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Original Article

A Modified eCura System to Stratify the Risk of Lymph Node Metastasis in Undifferentiated-Type Early Gastric Cancer After Endoscopic Resection

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

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

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Correspondence to
Il Ju Choi
Center for Gastric Cancer, Research Institute and Hospital, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 10408, Korea.
Email: cij1224@ncc.re.kr

ORCID iDs
Hyo-Joon Yang
https://orcid.org/0000-0002-0265-672X
Hyuk Lee
https://orcid.org/0000-0003-4271-7205
Tae Jun Kim
https://orcid.org/0000-0001-8101-9034
Da Hyun Jung
https://orcid.org/0000-0001-6668-3113
Kee Don Choi
https://orcid.org/0000-0002-2517-4109
Ji Yong Ahn
https://orcid.org/0000-0002-0030-3744
Wan Sik Lee
https://orcid.org/0000-0002-8021-6228
Seong Woo Jeon
https://orcid.org/0000-0002-9539-9389
Jie-Hyun Kim
https://orcid.org/0000-0002-9198-3326

ABSTRACT

Purpose: The original eCura system was designed to stratify the risk of lymph node metastasis (LNM) after endoscopic resection (ER) in patients with early gastric cancer (EGC). We assessed the effectiveness of a modified eCura system for reflecting the characteristics of undifferentiated-type (UD)-EGC.
Materials and Methods: Six hundred thirty-four patients who underwent non-curative ER for UD-EGC and received either additional surgery (radical surgery group; n=270) or no further treatment (no additional treatment group; n=364) from 18 institutions between 2005 and 2015 were retrospectively included in this study. The eCuraU system assigned 1 point each for tumors >20 mm in size, ulceration, positive vertical margin, and submucosal invasion <500 μm; 2 points for submucosal invasion ≥500 μm; and 3 points for lymphovascular invasion.
Results: LNM rates in the radical surgery group were 1.1%, 5.4%, and 13.3% for the low- (0–1 point), intermediate- (2–3 points), and high-risk (4–8 points), respectively (P-for-trend<0.001). The eCuraU system showed a significantly higher probability of identifying patients with LNM as high-risk than the eCura system (66.7% vs. 22.2%; McNemar P<0.001). In the no additional treatment group, overall survival (93.4%, 87.2%, and 67.6% at 5 years) and cancer-specific survival (99.6%, 98.9%, and 92.9% at 5 years) differed significantly among the low-, intermediate-, and high-risk categories, respectively (both P<0.001). In the

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Gwang Ha Kim
https://orcid.org/0000-0001-9721-5734
Jae Myung Park
https://orcid.org/0000-0002-1534-7467
Sang Gyun Kim
https://orcid.org/0000-0003-1799-9028
Woon Geon Shin
https://orcid.org/0000-0002-9851-5576
Young-Il Kim
https://orcid.org/0000-0002-2614-3419
Il Ju Choi
https://orcid.org/0000-0002-8339-9824

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

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high-risk category, surgery outperformed no treatment in terms of overall mortality (hazard ratio, 3.26; P=0.015).
Conclusions: The eCuraU system stratified the risk of LNM in patients with UD-EGC after ER. It is strongly recommended that high-risk patients undergo additional surgery.

Keywords: Stomach neoplasms; Undifferentiated-type histology; Endoscopic mucosal resection; Lymph node metastasis; Risk assessment

INTRODUCTION

Endoscopic resection (ER) is a minimally invasive treatment for early gastric cancer (EGC) that can preserve the quality of life [1,2]. However, pathological evaluation of ER specimens fails to meet the criteria for curative resection in 16.0%–23.5% of patients [3-7]. Consequently, additional radical gastrectomy with lymph node dissection is necessary for these patients because of the risk of lymph node metastasis (LNM) [8-11]. Nevertheless, only 5.1%–12.2% of these patients are diagnosed with LNM during surgery, highlighting the need for a more tailored approach [3-7]. In the case of differentiated-type EGC, the risk of LNM can be stratified using a scoring model called the "eCura system" [12]. Patients are categorized based on low-, intermediate-, or high-risk for LNM according to the risk scores assigned to each risk factor by the model. According to this model, high-risk patients are recommended to undergo radical surgery, while low-risk patients may be considered for close follow-up without additional treatment [12,13].

Undifferentiated-type (UD)-EGC requires more stringent criteria for curative ER because of its elevated risk of LNM compared to differentiated-type EGC [8-11]. Recently, we demonstrated the effectiveness of the eCura system in stratifying the risk of LNM in patients with UD-EGC who required additional surgery after ER [14]. Moreover, the eCura system is valuable in assessing the risk of cancer-specific mortality and cancer recurrence among patients who did not receive further treatment during follow-up after non-curative ER for UD [14]. However, because this system was initially developed based on a patient cohort where 85.2% had differentiated-type EGC, the criteria for risk factors of the eCura system, such as tumor size or depth of invasion, differ from those for curative resection of UD-EGC [10,12,15]. This suggests that the eCura system may underestimate the risk of LNM in UD-EGC.

Here, we conducted a multicenter cohort study to assess the effectiveness of a newly developed eCuraU system, modified from the original eCura system, in stratifying the risk of LNM in patients with UD-EGC following ER.

MATERIALS AND METHODS

Patient inclusion and follow-up

This study reanalyzed the previous multicenter retrospective cohort data collected from 18 centers in Korea [14,16]. Of 1,124 patients who underwent ER for UD-EGC between 2005 and 2015, 634 who did not fulfill the criteria for curative resection were included (**Supplementary Fig. 1**). Curative resection for UD EGC was defined as en bloc resection with negative horizontal and vertical resection margins, tumor size ≤2 cm, mucosal cancer, no ulcer in the tumor, and no lymphovascular invasion (LVI) [10,11]. Patients with a positive horizontal

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margin but otherwise meeting the curative resection criteria, a history of gastric cancer, synchronous gastric cancers, or advanced gastric cancer were excluded. Patients who were unable to follow-up or received additional endoscopic treatment after ER were also excluded. The included patients were divided into 2 groups: a radical surgery group, comprising patients who underwent additional gastrectomy with lymph node dissection, and a 'no additional treatment' group, comprising patients who did not receive any further treatment and were followed-up. In the no additional treatment group, the first endoscopy was performed 3 months after ER. Subsequently, both groups of patients underwent endoscopy and abdominal computed tomography at 6–12-month intervals during the initial 3 years, followed by annual examinations for at least 2 consecutive years [10,17]. The Institutional Review Boards (IRBs) of all participating hospitals, including Kangbuk Samsung Hospital (IRB No. 2017-09-035), approved the study protocol.

Data collection

Baseline and follow-up data, along with pathological information, were collected by reviewing medical records, as described in previous studies [14,16,18]. Pathological specimens were evaluated at each center according to the Japanese Gastric Cancer Association guidelines [19]. UD-EGC was defined as cases in which signet ring cell carcinoma, poorly differentiated adenocarcinoma, or mucinous adenocarcinoma constituted the entirety or more than 50% of the tumors [10,19]. Depth of submucosal invasion was categorized as <500 μm (SM1) or ≥500 μm (SM2) from the muscularis mucosa [10,19]. Lymphatic invasion was evaluated by hematoxylin and eosin (H&E) staining. The pathologist at each center decided whether to use immunohistochemical staining with the D2-40 monoclonal antibody to assess lymphatic invasion. H&E staining was used to assess the presence of vascular invasion without the use of special staining techniques.

Survival data on the date and cause of death were gathered from medical records and claims data (screened on March 31, 2019). Loss of health insurance was considered as a death from unknown causes [20,21]. Overall survival (OS) was defined as the duration between initial treatment and death from any cause, whereas cancer-specific survival (CSS) was defined as the duration between initial treatment and death from gastric cancer. We defined cancer recurrence as the occurrence of lymph node or distant recurrence, following the same definition described in the original eCura studies [12,14].

Modification of the eCura system

We modified the original eCura system to suit the characteristics of UD-EGC, resulting in the development of the eCuraU system. The original eCura system generated a risk score by assigning points to the following risk factors: 1 point for tumors >30 mm in size, 1 point for SM2, 3 points for lymphatic invasion, 1 point for venous invasion, and 1 point for positive vertical margin (VM) [12]. LNM risk was categorized based on the scores as low- (0–1), intermediate- (2–4), or high-risk (5–7). In the eCuraU system, we assigned the same scores as in the eCura system: 3 points for lymphatic invasion, 1 point for venous invasion, and 1 point for positive VM. However, we combined lymphatic and venous invasion into the LVI and assigned 3 points for LVI because the data could not be separated, as previously reported [14]. This decision aligns with that of a previous systematic review that indicated a similar risk of LNM between LVI and lymphatic invasion [22]. However, we assigned different scores to the eCuraU system for tumor size, submucosal invasion, and ulceration because the curative resection criteria suggested by the guidelines differ between differentiated-type and UD-EGC [8,10,11]. In the eCuraU system, we adjusted 1 point for tumor size >30 mm to >20 mm

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because UD-EGC >20 mm in size is associated with increased risk of LNM [23,24]. The score for submucosal invasion was revised from 1 point for SM2 to 1 point for SM1 and 2 points for SM2, because the risk of LNM in UD histology is increased in both SM1 and SM2 invasion [16,23]. Moreover, we added 1 point for the presence of ulceration because ulceration is a risk factor for LNM in UD-EGC [16,24]. In summary, for the eCuraU system, we assigned 1 point each for tumors >20 mm in size, ulceration, positive VM, and SM1; 2 points for SM2; and 3 points for LVI. Regarding LNM risk in each score stratum, instead of dividing it into low- (0–1), intermediate- (2–4), or high-risk (5–8), we categorized it as low- (0–1), intermediate- (2–3), or high-risk (4–8) [12].

Statistical analysis

The LNM rate in the radical surgery group was calculated for each of the eCuraU risk scores and categories and compared using the χ^2 test, whereas the Cochran-Armitage test was used to calculate the P-for-trend. Receiver operating characteristic (ROC) curves with 95% confidence intervals (CIs) for the eCura and eCuraU scores in the prediction of LNM were plotted with 1,000 bootstrap replications and compared using the DeLong test. We compared the sensitivity and false-negative rate for LNM between the eCura and eCuraU systems using McNemar's test. The original eCura study recommended radical surgery for high-risk patients and no additional treatment for low-risk patients, which implies that LNM can be detected in high-risk patients, but may be missed in low-risk patients [12]. Thus, we defined the sensitivity of both systems for LNM as the probability of identifying patients with LNM as high-risk, which was the number of high-risk patients with LNM divided by the number of overall patients with LNM in the radical surgery group. We also defined the false-negative rate as the probability of classifying patients with LNM as low-risk, which was the number of low-risk patients with LNM divided by the number of overall patients with LNM in the radical surgery group.

Survival data were plotted according to the eCuraU risk category using the Kaplan-Meier method and compared using the log-rank test. We estimated the hazard ratios (HRs) with 95% CI for survival and recurrence outcomes in patients in the low-, intermediate-, and high-risk categories of the eCuraU system using Cox regression analysis in the no additional treatment group. These models were adjusted for age, sex, American Society of Anesthesiologists (ASA) physical status, tumor location, and tumor histology (signet ring cell carcinoma or others). In addition, the adjusted HRs with 95% CI for survival outcomes, comparing patients in the radical surgery and no additional treatment groups were estimated for each of the low-, intermediate-, and high-risk categories of the eCuraU system.

Continuous variables were compared using the Kruskal-Wallis test, and categorical variables were compared using the χ^2, Fisher's exact, or Cochran-Armitage tests, as appropriate. P-values were 2-sided, and significance was set at the 0.05 level. All analyses were performed using R (version 4.2.2; The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

A total of 634 patients who did not undergo curative ER were included in the analysis. According to the eCuraU system, the radical surgery group (n=270) comprised 87 low-risk, 93 intermediate-risk, and 90 high-risk patients, whereas the no additional treatment group

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Table 1. Baseline characteristics of patients in the radical surgery and no additional treatment groups according to the risk categories of the eCuraU system*

Characteristics	Radical surgery group (n=270)				No additional treatment group (n=364)			
	Low risk (n=87)	Intermediate risk (n=93)	High risk (n=90)	P-value	Low risk (n=240)	Intermediate risk (n=95)	High risk (n=29)	P-value
Age (yr)	56.5 (51.3–65.2)	59.5 (52.8–67.7)	63.6 (54.0–70.6)	0.012	62.8 (52.4–72.4)	64.0 (53.6–72.6)	73.9 (68.2–79.3)	0.001
Male sex	51 (58.6)	58 (62.4)	63 (70.0)	0.274	138 (57.5)	58 (61.1)	17 (58.6)	0.838
ASA physical status				0.004†				0.009†
I	59 (67.8)	53 (57.0)	46 (51.1)		140 (58.3)	42 (44.2)	16 (55.2)	
II	28 (32.2)	38 (40.9)	37 (41.1)		90 (37.5)	44 (46.3)	7 (24.1)	
III–IV	0 (0.0)	2 (2.2)	7 (7.8)		10 (4.2)	9 (9.5)	6 (20.7)	
Tumor location				0.413				0.012
Upper third	39 (44.8)	34 (36.6)	44 (48.9)		95 (39.6)	28 (29.5)	14 (48.3)	
Middle third	41 (47.1)	46 (49.5)	37 (41.1)		131 (54.6)	51 (53.7)	13 (44.8)	
Lower third	7 (8.0)	13 (14.0)	9 (10.0)		14 (5.8)	16 (16.8)	2 (6.9)	
Tumor size (mm)	30.0 (24.0–40.0)	21.0 (16.0–34.0)	25.0 (18.0–34.8)	<0.001	27.0 (22.0–35.2)	24.0 (16.5–30.5)	24.0 (22.0–32.0)	0.001
Depth of invasion				<0.001				<0.001
Mucosa	73 (87.4)	19 (20.4)	3 (3.3)		218 (90.8)	19 (20.0)	4 (13.8)	
Submucosa <500 μm	11 (12.6)	19 (20.4)	17 (18.9)		22 (9.2)	26 (27.4)	2 (6.9)	
Submucosa ≥500 μm	0 (0.0)	55 (59.1)	70 (77.8)		0 (0.0)	50 (52.6)	23 (79.3)	
Histology				0.005‡				0.067‡
PD	60 (69.0)	77 (82.8)	73 (81.1)		146 (60.8)	62 (65.3)	21 (72.4)	
SRC	27 (31.0)	16 (17.2)	11 (12.2)		92 (38.3)	31 (32.6)	5 (17.2)	
Mucinous	0 (0.0)	0 (0.0)	6 (6.7)		2 (0.8)	2 (2.1)	3 (10.3)	
Lymphovascular invasion	0 (0.0)	8 (8.6)	68 (75.6)	<0.001	0 (0.0)	3 (3.2)	20 (69.0)	<0.001
Ulceration	0 (0.0)	14 (15.1)	13 (14.4)	0.001	9 (3.8)	21 (22.1)	7 (24.1)	<0.001
Positive vertical margin	1 (1.1)	15 (16.1)	38 (42.2)	<0.001	3 (1.3)	12 (12.6)	11 (37.9)	<0.001

Values 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 eCuraU system are assigned 0–1, 2–3, and 4–8 points, respectively, according to the sum of the following risk scores: 1 point each for tumors >20 mm in size, ulceration, positive vertical margin, and submucosal invasion <500 μm from the muscularis mucosa; 2 points for submucosal invasion ≥500 μm from the muscularis mucosa; and 3 points for lymphovascular invasion.
†Cochran-Armitage test was used to calculate the P-for-trend.
‡The proportion of patients with signet ring cell carcinoma was compared to that of patients with poorly differentiated or mucinous adenocarcinoma.

(n=364) comprised 240 low-risk, 95 intermediate-risk, and 29 high-risk patients. The mean age ± standard deviation of the overall cohort was 61.8±11.8 years, with 385 (60.7%) male patients. The patient demographics and baseline characteristics are presented in **Table 1**.

Risk stratification for LNM in the radical surgery group

Of the 270 patients in the radical surgery group, 18 (6.7%; 95% CI, 3.7–9.7) were confirmed to have LNM (**Table 2**). A significant increasing trend in the LNM rate was found with increasing eCuraU risk scores (P-for-trend<0.001). The high-risk patients had a significantly higher LNM rate than the low-risk patients (13.3% vs. 1.1%, P=0.002), whereas the intermediate-risk patients did not (5.4% vs. 1.1%, P=0.212). In the ROC analysis, the C-statistic of the eCuraU score was 0.723 (95% bootstrap CI, 0.589–0.832), indicating good discrimination (**Supplementary Fig. 2**); however, there was no significant difference from the original eCura score (0.687; 95% bootstrap CI, 0.558–0.815; P=0.240). The risk category was upgraded from low-risk to intermediate- or high-risk (n=64), or from intermediate-risk to high risk (n=62) in the eCuraU system compared with the original eCura system, but the risk category was not downgraded (**Table 3**). Among the 18 patients with LNM, the eCuraU system categorized 12 patients as high-risk and only one patient as low-risk. In contrast, the original eCura system categorized only 4 patients as high-risk and 4 patients as low-risk (**Supplementary Table 1**). Consequently, the eCuraU system showed a significant improvement in sensitivity (66.7% vs. 22.2%; McNemar P<0.001) and false-negative rate (5.5% vs. 22.2%; McNemar P<0.001) for LNM compared with the original eCura system (**Supplementary Table 2**).

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Table 2. LNM rate according to the eCuraU system in the radical surgery group

eCuraU*	Patients (n=270)	LNM (n=18)	Rate of LNM, % (95% CI)
Risk score			
0			
1	87	1	1.1 (0.0–3.4)
2	48	3	6.3 (0.0–13.4)
3	45	2	4.4 (0.0–10.7)
4	28	4	14.3 (0.5–28.1)
5	22	1	4.5 (0.0–14.0)
6	28	4	14.3 (0.5–28.1)
7	11	3	27.3 (0.0–58.7)
8	1	0	0.0 (NA)
Total	270	18	6.7 (3.7–9.7)
P-for-trend			<0.001
Risk category (score)			
Low (0–1)	87	1	1.1 (0.0–3.4)
Intermediate (2–3)	93	5	5.4 (0.7–10.1)†
High (4–8)	90	12	13.3 (6.2–20.5)‡
P-for-trend			0.012

LNM = lymph node metastasis; CI = confidence interval; NA = not applicable.
*Risk scores: 1 point each for tumors >20 mm in size, ulceration, positive vertical margin, and submucosal invasion <500 μm from the muscularis mucosa; 2 points for submucosal invasion ≥500 μm from the muscularis mucosa; and 3 points for lymphovascular invasion.
†The LNM rate was not significantly different between the intermediate- and low-risk patients (P=0.212).
‡The LNM rate was significantly higher in the high-risk patients than in the low-risk patients (P=0.002).

Table 3. LNM rates in upgraded, maintained, and downgraded cases in the eCuraU system compared to the original eCura system

LNM rate	eCuraU†							
	Low-risk		Intermediate-risk		High-risk		Overall	
	% (95% CI)	(no./total no.)	% (95% CI)	(no./total no.)	% (95% CI)	(no./total no.)	% (95% CI)	(no./total no.)
eCura*								
Low-risk	1.1 (0.0–3.4)	(1/87)	4.8 (0.0–10.2)	(3/63)	0.0 (not estimated)	(0/1)	2.6 (0.1–5.2)	(4/151)
Intermediate-risk	-		6.7 (0.0–16.1)	(2/30)	12.9 (4.3–21.5)	(8/62)	10.9 (4.4–17.6)	(10/92)
High-risk	-		-		14.8 (0.5–29.1)	(4/27)	14.8 (0.5–29.1)	(4/27)
Overall	1.1 (0.0–3.4)	(1/87)	5.4 (0.7–10.1)	(5/93)	13.3 (6.2–20.5)	(12/90)		

LNM = lymph node metastasis; CI = confidence interval.
*The low-, intermediate-, and high-risk categories of the eCura system are assigned 0–1, 2–4, and 5–7 points, respectively, according to the sum of the following risk scores: 1 point each for tumors >30 mm in size, positive vertical margin, and submucosal invasion ≥500 μm from the muscularis mucosa, and 3 points for lymphovascular invasion.
†The low-, intermediate-, and high-risk categories of the eCuraU system are assigned 0–1, 2–3, and 4–8 points, respectively, according to the sum of the following risk scores: 1 point each for tumors >20 mm in size, ulceration, positive vertical margin, and submucosal invasion <500 μm from the muscularis mucosa; 2 points for submucosal invasion ≥500 μm from the muscularis mucosa; and 3 points for lymphovascular invasion.

Survival and recurrence risk discrimination in the no additional treatment group

In the no additional treatment group, the OS was significantly different among the low-, intermediate-, and high-risk patients (P<0.001): 93.4%, 87.2%, and 67.6% at 5 years, respectively (**Fig. 1A**). However, this was not observed in the radical surgery group (P=0.404) (**Fig. 1B**). After adjusting for age, sex, ASA physical status, and tumor location and histology, the increasing eCuraU risk category was significantly associated with increasing HR for overall mortality (HR, 1.57; 95% CI, 1.07–2.28; P-for-trend=0.020) (**Table 4**).

CSS also differed significantly in the low-, intermediate-, and high-risk patients in the no additional treatment group (P<0.001): 99.6%, 98.9%, and 92.9% at 5 years, respectively (**Fig. 1C**). The increased HR for cancer-specific mortality was also significantly associated with the increasing eCuraU risk category in the no additional treatment group (HR, 5.45; 95% CI, 1.54–19.23; P-for-trend=0.008) (**Table 4**). CSS was also significantly different among the eCuraU risk categories in the radical surgery group (P=0.049) (**Fig. 1D**), but the significance was eliminated after adjusting for covariates (**Supplementary Table 3**). The cancer recurrence analysis showed similar results (**Table 4**, **Supplementary Table 3**, **Supplementary Fig. 3**).

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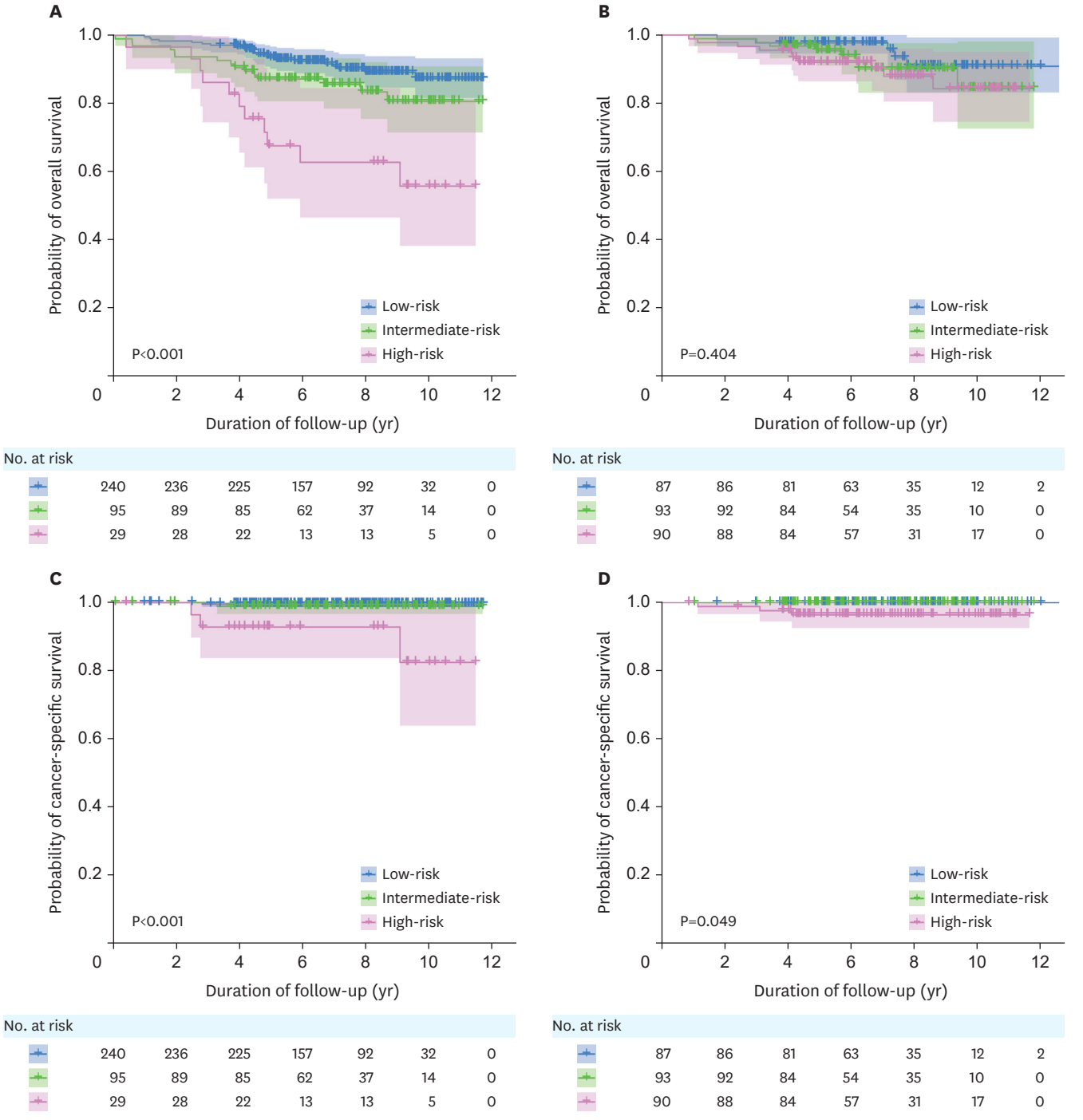

Fig. 1. Survival outcomes based on the risk categories of the eCuraU system. Overall survival in (A) the no additional treatment group and (B) the radical surgery group. Cancer-specific survival in (C) the no additional treatment group and (D) the radical surgery group.

Benefit of additional surgery for high-risk patients

The no additional treatment group was associated with a significant increase in overall mortality compared to the radical surgery group in the high-risk category after adjustment (HR, 3.26; 95% CI, 1.26–8.42; P=0.015) (**Table 5**). The adjusted HR for cancer-specific mortality and cancer recurrence comparing no additional treatment and radical surgery

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Table 4. Adjusted analysis* of hazards for mortality and recurrence according to risk categories of the eCuraU system in the no additional treatment group†

Risk category	Overall mortality					Cancer-specific mortality					Cancer recurrence				
	Person time at risk (mon)	No. of cases	HR	95% CI	P-value	Person time at risk (mon)	No. of cases	HR	95% CI	P-value	Person time at risk (mon)	No. of cases	HR	95% CI	P-value
Low-risk	20,641.1	22				20,641.1	1				14,308.2	2			
Intermediate-risk	7,954.3	15	1.57	0.78–3.14	0.199	7,954.3	1	2.80	0.17–45.88	0.472	5,175.2	2	3.52	0.48–25.70	0.215
High-risk	2,256.5	11	2.45	1.13–5.28	0.023	2,256.5	3	25.43	2.36–274.45	0.008	1,278.3	3	17.51	2.58–119.03	0.003
P-for-trend			1.57	1.07–2.28	0.020			5.45	1.54–19.23	0.008			4.19	1.58–11.15	0.004

HR = hazard ratio; CI = confidence interval.
*Hazard ratios were adjusted for age, sex, American Society of Anesthesiologists physical status, and tumor location and histology.
†The low-, intermediate-, and high-risk categories of the eCuraU system are assigned 0–1, 2–3, and 4–8 points, respectively, according to the sum of the following risk scores: 1 point each for tumors >20 mm in size, ulceration, positive vertical margin, and submucosal invasion <500 μm from the muscularis mucosa; 2 points for submucosal invasion ≥500 μm from the muscularis mucosa; and 3 points for lymphovascular invasion.

Table 5. 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 eCuraU system†

Risk category	Overall mortality					Cancer-specific mortality					Cancer recurrence				
	Person time at risk (mon)	No. of cases	HR	95% CI	P-value	Person time at risk (mon)	No. of cases	HR	95% CI	P-value	Person time at risk (mon)	No. of cases	HR	95% CI	P-value
Low-risk															
Radical surgery	7,790.3	5	1			7,790.3	0	1			5,490.3	0	1		
No additional treatment	20,641.1	22	0.54	0.17–1.69	0.292	20,641.1	1	1.06×10^{8}	0.00–Infinite	1.000	14,308.2	2	6.11×10^{9}	0.00–Infinite	0.999
Intermediate-risk															
Radical surgery	7,734.0	8				7,734.0	0				5,105.8	0			
No additional treatment	7,954.3	15	1.00	0.39–2.59	0.994	7,954.3	1	0.03	0.00–Infinite	1.000	5,175.2	2	3.90×10^{9}	0.00–Infinite	0.999
High-risk															
Radical surgery	7,609.4	10				7,609.4	3				5,223.9	4			
No additional treatment	2,256.5	11	3.26	1.26–8.42	0.015	2,256.5	3	4.76	0.78–29.21	0.092	1,278.3	3	3.61	0.71–18.41	0.122

HR = hazard ratio; CI = confidence interval.
*Hazard ratios were adjusted for age, sex, American Society of Anesthesiologists physical status, and tumor location and histology.
†The low-, intermediate-, and high-risk categories of the eCuraU system are assigned 0–1, 2–3, and 4–8 points, respectively, according to the sum of the following risk scores: 1 point each for tumors >20 mm in size, ulceration, positive vertical margin, and submucosal invasion <500 μm from the muscularis mucosa; 2 points for submucosal invasion ≥500 μm from the muscularis mucosa; and 3 points for lymphovascular invasion.

were 4.76 (95% CI, 0.78–29.21; P=0.092) and 3.61 (95% CI, 0.71–18.48; P=0.122), respectively. However, this association was not found in the low- or intermediate-risk patients.

DISCUSSION

In this large cohort study, we modified the original eCura system to develop an eCuraU system that reflects the characteristics of UD-EGC. Using the eCuraU system, we effectively stratified the risk for LNM in patients who underwent additional surgery after ER. The eCuraU system identified more patients with LNM as high-risk and fewer as low-risk than the original eCura system. Additionally, the system discriminated between the risk of survival and recurrence during follow-up in patients who received no additional treatment after non-curative ER. Moreover, higher OS, excluding cancer-specific outcomes, was associated with radical surgery than with no additional treatment in high-risk patients. These results suggest that the eCuraU system may be useful in stratifying LNM risk and assisting in the decision-making process regarding additional surgery after ER for UD-EGC.

The original eCura system was developed primarily for patients with differentiated-type EGC [12,15]. While an eCura score of 0 indicates curative ER for differentiated-type EGC, it also

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includes non-curative ER for UD-EGC. In the eCuraU system, we adjusted the risk categories to ensure that a score of 0 corresponded to a curative ER for UD EGC. Additionally, we have revised the intermediate-risk category from 2–4 to 2–3. With these revisions, the eCuraU system evaluated the risk of LNM more strictly than the original version; almost 50% of the patients in the radical surgery group were upgraded in their risk category in the eCuraU. The LNM rates among the 3 risk categories were more appropriately distinguished using the eCuraU system (1.1%, 5.4%, and 13.3% for low-, intermediate-, and high-risk, respectively) than using the original system (2.6%, 10.9%, and 14.8% for low-, intermediate-, and high-risk, respectively) [14]. The sensitivity and false-negative rate for LNM also improved with the system modifications.

In our analysis, the low-risk patients demonstrated an LNM rate of 1.1%, which is comparable to 2.5% in the initial eCura study and 2.6% in the validation study of the eCura system for UD-EGC [12,14]. Low-risk patients exhibited a 99.6% CSS rate and 0.5% cancer recurrence rate after 5 years of follow-up without additional treatment. Given that low-risk patients who underwent radical surgery achieved a 5-year CSS rate of 100.0%, the benefit of additional surgery was marginal. Therefore, low-risk patients found using the eCuraU system may be considered for close follow-up without additional treatment. However, it is important to note that LNM can still occur in low-risk patients in the eCuraU system because they did not undergo curative ER.

The high-risk patients under the eCuraU system demonstrated a 13.3% rate of LNM, which is comparable to those in the original eCura study (22.7%) and the validation study of the eCura system in UD-EGC (14.8%) [12,14]. Additionally, among high-risk patients in the no additional treatment group, the CSS rate was 92.9% at 5 years with a cancer recurrence rate of 9.8%. These rates were inferior to the 96.6% CSS and 5.0% cancer recurrence rate at 5 years observed among high-risk patients in the radical surgery group, although the adjusted HR for these outcomes when comparing the 2 groups was not statistically significant. Therefore, according to the eCuraU system, radical surgery is strongly recommended for high-risk patients after ER for UD-EGC. However, further evidence is required to substantiate this recommendation, as no statistically significant improvements in cancer-specific outcomes with radical surgery were observed in our study.

In the original eCura system, neither close follow-up nor radical surgery was recommended for the intermediate-risk patients [12,13]. However, we have previously suggested combining the intermediate- and high-risk patients of the eCura system into a single high-risk category in cases of UD-EGC, for which additional surgery is strongly recommended [14]. In the present study, according to the eCuraU system, we observed that intermediate-risk patients had a 5.4% LNM rate in the radical surgery group and a 98.9% 5-year CSS rate in the no additional treatment group. Therefore, decisions regarding additional surgery can be made on an individual basis, considering the surgical risk, as recommended in the original eCura study. However, caution should be exercised when dealing with cases of positive VM because the exact depth of invasion cannot be evaluated [19,25]. Although, statistically, a positive VM is considered a risk factor for LNM [12,16,22], it poses a risk of residual cancer in the submucosal or deeper layers, which can lead to local recurrence. Therefore, additional surgery may be warranted for patients with positive VM, even if they have an intermediate risk of LNM.

Our study had some limitations. First, our data were derived from a retrospective cohort, which has some inherent limitations. As ER for UD-EGC is still considered an experimental

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treatment in Korea [8,9,26], there may have been a selection bias in the choice between surgical resection and ER as the initial treatment, and between additional surgery and no additional treatment after ER. Second, the eCuraU system was not developed using statistical methods due to the limited sample size; rather, we modified the original eCura system based on existing evidence of the LNM risk, including findings from systematic reviews [12,16,22,24]. Nonetheless, our results derived from ER pathology specimens maintain clinical significance compared with prior larger-sized studies that relied on surgical specimens [24,27-29]. This stems from the finding that evaluating ER specimens allows better detection of LVI and submucosal invasion than evaluating surgical specimens [30]. Third, we used LVI as a surrogate for assessing lymphatic and venous invasion separately because routine immunohistochemical staining for lymphatic invasion was not feasible. This approach may have resulted in the misclassification of risk scores, as discussed in a previous study [14]. Fourth, our cohort was the development cohort for the eCuraU score but a validation cohort for the eCura system. To accurately compare the 2 risk scores, a comparison using a large external cohort that is not associated with the development of either score is required. A randomized controlled trial comparing endoscopic submucosal dissection and surgery in patients with UD-EGC in terms of survival outcomes is in progress (ClinicalTrials.gov No. NCT04890171) [31]. The analysis of trial data may provide more robust and reliable evidence, while minimizing the risks of selection and misclassification bias.

In conclusion, we have introduced a modified eCuraU system to stratify LNM risk after ER in patients with UD-EGC. Based on our findings, we strongly recommend that high-risk patients consider additional surgery, as it may improve cancer-specific outcomes. Conversely, low-risk patients may be suitable for close follow-ups without the need for additional treatment. Nevertheless, it is essential to conduct further prospective studies to validate our results and ascertain the effectiveness of the eCuraU system in guiding clinical decision-making.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Risk factor profile of the patients with lymph node metastasis diagnosed at additional surgery after non-curative endoscopic resection

Supplementary Table 2
Comparison of sensitivity and false negative rate for lymph node metastasis between the eCura and eCuraU system in the radical surgery group

Supplementary Table 3
Adjusted analysis* of hazards for mortality and recurrence according to risk categories of the eCuraU system in the radical surgery gGroup†

Supplementary Fig. 1
A flowchart of the study cohort.

Supplementary Fig. 2
Receiver operating characteristic curve to compare eCura and eCuraU in the prediction of lymph node metastasis in the radical surgery group. No significant difference was observed in the area under the curves of the 2 curves (DeLong, P=0.240).

Supplementary Fig. 3
Cancer recurrence according to the risk categories of the eCuraU system. (A) No additional treatment group. (B) Radical surgery group.

REFERENCES

1. Kim SG, Ji SM, Lee NR, Park SH, You JH, Choi IJ, et al. Quality of life after endoscopic submucosal dissection for early gastric cancer: a prospective multicenter cohort study. Gut Liver 2017;11:87-92. PUBMED | CROSSREF
2. Choi JH, Kim ES, Lee YJ, Cho KB, Park KS, Jang BK, et al. Comparison of quality of life and worry of cancer recurrence between endoscopic and surgical treatment for early gastric cancer. Gastrointest Endosc 2015;82:299-307. PUBMED | CROSSREF
3. Yang HJ, Kim SG, Lim JH, Choi J, Im JP, Kim JS, et al. Predictors of lymph node metastasis in patients with non-curative endoscopic resection of early gastric cancer. Surg Endosc 2015;29:1145-1155. PUBMED | CROSSREF
4. Kim ER, Lee H, Min BH, Lee JH, Rhee PL, Kim JJ, et al. Effect of rescue surgery after non-curative endoscopic resection of early gastric cancer. Br J Surg 2015;102:1394-1401. PUBMED | CROSSREF
5. Hatta W, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, 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. PUBMED | CROSSREF
6. Suzuki H, Oda I, Abe S, Sekiguchi M, Nonaka S, Yoshinaga 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. PUBMED | CROSSREF
7. Kawata N, Kakushima N, Takizawa K, Tanaka M, Makuuchi R, Tokunaga M, 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. PUBMED | CROSSREF
8. Kim TH, Kim IH, Kang SJ, Choi M, Kim BH, Eom BW, et al. Korean practice guidelines for gastric cancer 2022: an evidence-based, multidisciplinary approach. J Gastric Cancer 2023;23:3-106. PUBMED | CROSSREF

https://doi.org/10.5230/jgc.2024.24.e13

9. Park CH, Yang DH, Kim JW, Kim JH, Kim JH, Min YW, et al. Clinical practice guideline for endoscopic resection of early gastrointestinal cancer. Clin Endosc 2020;53:142-166. PUBMED | CROSSREF
10. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1-21. PUBMED | CROSSREF
11. Ono H, Yao K, Fujishiro M, Oda I, Uedo N, Nimura S, et al. Guidelines for endoscopic submucosal dissection and endoscopic mucosal resection for early gastric cancer (second edition). Dig Endosc 2021;33:4-20. PUBMED | CROSSREF
12. Hatta W, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, 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. PUBMED | CROSSREF
13. Hatta W, Gotoda T, Oyama T, Kawata N, Takahashi A, Yoshifuku Y, 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. PUBMED | CROSSREF
14. Yang HJ, Kim YI, Ahn JY, Choi KD, Kim SG, Jeon SW, et al. External validation of the eCura system for undifferentiated-type early gastric cancer with noncurative endoscopic resection. Gut Liver 2023;17:537-546. PUBMED | CROSSREF
15. Hirai Y, Abe S, Makiguchi ME, Sekiguchi M, Nonaka S, Suzuki H, et al. Endoscopic resection of undifferentiated early gastric cancer. J Gastric Cancer 2023;23:146-158. PUBMED | CROSSREF
16. Yang HJ, Jang JY, Kim SG, Ahn JY, Nam SY, Kim JH, 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. PUBMED | CROSSREF
17. Lee JH, Kim JG, Jung HK, Kim JH, Jeong WK, Jeon TJ, et al. Clinical practice guidelines for gastric cancer in Korea: an evidence-based approach. J Gastric Cancer 2014;14:87-104. PUBMED | CROSSREF
18. Yang HJ, Lee WS, Lee BE, Ahn JY, Jang JY, Lim JH, et al. Long-term outcomes of undifferentiated-type early gastric cancer with positive horizontal margins after endoscopic resection. Gut Liver 2021;15:723-731. PUBMED | CROSSREF
19. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101-112. PUBMED | CROSSREF
20. Kim JH, Kim YI, Ahn JY, Shin WG, Yang HJ, Nam SY, et al. Long-term outcomes of endoscopic resection followed by additional surgery after non-curative resection in undifferentiated-type early gastric cancer: a nationwide multi-center study. Surg Endosc 2022;36:1847-1856. PUBMED | CROSSREF
21. Ahn JY, Kim YI, Shin WG, Yang HJ, Nam SY, Min BH, et al. Comparison between endoscopic submucosal resection and surgery for the curative resection of undifferentiated-type early gastric cancer within expanded indications: a nationwide multi-center study. Gastric Cancer 2021;24:731-743. PUBMED | CROSSREF
22. Hatta W, Gotoda T, Kanno T, Yuan Y, Koike T, Moayyedi P, 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. PUBMED | CROSSREF
23. Hirasawa T, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, et al. Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. Gastric Cancer 2009;12:148-152. PUBMED | CROSSREF
24. Sekiguchi M, Oda I, Taniguchi H, Suzuki H, Morita S, Fukagawa T, et al. Risk stratification and predictive risk-scoring model for lymph node metastasis in early gastric cancer. J Gastroenterol 2016;51:961-970. PUBMED | CROSSREF
25. Park YS, Kook MC, Kim BH, Lee HS, Kang DW, Gu MJ, et al. A standardized pathology report for gastric cancer: 2nd edition. J Gastric Cancer 2023;23:107-145. PUBMED | CROSSREF
26. Eom SS, Choi W, Eom BW, Park SH, Kim SJ, Kim YI, et al. A comprehensive and comparative review of global gastric cancer treatment guidelines. J Gastric Cancer 2022;22:3-23. PUBMED | CROSSREF
27. Abdelfatah MM, Barakat M, Lee H, Kim JJ, Uedo N, Grimm I, et al. The incidence of lymph node metastasis in early gastric cancer according to the expanded criteria in comparison with the absolute criteria of the Japanese Gastric Cancer Association: a systematic review of the literature and meta-analysis. Gastrointest Endosc 2018;87:338-347. PUBMED | CROSSREF
28. Pyo JH, Shin CM, Lee H, Min BH, Lee JH, Kim SM, et al. A risk-prediction model based on lymph-node metastasis for incorporation into a treatment algorithm for signet ring cell-type intramucosal gastric cancer. Ann Surg 2016;264:1038-1043. PUBMED | CROSSREF
29. Kim SM, Min BH, Ahn JH, Jung SH, An JY, Choi MG, et al. Nomogram to predict lymph node metastasis in patients with early gastric cancer: a useful clinical tool to reduce gastrectomy after endoscopic resection. Endoscopy 2020;52:435-443. PUBMED | CROSSREF

30. Kim YI, Kook MC, Choi JE, Lee JY, Kim CG, Eom BW, 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. PUBMED | CROSSREF

31. Choi IJ. Comparison of endoscopic resection and surgery for early gastric cancer with undifferentiated histological type (ERASE-GC), identifier NCT04890171 [Internet]. Bethesda, MD: National Library of Medicine; 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT04890171?term=NCT04890171&draw=2&rank=1.