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ORIGINAL REPORT

Nomogram Predicting Long-Term Survival After D2 Gastrectomy for Gastric Cancer

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ABSTRACT

Purpose
The aim of this study was to combine clinicopathologic variables associated with overall survival after gastric resection with D2 lymphadenectomy (D2 gastrectomy) for gastric cancer into a prediction nomogram.

Patients and Methods
We retrospectively analyzed 7,954 patients who underwent D2 gastrectomy for gastric cancer at Seoul National University Hospital (SNUH) in Seoul, Korea. Two thirds of the patients were randomly assigned to the training set (n = 5,300), and one third were assigned to the validation set (n = 2,654). Multivariate analysis by Cox proportional hazards regression was performed using the training set, and the nomogram was constructed. Discrimination and calibration were performed using the SNUH validation set. Additional external validation was performed using the data set (n = 2,500) from Cancer Institute Ariake Hospital (CIAH) in Tokyo, Japan.

Results
The multivariate Cox model identified age at diagnosis, sex, location, depth of invasion, number of metastatic lymph nodes, and number of examined lymph nodes as covariates associated with survival. In the SNUH validation set, the nomogram exhibited superior discrimination power compared with the seventh American Joint Committee on Cancer TNM classification (Harrell's C-index, 0.78 *v* 0.69, respectively; $P < .001$). Calibration of the nomogram predicted survival corresponding closely with the actual survival. In the CIAH validation set, discrimination was good (C-index, 0.79), and the predicted survival was within a 10% margin of ideal nomogram.

Conclusion
We developed a nomogram predicting 5- and 10-year overall survival after D2 gastrectomy for gastric cancer. Validation using the SNUH and CIAH data sets revealed good discrimination and calibration, suggesting good clinical utility. The nomogram improved individualized predictions of survival.

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INTRODUCTION

Gastric cancer still remains the second most common cause of cancer-related death and is responsible for approximately one million deaths annually.[1] In Korea, gastric cancer is the most prevalent cancer and the second leading cause of cancer-related death.[2]

The only proven and potentially curative treatment for gastric cancer without distant metastasis is radical resection of the stomach combined with regional lymphadenectomy. Regarding D2 lymphadenectomy, a recently reported Dutch trial revealed that cancer-related death rates were lower in the D2 lymphadenectomy group.[3]

In 2010, the seventh edition of the American Joint Committee on Cancer (AJCC) TNM classification was published,[4] and this system stratified M0 gastric cancer into seven risk groups according to the pathologic depth of invasion and the number of metastatic lymph nodes. However, other factors such as age, sex, size of the tumor, and differentiation could be considered for predicting individualized survival. Nomograms have been developed to quantify risk by combining prognostic factors in some diseases.[5-7] However, nomograms predicting survival of gastric cancer are few in number, and one reported nomogram was based on a Western database.[8] This nomogram has been validated for accuracy in the Western population.[9-11]

In Korea, which has the highest incidence of gastric cancer in the world,[12] surgeons have accumulated substantial surgical experience, and gastric resection with D2 lymphadenectomy (D2

gastrectomy) is routinely performed with low morbidity and mortality rates.[13,14] On the basis of this surgical practice and data collection, the gastric cancer data set of Seoul National University Hospital (SNUH) in Seoul, Korea was reflected in revising the AJCC TNM classification for gastric cancer.[15]

The aim of the current study was to combine clinicopathologic variables that are associated with overall survival after D2 gastrectomy for gastric cancer into a prediction nomogram based on the data of a single large-volume institution. We also compared the discriminating value of the nomogram to that of the seventh AJCC TNM classification.

PATIENTS AND METHODS

Data Set

Between January 1, 1986, and December 31, 2007, among patients who underwent gastric cancer surgery at the Department of Surgery at SNUH, we collected data for 7,954 patients who satisfied the following inclusion criteria: the presence of primary gastric cancer; no combined malignancy; no preoperative chemotherapy; no distant metastasis; R0 resection (no residual macroscopic or microscopic tumor); more than 15 examined lymph nodes; and without one or more missing values.

This data set included patient demographics (age and sex), pathologic characteristics (location, size, gross type, histology, depth of invasion, number of metastatic lymph nodes, and number of examined lymph nodes), adjuvant chemotherapy, and follow-up data (follow-up duration and survival). The location of the tumor was categorized as upper third, middle third, or lower third by the center of the lesion. Adenocarcinoma of the esophagogastric junction within the stomach was categorized as upper third gastric cancer.[16] The size of the tumor was measured at the longest diameter. Gross type was categorized as early gastric cancer, advanced gastric cancer with Borrmann type I to III, or advanced gastric cancer with Borrmann type IV. The histologic subtype was categorized as differentiated type (papillary adenocarcinoma, well-differentiated tubular adenocarcinoma, and moderately differentiated tubular adenocarcinoma) or undifferentiated type (poorly differentiated tubular adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma). The depth of invasion was categorized as mucosa, submucosa, proper muscle, subserosa, serosa, or adjacent organ invasion. The number of metastatic lymph nodes was categorized according to the node grouping of the seventh AJCC TNM classification (zero, one to two, three to six, seven to 15, or $\geq$ 16 nodes). Adjuvant chemotherapy was categorized as received or not received. Follow-up data were collected from hospital records or the National Statistical Office data for patients who were lost to follow-up. The follow-up duration was measured from the time of surgery to the last follow-up date, and information regarding the survival status at the last follow-up was collected.

Construction of the Nomogram

For nomogram construction and validation, we randomly assigned two thirds of the patients to the training set (n = 5,300) and one third to the validation set (n = 2,654). The clinicopathologic characteristics of the training and validation sets were evaluated.

The proportional hazards (PH) assumption and linearity assumption in continuous variables (size, examined lymph nodes) were examined using restricted cubic splines.[17,18] Continuous variables were transformed to adequate form for fitting the PH and linearity assumptions. For the categorical variables, a log-log survival plot was used for identifying the PH assumption, and all variables were fitted to the PH assumption. Variables were selected by the forward stepwise selection method in the Cox PH regression model. On the basis of the predictive model with the identified prognostic factors, a nomogram was constructed for predicting 5- and 10-year overall survival.

Validation of the Nomogram

Nomogram validation consisted of discrimination and calibration by using the validation set. Discrimination was evaluated using a concordance index, which provides the probability that for two randomly selected patients, when one patient has an event before the other, this patient has a poorer predicted outcome as determined by the nomogram. Harrell's C-index, which is appropriate for censored data, was used for evaluating the discrimination.[18,19] In general, a C-index value greater than 0.75 is considered to represent relatively good discrimination. Calibration was performed by comparing the means of predicted survival with those of actual survival with observed Kaplan-Meier estimates after grouping of the nomogram predicted survival by decile.

The nomogram was validated by two validation sets. The first validation used the SNUH validation set (n = 2,654) by data-splitting method because the SNUH has a large enough internal database, and the second validation was performed using a data set from one of the most active Japanese institutes, Cancer Institute Ariake Hospital (CIAH), which has a large prospective database. We collected the CIAH validation set (n = 2,500), which satisfied the aforementioned inclusion criteria, and examined the clinicopathologic variables that were included in the nomogram.

Statistical significance was set as $P < .05$ in a two-tailed test. All statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC), SPSS version 19 (SPSS, Chicago, IL), and R software version 2.13.2 (http://www.r-project.org) with the design and survival packages. This study was approved by the Institutional Review Board of SNUH (H-1109-051-378).

RESULTS

The clinicopathologic characteristics for the training set (n = 5,300) and SNUH validation set (n = 2,654) are listed in Table 1. The mean numbers of examined lymph nodes were 32.4 $\pm$ 12.4 and 32.6 $\pm$ 12.9 nodes in the training set and validation set, respectively. In the training set and validation set, 69.5% and 70.3% of patients, respectively, had more than 25 lymph nodes examined.

After examination and transformation of variables to fit in the Cox PH regression model, variables were selected by the forward stepwise selection method ($P < .05$). Table 2 lists the selected variables with hazard ratios. The hazard ratios were significantly higher for older age, male sex, location of upper part of stomach, advanced depth of invasion, increased number of metastatic lymph nodes, and decreased number of examined lymph nodes. However, size, histology, gross type, and adjuvant chemotherapy were not found to be significant.

Figure 1 shows the nomogram predicting 5- and 10-year overall survival that was constructed based on selected variables with hazard ratios. The nomogram can assign the probability of survival by adding up the scores identified on the points scale for each variable. The total score projected to the bottom scale indicate the probability of 5- and 10-year survival.

Validation was performed by using the SNUH and CIAH validation sets. The clinicopathologic characteristics for the CIAH validation set (n = 2,500) are listed in Table 1. In the CIAH validation set, we examined clinicopathologic variables that were included in the nomogram.

In the SNUH validation set, Harrell's C-index was 0.78 (95% CI, 0.73 to 0.82). Figure 2 shows the calibration plot of the nomogram. The *x*-axis is the predicted survival calculated by the nomogram, and the *y*-axis is the actual survival estimated by the Kaplan-Meier method. The solid line represents the ideal reference line where predicted survival corresponds with the actual survival, and the dotted

Table 1. Demographic and Clinicopathologic Variables of the Training and Validation Sets

Variable	Training Set (n = 5,300) No. of Patients	%	SNUH Validation Set (n = 2,654) No. of Patients	%	CIAH Validation Set (n = 2,500) No. of Patients	%
Tumor size, cm						
Mean	4.4		4.4			
Standard deviation	2.6		2.7			
Examined LNs, No.						
Mean	32.4		32.6		38.5	
Standard deviation	12.6		12.9		16.0	
Age, years						
< 40	502	9.5	261	9.8	102	4.1
40-49	1,004	18.9	508	19.1	355	14.2
50-59	1,569	29.6	790	29.8	728	29.1
60-69	1,546	29.2	772	29.1	770	30.8
≥ 70	679	12.8	323	12.2	545	21.8
Sex						
Male	3,593	67.8	1,783	67.2	1,683	67.3
Female	1,707	32.2	871	32.8	817	32.7
Metastatic LNs, No.						
0	2,806	52.9	1,411	53.2	1,803	72.1
1-2	671	12.7	350	13.2	306	12.2
3-6	725	13.7	374	14.1	230	9.2
7-15	750	14.2	343	12.9	129	5.2
≥ 16	348	6.6	176	6.6	32	1.3
Gross type						
EGC	2,155	40.7	1,122	42.3		
AGC, Borrmann type I-III	2,855	53.9	1,370	51.6		
AGC, Borrmann type IV	290	5.5	162	6.1		
Depth of invasion						
Mucosa	1,130	21.3	554	20.9	927	37.1
Submucosa	991	18.7	540	20.4	701	28.0
Proper muscle	681	12.9	349	13.2	306	12.2
Subserosa	1,294	24.4	628	23.7	265	10.6
Serosa	1,135	21.4	553	20.8	281	11.2
Adjacent organ invasion	69	1.3	30	1.1	20	0.8
Location						
Upper	658	12.4	355	11.6	452	18.1
Middle	1,329	25.1	743	27.0	1,282	51.3
Lower	3,313	62.5	1,894	61.4	766	30.6
Histology						
Differentiated	2,427	45.8	1,230	46.4		
Undifferentiated	2,873	54.2	1,424	53.7		
Chemotherapy						
Yes	2,315	43.7	1,141	42.4		
No	2,985	56.3	1,553	57.6		

Abbreviations: AGC, advanced gastric cancer; CIAH, Cancer Institute Ariake Hospital; EGC, early gastric cancer; LN, lymph node; SNUH, Seoul National University Hospital.

lines represent a 10% margin of error. The actual survival corresponded closely with the predicted survival and was always within the 10% margin of error. We compared the discrimination of the nomogram with that of the seventh AJCC TNM classification. Nomogram discrimination was 0.78 (95% CI, 0.73 to 0.82), which was superior to that of the seventh AJCC TNM classification (0.69; 95% CI, 0.64 to 0.074; $P < .001$). Figure 3 illustrates the 5-year survival predicted by the nomogram in each stage of the seventh AJCC TNM classification. A wide range of predicted survival could be identified in each TNM stage. Furthermore, the range of predicted survival was wider for higher stages.

In the CIAH validation set, Harrell's C-index was 0.79 (95% CI, 0.73 to 0.85). Figure 4 shows the calibration plot of the nomogram. Although the actual survival was slightly higher than the predicted survival, it was within a 10% margin of nomogram prediction.

DISCUSSION

This study is significant because a large cohort of patients who underwent D2 gastrectomy that was verified in revision of the AJCC TNM classification was used to develop the nomogram. There are statistical

Table 2. Selected Variables According to the Cox Proportional Hazards Regression Model

Variable	Hazard Ratio	95% CI	*P*
Age, years			
< 40	Ref		
40-49	0.87	0.72 to 1.06	.178
50-59	1.09	0.91 to 1.30	.364
60-69	1.54	1.29 to 1.84	< .001
≥ 70	2.26	1.87 to 2.74	< .001
Sex			
Male	Ref		
Female	0.80	0.72 to 0.88	< .001
Location			
Upper	Ref		
Middle	0.83	0.72 to 0.96	.011
Lower	0.75	0.66 to 0.85	< .001
Depth of invasion			
Mucosa	Ref		
Submucosa	1.26	1.00 to 1.58	.051
Proper muscle	1.59	1.26 to 2.02	< .001
Subserosa	2.70	2.18 to 3.34	< .001
Serosa	3.35	2.69 to 4.16	< .001
Adjacent organ invasion	7.31	5.24 to 10.21	< .001
Metastatic LNs, No.			
0	Ref		
1-2	1.29	1.09 to 1.52	.003
3-6	2.05	1.76 to 2.39	< .001
7-15	3.25	2.80 to 3.77	< .001
≥ 16	5.63	4.73 to 6.71	< .001
$\sqrt{\text{Examined LNs}}$	0.91	0.87 to 0.95	< .001

Abbreviations: LN, lymph node; Ref, reference.

methods for internal validation such as cross-validation and bootstrap resampling; however, these methods have a theoretical probability of overinterpretation.[20] For this reason, external validation is essential for ensuring external applicability, although the predictive accuracy decreased in the external validation set. The most stringent external validation involves using a data set from other countries, whereas less stringent external validation involves using a data set from different institutions or a validation set by data-splitting method from the same institution.[18] In this study, we performed two kinds of external validation using a validation set that was independent from the training set in the same institution and a validation set from one of the most active Japanese institutes.

Compared with a previous nomogram based on a Western database, Lauren classification and size were excluded from this nomogram. In data collection, we did not include Lauren classification because missing data would have reduced the statistical power. In addition, Lauren classification was not significantly associated with survival in the multivariate analysis.[8] Another difference is that we used categorical variables for age and the number of metastatic lymph nodes for clinical convenience. Although continuous variables can preserve information more than categorical variables, drawing lines to points in the nomogram and adding points can be ambiguous and cumbersome. For this study, we categorized the number of metastatic lymph nodes by using statistical methods. However, discrimination was not much better than the lymph node grouping using the seventh AJCC TNM classification (results not shown).

In this study, we categorized the tumor location as upper third, middle third, and lower third gastric cancer. Although the seventh AJCC TNM classification regards adenocarcinoma of the esophagogastric junction as esophageal cancer, our previous study showed that adenocarcinoma of the esophagogastric junction within the stomach should be considered as gastric cancer.[16] Compared with Kattan's nomogram, the proportion of upper third gastric cancer was much smaller in this study (49.5% *v* 12.4%, respectively). Nevertheless, upper third gastric cancer similarly contributed to the nomogram as an indicator of poor prognosis. As a result, when the TNM stage is the same between two cohorts, the survival can differ because of variables that are not considered in TNM classification. However, using this nomogram with significant clinicopathologic variables

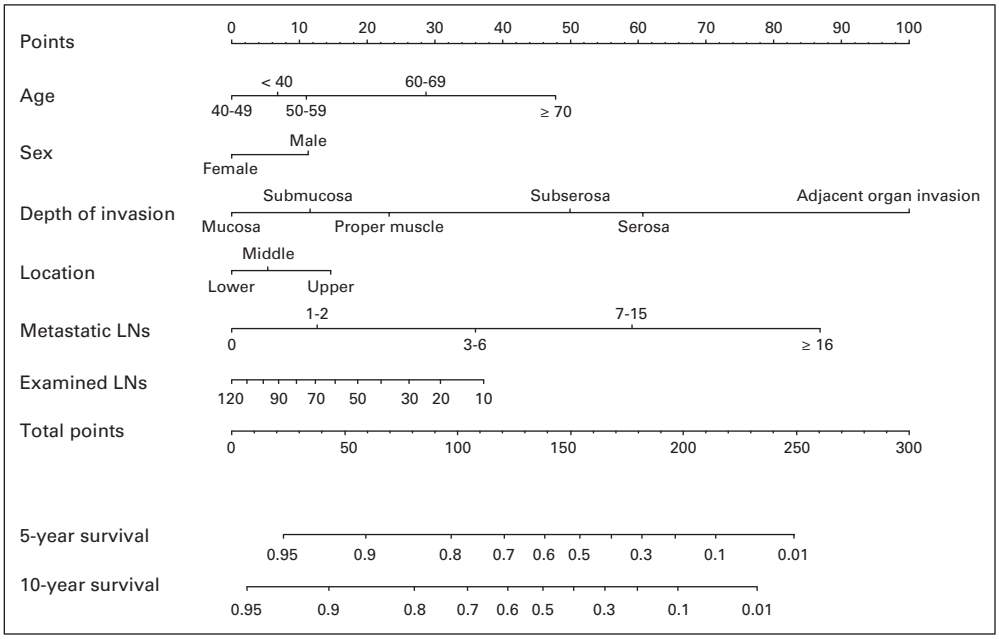

Fig 1. Nomogram predicting 5- and 10-year overall survival after D2 gastrectomy for gastric cancer. The nomogram is used by adding up the points identified on the points scale for each variable. The total points projected on the bottom scales indicate the probability of 5- and 10-year survival. LNs, lymph nodes.

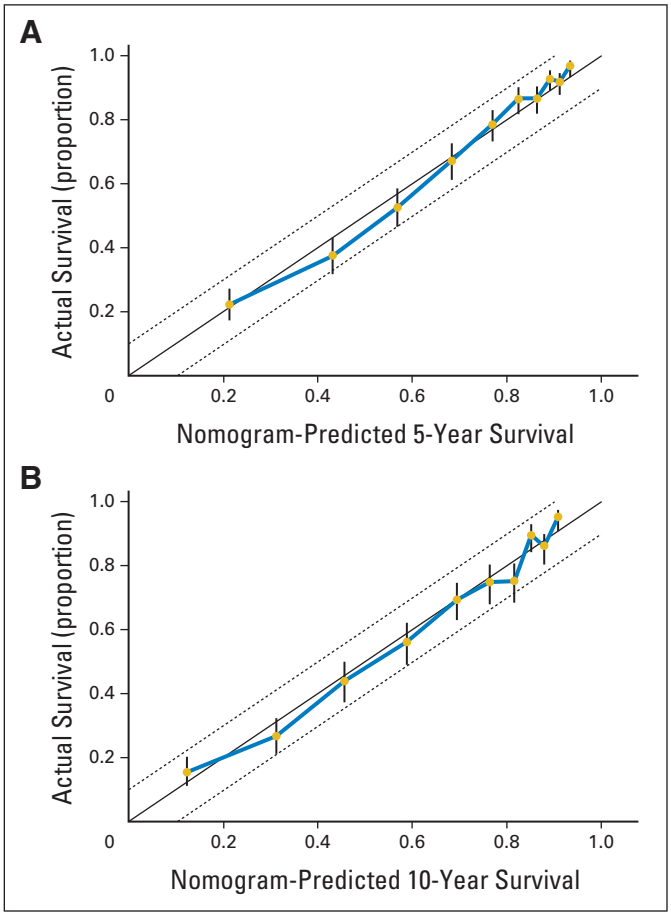

Fig 2. Calibration of the nomogram in the Seoul National University Hospital validation set. The *x*-axis represents the nomogram-predicted survival, and the *y*-axis represents actual survival and 95% CIs measured by Kaplan-Meier analysis. All predictions lie within a 10% margin of error (within the dashed line). (A) Five-year survival. (B) Ten-year survival.

including age, location of the tumor, number of examined lymph nodes, and so on, we demonstrated that patient survival can be more precisely predicted than when using TNM stage. In fact, Figure 3 demonstrates that patients with the same TNM stage had diverse survival.

For generalized use of the nomogram by other institutions or other regions, it is important to minimize the effect of differences in the surgical strategy and pathologic examination. In this study, we excluded patients when the number of examined lymph nodes was less than 16. The examination of at least 16 lymph nodes ensured the surgical quality of D2 lymphadenectomy and prevented stage migration effect. The sixth edition of the AJCC staging manual for gastric cancer recommends that at least 16 lymph nodes be examined for correct assessment of the lymph node status.[21] Several studies have reported that the examination of more than 15 lymph nodes improves the prediction of prognosis in gastric cancer.[22,23] Kong et al[24] reported that the survival rate increased as the number of examined lymph nodes increased by the stage migration effect. In this study, the mean numbers of examined lymph nodes were 32.4 and 32.6 in the training and validation sets, respectively. The proportion of patients with more than 25 examined lymph nodes was approximately 70% in each group. This result represents

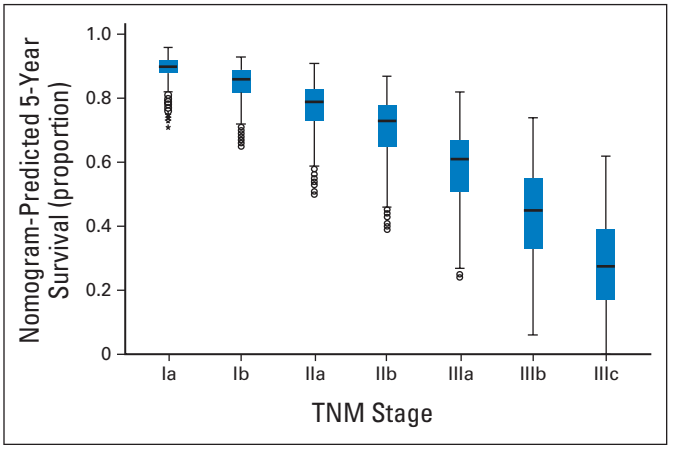

Fig 3. The box plot represents the distribution of nomogram-predicted 5-year survival according to seventh American Joint Committee on Cancer TNM classification. A wide range of predicted survival can be identified in each TNM stage.

the high relevance of D2 lymphadenectomy in this cohort compared with the Western study.

Regarding adjuvant chemotherapy in gastric cancer, there have been few randomized controlled trials, and no regimens have been

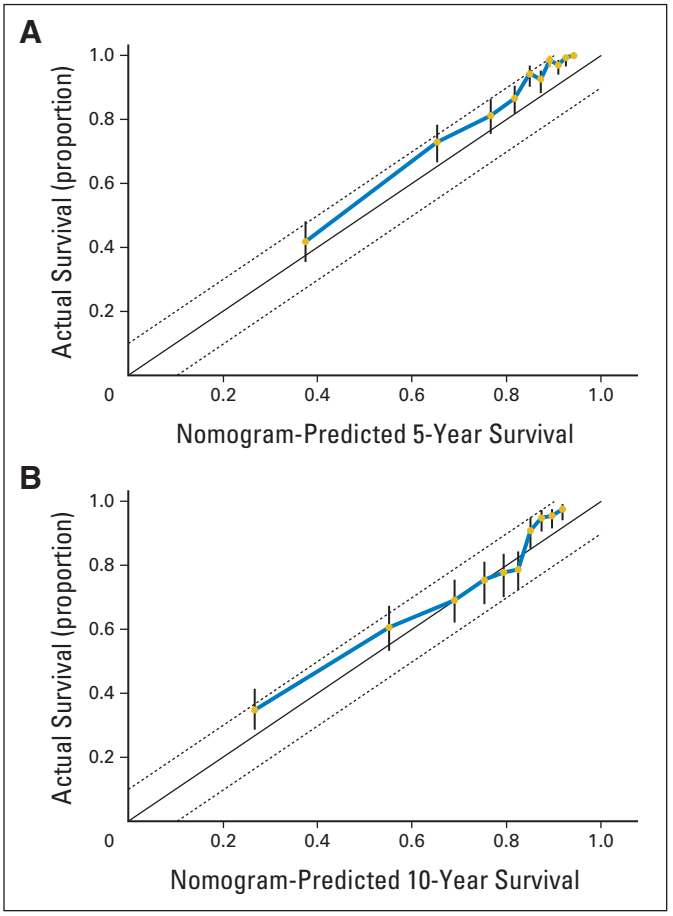

Fig 4. Calibration of the nomogram in the Cancer Institute Ariake Hospital validation set. The *x*-axis represents the nomogram-predicted survival, and the *y*-axis represents actual survival and 95% CIs measured by Kaplan-Meier analysis. All predictions lie within a 10% margin of error (within the dashed line). (A) Five-year survival. (B) Ten-year survival.

established as the standard after gastrectomy with D2 lymphadenectomy before 2007.[25] Recently, adjuvant oral fluoropyrimidine (S-1) after gastrectomy with D2 lymph node dissection exhibited a survival benefit in a large-scale randomized controlled trial.[25,26] Another phase III trial exhibited a benefit in 3-year disease-free survival after adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy compared with gastrectomy alone (74% *v* 59%, respectively; $P < .001$).[27] In this study, however, adjuvant chemotherapy failed to demonstrate significance in the Cox PH regression model and thus was excluded from the nomogram. In our institution, patients with stage II or III gastric cancer usually receive adjuvant chemotherapy with a relatively uniform protocol based on fluorouracil and platinum. Unlike randomized controlled trials for adjuvant chemotherapy, adjuvant chemotherapy was omitted only in patients with poor functional status and reluctant to receive chemotherapy. As a result, adjuvant chemotherapy is believed to have little significance as a variable in this study.

External validation in both the SNUH and CIAH validation sets demonstrated good discrimination power (Harrell's C-index, 0.78 and 0.79, respectively). Calibration using the SNUH validation set demonstrated that the actual survival corresponds closely with the predicted survival. In the CIAH validation set, the actual survival was slightly higher than the predicted survival, although it was within a 10% margin of nomogram prediction. The Japanese Gastric Cancer Association reported that the 5-year survival rate of patients with middle third gastric cancer was higher than that of patients with lower third gastric cancer (78.9% *v* 71.9%, respectively).[28] However, the score of middle third gastric cancer is higher than that of lower third gastric cancer in our nomogram. In addition, because the proportion of middle third gastric cancer was high (51.3%) in the CIAH validation set, the actual survival could be slightly higher than the predicted survival.

The present study has several limitations. First, patient comorbidity was not reflected in this nomogram. We expect that comorbidity will affect overall survival to some extent. However, because of the diversity of comorbidity, it is hard to create categorized variables and to quantify risk. According to a report of the National Statistical Office in Korea, in 2010, the most common cause of death in Korea was malignancy, and the next most common cause was cerebrovascular disease, which carried a 3.2-fold lower risk of death than cancer.[29] In this study, because patients with other malignancies were excluded from data collection, the impact of comorbidity on survival is expected to be minimal. Second, the time span for the data set is more than 20 years. A question might be raised about whether this nomogram can be applied to present patients. In our institution, however, overall strategies for D2 lymphadenectomy and pathologic examination have not changed during this period. Splenectomy was considered when the advanced gastric cancer was located at the upper third greater curvature side, and distal pancreatectomy was not routinely performed for D2 lymphadenectomy. Although, the overall survival was better in the later period, this was a result of the increased proportion of early gastric cancer diagnoses because of a nationwide screening program.[13]

In summary, we developed and externally validated a nomogram predicting 5- and 10-year overall survival after D2 gastrectomy for gastric cancer based on an Eastern database. The nomogram provides significantly better discrimination than the seventh AJCC TNM classification and also provides an individualized prediction of survival. The accuracy was validated by large data sets from Korean and Japanese institutes. We believe that this nomogram can be useful in Korea and Japan, where the incidence of gastric cancer is high and D2 gastrectomy is routinely performed. For the generalized use of this nomogram, validation by a Western cohort is required.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Kamangar F, Dores GM, Anderson WF: Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24:2137-2150, 2006
2. Lee HJ, Yang HK, Ahn YO: Gastric cancer in Korea. Gastric Cancer 5:177-182, 2002
3. Songun I, Putter H, Kranenbarg EM, et al: Surgical treatment of gastric cancer: 15-Year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 11:439-449, 2010
4. Edge SB, Byrd DR, Compton CC, et al: AJCC Cancer Staging Manual (ed 7). New York, NY, Springer, 2010
5. Kattan MW, Stapleton AM, Wheeler TM, et al: Evaluation of a nomogram used to predict the pathologic stage of clinically localized prostate carcinoma. Cancer 79:528-537, 1997
6. Gold JS, Gonen M, Gutierrez A, et al: Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localised primary gastrointestinal stromal tumour: A retrospective analysis. Lancet Oncol 10: 1045-1052, 2009
7. Keam B, Im SA, Park S, et al: Nomogram predicting clinical outcomes in breast cancer patients treated with neoadjuvant chemotherapy. J Cancer Res Clin Oncol 137:1301-1308, 2011
8. Kattan MW, Karpeh MS, Mazumdar M, et al: Postoperative nomogram for disease-specific survival after an R0 resection for gastric carcinoma. J Clin Oncol 21:3647-3650, 2003
9. Peeters KC, Kattan MW, Hartgrink HH, et al: Validation of a nomogram for predicting disease-specific survival after an R0 resection for gastric carcinoma. Cancer 103:702-707, 2005
10. Novotny AR, Schuhmacher C, Busch R, et al: Predicting individual survival after gastric cancer resection: Validation of a U.S.-derived nomogram at a single high-volume center in Europe. Ann Surg 243:74-81, 2006
11. Koc M, Dizen H, Ozalp N, et al: External validation of a US-derived nomogram that predicts individual survival after gastric cancer resection. Langenbecks Arch Surg 394:755-756, 2009
12. Lee J, Demissie K, Lu SE, et al: Cancer incidence among Korean-American immigrants in the United States and native Koreans in South Korea. Cancer Control 14:78-85, 2007
13. Ahn HS, Lee HJ, Yoo MW, et al: Changes in clinicopathological features and survival after gastrectomy for gastric cancer over a 20-year period. Br J Surg 98:255-260, 2011
14. Park DJ, Lee HJ, Kim HH, et al: Predictors of operative morbidity and mortality in gastric cancer surgery. Br J Surg 92:1099-1102, 2005

15. Ahn HS, Lee HJ, Hahn S, et al: Evaluation of the seventh American Joint Committee on Cancer/International Union Against Cancer Classification of gastric adenocarcinoma in comparison with the sixth classification. Cancer 116:5592-5598, 2010

16. Suh YS, Han DS, Kong SH, et al: Should adenocarcinoma of the esophagogastric junction be classified as esophageal cancer? A comparative analysis according to the seventh AJCC TNM classification. Ann Surg 255:908-915, 2012

17. Hess KR: Assessing time-by-covariate interactions in proportional hazards regression models using cubic spline functions. Stat Med 13:1045-1062, 1994

18. Harrell FE Jr: Regression Modeling Strategies with Application to Linear Models, Logistic Regression, and Survival Analysis. New York, NY, Springer Verlag, 2001

19. Harrell FE Jr, Lee KL, Mark DB: Multivariable prognostic models: Issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361-387, 1996

20. Iasonos A, Schrag D, Raj GV, et al: How to build and interpret a nomogram for cancer prognosis. J Clin Oncol 26:1364-1370, 2008

21. American Joint Committee on Cancer: Stomach, in: AJCC Cancer Staging Manual (ed 6). New York, NY, Springer Verlag, 2002

22. Smith DD, Schwarz RR, Schwarz RE: Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: Data from a large US-population database. J Clin Oncol 23:7114-7124, 2005

23. Shen JY, Kim S, Cheong JH, et al: The impact of total retrieved lymph nodes on staging and survival of patients with pT3 gastric cancer. Cancer 110:745-751, 2007

24. Kong SH, Lee HJ, Ahn HS, et al: Stage migration effect on survival in gastric cancer surgery with extended lymphadenectomy: The reappraisal of positive lymph node ratio as a proper N-staging. Ann Surg 255:50-58, 2012

25. Sakuramoto S, Sasako M, Yamaguchi T, et al: Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 357:1810-1820, 2007

26. Sasako M, Sakuramoto S, Katai H, et al: Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 29:4387-4393, 2011

27. Bang YJ, Kim YW, Yang HK, et al: Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): A phase 3 open-label, randomized controlled trial. Lancet 379:315-321, 2012

28. Isobe Y, Nashimoto A, Akazawa K, et al: Gastric cancer treatment in Japan: 2008 annual report of the JGCA nationwide registry. Gastric Cancer 14:301-316, 2011

29. National Statistical Office: Korean Statistical Information Service. http://kosis.kr/eng/

