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Development and validation of the Massachusetts General Hospital/ Memorial Sloan Kettering nomogram to predict overall survival of resected patients with pancreatic ductal adenocarcinoma treated with neoadjuvant therapy

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ABSTRACT

Background: Prognostication in patients undergoing resection for pancreatic ductal adenocarcinoma following neoadjuvant therapy remains challenging. In this study, we aimed to develop and validate a nomogram for the prediction of overall survival of these patients.

Methods: Patients who underwent neoadjuvant therapy followed by surgical resection at the Massachusetts General Hospital were analyzed (training cohort). Patients from Memorial Sloan Kettering were included as a validation cohort. A nomogram to predict overall survival was designed, trained, and subjected to internal (bootstrap) validation.

Results: A total of 325 patients were identified from Massachusetts General Hospital. Multivariable Cox regression analysis demonstrated that age (hazard ratio 1.828, 95% confidence interval 1.251–2.246; $P = .007$), serum carbohydrate antigen 19-9 $\geq$ 37 U/mL (HR 1.602, 95% confidence interval 1.187–3.258; $P = .015$), tumor size (hazard ratio 2.278, 95% confidence interval 1.405–4.368; $P = .003$), nodal status (hazard ratio 1.309, 95% confidence interval 1.108–2.439; $P = .032$), and R1 tumor resection (hazard ratio 1.481, 95% confidence interval 1.049–2.091; $P = .026$) were independent factors associated with overall survival. A nomogram that incorporated these significant prognostic factors was established. The calibration plots demonstrated high concordance between predictive nomogram values and actual overall survival for 1-year, 3-year, and 5-year overall survival. The model demonstrated excellent discriminatory power in both the Massachusetts General Hospital and Memorial Sloan Kettering cohorts, with adjusted Harrel's concordance index values of 0.729 and 0.712, respectively.

Conclusion: In this report, we established and validated a novel nomogram for predicting the survival of patients who underwent neoadjuvant therapy followed by pancreatectomy. This model allows clinicians to better estimate the survival of these specific patients.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer, and prognosis of patients with PDAC remains poor.[1–4] Curative-intent surgery for patients with resectable tumors plays a significant role in patients who experience long-term survival from this disease.[5,6] However, only 15%–20% will be deemed as resectable at the time of diagnosis. Even following negative-margin

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(R0) resection, PDAC disease recurrence rates remain high, with rates of recurrence approaching 80%.[7,8]

It is widely recognized that pancreatic cancer is both a locally invasive and systemic disease in most patients at presentation. In addition, patients often present with borderline-resectable and locally advanced disease. Thus, neoadjuvant therapy provides an opportunity to address more locally advanced tumors while treating early systemic micrometastases, all while ensuring that patients receive multimodal treatment, which is often more difficult to administer postoperatively. In addition, neoadjuvant therapy is associated with higher R0 and node-negative resections, which may influence long-term survival.[9–13] Currently, the two commonly utilized neoadjuvant regimens are FOLFIRINOX (5-FU, leucovorin, irinotecan, and oxaliplatin) and gemcitabine/nab-paclitaxel. While the choice of one versus the other is currently dependent on institutional and patient factors, both regimens outperform older combinations and single-agent therapies.[14–16]

The prognostic stratification of post-resection survival of patients with PDAC is currently based on the American Joint Committee on Cancer (AJCC) staging system.[17] Many studies have established predictive prognostic models to stratify patient survival using both clinical and pathological parameters.[18–21] However, many of these studies were performed in patients who underwent upfront surgery, including the widely utilized AJCC staging system. Prognostic stratification among patients who received neoadjuvant therapy followed by pancreatectomy is lacking. In terms of prognostic stratification, nomograms have been accepted as reliable tools to quantify risk by incorporating validated prognostic factors.[22–24] By creating a statistical predictive model, a nomogram gives rise to a numerical probability of a clinical event, such as overall survival (OS). Nomograms have been shown to be more precise, with greater discriminatory prognostic capacity than traditional tumor-nodes-metastasis (TNM) stages, and help guide counseling discussions and management strategies.[25,26]

In this study, we aimed to identify clinical and pathological parameters that independently influenced OS in patients with PDAC who underwent neoadjuvant chemotherapy, with or without radiation, followed by tumor resection. We then aimed to integrate these parameters into a nomogram model to assess OS. Finally, we sought to assess its reproducibility using an independent external validation cohort and evaluate the prognostic ability of the nomogram model compared with the eighth edition of the AJCC TNM staging system. The objective of this tool was to provide prognostic information that is specific to post-neoadjuvant, resected, pancreatic cancer patients to help determine prognosis more accurately and counsel patients accordingly.

Methods

The study was approved by the Ethics Committee of the Institutional Review Board of the Massachusetts General Hospital (MGH). Written informed consent was waived owing to the retrospective and deidentified nature of the study.

MGH cohort

Consecutive adult patients (≥18 years old) who underwent neoadjuvant therapy followed by pancreatectomy between March 1, 2007, to December 30, 2017, were considered for inclusion. All patients included had received neoadjuvant systemic chemotherapy, and some received radiation therapy as well. For most patients, FOLFIRINOX was administered as the standard of care in borderline or locally advanced PDAC. The definitions of borderline and locally advanced disease were determined by the National Comprehensive Cancer Network criteria. Radiographic imaging was performed during and following completion of chemotherapy, and surgical exploration was carried out with multidisciplinary input if no tumor progression was detected. Patients had no additional adjuvant chemotherapy routinely administered unless a recurrence was identified.

Next, patients' clinical data were retrospectively collected. Data included demographics, body mass index, and preoperative carbohydrate antigen 19-9 (CA 19-9) levels. Postoperative outcomes and treatment included the occurrence of major morbidity (Clavien-Dindo ≥ III) and 30-day mortality. Pathologic parameters were collected according to the eighth edition of the AJCC TNM staging system and included tumor stage, tumor size, extent of lymph node involvement, and tumor grade. Surgical resection margins closer than 1 mm were considered microscopically positive and denoted as R1. Follow-up data for all patients were obtained from their most recent medical review, including documented clinical examination and assessment of computed tomography (CT) scans. Patients' OS was calculated from the date of the index operation to the date of death or last contact. An independent biostatistician managed and maintained the collected data.

Memorial Sloan Kettering cohort

Patients who received neoadjuvant therapy and pancreatic surgery at Memorial Sloan Kettering (MSK) served as the independent external validation cohort. Consecutive individuals receiving neoadjuvant therapy (at least neoadjuvant chemotherapy as above) before surgery from January 1, 2014, to December 30, 2017, were identified from a local, prospectively maintained database. Similar inclusion and exclusion criteria to the MGH cohort were applied.

Construction of the nomogram

In the MGH cohort, survival curves were generated using Kaplan-Meier estimates for the different variables, which were compared using the log-rank test. Variables that achieved significance according to the authors were entered into the multivariable analysis using Cox regression modeling. Statistical analyses to identify independent prognostic factors were conducted in SPSS 25.0 (IBM Corp, Armonk, NY). Based on the multivariable analysis, a nomogram was formulated using R 2.14.1 analysis (R Foundation for Statistical Computing, Vienna, Austria) with the survival and rms packages.[27,28] A final model was selected using a backward step-down process, which used the Akaike information criterion as a stopping rule.[29]

Statistical analyses

The primary outcome was OS, which was calculated from the date of surgery to death. Patients who did not experience the main end point were censored at the last available follow-up. Disease and treatment characteristics were summarized using median and range for continuous variables, and frequency and percentages for categorical variables. Recurrence was identified through routine surveillance CT scans according to institutional protocols.

The model performance for predicting outcome was evaluated by calculating Harrel's concordance index (C-index).[30,31] Confidence intervals (CIs) for the C-index were calculated as 95% of the C-index distribution after resampling through bootstrap. The value of the C-index ranges from 0.5 to 1.0, with 0.5 indicating a random chance and 1.0 indicating a perfect ability to correctly discriminate the outcome with the model. Comparison of the C-index of 2 different models was based on previously described and validated

methods.[32] Calibration of the nomogram for 1-year, 3-year, and 5-year OS was performed by comparing the predicted survival with the observed survival after bias correction. In addition to numerically comparing the discrimination ability by C-index, areas under the receiver-operating characteristics (AUROC) curves for estimated OS were also used in both the MGH cohort and MSK validation cohort to compare the predictive performance of the nomogram with the most recent AJCC staging system.[33] Moreover, we sought to illustrate further the independent discriminatory ability of the nomogram by evenly grouping patients into different risk groups according to total risk scores (highest to lowest) in the MGH cohort. We determined cutoff values using AUROC curves and then plotted Kaplan-Meier curves in both MGH and MSK cohorts.

Results

Patient characteristics

A total of 325 patients met the criteria and were included in this study as the MGH training cohort. A total of 103 patients were included from MSK and served as the validation cohort. Patient demographics are detailed in Table I.

Table I
Patient and tumor characteristics

Variable	MGH Training Cohort ($n = 325$)	MSK Validation Cohort ($n = 103$)
Sex		
Female patients	153	51
Male patients	172	52
Age, y	66.2 (35–92)	65.4 (34–85)
ASA classification		
II	184	17
III	141	86
BMI kg/m^2	25.8 ± 6.2	26.5 ± 4.9
Serum CA-19-9 U/mL		
<37	157	26
≥37	168	77
Tumor and pathologic characteristics		
AJCC TNM stage		
I	85	57
II	200	29
III	40	17
Grade		
G1	38	6
G2	190	68
G3	88	23
G4	9	6
Neoadjuvant chemotherapy		
FOLFIRINOX	247	82
Gemcitabine-based regimen	72	21
Others	6	0
Neoadjuvant radiotherapy		
Yes	262	69
No	63	34
Tumor size, cm	2.58 ± 1.72	2.67 ± 1.05
Neural invasion		
Yes	94	26
No	231	67
Vascular invasion		
Yes	110	45
No	215	58
Nodal status		
0	177	57
1	89	19
2	59	27
Tumor resection		
R0	243	65
R1	82	38
Operation type		
Whipple	265	85
Distal pancreatectomy	60	18
Recurrence sites		
Local lymph nodes	62	52
Liver	23	18
Peritoneum	17	12
Lung	12	4
Other	27	16

AJCC, American Joint Committee on Cancer; *ASA*, American Society of Anesthesiologists; *BMI*, body mass index; *CA*, carbohydrate antigen; *MGH*, Massachusetts General Hospital; *MSK*, Memorial Sloan Kettering; *TNM*, tumor-node-metastasis.

Prognostic factors associated with overall survival

Cox proportional hazards models were used to quantify the prognostic factors associated with OS in patients with PDAC. The results of both univariable and multivariable analyses are shown in Table II. Following univariable analysis, a multivariable analysis was performed to evaluate factors that demonstrated statistical significance on univariable analysis. After adjusting for competing risk factors, age (hazard ratio [HR] 1.828, 95% CI 1.251–2.246; $P = .007$), serum CA-19-9 ≥ 37 U/mL (HR 1.602, 95% CI 1.187–3.258; $P = .015$), tumor size (HR 2.278, 95% CI 1.405–4.368; $P = .003$), nodal status (HR 1.309, 95% CI 1.108–2.439; $P = .032$), and R1 margin status (HR 1.481, 95% CI 1.049–2.091; $P = .026$) were identified as independent factors associated with OS. These independent factors were utilized for development of the nomogram.

Prognostic nomogram for overall survival

A nomogram that incorporated the significant prognostic factors was established (Figure 1). The MGH/MSK nomogram illustrated the relative contribution of the individual factors, including tumor size, age, serum CA-19-9 ≥ 37 U/mL, R1 margin status, and nodal status. Each factor was assigned a score based on its contribution and reflected on the point scale. By combining the aggregate score, a vertical corresponding estimate of OS can be determined.

Calibration and predictive value of the nomogram

The calibration plots reflected high concordance between predicted versus actual observed OS for 1-year, 3-year, and 5-year OS (Figure 2). The nomogram model revealed excellent discriminatory power in both the MGH training cohort and MSK validation cohort, with adjusted C-index values of 0.729 and 0.712, respectively. As shown in Figure 3, further AUROCs were performed to compare the predictive values of the established nomogram with the eighth AJCC TNM staging system using both the MGH training cohort and MSK validation cohort. In the MGH training cohort, the nomogram model showed a significantly improved predictive value (AUROC 0.729, 95% CI 0.686–0.772) than the eighth AJCC TNM staging system (AUROC 0.598, 95% CI 0.544–0.651; $P < .001$), shown in Figure 3, *A*. In the MSK validation cohort, the nomogram model also showed significantly improved predictive yield (AUROC 0.712, 95% CI 0.647–0.739) compared with the eighth AJCC TNM staging system (AUROC 0.582, 95% CI, 0.532–0.643; $P < .001$), as shown in Figure 3, *B*.

Performance of the nomogram in stratifying patient prognosis

By separating patients into 3 groups, we determined the cutoff values in the MGH training cohort according to total scores of 0 to 80, 81 to 120, and >120. Each group represented a distinct

Table II
Univariable and multivariable analysis of factors associated with death in patients with PDAC

Variable	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	2.313	1.279–4.183	.001	1.828	1.251–2.246	.007
Sex						
Female patients	Ref					
Male patients	1.033	0.755–1.413	.841			
ASA score						
II	Ref					
III	1.169	0.856–1.596	.328			
BMI	0.998	0.956–1.031	.886			
Serum CA-19-9						
<37 U/mL	Ref			Ref		
≥37 U/mL	2.627	1.243–4.128	.001	1.602	1.187–3.258	.015
Grade						
G1/G2	Ref					
G3/G4	1.114	0.759–1.285	.187			
Type of chemotherapy						
Non-FOLFIRINOX	Ref					
FOLFIRINOX	0.845	0.652–1.073	.718			
Neoadjuvant radiotherapy						
No	Ref					
Yes	0.862	0.466–1.593	.635			
Tumor size, cm	2.045	1.152–3.751	.001	2.278	1.405–4.368	.003
Perineural invasion						
No	Ref			Ref		
Yes	1.912	1.155–3.578	.007	1.021	0.943–1.102	.739
Vascular invasion						
No	Ref			Ref		
Yes	2.227	1.259–3.364	.001	1.237	0.868–1.764	.352
Nodal status						
0	Ref			Ref		
1	1.376	1.245–2.017	.012			
2	2.575	1.831–3.162	.001	1.309	1.108–2.439	.032
Tumor resection						
R0	Ref			Ref		
R1	2.774	1.652–5.475	.001	1.481	1.049–2.091	.026
Operation type						
Distal	Ref					
Whipple	0.653	0.408–1.045	.076			

ASA, American Society of Anesthesiologists; *BMI*, body mass index; *CA*, carbohydrate antigen; CI, confidence interval; *FOLFIRINOX*, 5-FU, leucovorin, irinotecan, and oxaliplatin; *HR*, hazard ratio; *PDAC*, pancreatic ductal adenocarcinoma.

prognosis, which is highlighted in Figure 4, *A*. After applying the same cutoff values to the MSK validation cohort, a similar, distinct stratification of patients was equally appreciated (Figure 4, *B*). These values and separations were all statistically significant.

Discussion

The present study examined a large cohort of patients who underwent neoadjuvant therapy with chemotherapy, with and without radiation therapy, followed by surgical resection to develop a novel nomogram model that can be used to accurately estimate the prognosis of patients with PDAC. In addition, the nomogram model was subsequently validated using a neoadjuvant cohort from a secondary institution. The objective of this tool was to provide prognostic information that is specific to patients with pancreatic cancer undergoing resection following neoadjuvant therapy to help determine prognosis more accurately and counsel patients accordingly.

In our study, the presented MGH/MSK nomogram demonstrated a highly accurate and predictive ability to estimate 1-year, 3-year, and 5-year survival of patients at both institutions. Furthermore, the nomogram also demonstrated superiority in the ability to reliably predict survival of patients who underwent neoadjuvant therapy compared with the eighth AJCC staging system, which does not routinely distinguish between neoadjuvant versus upfront resected patients. Finally, the nomogram model provided additional discriminatory survival prognostication based on total score, thereby helping stratify patients with management implications, including consideration for additional therapy, heightened surveillance, and enrollment in clinical trials.

Whether neoadjuvant therapy results in a survival benefit remains largely unknown.[34–36] Neoadjuvant therapy has been increasingly utilized in attempts to reduce margin-positive resection rates and downstage node-positive disease. In addition, PDAC is largely considered to be systemic in nature at diagnosis, and the use of systemic therapy is considered attractive. However, the benefit of neoadjuvant therapy most notably includes the ability to ensure delivery of much-needed multimodal therapy, given that the need for adjuvant therapy is minimized and which is often poorly tolerated and frequently omitted (25%–50% of patients) following pancreatectomy.[37] With added success in the use of neoadjuvant therapies, such as FOLFIRINOX and gemcitabine/nab-paclitaxel in locally advanced tumors, the concept continues to be explored for upfront resectable disease and is the subject of a United States multi-institutional prospective randomized controlled phase 3 trial today (Alliance A021806).[38] In a Japanese trial with patients receiving neoadjuvant chemotherapy with gemcitabine and S-1 compared with upfront surgery for resectable pancreatic cancer (Prep-01/JSAP-05), the benefit of neoadjuvant

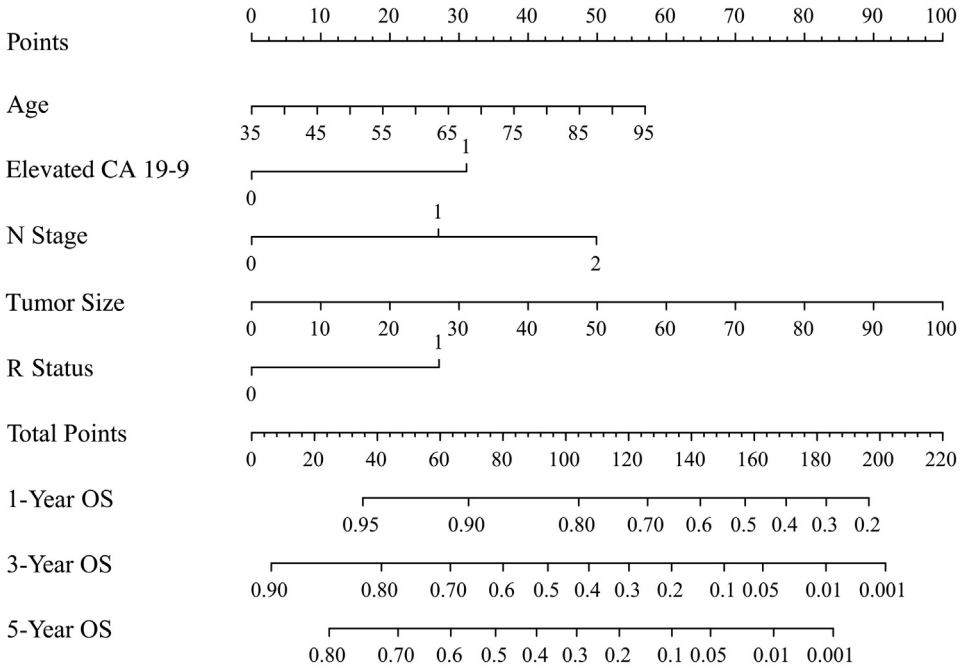

Figure 1. Prognostic MGH/MSK nomogram for patients with PDAC treated with neoadjuvant chemotherapy followed by surgical resection. *MGH*, Massachusetts General Hospital; *MSK*, Memorial Sloan Kettering; *PDAC*, pancreatic ductal adenocarcinoma.

therapy was demonstrated (median OS of 36.7 months in the neoadjuvant arm vs 26.6 months in the upfront surgery arm).[39] That randomized controlled trial also demonstrated a reduced rate of nodal positivity in the neoadjuvant cohort as well as a near 10% improvement in 2-year OS with neoadjuvant therapy. Importantly, the trial revealed the feasibility of neoadjuvant therapy, with no difference in operating time, bleeding events, operative technique, morbidity, or mortality.

Neoadjuvant therapy in the United States currently incorporates different treatment modalities, including neoadjuvant chemotherapy, radiation therapy, or a combination of both.[40–42] Given the variety of regimens utilized over time and between institutions, we chose to focus the present study on patients who received neoadjuvant chemotherapy at a minimum, given that radiation therapy utilization rates provide the greatest source of variation between institutions, and given that systemic therapy is a common denominator among institutions providing neoadjuvant therapy, thereby allowing maximal extrapolation of findings from this study among patients receiving neoadjuvant chemotherapy[15,43] Our current institutional practice selectively favors FOLFIRINOX in the first line, although no difference has been shown in efficacy between the Gemcitabine/nab-paclitaxel regimen in a randomized prospective setting.[44] However, in settings where patients are deemed slightly frailer and have demonstrated early, nonmetastatic progression or have 5-FU-based toxicities/intolerance, gemcitabine-based regimens have been utilized. The use of radiation therapy in the neoadjuvant setting continues to be debated and was, not surprisingly, inconsistently included in our analysis as a result. While initial trial data as designed and powered did not show a difference between treatment arms, long-term data from the PREOPANC trial demonstrated that preoperative chemoradiotherapy resulted in improved OS and a reduction in local recurrences.[45]

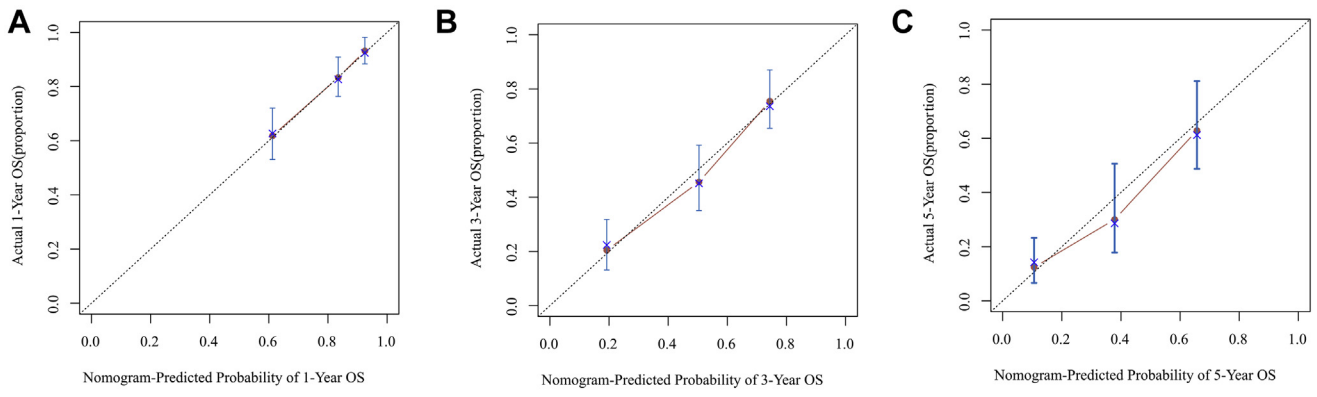

Figure 2. Calibration curves of predicted versus actual observed survival at 1-year, 3-years, and 5-years.

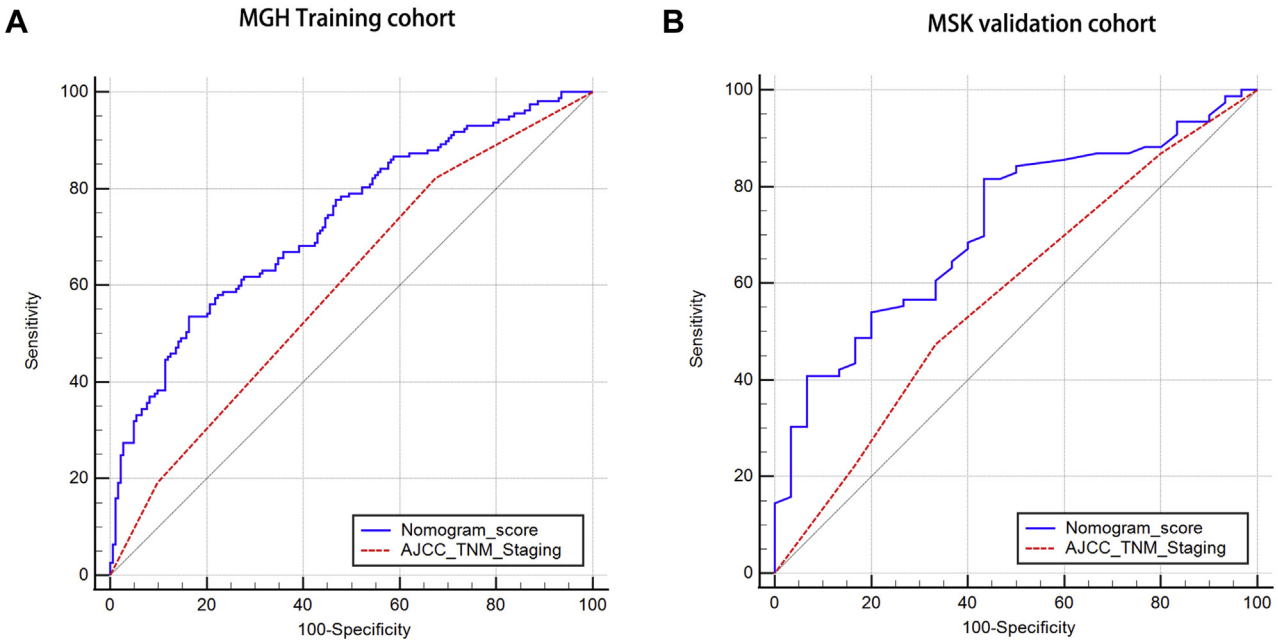

Figure 3. Comparison of the predictive value of the nomogram compared with the AJCC TNM staging. *AJCC*, American Joint Committee on Cancer; *TNM*, tumor-node-metastasis.

In a previous analysis from MGH, the authors utilized a similar concept to develop a prognostic scoring system (PANAMA score) for patients who had received induction chemotherapy followed by surgery for pancreatic cancer based on pathological parameters and CA 19-9 levels.[46] While the variables of interest were similar between the studies, the study provided 3 categories of risk stratification with excellent discriminatory power. The findings were subsequently validated with an independent cohort from Heidelberg, Germany. While this study utilizes a larger sample size and a high-volume United States tertiary referral center (MSK) as the independent external validation source, this study provides a continuous scale-based predictor with additional granularity and discriminatory power in the form of a nomogram, which may be extrapolated to all patients who undergo induction neoadjuvant systemic therapy to predict OS. Prior findings serve to further validate results used for the development of this neoadjuvant nomogram.

The strengths of this study are represented by the large neoadjuvant sample size and validation using an independent external population. Our nomogram achieved a C-index of 0.729 in the MGH cohort, and the strength of the model was then confirmed by a C-index of 0.712 in the external MSK validation cohort. In addition, the calibration plot demonstrated almost perfect accuracy in predicting 1-year, 3-year, and 5-year OS. Validation of the nomogram was essential to avoid overfitting of the model and determine generalizability. In our study, calibration plots showed optimal agreement between predicted and actual observed survival, which ensures the reliability and reproducibility of the established nomogram. While these findings were helpful, the power of this nomogram arguably arises from the significantly improved predictive potential compared with the eighth edition AJCC TNM staging system using both the MGH and MSK cohorts. This is critical given that the AJCC system does not adequately discriminate

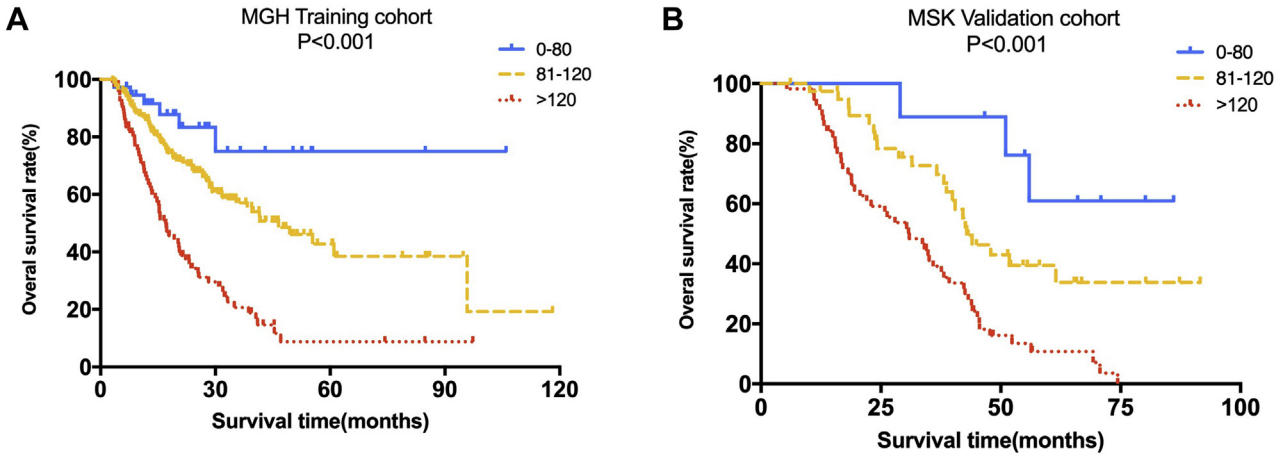

Figure 4. Group prognostication of OS using nomogram cutoff values. *OS*, overall survival.

between patients who underwent neoadjuvant therapy versus upfront resection.

The present study has several limitations. First, the current nomogram model was derived based on a population in the United States. Global application of findings relies on inclusion of Far-Eastern, South American, and European patients for additional validation. Second, this is a retrospective study in which selection biases are unavoidable, despite attempts to minimize these using large, independent cohorts of consecutive patients. Third, the recorded metrics do not include performance status and comorbidity profile, which are important determinants of survival following surgery. Finally, variability in neoadjuvant regimens could curtail broad application, including both variation between chemotherapy regimens as well as the use of radiation therapy. Due to the relatively small numbers of patients across different chemotherapy and radiation subgroups, validation of individual subgroups (for example, gemcitabine-based versus FOLFIRINOX) was not performed.

In conclusion, we established and validated a novel MGH/MSK nomogram for predicting the survival of patients who underwent neoadjuvant therapy followed by pancreatectomy. This model allows clinicians to estimate the survival of individual patients following neoadjuvant therapy more precisely in patients with pancreatic cancer. Future perspectives and staging systems should focus on the inclusion of novel biochemical and molecular biomarkers, which may be integrated into predictive prognostic models.

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Conflict of interest/Disclosure

The authors who have taken part in this study have nothing to disclose.

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