Development And Validation Of A Prognostic Nomogram For Overall And Disease-Specific Survival In Patients With Sarcomatoid Urothelial Carcinoma

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Abstract

Introduction: Sarcomatoid urothelial carcinoma (SUC) is a rare and aggressive variant of bladder cancer with limited data guiding prognosis. In this study, we present the first prognostic nomograms in the literature for 3- and 5- year overall survival (OS) and disease-specific survival (DSS), for patients with SUC derived from Survival, Epidemiology and End Results (SEER) database.

Materials and Methods: The SEER database was searched for patients with invasive (≥T1) disease, using the topography codes C67.0-C67.9 (bladder cancer), and the morphologic code 8122 (SUC). Patients included were randomly divided into a training (TC) and a validation cohort (VC) (7:3 ratio). Variables significantly associated with OS and DSS were identified with multivariate (MVA) Cox regression and were used to build the nomograms. Harrel's C-statistic with bootstrap resampling and calibration curves were used for internal (training cohort-TC) and external (validation cohort-VC) validation. Clinical utility of the nomograms was assessed with the decision curve analysis (DCA). Goodness of fit between the nomograms and the AJCC 8th edition staging system was compared with the likelihood ratio test (LRT).

Results: A total of 741 patients with SUC were included (507 TC, 234 VC). No statistically significant differences in baseline characteristics were identified between the two cohorts. Sex, SEER stage, radical cystectomy and chemotherapy were common variables for the OS and the DSS nomogram with the addition of age in the former. Optimism-corrected C-statistic for the nomograms was 0.68 and 0.67 for OS and DSS respectively. In comparison, C-statistic for AJCC was 0.59 for OS and 0.60 for DSS ($p<0.001$). Calibration curves constructed for the nomograms showed appropriate consistency between predicted and actual survival. The nomograms demonstrated optimal clinical utility in the DCA, outperforming the AJCC staging system, by maintaining a higher clinical NB than treat all, treat none and AJCC curves, across threshold probabilities.

Conclusion: We present the first prognostic nomograms developed patients with SUC. Our models demonstrated superior prognostic performance to the gold standard AJCC system, by utilizing a set of variables readily available in daily practice and may serve as useful tools for the individualized risk assessment of patients with this rare disease.

Keywords: nomograms, cystectomy; sarcomatoid bladder cancer; SEER program, urinary bladder neoplasms; urothelial carcinoma

Introduction

Sarcomatoid urothelial carcinoma (SUC) is a rare bladder tumor, classified as a histologic variant of urothelial origin, as per the latest WHO 2016 guidelines.[1] As its name implies, SUC demonstrates a mixture of histologic features of urothelial and mesenchymal ("sarcomatous") components[2], which initially led to its labelling as "carcinosarcoma".[3] Reported incidence of SUC varies anywhere between 0.1-0.3% of urinary bladder neoplasms[4], which make it one of the rarest tumor types of that organ. Observational data suggest a predilection for older adults compared to conventional UC[5], as well as an association with radiation and cyclophosphamide treatment.[6] Evidence from population-based studies and institutional series suggest that SUC confers a poorer prognosis compared to its conventional UC counterpart, with variable response to chemotherapy regimens[5]·[7], however a systematic approach to the development of a dedicated prognostication tool is lacking in the literature. In this study, we present novel prognostic nomogram for overall survival (OS) and disease-specific survival (DSS) designed for patients with SUC, by utilizing patient-level data from the Surveillance, Epidemiology, and End Results program (SEER), aiming to provide a useful clinical tool in the individualized risk assessment of patients with this rare bladder tumor.

Materials and Methods

A. Identification of patients in the SEER database

The SEER Research Plus database (18 registries/November 2020), is a National Cancer Institute (NCI) supported database with multiple participating institutions across the United States (US), providing demographic, clinicopathologic, treatment and outcomes data for patients diagnosed with any type of malignancy. Approval to use the database was obtained institutionally via the eRA Commons platform (https://www.era.nih.gov/era-training/era-commons.htm), after electronically signing the required data user agreement (DUA) for the fair use of data. All data

included in the SEER database are de-identified, in order to avoid breach of sensitive patient health information. In addition, although not explicitly required by the SEER Research Plus DUA, we elected to mask any cell values <11, as an extra precaution of avoiding identification of individuals listed in the database. No IRB approval was required for this study.

We searched the SEER Research Plus database with the case-listing method for patients diagnosed with SUC of the bladder, utilizing the International Classification of Disease topography codes for the urinary bladder (C67.0 - C67.9) and the morphologic code 8122 for SUC ("transitional cell carcinoma, spindle cell"). Inclusion criteria were: i)adult patients (≥18yo), ii) invasive tumors (≥T1), iii) confirmed by microscopic examination of a surgical specimen (local excision/TURBT or cystectomy), iv) available data for American Joint Committee on Cancer (AJCC) 8th edition staging and SEER staging, v)survival data available for >0 months. All AJCC staging classifications for editions 6th and 7th used for patients diagnosed in or after 2004 were manually extrapolated to the 8th edition, [8] while patients diagnosed before 2004 were excluded due to significant differences between AJCC 3rd TNM edition staging used in these cases, and subsequent AJCC editions, which did not allow for safe and accurate extrapolation.

B. Extracted variables

Demographic (age at initial diagnosis, gender, race, median income, rural vs metropolitan area), clinicopathologic (TNM stage, AJCC stage, SEER stage), treatment (radiation, radical cystectomy, chemotherapy) and survival data (months from diagnosis to death or last follow-up, status at last follow-up, cause of death) were extracted. AJCC staging 8th edition was utilized as described above. In addition, the SEER staging system which converts the four AJCC stages to three disease categories (Localized, Regional, Distant) was also utilized, modified by the authors to reflect the recent changes on the AJCC 8th edition. More specifically, patients with N3 disease as per AJCC 8th Edition, previously classified as M1 - metastatic stage IV disease on AJCC 6th and 7th edition, were also previously considered to be of Distant stage as per SEER. These patients were manually converted to Regional SEER stage to better reflect the prognostic significance of the new AJCC edition. Of note, the SEER database utilizes a combination of clinical and pathologic information from imaging, biopsies, TURBT, RC and autopsies to estimate TNM stage. For that reason, general terms T, N or M for a "composite stage", without the defining clinical (c) or pathologic (p) terms (e.g. cT, pT) were used. In addition, it should be noted that we approached chemotherapy and radiotherapy as a dichotomous

variable (patient received/did not receive therapy), without specifying whether this was in the (neo)adjuvant or palliative setting, because of the limitations in the reporting of systemic therapy/radiotherapy sequencing data. More specifically, although SEER Research Plus often provides data on whether the chemotherapy/radiotherapy was given prior/after surgery, neither the type of surgery nor the intent of systemic treatment is specified.

C. Statistical Analysis – Development of nomograms

Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY, IBM Corp. Released 2015) and R version 4.2.0. The following statistical packages were used in R: *survival, survminer, rms, rcorrcens, rmda*. Initially, patients fulfilling the eligibility criteria were randomly divided to two groups with a ratio of 7:3. The first group (~70% of the sample) was used as the training cohort and the second group (~30% of the sample was used as the validation cohort. A multivariate Cox proportional hazards model was utilized to identify variables associated with OS (time from bladder cancer diagnosis to death from any cause) and DSS (time from bladder cancer diagnosis to death from bladder cancer) in the training cohort. Selection of variables for the multivariate model was based on known factors associated with survival (e.g. AJCC stage, RC, chemotherapy, radiation), as well as clinical reasoning based on known literature, and not on factors significant on univariate analysis ("univariate pre-filtering"), as this approach has not been proven to improve stability of the model, with the additional risk of overlooking important adjustment variables needed for control in an etiologic model.[9]·[10] An alpha error of 5% (two-tailed) was set as the cutoff of statistical significance for all statistical tests utilized. Variables found to be non-significant in the multivariate Cox regression were eliminated with the backwards stepwise conditional approach to arrive to the final model, which was then used to build the nomograms for 3- and 5-year OS and DSS, using the following formula: $\boldsymbol{Probability\ of\ an\ event\ at\ time\ t=S_0(t)^{exp(\beta_1 x_1, \beta_2 x_2 \cdots)}}$, where β are the regression coefficients and x are the observed values of the covariates. $S_0(t)$ is called the baseline survival function and is also estimated from the data. Regression coefficients are used to construct the variable axes in the nomogram and S0 is used in the translation from total points to predicted probability.[11]

D. Statistical Analysis - Validation of nomograms and comparison with AJCC staging

Internal validation of the nomograms was performed on the training cohort and external validation on the validation cohort, by utilizing Harrel's C-index for censored data (rcorrcens function in R), which corresponds to the area under

the curve (AUC) in the Receiver-operating Characteristic curve (ROC curve).[12] To minimize overfitting bias, bootstrap resampling method (B=1000) was applied to both cohorts and only the optimism-corrected C-indices (with 95% confidence intervals) were reported for the nomograms. C-indices were also provided for the AJCC 8th edition in relation to OS and DSS prognosis with the same method (rcorrcens). C-index values range between 0.5 (discrimination not better than chance alone) and 1 (optimal discrimination), with values ~ 0.7 indicating a good prognostic model, 0.8 a strong prognostic model and 1 the perfect fit.[12]. In addition, we designed calibration curves estimating the association between survival predicted by nomogram and actual survival of the cohorts. In a perfectly fitting nomogram, the prediction is expected to lie on a 45-degree diagonal of the calibration curve.[13]

To further assess the goodness of fit of the nomograms in comparison to AJCC staging, we calculated the log likelihood for each model (lower log likelihood values suggests better fit), and then we utilized the likelihood ratio chi squared test, which compares the log likelihoods of different models and provides a p-value. Akaike Information Criterion (AIC), derived from the formula AIC = -2(log-likelihood) + 2K, with K as the number of model parameters, was also used to compare the models.[14] For the sake of that comparison, lower AIC values correspond to a model with a better fit. No p-value is calculated for differences in AIC. It should be noted that we did not directly compare the differences in the C-indices, because C-statistic has been associated with a lower power for discrimination among alternative models, as Harrel et al. have demonstrated.[15]

E. Statistical Analysis – Decision curve analysis and comparison with AJCC staging

Clinical utility and applicability of the nomograms was further assessed with the decision curve analysis (DCA) method, and compared with the AJCC 8th edition staging system, both in the training and the validation cohort. DCA is a method for assess the clinical benefit of a designated model, as well as its benefit or harm compared to standard strategies.[16] This is applied to nomograms by quantifying net benefits (NB) at different threshold probabilities. This method allows for the estimation of the NB to the patient if the prognostic nomogram vs. the AJCC 8th edition staging system is utilized. The curves of treat-all-patients scheme (highest clinical costs) and the treat-none scheme (no clinical benefit) are plotted as default references. A model is only clinically useful at threshold T if it has a higher NB than treat all and treat none, throughout a wide range of threshold probabilities.[16] In addition, we evaluated whether the

nomogram under study has a higher NB than the default AJCC strategy throughout threshold probabilities, by visual comparison of the curves.

Results

A. Baseline patient characteristics

We identified 741 patients fulfilling the eligibility criteria, diagnosed between 2004 - 2018. Clinicopathologic and treatment data are summarized on tables 1A-B. Males comprised 68% of the cohort. Median age of diagnosis was 71 years (IQR 64-81), with more than half of the patients diagnosed after the age of 70 (58%). The majority of patients were Caucasian Whites, married, with an annual income of >60k, coming from large metropolitan areas (>1million people). In terms of staging, most patients had muscle invasive disease (AJCC Stage II) +/- extravesical spread beyond the muscle wall and/or lymph node involvement (AJCC Stage III), with 11% of the patients being diagnosed with locally advanced/metastatic disease (AJCC Stage IV). Around half of the patients underwent radical cystectomy (RC, 48%), while chemotherapy and radiation was administered to 37% and 13% respectively. Median follow-up time was 64 months (95% CI; 56.3-71.7) in the entire cohort. Median OS was 12 months (95%CI; 9.8-14.2) and median DSS was 17 months (95% CI; 13.1-20.9).

After random sampling, 507 patients were included in the training cohort and 234 in the validation cohort (ratio ~7:3). No statistically significant differences in baseline patient characteristics were observed between the training and the validation cohort, table 1A-B. Survival outcomes were similar between the two different cohorts; median OS was 12 months (95% CI; 9.6-14.4) in the training cohort and 13 months (95% CI; 9.4-16.6) in the validation cohort, p = 0.660. Median DSS was 17 months (95% CI; 11.9-22.1) in the training cohort and 17 months (95% CI; 12.1-21.9) in the validation cohort, p=0.876.

B. Nomograms for OS and DSS

Results of the multivariate Cox regression for OS and DSS in the training cohort are shown in Tables 2A-B. Out of 11 variables inserted in the multivariate models (age, sex, race, marital status, median income, area of residence, tumor size, combined SEER stage, RC, chemotherapy, radiotherapy), six variables were selected for the final OS model (age, sex, tumor size, combined SEER stage, RC, chemotherapy regardless of intent) and five variables for the DSS model

(sex, tumor size, combined SEER stage, RC, chemotherapy regardless of intent) with the backwards stepwise conditional method. A nomogram predicting 3- and 5-year mortality was constructed based on the final model, both for OS and DSS, which are shown at Figure 1A-B. Points assigned to every variable category are shown at supplementary Table 1.

C. Internal and external validation of nomograms

In terms of internal validation, the C-indices (95% CI) for the OS and DSS nomograms in the training cohort were 0.68 (0.64 – 0.70) and 0.67 (0.62 - 0.69) respectively (optimism-corrected). In comparison, C-indices for OS and DSS prognostication based on the AJCC 8th edition were 0.59 (0.55 - 0.62) and 0.60 (0.57 - 0.63) respectively. The likelihood ratio test demonstrated a statistically significant difference between the nomogram and the AJCC model, favoring the nomogram, ($p<0.001$). Calibration curves for the nomograms in the training cohort, constructed for 3- and 5-year timepoints also demonstrated appropriate consistency between the prediction by our nomograms and actual survival, figure 2A-D.

External validation was confirmed with the calculation of the C-indices when the nomograms were applied to the validation cohort. C-indices for OS and DSS calculated from the nomograms were 0.66 (0.63-0.72) and 0.67 (0.63-0.73), respectively (optimism-corrected). In comparison, C-indices for OS and DSS calculated from the AJCC 8th edition were 0.59 (0.56 - 0.62) and 0.61 (0.58 to 0.65) respectively. The likelihood ratio test demonstrated a statistically significant difference between the nomogram and the AJCC model, favoring the nomogram, ($p<0.001$). Calibration curves for the nomograms in the validation cohort, constructed for 3- and 5-year timepoints also demonstrated appropriate consistency between the prediction by our nomograms and actual survival, figure 2E-H.

D. Decision Curve Analysis

The DCA method was utilized to evaluate the clinical benefit of the nomograms both on the training and the validation cohort. The nomogram demonstrated a consistently higher NB than treat all and treat none strategies, throughout a wide range of threshold probabilities, both for OS and DSS, a finding corroborating to its clinical applicability. In addition, DCA curves generated by the nomogram scoring were consistently of higher NB than the DCA curves

generated by the AJCC 8th edition, both for OS and DSS, corroborating to the prognostic superiority of the former, figure 3.

E. Application of the nomograms – Risk Stratification

The nomograms developed for OS and DSS were utilized to assign a score of cumulative risk points to each patient in the study (supplementary table 1). In terms of OS, the median score calculated by the nomogram was 111 (SD ±47). Patients were then stratified to the following risk groups: low (0-64), intermediate (65-110), high (111-160), very high (161+). In terms of DSS, the median score calculated by the nomogram was 77(SD ±41). Patients were then stratified to the following risk groups: low (0-30), intermediate (31-70), high (71-110), very high (111+). Kaplan-Meier curves were constructed both for OS and DSS based on the risk stratification provided by the nomogram, with statistically significant discrimination demonstrated between the different categories ($p<0.001$ for all strata), with higher risk categories associated with worse survival outcomes, supplementary figures 1-2.

Discussion

SUC is a rare histologic variant of urothelial carcinoma with limited data on survival outcomes. Given its rarity, most of the prognostic information are extrapolated by conventional urothelial carcinoma. Its rare incidence and possibly unique underlying biology calls for a personalized approach to patients with this disease, and highlights the need to go beyond the limited scope of anatomic spread-based staging of the TNM/AJCC system. In that regard we offer the first prognostic nomograms in the literature for OS and DSS in patients with SUC, developed and validated both internally and externally, on a retrospective cohort of SUC cases derived from the SEER database. Our nomograms are easy to use on daily clinical practice, by encompassing a combination of clinicopathologic (age, sex, tumor size, SEER stage) and treatment variables (radical cystectomy, chemotherapy regardless of intent), which are readily available regardless of the healthcare setting (academic, community). Every patient is assigned a set of points per condition satisfied (suppl Table 1) and the total number of points can be used to assign the patients to four different risk categories; low intermediate, high and very high risk. The discriminatory performance of this stratification was also successfully demonstrated by the constructed KM curves (suppl Figures) for OS and DSS. Overall, our nomograms may ideally serve as a unique prognostic tool, offering an individualized risk assessment in a population of patients diagnosed with a disease for which limited prognostic data exists.

In terms of internal and external validation, both nomograms demonstrated appropriate goodness of fit in the training and the validation cohort, with an optimism-corrected Harrel's C-statistic approaching 0.7 for both OS and DSS. The constructed calibration curves showed appropriate consistency between nomogram-predicted and actual OS/DSS, both in the training and the validation cohort. Our nomogram-based prognostic models were also found to have a significantly superior goodness of fit compared to the gold standard AJCC 8^{th} edition staging, which can be inferred by the numerically higher C-statistics and further confirmed with the lower AIC values as well as the statistically significant difference in log likelihoods, obtained with the likelihood ratio test. Furthermore, our nomograms showed optimal clinical utility in the DCA analysis, also outperforming the AJCC staging system, by maintaining a higher clinical NB than treat all, treat none and AJCC curves, across threshold probabilities. In addition, the KM curves stratified by the risk strata of the nomogram, showed a better discriminatory ability than AJCC, both in the training and the validation cohort.

Nomograms are increasingly utilized as a promising method with many advantages in prognostic assessment in oncology over the TNM system.[11] By providing a visual representation of complicated multivariate models, they are allowing a better interpretation of survival models and allow for easier integration of these models to daily clinical practice. In addition, unlike TNM, which is solely depending on the anatomical spread of the disease and does not account for the heterogeneity in clinical outcomes seen between patients of similar stages, nomograms are able to incorporate a combination of demographic, clinical, pathologic and treatment information and provide a comprehensive risk assessment for a specific outcome (e.g. risk of recurrence, death), at the level of the individual patient. They can inform a series of management decisions in oncology, e.g. by providing preoperative assessment of positive surgical margins and lymph node metastases for selection of patients requiring extensive surgery [17], estimating the likelihood of recurrence, cancer-specific and overall survival after an intervention[18] while also becoming extremely useful in assessing prognosis in rare histological types of cancer, for which prognostic information is based on extrapolation from more common histologic diagnoses.[19]

The limitations of our study are pertaining to the retrospective nature of the SEER database. These include selection bias due to lack of randomization, data heterogeneity due to cases from multiple institutions and a wide timeframe of diagnosis, predisposing to variable diagnostic and treatment modalities and surveillance plans across time and health-care facilities, as well as inconsistent documentation across of the cases in the database itself, due to user-specific attributes. AJCC system has also seen significant changes throughout history, impacting the interpretation of staging in older cases, as well as the safe extrapolation to the current 8th edition. In addition, in the majority of the cases SEER provides a composite stage for T, N and M with limited data distinguishing between the clinical and pathologic setting. This also limits the assessment of pathologic response of treatments such as neoadjuvant chemotherapy. In terms of the documented interventions, while there is satisfactory granularity of data pertaining to types of surgical procedures, the way of documenting the timing of chemotherapy and radiotherapy does not allow for an accurate estimation of the intent of the respective systemic treatments (neoadjuvant, adjuvant, palliative, chemoradiotherapy etc.). In addition, data on the exact chemotherapeutic regimen (e.g. cisplatin-based, carboplatin-based) are lacking. Lastly, no data on novel treatments such as immune checkpoint inhibitors, antibody-drug conjugates and other targeted treatments (e.g. erdafitinib), are not documented at all. Despite the above, to our knowledge, this is the first set of nomograms

developed for prognostic classification of patients with SUC, hoping to provide an individualized risk assessment to patients with this rare disease.

Conclusion

In this study, we present the first prognostic nomograms in the literature for OS and DSS designed for patients with SUC. The nomograms were both internally and externally validated in our training and validation cohort respectively, showing satisfactory discriminatory performance and an optimal net clinical benefit across a threshold of clinical probabilities. Based on the points generated by the nomograms, we also provided a risk stratification of SUC patients into four distinct categories (low, intermediate, high and very high), with appropriate separation of curves in the KM analysis. These nomograms were proven to be superior to the current gold standard of AJCC staging, in terms of prognostic performance and clinical utility. These nomograms could serve as a valuable tool in an individualized risk assessment in patients with SUC, while further validation at other independent cohorts, or possible prospective validation would be desirable.

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Tables and Figures

Table 1A – Demographic data of patients with SUC and comparison between Training and Validation cohorts

	Total (741)	**Training cohort (507)**	**Validation cohort (234)**	**p-value**
Variables	**N (%)**	**N (%)**	**N%**	
Age Category				.321
<60	105 (14)	67 (13)	38 (16)	
60 – 69	208 (28)	137 (27)	71(30)	
70 – 79	216 (29)	157 (31)	59 (25)	
80+	212 (29)	146 (29)	66 (28)	
Sex assigned at birth				.128
Male	502 (68)	334 (66)	168 (72)	
Female	239 (32)	173 (34)	66 (28)	
Race				.431
Non-hispanic White	590 (80)	411 (81)	179 (77)	
Hispanic	56 (8)	39 (8)	17 (7)	
Black	57 (8)	35 (7)	22 (9)	
API	35 (5)	20 (4)	15 (6)	
Other/NA	<11*	<11*	<11*	
Married				.382
No	332 (45)	233 (46)	99 (42)	
Yes	409 (55)	274 (54)	135 (56)	
Median Income				.415
<60.000	228 (31)	159 (31)	69 (30)	
60-74.000	310 (42)	204 (40)	106 (45)	
>75.000	203 (27)	144 (28)	59 (25)	
Area of residence				.935
>1.000.000 ppl	460 (62)	315 (62)	145 (62)	
<1.000.000 ppl	182 (25)	123 (24)	59 (25)	
Suburban/Rural	99 (13)	69 (14)	30 (13)	

Abbreviations: ppl – population, API - Asian/Pacific Islander, NA – not available

Table 1B - Clinicopathologic characteristics

	Total (741)	Training cohort (507)	Validation cohort (234)	
Variables	**N (%)**	**N (%)**		**P-value (χ^{2})**
Grade of tumor differentiation				.302
Well, Grade I	<11	<11	<11	
Moderate, Grade II	<11	<11	<11	
Poor, Grade III	169 (23)	110 (22)	59 (25)	
Anaplastic, Grade IV	448 (61)	310 (61)	138 (59)	
N/A	113 (15)	82 (16)	31 (13)	
Tumor size				.648
<5cm	247 (33)	163 (32)	84 (36)	
5 - 9.9cm	241 (33)	171 (34)	70 (30)	
10+cm	49 (7)	35 (7)	14 (6)	
NA	204 (28)	138 (27)	66 (28)	
T stage				.665
T1	148 (20)	96 (19)	52 (22)	
T2	313 (42)	211 (42)	102 (44)	
T3	176 (24)	127 (25)	49 (21)	
T4	97 (13)	67 (13)	30 (13)	
Tx/NA	<11	<11	<11	
N stage				.818
N0	589 (80)	409 (81)	180 (77)	
N1-3	126 (17)	81 (16)	45 (19)	
Nx	26 (4)	17(3)	<11	
M stage				.679
M0	662 (89)	455 (90)	207 (89)	
M1	74 (10)	48 (10)	26 (11)	
Mx	<11	<11	<11	
AJCC 8th edition				.782
I	137 (19)	89 (18)	48 (21)	
II	261 (35)	182 (36)	79 (34)	
III	260 (35)	180 (36)	80 (34)	
IV	83 (11)	56 (11)	27 (12)	
Combined SEER Stage				.935
Localized	398 (54)	271 (54)	127 (54)	
Regional	260 (35)	180 (35)	80 (34)	
Distant	83 (11)	56 (11)	27 (12)	
Surgical excision				.356
Radical Cystectomy	352 (48)	241 (48)	111 (47)	
Partial cystectomy	30 (4)	17 (3)	13 (6)	
Localized treatment/TURBT	359 (48)	249 (49)	110 (47)	
Chemotherapy				.120
No	464 (63)	327 (66)	137 (59)	
Yes	277 (37)	180 (36)	97 (42)	
Radiation				.930
No	648 (87)	443 (87)	205 (88)	
Yes	93 (13)	64 (13)	29 (12)	

Abbreviations: AJCC – american joint committee on cancer, TURBT – transurethral resection of bladder tumor, NA – not available

Table 2A – Multivariate Cox regression analysis for factors associated with overall survival (OS) in the training SUC cohort (full model and stepwise conditional model)

N=507	**Full Model**		**Backwards Stepwise Conditional**	
Variables	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
Age Category				
<60	REF		REF	
60 – 69	1.05 (0.71 – 1.57)	.804	1.08 (0.73 – 1.60)	.718
70 – 79	1.28 (0.88 – 1.88)	.201	1.32 (0.91 – 1.92)	.142
80+	1.78 (1.20 – 2.62)	*.004*	1.79 (1.22 – 2.63)	*.003*
Sex assigned at birth				
Male	REF		REF	
Female	1.19 (0.93 – 1.52)	.162	1.25 (1.00 – 1.56)	*.050*
Race				
Non-hispanic White	REF			
Hispanic	0.87 (0.57 – 1.33)	.527	-	
Black	1.25 (0.85 – 1.85)	.261	-	
API	0.70 (0.36 – 1.33)	.272	-	
Other	1.80 (0.24 – 13.41)	.857	-	
Marital Status				
Not married	REF		-	
Married	0.92 (0.73 – 1.17)	.504	-	
Median Income				
<60.000	REF		-	
60-74.000	0.94 (0.70 – 1.27)	.701	-	
>75.000	0.99 (0.71 – 1.39)	.978	-	
Area of residence			-	
>1.000.000 ppl	REF		-	
<1.000.000 ppl	1.22 (0.82 – 1.80)	.331	-	
Suburban/Rural	1.19 (0.80 – 1.78)	.381	-	
Tumor size				
<5cm	REF		REF	
5 - 9.9cm	1.45 (1.10 – 1.90)	*.008*	1.48 (1.13 – 1.94)	*.004*
10+cm	2.21 (1.44 – 3.38)	*<.001*	2.31 (1.52 – 3.49)	*<.001*
N/A	1.14 (0.85 – 1.53)	.385	1.16 (0.86 – 1.55)	.331
Combined SEER Stage				
Localized	REF		REF	
Regional	2.35 (1.80 – 3.07)	*<.001*	2.36 (1.82 – 3.06)	*<.001*
Distant	2.82 (2.02 – 3.94)	*<.001*	2.71 (1.96 – 3.75)	*<.001*
Radical Cystectomy				
No	REF		REF	
Yes	0.48 (0.37 – 0.64)	*<.001*	0.47 (0.36 – 0.62)	*<.001*
Chemotherapy				
No	REF		REF	
Yes	0.77 (0.60 – 0.98)	*.030*	0.77 (0.61 – 0.97)	*.024*
Radiation				
No	REF		-	
Yes	1.02 (0.73 – 1.42)	.908	-	

Abbreviations: SUC – sarcomatoid urothelial carcinoma, aHR – adjusted hazard ratio, CI – confidence interval, API - Asian/Pacific Islander, SEER – survival, epidemiology and end results program, AJCC – american joint committee on cancer, API – Asian/Pacific Islander

Table 2B – Multivariate Cox regression analysis for factors associated with disease-specific survival (DSS) in the training SUC cohort (full model and stepwise conditional model)

N=234	**Full Model**		**Stepwise Conditional**	
Variables	**aHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
Age Category				
<60	REF		-	
60 – 69	0.90 (0.59 – 1.36)	.607	-	
70 – 79	1.02 (0.68 – 1.53)	.915	-	
80+	1.29 (0.85 – 1.94)	.232	-	
Sex assigned at birth				
Male	REF		REF	
Female	1.25 (0.95 – 1.64)	.109	1.35 (1.05 – 1.72)	*.019*
Race				
Non-hispanic White	REF			
Hispanic	0.76 (0.47 – 1.22)	.254	-	
Black	1.07 (0.68 – 1.68)	.778	-	
Asian	0.67 (0.32 – 1.39)	.348	-	
Other	2.68 (0.35 – 19.75)	.348	-	
Marital Status				
Not married	REF		-	
Married	0.87 (0.67 – 1.13)	.306	-	
Median Income				
<60.000	REF		-	
60-74.000	0.95 (0.68 – 1.32)	.758	-	
>75.000	0.93 (0.64 – 1.36)	.717	-	
Area of residence			-	
>1.000.000 ppl	REF		-	
<1.000.000 ppl	1.56 (0.99 – 2.45)	.053	-	
Suburban/Rural	1.39 (0.88 – 2.19)	.163	-	
Tumor size				
<5cm	REF		REF	
5 - 9.9cm	1.35 (1.00 – 1.84)	.053	1.45 (1.08 – 1.95)	*.015*
10+cm	2.49 (1.58 – 3.93)	*<.001*	2.58 (1.65 – 3.99)	*<.001*
N/A	1.05 (0.75 – 1.47)	.777	1.08 (0.78 – 1.50)	.653
Combined SEER Stage				
Localized	REF		REF	
Regional	2.30 (1.71 – 3.11)	*<.001*	2.35 (1.76 – 3.16)	*<.001*
Distant	3.30 (2.30 – 4.74)	*<.001*	3.15 (2.22 – 4.48)	*<.001*
Radical Cystectomy				
No	REF		REF	
Yes	0.50 (0.37 – 0.68)	*<.001*	0.44 (0.34 – 0.59)	*<.001*
Chemotherapy				
No	REF		REF	
Yes	0.73 (0.56 – 0.96)	*.025*	0.73 (0.56 – 0.93)	*.012*
Radiation				
No	REF		-	
Yes	1.10 (0.77 – 1.59)	.596	-	

Abbreviations: SUC – sarcomatoid urothelial carcinoma, aHR – adjusted hazard ratio, CI – confidence interval, API - Asian/Pacific Islander, SEER – survival, epidemiology and end results program ,AJCC – american joint committee on cancer, API – Asian/Pacific Islander

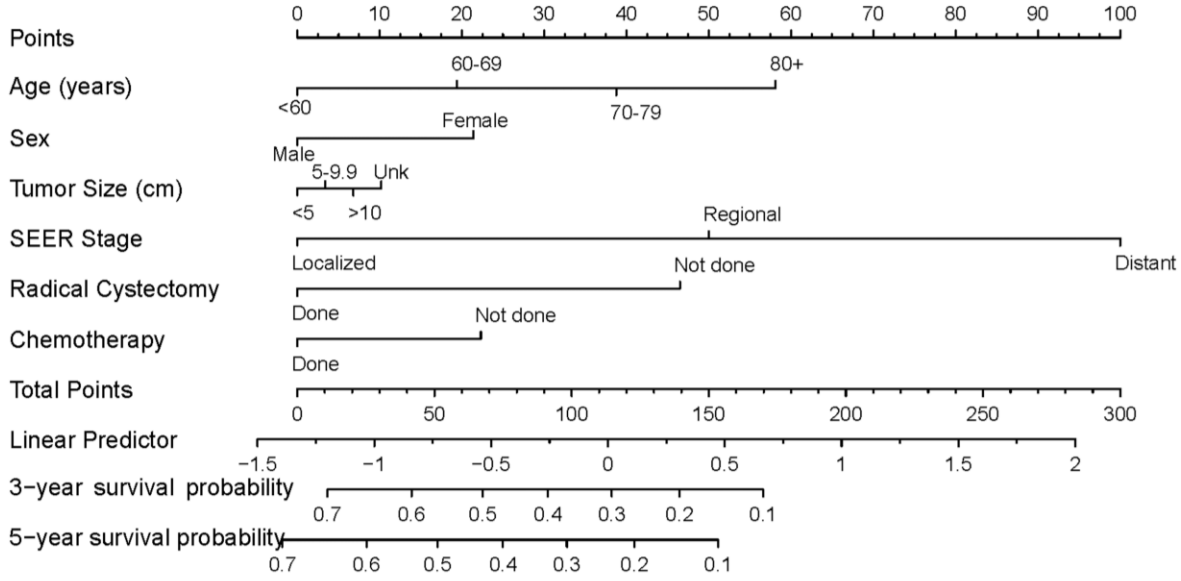
Table 3 - Comparison between the nomograms and the AJCC 8th edition as prognostic models for OS, DSS

	Nomogram	AJCC	P-value (LR χ^2 test)
Training cohort OS			
C-statistic (95% CI)	0.68 (0.64 – 0.70)	0.59 (0.55 - 0.62)	-
Log likelihood	-1926.86	-1962.345	*<.001*
AIC	3865.721	3926.691	-
Training cohort DSS			
C-statistic (95% CI)	0.67 (0.62 - 0.69)	0.60 (0.57 - 0.63)	-
Log likelihood	-1551.855	-1568.593	*<.001*
AIC	3113.709	3139.185	-
Validation cohort OS			
C-statistic (95% CI)	0.66 (0.63-0.72)	0.59 (0.56 - 0.62)	-
Log likelihood	-752.0144	-770.7571	*<.001*
AIC	1516.029	1543.514	-
Validation cohort DSS			
C-statistic (95% CI)	0.67 (0.63 - 0.73)	0.61 (0.58 - 0.65)	-
Log likelihood	-608.56	-770.7571	*<.001*
AIC	1227.12	1543.514	-

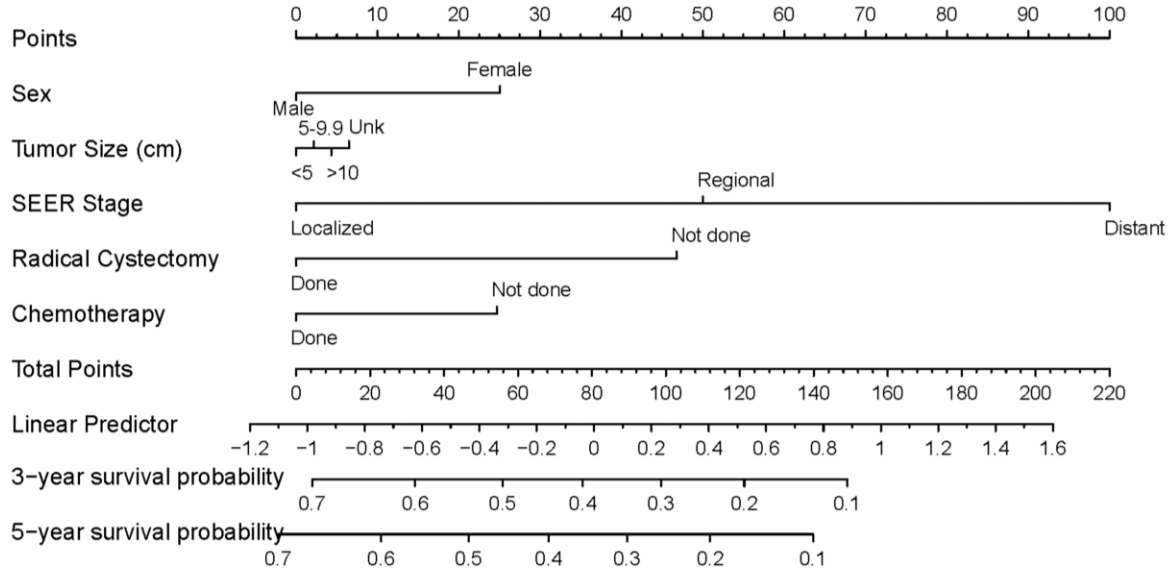
Abbreviations: OS – overall survival, DSS – disease-specific survival, AJCC – american joint committee for cancer, LR – likelihood ratio, CI – confidence interval, AIC – Akaike information criterion

Figures

Figure 1: A – Prognostic nomogram for 3- and 5- year overall survival (OS), B – Prognostic nomogram for disease-specific survival (DSS)



A



B

Figure 2 – Calibration curves for the nomograms. A-B) 3- and 5-year overall survival (OS) in the training cohort, C-D) 3- and 5-year disease-specific survival (DSS) in the training cohort, E-F) 3- and 5-year OS in the validation cohort, G-H) 3- and 5-year DSS in the validation cohort

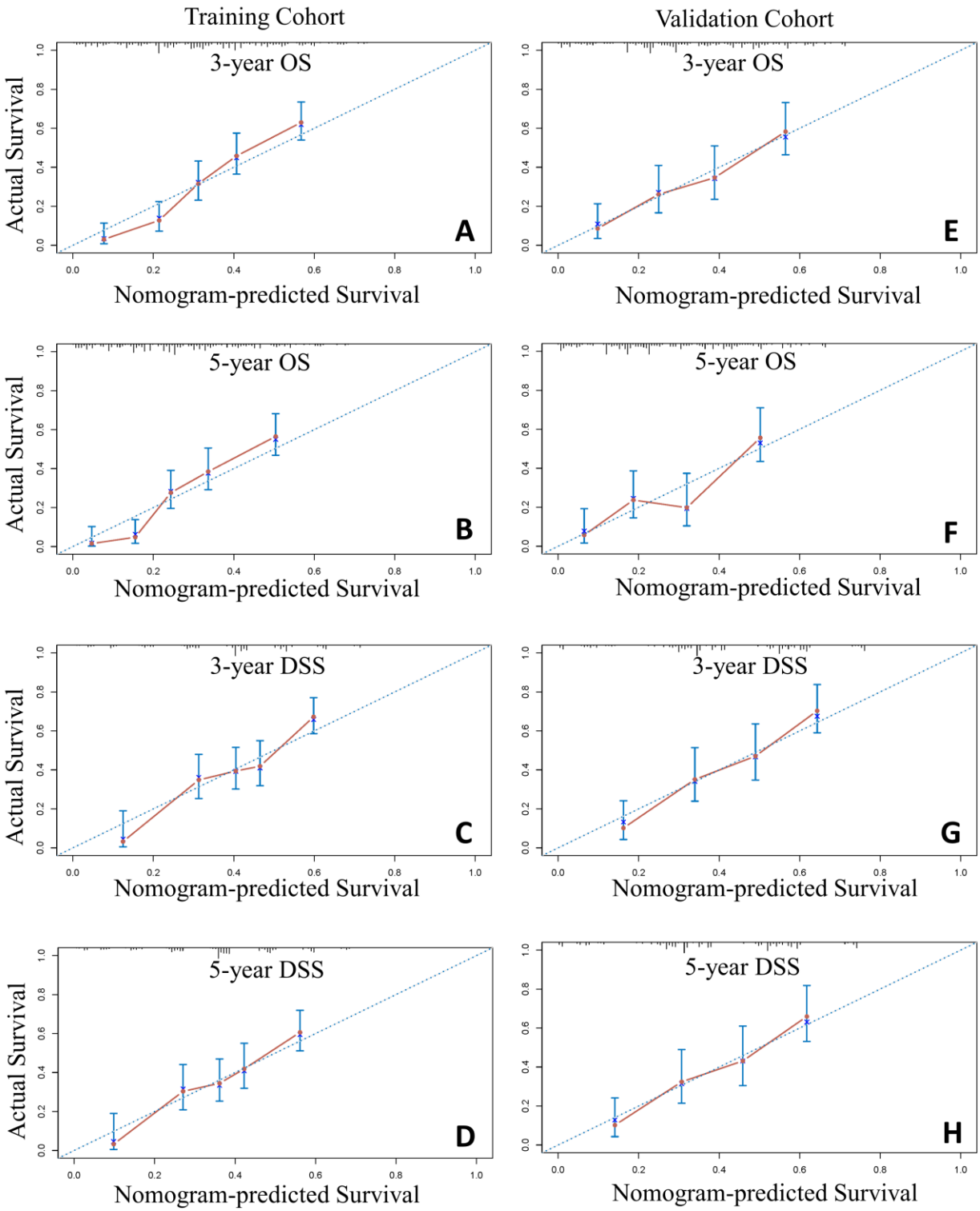
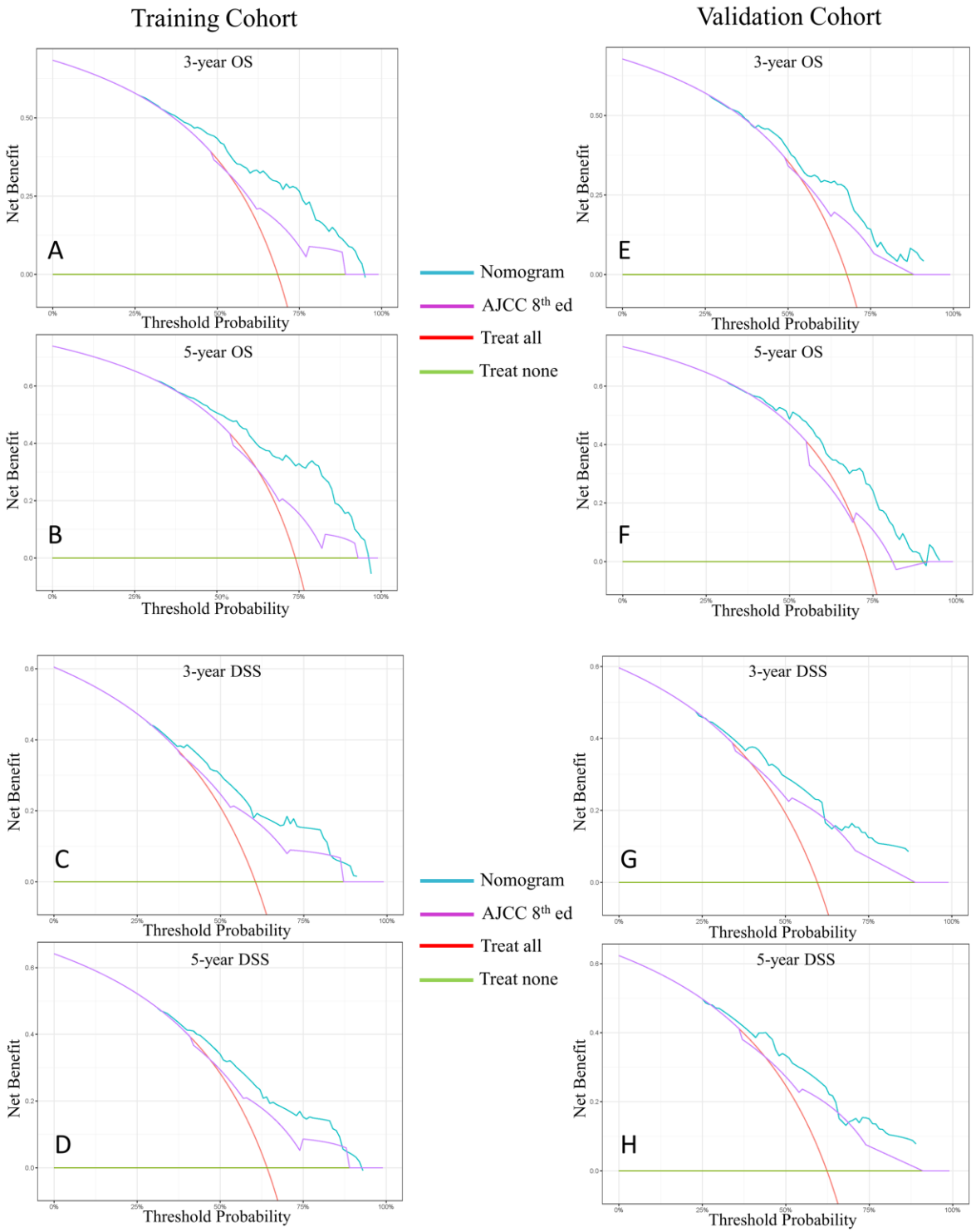


Figure 3 – Decision curve analysis for nomograms and AJCC 8th edition. A-B) 3- and 5-year overall survival (OS) in the training cohort, C-D)3- and 5-year disease-specific survival (DSS) in the training cohort, E-F) 3- and 5-year OS in the validation cohort, G-H) 3- and 5-year DSS in the validation cohort



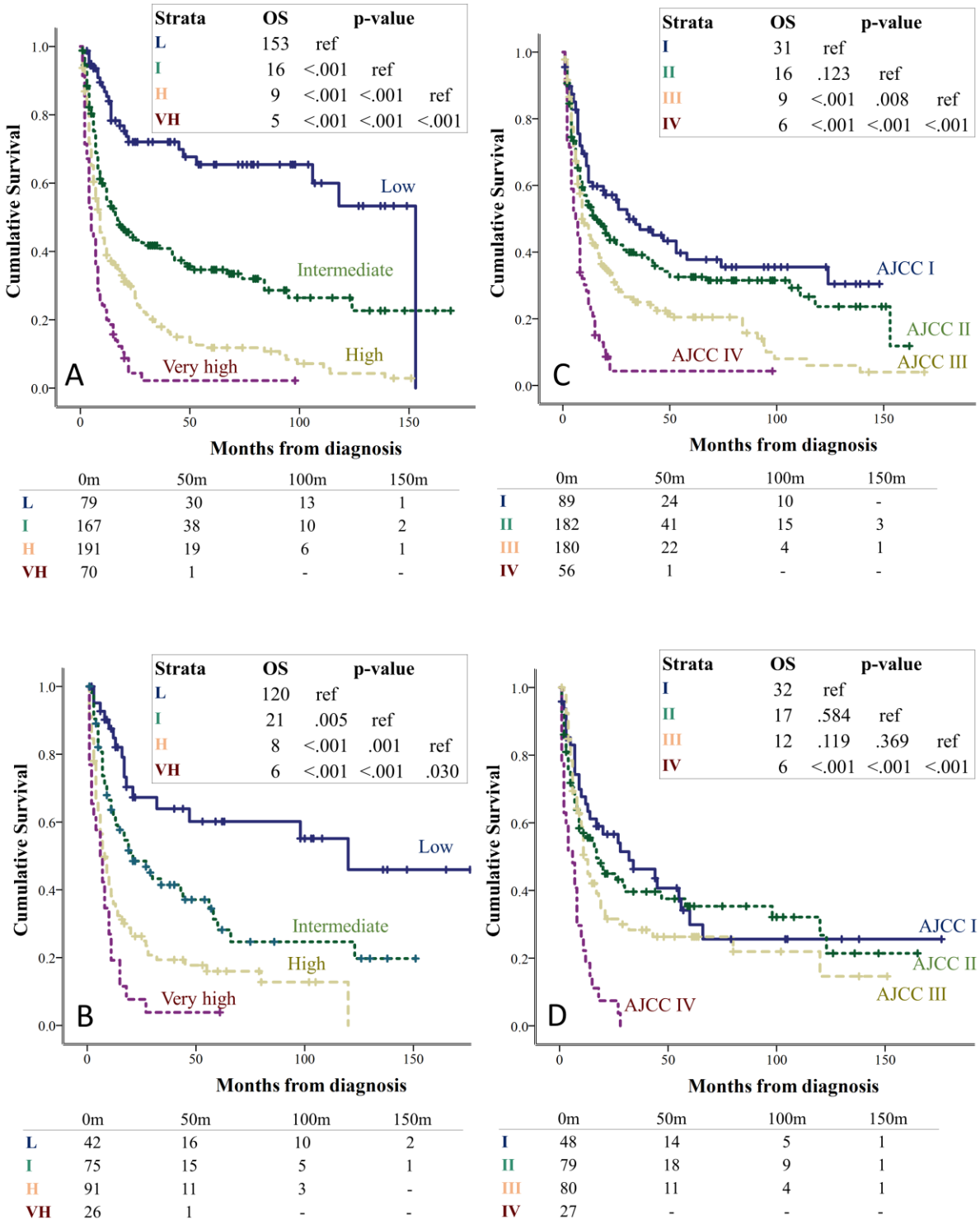
Supplementary material

Table 1 – Nomogram points

Variables		OS points	DSS points
Age Category			
	<60	0	-
	60 – 69	19	-
	70 – 79	39	-
	80+	58	-
Sex assigned at birth			
	Male	0	0
	Female	21	25
Tumor size			
	<5cm	0	0
	5-9.9cm	3	2
	≥10cm	7	4
	Unknown	10	6
SEER Stage			
	Localized	0	0
	Regional	50	50
	Distant	100	100
Radical cystectomy			
	Done	0	0
	Not done	46	47
Chemotherapy			
	Done	0	0
	Not done	22	25
Risk categories			
	Low	0-64	0-30
	Intermediate	65-110	31-70
	High	111-160	71-110
	Very High	161+	111+

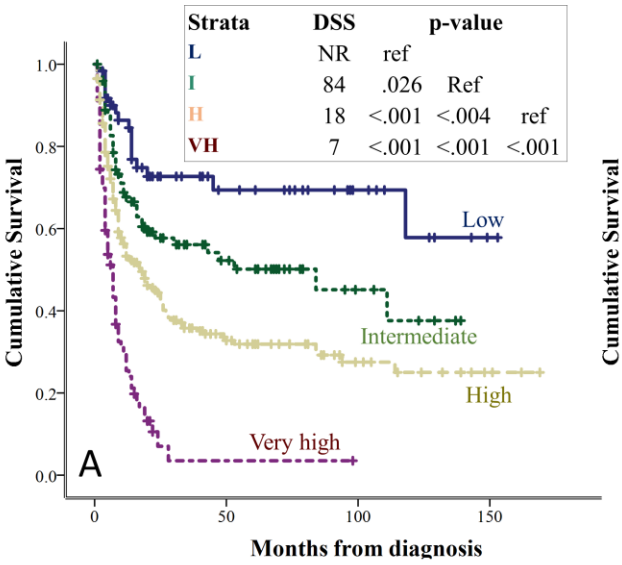
Abbreviations: SEER – survival, epidemiology and end results, OS – overall survival, DSS – disease-specific survival

Figure 1 – Kaplan-Meier curves for overall survival (OS). A) Nomogram (training cohort), B) Nomogram (validation cohort), C) AJCC (training cohort), D) AJCC (validation cohort)

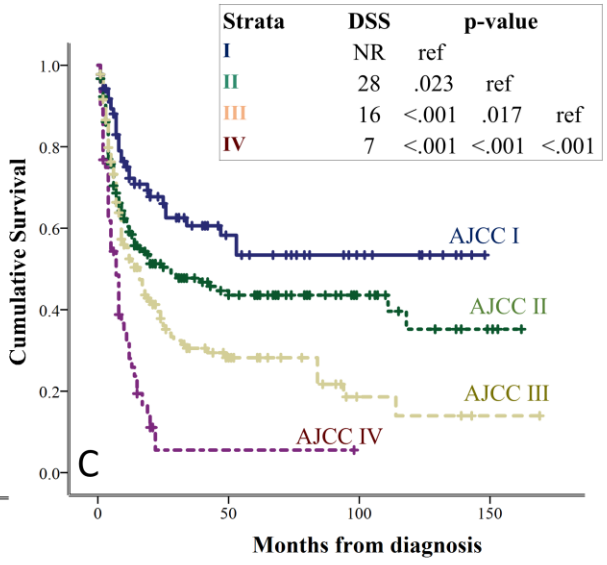


Abbreviations: L – low risk, I – intermediate risk, H – high risk, VH – very high risk

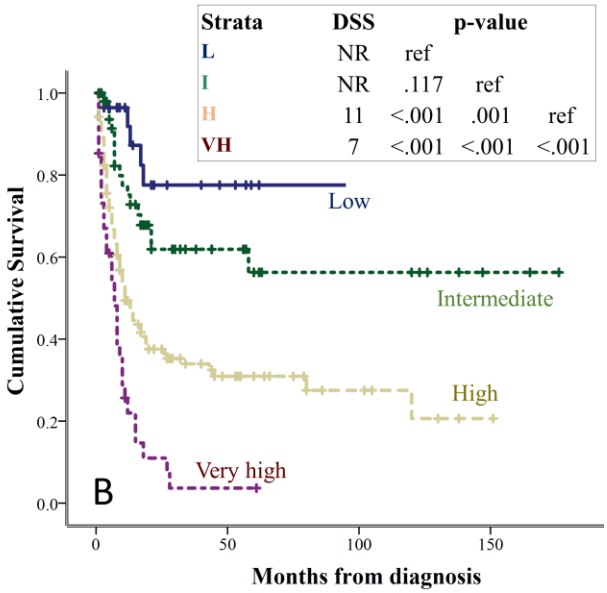
Figure 2 - Kaplan-Meier curves for disease-specific survival (DSS). A) Nomogram (training cohort), B) Nomogram (validation cohort), C) AJCC (training cohort), D) AJCC (validation cohort)



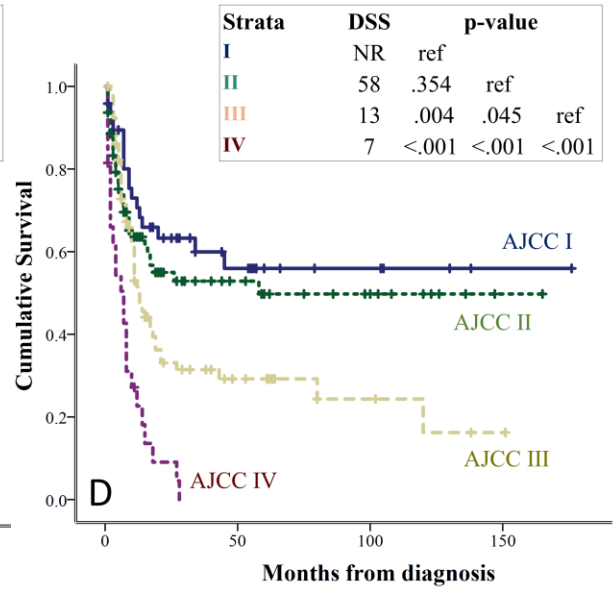
	0m	50m	100m	150m
L	61	20	9	1
I	100	26	7	-
H	256	41	13	2
VH	90	1	-	-



	0m	50m	100m	150m
I	89	24	10	-
II	182	41	15	3
III	180	22	4	1
IV	56	1	-	-



	0m	50m	100m	150m
L	29	11	5	-
I	51	13	7	2
H	120	18	6	1
VH	34	1	-	-



	0m	50m	100m	150m
I	48	14	5	1
II	79	18	9	1
III	80	11	4	1
IV	27	-	-	-

Abbreviations: L – low risk, I – intermediate risk, H – high risk, VH – very high risk