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Original Article

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Stratifying Risk of Lymph Node Metastasis After Non-Curative Endoscopic Submucosal Dissection of Early Gastric Cancer: Comparison of the eCura System and Elderly Criteria

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ABSTRACT

Purpose: The novel curability criteria for elderly (EL) patients have been proposed to stratify their risk of lymph node metastasis (LNM), following non-curative endoscopic submucosal dissection (ESD) for early gastric cancer (EGC). Hence, this study aimed to evaluate the effectiveness of the EL criteria and compare them with those of the well-known eCura system.
Materials and Methods: A retrospective analysis was performed on 143 patients who did not meet the curative ESD criteria at a tertiary hospital in Korea between 2011 and 2022. Of these, 102 underwent additional surgery, while 41 were followed up without further treatment. The LNM rates based on the EL and eCura systems were stratified and compared.
Results: In the surgery group, 29.4% (30/102) patients were classified as EL-low (EL-L) and 70.2% (72/102) as EL-high (EL-H). The LNM rates (95% confidence interval) were 0.0% (0.0–11.6) and 9.7% (4.0–19.0) for EL-L and EL-H, respectively (P=0.102). EL-L was closely aligned with the eCura low-risk category, with a similar patient proportion (32.4%) and an LNM rate of 0.0% (0.0–10.6). The eCura system classified 94.1% (48/51) of the EL-L patients as low-risk, with an 86% concordance rate (123/143). Discordant cases included patients with positive vertical margins, but without other risk factors, who were classified as EL-H without LNM.
Conclusions: Patients with EL-L showed no LNM, and the EL criteria demonstrated high concordance with the eCura system. The EL criteria may be as effective as the eCura system in identifying low-risk patients after non-curative ESD for EGC.

Keywords: Stomach neoplasms; Endoscopic mucosal resection; Lymphatic metastasis; Risk assessment

INTRODUCTION

Endoscopic submucosal dissection (ESD) has become the first-line treatment for early gastric cancer (EGC) with minimal risk of lymph node metastasis (LNM) in Korea [1,2], Japan [3,4], and more recently, in Western countries [5,6]. However, approximately 15%–20% of resections fail to meet the curative criteria upon the pathological evaluation of the resected

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Conceptualization: Y.H.J.; Data curation: K.T.W., Y.H.J., L.G., P.S.K., J.Y.S., P.J.H., P.D.I., S.C.I.; Formal analysis: K.T.W., Y.H.J.; Funding acquisition: Y.H.J.; Resources: Y.H.J.; Supervision: Y.H.J.; Writing - original draft: K.T.W., Y.H.J.; Writing - review & editing: K.T.W., Y.H.J., L.G., P.S.K., J.Y.S., P.J.H., P.D.I., S.C.I.

specimens, and are considered non-curative [7-11]. For non-curative ESD cases, additional surgery is recommended as the standard treatment [1,3,4]. Nevertheless, for patients with an elevated surgical risk, such as those of advanced age or with significant comorbidities, assessing the risk of LNM may aid in deciding between subsequent surgery and close observation [12-14]. The eCura system is a risk stratification tool for assessing LNM risk after non-curative ESD for EGC [13,15]. This system is used to classify patients into low, intermediate, and high-risk categories. Close observation rather than additional surgery is recommended for patients in the low-risk category. This system has been externally validated in patients with undifferentiated-type EGC [16], and modified for such patients [17] as well as Western populations [18].

According to the recently proposed novel curability criteria for the elderly (EL), patients (aged ≥75 years) [19], and those undergoing non-curative ESD are classified as EL-low (EL-L) or EL-high (EL-H) risk patients. Additional surgery is not recommended for EL-L patients because among them, the 5-year gastric cancer mortality is only 0.9%. However, this study did not report LNM rates in patients who underwent non-curative ESD based on the EL criteria. Furthermore, differences between the EL criteria and eCura system in risk stratification for LNM after non-curative ESD have not been examined.

Therefore, this study aimed to evaluate the effectiveness of the EL criteria in stratifying the risk of LNM following non-curative ESD for EGC in an independent cohort, and compare these criteria with the eCura system.

MATERIALS AND METHODS

Patients

This retrospective study involved consecutive patients who underwent ESD for EGC at the Kangbuk Samsung Hospital, Seoul, Korea, between September 2011 and December 2022. Patients who experienced non-curative ESD were included in the analysis. Non-curative ESD was defined as a resection not fulfilling the criteria for curative ESD, that as per Korean and Japanese guidelines [1,3,4], was defined as en bloc resection with a negative horizontal margin (HM), negative vertical margin (VM), and absence of lymphatic and venous invasion. It included the following conditions: 1) differentiated-type histology, pT1a, any tumor size, and without ulceration; 2) undifferentiated-type histology, pT1a, tumor size of ≤2 cm, and without ulceration; 3) differentiated-type histology, pT1a, tumor size of ≤3 cm, and with ulceration; 4) differentiated-type histology, pT1b with <500 μm from the muscularis mucosa (SM1), and tumor size of ≤3 cm. For differentiated-type EGC with SM1 invasion, the resection was classified as non-curative if an undifferentiated-type component was present in the submucosal area [3]. The exclusion criteria were: resection with a positive HM, but meeting the other curative criteria; loss to follow-up without a post-ESD visit; history of gastric cancer; multiple EGCs with non-curative ESD; laparoscopic lymph node dissection without gastrectomy after non-curative ESD; and muscularis propria invasion during additional surgery after non-curative ESD.

Following non-curative ESD, additional gastrectomy with lymph node dissection was recommended for all patients according to clinical guidelines [1,3,4]. Patients who underwent additional surgeries formed the surgery group. These patients were monitored using endoscopy and abdominal computed tomography every 6–12 months for 3 years,

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followed by annual assessments for up to 5 years post-surgery. Patients who did not undergo surgery owing to advanced age, comorbidities, or personal refusal were included in the follow-up group. These patients underwent upper endoscopy 3 months post-ESD, and were subsequently subject to the same surveillance schedule as in the surgery group. This study was approved by the Institutional Review Board (IRB) of Kangbuk Samsung Hospital (IRB number: 2024-05-003), and the requirement for informed consent was waived.

ESD procedure and pathological evaluation

ESD was performed by experienced endoscopists through: 1) tumor marking; 2) submucosal injection, followed by mucosal incision outside the markings;3) submucosal dissection using ESD knives, including an insulated-tip knife 2 (IT2; Olympus Medical Systems, Tokyo, Japan); 4) post-ESD ulcer management, including hemostasis of the visible vessels using hemostatic forceps.

The resected specimens were processed and evaluated by experienced pathologists following Japanese guidelines [20]. Pathological mapping was performed at 2-mm intervals. The tumor size, invasion depth, presence of ulceration, and resection margins were assessed. Submucosal invasion was classified as SM1 (if <500 μm from the muscularis mucosa) or SM2 (if ≥500 μm) [3,20]. Papillary, well-differentiated tubular, and moderately differentiated tubular adenocarcinomas were classified as having differentiated-type histology [3,20]. Poorly differentiated (solid and non-solid types), signet-ring cell, and mucinous adenocarcinomas were categorized as having undifferentiated-type histology. Lymphatic and venous invasion were assessed using hematoxylin-eosin staining, whereas immunohistochemical staining (D2-40 monoclonal antibody) was used to evaluate lymphatic invasion at the discretion of the pathologists [21].

Risk stratification for LNM

Two risk stratification systems were used to predict LNM following non-curative ESD in patients with EGC. The eCura system assigned 1 point each for tumor size >3 cm, SM2, venous invasion, and positive VM, whereas lymphatic invasion was assigned 3 points [13,15]. Based on the total score, patients were categorized into low (0–1), intermediate (2–4), and high (5–7) risk categories for LNM.

EL criteria were also applied [19]. Patients were classified as EL-H if they met any of the following conditions: 1) presence of lymphovascular invasion (LVI); 2) positive VM; or 3) undifferentiated-type EGC, pT1b, and tumor size of >3 cm. Those who did not meet these conditions were classified as EL-L, which included patients with negative LVI and VM, but who had: 1) differentiated-type EGC with SM2 or tumor size of >3 cm; or 2) undifferentiated-type EGC with pT1a with any size, or pT1b with tumor size of ≤3 cm.

Outcome evaluation

The primary outcome was the LNM rate in the surgical specimens of patients who underwent additional surgery following non-curative ESD. Overall survival was defined as the duration from the date of ESD to death from any cause based on medical records and claims data as of July 31, 2024 [16,17]. Loss of insurance owing to death was classified as death from an unknown cause. Disease-specific survival was defined as the time from the date of ESD to death from gastric cancer.

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Data collection and statistical analysis

Data on clinical characteristics, pathological findings, surgical outcomes, and follow-up outcomes were collected by reviewing medical records.

Categorical variables were compared using the χ^2 test or Fisher's exact test, and trend analysis was performed using the Cochran–Armitage test. Continuous variables were analyzed using the Student's t-test or the Mann–Whitney test as appropriate.

The LNM rate was analyzed according to the eCura system and EL criteria, and comparisons were made across risk categories within each system. The agreement rate for categorizing low-risk patients was defined as the percentage of patients classified as low-risk by both systems, or not classified as low-risk by either system. The predictive performances of these risk stratification systems were compared using receiver operating characteristic (ROC) analysis. The area under the curve (C-statistics) with a 95% confidence interval (CI) was estimated using 1,000 bootstrap resampling, and the 2 systems were compared using the DeLong test. Survival outcomes were evaluated using the Kaplan–Meier analysis, and groups were compared using the log-rank test. All statistical analyses were performed using the R statistical software package (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

During the study period, 1,201 patients underwent ESD for 1,271 EGCs. Of these patients, 243 (20.2%) were identified as non-curative (**Fig. 1**), and 100 were excluded from the analysis for the following reasons: positive HM without other non-curative factors (n=49), loss to follow-up (n=32), history of gastric cancer (n=11), multiple non-curative ESDs (n=2), laparoscopic lymph node dissection (n=1), or invasion of the muscularis propria in additional surgery (n=5). Consequently, 143 patients were included in the analysis. Among them, 102 (71.3%) who underwent additional radical gastrectomy with lymph node dissection were included in the surgery group, whereas the remaining 41 who were followed up without further treatment comprised the follow-up group.

The mean age ± standard deviation of the overall cohort was 65.8±10.6 years, with 71.3% of the patients being male (**Table 1**). The surgery group demonstrated significantly higher rates of SM2 (68.6% vs. 24.4%, P<0.001) and lymphatic (52.0% vs. 12.2%, P<0.001) invasion than the follow-up group. However, no other significant differences were observed between the 2 groups.

LNM rates according to risk stratification in the surgery group

In the surgery group, 7/102 patients had LNM upon additional surgery, yielding an overall LNM rate of 6.9% (95% CI, 2.8–13.6).

Risk stratification was initially performed using the eCura system (**Table 2**), which revealed a significant increase in LNM rates with higher eCura scores (P-for-trend<0.001). Based on the eCura classification, 33 patients (32.4%) were categorized as low-risk, 46 (45.1%) as intermediate-risk, and 23 (22.5%) as high-risk. The respective LNM rates (95% CI) were 0.0% (0.0–10.6), 2.2% (0.1–11.5), and 26.1% (10.2–48.4) for low, intermediate, and high-risk patients, respectively, showing a significant trend across the risk groups (P-for-trend<0.001).

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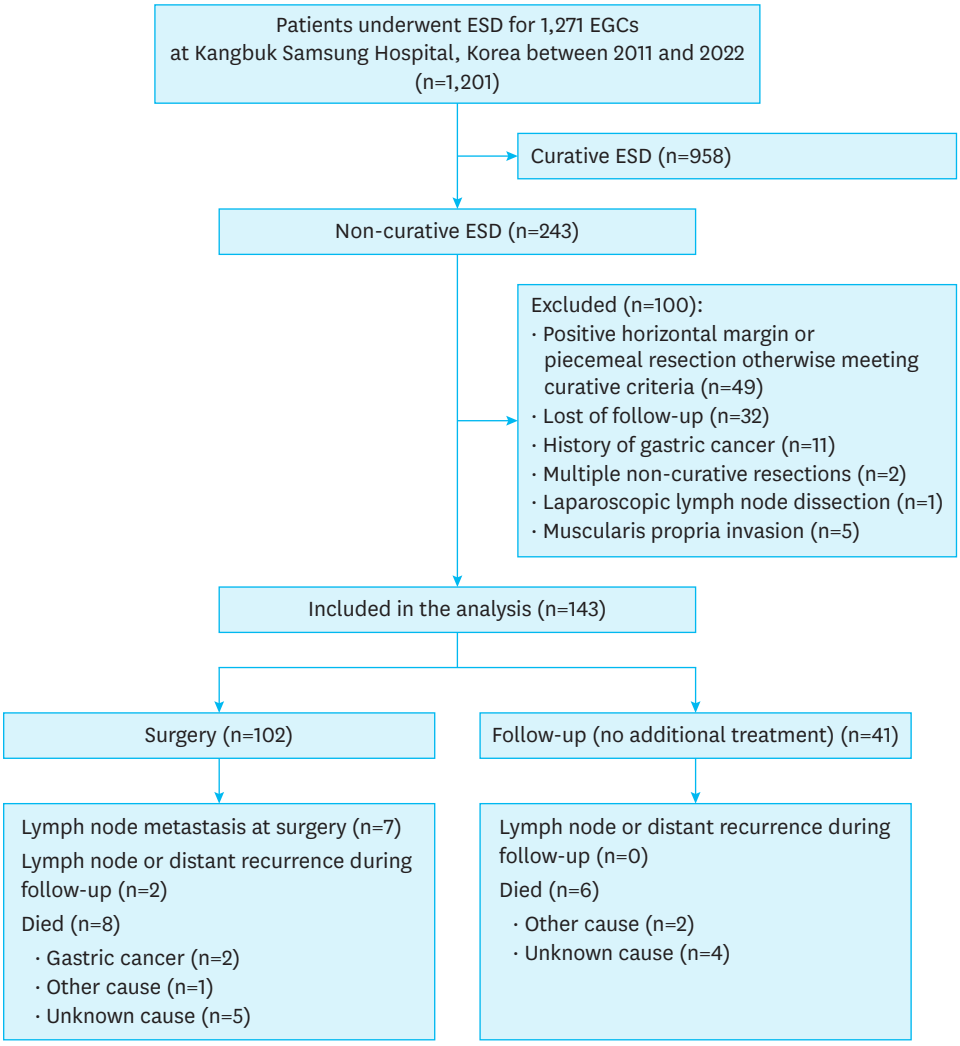

Fig. 1. Flowchart of patients.
ESD = endoscopic submucosal dissection; EGC = early gastric cancer.

Subsequently, the EL criteria were applied to stratify the LNM risk. Based on these criteria, 30 (29.4%) patients were classified as EL-L, a proportion similar to that in the eCura low-risk category. The remaining 72 (70.6%) were classified as EL-H. The LNM rate (95% CI) in the EL-L patients was 0.0% (0.0–11.6), which was also comparable to that in eCura low-risk patients. Among the EL-H patients, the rate in was 9.7% (4.0–19.0); however, the difference between EL-L and EL-H did not reach statistical significance owing to the small sample size (P=0.102). Upon further categorization, LNM was detected only in EL-H patients with LVI. Patients with positive or undetermined VM but without LVI, and one patient with undifferentiated-type histology, submucosal invasion, and tumor size of >3 cm exhibited no LNM.

Comparison of the eCura system and EL criteria for risk stratification

The concordance between the eCura system and EL criteria was assessed by cross-tabulating patient distribution according to the eCura risk categories against the EL classification (**Tables 3** and **4**). Among the patients with non-curative ESD, 94.1% (48/51) of those classified as EL-L were also categorized as low-risk by the eCura system, while EL-H comprised eCura

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Table 1. Baseline characteristics of patients

Characteristics	Overall (n=143)	Surgery (n=102)	Follow-up (n=41)	P-value
Age (yrs)	65.8±10.6	65.6±10.3	66.4±11.5	0.654
Sex				0.473
Female	41 (28.7)	31 (30.4)	10 (24.4)	
Male	102 (71.3)	71 (69.6)	31 (75.6)	
ASA physical status				0.605*
I	51 (35.7)	36 (35.3)	15 (36.6)	
II	88 (61.5)	65 (63.7)	23 (56.1)	
III–IV	4 (2.8)	1 (1.0)	3 (7.3)	
Tumor location				0.120
Upper third	23 (16.1)	18 (17.6)	5 (12.2)	
Middle third	61 (42.7)	38 (37.3)	23 (56.1)	
Lower third	59 (41.3)	46 (45.1)	13 (31.7)	
Tumor size (mm)	24.5±10.8	24.6±10.8	24.3±11.1	0.891
Depth of invasion				<0.001
Mucosa	42 (29.4)	18 (17.6)	24 (58.5)	
Submucosa <500 μm	21 (14.7)	14 (13.7)	7 (17.1)	
Submucosa ≥500 μm	80 (55.9)	70 (68.6)	10 (24.4)	
Histology†				0.895
Differentiated type	100 (69.9)	71 (69.6)	29 (70.7)	
Undifferentiated type	43 (30.1)	31 (30.4)	12 (29.3)	
Lymphatic invasion	58 (40.6)	53 (52.0)	5 (12.2)	<0.001
Venous invasion	1 (0.7)	1 (1.0)	0 (0.0)	1.000
Ulceration	2 (1.4)	2 (2.0)	0 (0.0)	1.000
Positive vertical margin	51 (35.7)	35 (34.3)	16 (39.0)	0.595

Values are presented as mean ± standard deviation or number (%).
ASA = American Society of Anesthesiologists.
*The Cochran-Armitage test was used to calculate P-for-trend.
†Differentiated type included papillary, well-differentiated tubular, and moderately differentiated tubular adenocarcinomas. Undifferentiated type included poorly differentiated (solid and non-solid type), signet-ring cell, and mucinous adenocarcinomas.

low, intermediate, and high-risk patients. The overall agreement rate between the 2 systems for categorizing low-risk patients was 86% (123/143). In the surgery group, the concordance rate between the 2 systems for low-risk classification was 93% (95/102). Notably, no LNM was detected among patients classified as low-risk by either system. LNM was exclusively diagnosed among patients classified as intermediate or high-risk by the eCura system, and as EL-H by the EL criteria. Discrepancies between the EL criteria and eCura system were found in 20 patients (**Supplementary Table 1**). Totally, 85% (17/20) patients were positive for VM without other eCura risk factors because they were classified as EL-H by the EL criteria, but low-risk by the eCura system. Among these 17 patients, the VM was indeterminate rather than positive in 10, and the tumor was confined to the mucosa in 11; however, all exhibited no LNM during surgery or follow-up.

ROC analysis showed that the eCura system had a better predictive performance for LNM (C-statistics, 0.864; 95% bootstrap CI, 0.754–0.937) than the EL criteria (0.658; 95% CI, 0.611–0.705; P<0.001) (**Fig. 2**). However, the 2 systems exhibited minimal differences in classifying low-risk patients. The better performance of the eCura system was primarily owing to its ability to distinguish between high and intermediate-risk patients.

Follow-up outcomes according to risk stratification

Patients were followed up for a median of 70.4 months (interquartile range, 42.9–108.4). There were no significant differences in overall survival between the surgery and follow-up groups, with 5-year survival rates of 96.6% and 89.9%, respectively (P=0.444) (**Supplementary Fig. 1A**). During follow-up, 2 patients in the surgery group experienced

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Table 2. Lymph node metastasis rate according to the eCura system and EL criteria in the surgery group

Risk model	Patients (n=102)	LNM (n=7)	Rate of LNM (% [95% CI])
eCura*			
Risk score			
0	5	0	0.0 (0.0–52.2)
1	28	0	0.0 (0.0–12.3)
2	14	0	0.0 (0.0–23.2)
3	15	0	0.0 (0.0–21.8)
4	17	1	5.9 (0.1–28.7)
5	17	4	23.5 (6.8–49.9)
6	6	2	33.3 (4.3–77.7)
7	0	0	0.0 (not estimated)
P-for-trend			<0.001
Risk category (score)			
Low (0–1)	33	0	0.0 (0.0–10.6)
Intermediate (2–3)	46	1	2.2 (0.1–11.5)
High (4–8)	23	6	26.1 (10.2–48.4)
P-for-trend			<0.001
EL†			
Non-curative category			
Diff, SM2 or >3 cm	17	0	0.0 (0.0–19.5)
Undiff, M or SM ≤3 cm	13	0	0.0 (0.0–24.7)
Undiff, SM, >3 cm	1	0	0.0 (0.0–97.5)
VM1/VMX (LVI [–])	18	0	0.0 (0.0–18.5)
LVI (+)	53	7	13.2 (0.0–11.6)
Elderly risk category			
EL-L	30	0	0.0 (0.0–11.6)
EL-H	72	7	9.7 (4.0–19.0)
P-value			0.102

EL = elderly; LNM = lymph node metastasis; CI = confidence interval; Diff = differentiated type, SM2 = submucosal invasion ≥500 μm from the muscularis mucosa; Undiff = undifferentiated type; M = mucosa; SM = submucosa; VM1 = positive vertical margin; VMX = indeterminate vertical margin; LVI = lymphovascular invasion; EL-L = elderly-low; EL-H = elderly-high; EGC = early gastric cancer.
*eCura model assigned 1 point each for tumor size of >3 cm, SM2, venous invasion, and positive VM, and 3 points for lymphatic invasion.
†EL-L were patients with negative LVI and vertical margin but who either had 1) differentiated-type EGC with SM2 or tumor size of >3 cm, or 2) undifferentiated-type EGC with pT1a with any size or pT1b with tumor size of ≤3 cm. EL-H included 1) presence of LVI, 2) VM1, or 3) undifferentiated-type EGC, pT1b, and tumor size of >3 cm.

lymph node or distant recurrence, and subsequently died from gastric cancer, whereas no patients in the follow-up group developed these events. Disease-specific survival did not differ significantly between the surgery and follow-up groups, with 5-year survival rates

Table 3. Comparison of the eCura system and EL criteria in the risk stratification of patients after non-curative endoscopic submucosal dissection

Overall cohort	EL*		
	EL-L	EL-H	Overall
eCura†			
Low risk	48 (94.1)	17 (18.5)	65
Intermediate risk	3 (5.9)	50 (50.3)	53
High risk	0 (0.0)	25 (27.2)	25
Overall	51	92	143

Values are presented as number (%).
EL = elderly; EL-L = elderly-low; EL-H = elderly-high; SM2 = submucosal invasion ≥500 μm from the muscularis mucosa; EGC = early gastric cancer.
*EL-L were patients with negative lymphovascular invasion and vertical margin but who either had 1) differentiated-type EGC with SM2 or tumor size of >3 cm or 2) undifferentiated-type EGC with pT1a with any size, or pT1b with tumor size of ≤3 cm. EL-H included 1) presence of lymphovascular invasion, 2) positive vertical margin, or 3) undifferentiated-type EGC, pT1b, and tumor size of >3 cm.
†eCura model assigned 1 point each for tumor size of >3 cm, SM2, venous invasion, and positive vertical margin, and 3 points for lymphatic invasion.

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Table 4. Comparison of the eCura system and EL criteria in the risk stratification of patients after non-curative endoscopic submucosal dissection

Surgery group (LNM rate)	EL*					
	EL-L		EL-H		Overall	
	% (95% CI)	n/N	% (95% CI)	n/N	% (95% CI)	n/N
eCura†						
Low risk	0.0 (0.0–12.3)	0/28	0.0 (0.0–52.2)	0/5	0.0 (0.0–10.6)	0/33
Intermediate risk	0.0 (0.0–84.2)	0/2	2.7 (0.1–12.0)	1/44	2.2 (0.1–11.5)	1/46
High risk	0.0 (not estimated)	0/0	26.1 (10.2–48.4)	6/23	26.1 (10.2–48.4)	6/23
Overall	0.0 (0.0–11.6)	0/30	9.7 (4.0–19.0)	7/72	6.9 (2.8–13.6)	7/102

EL = elderly; LNM = lymph node metastasis; EL-L = elderly-low; EL-H = elderly-high; CI = confidence interval; SM2 = submucosal invasion ≥500 μm from the muscularis mucosa; EGC = early gastric cancer.
*EL-L were patients with negative lymphovascular invasion and vertical margin but who either had 1) differentiated-type EGC with SM2 or tumor size of >3 cm or 2) undifferentiated-type EGC with pT1a with any size, or pT1b with tumor size of ≤3 cm. EL-H included 1) presence of lymphovascular invasion, 2) positive vertical margin, or 3) undifferentiated-type EGC, pT1b, and tumor size of >3 cm.
†eCura model assigned 1 point each for tumor size of >3 cm, SM2, venous invasion, and positive vertical margin, and 3 points for lymphatic invasion.

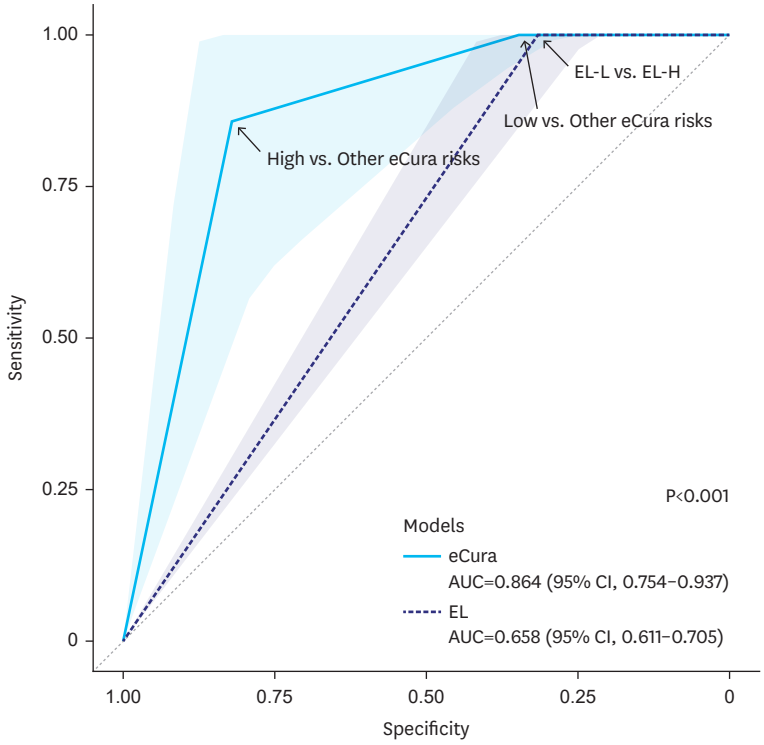

Fig. 2. Receiver operating characteristic curve to compare the EL criteria and eCura system in the prediction of lymph node metastasis in the surgery group. The area under the curve (C-statistics) with a 95% confidence interval was estimated using 1,000 bootstrap resampling, and compared between the systems using the DeLong test (P<0.001).
EL-L = elderly-low; EL-H = elderly-high; AUC = area under the curve; CI = confidence interval.

of 97.5% and 100.0%, respectively (P=0.347) (**Supplementary Fig. 1B**). In the follow-up group, the eCura system and EL criteria discriminated overall survival significantly (P<0.001 and P=0.013, respectively) (**Supplementary Fig. 2**). However, as no lymph node or distant recurrence was observed in the follow-up group, there were no significant differences in disease-specific survival based on the eCura system or the EL criteria.

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DISCUSSION

This study evaluated the effectiveness of the EL criteria in stratifying LNM risk in patients who experienced non-curative ESD for EGC. These results were compared with those obtained using the eCura system. Its findings revealed that EL-L was similar to the eCura low-risk category in terms of the proportion of patients and LNM rate. The 2 systems demonstrated a high agreement rate in identifying low-risk patients, which was supported by ROC analysis. However, patients with positive VM, but no other risk factors, accounted for many of the discrepancies between the 2 systems. These patients were classified as EL-H, but had no LNM during surgery or follow-up.

The EL criteria were developed based on a cohort study of 3,131 patients who underwent surgery for EGC [14,19]. This study originally suggested an 11-point risk-scoring model for LNM, which included tumor size, invasion depth, histological type, ulceration, and LVI as risk factors [14]. This model was recently revised into a risk table format that can be integrated with the conventional curability criteria table [3,22,23], categorizing patients as EL-L with an LNM rate of <10% or EL-H with an LNM rate of ≥10% [19]. However, this 10% cutoff may be lower in patients who underwent ESD rather than surgery as their initial treatment, given the more accurate pathological assessment of ESD specimens over surgical ones for detecting submucosal invasion or LVI [24]. This study evaluated LNM rates using the EL criteria based on pathological findings from ESD. No LNM was detected among the EL-L patients during surgery although the CI was wide owing to the small sample size. Additionally, the EL-L patients were found to comprise approximately 30% of the non-curative ESD cases. The LNM rate and patient distribution were comparable to those classified as low-risk by the eCura system, which estimates an LNM rate of <3% [13,16]. This suggests that the LNM rate among EL-L patients could be <3% following non-curative ESD for EGC.

The EL criteria and eCura system showed a high level of agreement in identifying low-risk patients, with 94.1% of EL-L patients classified as low-risk by the eCura system. This concordance was supported by the ROC analysis. Although the predictive performance of the EL criteria was inferior to that of the eCura system, the thresholds for distinguishing low-risk patients were close. This suggests that either system could be used to identify patients with a low LMN risk (<3%) following non-curative ESD. Moreover, patients classified as low-risk by either system did not develop LNM, whereas those classified as non-low-risk by both systems did. These findings indicate that the 2 systems may complement each other in LNM risk stratification, potentially increasing the proportion of low-risk patients and reducing unnecessary surgery.

A crucial difference between the 2 systems lies in their interpretation of the significance of positive VM in LNM risk. The eCura system stratifies patients with positive VM based on the presence of additional risk factors [13], whereas EL criteria classify all patients with positive VM as high-risk, regardless of other risk factors [19]. Hence, patients with positive VM but without other eCura risk factors, such as SM2 invasion, LVI, or large (>3 cm) tumor size, are classified as low-risk by the eCura system, but EL-H by EL criteria. In this study, only 5/17 patients in this category underwent additional surgery, and all 17 patients had no LNM during surgery, or developed lymph node or distant recurrence during follow-up. This is consistent with the observation in a previous study, indicating that the LNM risk among patients with positive VM is influenced by additional risk factors, such as tumor size, undifferentiated-type histology, invasion depth, and evident tumor exposure [25]. In this study, many of the lesions

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in this category were intramucosal or had indeterminate VM, possibly caused by lesion damage during ESD, rather than by deep submucosal invasion. These findings suggest that in cases where positive or indeterminate VM results from technical issues during ESD, the LNM risk may be lower than those in the other EL-H cases [26]. Notably, this study's 35.7% proportion of positive VM seemed higher than those reported in previous studies (14.2%–30.7%) [7-11]. This discrepancy may be attributable to insufficient submucosal dissection depth in this study. Therefore, further investigations with larger cohorts are needed to better evaluate the risk of LNM in EL-H patients with positive VM, but without other risk factors. Nevertheless, caution should always be exercised because the exact depth of invasion cannot be accurately estimated in cases of positive VM [20,27].

This study had some limitations. First, its retrospective design limited data collection, particularity regarding follow-up outcomes. Many deaths were owing to unknown causes, which may have contributed to the underestimation of gastric cancer mortality. Second, its sample size was smaller than those used to develop the eCura system or EL criteria [13,14,19], reducing the statistical power to differentiate LNM rates between EL-L and EL-H, with wide CIs for these rates. The analysis of discrepant cases between the 2 systems was also limited. Therefore, further large-scale studies are required to validate these findings. Lastly, and most importantly, it applied the EL criteria to patients with EGC across all age groups, despite these criteria being specifically designed for patients aged ≥75 years. While this study aimed to evaluate the effectiveness of the EL criteria in stratifying the risk of LNM after non-curative ESD for EGC, it is crucial to emphasize that its findings do not imply that the EL criteria are universally applicable to patients of all age groups.

In conclusion, this study showed that EL-L patients had no LNM detected following non-curative ESD for EGC. The EL criteria demonstrated high concordance with the eCura system in identifying low-risk patients. These findings suggest that the EL criteria may be as effective as the eCura system in identifying low-risk patients after non-curative ESD for EGC. However, further studies are warranted to more accurately assess the risk of LNM in patients with positive VM but without other risk factors.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Risk factor profiles of patients classified into different risk categories by the eCura and EL systems

Supplementary Fig. 1

Survival outcomes according to additional treatment after non-curative endoscopic submucosal dissection for early gastric cancer. (A) Overall survival in the surgery and follow-up groups. (B) Disease-specific survival in the surgery and follow-up groups.

Supplementary Fig. 2

Overall survival based on the risk stratification systems in the follow-up group. (A) Overall survival according to the eCura risk categories. (B) Overall survival according to the elderly criteria.

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