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Validation of the Memorial Sloan Kettering Gastric Cancer Post-Resection Survival Nomogram: Does It Stand the Test of Time?

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Abstract

Background: The MSK nomogram combined both gastroesophageal junction (GEJ) and gastric cancer patients and was created in an era from patients who generally did not receive neoadjuvant chemotherapy. We sought to re-evaluate the MSK nomogram in the era of multidisciplinary treatment for GEJ and gastric cancer.

Study design: Using data on patients who underwent R0 resection for GEJ or gastric cancer between 2002 and 2016, the C-index of prediction for disease-specific survival (DSS) was compared between the MSK nomogram and the AJCC 8th edition staging system after segregating patients by tumor location (GEJ or gastric cancer) and neoadjuvant treatment. A new nomogram was created for the group for which both systems poorly predicted prognosis.

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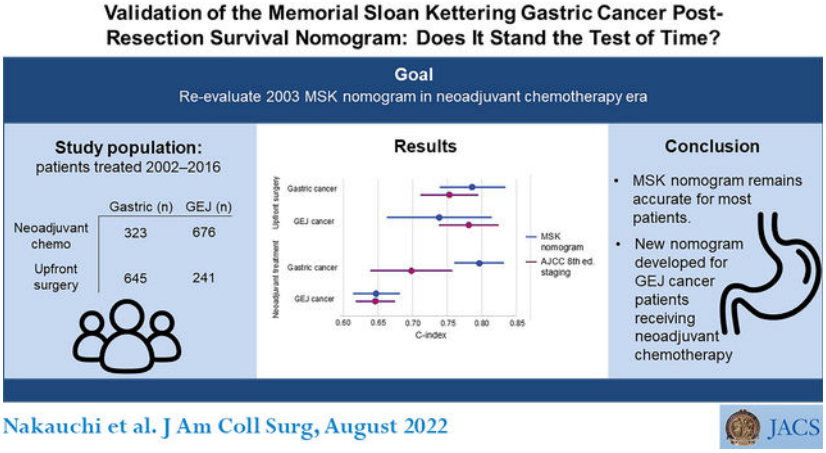
Results: During the study period, 886 patients (645 gastric and 241 GEJ cancer) underwent upfront surgery, and 999 patients (323 gastric and 676 GEJ) received neoadjuvant treatment. Compared with the AJCC staging system, the MSK nomogram demonstrated a comparable C-index in gastric cancer patients undergoing upfront surgery (0.786 vs. 0.753) and a better C-index in gastric cancer patients receiving neoadjuvant treatment (0.796 vs. 0.698). In GEJ cancer patients receiving neoadjuvant chemotherapy, neither the MSK nomogram nor the AJCC staging system performed well (C-indices 0.647 and 0.646). A new GEJ nomogram was created based on multivariable Cox regression analysis and was validated with a C-index of 0.718.

Conclusions: The MSK gastric cancer nomogram's predictive accuracy remains high. We developed a new GEJ nomogram that can effectively predict DSS in patients receiving neoadjuvant treatment.

Graphical Abstract



Précis:

Re-evaluation of the 2003 Memorial Sloan Kettering nomogram revealed continued predictive accuracy for all gastric cancer patients and gastroesophageal junction (GEJ) cancer patients undergoing upfront operation. A new nomogram was created and validated for GEJ cancer patients receiving neoadjuvant chemotherapy.

Keywords

prognostic prediction; preoperative chemotherapy

Introduction

Gastric and GEJ cancers are one of the most common cancer and leading cause of cancer-related deaths in the world (1) and have a heterogenous presentation.(2) Perioperative chemotherapy with or without radiotherapy is now the standard treatment for locally advanced gastric and GEJ cancer based on the results of several phase III trials demonstrating benefit over surgery alone in Western countries.(3–6) Predicting prognosis for patients with cancer takes an important role in treatment planning and patient counseling.

The prognosis of patients with gastric or GEJ cancer is generally estimated according to the American Joint Committee on Cancer (AJCC) staging system,(2, 7) which consists of tumor depth, nodal status, and presence of metastasis. Although survival curves by stage separate well, individual outcomes vary widely, especially among patients with pathological stage II or III disease.(8) To improve the accuracy of prognostic prediction, a nomogram for gastric cancer was first developed by researchers at Memorial Sloan Kettering Cancer Center (MSK) in 2003, based on data from 1173 patients who underwent curative resection between 1985 and 2002.(8) This nomogram included 8 variables: sex, age, primary site, Lauren classification, tumor size, number of positive nodes, number of negative nodes, and pathological tumor depth. Several studies have since validated the utility of this nomogram at other institutions and internationally.(9–11) Since then other centers, mostly from Asian countries, have published variations on this nomogram, including at least 13 for gastric (12–24) and 2 for GEJ cancer,(25, 26) which incorporate different combinations of variables.

The inclusion of both GEJ and gastric cancer patients in the MSK nomogram contrasts with other prognostic tools. AJCC guidelines recommend using the staging system for esophageal adenocarcinoma for GEJ adenocarcinomas with an epicenter located within 2 cm of the anatomical GEJ and the gastric cancer staging system for any tumors with an epicenter located greater than 2 cm below the anatomical GEJ.(7) Nomograms from Asian countries have included only gastric cancer patients(12, 14–19, 21) because the incidence of GEJ cancer in Asia is low.

In addition, few patients included in the development of the MSK nomogram received neoadjuvant chemotherapy, as it was created before widespread adoption of perioperative therapy in 2005.(4) Nomograms from Asian countries are not likely to be more accurate, as they are based on data from patients who rarely receive neoadjuvant chemotherapy(12, 14–19, 21) because adjuvant chemotherapy following curative resection is the standard treatment for advanced disease in these countries.(27, 28) Given the significant changes in the treatment and outcomes of patients with GEJ and gastric cancers in the 18 years since the publication of the original MSK nomogram, we aimed to evaluate the predictive value of the nomogram in the era of multidisciplinary treatment. Our hypothesis was that because the nomogram was based on post-resection pathological variables, the introduction of neoadjuvant therapy would not affect its prognostic value.

Methods

Patient characteristics and clinicopathological data

All patients were treated in accordance with the Declaration of Helsinki, and this retrospective review was approved by the MSK institutional review board (protocol #19-111). Demographic, clinicopathological, and treatment information was collected from the prospectively maintained surgical GEJ and gastric cancer database and electronic medical records. Inclusion criteria were histologically confirmed GEJ or gastric adenocarcinoma and curative-intent resection between January 2002 and December 2016. Exclusion criteria were pathological stage IV disease, resection for remnant GEJ or gastric cancer, non-curative resection, and wedge resection without lymph node dissection.

Tumor location was classified as GEJ or gastric in the final pathological report by a dedicated gastrointestinal pathologist in accordance with the 8th edition of the AJCC staging system; tumors with an epicenter located < 2 cm into the gastric cardia were classified as GEJ cancer.(7) GEJ cancers with > 75% of the tumor located above or below the anatomical GEJ were classified as upper or lower GEJ tumors, respectively; others were classified as a middle GEJ cancer. Tumor depth (T stage), lymph node status (N status), and TNM stage were classified according to the 8th edition of the AJCC staging system.(2, 7) Tumor size and vascular invasion were collected from the final pathologic report. CT scan of the chest, abdomen, and pelvis, as well as endoscopic ultrasonography and PET scans when available, were used for clinical staging. Patients underwent staging laparoscopy before treatment to rule out occult metastatic disease, classified as biopsy-proven peritoneal carcinomatosis or positive peritoneal cytology.

In general, GEJ and gastric cancer patients with clinical T ≥ 3 and/or node-positive disease were offered neoadjuvant treatment. The regimen of neoadjuvant treatment was selected on the basis of guideline recommendations or trial regimens. For patients with GEJ cancer, a platinum-based doublet regimen (e.g. carboplatin/paclitaxel, cisplatin/paclitaxel, or cisplatin/irinotecan) with or without concurrent radiotherapy of 41.4–50.4 Gy or an epirubicin-based triplet regimen (e.g. epirubicin/cisplatin/5-fluorouracil, epirubicin/cisplatin/capecitabine, or epirubicin/oxaliplatin/capecitabine) was administered. For patients with gastric cancer, an epirubicin-based triplet regimen or FOLFOX (5-fluorouracil/oxaliplatin/leucovorin) was predominantly administered. A transthoracic approach including Ivor-Lewis esophagectomy with two-field lymphadenectomy was commonly performed for patients with GEJ cancer. A transabdominal approach with one-field lymphadenectomy was performed for patients with GEJ cancer mainly located at the abdominal esophagus or distally. In terms of extent of abdominal lymphadenectomy, D2 dissection, indicated for patients with advanced cancer, included perigastric nodes and nodes along the celiac trunk, left gastric artery, common hepatic artery, splenic artery, proper hepatic artery, and portal vein. D1 dissection, indicated for patients with clinical T1N0 cancer, included perigastric nodes. D2 dissection was commonly indicated for patients with gastric cancer, and D1 or D1+ dissection was indicated for patients with early gastric cancer. Among GEJ cancer patients, mediastinal lymphadenectomy included periesophageal, infracarinal, and hilar nodes when a transthoracic approach was used (with upper paratracheal and/or cervical lymphadenectomy if the tumor extended proximally to the mid esophagus); lower mediastinal nodes up to the level of the proximal margin and pericardial nodes were included with a transabdominal approach. Pathological chemotherapy response was assessed by an experienced gastric cancer pathologist on a scale from 0 to 100%. Neutrophil-to-lymphocyte ratio (NLR) and hemoglobin and albumin were measured prior to initiation of any treatment for GEJ or gastric cancer.

Follow-up

Follow-up after resection consisted of visits to the outpatient department and included blood tests including complete blood count and chemistry panel, as well as a CT scan of the chest, abdomen, and pelvis every 3–6 months for the first 2 years and annually for years 3–5 after surgery. Survival was measured from the date of surgery to the date of death from any cause

or last follow-up, whichever occurred first. For disease-specific survival (DSS), death from recurrence of primary GEJ or gastric cancer was considered an event and death from other causes was considered as censored.

Statistical analysis

Patients were divided into 4 groups according to gastric vs. GEJ cancer and receipt or non-receipt of neoadjuvant treatment. Categorical variables were compared using chi-square test or Fisher's exact test, and continuous variables using a Mann-Whitney U test. The accuracy of survival predictions was compared between our previous nomogram and the AJCC 8th edition staging system for each group.(2, 7) Survival curves were estimated by Kaplan-Meier methods and compared by log-rank test. Univariable and multivariable analyses for survival were performed by Cox regression analysis. Variables with p values of < 0.2 in univariable analysis were included in the multivariable analysis.

As the prior nomogram did not include patients receiving neoadjuvant treatment, which can lead to downstaging, we built a new nomogram using independently significant variables in the multivariable analysis and clinically important variables, for which the dataset was divided into a training and validation set at a 3 to 1 ratio.

Data were expressed as median (interquartile range [IQR]), odds ratio (OR; 95% confidence interval), or hazard ratio (HR; 95% confidence interval), unless otherwise stated. Missing variables were indicated as unknown and multivariable analysis did not include cases in which variables in the model were missing. P values of < 0.05 (two-tailed) were considered to be statistically significant. Statistical analyses were performed using SPSS® software version 25 (IBM, Armonk, New York, USA) or R version 3.6 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Of the 2,028 patients who underwent surgery for GEJ or gastric adenocarcinoma between January 2002 and December 2016, 1,885 patients were included in this study. Of these, 886 patients (645 [73%] gastric cancer and 241 [27%] GEJ cancer patients) underwent upfront surgery and 999 patients (323 [32%] gastric cancer and 676 [68%] GEJ cancer patients) received neoadjuvant treatment (Supplemental Digital Content 1). Approximately half of GEJ tumors were located in the middle of the anatomical GEJ and approximately half of gastric tumors were located in the lower third of the stomach (Table 1). In patients receiving neoadjuvant treatment, chemoradiotherapy was given almost exclusively to GEJ patients (84%), with only a very small number of gastric cancer patients receiving chemoradiotherapy (n = 4, 1.2%). The use of neoadjuvant chemoradiotherapy was more frequent in GEJ patients with tumors in the upper or middle GEJ (71% vs. 36% among those with tumors in the lower GEJ). GEJ cancer patients had lower T and N status compared to gastric cancer patients regardless of neoadjuvant treatment, as well as more differentiated tumors, less vascular invasion, less perineural invasion, and higher NLR, hemoglobin, and

albumin ($p < 0.001$ for all; Table 1). The distribution of TNM stages in the 4 subgroups is shown in Supplemental Digital Content 2.

Disease-specific survival

After a median follow-up of 42 months (IQR 20–70), 5-year DSS was 81% and 76% for gastric and GEJ cancer patients undergoing upfront surgery, respectively. For patients receiving neoadjuvant therapy, 5-year DSS was 67% and 53% for gastric and GEJ cancer patients, respectively (Fig. 1). DSS in each group according to AJCC TNM stage is shown in Supplemental Digital Content 3 and 4. In gastric cancer patients receiving neoadjuvant treatment, 31 (9.6%) patients had pathological complete response at the primary site (ypTCR). Five-year DSS for such patients was 92% (Supplemental Digital Content 4a). In GEJ cancer patients receiving neoadjuvant treatment, 128 (18.9%) patients had ypTCR.

Evaluation of previous MSK nomogram and AJCC staging system

The C-index of the MSK nomogram for predicting DSS in the entire cohort was 0.756 (95% CI 0.736–0.776, Figure 2). In the upfront surgery cohort, the MSK nomogram demonstrated a slightly higher C-index in gastric cancer patients compared with AJCC staging, whereas AJCC staging demonstrated a somewhat higher C-index in GEJ cancer patients compared with the MSK nomogram, though 95% CIs overlapped for both comparisons. In patients receiving neoadjuvant treatment, the MSK nomogram again had a higher C-index in gastric cancer patients compared with AJCC staging, while both the AJCC staging and the MSK nomogram demonstrated low predictive value in GEJ cancer patients (C-index 0.647 and 0.646, respectively, Fig. 2).

Revised nomogram for GEJ patients receiving neoadjuvant treatment

From the 676 GEJ cancer patients who received neoadjuvant treatment, training and validation sets were created. There was no significant difference in clinicopathological characteristics between the two groups (Supplemental Digital Content 5). In the training set, independently significant predictors for worse DSS identified by multivariable Cox regression analysis included number of positive nodes (HR 1.08, $p = 0.003$), poorly differentiated tumors (HR 1.48, $p = 0.018$), vascular invasion (HR 1.78, $p = 0.003$), neoadjuvant radiation (HR 1.88, $p = 0.005$), and NLR ≥ 5.0 (HR 1.62, $p = 0.036$). Predictors of improved DSS included ≥ 30 negative nodes (HR 0.54, $p = 0.026$) and pathological treatment response ≥ 30% (HR 0.60, $p = 0.014$) and ≥ 90% (HR 0.52, $p = 0.031$) (Table 2).

The C-index for the prediction model incorporating these 7 variables was 0.665 [95% CI 0.635–0.696]. A nomogram was created that added age and ypT status to these factors, resulting in a model with 9 variables and a C-index of 0.669 [95% CI 0.619–0.673] in the training set and 0.718 [95% CI 0.672–0.764] in the validation set (Fig. 3), both higher than the C-indices for the AJCC staging system in each set. The calibration plot of the new nomogram showed a high degree of similarity between the actual and estimated DSS at 3, 5, and 9 years after surgery (Fig. 4).

Discussion

Management of gastric and GEJ cancers has changed significantly since the publication of the classic MSK nomogram in 2003, particularly with the addition of neoadjuvant therapy prior to resection for most patients. We therefore sought to re-evaluate the prognostic and predictive value of the MSK nomogram for patients treated under the current standard of care and compared it to that of the AJCC 8th edition staging system. The MSK nomogram prevailed in providing reliable prognostic prediction for DSS in patients who did not receive neoadjuvant treatment, with a C-index of 0.786 and 0.738 in gastric and GEJ cancer patients, respectively, within the range of C-indices of other published nomograms for gastric cancer, 0.68 to 0.87.(12, 14, 15, 17–19) This similarity likely reflects its inclusion of many of the same clinicopathological variables(8) as other nomograms, namely age, sex, tumor location, tumor size, number or status of metastatic lymph nodes, and pathological tumor depth.(12, 14–16, 18)

For GEJ cancer patients treated with upfront surgery, the AJCC staging system provided relatively better prediction compared with the MSK nomogram. This superior accuracy likely reflects the AJCC system's incorporation of 10 categories (i.e., Stage 0 to IVB), including tumor grade for Stage IA to IIA disease,(7) which accounted for 60.2% of GEJ cancer patients in this study.

The previous MSK nomogram showed significantly better performance in gastric cancer patients receiving neoadjuvant treatment when compared with the AJCC staging system despite the fact that it was created in an era when neoadjuvant treatment was not widely applied (C-index 0.796 vs. 0.698). Only one nomogram for such patients was reported from China, which consisted of body mass index, tumor location, pathological T stage, and pathological N status and had a C-index of 0.74,(24) lower than that of the MSK nomogram in the current study. Although neither the Chinese nor the MSK nomogram include variables reflecting the effect of neoadjuvant treatment, they predict prognosis fairly accurately. Pathological response after neoadjuvant chemotherapy has been reported not to be an independent predictor of overall survival in gastric cancer patients.(4) Thus, post-resection variables such as ypT and N status predict survival regardless of receipt of neoadjuvant chemotherapy.

The survival of gastric cancer patients with pathological complete response (ypTCR) following neoadjuvant chemotherapy cannot be estimated using either the MSK nomogram or the AJCC staging system. The present study showed a very good prognosis for ypTCR patients; however, only 31 patients with ypTCR were identified, limiting the applicability of this finding. As more such patients are identified, the nomogram could be further revised in the future.

We created a new nomogram for GEJ cancer patients receiving neoadjuvant treatment and demonstrated its prognostic accuracy (C-index 0.718), comparable to that of the AJCC staging system. It proved more accurate compared with another nomogram for GEJ cancer patients treated with neoadjuvant chemoradiotherapy, which was developed using data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer

Institute and had a C-index of 0.61.(26) Its accuracy cannot be compared with the other GEJ cancer nomogram reported by Zhou et al., also based on SEER data, because it did not include information on neoadjuvant treatment.(25) In addition, these 2 nomograms predicted overall survival, whereas our study focused on DSS, an endpoint that is not available from administrative databases.

In this study, we also analyzed NLR as a candidate variable given the results of multiple studies including our previous study,(29) demonstrating an association between high NLR and poor survival in several cancers.(30) NLR was an independent predictor for DSS in GEJ cancer patients receiving neoadjuvant treatment, similar to Choi et al.'s findings in a nomogram for gastric cancer patients.(21) NLR is a readily available marker in clinical practice, as it can be calculated easily from a complete blood count.

The previous MSK nomogram and new GEJ nomogram reported here, similar to most published nomograms, are based on regression models, partially overcoming the problem of heterogeneity in stage.(31) These models are limited by their focus on specific variables, as they cannot account for the effects of combination. More sophisticated approaches using artificial intelligence can now account for combinatorial interactions,(31–33) including a recent nomogram that predicts the number of lymph node metastases in locally advanced gastric cancer,(34) which could improve the performance of prognostic prediction models.

There are several limitations to this study. Selection bias is inherent in any retrospective study design. Patients received a number of neoadjuvant chemotherapy regimens because recommendations changed during the 15-year study period, and chemotherapy dose intensity was not available. In addition, improved efficacy of newer chemotherapy regimens, in addition to the use of targeted therapy and checkpoint blockade for patients who experienced recurrence during the follow-up period, may have affected disease-specific outcomes. Increasing use of these new regimens, including in the neoadjuvant setting, could affect survival, calling for future re-assessment of the previous MSK nomogram and the new GEJ cancer nomogram. The new nomogram for GEJ in the present study was created and validated using data from the same group of 676 patients and should be externally validated using data from a larger cohort in the future. Finally, because more than 90% of the patients in the cohort used to develop the new GEJ cancer nomogram were white, it should be validated in cohorts of other ethnic backgrounds.

Conclusions

This study shows that the classic MSK gastric cancer nomogram continues to provide accurate prognostic information for patients treated with modern regimens that include neoadjuvant chemotherapy and chemoradiotherapy. Additionally, we developed a new GEJ nomogram that can more effectively predict DSS in patients receiving neoadjuvant treatment and help to individualize prognostic assessment and clinical decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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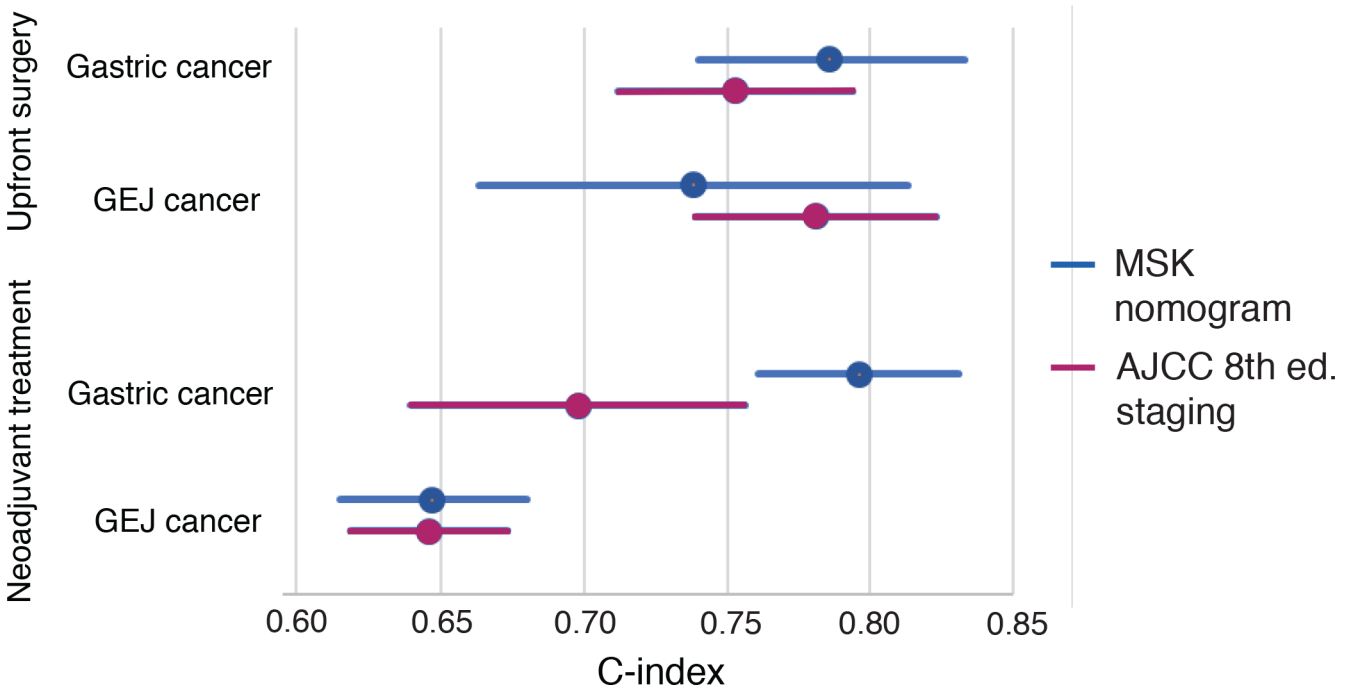


Figure 1.
Disease-specific survival (DSS) according to tumor site (gastroesophageal junction [GEJ] vs. gastric) and receipt of neoadjuvant treatment (Tx).

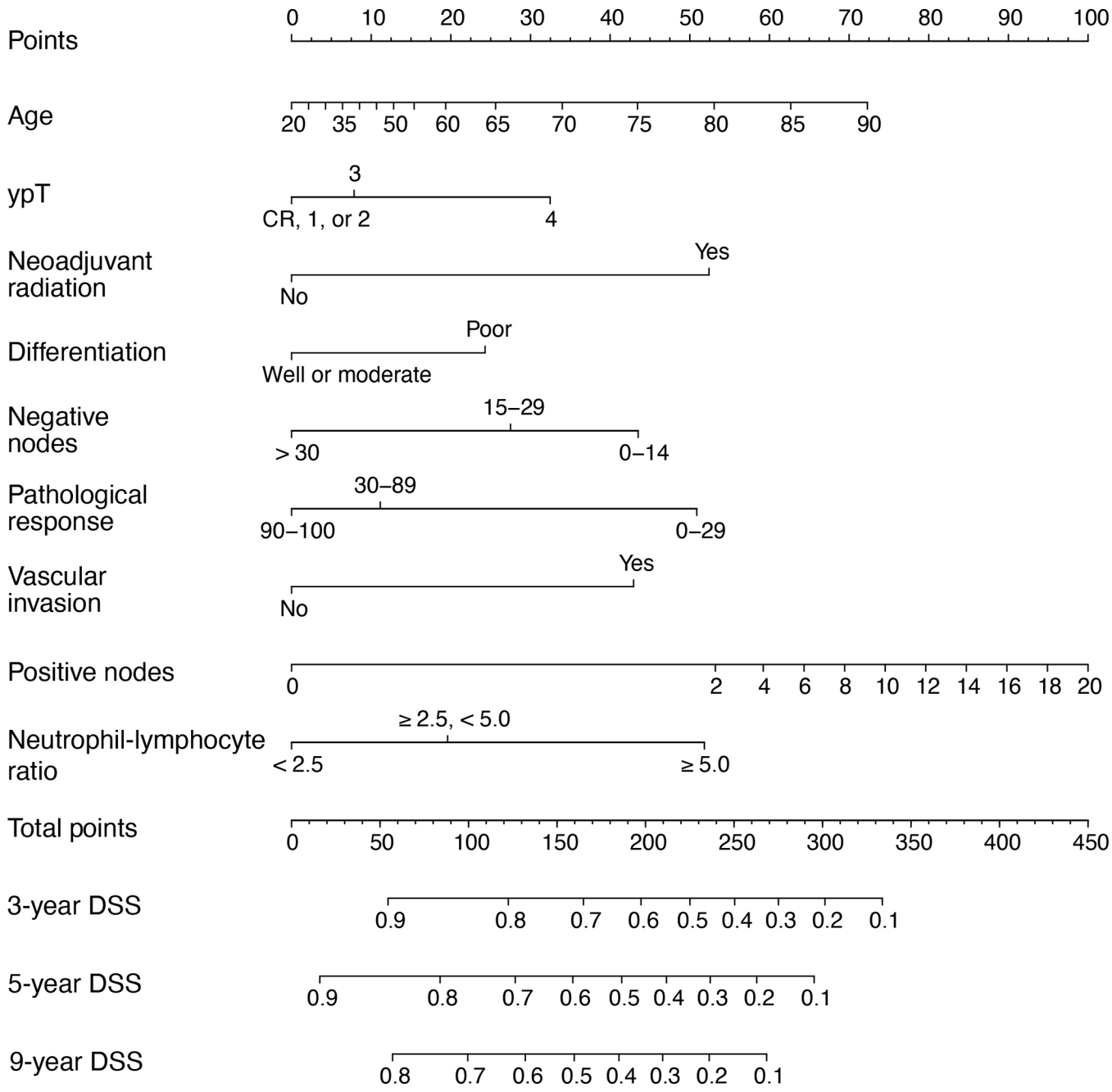
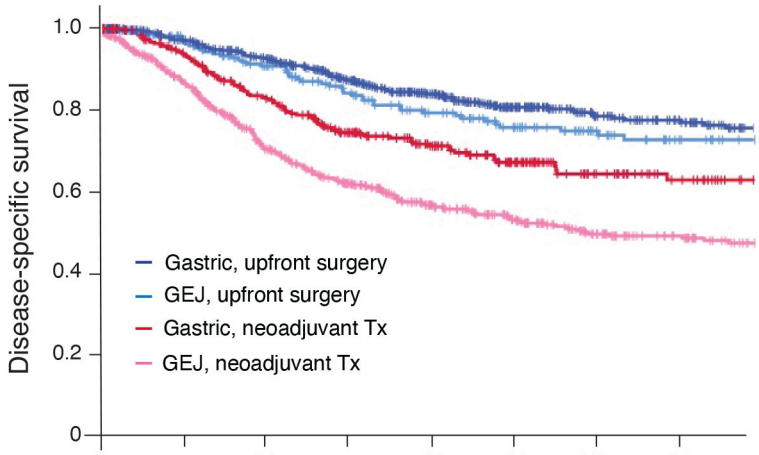


Figure 2.

Concordance index (C-index) of the Memorial Sloan Kettering (MSK) gastric cancer nomogram and the American Joint Committee on Cancer (AJCC) 8th edition TNM staging system for gastroesophageal junction (GEJ) and gastric cancer patients who did or did not receive neoadjuvant treatment. Bars represent 95% CIs.



	5-year DSS (%)	No. at risk							
Gastric, upfront surgery	80.7	645	563	500	405	320	232	165	134
GEJ, upfront surgery	75.8	241	200	175	146	120	98	73	57
Gastric, neoadjuvant Tx	67.2	323	276	228	177	139	99	59	42
GEJ, neoadjuvant Tx	53.2	676	536	395	312	229	175	118	93

Figure 3.

New nomogram for gastroesophageal junction cancer patients receiving neoadjuvant treatment. CR, complete response; DSS, disease-specific survival

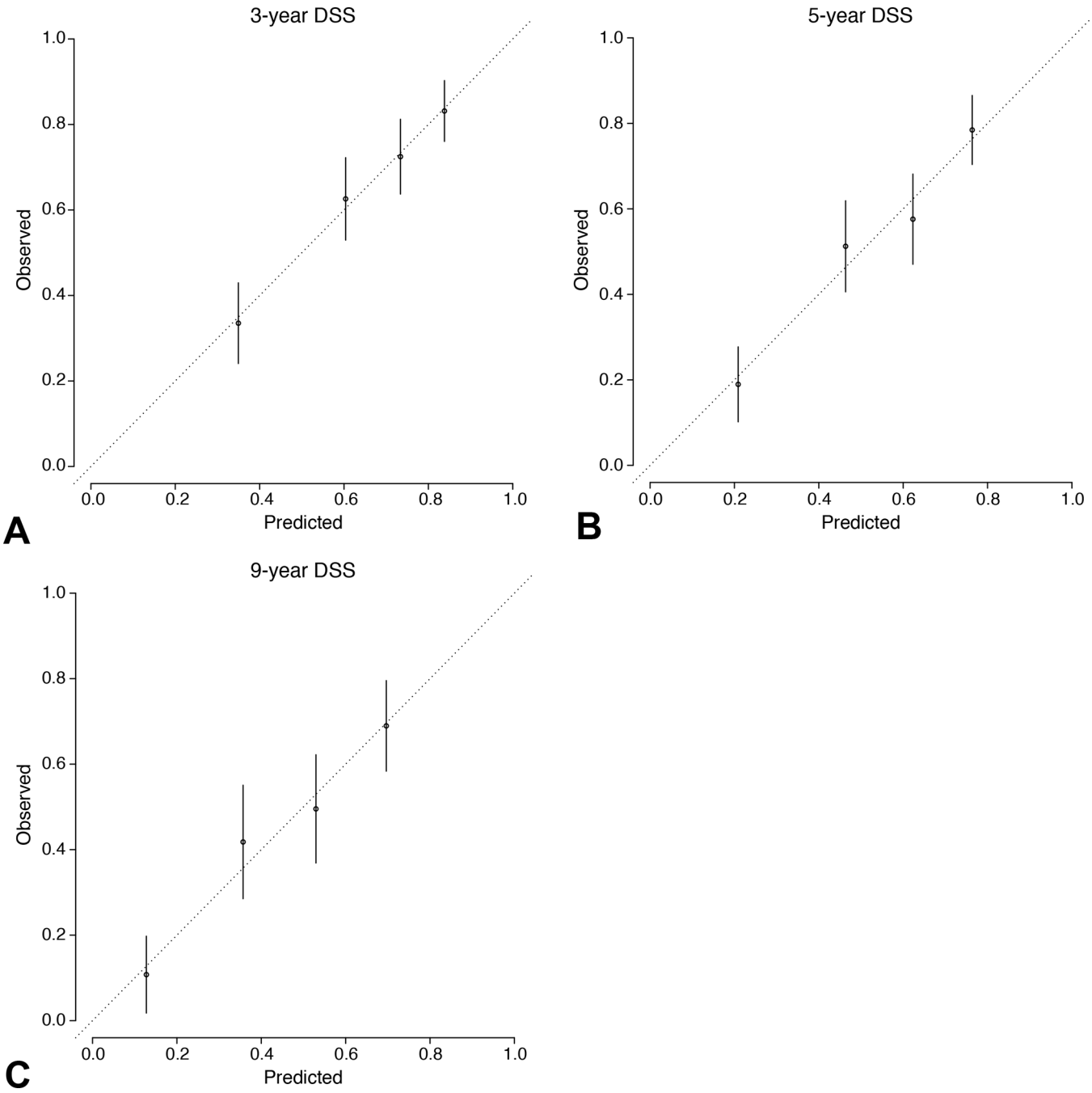


Figure 4.

Calibration curve comparing the nomogram's prediction of survival vs observed survival (mean, 95% CI for each quartile) at (**A**) 3, (**B**) 5, and (**C**) 9 years after operation. DSS, disease-specific survival.

Table 1.

Patient Characteristics

Characteristic	Entire (n = 1,885)	Upfront operation (n = 846)		Neoadjuvant treatment (n = 999)		p Value
		Gastric (n = 645)	GEJ (n = 241)	Gastric (n = 323)	GEJ (n = 676)	
Sex, m, n (%)	1,283 (68.1)	344 (53.3)	198 (82.2)	182 (56.3)	559 (82.7)	<0.001
Age, y, median (IQR)	65 (56–73)	68 (56–77)	68 (60–74)	63 (53–70)	62 (56–69)	<0.001
Race, n (%)						<0.001
White	1,519 (80.6)	456 (70.7)	223 (92.5)	218 (67.5)	622 (92.0)	
Asian	181 (9.6)	106 (16.4)	8 (3.3)	44 (13.6)	23 (3.4)	
Black	98 (5.2)	48 (7.4)	3 (1.2)	35 (10.8)	12 (1.8)	
Other/unknown	87 (4.6)	35 (5.4)	7 (2.9)	26 (8.0)	19 (2.8)	
Location, n (%)						-
Upper GEJ	151 (8.0)	-	38 (15.8)	-	113 (16.7)	
Middle GEJ	546 (29.0)	-	118 (49.0)	-	428 (63.3)	
Lower GEJ	220 (11.7)	-	85 (35.3)	-	135 (20.0)	
Upper stomach	105 (5.6)	55 (8.5)	-	50 (15.5)	-	
Middle stomach	337 (17.9)	214 (33.2)	-	123 (38.1)	-	
Lower stomach	479 (25.4)	334 (51.8)	-	145 (44.9)	-	
Whole stomach	47 (2.5)	42 (6.5)	-	5 (1.5)	-	
Neoadjuvant therapy, n (%)						
Chemotherapy only	425 (22.5)	0 (0)	0 (0)	319 (98.8)	106 (15.7)	
Chemoradiotherapy	574 (30.5)	0 (0)	0 (0)	4 (1.2)	570 (84.3)	
None	886 (47.0)	645 (100)	241 (100)	0 (0)	0 (0)	
Adjuvant treatment, n (%)						<0.001
Chemotherapy only	290 (15.4)	84 (13.0)	19 (7.9)	136 (42.1)	51 (7.5)	
Chemoradiotherapy	94 (5.0)	48 (7.4)	21 (8.7)	16 (5.0)	9 (1.3)	
Radiotherapy only	6 (0.3)	0 (0)	0 (0)	4 (1.2)	2 (0.3)	
None	1,495 (79.3)	513 (79.5)	201 (83.4)	167 (51.7)	614 (90.8)	
Type of operation, n (%)						<0.001
Ivor-Lewis	780 (41.4)	0 (0)	181 (75.1)	0 (0)	599 (88.6)	

Characteristic	Entire (n = 1,885)	Upfront operation (n = 846)		Neoadjuvant treatment (n = 999)		p Value
		Gastric (n = 645)	GEJ (n = 241)	Gastric (n = 323)	GEJ (n = 676)	
Total gastrectomy	408 (21.6)	167 (25.9)	51 (21.2)	113 (35.0)	77 (11.4)	
Proximal gastrectomy	23 (1.2)	10 (1.6)	9 (3.7)	4 (1.2)	0 (0)	
Distal gastrectomy	674 (35.8)	468 (72.6)	0 (0)	206 (63.8)	0 (0)	
Pathological T stage, n (%)						<0.001
1a	264 (14.0)	171 (26.5)	52 (21.6)	14 (4.3)	27 (4.0)	
1b	412 (21.9)	178 (27.6)	103 (42.7)	32 (9.9)	99 (14.6)	
2	261 (13.8)	60 (9.3)	32 (13.3)	44 (13.6)	125 (18.5)	
3	544 (28.9)	111 (17.2)	39 (16.2)	112 (34.7)	282 (41.7)	
4a	227 (12.0)	116 (18.0)	15 (6.2)	83 (25.7)	13 (1.9)	
4b	18 (1.0)	9 (1.4)	0 (0)	7 (2.2)	2 (0.3)	
Complete response	159 (8.4)	-	-	31 (9.6)	128 (18.9)	
Pathological N status, n (%)						<0.001
0	1,099 (58.3)	406 (62.9)	160 (66.4)	152 (47.1)	381 (56.4)	
1	353 (18.7)	91 (14.1)	48 (19.9)	59 (18.3)	155 (22.9)	
2	246 (13.1)	73 (11.3)	16 (6.6)	51 (15.8)	106 (15.7)	
3a	154 (8.2)	59 (9.1)	16 (6.6)	48 (14.9)	31 (4.6)	
3b	33 (1.8)	16 (2.5)	1 (0.4)	13 (4.0)	3 (0.4)	
No. of dissected nodes, median (IQR)	22 (17–30)	21 (16–31)	22 (16–30)	25 (18–33)	22 (17–28)	<0.001
No. of positive nodes, median (IQR)	0 (0–2)	0 (0–2)	0 (0–1)	1 (0–5)	0 (0–2)	<0.001
Tumor size, cm, median (IQR)	2.5 (1.4–4.5)	2.6 (1.3–4.6)	2.2 (1.5–3.5)	3.5 (2.0–6.0)	2.5 (0.7–4.2)	<0.001
Pathological response, %, median (IQR)	-	-	-	40 (10–80)	80 (40–95)	<0.001
Lauren type, n (%)						<0.001
Intestinal	956 (50.7)	308 (47.8)	137 (56.8)	146 (45.2)	365 (54.0)	
Diffuse	381 (20.2)	209 (32.4)	16 (6.6)	104 (32.2)	52 (7.7)	
Mixed	285 (15.1)	121 (18.8)	25 (10.4)	68 (21.1)	71 (10.5)	
Unknown	263 (14.0)	7 (1.1)	63 (26.1)	5 (1.5)	188 (27.8)	
Differentiation, n (%)						<0.001
Well	113 (6.0)	66 (10.2)	21 (8.7)	6 (1.9)	20 (3.0)	

Characteristic	Entire (n = 1,885)	Upfront operation (n = 846)		Neoadjuvant treatment (n = 999)		p Value
		Gastric (n = 645)	GEJ (n = 241)	Gastric (n = 323)	GEJ (n = 676)	
Moderate	862 (45.7)	228 (35.3)	146 (60.6)	98 (30.3)	390 (57.7)	
Poor	822 (43.6)	344 (53.3)	66 (27.4)	207 (64.1)	205 (30.3)	
Unknown	88 (4.7)	7 (1.1)	8 (3.3)	12 (3.7)	61 (9.0)	
Vascular invasion, n (%)						<0.001
No	1,143 (60.6)	372 (57.7)	147 (61.0)	163 (50.5)	461 (68.2)	
Yes	733 (38.9)	270 (41.9)	94 (39.0)	156 (48.3)	213 (31.5)	
Unknown	9 (0.5)	3 (0.5)	0 (0)	4 (1.2)	2 (0.3)	
Neutrophil-lymphocyte ratio, median (IQR)	2.8 (2.0–3.9)	2.5 (1.8–3.5)	2.6 (2.1–3.7)	2.5 (1.9–3.4)	3.3 (2.3–4.8)	<0.001
Hemoglobin, median (IQR)	12.7 (11.4–13.9)	12.7 (11.4–13.8)	13.6 (12.4–14.6)	12.0 (10.9–13.3)	12.8 (11.4–14.0)	<0.001
Albumin, median (IQR)	4.2 (3.9–4.4)	4.2 (4.0–4.4)	4.3 (4.1–4.5)	4.1 (3.8–4.3)	4.2 (3.9–4.4)	<0.001

p Values compare gastric vs GEJ cancer patients.

IQR, interquartile range; GEJ, gastroesophageal junction

Table 2.

Factors Associated with Disease-Specific Survival in the Training Set

Factor	Univariable			Multivariable		
	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.01	1.00–1.02	0.189	1.01	1.00–1.03	0.071
Sex, f	1.12	0.79–1.57	0.523	-	-	-
Race						
White	1	-	-	1	-	-
Non-White	0.69	0.39–1.21	0.191	0.88	0.48–1.62	0.672
Tumor location						
Upper GEJ	1	-	-	-	-	-
Middle GEJ	1.02	0.67–1.55	0.936	-	-	-
Lower GEJ	1.04	0.64–1.69	0.881	-	-	-
ypT						
1	1	-	-	1	-	-
2	1.16	0.71–1.89	0.556	0.77	0.45–1.33	0.343
3	1.78	1.19–2.65	0.005	0.90	0.54–1.50	0.683
4	4.07	1.93–8.57	<0.001	1.29	0.51–3.27	0.596
Complete response	0.88	0.53–1.46	0.616	0.67	0.33–1.34	0.256
No. of positive lymph nodes	1.12	1.08–1.16	<0.001	1.08	1.03–1.13	0.003*
No. of negative lymph nodes						
<15	1	-	-	1	-	-
≥15, <30	0.59	0.43–0.82	0.001	0.86	0.58–1.28	0.468
≥30	0.36	0.23–0.57	<0.001	0.54	0.32–0.93	0.026*
Differentiation						
Well/moderately	1	-	-	1	-	-
Poorly	1.31	0.99–1.75	0.064	1.48	1.07–2.05	0.018*
Vascular invasion	2.36	1.79–3.10	<0.001	1.78	1.23–2.60	0.003
Tumor size, cm	1.09	1.03–1.15	0.004	1.00	0.92–1.09	0.993
Neoadjuvant therapy						
Chemotherapy only	1	-	-	1	-	-
Chemoradiotherapy	1.34	0.91–1.97	0.137	1.88	1.21–2.94	0.005*
Adjuvant therapy						
None	1	-	-	-	-	-
Chemotherapy only	0.89	0.54–1.45	0.631	-	-	-
Chemoradiotherapy/radiotherapy	0.93	0.38–2.26	0.871	-	-	-
NAC response rate						
<30%	1	-	-	1	-	-
≥30%, <90%	0.61	0.43–0.86	0.005	0.60	0.40–0.90	0.014*
≥90%	0.41	0.28–0.58	<0.001	0.52	0.29–0.94	0.031*

Factor	Univariable			Multivariable		
	HR	95% CI	p Value	HR	95% CI	p Value
Neutrophil-lymphocyte ratio						
<2.5	1	-	-	1	-	-
≥ 2.5, <5.0	1.38	0.98–1.94	0.065	1.30	0.90–1.88	0.156
≥ 5.0	1.75	1.18–2.59	0.005	1.62	1.03–2.54	0.036*

*Statistically significant

GEJ, gastroesophageal junction; NAC, neoadjuvant chemotherapy