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External Validation of an Eastern Asian Nomogram for Survival Prediction After Gastric Cancer Surgery in a European Patient Cohort

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Abstract: Several nomograms for survival prediction after curative gastric cancer surgery have been published over the recent years. Previous validation studies failed to prove applicability of Eastern Asian nomograms in Western patients. Here we present data on a validation analysis of a newly developed Korean nomogram in a German patient cohort.

Among a total of 2771 patients having been treated in the Department of Surgery of the Technische Universitaet Muenchen from 1982 to 2008, 908 patients were eligible to undergo this analysis. Patients were treated according to Japanese Gastric Cancer guidelines and followed up on a regular basis for at least 60 months postoperatively. Baseline characteristics were compared using χ^2-testing. Survival analyses were computed with the Kaplan–Meier method and multivariate regression analysis models. The C-statistics and Hosmer–Lemeshow chi-square statistics were computed for comparisons of the nomogram's predictive ability.

All baseline characteristics were significantly different ($P < 0.0001$) between Korean and German patients except Union Internationale Contre le Cancer-stages ($P = 0.427$). Multivariate regression analysis revealed the same predictive factors for overall survival in the German and Korean cohorts, respectively, with the exception of tumor size >10 cm and an exclusive correlation of whole stomach spread and pN1-stage for German patients only. The C-index was 0.76, representing an adequate value for predictability of the Korea nomogram in German patients. The Hosmer–Lemeshow statistic implied applicability of the nomogram in the TUM-cohort.

A newly developed multicenter Korean nomogram for survival prediction after curative gastric cancer surgery may be applicable for estimating survival prognosis in Western (European) patients.

(*Medicine* 94(52):e2406)

Abbreviations: AEG = adenocarcinoma of the esophago-gastric junction, AJCC = American Joint Commission on Cancer, CEA = carcino-embryonic antigene, CI = confidence interval, CT = computed tomography, EGD = esophago-gastro-duodenoscopy, GC = gastric cancer, H-L = Hosmer–Lemeshow, KNDS = Korean Nomogram Development Set, LVII = ymphatic vessel infiltration, MSKCC = Memorial Sloan Kettering Cancer Center, OS = overall survival, ROC = receiver operating characteristic, SNUH = Seoul National University Hospital, TNM = tumor node metastasis, TUM = Technische Universitaet Muenchen, UICC = Union Internationale Contre le Cancer, US = United States.

BACKGROUND

Despite decreasing incidence and recent improvements in treatment concepts gastric cancer remains one of the most common cancer entities worldwide with highest incidence rates in eastern Asian countries such as Korea and Japan.[1] Adequate oncologic resection is the only option of treatment with curative intent.[2] However, in order to define prognostic factors or to decide for adjuvant treatment concepts, prediction of post-operative survival is considered to be of utmost importance. The most commonly used tool is the TNM classification, edited by the Union International Contre le Cancer (UICC) and American Joint Commission on Cancer (AJCC).[3] In 2010, the most recent 7th edition was published. Despite several improvements over the sixth edition, survival prediction appeared to be suboptimal under certain circumstances.[4] As an alternative, nomograms were proposed to provide more accurate survival prediction because not only factors involving tumor extension to locoregional lymph nodes and distant organs but also predictive factors such as number of dissected lymph nodes, tumor size, lymphatic vessel infiltration (LVI), and tumor location represent prognostic factors in gastric cancer surgery.[5–11] One of the first nomograms was developed in the US[5] and cross-validated in 2 European institutions.[6,7] Among them was a cohort from the Department of Surgery of the Technische Universitaet Muenchen (TUM).[6] It was demonstrated that the US-nomogram was applicable also for European

Editor: Patrick Wall.
Received: August 19, 2015; revised: December 1, 2015; accepted: December 9, 2015.
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This manuscript fully consists of original material, which has not been published or submitted to another journal. All authors declare that they participated in the analysis as specified below and that they have seen and approved the final version.
No funds or grants or company gifts have been received, nor has the article been written by a third party. Data acquisition and analysis was performed according to local ethic standards and GCP guidelines.
This work was supported by the National Cancer Center Fund, Republic of Korea (Grant No. 1410140-1).
The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000002406

patients. In contrast, the nomogram did not prove to be applicable in Eastern Asian (Korean) patients due to possibly different treatment strategies, tumor location, or ethnic differences.[8] In consequence, Korean-specific nomograms were developed respecting local circumstances.[9,10,11] These nomograms were only cross-validated in Japanese cohorts so far.[9] Further general applicability of the Korean nomograms was considered questionable due to the high specialization of the reporting centers, which developed the nomograms.[11] Therefore, Eom et al[11] developed a nomogram based on multicentric data (8 institutions) with a Korean cross-validation study. This nomogram was constructed using a multivariate Cox proportion hazard regression model of potential survival-related factors. Here, a line is drawn according to any of the clinicopathologic factors to an axis indicating specific score values. After adding the respective values, the sum value displays the probability of 5-year survival by connecting the score value with the 5-year survival axis. It was demonstrated that survival prediction was accurate not only in specialized centers but also in general hospitals. However, the authors concluded that validation in Western patients is deemed to be useful considering general applicability of the tool. In order to obtain comparable results, treatment strategies are considered to be similar between the centers.

Here we report of a validation study for the multicenter Korean nomogram in gastric cancer patients having undergone primary curative oncologic surgery at the Department of Surgery of the TUM.

PATIENTS AND METHODS

The prospectively documented gastric cancer database was reviewed for patients having undergone gastric cancer surgery with curative intent between 1982 and 2008 at the surgical department of the TUM. Data were obtained from the medical records and transferred to the institutional database as soon as the patients were discharged from inpatient hospital care. Eligibility criteria were: histologically proven gastric cancer, R0-resection. Exclusion criteria were: metastatic disease, neoadjuvant/perioperative chemotherapy, extension to the distal esophagus, gastric stump cancer, hospital mortality within 30 days, loss of follow-up within a 60-month period and residual cancer after surgery (R1/R2). The exclusion criteria were the same as in the original Korean patient cohort. The dataset consisted of patients' age, sex, tumor size, location (upper, middle, lower third), histological type (differentiated type: papillary, well-differentiated, and moderately differentiated tubular adenocarcinoma; undifferentiated type: poorly differentiated tubular adenocarcinoma, signet ring cell carcinoma, mucinous adenocarcinoma, and undifferentiated adenocarcinomas), lymphovascular invasion, pT-, pN-, and UICC-stage, extent of lymph node dissection and follow-up period with survival status.

All surgical procedures were performed according to the Japanese guidelines for GC-treatment.[12] Lymph node dissection was categorized as D1 plus or D2 as defined by the Japanese treatment guidelines.[13] T- and N-stages were evaluated according to the 7th AJCC/UICC tumor-node-metastasis (TNM) classification.[3] None of the patients received adjuvant chemotherapy. Patients were followed up after surgery regularly according to institutional guidelines including physical examinations, laboratory tests (CEA), endoscopy, and computed tomography (CT). The examinations were scheduled every 6 months for the first 3 years and annually for the next 2 years. Follow-up time was determined from the day of surgery to the last follow-up date. IRB approval was obtained according to local regulations for retrospective analyses.

The control group consisted of the patients having been included in the Multicenter Korean nomogram development set published before.[11] Intergroup comparisons were analyzed by χ^2-testing, continuous variables are presented as mean ± standard deviation. T tests or Wilcoxon tests were used whenever appropriate. Risk calculation according to the proposed nomogram (Figure 1) was performed for every patient. The hazard ratio and corresponding 95% confidence interval [CI]) for each of the potential risk factors was estimated by a Cox proportional hazard regression model. The Korean patient group was used as the development set, and the German patient group as the validation set. All of the statistical analyses with respect to the model's performance were performed in the German patients cohort. The previously developed model was validated in the German cohort with respect to its discrimination ability using C-statistics and its calibration ability using Hosmer–Lemeshow (H-L) chi-square statistics. The discriminative power depends on the ability of a model to correctly distinguish between nonevents and events, which can be quantified by calculating the C-statistic developed for the respective survival model.[13] The C-statistic is a measure that is analogous to the receiver operating characteristic (ROC) curve, which indicates the probability that a model produces higher risks for those who

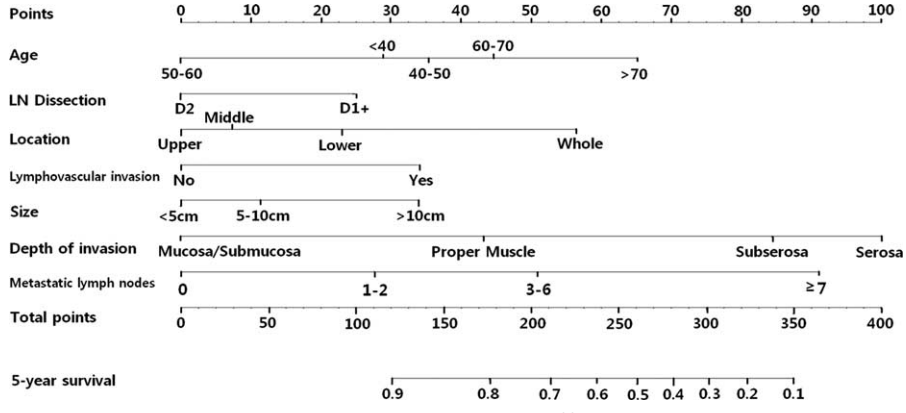


FIGURE 1. Multicenter Korean survival nomogram as proposed by Eom et al.[11]

develop events compared with those who do not develop events. H-L chi-square statistic[13] measures how closely the predicted probabilities agree numerically with the actual outcomes. This chi-square statistic was calculated by categorizing the data into 5 groups (quintiles) based on the predicted probabilities that are generated by the model in ascending order. For each quintile, the average predicted probabilities were compared to the event rate estimated by the Kaplan–Meier method. The statistical analysis was carried out in analogy to the Korean validation cohort in the Eom paper.[11]

Two-sided P values < 0.05 were considered statistically significant. All data were analyzed by the SAS software version 9 (SAS Institute Inc., Cary, NC, USA). All of the results were interpreted by a specialist in biostatistics (BH Nam). This analysis was approved by the local institutional review board (Ethikkommission der Fakultaet für Medizin der Technischen Universitaet Muenchen).

RESULTS

Patients

A total of 2771 patients underwent surgery for gastric cancer at TUM between 1982 and 2008. Among these patients, 659 patients with neoadjuvant/perioperative chemotherapy, 33 with neoadjuvant chemoradiation, 84 with R1-resection, 257 with R2-resection, 291 patients with metastatic disease, 307 with adenocarcinoma of the esophagogastric junction (AEG), 19 carcinomas of the gastric remnant, 42 patients with in-hospital mortality, 75 patients without resection (open&close), and 96 patients with a follow-up of <60 months were excluded from the analysis. Finally 908 patients were enrolled in this validation analysis. The control cohort consisted of 1579 patients and was published before.[11]

Baseline characteristics of the cohorts are depicted in Table 1. Apart from AJCC/UICC stages, the TUM cohort was different in almost all analyzed parameters compared to Korean patients. TUM patients were significantly older ($P < 0.0001$) and the amount of female patients was considerably higher ($P < 0.001$). Tumor size tended to be smaller in German patients ($P < 0.0001$) and tumors tended to be located in the more proximal parts of the stomach ($P < 0.0001$). Tumors were more undifferentiated compared to Korean patients and LVI was less frequent in German patients ($P < 0.0001$, respectively). T-stages were more advanced in the TUM cohort ($P < 0.0001$), whereas lymph node metastases were diagnosed more frequently in Koreans ($P < 0.0001$). The extent of lymph node dissection was significantly different: Almost all the Korean patients received a D2 dissection whereas in contrast D1 + dissection was performed more frequently in the German cohort ($P < 0.0001$). Therefore, the amount of patients with <15 retrieved lymph nodes is significantly higher compared to the Korean-Multicenter cohort ($P < 0.0001$). No patient in the German group received adjuvant chemotherapy. There was no missing data for all variables of interest which were described above.

Median overall follow-up was 64.7 months (1–218), 74 (8–214 months) for survivors and 25.9 (1–218) months for deceased patients in the German cohort. Median follow-up was significantly longer compared to the Korean cohort (52 [1–105] months overall, 57 [1–105] months for survivors, 18 [1–100] months for nonsurvivors, $P < 0.0001$). During the follow-up period 398 patients (43.8%) died (351/1579 [23.4%] in the Korean cohort, $P < 0.0001$).

In the univariate model age (older than 70 years), tumor size (above 5 cm), location in the upper third and tumor-involvement of the whole stomach, undifferentiated histology, LVI, pT-, pN-stage, and D1+ dissection were significantly related to survival. Multivariate regression analysis revealed age (older than 70 years), tumor extension to the complete stomach, presence of LVI, pT- and pN-stage to be significantly related to overall survival. The prognostic factors were almost comparable in the Korean cohort. In Korean patients tumor size >10 cm was related to worse overall survival exclusively and pN1-stage was not predictive for OS in contrast to the TUM cohort. Results from multivariate regression analysis are depicted in Table 2.

The validation of the Korean nomogram in the TUM cohort was performed by evaluating the performance of the model with respect to its discrimination and calibration abilities. The C-index was 0.761 (95% CI, 0.735–0.787). The H-L chi-square statistic was 2.16, and the calibration plot (predicted and actual events [deaths]) according to the respective quintiles is presented in Figure 2 ($P = 0.989$). Only slight over- and underestimations of event probabilities were noted (Figure 2). The ratios between expected and observed risks for each quintile range from 84% to 107% of the predicted value. Figure 3 shows the Kaplan–Meier estimates according to their respective quintiles ($P < 0.0001$). An even distribution of the survival curves can be noted. Each stage was significantly different from each other (Group 1 vs Group 2: $P < 0.0001$; Group 2 vs Group 3: $P = 0.0018$; Group 3 vs Group 4: $P = 0.015$; Group 4 vs Group 5: $P < 0.0001$).

DISCUSSION

Despite decreasing incidence gastric cancer remains 1 of the most common malignancies worldwide with a special focus on eastern Asia (Korea, Japan, and China).[14,15] Therefore, uniform staging methods are of utmost importance to compare treatment outcomes and treatment results from randomized controlled trials between different parts of the world. The most commonly used staging system is the TNM system proposed by the UICC/AJCC.[16] However, several authors demonstrated before that survival probabilities may vary within the respective UICC/AJCC stages and that survival predictability has not necessarily improved after revision of the sixth edition.[4] Furthermore predictive factors such as tumor location, tumor size, extent of lymph node dissection, and presence of LVI are not covered by classical TNM staging. Therefore, more uniform staging methods are required omitting those possible drawbacks.

A conceivable option to resolve this issue is the development of nomograms. The best known nomogram was developed at the Memorial Sloan Kettering Cancer Center in the United States[5] and validated in cohorts across the world with different outcomes.[6–8] Validation studies in Germany[6] and the Netherlands[7] revealed its applicability in the Western hemisphere whereas the MSKCC-nomogram failed to adequately predict survival in Korean patients.[8] That is why several nomograms have been developed by Korean institutions.[9–11] The SNUH-nomogram was externally validated not only in Korea itself but also in Japan,[9] whereas the Seoul-St Mary's nomogram was only validated internally.[10] However, those nomograms were criticized to be exclusively based on specialized institutional data.[11] They only incorporated patients having undergone open surgery and D2-lymphadenctomy by very specialized surgeons with high caseload. The nomograms were criticized not to be

TABLE 1. Demographic and Clinicopathological Characteristics of the KNDS and TUM Cohorts

		KNDS (n = 1579)	TUM (n = 908)	
Factors	**Subgroup**	**No. of Patients (%)**	**No. of Patients (%)**	***P***
Age, y	<40	115 (7.3)	31 (3.4)	<0.0001
	40–49	257 (16.3)	94 (10.4)	
	50–59	382 (24.2)	191 (21.0)	
	60–69	547 (34.6)	275 (30.3)	
	≥70	278 (17.6)	317 (34.9)	
Sex	Male	1079 (68.3)	528 (58.1)	<0.0001
	Female	500 (31.7)	380 (41.9)	
Tumor size, cm	<5.0	854 (54.1)	552 (60.8)	<0.0001
	5.0–9.9	582 (36.9)	317 (34.9)	
	≥10.0	143 (9.1)	39 (4.3)	
Location	Upper	256 (16.2)	257 (28.3)	<0.0001
	Middle	512 (32.4)	274 (30.2)	
	Lower	771 (48.8)	366 (40.3)	
	Whole	40 (2.5)	11 (1.2)	
Histological type*	Differentiated	625 (39.6)	290 (31.9)	<0.0001
	Undifferentiated	954 (60.4)	618 (68.1)	
LVI	Absent	812 (51.4)	736 (81.1)	<0.0001
	Present	769 (48.6)	172 (18.9)	
pT†	pT1	593 (37.6)	374 (41.2)	<0.0001
	pT2	597 (37.8)	124 (13.7)	
	pT3	346 (21.9)	230 (25.3)	
	pT4	43 (2.7)	180 (19.8)	
pN†	pN0	797 (50.5)	543 (59.8)	<0.0001
	pN1	129 (8.2)	219 (24.1)	
	pN2	84 (5.3)	94 (10.4)	
	pN3	569 (36.0)	52 (5.7)	
UICC†	I	786 (49.7)	435 (47.9)	0.427
	II	369 (23.4))	233 (25.7)	
	III	424 (26.9)	240 (26.4)	
	IV	0 (0.0)	0 (0.0)	
Extent of LND	D1 plus	123 (7.8)	301 (33.1)	<0.0001
	D2	1456 (92.2)	607 (66.9)	
No. of harvest LN	<15	39 (2.5)	56 (6.2)	<0.0001
	15–29	406 (25.7)	363 (40.0)	
	30–44	615 (39.0)	313 (34.5)	
	≥45	519 (32.9)	176 (19.4)	
Adjuvant CTx	No	966 (61.2)	908 (100.0)	<0.0001
	Yes	613 (38.8)	0 (0.0)	

CTx = Chemotherapy, KNDS = Multicenter Korean Nomogramm Development Set, LN = Lymph Nodes, LND = lymph node dissection, LVI = lymphatic vessel infiltration, TUM = validation cohort of the Surgical Department of the Technische Universitaet Muenchen, Germany, UICC = Union Internationale Contre le Cancer.

* Differentiated = papillary type, G1/G2 tubular type; Undifferentiated = G3/G tubular, mucinous and signet ring cell type.

† According to AJCC/UICC 7th ed.

applicable to stage adopted lymph node dissection (D1 + β) in early gastric cancer patients concluding that ''previous nomograms are not suited for more than half of the gastric cancer patients in Korea.''[11] Due to that criticism the Korean multicenter data incorporated data from 8 different institutions with different case load and also reduced lymphadenectomy cases (D1 + β gastrectomy due to EGC).[11] The authors concluded that their multicenter-nomogram was suitable for survival prediction in specialized and local hospitals in Korea. Similar to the developers of the SNUH-nomogram the authors concluded that despite successful external validation within Korea and Japan, a confirmation of the results in a Western patient cohort was required in order to obtain general applicability.

Comparison between the Korean and the German group revealed marked differences in baseline characteristics except for the distribution of UICC stages. This is in concordance with previously published data comparing Eastern Asian and Western cohorts.[8,17,18] It is well known that Korean patients are significantly younger at the time of diagnosis and treatment compared to Western patients.[2] The amount of patients older than 70 years was twice as high in the German cohort. Additionally a preponderance of proximal tumor locations was noted and is congruent with other studies.[8,17,18] Tumor stages were more advanced in the Western cohort. Almost half of the German patients presented with pT3/pT4 tumors. These facts may basically be related to and explained by the existence of a

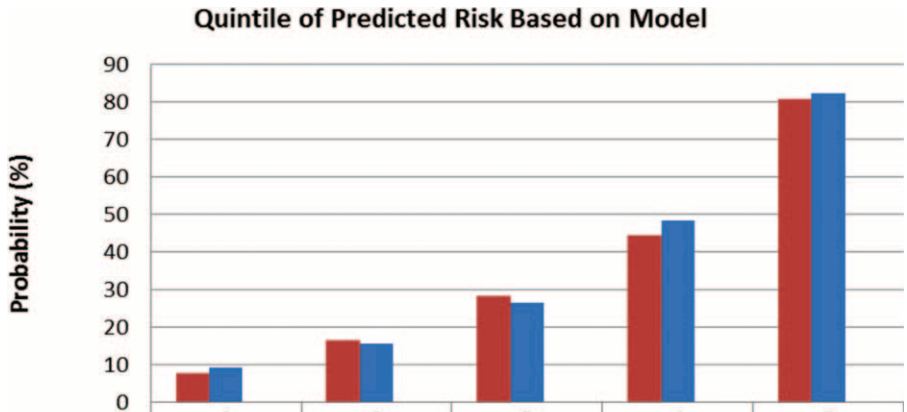
TABLE 2. Risk Factors for Overall Survival Comparing Korean and German Patients (Cox Proportional Hazards Regression Model)

		KNDS						TUM					
		Univariate			Multivariate			Univariate			Multivariate		
		HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Age, y	<40	1			1			1			1		
	40–49	1.09	0.67–1.78	0.720	1.09	0.67–1.78	0.729	0.62	0.29–1.32	0.214	0.83	0.39–1.78	0.62
	50–59	0.70	0.43–1.14	0.153	0.68	0.42–1.11	0.122	0.94	0.48–1.83	0.850	1.13	0.57–2.23	0.72
	60–69	1.19	0.77–1.86	0.436	1.24	0.79–1.94	0.357	1.44	0.76–2.74	0.269	1.80	0.94–3.46	0.08
	≥70	1.88	1.19–2.97	0.007	1.63	1.02–2.59	0.040	2.24	1.19–2.24	0.013	2.87	1.51–5.47	0.001
Sex	Male	1						1					
	Female	0.96	0.76–1.20	0.712				0.86	0.73–1.05	0.143			
Tumor	<5.0	1			1			1					0.78
Size, cm	5.0–9.9	2.80	2.20–3.56	<0.001	1.16	0.89–1.53	0.275	2.33	1.90–2.86	<0.0001			0.97
	≥10.0	5.43	4.01–7.36	<0.001	1.58	1.11–2.24	0.011	4.7	3.22–6.87	<0.0001			0.51
Location	Lower	1			1			1			1		
	Upper	0.89	0.65–1.22	0.470	0.74	0.53–1.01	0.059	2.02	1.56–2.56	<0.0001	1.24	0.97–1.59	0.092
	Middle	0.91	0.71–1.16	0.439	0.81	0.63–1.04	0.101	1.19	0.92–1.55	0.182	0.95	0.73–1.24	0.72
	Whole	4.12	2.70–6.27	<0.001	1.57	0.97–2.53	0.067	3.59	1.83–7.07	<0.0001	2.08	1.04–4.17	0.038
Histological type	Differentiated	1						1					
	Undifferentiated	1.59	1.27–2.00	<0.001				1.330	1.07–1.65	0.011			0.91
LVI	Absent	1			1			1			1		
	Present	4.89	3.78–6.34	<0.001	1.58	1.17–2.14	0.003	2.83	2.28–3.51	<0.0001	1.45	1.13–1.85	0.003
pT	1	1			1			1			1		
	2	4.15	2.85–6.03	<0.001	1.79	1.16–2.76	0.009	2.29	1.61–3.27	<0.0001	1.71	1.18–2.46	0.004
	3	11.24	7.80–16.20	<0.001	3.11	1.97–4.92	<0.001	3.30	2.48–4.39	<0.0001	1.85	1.33–2.57	<0.001
	4	13.89	8.26–23.37	<0.001	3.73	2.11–6.96	<0.001	7.45	5.63–9.85	<0.0001	3.64	2.61–5.07	<0.001
pN	0	1			1			1			1		
	1	2.41	1.43–4.07	0.001	1.45	0.84–2.50	0.183	2.33	1.83–2.95	<0.0001	1.55	1.18–2.04	0.002
	2	4.06	2.47–6.67	<0.001	1.98	1.16–3.38	0.012	4.44	3.34–5.91	<0.0001	2.31	1.64–3.25	<0.001
	3	8.87	6.61–11.90	<0.001	3.40	2.34–4.94	<0.001	8.22	5.92–11.42	<0.0001	4.61	3.17–6.70	<0.001
Extent of LND	D2	1						1					
	D1 plus	1.44	1.02–2.04	0.038			0.071	0.76	0.61–0.944	0.013			0.34
No. of harvested LNs	<15	1						1					
	15–29	1.41	0.57–3.49	0.456				0.78	0.51–1.17	0.226			
	30–44	1.92	0.79–4.69	0.151				0.87	0.57–1.31	0.491			
	≥45	2.13	0.87–5.21	0.098				1.15	0.75–1.76	0.524			
Chemotherapy	No	1						n.a.					
	Yes	3.42	2.74–4.26	<0.001				n.a.					

CI = confidence interval, HR = hazards ratio, KNDS = Multicenter Korean Nomogramm Development Set, LND = lymph node dissection, LVI = lymphatic vessel infiltration, n.a. = not available, TUM = validation cohort of the Surgical Department of the Technische Universitaet Muenchen, German.

national screening program in Korea,[19] which is accessible from the age of 40 and inexistent in Germany, where EGD is only performed in case of symptoms or positive family history.[20] However, distribution of the AJCC/UICC stages was not different between the 2 groups. Nonsurprisingly the amount of patients having undergone D2-dissection is significantly higher in the Korean cohort and represented by the significantly higher number of harvested lymph nodes. D2-dissection has only been implemented in Europe as a standard of care since publication of the long-term results of the Dutch trial.[21] Nonetheless the authors of the nomogram emphasized the applicability of the nomogram also for patients not having undergone D2-dissection due to more limited disease stages. Interestingly the type of lymph-node dissection did not have any significant correlation to overall survival in both of the analyzed cohorts. Analysis of prognostic factors revealed the same predictors of overall survival as in the Korean cohort with the following exceptions: Tumor size >10 cm was not related to OS in the German cohort. Tumor involvement of the whole stomach was exclusively related to OS in the TUM patients which, however, implies a tumor size >10 cm. Interestingly, limited metastasis to 1 or 2 lymph nodes was an independent predictor of OS only in the German patient cohort. This may be explained by a more aggressive tumor phenotype which may be represented by more advanced pT-stages. All other survival predictors were comparable.

Finally, comparative analysis of the predictive abilities of the Korean nomogram in the German patient cohort demonstrated its validity. C-statistics were used as goodness-of-fit measure to discriminate expected and actual events.[13] C-values of 0.7 to 0.8 generally indicate moderately good discrimination and excellent discriminative ability is indicated by values over 0.8. The c-index of 0.76 may be interpreted as an acceptable value for predictability of the nomogram in Western patients. The c-index in the Korean cross-validation was 0.83. The nomogram is considered to be more accurate the higher the value of the c-index is. The lower value in the German cohort thus means a decreased predictability compared to the Korean



	1	2	3	4	5
Observed	7.778	16.609	28.278	44.505	80.851
Predicted	9.24	15.758	26.506	48.485	82.208
Ratio(O/E)	84.178	105.402	106.685	91.791	98.349

FIGURE 2. Calibration plot of predicted and actual events (deaths) according to the quintiles in the Hosmer–Lemeshow statistic. X-axis represents the quintiles, Y-axis the event probability. H-L type $\chi^2 = 2.162$ ($P = 0.989$). C-index = 0.761 (95% CI 0.735–0.787). The observed and expected event probabilities and their respective ratios (O/E) are depicted according to the respective quintiles in the German validation cohort. CI = confidence interval.

validation set. This may be represented by ethnic and biologic differences, which are not considered in the statistical model. However, goodness-of-fit analysis by H-L chi-square statistic revealed no statistical difference in the German validation. This result indicates that the predictive ability of the nomogram does not significantly differ from the observed OS. Further, stage distribution according to the predicted quintiles revealed a homogenous distribution of the survival curves with statistically significant differences over all stages. This staging system might be an additional tool to the conventional TNM-staging for survival prediction. Therefore, we conclude that this Korean nomogram may be applicable in Western patients. This stands in marked contrast to the popular MSKCC-nomogram, which failed to predict survival in comparison between Korean and US patients.[8] Reasons for this may be that the MSKCC-nomogram incorporated slightly different parameters like Lauren histotype and a differentiation between positive and negative lymph nodes. Not only the Lauren histotype but also stage distribution was significantly different between Korean and US patients.[8] Further the amount of patients with a number of <15 retrieved lymph nodes was 22% in the MSKCC cohort compared with 6% in this analysis.

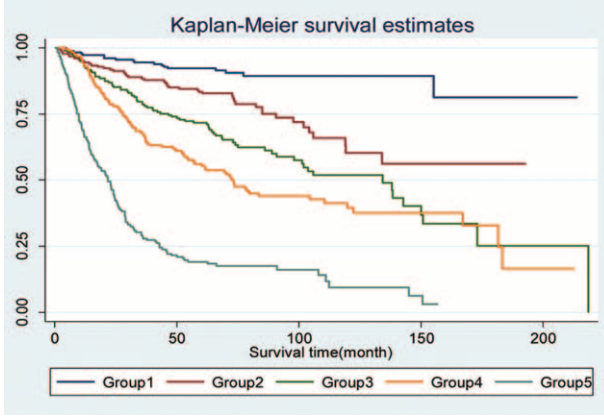


FIGURE 3. Kaplan–Meier survival plots according to the respective quintiles in the German validation cohort ($P < 0.0001$). Group 1 vs Group 2: $P < 0.0001$; Group 2 vs Group 3: $P = 0.0018$; Group 3 vs Group 4: $P = 0.015$; Group 4 vs Group 5: $P < 0.0001$.

The results of this analysis are comparable to the results of the SNUH nomogram.[9] However, the construction- and validation-datasets are based on a single-center cohort with patients having undergone D2-dissection only. This does not reflect surgical reality in these days as more stage-adopted resection is performed in Korea (ie, D1 + β dissection for early gastric cancer).[22] Finally the SNUH-nomogram was only validated in a specialized Japanese single-center cohort.[9] Despite its similarities with the SNUH-nomogram this multicenter nomogram is not only applicable in specialized Korean centers but also in general hospitals and maybe in Western (European) collectives. The predictability of the Korean multicenter-nomogram in the TUM cohort also reflects the necessity to treat patients in specialized institutions, especially in Western countries. This again stirs up the debate if centralization to specialized hospitals for specific types of cancers improves oncologic outcomes. From the authors point of view the answer must be yes.

This analysis certainly has several limitations due to its retrospective character. Biological and ethnical factors are possible confounders which could not be addressed. Further, patients having undergone neoadjuvant/perioperative chemotherapy were excluded from this analysis which may have led to a selection bias. The reason for excluding these patients was that neoadjuvant regimens in the reported period (1982–2008) were not standardized and applied on an irregular basis. The regimens applied here were very heterogenous. Further ''neoadjuvant'' chemotherapy at that time was applied to technically irresectable patients who would not have met the inclusion criteria for this analysis. Since neoadjuvant chemotherapy has become a standard of treatment in Europe[23]

these results will have to be reanalyzed in the future. Further the general applicability of the nomogram in German community hospitals may not be guaranteed due to the specialization of the TUM in gastric cancer treatment and a centralization effect.

Conclusively this validation analysis of a Korean multicenter nomogram for survival-prediction after curative gastric cancer surgery demonstrated its applicability in a specialized Western treatment center for gastric cancer. Further study is needed to obtain data on generalized applicability in Western gastric cancer patients.

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