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ORIGINAL ARTICLE

Development of a predictive model for extragastric recurrence after curative resection for early gastric cancer

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Abstract

Background Stratification of patients who undergo curative resection for early gastric cancer (EGC) is warranted due to the heterogeneity in the risk of developing extragastric recurrence (EGR). Therefore, we aimed to stratify the need for postoperative surveillance for EGR detection in patients with EGC by developing a model for predicting EGR-free survival.

Methods This retrospective cohort study included patients who underwent postoperative surveillance after curative resection of EGC ($n=4149$). Cox proportional hazard models were used to identify predictors to build a model for predicting EGR-free survival. Bootstrap-corrected c-index and calibration plots were used for internal and external ($n=2148$) validations.

Results A risk-scoring system was constructed using variables significantly associated with EGR-free survival: pathologic T stage (pT1b[sm1], hazard ratio [HR] 4.928; pT1b[sm2], HR 5.235; pT1b[sm3], HR 7.748) and N stage (pN1, HR 4.056; pN2, HR 9.075; pN3, HR 30.659). Patients were dichotomized into a very-low-risk group or a low-or-greater-risk group. The 5-year EGR-free survival rates differed between the two groups (99.9 vs. 97.3%). The discriminative performance of the model was 0.851 (Uno's c-index) and 0.751 in the internal and external cohorts, respectively. The calibration slope was 0.916 and 1.131 in the internal and external cohorts, respectively.

Conclusions Our model for predicting EGR-free survival based on the pathologic T and N stages may be useful for stratifying patients who have undergone curative surgery for EGC. The results suggest that patients in the very-low-risk group may be spared from postoperative surveillance considering their extremely high EGR-free survival rate.

Keywords Stomach neoplasms · General surgery · Watchful waiting · Treatment outcome · Retrospective studies

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Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related mortality globally, with an estimated > 1 million new cases and 783,000 deaths in 2018 [1]. Notably, the detection rates of early gastric cancer (EGC) in Eastern Asia have been increasing due to the introduction of nationwide endoscopy-based cancer-screening programs [2, 3]. For EGC, gastrectomy with lymph node (LN) dissection remains the standard treatment and is associated with an excellent 5-year overall survival rate (> 97%) [4, 5]. After curative resection of EGC, patients undergo surveillance for the early detection of either gastric recurrence (GR) or extragastric recurrence (EGR) [5–10]. Gastroscopy is performed to detect GR, whereas computed tomography (CT) or ultrasound is performed to detect EGR [5, 6, 10]. However, the incidence of EGR after curative resection of EGC has been reported to be as low as 1–2% [11–13]. Moreover, the risk of developing EGR appears to significantly differ among patients, with even lower risk reported in some patients [14, 15]. Considering the medical costs of imaging surveillance, safety issues such as the potential radiation hazard, and the attendant psychological burden [16–19], identification of patients with a very low risk of EGR and sparing them from postoperative surveillance is clinically important. In this regard, Seo et al. recently reported a risk-scoring system for predicting the risk of EGR after curative resection of EGC and suggested avoiding surveillance in patients with low risk [14]. However, the predictors reported by them included indications for endoscopic submucosal dissection (ESD), which are complex to assess and may not be intuitively applied to surgical specimens. Moreover, ultrasound, which has been recommended as an imaging modality for postoperative surveillance in East Asian patients with EGC [5, 6], was not addressed in that study, and the validation cohort ($n = 430$) was relatively smaller than the derivation cohort ($n = 3162$).

Therefore, we aimed to develop a new model for predicting EGR-free survival after curative resection of EGC and to stratify the need for postoperative surveillance according to the predicted risk of developing EGR.

Methods

This retrospective study was approved by the institutional review boards of Seoul National University Hospital (H-1901-125-1005) and Seoul National University Bundang Hospital (B-1905/538-403); the requirement for informed consent was waived.

Patients

We searched the surgery database of Seoul National University Hospital to identify 4662 consecutive patients who underwent total or subtotal gastrectomy for EGC between January 2003 and December 2013. We excluded patients who met the following criteria: (1) showed other remote or concurrent malignancy ($n = 336$), (2) did not undergo postoperative surveillance at our hospital ($n = 107$), (3) previously underwent curative ESD for EGC ($n = 61$), (4) showed a positive resection margin in the surgical specimen ($n = 5$), or (5) had distant metastasis at initial presentation ($n = 4$). The remaining 4149 patients who underwent curative resection of EGC were included as a derivation cohort. For external validation, the data of 2423 patients who underwent surgical resection for EGC in Seoul National University Bundang Hospital were reviewed. After excluding 275 patients according to the same criteria as those applied for the derivation cohort, 2148 patients were included in a validation cohort (Fig. 1).

Baseline characteristics

The following clinicopathologic variables were collected: age and sex of the patients, type of surgery (total or subtotal gastrectomy), extent of lymphadenectomy (D1, D1+, or D2), number of dissected LNs, pathological information of EGC (multiplicity, size, location, macroscopic type, presence of ulcers, World Health Organization [WHO] histological subtype, Lauren classification, Ming classification, pathologic T [pT] stage, pathologic N [pN] stage, lymphovascular invasion [LVI], perineural invasion, and resection margin distance). The tumor location was categorized as the upper, middle, or lower third of the stomach according to the center of the tumor. The dominant macroscopic type of tumor was assessed on surgical specimens by pathologists and classified as EGC type I, IIa/IIb/IIc, or III. Histological classification of EGC was performed using the WHO, Lauren, or Ming classification. The WHO histological subtype was evaluated as follows: papillary adenocarcinoma; well-, moderately-, or poorly-differentiated tubular adenocarcinoma; mucinous adenocarcinoma; poorly cohesive adenocarcinoma; or other uncommon variants [20]. According to the Lauren and Ming classification systems, tumors were categorized into intestinal, diffuse, or mixed types and into infiltrative or expanding types, respectively [21, 22]. pT stage and pN stages were classified according to the American Joint Committee on Cancer (AJCC) 8th edition with further categorization of submucosal invasion (i.e., pT1b) into sm1, sm2, and sm3 [23, 24]. A positive LVI was defined by the presence of tumor cells in an endothelial cell-lined space. Perineural invasion was considered as positive when tumor cells were

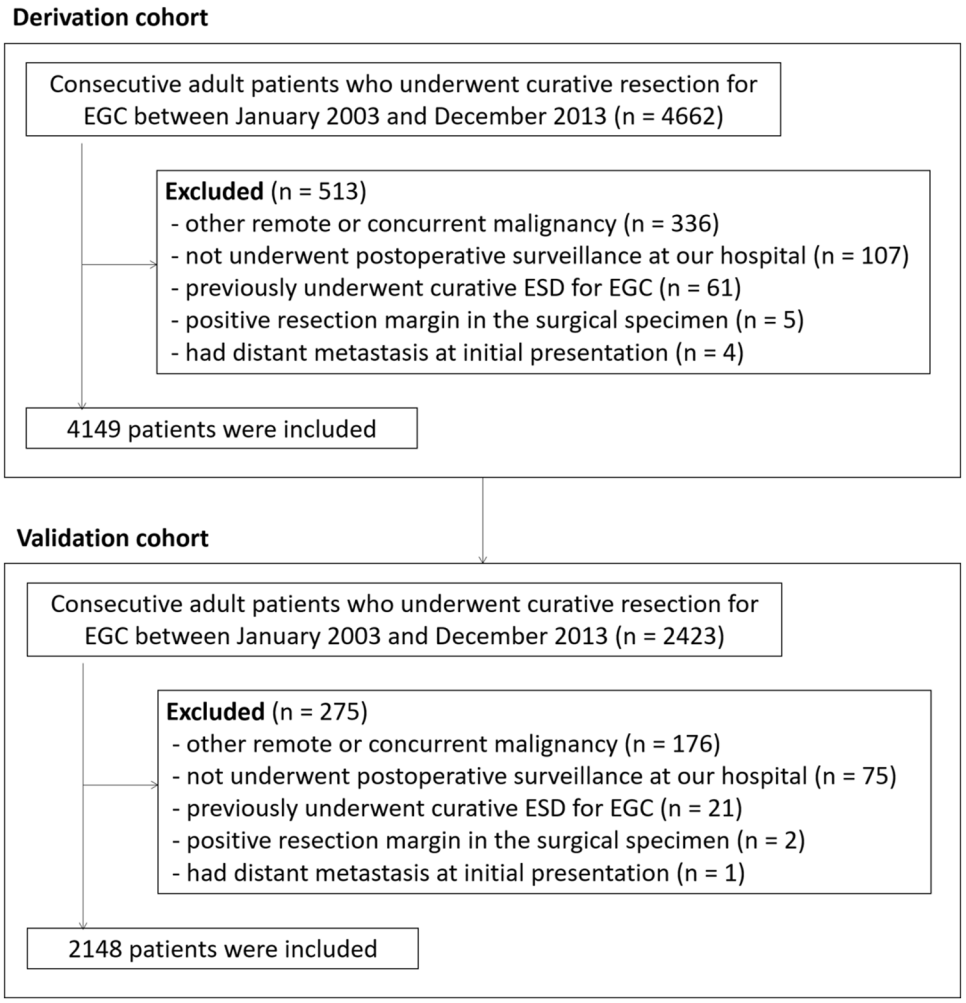

Fig. 1 Flow diagram of the study population

present in the perineurium or neural fascicles. The resection margin distance was defined as the distance of tumor cells to the closest resection margin.

Follow-up assessments

A routine postoperative follow-up protocol of our institutions consists of medical and laboratory examinations, including measurement of tumor marker levels, 1 and 6 months after surgery, every 6 months for the first 3 years, and then annually for the next 2 years. Abdominopelvic CT or ultrasound is alternatively performed every 6 months for 5 years. Gastroscopy is performed annually for 5 years. At each institution, electronic medical records and formal reports of abdominopelvic CT, ultrasound, and gastroscopy of the patients were reviewed to assess the presence of EGR/GR. EGR was defined by the detection of metastatic tumors at locations outside the stomach (e.g., liver or LN). The reference standards for EGR included pathological confirmation and the results of follow-up imaging examinations. GR was defined as endoscopically performed biopsy-proven malignancy around the anastomosis site. EGR-free survival was defined as the interval between the date of resection and the date of follow-up imaging examination in which EGR was detected or the date of the last follow-up imaging examination before November 30, 2020. As our primary aim was to assess the role of imaging surveillance, we focused on the events that were identifiable at imaging examinations but not death.

Statistical analysis

Continuous variables were presented as median values (ranges), and categorical variables were presented as numbers (percentages). To identify the variables associated with EGR-free survival, Cox proportional hazard regression analyses were performed. The linearity and proportional hazard assumption for a continuous predictor was checked using cumulative sums of martingale residuals and the Kolmogorov-type supremum test. The proportional hazard assumption for a categorical predictor was checked using the Log (−Log [survival]) plot and the time-by-covariate interaction. The

penalized partial likelihood, the so-called Firth's correction, was applied for some categorical predictors with categories showing zero recurrence to properly estimate the hazard ratio (HR). Variables with P values < 0.10 in the univariable analyses were included in the multivariable analysis to determine independent variables associated with EGR-free survival. The internal validity of the prediction model was assessed using the c-statistic, calibration plot, and calibration slope using the bootstrap approach with 1000 bootstrap resamples. Based on the risk score calculated from the prediction model, risk stratification was performed using unbiased recursive partitioning [25]. In this approach, patients are classified into several risk groups that show significantly different recurrences. The 5- and 10-year EGR-free survival rates for each risk group were estimated using the Kaplan–Meier method. Although postoperative surveillance was performed for 5 years according to our protocol, 10-year EGR-free survival rates were additionally estimated because the EGR rate of EGC is very low. The risk stratification was validated by comparing EGR-free survival among groups using the log-rank test in the validation cohort. Among the groups with different EGR-free survival rates, those with the lowest risk of developing EGR became our focus, since we aimed to investigate the possibility of sparing postoperative surveillance in these patients. After designating the other groups with higher risk into one group, EGR-free survival rates were compared between the two groups (lowest versus higher risk) using the log-rank test. Comparison of EGR-free survival rates was also performed according to the AJCC TNM staging system as follows: IA (pT1aN0, pT1bN0); IB (pT1aN1, pT1bN1); IIA (pT1aN2, pT1bN2); IIB (pT1aN3a, pT1bN3a); and IIIB (pT1aN3b, pT1bN3b) [23]. Subgroup analysis was performed in patients with node-negative EGCs because omitting postoperative surveillance may be more feasible in these patients than in patients with node-positive EGCs. In addition, the validity of the risk-scoring system proposed by Seo et al. was assessed and compared with the suggested prediction model using Uno's c-index and calibration slope with the validation cohort.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value < 0.05 was considered to be statistically significant.

Results

Baseline characteristics

The baseline characteristics of the patients in the derivation and validation cohorts are presented in Table 1, and the clinicopathologic characteristics of the patients without

Table 1 Comparison of baseline characteristics between the derivation cohort and validation cohort

Characteristics	Derivation cohort (n = 4149)	Validation cohort (n = 2148)
Age, years	59 (50–67)	60 (50–68)
Male	2482 (59.8)	1430 (66.6)
Type of surgery		
Subtotal gastrectomy	3785 (91.2)	1983 (92.3)
Total gastrectomy	364 (8.8)	165 (7.7)
Extent of lymphadenectomy		
D1	199 (4.8)	60 (2.8)
D1+	2611 (62.9)	1045 (48.6)
D2	1339 (32.3)	1043 (48.6)
Tumor multiplicity	288 (6.9)	119 (5.5)
Tumor size, cm	2.4 (1.6–3.6)	2.4 (1.6–3.5)
Resection margin distance, mm	2.6 (1.6–3.7)	2.0 (1.1–3.1)
Tumor location		
Upper third	422 (10.2)	259 (12.1)
Middle third	1151 (27.7)	527 (24.5)
Lower third	2276 (62.1)	1362 (63.4)
Macroscopic type		
EGC-I	162 (3.9)	97 (4.5)
EGC-IIa	489 (11.8)	278 (12.9)
EGC-IIb	495 (11.9)	307 (14.3)
EGC-IIc	2919 (70.4)	1414 (65.8)
EGC-III	84 (2.0)	52 (2.4)
Ulcers	333 (8.0)	352 (16.4)
WHO histological subtype		
Papillary ADC	31 (0.7)	8 (0.4)
W/D tubular ADC	864 (20.8)	442 (20.6)
M/D tubular ADC	1327 (32.0)	739 (34.4)
P/D tubular ADC	698 (16.8)	377 (17.6)
Mucinous ADC	42 (1.0)	16 (0.7)
Poorly cohesive carcinoma	1187 (28.7)	566 (26.4)
Others	0	0
Lauren classification		
Intestinal	2398 (57.8)	1267 (59.0)
Diffuse	1401 (33.8)	788 (36.7)
Mixed	350 (8.4)	93 (4.3)
Ming classification		
Infiltrative	2932 (70.7)	1266 (58.9)
Expanding	669 (16.1)	877 (40.9)
Not classifiable	548 (13.2)	5 (0.2)
Lymphovascular invasion	558 (13.4)	312 (14.5)
Perineural invasion	82 (2.0)	47 (2.2)
Pathologic T stage		
pT1a	2240 (54.0)	1145 (53.3)
pT1b, sm1	584 (14.1)	307 (14.3)
pT1b, sm2	779 (18.8)	311 (14.5)
pT1b, sm3	546 (13.1)	385 (17.9)

Table 1 (continued)

Characteristics	Derivation cohort ($n=4149$)	Validation cohort ($n=2148$)
Pathologic N stage		
pN0	3777 (91.1)	1898 (88.4)
pN1	242 (5.8)	196 (9.1)
pN2	96 (2.3)	29 (1.4)
pN3	34 (0.8)	25 (1.2)
pN3a	27 (0.6)	20 (1.0)
pN3b	7 (0.2)	5 (0.2)

Data are presented as medians (interquartile ranges) or numbers (percentages)

EGR extragastric recurrence, *EGC* early gastric cancer, *WHO* World Health Organization, *ADC* adenocarcinoma, *W/D* well differentiated, *M/D* moderately differentiated, *P/D* poorly differentiated, *sm* submucosal

Table 2 Details of extragastric recurrence detected after curative resection for early gastric cancer in the derivation cohort

Involved organ	Patient number	Imaging modality
Lymph node	23	CT (20), ultrasound (3)
Liver	17	CT (13), ultrasound (4)
Peritoneum	5	CT (4), ultrasound (1)
Ovary	4	CT (3), ultrasound (1)
Peritoneum, ovary	3	CT (3)
Bone	2	CT (2)
Duodenum	2	CT (1), ultrasound (1)
Lymph node, lung	1	CT (1)
Liver, peritoneum	1	CT (1)
Liver, bone	1	CT (1)
Pancreas	1	CT (1)
Lung	1	CT (1)

CT computed tomography

and with EGR are demonstrated in Online Resource 1. In both the derivation and validation cohorts, the tumors of patients with EGR were slightly larger, more frequently demonstrated mixed Lauren classification and LVI, and had higher pT and pN stages (P values ≤ 0.028).

Extragastric recurrence

In the derivation cohort, the patients were followed up for a median period of 66.0 months (range 1–210 months). During the entire follow-up period, EGRs were detected in 1.5% (61/4149; 95% confidence interval [CI] 1.1–1.9%) of the patients. LNs and liver were the two most common organs involved by EGR (Table 2). EGRs were detected using CT ($n=51$) or ultrasound ($n=10$) and were confirmed by pathology ($n=36$) or follow-up imaging ($n=25$). The patients with EGR received the following treatments: chemotherapy ($n=43$), supportive care ($n=12$), radiation therapy ($n=2$), surgical resection ($n=2$), or unknown due to follow-up loss ($n=2$). Of note, there were three patients with pT1aN0 EGC who developed EGR. The organs with EGR in each patient were as follows: patient 1, liver; patient 2, liver and LNs; patient 3, liver, LNs, peritoneal seeding, and lungs. Patient 2 also developed GR as well as EGR. The information on *Helicobacter pylori* infection status was available in one patient in the validation cohort in whom mild association with *H. pylori* was discovered. Regarding immunohistochemical staining results, one patient in the derivation cohort demonstrated the following profiles: epidermal growth factor receptor, faint positive (+/3); cadherin 17, positive; CD44, positive in 5%; thymidylate synthase, positive in 15%; and forkhead box P3, positive (++/3) in tumor-infiltrating lymphocytes. The results of another patient in the validation cohort were as follows: p53, negative; human mutL homolog 1, positive; epidermal growth factor receptor, negative; Laminin-r2, focal positive; cytokeratin, negative.

In terms of GR, there were 25 patients with GR only ($n=18$) or with both EGR and GR ($n=7$). All GRs were confirmed by endoscopically performed biopsy. Patients with GR only received remnant total gastrectomy ($n=13$), chemotherapy ($n=3$), or ESD ($n=2$). The EGR-free survival rates according to the TNM staging system are presented in Online Resource 1.

Development of a predictive model for EGR

Univariable and multivariable Cox regression analyses revealed that pT and pN stage were independently associated with EGR-free survival (Online Resource 1). pN3a and pN3b stages were grouped into the pN3 stage considering the small number of patients in each stage (27 and 7 patients, respectively). On the basis of these results, we constructed a model to predict EGR-free survival using the pT stage (pT1b[sm1]: HR = 4.928, 95% CI 1.703–14.263; pT1b[sm2]: HR = 5.235, 95% CI 2.024–13.543; pT1b[sm3]: HR = 7.748, 95% CI 3.016–19.903) and pN stage (pN1: HR = 4.056, 95% CI 1.966–8.368; pN2: HR = 9.075, 95% CI 4.374–18.828; pN3: HR = 30.659, 95% CI 14.654–64.147). The beta coefficients of the predictive model were multiplied by 10 for the ease of calculation to yield scores to predict the risk of developing EGR as follows: 16 for pT1b(sm1), 17 for pT1b(sm2), and 20 for pT1b(sm3); 14 for pN1, 22 for pN2, and 34 for pN3. The total score for each patient ranged from 0 (pT1aN0) to 54 (pT1b[sm3]N3). Among the patients with node-negative EGCs (i.e., pN0 stage), patients with pT1a had a risk score of 0, whereas patients with pT1b had a risk score ranging from 16 (pT1b[sm1]) to 20 (pT1b[sm3]). On the basis of these scores, the patients in the derivation

cohort were classified into four groups: high-risk ($n=73$), moderate-risk ($n=237$), low-risk ($n=1615$), and very-low-risk group ($n=2224$), with cutoff scores of 39, 30, and 14, respectively (Table 3). The EGR-free survival rates for each group are presented in Fig. 2 and Online Resource 1. In the very-low-risk group, EGR was found in two patients with pT1aN0 stage EGC (0.1% [2/2196]; 95% CI 0.1–0.1%) and not in the patients with pT1aN1 stage EGC (0% [0/28]; 95% CI 0–12.3%). When the patients were dichotomized into the very-low-risk group (score ≤ 14) ($n=2224$) and the low-or-greater-risk group (score > 14) ($n=1925$), the 5-year EGR-free survival rates were 99.9% (95% CI 99.7–100%) in the very-low-risk group and 97.3% (95% CI 96.5–98.1%) in the low-or-greater risk group, respectively (Fig. 3). The 10-year EGR-free survival rates were 99.9% (95% CI 99.7–100%) in the very-low-risk group and 95.2% (95% CI 93.6–96.7%) in the low-or-greater-risk group, respectively. Meanwhile, when the patients were dichotomized into the pT1aN0 ($n=2196$) and above pT1aN0 groups ($n=1953$), the 5- and 10-year EGR-free survival rates were both 99.9%

Table 3 Categorization of the patients according to the risk of developing extragastric recurrence

Group	Score	pT and pN stage	Derivation cohort		Validation cohort	
			Number of patients (%)	Number of extragastric recurrence	Number of patients (%)	Number of extragastric recurrence
Very low risk	≤ 14	pT1aN0, pT1aN1	2224 (53.6)	2	1139 (53.0)	1
Low risk	15–30	pT1aN2, pT1b(sm1)N0, pT1b(sm1)N1, pT1b(sm2)N0, pT1b(sm3)N0	1615 (38.9)	23	821 (38.2)	6
Moderate risk	31–39	pT1aN3, pT1b(sm1)N2, pT1b(sm2)N1, pT1b(sm2)N2, pT1b(sm3)N1	237 (5.7)	19	150 (7.0)	4
High risk	≥ 40	pT1b(sm1)N3, pT1b(sm2)N3, pT1b(sm3)N2, pT1b(sm3)N3	73 (1.8)	17	38 (1.8)	7

pT stage pathologic T stage, *pN stage* pathologic N stage

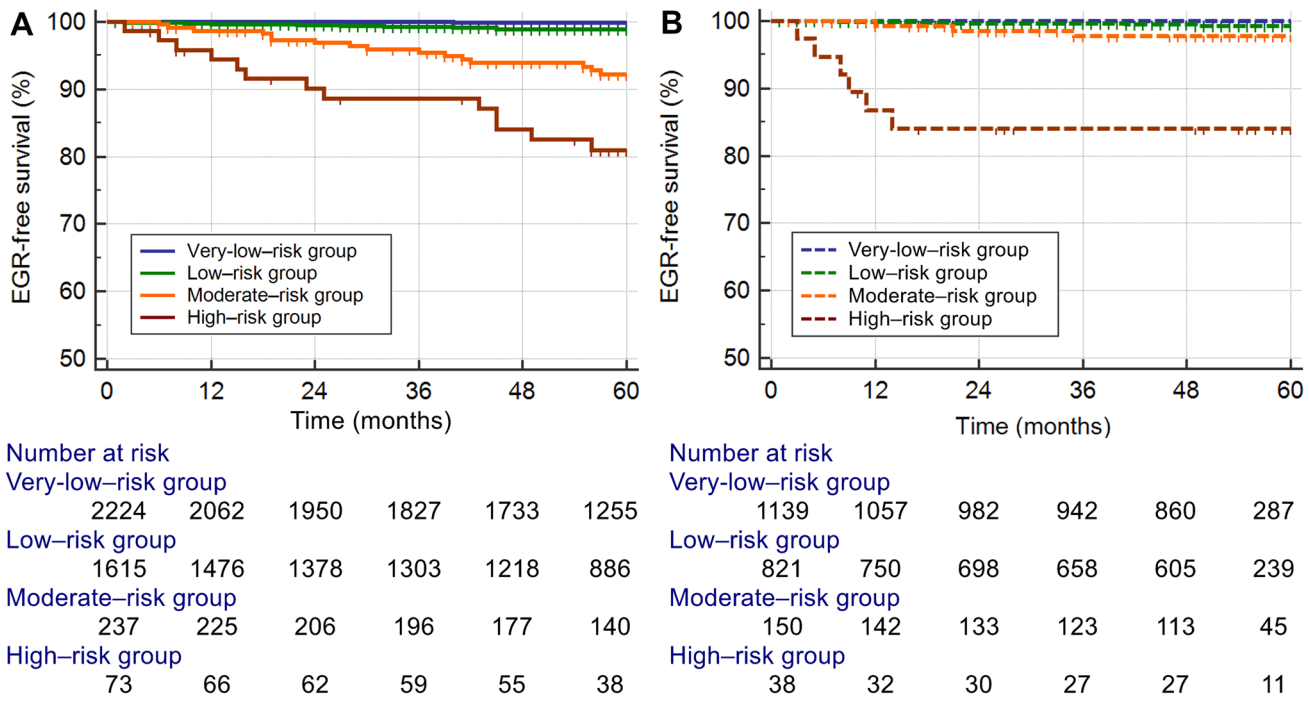

Fig. 2 Extragastric recurrence-free survival probability of the four risk groups categorized according to the prediction model in the **a** derivation cohort ($n=4149$, solid line) and **b** validation cohort ($n=2148$, dotted line). Blue, very-low-risk group; green, low-risk group; orange, moderate-risk group; and brown, high-risk group

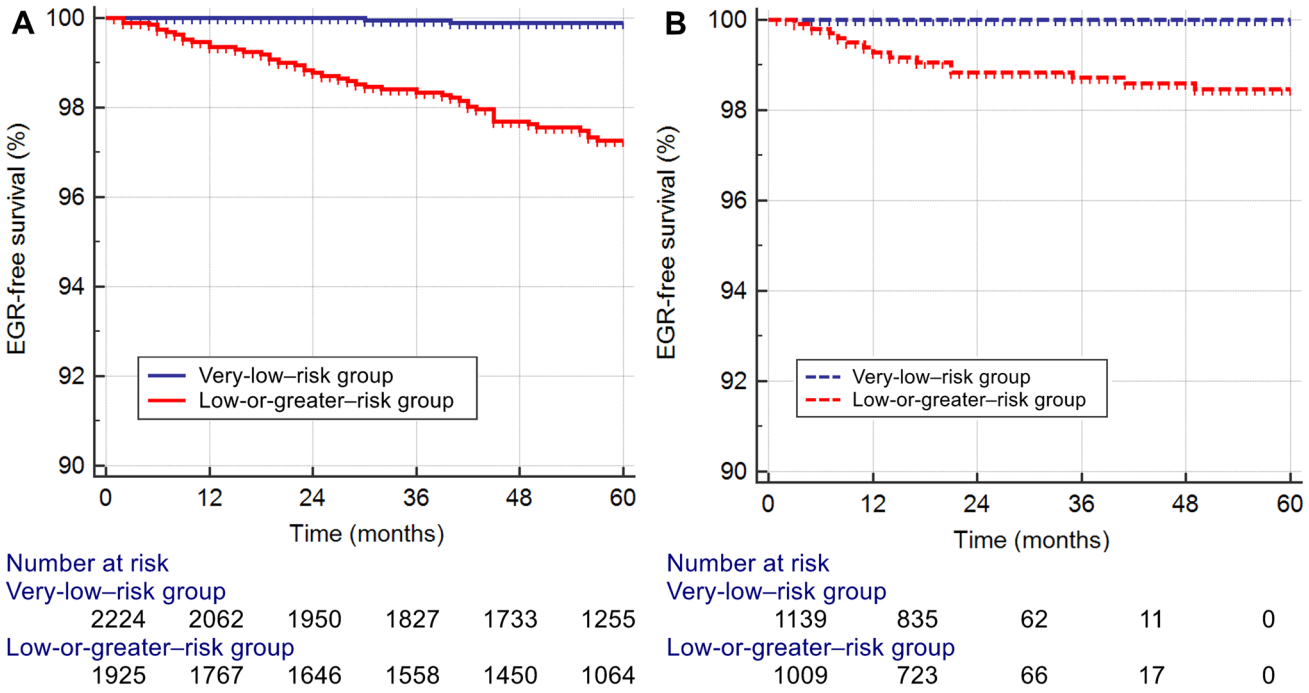

Fig. 3 Extragastric recurrence-free survival probability of the two risk groups (very low risk vs. low or greater risk) in the **a** derivation cohort (solid line) and **b** validation cohort (dotted line). Blue, very-low-risk group; red, low-or-greater-risk group

(95% CI 99.7–100%) in the pT1aN0 group and 97.3% (95% CI 96.5–98.1%) and 95.3% (95% CI 93.8–96.8%) in the above pT1aN0 group, respectively ($P < 0.001$ for both).

Validation of the predictive model

In the validation cohort, 5-year EGR-free survival rates in the very-low- and low-or-greater-risk groups were 100% (95% CI 100–100%) and 98.5% (95% CI 97.7–99.3%), respectively ($P < 0.001$) (Fig. 3). The 10-year EGR-free survival rates were 98.8% (95% CI 96.4–100%) in the very-low-risk group and 96.2% (95% CI 93.5–98.9%) in the low-or-greater-risk group. In the very-low-risk group, EGR was detected in one patient who had pT1aN0 stage EGC (0.1% [1/1102]; 95% CI 0–0.5%) but not in the patients with pT1aN1 stage EGC (0% [0/37]; 95% CI 0–9.5%). The discriminating power of our model for predicting EGR-free survival assessed using Uno's c-index was 0.869 (95% CI 0.826–0.911; bootstrap-corrected, 0.851) for the derivation cohort and 0.751 (95% CI 0.466–1.036) for the validation cohort. The calibration of the model also appeared to be proper: the calibration slope was 1.000 (95% CI 0.842–1.158; bootstrap-corrected: 0.916) for the derivation cohort and 1.131 (95% CI 0.829–1.433) for the validation cohort, even though a slightly underestimated recurrence was observed in the bottom quarter of the risk of recurrence in the validation cohort (Fig. 4). The predictive performance with our model was superior to that of a previously reported risk-scoring system by Seo et al. [14] which showed Uno's c-index of 0.626 (95% CI 0.305–0.947) and a calibration slope of 0.179 (95% CI 0.110–0.247) in the validation cohort ($P < 0.001$ for both).

Development and validation of a predictive model for EGR in patients with node-negative EGCs

In patients with node-negative EGCs, Cox regression analyses revealed that age and pT stage were independently associated with EGR-free survival (Online Resource 1). However, incorporating age into a predictive model may increase complexity. Furthermore, when we compare a predictive model consisting of both age and pT stage with another model consisting of pT stage, no significance difference in predicting EGR between the two models was revealed (Uno's c-index, 0.832 [95% CI 0.732–0.932] vs. 0.803 [95% CI 0.715–0.891], $P = 0.065$). Accordingly, we constructed a model to predict EGR-free survival using pT stage only that categorized patients into a low-risk group with pT1a stage EGC ($n = 2196$) and a high-risk group with pT1b stage EGC ($n = 1581$). The 5- and 10-year EGR-free survival rates were 99.9% (95% CI 99.7–100%) for both in the low-risk group, and 98.8% (95% CI 98.2–99.4%) and 97.4% (95% CI 96.1–98.7%) in the high-risk group, respectively ($P < 0.001$). In the validation cohort, the 5- and 10-year EGR-free survival rates in the low- and high-risk groups were 100% (95% CI 100–100%) and 98.7% (95% CI

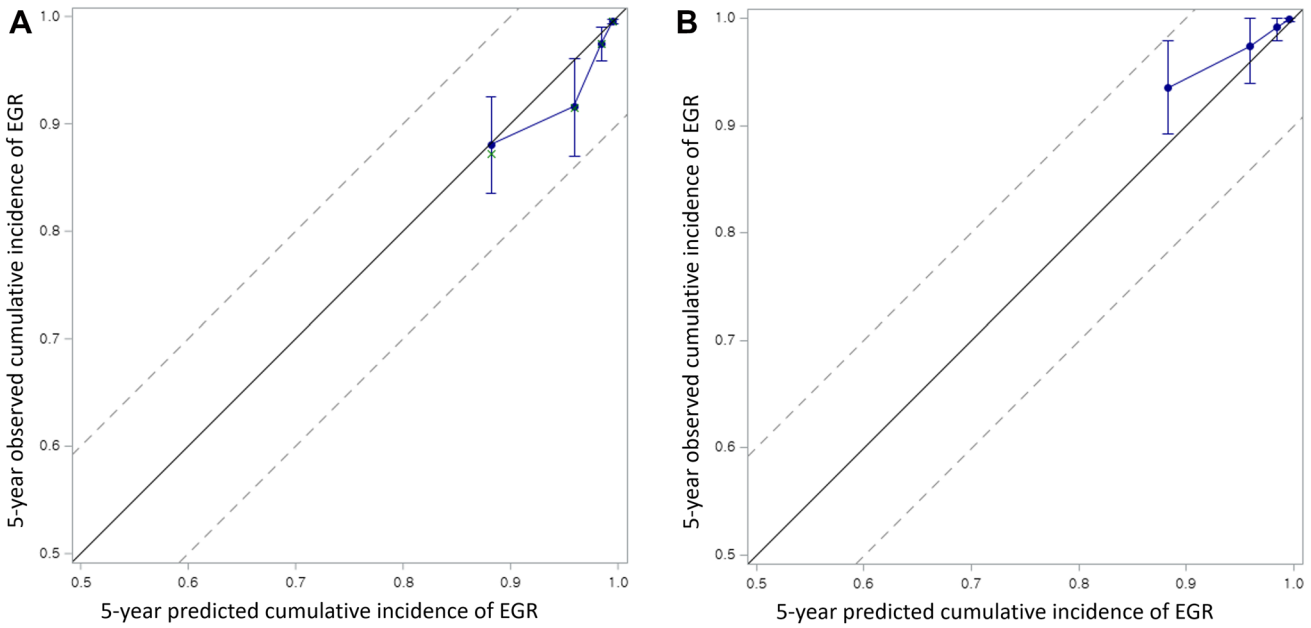

Fig. 4 Calibration plots of **a** derivation cohort and **b** validation cohort. *EGR* extragastric recurrence

96.3–100%) in the low-risk group, respectively, and 99.4% (95% CI 98.8–100%) and 98.2% (95% CI 95.8–100%) in the high-risk group, respectively ($P = 0.049$) (Online Resource 1).

Discussion

In this study, we developed a predictive model based on pT and pN stages for EGR after curative resection of EGC and categorized patients into very-low- and low-or-greater-risk groups. The very-low-risk group contained more than half of the patients (53.6%, 2224/4149), but had a 5-year EGR-survival rate of 99.9%, which was significantly better than the value of 97.3% in the low-or-greater-risk group. Considering that the majority of the patients (> 50%) in both the derivation and validation cohorts belonged to the very-low-risk group, their exemption from postoperative imaging surveillance would have a profound clinical impact in terms of medical costs, radiation hazards, adverse reactions associated with iodinated contrast media, and the psychological burden on patients. Our model is easy to use because it requires only two variables (pT and pN stages) that are readily obtainable from routine pathological reports of surgical specimens. The predictive accuracy of our model was validated both internally and externally and was also demonstrated to be superior to that of a previously reported predictive model.

Although there is no evidence that postoperative surveillance after curative resection of EGC is cost-effective or prolongs patients' survival, follow-up imaging examinations are recommended by major guidelines for the early detection of recurrence [5, 6, 8]. However, considering the economic and psychological burden associated with imaging surveillance, the radiation hazards associated with contrast-enhanced CT, and the potential adverse reactions associated with iodinated contrast media [16–19, 26], an exact stratification of patients who are benefited by imaging surveillance according to the risk of recurrence is imperative. Unfortunately, there has been only one study that provided a cutoff value for the incidence of EGR to justify imaging surveillance in patients who underwent curative resection of EGC. Generally, imaging surveillance to detect recurrence is recommended up to 5 years after curative surgery in patients with malignancy because recurrence is infrequent afterward [27]. In our study, the 5-year EGR-free survival rate of the very-low-risk group was 99.9 and 100% in the derivation and validation cohorts, respectively. Notably, the very-low-risk group consisted of patients with pT1aN0 and pT1aN1 stage disease. Although the patients with pT1aN1 stage disease showed no EGR for 5 years, the small number of these patients (28 and 37 patients in the derivation and validation cohort, respectively) may be responsible for this result, especially considering that the upper margin of 95% CI was up to approximately 10% in both derivation and validation cohorts. Furthermore, the result of the subgroup analysis in patients with pN0 EGC also revealed that patients with pT1aN0 EGC demonstrated significantly lower risks of EGR compared with patients with pT1bN0

EGC. Therefore, we cautiously suggest that postoperative imaging surveillance for EGR may be spared in the subset of patients with pT1aN0 EGC since they were negative for both independent risk factors for EGR (i.e., pT and pN stage).

According to a recent study, the following five variables were associated with EGR: disease beyond the ESD indications, LN metastasis, male sex, positive LVI, and elevated macroscopic type of EGC [14]. Among these variables, disease beyond the ESD indications and LN metastasis are associated with pT and pN stages, respectively. However, as a composite outcome, the ESD indications are not readily retrievable from medical records and have to be assessed through a complex process by considering the depth of invasion, size, and differentiation of tumor, and the presence of ulcers [28–30]. Moreover, assessment of "disease beyond the ESD indications" in patients who have already undergone curative resection of EGC might not fit well with routine clinical practice because the ESD indications were established to recommend rescue surgery after non-curative endoscopic resection. Regarding LN metastasis, which has been traditionally validated as a prognostic factor in patients with EGC [12], we used the pN stages from pN0 to pN3 to provide a stratified risk of EGR in a more elaborate manner whereas the previous study used a simple dichotomization of LN metastasis into presence or absence [14]. Even though we developed a simpler model based on classical prognostic factors in comparison with the previously proposed model [14], we believe that our predictive model is noteworthy since our results showed significantly better prediction performance for the development of EGR.

There are a few limitations in this study. First, selection bias may have been present due to the retrospective nature of this study. Second, although most patients adhered to the routine protocol of postoperative surveillance, there have been slight variations in the follow-up protocol among clinicians and/or institutions due to the relatively long study period from 2003 to 2020. Third, although stratification of outcomes according to the TNM staging system works well within each region [31], regional differences in the prognosis of patients with EGC should be taken into consideration (e.g., Korea/Japan vs. Western countries). Therefore, the generalization of our results to patients in Western or other Asian countries must be implemented carefully. Lastly, the performance of the predictive model may have been affected by the low incidence of EGR after curative resection of EGC.

In conclusion, we developed an easy-to-use predictive model for predicting EGR after curative resection of EGC using pT and pN stage, which are readily obtainable from routine pathological reports. This model showed good predictive performance in both internal and external cohorts. The patients who underwent curative surgery for EGC of pT1aN0 stage might be spared from postoperative imaging surveillance since their risk of developing EGR is extremely low.

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