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Seminars Article

Hospital length of stay following radical cystectomy for muscle-invasive bladder cancer: Development and validation of a population-based prediction model

Mohamed D. Ray-Zack, M.B.B.S.[a], Yong Shan, Ph.D.[a], Hemalkumar B. Mehta, Ph.D.[b], Xiaoying Yu, Ph.D.[c], Ashish M. Kamat, M.D.[d], Stephen B. Williams, M.D.[a,*]

[a] Department of Surgery, Division of Urology, The University of Texas Medical Branch, Galveston, TX
[b] Department of Surgery, The University of Texas Medical Branch at Galveston, Galveston, TX
[c] Department of Preventative Medicine and Community Health, The University of Texas Medical Branch at Galveston, Galveston, TX
[d] Department of Urology, The University of Texas MD Anderson Cancer Center, Houston, TX

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Abstract

Objective: Length of hospital stay for patients following radical cystectomy is an important determinant for improved quality of care. We sought to develop and validate a predictive model for length of hospital stay following radical cystectomy.

Methods: Patients aged 66 to 90 years diagnosed with clinical stage T2-4a muscle-invasive bladder cancer who underwent radical cystectomy were included from January 1, 2002 through December 31, 2011 using the Surveillance, Epidemiology, and End Results (SEER)-Medicare data. Linear regression analyses were used to develop and validate a predictive model for length of hospital stay.

Results: A total of 2,448 patients met inclusion criteria. After random assignment, 1,224 patients were included in the discovery cohort and 1,224 patients included in the validation cohort. The cohorts were well balanced with no significant difference in any of the preoperative variables. A best model was developed using marital status, Surveillance, Epidemiology, and End Results (SEER) region, clinical stage, Charlson comorbidity index, logarithm of hospital cystectomy volume, and use of neoadjuvant chemotherapy in a backward selection to predict the length of stay. There was robust internal validation (sum square error (SSE): 258.1 vs. predicted sum of squares (PRESS): 264.0 at SLS = 0.10), consistent with the external validation (average square error (ASE): discovery (0.248) vs. validation (0.258)) cohort. The strength of the model in predicting length of stay for the entire cohort was ($R^2 = 0.048$).

Conclusion: In this large population-based study, we developed and validated a model to predict length of hospital stay following radical cystectomy. Identification of at-risk patients for prolonged hospital stay may aid in targeted interventions to reduce length of stay, improve quality of care, and decrease healthcare costs.

Keywords: Bladder cancer; Radical cystectomy; Hospital stay; Prediction; Model; SEER

1. Introduction

Nearly 81,190 bladder cancer cases and 17,240 associated deaths are estimated in the United States in 2018 [1]. Radical cystectomy with extended pelvic lymphadenectomy is recommended for patients with muscle-invasive bladder cancer [2]. Despite these longstanding guidelines, radical cystectomy is markedly underused as historically only 21% of patients with muscle-invasive disease are offered this potentially curative surgery [3]. Given concerns regarding the non-negligible morbidity and mortality associated with this complex surgery, along with patients more often being elderly with increased comorbidities, identifying determinants to improve outcomes are needed. One of the potential surrogates for improved quality of care defined by the Center for Medicare and Medicaid Services (CMS)

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*Corresponding author. Tel: +1-409-747-7333; Fax: +1-409-772-0088.
E-mail address: stbwilli@utmb.edu (S.B. Williams).

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includes length of stay. Prolonged hospital stays were historically associated with increased adverse events, subsequent utilization of healthcare resources, as well as associated cost of care, particularly following major cancer surgeries [4]. While some factors, such as patient age and racial background, were observed as independent predictors of prolonged hospital stays, there is no comprehensive model to accurately predict length of stay for patients following radical cystectomy [5,6]. The purpose of the present study was to develop and validate a predictive model which may identify at-risk patients to develop targeted interventions to reduce length of stay.

2. Patients and methods

2.1. Data source

We used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data from the National Cancer Institute [7]. SEER database contains information on patient demographics, cancer characteristics (stage, grade, histology), and patient follow-up information. The Medicare database contains information on inpatient and outpatient claims. The study was deemed exempt by the Institutional Review Board at The University of Texas Medical Branch at Galveston.

2.2. Ascertainment of study cohort

Using SEER-Medicare, we included 66 to 90 years old patients with clinical stage II-IVa bladder cancer (transitional cell or urothelial carcinoma) from January 1, 2002 through December 31, 2011. Medicare claims that data were available through December 31, 2013 [3]. Patients who did not undergo radical cystectomy as primary treatment were excluded. We restricted the study sample to patients who had Medicare Fee-for-Service coverage with available Medicare Part A and Part B claims data. The final cohort consisted of 2,448 patients randomly divided into discovery (n = 1,224) and validation cohorts (n = 1,224) (Fig. 1).

2.3. Identification of bladder cancer treatment

Radical cystectomy was identified using Current Procedural Terminology (CPT) codes that are indicative of radical cystectomy, including both open and robot-assisted laparoscopic surgery, with or without pelvic lymph node dissection. The radical cystectomy group included patients who underwent surgery alone or in combination with chemotherapy.

2.4. Study covariates

For the patients included, we determined patient age at diagnosis of bladder cancer, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and non-Hispanic other races), marital status (single, married, and unknown), census region (Northeast, South, Midwest, and West), and patients' neighborhood socioeconomic characteristics. Educational level was defined according to the percentage of residents who had at least 4 years of college education. County-level median household income was acquired via linkage to the Area Health Resource File and then divided into quartiles. Pre-existing comorbidities were quantified using the Klabunde modification of the Charlson Comorbidity Index during the year before cancer diagnosis [8]. The Klabunde modification incorporates the diagnostic and procedure data contained in hospital claims and physician/outpatient claims into the comorbid conditions identified by the Charlson comorbidity index [9]. We calculated radical cystectomy hospital volume by aggregating the number of procedures performed from 2002 to 2011. Length of hospital stay was defined as index hospital stay in days from date of admission to date of discharge following radical cystectomy.

2.5. Statistical analysis

Descriptive statistics for patient and bladder cancer characteristics were summarized using the Student's t-test, Pearson Chi-square test, and Analysis of Variance (ANOVA). Univariate analyses were conducted to determine the association of length of hospital stay with the covariates described above, using the Student's t-test and Pearson Chi-square test for continuous and categorical variables, respectively. To examine factors that predict length of stay, we created multivariate linear models that incorporated patient age, sex, race/ethnicity, household income, educational level, census region, cancer stage, neoadjuvant chemotherapy use, year of surgery, and comorbidity score. We also assessed hospital volume as a continuous variable, which has been known to impact in-hospital mortality and length of hospital stay [10]. We incorporated covariates that were clinically meaningful or associated with length of stay in univariate models at an alpha level of 0.10 or lower into our multivariable models.

Length of stay had a curvilinear distribution which the Cox-Box procedure confirmed logarithmic transformation to improve linear and normality assumptions. Hospital cystectomy volume during the study period was assessed with logarithmic transformation in order to improve the normality assumption for the outcomes variable (length of stay). Multi-collinearity was assessed for variables introduced into the model. There were no collinear variables. A best model selection in a backward fashion was performed.

Using the discovery cohort, we fitted the following linear regression model via the least squares method to predict length of stay using backward selection with significance level to stay (SLS) = 0.1:

$Y_i = \beta_0 + \beta_1$ (marital status: married vs. single) + β_2 (marital status: unknown vs. single) + β_3 (SEER region:

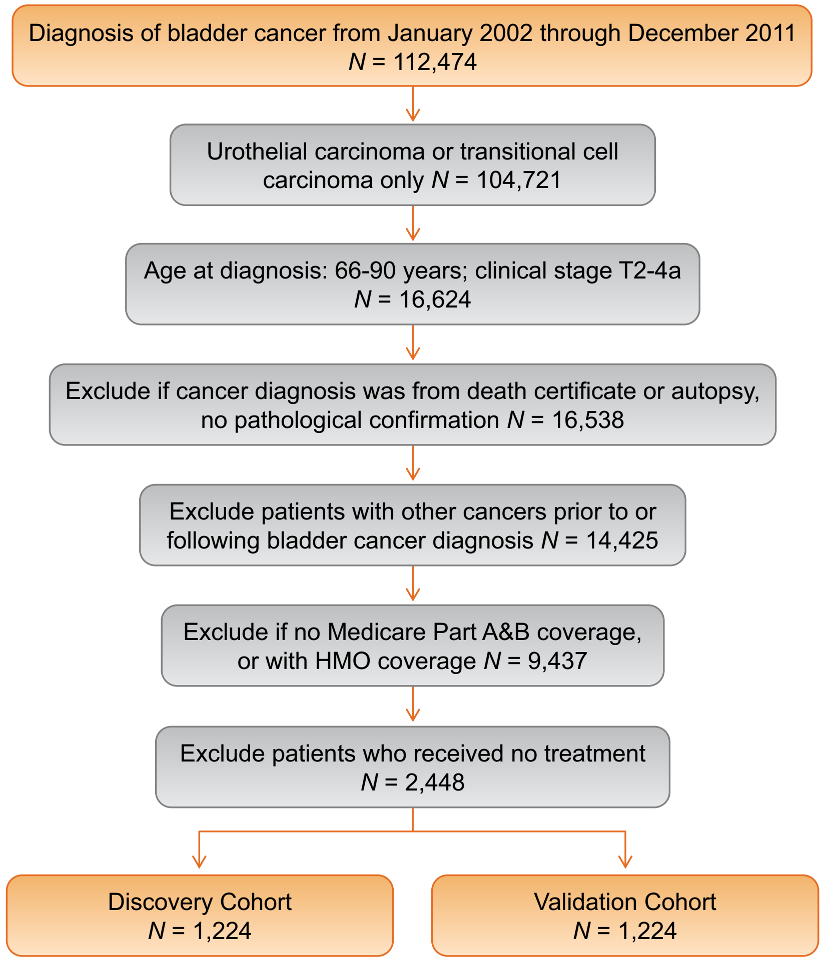

Fig. 1. Patient selection process.

Northeast vs. West) + β_4 (census region: Midwest vs. West) + β_5 (census region: South vs. West) + β_6 (cancer stage: III vs. II) + β_7 (cancer stage: IV vs. II) + β_8 (Charlson comorbidity index: 1 vs. 0) + β_9 (Charlson comorbidity index: 2 vs. 0) + β_{10} (Charlson comorbidity index: 3+ vs. 0) + β_{11} (logarithm of hospital volume) + β_{12} (neoadjuvant chemotherapy ise: no vs. yes) + E, where Y_i = predicted logarithm length of stay. To improve upon the normality assumption, length of stay was log transformed. Each predictor was assessed similarly for outliers using studentized residual and Cook's D tests. Hospital volume was subsequently log transformed with improved residuals. We refitted the model for each of the independent variables described above and performed tests for interaction, taking into account missing predictors. Table 2 shows how coefficients β_0 through β_{12} yield the following estimates of interest: length of stay according to marital status, region, stage, comorbidity, hospital volume, and neoadjuvant chemotherapy use, respectively.

To validate the predictive accuracy of the model developed using the discovery cohort, the model was internally validated comparing the average square error (ASE) with the prediction sum of squares (PRESS). External validation was performed with the validation cohort comparing the ASE from the discovery cohort with the mean square prediction error (MSPR) from the validation cohort. After validation, we applied the discovery cohort model to the entire overall cohort (n = 2,448) and calculated the adjusted R^2 and shrinkage of external R^2 between observed data vs. predicted values.

All statistical tests were 2-sided, and all analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC). Statistical significance was defined as $P < 0.05$.

3. Results

Patient demographics in the discovery and validation cohorts are summarized in Table 1. Overall, 1,224 (50.0%) and 1,224 (50.0%) of the 2,448 patients who underwent radical cystectomy for muscle-invasive bladder cancer were included in the discovery and validation cohorts, respectively. Patients were similar across all demographic and clinical predictors except for census region. Patients in the validation cohort were more often from the West (41.8% vs. 40.6%) and South (25.5% vs. 23.9%) than patients in the discovery cohort ($P = 0.062$).

Table 1
Patient demographic and clinical characteristics in the discovery and validation cohorts

		Discovery			Validation		
Category	*n*	No.	%	*n*	No.	%	*P* value
Year of diagnosis	1224			1224			
2002		126	10.3		130	10.6	0.116
2003		116	9.5		146	11.9	
2004		149	12.2		125	10.2	
2005		143	11.7		139	11.4	
2006		108	8.8		135	11.0	
2007		128	10.5		108	8.8	
2008		135	11.0		110	9.0	
2009		111	9.1		105	8.6	
2010		111	9.1		114	9.3	
2011		97	7.9		112	9.2	
Age (mean ± SD)	1224	75.0 ± 5.8		1224	75.3 ± 5.8		0.338
Sex	1224			1224			
Male		744	60.8		772	63.1	0.244
Female		480	39.2		452	36.9	
Race/ethnicity	1224			1224			
Non-Hispanic White		1073	87.7		1063	86.7	0.910
Non-Hispanic Black		51	4.2		52	4.3	
Hispanics		41	3.4		47	3.8	
Other		59	4.8		62	5.1	
Marital status	1224			1224			
Single		174	14.2		167	13.6	0.579
Married		758	61.9		743	60.7	
Unknown		292	23.9		314	25.7	
Census region	1224			1224			
West		497	40.6		512	41.8	0.062
Northeast		275	22.5		283	23.1	
Midwest		159	13.0		117	9.6	
South		293	23.9		312	25.5	
Median household income, $	1224			1224			
≤23,364		275	22.5		255	20.8	0.586
23,365−31,906		309	25.3		317	25.9	
31,907−41,719		310	25.3		298	24.4	
≥41,720		330	27.0		354	28.9	
Educational level, %	1224			1224			
≤20.95		328	26.8		353	26.8	0.612
20.96−26.61		305	24.9		303	24.8	
26.62−32.54		284	23.2		262	21.4	
≥32.55		307	25.1		306	25.0	
Cancer stage	1224			1224			
II		470	38.4		496	40.5	0.231
III		400	32.7		361	29.5	
IV		354	28.9		367	30.0	
Charlson Comorbidity Index	1224			1224			
0		704	57.5		681	55.6	0.820
1		317	25.9		329	26.9	
2		116	9.5		124	10.1	
3+		87	7.1		87	7.4	
Neoadjuvant chemotherapy use	1224			1224			
Yes		197	16.1		188	15.4	0.617
No		1027	83.3		1036	84.6	
Hospital volume, procedures (mean ±SD)	1034	20.5 ± 21.1		1038	19.9 ± 20.3		0.521
Length of stay, days (mean ± SD)	1136	11.5 ± 8.7		1149	11.7 ± 8.4		0.601

SD = standard deviation.

Descriptive analyses using the *t*-test and Chi-square for continuous and categorical variables were performed. Length of stay had a curvilinear distribution which the Cox-Box procedure confirmed logarithmic transformation to improve linear and normality assumptions. Hospital cystectomy volume during the study period was assessed with logarithmic transformation in order to improve the normality assumption for the outcomes variable (length of stay).

Multi-collinearity was assessed for variables introduced into the model. There were no collinear variables. A best model selection in a backward fashion was performed.

Table 2 shows how coefficients β_0 through β_{12} yielded the following estimates of interest: logarithm length of stay predicted according to marital status, region, stage, comorbidity, logarithm hospital volume, and neoadjuvant chemotherapy use, respectively. Normality and variance assumptions were not violated. Tests for effect modification were performed for all possible interaction terms. There were no significant interactions. Internal validation was confirmed with PRESS = 264.0 at SLS = 0.10, which was close to the SSE = 258.1. External validation was performed in the validation cohort [ASE: discovery (0.248) vs. validation (0.258)]. We compared the squared correlation coefficient between observed ($R^2 = 0.048$) vs. predicted values using the model ($R^2 = 0.020$) which gave a difference (shrinkage) of 0.028.

4. Discussion

We developed and validated a predictive model for length of hospital stay following radical cystectomy. The model performed well as shown by the robust internal and external validation enhancing generalizability and applicability of the model. With the need to improve quality and outcomes of care at decreased costs, models such as the one developed and validated in the present may identify potential at-risk patients and measures to decrease length of stay following surgery.

Table 2
Model using backward selection applying the final model to the entire cohort*

Parameter	Estimate	SE
β_0 Intercept	2.343	0.061
Marital status		
Single (reference)	–	-
β_1 Married	−0.013	0.046
β_2 Unknown	0.087	0.054
Census region		
West (reference)	-	-
β_3 Northeast	0.007	0.041
β_4 Midwest	−0.006	0.049
β_5 South	−0.119	0.041
Cancer stage		
II (reference)	-	-
β_6 III	0.009	0.037
β_7 IV	0.116	0.040
Charlson Comorbidity Index		
0 (reference)	-	-
β_8 1	0.024	0.037
β_9 2	0.084	0.057
β_{10} 3+	0.170	0.063
β_{11} (logarithm of hospital volume)	−0.036	0.013
Neoadjuvant chemotherapy use	−0.117	0.043
Yes (reference)	-	-
β_{12} No	−0.116	0.043

* Significance level to stay (SLS) = 0.10.

Our study has several important findings. First, we identified predictors associated with length of stay following radical cystectomy. Prior studies have shown patient factors and hospital volume to be important determinants of length of stay [10]. Prolonged hospital stay occurs more often among particular patients, such as those of older age and black race [5,6]. In this study, adjusting for other variables, e.g. Charlson Comorbidity Index = 1 vs. 3+ had a 1.02- and 1.19-fold increased median hospital stay when compared to patients with no comorbidity, respectively (the log of hospital stay converted back using exponential function). Moreover, for each 2-fold increase in the number of radical cystectomies performed at a hospital, there would be a 2.5% decrease in median days spent in the hospital. We also noted that married patients had a shorter length of hospital stay as compared to single patients. Prior studies have showed that greater social support improves patient survival following radical cystectomy [11]. Our results provide further evidence confirming that marital status also predicts decreases in the length of hospital stay. In clinical settings, understanding those predictors is relevant for patient education, decision making regarding in-hospital treatment course, and planning of appropriate patient disposition upon discharge from the hospital. Controlling and predicting hospital stay may allow for more efficient use of hospital resources, contributing to regional and national efforts to limit excess healthcare spending.

Second, we observed that the clinical stage of bladder cancer along with geographic heterogeneity of patient residence in the United States predicted length of hospital stay. These findings are consistent with our prior studies regarding use of radical cystectomy and worse survival associated with more advanced disease [9,12]. Patients with more advanced disease may present as more challenging cases, which may lead to increased time to convalescence and thus an increase in time for postoperative recovery and overall length of hospital stay. Other studies also observed geographic heterogeneity in use of radical cystectomy [3]. While no study to date addressed length of hospital stay and census region as a potential determinant, varying practice of bladder cancer care and radical cystectomy according to geographic region are well known [13]. Our prediction model found patients residing in the Midwest and South regions of the United States to have shorter length of hospital stay when compared to the West. Identification of where high volume surgeons and hospitals reside may elucidate these findings.

Third, we developed a model with robust internal and external validation. We used preoperative factors associated with use of radical cystectomy and complications, which may prolong hospital stay [3,9]. While the model performed well, the lower strength of model as indicated by the weak correlation coefficient suggests other unmeasured factors need to be explored in order to further enhance the generalizability of the model (i.e., distance to radical cystectomy provider). Taking this into account, we provide a generalizable, easy-to-use predictive model with predictors available to providers derived from a large population-based database, which can aid in identification of at-risk patients for targeted interventions to decrease overall length of stay, and improve other outcomes such as survival. For example, a married patient with minimal comorbidities (i.e., CCI 1) and cT3 bladder cancer who does not undergo neoadjuvant radical cystectomy at a hospital in the South which performs 20 cystectomies per year will have a predicted length of stay of 9.7 days. Conversely, a married patient with significant comorbidities (i.e., CCI 3+) and cT3 bladder cancer who does not undergo neoadjuvant radical cystectomy at a hospital in the Northeast which performs 5 cystectomies per year will have a predicted a length of stay of 23.3 days.

Our findings must be interpreted within the context of the study design. First, patients identified in the present study were 66 years and older, and findings may not be applicable to younger patients. However, a majority of patients diagnosed with bladder cancer are in the sixth decade of life and we provide a contemporary analysis of utilization rates for this disease [14]. Second, there is level-one evidence to support neoadjuvant chemotherapy use with significant downstaging and improved survival benefit at radical cystectomy [15]. While approximately only 16% of radical cystectomy patients received neoadjuvant chemotherapy in the overall cohort, we noticed increased overall length of stay, consistent with prior studies noting toxicity and morbidity associated with surgery following chemotherapy [16,17]. Third, the study is retrospective in nature with inherent selection bias. While the purpose of the study was to discover and validate a predictive model for length of stay following surgery, we acknowledge the limitations in using this study design as some patients might have undergone surgery for palliative intent rather than primary treatment. While clinical trials overcome concerns of internal validity, there remain concerns regarding external validity and generalizability of findings from clinical trial enrollees [18,19]. Our analysis has the advantage of providing a contemporary and generalizable assessment for the length of hospital stay among a large number of elderly patients. Further validation in single centers and other large datasets (i.e., National Cancer Database) are needed to confirm the prediction of this model. Fourth, we provide a population-based assessment for length of stay using administrative claims data. SEER database lacks specific endpoints corresponding to use of early recovery after surgery (ERAS) pathways such as limiting narcotic medications, limiting perioperative fluids, administration of bowel motility agents (e.g., alvimopan), and immediate advancement of diet, all of which were not assessed in the present study. Fifth, a sample size or power calculation was not performed a priori, however, our sample size compares well with prior observational studies. Lastly, there was no adjustment for within-center correlations or within-surgeon correlations of length of stay.

5. Conclusions

In this large population-based study, we developed and validated a model to predict length of hospital stay following radical cystectomy. Patients who are unmarried, increased comorbidities, advanced clinical stage, received neoadjuvant chemotherapy, and underwent radical cystectomy at lower-volume hospitals in the West census region of the United States were at greater risk for prolonged hospital stay following surgery. Refinement of the model with inclusion of additional confounders may further enhance the robustness of the model. Identification of at-risk patients for prolonged hospital stay using this model may aid in the identification of interventions to decrease length of stay, improve quality of care, enhance utilization of resources, and decrease overall healthcare costs.

Conflicts of interest

None.

Acknowledgments

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References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA: Cancer J Clin 2018;68:7–30.

[2] Clark PE, Agarwal N, Biagioli MC, Eisenberger MA, Greenberg RE, Herr HW, et al. Bladder cancer. J Natl Compr Cancer Netw 2013;11:446–75.

[3] Gore JL, Litwin MS, Lai J, Yano EM, Madison R, Setodji C, et al. Use of radical cystectomy for patients with invasive bladder cancer. J Natl Cancer Inst 2010;102:802–11.

[4] Aloia TA. Predicting adverse outcomes after complex cancer surgery. Ann Surg Oncol 2010;17:2260–1.

[5] Meng X, Press B, Renson A, Wysock JS, Taneja SS, Huang WC, et al. Discriminative ability of commonly used indexes to predict adverse outcomes after radical cystectomy: comparison of demographic data, american society of anesthesiologists, modified charlson comorbidity index, and modified frailty index. Clin Genitourin Cancer 2018;16:e843–50.

[6] Gild P, Wankowicz SA, Sood A, von Landenberg N, Friedlander DF, Alanee S, et al. Racial disparity in quality of care and overall survival among black vs. white patients with muscle-invasive bladder cancer treated with radical cystectomy: a national cancer database analysis. Urol oncol 2018;36:469.e1−11.

[7] Weir HK, Johnson CJ, Mariotto AB, Turner D, Wilson RJ, Nishri D, et al. Evaluation of North American Association of Central Cancer Registries' (NAACCR) data for use in population-based cancer survival studies. J Natl Cancer Inst Monogr 2014;2014: 198–209.

[8] Klabunde CN, Potosky AL, Legler JM, Warren JL. Development of a comorbidity index using physician claims data. J Clin Epidemiol 2000;53:1258–67.

[9] Williams SB, Huo J, Chamie K, Hu JC, Giordano SH, Hoffman KE, et al. Underutilization of radical cystectomy among patients diagnosed with clinical stage t2 muscle-invasive bladder cancer. Eur Urol Focus 2016:online.

[10] Konety BR, Dhawan V, Allareddy V, Joslyn SA. Impact of hospital and surgeon volume on in-hospital mortality from radical cystectomy: data from the health care utilization project. J Urol 2005;173: 1695–700.

[11] Sammon JD, Morgan M, Djahangirian O, Trinh QD, Sun M, Ghani KR, et al. Marital status: A gender-independent risk factor for poorer survival after radical cystectomy. BJU Int 2012;110:1301–9.

[12] Williams SB, Huo J, Kosarek CD, Chamie K, Rogers SO Jr., Williams MA, et al. Population-based assessment of racial/ethnic differences in utilization of radical cystectomy for patients diagnosed with bladder cancer. Cancer Causes Control: CCC 2017;28:755–66.

[13] Gore JL, Litwin MS, Lai J, Yano EM, Madison R, Setodji C, et al. Use of radical cystectomy for patients with invasive bladder cancer. J Natl Cancer Inst 2010;102:802–11.

[14] Cancer facts & figures 2017. Atlanta: American Cancer Society; 2017.

[15] Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.

[16] Booth CM, Siemens DR, Li G, Peng Y, Tannock IF, Kong W, et al. Perioperative chemotherapy for muscle-invasive bladder cancer: a population-based outcomes study. Cancer 2014;120:1630–8.

[17] Cahn DB, Handorf EA, Ghiraldi EM, Ristau BT, Geynisman DM, Churilla TM, et al. Contemporary use trends and survival outcomes in patients undergoing radical cystectomy or bladder-preservation therapy for muscle-invasive bladder cancer. Cancer 2017;123:4337–45.

[18] Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA 2004;291:2720–6.

[19] Lewis JH, Kilgore ML, Goldman DP, Trimble EL, Kaplan R, Montello MJ, et al. Participation of patients 65 years of age or older in cancer clinical trials. J Clin Oncol 2003;21:1383–9.