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Scientific Article

A Predictive Nomogram for Development of Lymph Node Metastasis in Muscle-Invasive Bladder Cancer Following Neoadjuvant Therapy

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Purpose: Pelvic lymph node metastases (ypN+) after multiagent neoadjuvant chemotherapy (NAC) is a poor prognostic sign in nonmetastatic muscle-invasive bladder cancer (nmMIBC). We sought to create a nomogram predicting probability of ypN+ after NAC for cN0 nmMIBC and determine association with overall survival (OS).

Methods and Materials: We reviewed the National Cancer Database for patients with cT2-4N0M0 urothelial carcinoma of the bladder receiving multiagent NAC and surgery from 2004 to 2020. Following a data split, univariate logistic regression identified variables associated with ypN+ at $P < .05$. Eligible variables were used for multivariate logistic regression and nomogram generation. A threshold for 95% sensitivity defined high- and low-risk groups for ypN+. Fine−Gray models assessed ypN+ risk group and OS, accounting for competing risks of surgical mortality.

Results: A total of 6194 patients were identified with a median follow-up of 39.5 months (interquartile range [IQR], 20.5-67.2 months). Most patients had high-grade (97.7%) cT2 disease (70.8%) with nonpapillary urothelial histology (67.3%) and initiated NAC at a median of 41.0 days after diagnosis (IQR, 28.0-59.0 days).The nomogram included age in decades (odds ratio [OR], 0.94; 95% confidence interval [CI], 0.87−1.03; $P = .172$), weeks from diagnosis to NAC (OR, 1.02; 95% CI, 1.01-1.04; $P = .004$), nonpapillary histology (OR, 1.17; 95% CI, 0.99-1.39; $P = .068$), and clinical T-stage. Within the testing cohort, ypN+ was found in 392 (22.8%) high-risk and 12 (8.0%) low-risk patients ($P < .001$), with median OS of 36.1 and 74.0 months, respectively ($P < .001$). High-risk patients had worse OS despite competing risks of 30-day (subdistribution hazard ratio [SHR], 1.80; 95% CI, 1.49-2.18; $P < .001$) and 90-day surgical mortality (SHR, 1.68; 95% CI, 1.39-2.04; $P < .001$).

Conclusions: This is the first study to provide a tool for predicting ypN+ and prognosticate worse OS in primarily high-grade nmMIBC and could select patients for alternative neoadjuvant therapy and facilitate future study.

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The authors do not own these data and hence are not permitted to share them in the original form. Data can be made independently available upon request from the American College of Surgeons National Cancer Database.

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Introduction

Annually, nearly 573,000 bladder cancer cases are diagnosed worldwide, with approximately 81,180 in the United States in 2022. Of these, 15% to 30% are muscle-invasive.[1-4] Despite advancements in the management of nonmetastatic muscle-invasive bladder cancer (nmMIBC), the mortality rate has seen minor improvements, causing approximately 4.4 deaths per 100,000 standard population in the United States since 1987.[4]

Standard of care therapy for nmMIBC includes neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy. At the time of surgery, nearly 20% of patients who undergo neoadjuvant chemotherapy (NAC) may have residual nodal disease (ypN+). Patients with ypN+ experience a higher recurrence rate, worse prognoses, and shorter overall survival (OS) when compared with patients who achieve a complete nodal response.[5-7] Efforts to improve these outcomes through the administration of additional adjuvant chemotherapy have been unsuccessful to date.[6,8-10] While other adjuvant treatments remain under investigation, adjuvant therapy with the checkpoint inhibitor (CPI), nivolumab, has been shown to improve disease-free survival. However, these benefits may only apply to a minority of patients and improvement in OS with CPIs remains uncertain.[11,12] Neoadjuvant CPI approaches have shown promise in early phase 2 trials; however, they also remain experimental (NCT04700124, NCT03775265).[13,14]

Current neoadjuvant treatment strategies and clinical trials on nmMIBC largely employ a one-size-fits all approach and overlook disease heterogeneity, suggesting a need to develop prognostic tools to guide patient selection in nmMIBC and assist with delivery of personalized therapies. These efforts may identify which patients would benefit from an escalation or deviation in neoadjuvant therapies, and could prove especially useful in those with ypN+. As such, this study aimed to create a nomogram to predict ypN+ and correlate this with OS in clinically node-negative (cN0) nmMIBC patients treated with NAC and surgical resection.

Methods and Materials

Using the National Cancer Database (NCDB), which captures data from over 1500 Commission on Cancer-accredited facilities, we identified all nmMIBC patients with cT2-4 N0 M0 disease from 2004 to 2020. Only those with papillary or nonpapillary urothelial (transitional cell) histologies, complete clinical TNM staging (American Joint Committee on Cancer [AJCC] sixth to eighth edition), and treatment with multiagent NAC and surgery with pelvic lymph node dissection were included.[15] Patients with nonurothelial histologies, history of prior malignancies, or receipt of other neoadjuvant (ie, immunotherapy) or intraoperative therapies were excluded. Patients with clinical node-positive disease at diagnosis were removed to select a cohort where ypN+ represents true pathologic upstaging of disease. Information regarding specific chemotherapeutic agents employed is unavailable in the NCDB.

Baseline characteristics including age, sex, race, Charlson−Deyo Score, insurance status, time to NAC initiation, time to surgery, and follow-up duration were recorded. The Charlson−Deyo Score is a validated performance status metric of medical comorbidities used to quantify 10-year mortality risk.[16,17] Other cancer-specific variables such as histologic grade, histologic subtype (papillary vs nonpapillary), tumor size, tumor location, and AJCC TNM staging (sixth to eighth edition) were also obtained. For simplicity, patients were not restaged despite subtle differences between the sixth through eighth editions (Table E1). Lastly, survival measures were collected, including OS, 30-day and 90-day surgical mortality.

This work follows TRIPOD and STROBE guidelines for prediction model development and retrospective studies, respectively (File E1).[18,19]

Statistical analysis

All analysis was performed using Stata version 13.1 (StataCorp LC). Baseline patient, cancer, and outcome variables were summarized with descriptive statistics. Patients were then stratified by ypN status with differences in baseline characteristics assessed using chi-square, 2-sided t tests, or Mann−Whitney U tests where appropriate. Following a 70:30 training to testing data split, variables were assessed as risk factors for ypN+ using univariate logistic regression. Variables with P value $<.05$ were eligible for inclusion, and after omission of collinearity, a final multivariate logistic model was used for nomogram derivation. Additional methodology for the collinearity assessment is described in Figure E1. Calibration plots were constructed using a forward-selected fractional polynomial to model expected versus observed probabilities for ypN+ with calculation of Wald confidence intervals. The likelihood ratio test was then used to assess model goodness-of-fit.[20] Area under the receiver operating characteristics curve (AUC) was used to assess model discrimination. Using this nomogram, an empirical risk threshold at 95% sensitivity was established to stratify patients as high- or low-risk for ypN+ with assessments of performance using chi-square and log-rank tests for ypN+ and OS, respectively. Decision curve analysis provided theoretical values of net benefit with escalation of therapy across the range of predicted probabilities of ypN+. Decision curve analysis examines the net benefit of a proposed

intervention across a range of threshold probabilities for a prediction model by measuring an adjusted difference in the proportion of true and false positives, whereby the range of net benefit values may be assessed graphically relative to 2 reference scenarios where all or no patients receive the same proposed treatment.[21]

Lastly, to determine how nomogram probability of ypN+ correlates with OS, Fine−Gray models were constructed accounting for competing risks of 30-day and 90-day surgical mortality, and controlled for patient age and medical comorbidity. Follow-up time for survival outcomes was defined from time of diagnosis to final follow-up or death, whereas patients experiencing a competing event were interval censored. Proportional hazards assumptions were checked by creating an interaction term with the natural log of time (in months) where significant interactions were retained as a time-varying covariate (Table E2). Subdistribution hazard ratios were then calculated with their associated 95% confidence intervals (CIs) to determine the effect of each covariate on the primary outcome of nonsurgical death and were summarized using cumulative incidence curves. Statistical significance was established at $P < .05$.

Results

At a median follow-up of 39.5 months (interquartile range [IQR], 20.5-67.2 months), 6194 patients were identified for study. Most patients were male (68.0%) and Caucasian (91.3%), with a Charlson−Deyo Score of 0 (73.7%). Median age was 65.0 years (IQR, 58.0-71.0 years). Patients with ypN+ were marginally younger, with a median age of 64.0 years (IQR, 58.0-70.0), whereas ypN− patients had a median age of 65.0 years (IQR, 58.0-71.0, $P = .018$). There were no differences in sex, race, or comorbidity status.

For tumor characteristics, most had cT2 disease (70.8%), with nonpapillary urothelial histology (67.3%). Median tumor size was 4.0 cm (IQR, 2.7-5.5 cm) with most patients having tumors overlapping multiple sites within the bladder (21.1%). Patients initiated NAC at a median of 41.0 days after bladder cancer diagnosis (IQR, 28.0-59.0 days) followed by surgery at a median of 156.5 days (IQR, 129.5-188.0 days). Most patients received a radical cystectomy or pelvic exenteration (93.8%) and had a median of 16 lymph nodes removed (IQR, 10-25 nodes). Patients with ypN+ had more nonpapillary histology ($P < .001$), larger tumors ($P < .001$), higher T-stage ($P < .001$), and greater delays in initiation of chemotherapy ($p<0.001$) (Table 1).

On univariate logistic regression, age in decades (odds ratio [OR], 0.93; 95% CI, 0.87-0.99; $P = .022$), clinical T-stage, and nonpapillary urothelial histology (OR, 0.75; 95% CI, 0.65-0.85; $P < .001$) were significantly associated with ypN+. Odds of ypN+ increased with increasing clinical T-stage, with cT2a associated with the lowest risk (OR, 0.54; 95% CI, 0.38-0.74; $P < .001$) and cT4b associated with the highest risk (OR, 3.92; 95% CI, 2.33-6.58; $P < .001$). Other treatment variables associated with ypN+ included time (in weeks) to NAC initiation (OR, 1.03; 95% CI, 1.01-1.04; $P < .001$) and surgical resection (OR, 0.98; 95% CI, 0.98-0.99; $P < 0.001$).

Given concerns for collinearity between time to chemotherapy initiation and time to surgery, as well as age and insurance status, age and time to chemotherapy were chosen as candidates for the final model (Figure E1). Similarly, tumor location was omitted because of a high prevalence of missing data. Lastly, given the intended purpose of designing a nomogram for use prior to surgery, treatment variables of surgery type and duration of follow-up were also omitted. The final multivariate model included patient age in decades, clinical T-stage, time to NAC in weeks, and nonpapillary (vs papillary) histology (Table 2). The nomogram (Fig. 1) showed AUC = 0.644 and 0.645 in training and testing cohorts with model calibration noted between predicted probabilities of 10% to 60% (Figure E2).

A threshold nomogram probability of 13.2% provided 95% sensitivity. Within the training cohort, 3922 (90.7%) patients had predicted probabilities of ypN+ above this threshold and were deemed high-risk, whereas 402 (9.3%) patients fell below the threshold and were designated low-risk. Of high-risk patients, 830 (21.2%) had ypN+, whereas 43 (10.7%) low-risk patients had ypN+ ($P < .001$). Similarly, within the validation cohort, 1720 (92.0%) and 150 (8.0%) were identified as high- and low-risk, with ypN+ found in 392 (22.8%) and 12 (8.0%) patients, respectively ($P < .001$). Decision curve analysis showed benefit to theoretical therapy escalation between 13.0% and 40.0% threshold probabilities (Fig. 2). Other potential probability thresholds are provided in Table E3 with example scenarios on how to apply these findings shown in File E2.

Within the training cohort, high-risk patients had a lower median OS when compared to low-risk patients (36.4 vs 69.8 months, $P < .001$). A similar difference in median OS for high- and low-risk patients was seen in the validation cohort (36.1 vs 74.0 months, $P < .001$). Those at high-risk for ypN+ had a worse OS even when accounting for age, Charlson−Deyo Score, and competing risks of surgical mortality. High-risk patients had an 80% (95% CI, 1.49-2.18; $P < .001$) and 69% (95% CI, 1.39-2.04; $P < .001$) greater subdistribution hazard of nonperioperative death when accounting for 30- and 90-day surgical mortality, respectively (Table 3). Cumulative incidence curves for nonsurgical death by ypN+ risk group are displayed in Figure E3.

Table 1 Baseline patient, tumor, and treatment characteristics

	Overall cohort (N = 6194)		ypN+ (n = 1277)		ypN− (n = 4917)		
	n / Median	% / (IQR)	n / Median	% / (IQR)	n / Median	% / (IQR)	*P* value
Patient characteristics							
Demographics							
Age	65.0	(58.0-71.0)	64.0	(58.0-70.0)	65.0	(58.0-71.0)	**.018**
Female sex	1983	32.0	437	34.2	1546	31.4	.058
Race							
White	5609	91.3	1149	90.8	4460	91.4	.730
Black	362	5.9	80	6.3	282	5.8	
Other	172	2.8	37	2.9	135	2.8	
Insurance status							
No insurance	145	2.4	32	2.5	113	2.3	.076
Private insurance	2547	41.6	522	41.2	2025	41.7	
Medicaid	410	6.7	105	8.3	305	6.3	
Medicare	2913	47.6	580	45.8	2333	48	
Other government	109	1.8	27	2.1	82	1.7	
Charlson−Deyo score							
0	4563	73.7	937	73.4	3626	73.7	.367
1	1119	18.1	234	18.3	885	18	
2	335	5.4	77	6.0	258	5.3	
≥ 3	177	2.9	29	2.3	148	3.0	
Tumor characteristics							
Bladder location							
Trigone	352	5.7	69	5.4	283	5.8	**<.001**
Dome	251	4.1	31	2.4	220	4.5	
Lateral wall	1121	18.1	198	15.5	923	18.8	
Anterior wall	227	3.7	36	2.8	191	3.9	
Posterior wall	485	7.8	91	7.1	394	8.0	
Bladder neck	125	2.0	31	2.4	94	1.9	
Ureteric orifice	78	1.3	18	1.4	60	1.2	
Urachus	1	0.0	0	0.0	1	0.0	
Overlapping lesion	1304	21.1	332	26.0	972	19.8	
Bladder NOS	2250	36.3	471	36.9	1779	36.2	
Histology							
Nonpapillary	4170	67.3	923	72.3	3247	66.0	**<.001**
Papillary	2024	32.7	354	27.7	1670	34.0	
Grade							
1	21	0.6	7	0.9	14	0.5	.252
2	61	1.7	14	1.8	47	1.7	
3	1308	36.4	302	38.6	1006	35.8	
4	2200	61.3	459	58.7	1741	62.0	

(*continued on next page*)

Table 1 (*Continued*)

	Overall cohort (N = 6194)		ypN+ (n = 1277)		ypN− (n = 4917)		
	n / Median	% / (IQR)	n / Median	% / (IQR)	n / Median	% / (IQR)	*P* value
Tumor size	40.0	(27.0-55.0)	47.5	(30.0-60.0)	40.0	(26.0-52.0)	**<.001**
Number of nodes dissected	16.0	(10.0-25.0)	16.0	(10.0-25.0)	16.0	(10.0-25.0)	.200
Number of pathologic nodes positive	0.0	(0.0 - 0.0)	2.0	(1.0-4.0)	0.0	(0.0 - 0.0)	**<.001**
AJCC clinical T stage							
T2 NOS	3527	56.9	576	45.1	2951	60.0	**<.001**
T2a	444	7.2	42	3.3	402	8.2	
T2b	415	6.7	67	5.3	348	7.1	
T3 NOS	492	7.9	92	7.2	400	8.1	
T3a	451	7.3	163	12.8	288	5.9	
T3b	268	4.3	98	7.7	170	3.5	
T4 NOS	96	1.6	38	3.0	58	1.2	
T4a	441	7.1	175	13.7	266	5.4	
T4b	60	1.0	26	2.0	34	0.7	
AJCC edition							
6th	708	11.4	220	17.2	488	9.9	**<.001**
7th	3395	54.8	657	51.5	2738	55.7	
8th	2091	33.8	400	31.3	1691	34.4	
Treatment Variables							
Surgery type							
Local excision or surgery NOS	68	1.1	28	2.2	40	0.8	**<.001**
Partial cystectomy	144	2.3	16	1.3	128	2.6	
Simple/Total/Complete cystectomy	155	2.5	24	1.9	131	2.7	
Radical cystectomy	2992	48.3	592	46.4	2400	48.8	
Pelvic exenteration	2820	45.5	610	47.8	2210	44.9	
Cystectomy NOS	15	0.2	7	0.5	8	0.2	
Time to chemotherapy (d)	41.0	(28.0-59.0)	43.0	(29.0-63.0)	40.0	(27.0-57.0)	**<.001**
Time to definitive surgery (d)	156.5	(129.5-188.0)	153.5	(121.0-188.0)	158.0	(132.0-188.0)	**<.001**
Duration of follow-up (mo)	39.5	(20.5-67.2)	20.8	(12.2-36.0)	44.0	(25.2-72.8)	**<.001**

Abbreviations: IQR = interquartile range; NOS = not otherwise specified; ypN+ = occult pathologic nodal metastasis; ypN- = no pathologic nodal metastasis.
P values were calculated using a combination of chi-square, Fisher's exact test, and Wilcoxon rank sum, where applicable. Bolded values indicate statistical significance at $P < .05$.

Discussion

We present a nomogram capable of risk-stratifying patients for ypN+ in primarily high-grade cN0 nmMIBC patients after multiagent NAC and resection with pathologic nodal staging, based on histologic subtype, age at diagnosis, clinical T-stage, and time to chemotherapy initiation. These findings are particularly valuable since those stratified as high-risk had worse survival outcomes despite confounders of age, medical comorbidity, and perioperative mortality. To our knowledge, this is the first nomogram capable of predicting ypN+ with prognostic utility in a nmMIBC cohort treated with NAC and surgical resection, and thus provides a potential tool for investigation of NAC escalation or alternatives to traditional cisplatin-based therapies.[22,23]

Compared to historic literature, our nomogram demonstrates similarities with risk factors for generalized

Table 2 Univariate and multivariate logistic regressions for occult pathologic nodal metastasis

	ypN+						
	OR	**95% CI**	***P* value**		**OR**	**95% CI**	**p-value**
Demographics				Tumor size	1.00	(1.00-1.00)	0.111
Age	**0.99**	**(0.99-1.00)**	**.022**	Number of nodes dissected	1.00	(0.99-1.00)	0.223
Female sex	1.13	(1.00-1.29)	.058	Histology			
White race (vs all others)	0.92	(0.75-1.13)	.427	Nonpapillary (vs papillary)	**1.34**	**(1.17-1.54)**	**< 0.001**
Insurance status (vs Medicaid)				Grade (vs grade = 1)			
No insurance	0.82	(0.52-1.29)	.396	2	0.60	(0.20-1.76)	0.350
Private insurance	**0.75**	**(0.59-0.95)**	**.019**	3	0.60	(0.24-1.50)	0.275
Other government	0.96	(0.59-1.56)	.858	4	0.53	(0.21-1.31)	0.170
Medicare	**0.72**	**(0.57-0.92)**	**.008**	**Treatment variables**			
Charlson−Deyo score (vs score = 0)				Surgery type (vs radical cystectomy)			
1	1.02	(0.87-1.20)	.780	Local excision or surgery NOS	**2.84**	**(1.74-4.64)**	**< 0.001**
2	1.15	(0.89-1.50)	.286	Partial cystectomy	**0.51**	**(0.30-0.86)**	**0.012**
≥3	0.76	(0.51-1.14)	.180	Simple/Total/Complete cystectomy	0.74	(0.48-1.16)	0.190
Tumor characteristics				Pelvic exenteration	1.12	(0.99-1.27)	0.083
Tumor location (vs trigone)				Cystectomy NOS	**3.55**	**(1.28-9.82)**	**< 0.001**
Bladder dome	**0.58**	**(0.37-0.91)**	**.019**	Time to chemotherapy (d)	**1.00**	**(1.00-1.01)**	**< 0.001**
Lateral wall	0.88	(0.65-1.19)	.410	Time to definitive surgery (d)	**1.00**	**(1.00-1.00)**	**< 0.001**
Anterior wall	0.77	(0.50-1.20)	.255	Duration of follow-up (mo)	**0.98**	**(0.97-0.98)**	**< 0.001**
Posterior wall	0.95	(0.67-1.34)	.760				
Bladder neck	1.35	(0.83-2.19)	.221				
Ureteric orifice	1.23	0.68-2.22)	.490	**Nomogram multivariate model**			
Urachus	-	-	-	Age	0.99	(0.99-1.00)	0.172
Overlapping lesion of bladder	**1.40**	**(1.05-1.87)**	**.023**	AJCC clinical T stage (vs T2 NOS)			
Bladder, NOS	1.09	(0.82-1.44)	.567	T2a	**0.56**	**(0.37-0.84)**	**0.005**
AJCC clinical T stage (vs T2 NOS)				T2b	1.15	(0.83-1.61)	0.391
T2a	**0.54**	**(0.38-0.74)**	**<.001**	T3 NOS	1.14	(0.84-1.54)	0.395
T2b	0.99	(0.75-1.30)	.922	T3a	**2.91**	**(2.25-3.77)**	**< 0.001**
T3NOS	1.18	(0.92-1.50)	.187	T3b	**3.26**	**(2.36-4.52)**	**< 0.001**
T3a	**2.90**	**(2.35-3.58)**	**<.001**	T4 NOS	**4.00**	**(2.35-6.81)**	**<0.001**
T3b	**2.95**	**(2.27-3.85)**	**<.001**	T4a	**3.19**	**(2.45-4.16)**	**< 0.001**
T4NOS	**3.36**	**(2.21-5.10)**	**<.001**	T4b	**4.22**	**(2.12-8.40)**	**< 0.001**
T4a	**3.37**	**(2.73-4.16)**	**<.001**	Time to chemotherapy (d)	**1.00**	**(1.00-1.01)**	**0.004**
T4b	**3.92**	**(2.33-6.58)**	**<.001**	Nonpapillary (vs papillary)	1.17	(0.99-1.39)	0.068

Abbreviations: CI = Confidence Interval; NOS = Not otherwise specified; OR = Odds Ratio; ypN+ = Occult pathologic nodal metastasis.
Calculation of *P* values and odds ratios was performed using a combination of univariate and multivariate logistic regression. Multivariate model results are derived from training data cohort. Bolded values indicate statistical significance at $P < .05$

pathologic nodal involvement (pN+) in nmMIBC. Younger age has been reported as a risk factor for pN+, where genomic tumor features predispose to more advanced clinical presentations.[24] Similarly, features such as delayed receipt of chemotherapy or higher clinical T-stage suggest potential for cancer progression or more advanced disease, and could also contributes to a greater risk of pN+.[25,26] In comparison, papillary urothelial histology is considered less aggressive and is rarely associated with muscle-invasive and/or regional lymphatic disease.[27] As such, although higher rates of ypN+ in nonpapillary urothelial histologies was expected, it was unanticipated that

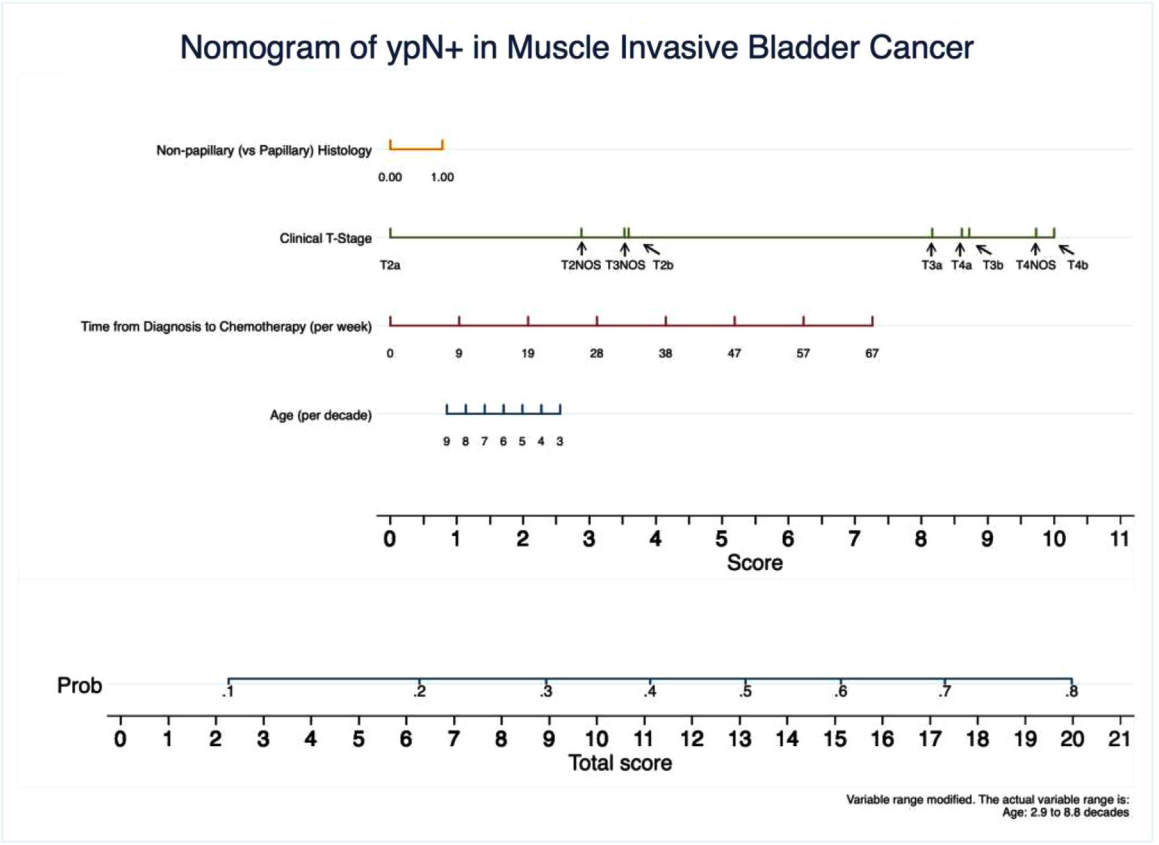

Figure 1 Nomogram for risk of occult pathologic nodes in muscle Invasive bladder cancer.
Nomogram depicting selected variables for prediction of ypN+ in patients receiving neoadjuvant multiagent chemotherapy and surgical resection with pathologic nodal staging.
Age range was adjusted for simplicity. True range of ages in this study was from 29 to 88 years.
Nonpapillary = +0.8 points for nonpapillary histology; time from diagnosis to chemotherapy (days) = +0.75 points per 47 days; T2a = +0 points; T2NOS = +2.9 points; T3NOS = +3.5 points; T2b = +3.6 points; T3a = +8.2 points; T3b = +8.7 points; T4a = +8.6 points; T4NOS = +9.7 points; T4b = +10.0 points; age = −0.25 points per decade (minimum = 90 years is 0.75 points; maximum = 29 years is 2.5 points).
Abbreviations: ypN+ = occult pathologic nodal metastasis; NP = nonpapillary; P = papillary; NOS = not otherwise specified.

a third of eligible muscle-invasive cases would include papillary variants. In 2016, the WHO classification for bladder cancer was restructured to place emphasis on the grade and morphology of primary lesions, where papillary variants largely constitute low-grade noninvasive disease.[28] One reason for this discrepancy could be explained by progression from noninvasive to muscle-invasive disease. High-grade urothelial lesions, which comprise 97% of the papillary cases here, pose greater recurrence risks. Estimated recurrence rates are up to 62% 1 year after initial treatment for high-grade papillary lesions with 40% to 60% of these cases reflecting muscle-invasive disease.[29,30] Although our nomogram suggests these patients are still at lower risk for ypN+, this reflects the importance of histologic grade in overall disease prognosis.

Given this, histologic grade is noticeably absent from our nomogram despite prior reports noting association with pN+.[26,31] Assessment of our cohort revealed that 98% patients comprised high-grade histology. This suggests low statistical power given an insufficient number of low-grade observations; however, it highlights the potential for misclassification of histologic grade at the time of diagnosis. Specifically, a diagnosis of nmMIBC implies the presence of sufficient dedifferentiation to allow penetration into the muscularis propria, such that recent ESMO guidelines recommend all cases of nmMIBC be considered high-grade.[31] This suggests that inclusion of histologic grade in predictions of ypN+ is potentially unnecessary because of less heterogeneity seen in muscle-invasive disease. The minority of our cohort comprising low-grade nmMIBC is thus unexpected, but highlights potential limitations of this study, including variation in grading practice by pathologists, errors in data entry, and the retrospective design.

Previous nomograms for nmMIBC exclude patients receiving NAC and/or were assessed in heterogeneous cohorts such that adoption into practice has been limited. However, these nomograms assert strengths of higher relative predictive accuracy for outcomes of pN+.[26,32,33] This is demonstrated by the nomogram by Wu et al,[32] which shows that inclusion of clinicopathologic and genomic variables allowed precise detection of pN+ in non

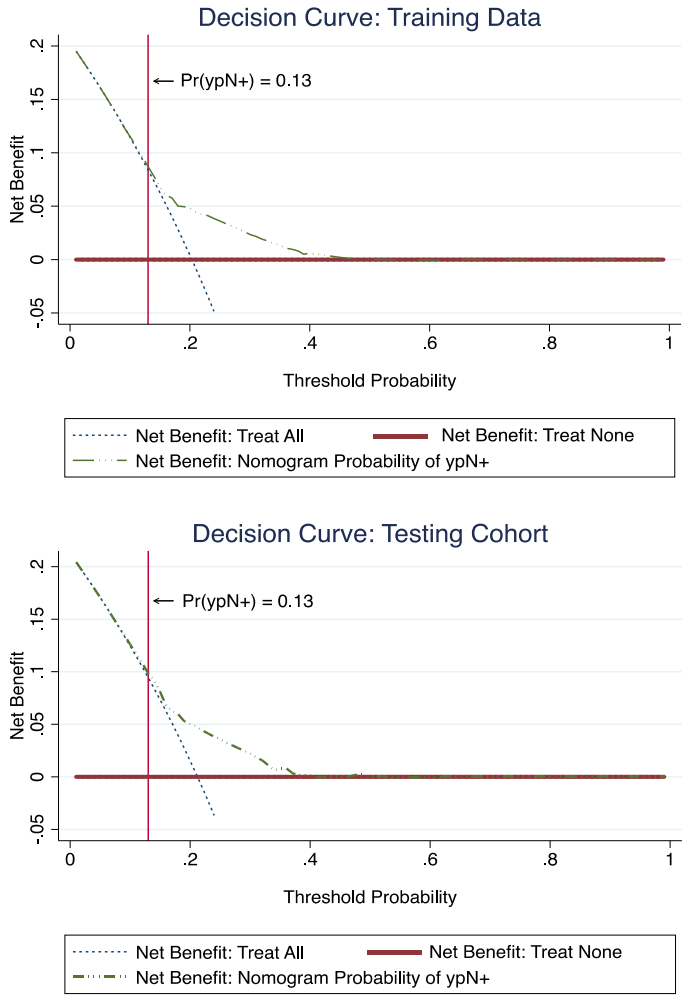

Figure 2 Decision curve analysis for selecting theoretical treatment for nomogram predicted probability of ypN+.
Decision curve analysis assesses the efficacy of a model in dictating treatment by drawing comparisons to hypothetical scenarios of treating all versus no patients. This is performed across a range of all threshold probabilities (X-axis) and using a metric called net benefit (Y-axis). Here, the decision curve analysis demonstrates relative benefit of selecting a theoretical treatment using the present nomogram at predicted probabilities ranging from approximately 13.0% to 40.0% for both training (top) and testing (bottom) cohorts. Further explanation on decision curve analyses and examples on how this may be hypothetically applied are listed in File E2. Pr(ypN+) = predicted nomogram probability of ypN+; ypN+ = occult pathologic nodal metastasis.

−muscle-invasive disease across training and validation cohorts (AUC, 0.840-0.886). Although differences in relative accuracy between nomograms could be attributed to study design, the decision to include detailed tumor-specific features holds merit when considering the genomic and molecular heterogeneity reported in nmMIBC.[34] For instance, bladder tumors with mutations in ERCC2, a helicase used in nucleotide excision repair, have demonstrated a high degree of sensitivity to cisplatin-based regimens and suggests assessments of mutational profiles may allow better predictions of ypN+.[35-37] As knowledge surrounding genomic signatures evolves and newer assays are developed, it is valuable to understand how such information may be harnessed to predict and identify therapies for nmMIBC and would likely benefit those with ypN+ disease.

Given the low AUC, predictions from our nomogram would benefit from validation and refinement prior to implementation in clinical practice. Doing so may allow clinicians to identify which patients could benefit from treatment escalation or alteration with novel approaches.[11-13,38-41] To illustrate how this nomogram could be useful in such scenarios, examining other non-standard neoadjuvant approaches, such as radiation therapy, is informative. For instance, when used in definitive chemoradiation or selective bladder preservation paradigms, radiation therapy is subject to controversy regarding elective treatment of pelvic lymph nodes. Extrapolating, we suspect a similar debate could arise if investigating neoadjuvant radiation for nmMIBC.[42] Here, our proposed nomogram presents with 2 potential clinical opportunities. First it could improve selection of a higher risk cohort benefiting from trials involving neoadjuvant treatment escalation. Additionally, it could identify which patients could potentially benefit from elective nodal irradiation or adjuvant radiation.[43] In such a setting, we

Table 3 Fine–Gray models for overall survival with surgical mortality competing risks

Overall survival (30-day surgical mortality as competing risk)			
	SHR	**95% CI**	***P* value**
Charlson–Deyo score (vs score = 0)			
1	**1.14**	**(1.01-1.30)**	**.042**
2*	**1.13**	**(1.06-1.21)**	**<.001**
≥3	1.03	(0.75-1.41)	.847
Age	**1.02**	**(1.02-1.03)**	**<.001**
High risk of ypN+ (vs low risk)	**1.80**	**(1.49-2.18)**	**<.001**
Overall survival (90-day surgical mortality as competing risk)			
	SHR	**95% CI**	***P* value**
Charlson–Deyo score (vs score = 0)			
1*	1.02	(0.98-1.07)	.303
2*	**1.13**	**(1.06-1.21)**	**.001**
≥3	1.11	(0.81-1.52)	.532
Age*	**1.01**	**(1.00-1.01)**	**<.001**
High risk of ypN+ (vs low risk)	**1.69**	**(1.39-2.04)**	**<.001**

Abbreviations: CI = confidence interval; SHR = subdistribution hazard ratio; ypN+ = occult pathologic nodal metastasis.
*Variable interacted with the natural log of time (in months) as nonproportional hazards assumption was not met; High risk of ypN+ = defined as a nomogram predicted probability of ypN+ > 13.2%.
Subdistribution hazard ratios for overall survival were calculating using Fine–Gray models controlling for 30- and 90-day surgical mortality as a competing risk. Bolded values indicate statistical significance at $P < .05$

would also recommend a different probability threshold to define high- and low-risk groups, as the current threshold for high-risk selection could be overly sensitive.

A detailed decision curve analysis illustrates how the sensitivity, specificity, and other parameters change with different nomogram threshold selection methods (Table E3). A discussion of how to use/interpret a decision curve analysis is in File E2. Raising the required nomogram score to be considered high-risk for ypN+ would lead to fewer patients meeting this threshold, but with greater prevalence of true ypN+ disease. This however, comes with a tradeoff of increased risk of false negatives, such that the low-risk cohort may also have more ypN+ disease. A similar approach could be applied to investigation of other new or emerging therapies to address ypN+ disease in nmMIBC as well but caution its utilization prior to further validation and refinement.

With validation, these results could also provide a means to prognosticate OS for those diagnosed with nmMIBC. The inferior median OS of 36 months found in high-risk patients for ypN+ is consistent with previous studies suggesting a median OS around 13 to 30 months.[5-7,44-46] The small difference in OS could be explained by differences in staging used in this study, as the AJCC sixth edition classifies subepithelial prostatic urethra invasion as cT4 disease, whereas later editions now recognize this feature as cT1. This suggests bias toward improved survival as those with cT1 disease likely have a better prognosis. Other causes may include the heterogeneity in surgical resections or lack of information highlighting the number of cycles or types of chemotherapeutic agents prescribed. This suggests benefit from further model refinement, and implies that application of these findings in an appropriately staged and selected cohort could prognosticate a worse survival than reported here. Indeed, post hoc analysis excluding those staged under the AJCC sixth edition and removing limited surgeries revealed a median OS of 33.5 months for patients identified as high-risk for ypN+, and is more in line with previous reports.

This study is not without limitations, most of which are because of the retrospective design and inherent limitations of the NCDB. This includes potentials for selection bias, data entry errors, and variation in NAC and staging across the study interval. Although most of these are unavoidable given study design, this also includes bias caused by clustering in treatment or outcomes by facility. In addition, specific details surrounding the delivery of chemotherapy are unavailable in the NCDB, such as the specific number of cycles delivered or type of agent. Other patient risk factors are absent, such as smoking status. The omission of these minutiae likely contributes to the modest AUC reported here, and consequently, we emphasize that these findings should not be used to provide a precise assessment of ypN+, but rather as a risk stratification tool to screen out patients of relatively low-risk of

ypN+. Next, it should be emphasized that these results only apply to urothelial carcinoma nmMIBC and cannot be applied to nonurothelial MIBC. Irrespective, these results highlight our nomogram's utility by identifying those at greater risk of ypN+ with prognostication of OS in a nmMIBC cohort treated with standard therapy, and may aid selection of patients for future trials investigating escalated or alternative neoadjuvant treatment approaches.

Conclusions

This study provides a nomogram for identification of primarily high-grade cN0 nmMIBC patients treated with multiagent NAC and surgical resection who are at greater risk for development of ypN+ and significantly worse OS, using age at diagnosis, clinical T-stage, time to starting treatment, and nonpapillary tumor histology. Although such findings need validation prior to implementation, nomogram threshold probabilities of 13% to 40% for ypN + could select patients likely to benefit from escalated or altered neoadjuvant treatment. These predictions may be improved with consideration of further clinicopathologic, radiomic, or genomic variables, while providing rationale for future clinical trial design.

Disclosures

Arash Rezazadeh reports a relationship with ECOM Medical that includes: equity or stocks. Arash Rezazadeh reports a relationship with Exelixis Inc that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Arash Rezazadeh reports a relationship with AstraZeneca Pharmaceuticals LP that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Arash Rezazadeh reports a relationship with Bayer Corporation that includes: consulting or advisory, funding grants, and travel reimbursement. Arash Rezazadeh reports a relationship with Pfizer that includes: consulting or advisory, funding grants, and travel reimbursement. Arash Rezazadeh reports a relationship with Novartis that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Arash Rezazadeh reports a relationship with Genentech that includes: consulting or advisory, funding grants, speaking and lecture fees, and travel reimbursement. Arash Rezazadeh reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory, funding grants, and speaking and lecture fees. Arash Rezazadeh reports a relationship with EMD Serono Inc that includes: consulting or advisory and speaking and lecture fees. Arash Rezazadeh reports a relationship with Immunomedics that includes: consulting or advisory and funding grants. Arash Rezazadeh reports a relationship with Gilead Sciences Inc that includes: consulting or advisory and speaking and lecture fees. Arash Rezazadeh reports a relationship with Janssen Pharmaceuticals Inc that includes: funding grants, speaking and lecture fees, and travel reimbursement. Arash Rezazadeh reports a relationship with Astellas Medivation that includes: funding grants, speaking and lecture fees, and travel reimbursement. Arash Rezazadeh reports a relationship with Sanofi-Aventis US LLC that includes: speaking and lecture fees. Arash Rezazadeh reports a relationship with Eisai Inc that includes: funding grants, speaking and lecture fees, and travel reimbursement. Arash Rezazadeh reports a relationship with Amgen Inc that includes: speaking and lecture fees. Arash Rezazadeh reports a relationship with Exelixis Inc that includes: funding grants, speaking and lecture fees, and travel reimbursement. Arash Rezazadeh reports a relationship with Merck & Co Inc that includes: speaking and lecture fees. Arash Rezazadeh reports a relationship with Astellas Pharma US Inc that includes: funding grants, speaking and lecture fees, and travel reimbursement. Arash Rezazadeh reports a relationship with AVEO Oncology that includes: speaking and lecture fees. Arash Rezazadeh reports a relationship with MacroGenics Inc that includes: funding grants. Arash Rezazadeh reports a relationship with Myovant Sciences Inc that includes: speaking and lecture fees. Arash Rezazadeh reports a relationship with BeyondSpring Inc that includes: funding grants. Arash Rezazadeh reports a relationship with BioClin Therapeutics that includes: funding grants. Arash Rezazadeh reports a relationship with Clovis Oncology that includes: funding grants. Arash Rezazadeh reports a relationship with Bavarian Nordic Inc that includes: funding grants. Arash Rezazadeh reports a relationship with Seagen Inc that includes: funding grants and speaking and lecture fees. Arash Rezazadeh reports a relationship with Epizyme Inc that includes: funding grants. Nataliya Mar reports a relationship with Seagen Inc that includes: speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101671.

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