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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

A Nomogram to Predict Overall Survival and Disease-Free Survival After Curative Resection of Gastric Adenocarcinoma

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ABSTRACT

Background. The American Cancer Society projects there will be over 22,000 new cases, resulting in nearly 11,000 deaths, related to gastric adenocarcinoma in the US in 2014. The aim of the current study was to find clinicopathologic variables associated with disease-free survival (DFS) and overall survival (OS) following curative resection of gastric adenocarcinoma, and create a nomogram for individual risk prediction.

Methods. A nomogram to predict DFS and OS following surgical resection of gastric adenocarcinoma was constructed using a multi-institutional cohort of patients who underwent surgery for primary gastric adenocarcinoma at seven major institutions in the US between January 2000 and August 2013. Discrimination and calibration of the nomogram were tested by C-statistic, Kaplan–Meier curves, and calibration plots.

Results. A total of 719 patients who underwent surgery for primary gastric adenocarcinoma were included in the study. Using the backward selection of clinically relevant variables with Akaike information criteria, age, sex, tumor site, depth of invasion, and lymph node ratio (LNR) were selected as factors predictive of OS, while age, tumor site, depth of invasion, and LNR were incorporated in the prediction of DFS. A nomogram was constructed to predict OS and DFS using these variables. Discrimination and calibration of the nomogram revealed good predictive abilities (C-index, DFS 0.711; OS 0.702).

Conclusion. Independent predictors of recurrence and death following surgery for primary gastric adenocarcinoma were used to create a nomogram to predict DFS and OS. The nomogram was able to stratify patients into prognostic groups, and performed well on internal validation.

Although there has been a steady decline in the mortality rate associated with gastric cancer over the past 30 years, it still remains the second most common cause of cancer-related deaths worldwide.[1–3] In the US, the American Cancer Society estimates that there will be over 22,000 new gastric cancer cases, resulting in nearly 11,000 deaths, in 2014.[3] Surgical resection remains the best hope for long-term survival.[4] Unfortunately, recurrence of the disease occurs in approximately 20–50 % of all patients following gastric resection.[5–9] In turn, 5-year overall survival (OS) estimates for patients with gastric cancer range from 5 to 90 %, depending on the stage of disease at

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presentation.[10–17] While several clinicopathological features have been associated with the risk of tumor recurrence and long-term survival, accurate stratification of patient prognosis remains a challenge.

Reliable estimation of the risk of recurrence and death following surgical resection of gastric adenocarcinoma is important to both patients and physicians. Such information may inform decisions regarding perioperative adjuvant therapy and frequency of surveillance, as well provide patients with desired information about their long-term prognosis. Currently, the American Joint Committee on Cancer (AJCC) classification schema is used to stage patients with gastric cancer based on the depth of tumor invasion, number of metastatic lymph nodes, and distant metastasis.[18] Although the AJCC classification is helpful for the general prediction of survival, its use may be limited in the clinical setting. Specifically, the application of cancer staging systems that are derived from and designed to stratify populations of patients may not be as applicable to determining the prognosis of an individual patient.[19–24] Rather, a number of studies have suggested that nomograms may be a useful tool to predict long-term prognosis using a simple graphical representation.[25] While the Memorial Sloan Kettering Cancer Center (MSKCC) has proposed a nomogram for gastric adenocarcinoma,[26] it has not been validated in a large independent cohort of patients from the US. The MSKCC nomogram was also based on only a single institutional experience and included patients from the 1980s. In addition, the MSKCC nomogram only assessed whether lymph nodes were 'negative' or 'positive'. However, more current data suggest that lymph node ratio (LNR), as well as the total number of lymph nodes examined (TNLE) may be important prognostic factors in gastric cancer.[27] Therefore, the aim of the current study was to create a novel nomogram to predict OS and disease-free survival (DFS) following surgical resection of gastric adenocarcinoma in a large, contemporary, multi-institutional cohort of patients. In addition, we sought to internally validate the current nomogram, as well as assess its prognostic performance relative to the previously proposed MSKCC nomogram.

METHODS

Patient Population and Data Collection

Using a multi-institutional database, 965 patients who underwent gastric resection between 2000 and 2013 at one of the seven major institutions participating in the US Gastric Cancer Collaborative were identified (Johns Hopkins Hospital, Baltimore, MD; Emory University, Atlanta GA; Stanford University, Stanford, CA; Washington University, St. Louis, MO; Wake Forest University, Winston-Salem, NC; University of Wisconsin, Madison, WI; The Ohio State University, Columbus, OH). Only patients who had a primary diagnosis of gastric adenocarcinoma and who underwent curative-intent surgery were included. Patients who died within 90 days of surgery, those patients with residual disease (either microscopically [R1] or macroscopically positive [R2]) and/or patients with AJCC stage IV gastric adenocarcinoma were excluded, leaving 719 patients in the study cohort. The Institutional Review Board at each participating institution approved this study.

Standard demographic and clinicopathologic data were collected, including age, sex, family history of gastric adenocarcinoma, body mass index (BMI), tumor size, tumor location, histological type and grade of tumor, depth of invasion, number of lymph nodes harvested, number of metastatic lymph nodes identified, presence of lymphovascular invasion (LVI) or perineural invasion (PNI), and final AJCC pathological stage of disease.[18] Treatment and operative details included extent of resection (partial vs. total gastrectomy) and lymphadenectomy (D1 vs. D2), as well as information on chemotherapy and radiotherapy. The primary outcome of interest was long-term DFS and OS. Date of last follow-up or death, recurrence-related information, and vital status were also collected.

Statistical Methods

Summary statistics for the study population were presented as percentages or as median values with interquartile range (IQR). DFS and OS for the entire study population were generated using the Kaplan–Meier method, and differences in DFS and OS were examined using the log-rank test. Clinically important variables associated with OS and recurrence risk were evaluated for inclusion into the nomogram. Continuous predictors such as age and tumor size were incorporated using restricted cubic splines to maximize the Wald χ^2 statistic. LNR, defined as the number of metastatic lymph nodes divided by the total number of nodes examined, was included in the model to maximize performance of the nomogram. The association of relevant clinicopathologic variables with DFS and OS were assessed using Cox proportional hazards models; backward stepwise selection with the Akaike information criterion (AIC) was used to identify variables for the multivariable Cox proportional hazards model. Selected variables were then incorporated into the nomogram. Model performance was evaluated by assessing discrimination with Harrell's C-index,[28] calibration plots using a bootstrapped sample, and plotting Kaplan–Meier curves over the quartiles of prediction by nomogram. The model was validated using bootstrapped resampling to quantify any overfitting. For determining disease-specific survival (DSS) based on the MSKCC nomogram, the predicted probability of death at

TABLE 1 Variables associated with overall survival according to the Cox proportional hazards regression model

Variable	Univariable analysis			Multivariable analysis		
Prognostic factor	HR	95 % CI	*p* value	HR	95 % CI	*p* value
Factors selected						
Age	1.01	1.00–1.02	0.02	1.39	1.01–1.91	<0.001
Male	1.01	0.80–1.27	0.94	1.07	0.84–1.36	0.56
Site						
Antrum/pyloric	Ref	–	–	Ref	–	–
Proximal/upper third	1.00	0.72–1.38	0.99	1.03	0.74–1.43	0.87
Body/middle third	1.02	0.78–1.33	0.89	1.12	0.85–1.48	0.43
GEJ	1.66	1.07–2.56	0.02	2.13	1.36–3.36	0.001
Lymph node ratio	6.16	4.29–8.85	<0.001	3.91	2.59–5.90	<0.001
Depth of Invasion						
T1	Ref	–	–	Ref	–	–
T2	1.80	1.16–2.79	0.009	1.53	0.97–2.42	0.35
T3	2.70	1.89–3.84	<0.001	2.06	1.41–3.01	<0.001
T4	4.19	2.91–6.02	<0.001	2.49	1.59–3.90	<0.001
Factors not selected						
Tumor size	1.08	1.05–1.11	<0.001			
Lauren						
Mixed type	Ref	–	–			
Intestinal type	1.26	0.51–3.07	0.62			
Diffuse type	1.57	0.63–3.93	0.33			
Family history of gastric cancer	0.95	0.62–1.45	0.80			
BMI	0.99	0.96–1.01	0.24			
Moderate to poor grade	1.15	0.90–1.47	0.26			
D2 lymphadenectomy	0.83	0.65–1.05	0.12			
LVI	2.20	1.72–2.81	<0.001			
PNI	2.01	1.54–2.62	<0.001			

HR hazard ratio, *CI* confidence interval, *GEJ* gastroesophageal junction, *BMI* body mass index, *LVI* lymphovascular invasion, *PNI* perineural invasion

5 years was calculated using the nomogram (http://nomograms.mskcc.org/Gastric/ROResection.aspx) for each patient.

Statistical analyses were performed with STATA version 12.0 (StataCorp, College Station, TX, USA), and R version 3.0.3 (http://www.r-project.org). All tests were two-sided and a p value < 0.05 was considered statistically significant.

RESULTS

Demographic and Clinicopathologic Characteristics

Median patient age was 66 years (IQR 56–74) and 58 % (n = 415) of patients were male (electronic supplementary Table 1). Most tumors were located in the antrum (n = 267, 37.9 %) or body (n = 256, 36.4 %), while fewer were at the gastroesophageal junction (n = 47, 6.7 %). Median BMI was 25.2 kg/m^2 (IQR 22.1–28.9). Prior to surgery, a subset of patients underwent neoadjuvant chemotherapy (n = 140, 19.5 %), while over one-half of patients (n = 367, 54.9 %) underwent adjuvant chemotherapy following resection, and one-third of patients (32.5 %) received adjuvant chemoradiotherapy. At the time of surgery, the majority of patients underwent a partial gastrectomy (n = 430, 60.1 %), with the remaining 39.9 % (n = 285) undergoing a total gastrectomy. The extent of lymphadenectomy was D1 in 244 (35.7 %) patients and D2 in 440 (64.3 %) patients.

On pathology, median tumor size was 4.0 cm (IQR 2.2–6.5). The majority of patients had moderately to poorly differentiated tumors (n = 462, 66.7 %), while the remaining patients had moderately or well-differentiated tumors (n = 231, 33.3 %). The incidence of LVI and PNI were 42.1 % (n = 270) and 28.4 % (n = 150), respectively. With regard to tumor type, 28 % (n = 136) of patients had a diffuse-type tumor, while the remaining tumors were either intestinal (n = 332, 68.3 %) or mixed

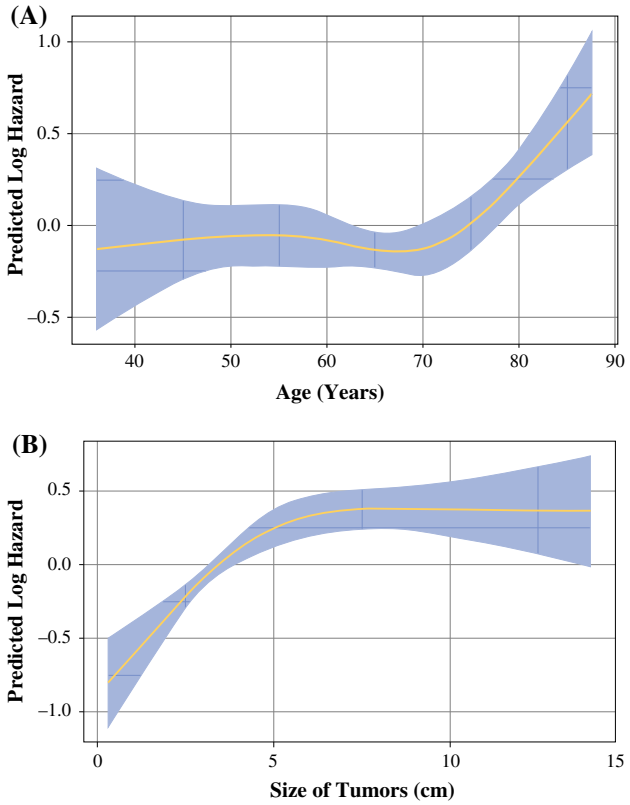


FIG. 1 Transformation of continuous variables in univariate analysis using restricted cubic splines relating to **a** age and **b** tumor size

type (n = 18, 3.7 %). Most tumors were locally advanced and penetrated the subserosal (T3 tumors: n = 235, 33.1 %) or serosal (T4 tumors: n = 186, 26.2 %) layer. Lymph node metastasis was common (n = 413, 58.7 %); the median of the TNLE was 17 (IQR 11–25). Based on the 7th edition AJCC staging system, patients with stage III disease were the most common (n = 294, 41.3 %); approximately one-third of patients had either stage I (n = 228, 32.0 %) or stage II (n = 190, 26.7 %) disease.

The median follow-up for our cohort was 18.3 months. During follow-up, 213 (29.6 %) patients recurred and 299 (41.6 %) patients died. Median DFS was 35.6 months (95 % CI 27.9–39.9) and median OS was 44.5 months (95 % CI 37.4–53.9). The 1-, 3- and 5-year DFS was 73.7, 48.9, and 38.2 %, while OS was 81.4, 54.6, and 42.6 %, respectively.

Model Specifications and Predictors of Overall and Disease-Free Survival

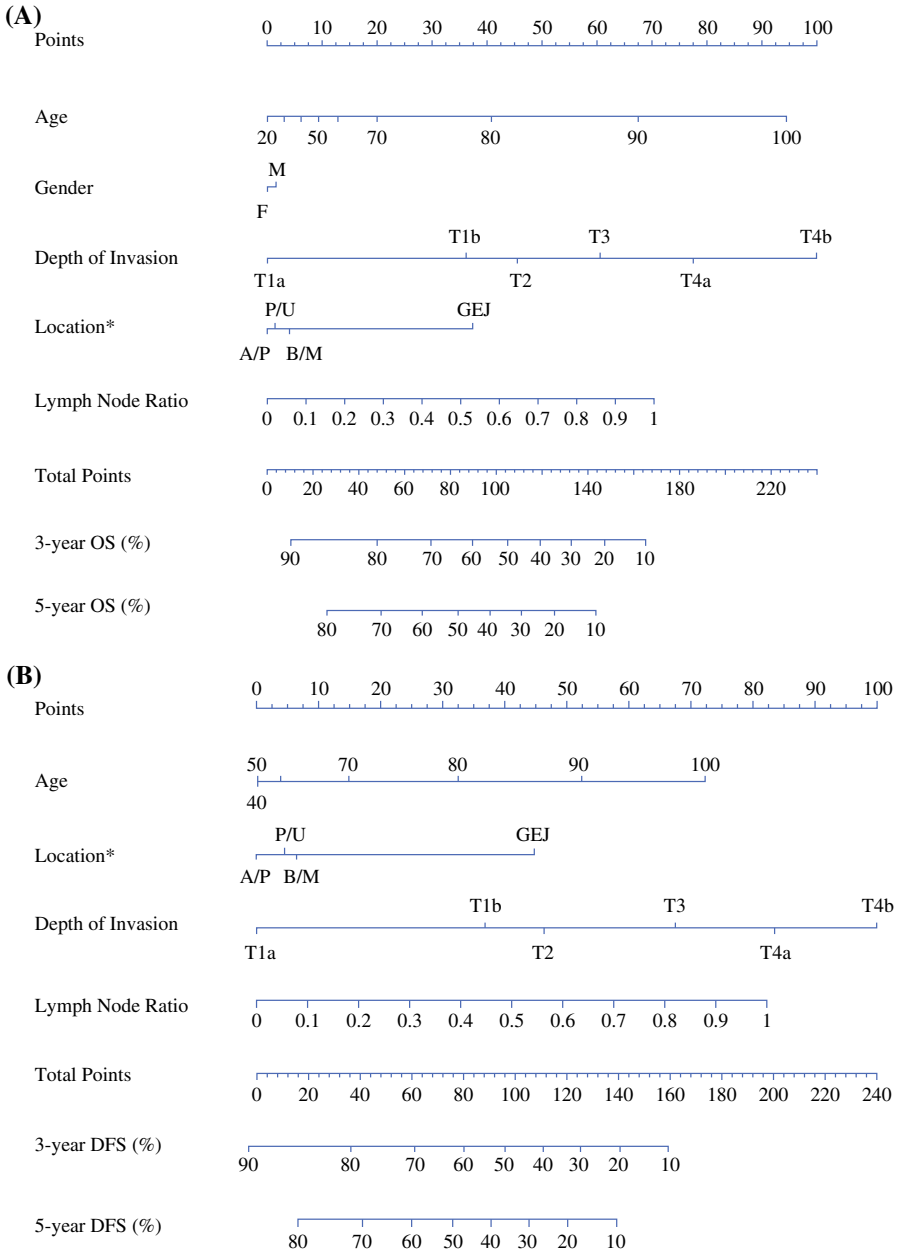
Standard demographic and tumor characteristic variables associated with recurrence and survival for gastric adenocarcinoma were selected for analysis.[26,29–31] Backward stepwise selection using the AIC in Cox proportional hazards regression modeling identified five variables that had the strongest association with outcome—age, sex, tumor site, depth of invasion, and LNR. The hazard ratios (HRs) for the univariable and multivariable Cox proportional hazards regression analysis for candidate and selected variables are shown in Table 1. On multivariable analysis, age (HR 1.39, 95 % CI 1.01–1.91), tumor site (reference: antrum, gastroesophageal junction HR 2.13, 95 % CI 1.36–3.36), depth of invasion (reference: T1, T3 HR 2.06, 95 % CI 1.41–3.01; T4 HR 2.49, 95 % CI 1.59–3.90) and LNR (HR 3.91, 95 % CI 2.59–3.90) were each independently associated with OS (all $p < 0.05$). The HRs for the univariable and multivariable Cox proportional hazards regression analysis associated with DFS revealed similar results as those for OS (electronic supplementary Table 2). Backward stepwise selection using the AIC in Cox proportional hazards regression modeling identified four variables associated with DFS.

Continuous variables (age, tumor size, and LNR) were explored using restricted cubic splines, piecewise linear model, and categorization. Both age and tumor size had non-linear effects on the HR of OS. Sensitivity analyses revealed a maximization of Wald χ^2 with four knots for tumor size ($\chi^2 = 34.23$) and age ($\chi^2 = 18.11$). The log-relative hazards of death were relatively homogenous below approximately 70 years of age and above approximately 6 cm for tumor size and (Fig. 1). LNR showed a linear effect on HR for OS.

Nomogram

A nomogram to predict OS of patients with gastric adenocarcinoma following surgical resection is shown in Fig. 2. The nomogram was developed based on the five independent prognostic markers—age, sex, tumor site, depth of invasion, and LNR. Each factor in the nomogram was assigned a weighted number of points, and the sum of points for each patient was associated with a specific predicted 3- and 5-year OS. Using the nomogram, a higher score was associated with worse prognosis. For example, a 70-year-old man with T2-stage gastric adenocarcinoma of the gastroesophageal junction with an LNR of 0.3 would have a total of 127 points (age = 20 points, male = 2 points, location = 40 points, depth of invasion = 45 points, and LNR = 20 points). For this patient, the predicted 3-year OS was 30 %, and the predicted 5-year OS was 17 %.

Discrimination ability was assessed by dividing the predicted probability of DFS and OS into quartiles. DFS and OS stratified by quartile were then used to plot Kaplan–Meier curves (Fig. 3). Patients with the lowest predicted 5-year DFS (Quartile 4) did substantially worse (5-year DFS = 7.2 %) than those patients in quartiles 1–3 (5-year DFS = 66.6, 44.8, and 30.6 % respectively) [$p < 0.001$]. Median 5-year DFS predicted by the



*Location: A/P, Antrum/Pylorus; P/U, Proximal/Upper 1/3; B/M, Body/Mid 1/3; GEJ, Gastroesophageal Junction

FIG. 2 Nomogram for predicting **a** overall survival and **b** disease-free survival of patients following resection of primary gastric adenocarcinoma. *M* male, *F* female, *GEJ* gastroesophageal junction, *A/P* antrum/pylorus, *P/U* proximal/upper third, *B/M* body/mid third, *OS* overall survival, *DFS* disease-free survival

nomogram was 6.4 % (95 % CI 2.7–12.1) in quartile 4, and 67.3 % (95 % CI 62.2–75.9), 46.9 % (95 % CI 42.0–51.2), and 27.2 % (95 % CI 21.6–32.5) in quartiles 1, 2, and 3, respectively. Similarly, patients with the lowest predicted 5-year OS (Quartile 4) did substantially worse (5-year OS 12.0 %) than those in quartiles 1–3 (5-year OS 68.2, 50.4, and 32.8 %, respectively) [$p < 0.001$]. Compared with actual survival based on Kaplan–Meier tables, median 5-year OS predicted by the nomogram revealed good estimation: 10.8 % (95 % CI 5.4–16.3) in quartile 4 versus 68.2 % (95 % CI 63.3–76.8), 50.2 % (95 % CI 45.8–55.0, and 32.0 % (95 % CI 26.6–36.9) in quartiles 1, 2 and 3.

Model Performance

Discrimination ability of the final model for OS and DFS was assessed using the C-statistic (C-index: 0.702 and 0.711, respectively) [electronic supplementary Table 3]. The 40-sample bootstrapped calibration plot for the prediction of 5-year OS is shown in Fig. 4. The calibration plots revealed good prediction of 5-year DFS and OS. Bootstrap validation of accuracy of the model with 150 iterations revealed minimal evidence of model overfit. Of note, the relative performance of the nomogram was comparable among patients treated with different perioperative adjuvant therapies (C-statistic: OS, whole cohort

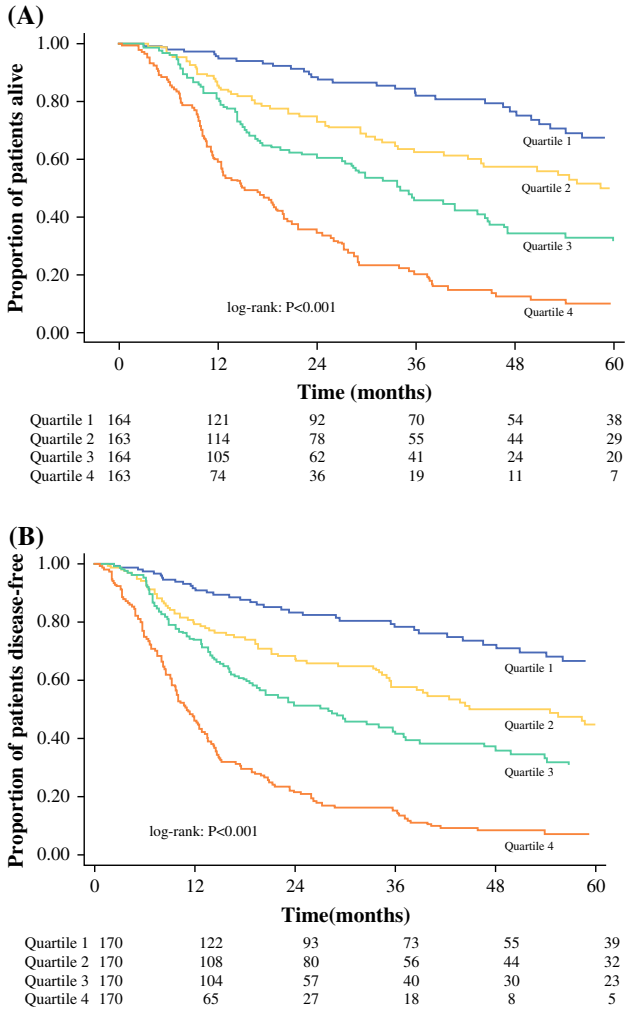


FIG. 3 Kaplan–Meier curves demonstrating **a** overall survival and **b** disease-free survival for patients following resection for primary gastric adenocarcinoma according to quartiles of predicted overall survival or disease-free survival

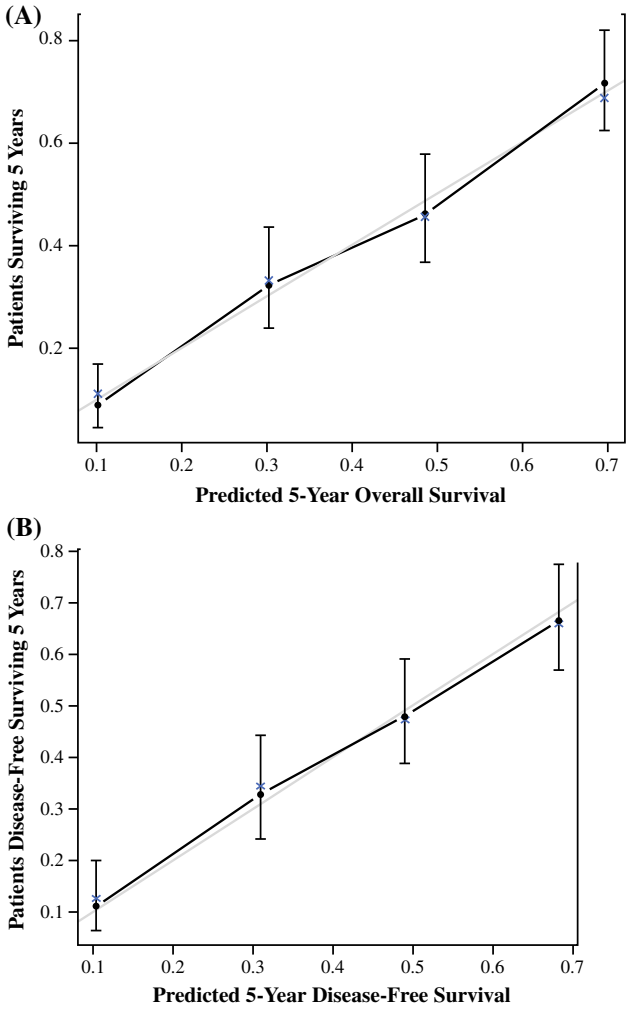


FIG. 4 Calibration plot comparing predicted and actual **a** overall survival and **b** disease-free survival probabilities at 5-year follow-up

0.70, only neoadjuvant cohort 0.71, only adjuvant cohort 0.69; DFS, whole cohort 0.71, only neoadjuvant cohort 0.72, only adjuvant cohort 0.70). The C-statistics for OS based on the AJCC staging system and MSKCC Nomogram were 0.691 and 0.667, respectively. While C-statistics for DFS revealed slightly better prediction based on the current nomogram, as well as the AJCC staging system and MSKCC nomogram (C-index: 0.711, 0.681, and 0.685, respectively).

DISCUSSION

Globally, gastric adenocarcinoma is the second leading cause of cancer-related death worldwide.[1] Complete surgical resection remains the treatment modality of choice for primary gastric adenocarcinoma without metastasis;[4] however, 20–50 % of patients experience recurrence after curative surgery.[7,31] Outcomes following surgery for gastric adenocarcinoma are therefore heterogeneous. Accurate prognostication is essential to select patients for perioperative therapy and to inform patients and family members of their prognosis. In this study, we describe a nomogram that accurately predicts an individual's DFS and OS following R0 resection of a primary gastric adenocarcinoma according to five clinically available variables—age, sex, tumor site, depth of invasion, and lymph node metastasis. The study is notable for having utilized a large, multi-institutional contemporary cohort of patients to derive the nomogram. In turn, the nomogram performed well, with good discriminatory prognostic ability, and therefore may be helpful to individualized treatment decisions and postoperative counseling.

Prognostic nomograms are useful as they are relatively easy to read with a simple graphic, they enable the incorporation/combination of multiple relevant clinical

predictors, and can be applied to individual patients. Nomograms directly quantify individual patient risk based on statistically derived prognostic variables rather than placing patients into prognostic groups. The variables used in our predictive nomogram included age, tumor site, depth of invasion, and lymph node metastasis, which have been associated with long-term survival in other studies.[29,31,32] Interestingly, compared with the MSKCC nomogram, Lauren classification and tumor size were not included in our nomogram according to stepwise selection based on AIC. While the lack of association of Lauren classification and survival may have been related to the relatively high frequency of patients without reported Lauren histology type ($\approx$ 30 %), other investigators have similarly reported a lack of association between Lauren histotype and tumor size with survival on multivariable analysis.[26,33–36] In addition, the current study is the first nomogram to incorporate LNR, which has been noted to be superior in assessing prognosis compared with simple lymph node status alone.[27] In fact, we noted that including the number of non-metastatic/metastatic lymph nodes in conjunction with the number of lymph nodes evaluated (LNR) maximized the Wald χ^2 and showed better performance.

The proposed nomogram demonstrated good discrimination, with a C-statistic of 0.70 for OS. The median predicted 5-year survival by nomogram was similar to actual survival calculated from the Kaplan–Meier test. In comparison, while the discrimination of the AJCC staging system was comparable (C-statistic 0.69), the prognostic power of the MSKCC nomograms was worse (C-statistic 0.67). Although our nomogram requires external validation, the proposed nomogram had very good internal validation on bootstrapping and appears to be superior to the MSKCC nomogram in predicting OS, which may be due to the incorporation of LNR in the prediction model.

The current study had several limitations. Collaborating with multiple institutions limited the ability to easily standardize diagnostic and treatment criteria. Although this is a possible limitation, it is also a strength of our study as it contributes to the generalizability of the data. The overall low incidence of gastroesophageal junction tumors may have been related to reporting bias as the study was based on a multi-institutional 'gastric' database. Some gastroesophageal tumors at the respective institutions may have been characterized as 'esophageal' and may have therefore been underreported. Finally, as noted, while the nomogram was internally validated using bootstrapped calibration and cross-validation, future studies are needed to externally validate the proposed nomogram.

CONCLUSIONS

Five independent prognostic variables, such as age, sex, tumor site, depth of invasion, and LNR, were incorporated into a nomogram to predict outcome. The nomogram was able to stratify patients into prognostic groups, and performed well on internal validation. Future studies are warranted to externally validate the proposed nomogram to establish its value in the prediction of DFS and OS following curative resection for gastric adenocarcinoma.

DISCLOSURE Yuhree Kim, Gaya Spolverato, Aslam Ejaz, Malcolm H. Squires, George Poultsides, Ryan C. Fields, Mark Bloomston, Sharon M. Weber, Konstantinos Votanopoulos, Alexandra W. Acher, Linda X. Jin, BS, William G. Hawkins, Carl Schmidt, David Kooby, David Worhunsky, Neil Saunders, Edward A. Levine, Clifford S. Cho, Shishir K. Maithel, Timothy M. Pawlik have nothing to disclose.

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