

External validation of nomogram for the prediction of recurrence after curative resection in early gastric cancer

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Background: Nomograms are statistics-based tools that provide the overall probability of a specific outcome. In our previous study, we developed a nomogram that predicts recurrence of early gastric cancer (EGC) after curative resection. We carried out this study to externally validate our EGC nomogram.

Patients and methods: The EGC nomogram was established from a retrospective EGC database that included 2923 consecutive patients. This nomogram was independently externally validated for a cohort of 1058 consecutive patients. For the EGC nomogram validation, we assessed both discrimination and calibration.

Results: Within the follow-up period (median 37 months), a total of 11 patients (1.1%) experienced recurrence. The concordance index (c-index) was 0.7 ($P = 0.02$) and the result of the overall C index was 0.82 [$P = 0.006$, 95% confidence interval (CI) 0.59–1.00]. The goodness of fit test showed that the EGC nomogram had significantly good fit for 1- and 2-year survival intervals ($P = 0.998$ and 0.879 , respectively). The actual and predicted survival outcomes showed good agreement, suggesting that the survival predictions from the nomogram are well calibrated externally.

Conclusions: A preexisting nomogram for predicting disease-free survival (DFS) of EGC after surgery was externally validated. The nomogram is useful for accurate and individual prediction of DFS, patient prognostication, counseling, and follow-up planning.

Key words: early gastric cancer, external validation, nomogram

introduction

Early gastric cancer (EGC) has been defined as an adenocarcinoma that is confined to the mucosa or submucosa, regardless of the size or presence of lymph node metastasis. Recent developments in diagnosis and the introduction of national mass screening programs have allowed increased detection of EGC, and these patients account for 40%–50% of operations carried out for gastric carcinoma in Japan and Korea [1, 2]. Patients with EGC generally have an excellent prognosis after curative resection (R0) with 5-year survival rates of approximately 90%. However, recurrence can still occur after curative resection of EGC, with a rate of 1.4%–7.0% [3–8]. Some studies have evaluated the independent risk factors for recurrence of EGC, but the number of patients with recurrence in these studies was too small to provide reliable results [6–9]. In particular, the prediction of recurrence of EGC after R0 resection has not been studied.

We attempted to identify independent risk factors for predicting recurrence of EGC after curative resection. According to results of our previous study [10], elevated gross type and presence of lymph node metastasis were shown to be independent risk factors for overall recurrence. On the basis of findings from this study, our institution developed a nomogram that estimates the disease-specific survival rate of each patient at 2, 5, and 10 years after curative resection for EGC (Figure 1).

Nomograms are statistics-based tools that provide the overall probability of a specific outcome [11]. In clinical practice, it is important to predict prognosis in order to decide the further treatment plan or follow-up duration. Nomograms, which can incorporate more clinicopathologic parameters than the staging system by reflecting not only the tumor characteristics but also the host status, can provide the clinician with a better estimation of the prognosis of an individual patient. Another potential benefit of the nomogram is that, with a simple graphical representation of a statistical predictive model, it generates a numerical probability of a clinical event. However, one should be cautious about extrapolating from regression

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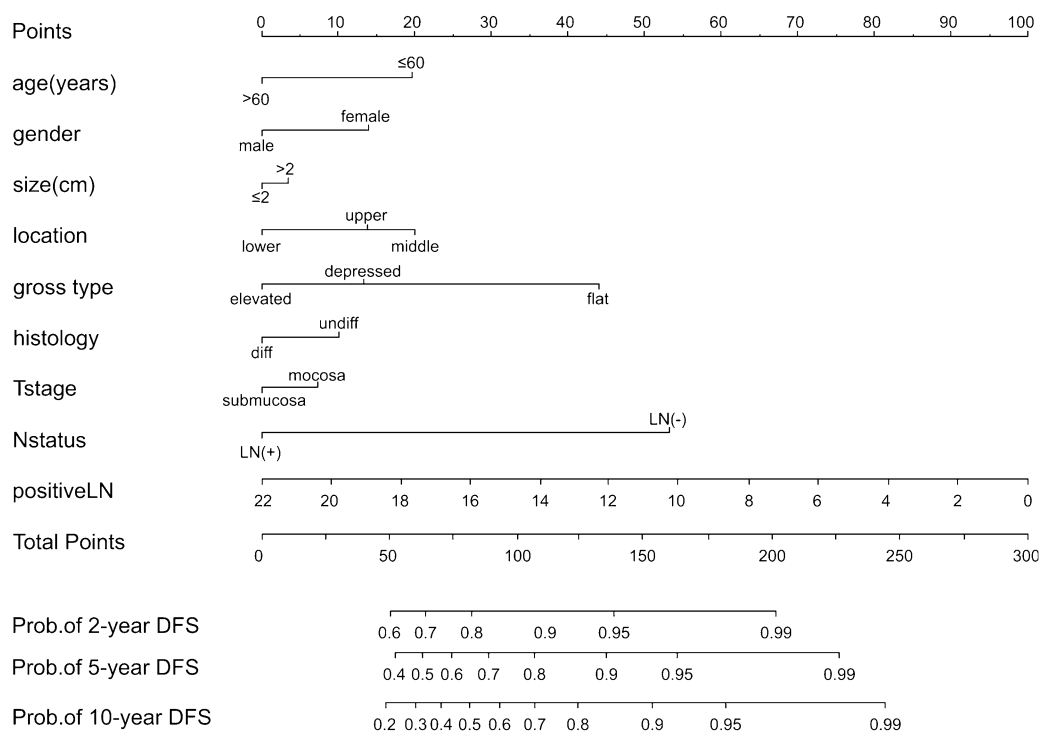


Figure 1. Instructions of early gastric cancer nomogram. Find the position of each variable on the corresponding axis and draw a line to the ‘Points’ axis to determine the number of points for each variable. Add the points for all the variables together and draw a line from the ‘Total points’ axis to determine the survival probabilities at the bottom, assuming no death from other causes. DFS, disease-free survival.

models built on different populations because a nomogram derived from one population may not be applicable to a new population. Therefore, external validation is essential to ensure that the nomogram is universally applicable in practice.

The aim of the present study was to externally validate this EGC nomogram in patients from another independent data set.

materials and methods

patients

A patient cohort from the EGC database at the Department of Surgery and Gastric Cancer Clinic, Yonsei University Health System (YUHS) in Seoul, Korea, was used to evaluate the validity of the EGC nomogram. Between May 2005 and April 2007, a consecutive series of 1058 patients with EGC who underwent curative resection at the Severance Hospital, YUHS, were retrospectively reviewed.

definitions

The variables required for the EGC nomogram were age, gender, tumor size, location, gross type, histological differentiation, depth of invasion, lymph node metastasis, and number of positive nodes. By using these clinicopathologic factors, the practical usage of the EGC nomogram is available in the Hyper Text Markup Language format shown in Figure 2.

The standard operation for EGC was a total or subtotal gastrectomy with D2 lymph node dissection in accordance with the rules of the Japanese Research Society for Gastric Cancer (JRS GC). Curative resection was defined as no tumor remaining after removal, both macroscopically and microscopically.

The gross appearance was classified according to JRS GC standard: type I and IIa were regarded as elevated type; type IIb as flat type; and type IIc and III as depressed type. A mixed type was recorded according to the type of the largest area.

The histological type was classified into two main categories: differentiated type, including papillary adenocarcinoma and well- and moderately differentiated tubular adenocarcinoma, and undifferentiated type, including poorly differentiated tubular adenocarcinoma, mucinous adenocarcinoma, and signet ring cell adenocarcinoma.

After being discharged from the hospital, the patients were started on a regular follow-up program. Patients were followed up every 3 months during the first 2 years, every 4 months during the third year, every 6 months during the fourth and fifth years, and once every year thereafter.

Recurrence was confirmed by physical findings, radiological studies, endoscopic examination with biopsy, and surgery if indicated. Disease that recurred within 24 months from the time of the operation was defined as an early recurrence. Disease-free survival (DFS) was defined as time of operation to time of recurrence.

data analysis

The patients’ features and clinical characteristics were analyzed using the two-tailed Student’s *t*-test for continuous variables and χ^2 test for categorical variables. DFS was estimated using the Kaplan–Meier method.

Nomogram validation consisted of discrimination and calibration. First, discrimination was quantified with the concordance index (*c*-index). Discrimination refers to a nomogram model’s ability to correctly distinguish the two classes of outcome. A model with good discrimination ability produces higher predicted probabilities for subjects who had events than for subjects who did not have events. The area under the Receiver Operating Characteristic (ROC) curve is one of the most commonly used measures for model discrimination. To further evaluate the discrimination of the nomogram model, we considered a time-to-event-based survival time model with censored observations such as the Cox regression model. Thus, for our nomogram discrimination, we used the overall *C* index introduced by Harrell as a natural extension of the ROC curve area to survival analysis [12, 13]. Second, we assessed calibration that compares the predicted

Age <=60 >60**Gender** Male Female**Tumor Size** <=2 >2**Location** upper middle lower**Gross** elevated depressed flat**Patho.** diff. undiff.**T stage** mucosa submucosa**N status** LN(-) LN(+)**positive LN** 0 2 4 6 8 10 12 14 16 18 20 22

Total Score	119
Probability of 2-year DFS	0.9105308801306521
Probability of 5-year DFS	0.8352721848092088
Probability of 10-year DFS	0.7477529322977472

Figure 2. The early gastric cancer nomogram available in Hyper Text Markup Language format.

probability of DFS with the actual survival. We used a Poisson log-linear model as an approximation to the survival time model in investigating the asymptotic behavior of the statistic based on the framework of a goodness of fit statistic for generalized linear models [12]. In addition, another calibration measure was carried out by grouping patients according to their nomogram-predicted probabilities and then comparing the mean of the group with the observed Kaplan–Meier DFS estimate.

SPSS 17.0 (SPSS, Chicago, IL) was used for the statistical analyses. In all statistical analyses, a *P* value <0.05 was considered significant.

results

patient characteristics

Of 1058 patients who had undergone curative resection for EGC between May 2005 and April 2007, 115 (10.9%) were lost to follow-up due to insufficient information. Among the remaining 943 patients, data for all the necessary variables were available for 930 patients. Descriptive statistics for the external validation dataset are summarized and compared with those for the nomogram development dataset in Table 1. The differences between the two cohorts were a relatively older age and smaller tumor size in the external validation set compared with the nomogram development set: median age 58 years (range 19–91) and tumor size 2.5 cm (± 1.7) in the external validation set compared with 57 years (range 23–89) and 2.7 cm (± 1.6) in

Table 1. Descriptive statistics of early gastric cancer patient cohorts from nomogram development set and external validation set. The two cohorts demonstrated statistical differences in terms of age, tumor size, tumor location, and histology.

	Nomogram development set (<i>n</i> = 2923)	External validation set (<i>n</i> = 930)	<i>P</i> value
Age (years)			<0.0001
Median (range)	57 (19–91)	58 (23–89)	
Gender, <i>n</i> (%)			0.372
Male	1912 (65.4)	622 (66.9)	
Female	1011 (34.6)	308 (33.1)	
Tumor size (cm)			<0.0001
Mean \pm SD	2.5 \pm 1.7	2.7 \pm 1.6	
Tumor location, <i>n</i> (%)			<0.0001
Upper	362 (12.4)	57 (6.1)	
Middle	1406 (48.1)	348 (37.4)	
Lower	1155 (39.5)	525 (56.5)	
Gross appearance, <i>n</i> (%)			0.832
Elevated	444 (15.2)	139 (14.9)	
Nonelevated	2403 (82.2)	791 (85.1)	
Histology, <i>n</i> (%)			0.027
Differentiated	1435 (49.1)	500 (53.8)	
Undifferentiated	1435 (49.1)	430 (46.2)	
Depth of invasion, <i>n</i> (%)			0.111
Mucosa	1485 (50.8)	505 (54.3)	
Submucosa	1438 (49.2)	425 (45.7)	
Lymph node status, <i>n</i> (%)			0.529
Negative	2601 (89.0)	834 (89.7)	
Positive	322 (11.0)	96 (10.3)	

SD, standard deviation.

the nomogram development set. In addition, a lower tumor location and more undifferentiated histology were observed in the external validation set. The two cohorts were similar in other clinicopathologic factors.

Among 930 patients, 11 (1.1%) experienced recurrence during the follow-up period. The median time to recurrence was 26.4 months (range 10.7–39.0 months) and four patients (36.4%) had recurrence within 2 years. Hematogenous recurrence was the predominant recurrence pattern; 7 (63.6%) of 11 recurred EGC patients had hematogenous recurrence, whereas 4 had locoregional recurrence. Table 2 shows a comparison of characteristics between the ‘no recurrence group’ and the ‘recurrence group’ in the external validation set. The recurrence group had a higher rate of lymph node metastasis (54.5%) compared with that of the no recurrence group (9.9%). The difference in lymph node status between these two groups was statistically significant (*P* = 0.003).

nomogram

The mean nomogram score of the nomogram development set and the external validation set is shown in Figure 3. The nomogram development set had a slightly higher nomogram score (208 ± 34.4) than the external validation set (203.7 ± 32.7 , *P* \leq 0.0001). Among the external validation set,

Table 2. Comparison between no recurrence group and recurrence group in external validation set. The lymph node status was significantly different between these two groups ($P = 0.003$)

	No recurrence group ($n = 919$)	Recurrence group ($n = 11$)	P value
Age (years)			0.058
Median (range)	58 (23–89)	64 (49–77)	
Gender, n (%)			0.112
Male	612 (66.6)	10 (91.9)	
Female	307 (33.4)	1 (9.1)	
Tumor size (cm)			0.322
Mean \pm SD	2.7 ± 1.6	3.2 ± 1.7	
Tumor location, n (%)			0.772
Upper	56 (6.1)	1 (9.1)	
Middle	344 (37.4)	4 (36.4)	
Lower	519 (56.5)	6 (54.5)	
Gross appearance, n (%)			0.999
Elevated	138 (15.0)	1 (9.1)	
Nonelevated	781 (85.0)	10 (91.9)	
Histology, n (%)			0.999
Differentiated	494 (53.8)	6 (54.5)	
Undifferentiated	425 (46.2)	5 (45.5)	
Depth of invasion, n (%)			0.124
Mucosa	502 (54.6)	3 (27.3)	
Submucosa	417 (45.5)	8 (72.7)	
Lymph node status, n (%)			0.003
Negative	828 (90.1)	5 (45.5)	
Positive	91 (9.9)	6 (54.5)	

SD, standard deviation.

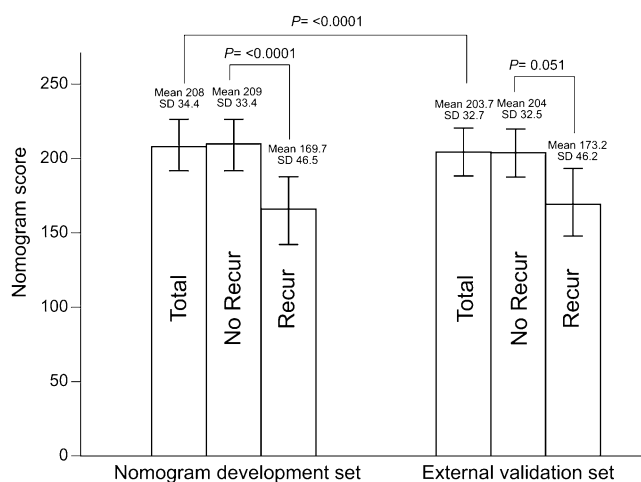


Figure 3. Comparison of the early gastric cancer nomogram score between the groups.

the mean nomogram score of the recurrence group was lower than that of the no recurrence group (173.2 ± 46.2 versus 204 ± 32.5 , respectively); however, this difference was not statistically significant ($P = 0.051$).

To compare the nomogram-predicted outcome with the actual outcome, patients in the external validation set were divided into three risk groups according to their nomogram

score that predicted the probability of DFS. These cut-off points were determined on the basis of the mean nomogram score of the no recurrence group (209 ± 33.4) and the recurrence group (169.7 ± 46.5) in the nomogram development set as follows: high risk (<170 points, 102 patients), intermediate risk (170 – 209 points, 427 patients), and low risk (>209 points, 401 patients). The descriptive statistics for the three subgroups are listed in Table 3.

nomogram validation

When applied to the external validation set, the EGC nomogram achieved a c -index of 0.70 ($P = 0.02$), meaning that the accuracy of the nomogram for predicting recurrence is 70%. In addition, we carried out further discrimination using the overall C index, which is the extension of C statistics to survival analysis. The result of the overall C index at the 2-year survival interval was 0.82 ($P = 0.006$, 95% CI 0.59–1.00), which means that the accuracy of the EGC nomogram for predicting 2-year DFS rate is 82%.

Next, χ^2 goodness of fit analysis was carried out for calibration, in which $P > 0.05$ would indicate a significant good fit. The goodness of fit test showed that the nomogram model had significantly good fit at 1- and 2-year survival intervals ($\chi^2 = 4.0995$, $P = 0.998$ and $\chi^2 = 11.7679$, $P = 0.879$, respectively), which means that the EGC nomogram is accurate in predicting individual 1- and 2-year DFS in the external validation set.

A subsequent calibration of the EGC nomogram was assessed by comparing the nomogram-predicted DFS with the actual survival in subgroups divided according to their nomogram score. The predictions derived from the EGC nomogram were then divided into three groups depending on their points. A Kaplan–Meier DFS curve showed a significant difference among these three subgroups ($P = 0.001$). Especially, in comparison with the DFS curve between the ‘high-risk group’ and ‘low-risk group’, the DFS of the low-risk group was statistically significantly higher than that of the high-risk group (93.4% 4-year DFS in high-risk group versus 99.2% 4-year DFS in low-risk group) (Figure 4). In addition, when we divided the total patients of the external validation set into two groups depending on whether the nomogram score was lower or greater than 170, patients with a score <170 points (high-risk group) also showed worse actual DFS compared with patients who had a score >170 (intermediate-risk group + low-risk group) (Figure 5).

discussion

The recurrence-predicting EGC nomogram that was originally developed in the Yonsei Cancer Center, YUHS, combines clinicopathological and operative parameters to predict DFS at 2, 5, and 10 years from curative resection of EGC. The EGC nomogram was previously internally validated for accuracy [10]. This study has provided external validation for our EGC nomogram.

In the current study, the overall recurrence rate of EGC after D2 gastrectomy was 1.1%, which was relatively lower than results of previous reports [3–8] including our previous study

Table 3. Stratification into three risk groups depending on nomogram score.

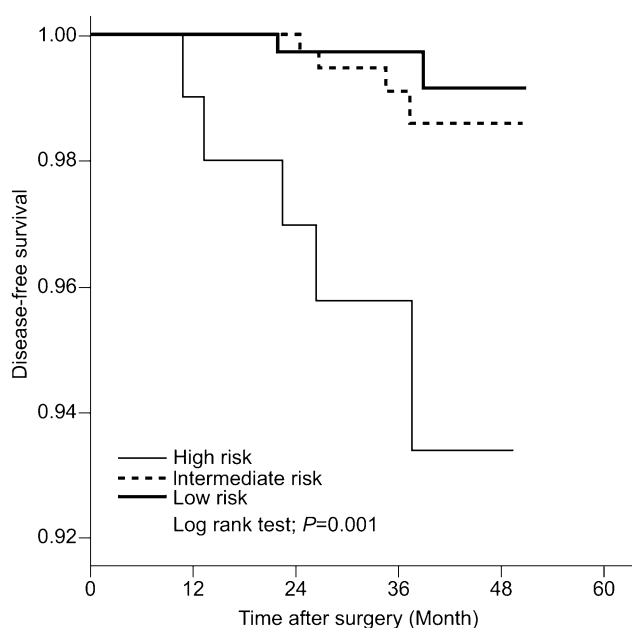
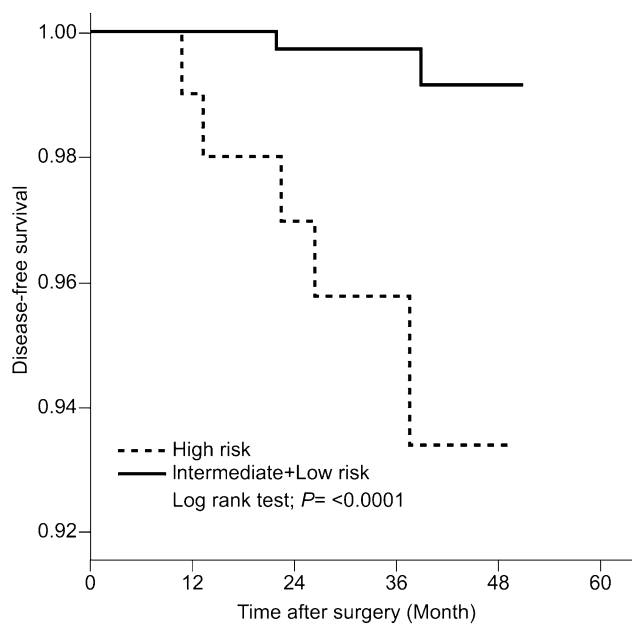
	High-risk group (n = 102)	Intermediate-risk group (n = 427)	Low-risk group (n = 401)
Age (years)			
Median (range)	62.5 (36–81)	63 (28–89)	52 (23–84)
Gender, n (%)			
Male	82 (80.4)	338 (79.2)	202 (50.4)
Female	20 (19.6)	89 (20.8)	199 (49.6)
Tumor size (cm)			
Mean ± SD	3.0 ± 1.7	2.6 ± 1.5	2.7 ± 1.6
Tumor location, n (%)			
Upper	2 (2.0)	28 (6.6)	27 (6.7)
Middle	23 (22.5)	88 (20.6)	237 (59.1)
Lower	77 (75.5)	311 (72.8)	137 (34.2)
Gross appearance, n (%)			
Elevated	34 (33.3)	88 (20.6)	17 (4.2)
Nonelevated	68 (66.7)	339 (79.4)	384 (95.8)
Histology, n (%)			
Differentiated	69 (67.6)	288 (67.4)	143 (35.7)
Undifferentiated	33 (32.4)	139 (32.6)	258 (64.3)
Depth of invasion, n (%)			
Mucosa	10 (9.8)	229 (53.6)	266 (66.3)
Submucosa	93 (90.2)	198 (46.4)	135 (33.7)
Lymph node status, n (%)			
Negative	29 (28.4)	406 (95.1)	399 (99.5)
Positive	73 (71.6)	21 (4.9)	2 (0.5)
Total score of nomogram			
Mean ± SD	140.2 ± 22.5	192.2 ± 11.4	232.0 ± 16.0
Recurrence	5	4	2

The predictions derived from the nomogram were divided into three groups depending on their scores: high risk (<170 points, 102 patients), intermediate risk (170–209 points, 427 patients), and low risk (>209 points, 401 patients).

SD, standard deviation.

(5-year DFS = 2.7%) [10]. This might be due to the relatively short follow-up duration of the current study. The median time to recurrence in the patients of the external validation set was 26.4 months, which was similar to that in the nomogram development set (26.5 months). The clinicopathologic characteristics and DFS observed in the nomogram development cohorts and external validation cohorts were similar.

The prognosis after curative resection for EGC is currently estimated using TNM (tumour–node–metastasis) staging from the American Joint Committee on Cancer [14]. The stage groupings are based on the depth of tumor invasion and the number of lymph node metastases and stratify patients into risk groups. However, this system does not provide sufficient estimates for recurrence risk and survival outcomes because most patients with EGC are diagnosed at an early stage (stage I or II) and the recurrence rate of EGC after curative resection is rare. In contrast to the staging system, prognostic nomograms are designed explicitly for prediction [11]. They do not produce risk groups; instead, they attempt to combine all proven prognostic factors and quantify risk as precisely as possible.

**Figure 4.** Comparison of Kaplan–Meier disease-free survival curve of patients stratified into three risk groups depending on their nomogram score.**Figure 5.** Comparison of Kaplan–Meier disease-free survival curve of patients stratified into two risk groups depending on their nomogram score.

Prognostic nomograms have been developed and validated for prostate cancer, sarcoma, pancreatic cancer, and gastric cancer [15–21]. Nomograms are able to evaluate a large number of significant variables to better predict an individual patient's outcome. Improved prediction of patient outcome would be useful for counseling patients and scheduling patient follow-up, especially for the rare incidence of recurrence in EGC patients.

The EGC nomogram carried out well when applied to the external validation set, with good individual discriminatory

properties and a good overall calibration. The validation was accomplished by comparing the nomogram predictions for each patient in the external validation set with actual outcome. The *c*-index was 0.70 when the EGC nomogram was applied to the external validation set ($n = 930$). The *c*-index of 0.70 in the external validation set means that the recurrence-predicting accuracy of the nomogram is 70%. It is considered significant.

We evaluated further discrimination methods to improve and enhance the predictive accuracy of the EGC nomogram. Although the nomogram discriminated well among patients in the external validation sets by using only nomogram score and status of recurrence, insufficient number of recurrences occurred due to the relatively short follow-up duration of this study. Measuring discrimination in survival analyses such as the Cox regression model is more difficult and ambiguous than in logistic regression. Therefore, we evaluated the discrimination of our EGC nomogram using the overall discrimination index *C* (overall *C*), which was introduced by Harrell et al. [22]. The overall *C* is a natural extension of the ROC curve area to survival analysis and its development was motivated by the extension of the concept of the ROC curve area viewed through the Mann–Whitney statistic. It measures the probability of concordance (agreement) between the predicted and observed outcomes in terms of length of survival of any two subjects. The estimated value of the overall *C* at the 2-year survival interval of our series was found to be 0.82 ($P = 0.006$, 95% CI 0.59–1.00), which means the recurrence-predicting accuracy of the EGC nomogram is 82%. Although not perfect, this represents an encouraging level of predictive accuracy.

Calibration describes how closely the predicted probabilities agree numerically with the actual outcomes. The goodness of fit test showed that the nomogram model had a significantly good fit at 1- and 2-year survival intervals ($P = 0.998$ and 0.879 , respectively). In addition, this was verified by a linear analysis after grouping patients according to their nomogram-predicted probabilities and then comparing the mean of the group with the observed survival estimate. The predictions derived from the nomogram were then divided into three groups depending on their score, and the points defining each group were arbitrarily determined on the basis of the mean nomogram score of the no recurrence group and recurrence group in the nomogram development set. The actual DFS of the high-risk group (<170 points) was worst among the three subgroups, as shown in the results. In addition, when we divided the total patients of the external validation set into two groups depending on whether the nomogram score was lower or greater than 170, patients with a score <170 points (high-risk group) also showed worse actual DFS compared with patients who had a score >170 (intermediate-risk group + low-risk group). Therefore, the actual and predicted survival outcomes showed good agreement, suggesting that the survival predictions from the nomogram are well calibrated externally.

The EGC nomogram showed a clear correlation between nomogram score and predicted DFS in patients with nomogram score <170. It indicated that a patient with a lower nomogram score had worse predicted DFS than patients with nomogram score <170, whereas predicted DFS was not proportional to the increase in nomogram score in patients

with a nomogram score >170 points (data not shown). It could be interpreted that the EGC nomogram is useful for predicting recurrence of EGC in patients with a nomogram score <170.

There are some limitations to our study. Despite its widespread use, the Cox model may have difficulty representing complex relationships, such as interactions in which a variable has a different effect depending on the level(s) of other variable(s). In addition, it is impossible to include enough predictive variables in a nomogram to give absolute predictions. Known variables may not be included because of the lack of numbers or observations, even though they are considered important in some analyses. However, by taking into account a greater number of known factors, this postresection nomogram allows for a more realistic approximation of whether an individual patient will suffer recurrence within a defined period of time.

The ethnic group is also an important factor that cannot be overlooked for prediction of EGC. This EGC nomogram derived from one population (Korean) might not be applicable to a different population (i.e. western countries). As our understanding of the disease progresses, additional clinical, pathologic, and biologic markers can be incorporated to further refine this predictive tool.

conclusion

Our preexisting nomogram for predicting recurrence-free survival of EGC after surgery was externally validated in this study. For the individual patient, the nomogram predicts the likelihood that a population of similar patients will survive for a defined period of time. Although this is only a likelihood, the nomogram provides a more accurate prediction of what the patient might expect, as it takes into account factors that are not included in a simple median survival analysis. For the clinician, the nomogram might be helpful in tailoring follow-up schedules or novel therapeutic strategies.

disclosure

The authors declare no conflict of interest.

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