first level of selection bias occurs at choosing the initial treatment. Although ER for UD EGC is regarded as an absolute indication in the recent Japanese guidelines,[3,4] it is still considered an expanded indication, and surgery is the standard treatment in the most recent Korean guidelines.[1,2] The other level of selection bias comes in choosing the additional treatment after noncurative ER. OS outcomes could be easily affected by those selection biases even after adjustment for age, sex, and ASA scores because gastric cancer recurrence or death were relatively rare events. In addition, the sample size was insufficient for the high-risk category. Therefore, further prospective randomized controlled trial with standardized inclusion criteria is necessary to minimize the selection bias. Currently, a Korean multicenter randomized controlled trial is ongoing to compare survival outcomes of endoscopic submucosal dissection for UD EGC meeting the expanded indication with those of surgery (ClinicalTrials.gov number, NCT04890171).[30] Third, D2-40 staining was performed only in some patients, so it might result in false-negative results for lymphatic invasion. Moreover, venous invasion data were not available separately because special staining or IHC staining was not performed. In addition, the lack of a central pathology review might have introduced a misclassification bias.

In conclusion, in this external validation study, our data suggested that the eCura system can be applied during the clinical decision-making process after noncurative ER for patients with UD EGC. Close follow-up without additional treatment may be considered for patients in the low-risk category, while additional radical surgery should be strongly recommended for patients in the intermediate- and high-risk categories.

CONFLICTS OF INTEREST

J.H.K. and G.H.K. are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

ACKNOWLEDGEMENTS

This research was supported by a grant of Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HC20C0123).

The authors gratefully acknowledge the invaluable contributions of the following investigators to the data collection process: Jae-Young Jang, MD, PhD, Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Korea; Su Youn Nam, MD, PhD, Gastroenterology, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea; Byung-Hoon Min, MD, PhD, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; Bong Eun Lee, MD, PhD, Department of Internal Medicine, Pusan National University College of Medicine, Busan, Korea; Moon Kyung Joo, MD, PhD, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea; Hang Lak Lee, MD, PhD, Division of Gastroenterology, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea; Tae-Geun Gweon, MD, PhD, Division of Gastroenterology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, Korea; Moo In Park, MD, PhD, Department of Internal Medicine, Kosin University College of Medicine, Busan, Korea; Jeongmin Choi, MD, PhD, Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea; and Chung Hyun Tae, MD, PhD, Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, Korea.

AUTHOR CONTRIBUTIONS

Study concept and design: H.J.Y., Y.I.K., I.J.C. Data acquisition: all authors. Data analysis and interpretation: H.J.Y., Y.I.K., I.J.C. Drafting of the manuscript: H.J.Y., I.J.C. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: H.J.Y., Y.I.K. Obtained funding: I.J.C. Administrative, technical, or material support: H.J.Y., Y.I.K., I.J.C. Study supervision: I.J.C. Approval of final manuscript: all authors.

ORCID

Hyo-Joon Yang https://orcid.org/0000-0002-0265-672X
Young-Il Kim https://orcid.org/0000-0002-2614-3419
Ji Yong Ahn https://orcid.org/0000-0002-0030-3744
Kee Don Choi https://orcid.org/0000-0002-2517-4109
Sang Gyun Kim https://orcid.org/0000-0003-1799-9028
Seong Woo Jeon https://orcid.org/0000-0002-9539-9389
Jie-Hyun Kim https://orcid.org/0000-0002-9198-3326
Sung Kwan Shin https://orcid.org/0000-0001-5466-1400
Hyuk Lee https://orcid.org/0000-0003-4271-7205
Wan Sik Lee https://orcid.org/0000-0002-8021-6228
Gwang Ha Kim https://orcid.org/0000-0001-9721-5734
Jae Myung Park https://orcid.org/0000-0002-1534-7467
Woon Geon Shin https://orcid.org/0000-0002-9851-5576
Il Ju Choi https://orcid.org/0000-0002-8339-9824

SUPPLEMENTARY MATERIALS

Supplementary materials can be accessed at https://doi.org/10.5009/gnl220333.

REFERENCES

1. Guideline Committee of the Korean Gastric Cancer Association (KGCA), Development Working Group & Review Panel. Korean practice guideline for gastric cancer 2018: an evidence-based, multi-disciplinary approach. J Gastric Cancer 2019;19:1-48.
2. Park CH, Yang DH, Kim JW, et al. Clinical practice guideline for endoscopic resection of early gastrointestinal cancer. Clin Endosc 2020;53:142-166.
3. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1-21.
4. Ono H, Yao K, Fujishiro M, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Dig Endosc 2021;33:4-20.
5. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: gastric cancer [Internet]. Plymouth Meeting: NCCN; c2021 [cited 2021 Nov 20]. Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1434
6. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015;47:829-854.
7. Banks M, Graham D, Jansen M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut 2019;68:1545-1575.
8. Yang HJ, Kim SG, Lim JH, et al. Predictors of lymph node

metastasis in patients with non-curative endoscopic resection of early gastric cancer. Surg Endosc 2015;29:1145-1155.
9. Kim ER, Lee H, Min BH, et al. Effect of rescue surgery after non-curative endoscopic resection of early gastric cancer. Br J Surg 2015;102:1394-1401.
10. Hatta W, Gotoda T, Oyama T, et al. Is radical surgery necessary in all patients who do not meet the curative criteria for endoscopic submucosal dissection in early gastric cancer? A multi-center retrospective study in Japan. J Gastroenterol 2017;52:175-184.
11. Suzuki H, Oda I, Abe S, et al. Clinical outcomes of early gastric cancer patients after noncurative endoscopic submucosal dissection in a large consecutive patient series. Gastric Cancer 2017;20:679-689.
12. Kawata N, Kakushima N, Takizawa K, et al. Risk factors for lymph node metastasis and long-term outcomes of patients with early gastric cancer after non-curative endoscopic submucosal dissection. Surg Endosc 2017;31:1607-1616.
13. Kusano C, Iwasaki M, Kaltenbach T, Conlin A, Oda I, Gotoda T. Should elderly patients undergo additional surgery after non-curative endoscopic resection for early gastric cancer? Long-term comparative outcomes. Am J Gastroenterol 2011;106:1064-1069.
14. Oda I, Gotoda T, Sasako M, et al. Treatment strategy after non-curative endoscopic resection of early gastric cancer. Br J Surg 2008;95:1495-1500.
15. Hatta W, Gotoda T, Oyama T, et al. A scoring system to stratify curability after endoscopic submucosal dissection for early gastric cancer: "eCura system". Am J Gastroenterol 2017;112:874-881.
16. Hatta W, Gotoda T, Oyama T, et al. Is the eCura system useful for selecting patients who require radical surgery after noncurative endoscopic submucosal dissection for early gastric cancer? A comparative study. Gastric Cancer 2018;21:481-489.
17. Bang CS, Baik GH, Shin IS, et al. Endoscopic submucosal dissection for early gastric cancer with undifferentiated-type histology: a meta-analysis. World J Gastroenterol 2015;21:6032-6043.
18. Takizawa K, Ono H, Hasuike N, et al. A nonrandomized, single-arm confirmatory trial of expanded endoscopic submucosal dissection indication for undifferentiated early gastric cancer: Japan Clinical Oncology Group study (JCOG1009/1010). Gastric Cancer 2021;24:479-491.
19. Oka S, Tanaka S, Higashiyama M, et al. Clinical validity of the expanded criteria for endoscopic resection of undifferentiated-type early gastric cancer based on long-term outcomes. Surg Endosc 2014;28:639-647.
20. Abe S, Oda I, Suzuki H, et al. Short- and long-term outcomes of endoscopic submucosal dissection for undifferentiated early gastric cancer. Endoscopy 2013;45:703-707.
21. Yang HJ, Jang JY, Kim SG, et al. Risk factors of lymph node metastasis after non-curative endoscopic resection of undifferentiated-type early gastric cancer. Gastric Cancer 2021;24:168-178.
22. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101-112.
23. Lee JH, Kim JG, Jung HK, et al. Clinical practice guidelines for gastric cancer in Korea: an evidence-based approach. J Gastric Cancer 2014;14:87-104.
24. Kim JH, Kim K, Park SJ, et al. Comparative effectiveness of abdominal versus laparoscopic radical hysterectomy for cervical cancer in the postdissemination era. Cancer Res Treat 2019;51:788-796.
25. Kang HJ, Chung H, Kim SG, et al. Synergistic effect of lymphatic invasion and venous invasion on the risk of lymph node metastasis in patients with non-curative endoscopic resection of early gastric cancer. J Gastrointest Surg 2020;24:1499-1509.
26. Sekiguchi M, Sekine S, Oda I, et al. Risk factors for lymphatic and venous involvement in endoscopically resected gastric cancer. J Gastroenterol 2013;48:706-712.
27. Hatta W, Gotoda T, Kanno T, et al. Prevalence and risk factors for lymph node metastasis after noncurative endoscopic resection for early gastric cancer: a systematic review and meta-analysis. J Gastroenterol 2020;55:742-753.
28. Yang HJ, Nam SY, Min BH, et al. Clinical outcomes of endoscopic resection for undifferentiated intramucosal early gastric cancer larger than 2 cm. Gastric Cancer 2021;24:435-444.
29. Kim YI, Kook MC, Choi JE, et al. Evaluation of submucosal or lymphovascular invasion detection rates in early gastric cancer based on pathology section interval. J Gastric Cancer 2020;20:165-175.
30. Choi IJ, Kim YI. Comparison of endoscopic resection and surgery for early gastric cancer with undifferentiated histological type (ERASE-GC) [Internet]. Identifier No. NCT04890171. Available from: https://clinicaltrials.gov/ct2/show/NCT04890171?term=NCT04890171&draw=2&rank=1