Predictors of Outcome in Bladder Cancer

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Abstract

Tumor stage and grade have largely been responsible for directing treatment algorithms in bladder cancer. However, the considerable heterogeneity of tumor biology in bladder cancer is incompletely characterized by stage and grade alone, and recent efforts to improve predictive models in bladder cancer may significantly improve accuracy and calibration. This article addresses how current nomograms and risk tables may be best used to individualize bladder cancer management. (*J Natl Compr Canc Netw* 2014;12:1549–1554)

A diagnosis of bladder cancer encompasses a wide variety of clinical entities, characterized by a range of genotypes and phenotypes, each with a unique susceptibility to various treatment modalities, rate of disease progression, and prognosis. The development of management strategies that appropriately treat the heterogeneity of clinical entities remains challenging. Ideally, clinicians would offer individualized treatment using risk stratification instruments based on readily available clinical information.

Accepted clinical guidelines, including the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), have traditionally used clinical stage and grade in the development of algorithms, based on the AJCC TNM staging classification[1] because of the wide availability and acceptance of these prognostic tools. Of course, stage and grade alone cannot capture the full heterogeneity of bladder cancer, and in multivariable models, several additional variables have offered incremental predictive discrimination. Risk stratification instruments, such as risk tables and nomograms, can incorporate these important clinical variables and weigh their relative importance based on the results of multivariable statistical models. Risk tables and nomograms use hazard ratios from multivariable analyses to devise a simple scoring system that predicts prognosis. However, nomograms can use both continuous variables (eg, age) and categorical variables (eg, presence of carcinoma in situ [CIS], T stage), whereas risk tables require categorical variables. Although incorporating multiple variables improves accuracy, including excessive numbers of predictors may render the nomogram unwieldy for clinical use, and thus, successful instruments achieve balance between simplicity and predictive value.

In patients with bladder cancer, risk stratification instruments allow rational decision-making in the absence of high-level evidence. These instruments may be of value in predicting which patients are likely to benefit from aggressive therapy, which therapy should be initiated, and when. This article discusses the current status of predictive models in bladder cancer and their potential to improve patient care.

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Predicting Recurrence and Progression of Non–Muscle-Invasive Bladder Cancer

Although non–muscle-invasive bladder cancer (NMIBC) represents a heterogenous cluster of phenotypes, in general it is characterized by high recurrence rates and infrequent, although potentially devastating, progression to muscle-invasive bladder cancer (MIBC).[2] Traditionally, patients with NMIBC undergo endoscopic tumor resec-

tion followed by frequent cystoscopic evaluation to screen for recurrence. Not surprisingly, surveillance of NMIBC adds considerable expense to the management of bladder cancer. Svatek et al[3] identified improvements in surveillance strategies for bladder cancer as one of the most important ways to decrease unnecessary procedures and reduce overall health care costs.

To optimize bladder cancer surveillance, risk stratification tools based on post hoc analyses of randomized clinical trials have been developed. The EORTC risk tables use tumor size, stage, grade, multifocality, previous recurrences, and presence of CIS to model risk of recurrence and progression.[4] The training cohort comprised 2596 patients from phase III EORTC studies evaluating the effectiveness of prophylactic intravesical therapy after transurethral resection (TUR) for patients with NMIBC. Of note, few patients in the training cohort underwent bacillus Calmette-Guérin (BCG) therapy, and patients with CIS alone were excluded. The European Association of Urology guideline panel has operationalized these EORTC risk tables by defining risk strata for recurrence and progression for patients with NMIBC[5] (Table 1) to facilitate treatment and surveillance recommendations, such as which patients merit early cystectomy and how often they should be monitored with surveillance.[4]

In the post-BCG setting, Fernandez-Gomez et al[6] evaluated participants in the 4 Spanish Urological Club for Oncological Treatment (CUETO) randomized trials to identify risk factors for recurrence and progression. Similar to the EORTC risk tables, the authors developed separate scoring systems for recurrence and progression. Factors associated with recurrence after BCG included female sex, history of recurrence, multiplicity, and presence of CIS, with a recurrence rate ranging from 20.98% to 67.61% at 5 years, depending on these factors. Progression was associated with age, history of recurrence, high-grade disease, T1 stage rather than Ta, and recurrence at first cystoscopy after BCG treatment. Risk of progression was 3.76% for the lowest-risk patients and as high as 33.57% at 5 years for the highest-risk. Notably, most patients included in the CUETO development cohort received maintenance BCG, and the resulting risk tables may not be accurate for patients who undergo an induction course of BCG alone.

In the EORTC and CUETO risk tables, the training cohorts differed with regard to patient characteristics and treatment patterns. Few patients included in the EORTC training cohort received BCG, whereas 62.4% of patients in the CUETO risk tables received at least 10 doses of BCG. Because BCG is known to reduce the risk of disease recurrence (and may delay disease progression), it is not surprising that the predicted rates of recurrence and progression are lower in the CUETO tables. Furthermore, external validation in routine practice settings has

Table 1 Predicted Probability of Recurrence and Progression at 1 and 5 Years Based on the EORTC Risk Tables

Recurrence Score	Probability of Recurrence at 1 y (95% CI)	Probability of Recurrence at 5 y (95% CI)	Recurrence Risk Group[a]
0	15% (10–19)	31% (24–37)	Low risk
1–4	24% (21–26)	46% (42–49)	Intermediate risk
5–9	38% (35–41)	62% (58–65)	Intermediate risk
10–17	61% (55–67)	78% (73–84)	High risk
Progression Score	**Probability of Progression at 1 y (95%CI)**	**Probability of Progression at 5 y (95% CI)**	**Progression Risk Group**
0	0.2% (0–0.7)	0.8% (0–1.7)	Low risk
2–6	1.0% (0.4–1.6)	6.0% (5.0–8.0)	Intermediate risk
7–13	5.0% (4.0–7.0)	17.0% (14.0–20.0)	High risk
14–23	17.0% (10.0–24.0)	45.0% (35.0–55.0)	High risk

Electronic calculator is available at http://www.eortc.be/tools/bladdercalculator/.

[a]Low-, intermediate-, and high-risk groups were defined based on recurrence score and used in the European Association of Urology guidelines on non–muscle-invasive urothelial carcinoma of the bladder.

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demonstrated mediocre performance,[7–10] with both instruments overestimating the risk of recurrence and progression, particularly in high-risk patients.[8] In a validation study of the EORTC and CUETO risk tables in 4689 patients, Xylinas et al[8] showed that the discriminations for disease recurrence and progression were 0.597 and 0.662, respectively, for the EORTC risk tables, and 0.523 and 0.616, respectively, for the CUETO tables. Notably, only 11% of patients underwent BCG treatment, although accuracy and calibration of the CUETO tables were suboptimal even when stratifying for these patients (concordance index, 0.597 and 0.645 for recurrence and progression, respectively). The low accuracy found in external validation likely extends from tumor biology that is incompletely characterized by the risk tables and differences in treatment and surveillance patterns even between centers of excellence.

The EORTC and CUETO risk tables allow identification of patients with NMIBC at high risk for recurrence and progression to facilitate selection of those who would benefit from early cystectomy. In addition, surveillance cystoscopy schedules may be individualized based on the EORTC or CUETO risk score.

Muscle-Invasive Bladder Cancer

Patient Selection for Neoadjuvant Chemotherapy

A landmark randomized controlled trial published in 2003 (SWOG-8710) demonstrated that patients treated with 3 cycles of methotrexate, vinblastine, doxorubicin, and cisplatin before radical cystectomy (RC) experienced a survival advantage over patients randomized to RC alone (77 vs 46 months).[11] However, use of neoadjuvant chemotherapy (NAC) remains low, and selecting the subset of patients most likely to benefit from NAC has proven difficult. Patients with organ-confined MIBC have experienced excellent oncologic outcomes absent the use of NAC (5-year disease-specific survival of ≈80%).[12] Thus, the greatest benefit of NAC likely occurs in patients with pT3 or greater disease who experience downstaging after chemotherapy. Owing to limitations in clinical and radiographic staging, many patients considered T2 or less before cystectomy will be upstaged (up to 73% according to some authors).[13] Furthermore, considerable toxicity is associated with cisplatin-based chemotherapy,[11] with grade 3 and 4 toxicity seen in 35% and 37% of patients, respectively. To preserve the benefits of NAC while minimizing unnecessary toxicity, risk-stratification tools have been developed to predict advanced pathologic stage at cystectomy using preoperative variables.

Green et al[14] developed a nomogram to predict risk of non–organ-confined disease at RC, thereby defining a subset of patients who may benefit most from NAC. The authors studied 201 patients from a single institution with clinically organ-confined disease who had not received NAC. Factors associated with upstaging to either pT3 or greater or N+ disease at the time of cystectomy in a multivariable model included stage at TUR of a bladder tumor (TURBT), presence of lymphovascular invasion in the TURBT specimen, and suggestion of non–organ-confined disease on preoperative imaging. The resulting nomogram was highly accurate in predicting non–organ-confined disease (area under the curve, 0.828), although external validation is necessary to determine its accuracy in other populations.[14] The authors included a decision curve analysis to assist clinicians in determining whether to administer NAC; for instance, if clinicians would only like to treat patients with a 30% or greater likelihood of non–organ-confined disease, the Green nomogram would allow these patients to be selected based on preoperative characteristics.

Other groups have also developed predictive models to determine the likelihood of response to NAC. For example, at The University of Texas MD Anderson Cancer Center, low- and high-risk bladder cancer groups have been defined based on prior studies of adjuvant chemotherapy,[15] and the criteria now include results of axial imaging, examination under anesthesia, and TUR. Specifically, MD Anderson defines high-risk disease as the presence of a palpable mass or local invasion (≥cT3b) on examination, presence of hydroureteronephrosis on imaging, or histologic evidence of lymphovascular invasion, micropapillary, and/or neuroendocrine features at TURBT.[15] Absent any of these features, the patient is considered low risk. Culp et al[16] assessed oncologic outcomes in a cohort of 297 patients who underwent RC without NAC at MD Anderson. The authors hypothesized that patients in the low-risk group could be spared the toxicity of NAC without compromising oncologic outcomes. Patients with low-risk disease before surgery had a 5-year

disease-specific survival rate of 82.7% compared with 68.2% for patients with any high-risk feature. Notably, 49.2% of patients considered low risk were upstaged to high risk at RC, including 29.6% with nodal disease. The only identifiable factor predictive of upstaging to high-risk disease was preoperative anemia. The authors acknowledge that a concern in implementing this paradigm into clinical practice is that the patients with low-risk preoperative characteristics who were upstaged would miss their chance for NAC. However, the authors point out that these patients are candidates for adjuvant chemotherapy and maintain a high 5-year disease-specific survival rate (>80%).[15]

The NCCN Guidelines for Bladder Cancer currently recommend that NAC be considered in all patients with MIBC (to view the most recent version of these guidelines, visit NCCN.org).[17] Nomograms and risk tables may identify patients most likely to benefit from chemotherapy, while sparing those who are unlikely to benefit from experiencing the morbidity associated with chemotherapy.

Predicting Risk of Recurrence After RC

The International Bladder Cancer Nomogram Consortium (IBCNC) sought to develop a prognostic tool that was globally generalizable based on patients treated with RC at centers of excellence worldwide.[18] The resulting nomogram, based on data from 9064 patients, was designed to predict 5-year progression-free probability after RC alone and was applicable to any bladder cancer histology. The variables chosen for the nomograms (sex, age, pathologic stage, histologic type, lymph node status, time from diagnosis to RC, and histologic grade) were selected a priori based on previous series and available data; they were not confirmed to have prognostic significance in multivariable analysis of the nomogram patient cohort. On internal validation of the nomogram using bootstrapping, the concordance index was calculated to be 0.75, which means that given any 2 patients, the probability was that the nomogram would correctly predict the patient with the first recurrence in 75% of instances. This discriminatory power is significantly superior to the AJCC TNM staging system (concordance index, 0.68) and the standard pathologic stage subgroupings (concordance index, 0.62).[18]

Strengths of the IBCNC calculator include the global patient population (23.6% of patients were from Mansoura University in Egypt) and the inclusion of various MIBC histologic types. However, as a consequence of this heterogeneity, the patient cohort came from a variety of treatment paradigms with no central pathology review. Furthermore, the data collection differed between institutions. Hence, the nomogram design was limited to variables available at all centers (eg, lymphovascular invasion, presence of CIS, and radiographic findings were not available). Also, because of limitations in data collection, nodal status could only be recorded as positive or negative, without regard to the number of positive nodes or the number of nodes removed.[19]

The Bladder Cancer Research Consortium (BCRC) has developed nomograms for disease recurrence[20] and disease-specific and overall survivals[21] using a large multi-institutional cohort of patients treated with RC in the United States. In addition to the clinical variables included in the IBCNC nomogram, the BCRC nomogram for recurrence includes the presence of lymphovascular invasion, CIS found in the pathology specimen, and use of chemotherapy or radiation therapy, yielding an excellent predictive accuracy (0.780) on internal validation. Notably, unlike the IBCNC nomogram, patients with nonurothelial carcinoma were excluded. Despite these differences, the BCRC and IBCNC nomograms have both performed well in external validation cohorts.[22–24] In a study from 2 European institutions, the predictive accuracy for the BCRC and IBCNC nomograms was found to be 0.84 and 0.86, respectively.[22] In an external validation study from the United States, the BCRC calculator showed slightly better calibration than the IBCNC calculator (concordance index, 0.77 vs 0.70).[23] The addition of clinical parameters, such as functional status, comorbidities, and smoking history, have been reported to improve the accuracy of nomograms predicting disease-specific survival further,[25] although head-to-head external validation studies are required to determine if the increased complexity improves accuracy over the BCRC and IBCNC nomograms.

Whether post-RC nomograms will gain widespread acceptance remains unclear. In addition to improved patient counseling and clinical trial design, post-RC nomograms may improve patient selection for adjuvant chemotherapy.[26,27] The current NCCN Guidelines for Bladder Cancer recommend consideration of adjuvant chemotherapy based on pathologic

stage (pT3, pT4, or N+ disease),[17] and recent meta-analyses suggest a particular benefit among patients with N+ disease.[28] However, the meta-analyses to date have relied on few patients, limiting the statistical power to detect small differences in subgroup analyses. Thus, whether post-RC nomograms are able to better align patients with treatment strategies more accurately than TNM staging should be validated in future studies.

The BCRC nomogram, IBCNC nomograms, and SPARC (Survival Prediction After Radical Cystectomy) score aim to individualize the risk of recurrence after RC. Potential benefits include improved patient counseling and improved selection of candidates for adjuvant chemotherapy, although further study is needed to demonstrate improvement over TNM staging.

Success of Bladder-Sparing Techniques

Candidates for bladder-sparing techniques traditionally have been patients with small tumors (<5 cm), cT2 disease, absence of extensive CIS, absence of hydronephrosis, and no evidence of pelvic lymphadenopathy, and those who undergo a complete TURBT.[17,29] These recommendations are derived from unadjusted models, wherein absence of any one of these clinical factors was associated with failure of multimodality therapy. Coen et al[30] sought to develop more sophisticated instruments to determine whether additional patients who do not meet traditional inclusion criteria should be considered for bladder-sparing treatment. The authors fit nomograms to predict complete response, disease-specific survival, and bladder-intact disease-free survival based on 325 patients who underwent bladder-sparing treatment at a single institution. The investigators included clinical T stage, grade, presence of hydronephrosis, age, TURBT completeness, and sex in the model. The authors found that extent of TURBT was predictive of complete response but not disease-specific survival. Preoperative hydronephrosis, on the other hand, was predictive of both lower disease-specific survival and incomplete response. Pending external validation, it is possible that the nomogram may be used to identify ideal patients for trimodality therapy.

Predicting Morbidity and Mortality After RC

Given the considerable morbidity and mortality associated with RC,[31,32] patients with MIBC considering treatment options must carefully balance the risks of surgery against the potential oncologic benefit. Nearly 75% of patients with bladder cancer are older than 65 years,[33] and an alarmingly high proportion have significant medical comorbidities. Individualizing the risk of morbidity or mortality after RC remains challenging, although several authors have attempted to improve tools for predicting mortality risk after RC. Morgan et al[34] developed a nomogram to predict 90-day mortality in patients older than 75 years using preoperative variables. The authors found age, Charlson comorbidity index, clinical T2 or greater disease, and preoperative albumin to be significantly associated with 90-day mortality in a multivariable model. A nomogram using these variables obtained a predictive accuracy of 75%, with a concordance index of 71% on internal validation. A similar nomogram developed in a European population predicts 90-day mortality risk in patients of all ages who undergo RC, with an internal predictive accuracy of 78.8%.[35] The factors used in the nomogram are age, presence of metastatic disease, hospital cystectomy volume, and American Society of Anesthesiologists score. Although both preoperative nomograms showed promising accuracy in the development cohort, neither has been externally validated. Importantly, they do point out the need to consider factors such as age, comorbidity, nutritional status, and hospital experience in assessing the risk/benefit ratio of RC. Considering the significant risk of morbidity and mortality after RC, these tools may enable individualized treatment decision-making in an attempt to optimize the risk/benefit ratio in bladder cancer treatment.

Conclusions

Bladder cancer remains a heterogeneous disease with heterogeneous outcomes. Although stage and grade offer considerable predictive discrimination, the addition of other clinicopathologic parameters clearly may improve the ability to individualize bladder cancer management. Through weighing the relative importance of multiple tumor- and patient-specific variables, bladder cancer risk tables and nomograms provide individualized risk assessment that can be used to predict patient-specific outcomes. In particular, nomograms for NMIBC allow the identification of patients at high risk of disease progression who are ideal candidates for early cystectomy. Nomograms

for MIBC better select the patients who will benefit from NAC or adjuvant chemotherapy, determine which patients can safely tolerate RC, and identify which patients should be referred for bladder-sparing approaches. Future efforts are needed to develop predictive models to guide other important decisions for patients with bladder cancer, such as those to predict quality of life, functional recovery after treatment, and risk of readmission. In aggregate, these predictive models will facilitate truly rational decision-making for patients with bladder cancer.

References

1. Edge S, Byrd DR, Compton CC, et al, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010.
2. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49:466–477.
3. Svatek RS, Hollenbeck BK, Holmang S, et al. The economics of bladder cancer: costs and considerations of caring for this disease [published online ahead of print January 21, 2014]. Eur Urol, doi: 10.1016/j.eururo.2014.01.006.
4. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol 2013;64:639–653.
5. Babjuk M, Oosterlinck W, Sylvester R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder, the 2011 update. Eur Urol 2011;59:997–1008.
6. Fernandez-Gomez J, Solsona E, Unda M, et al. Prognostic factors in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: multivariate analysis of data from four randomized CUETO trials. Eur Urol 2008;53:992–1001.
7. Fernandez-Gomez J, Madero R, Solsona E, et al. The EORTC tables overestimate the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: external validation of the EORTC risk tables. Eur Urol 2011;60:423–430.
8. Xylinas E, Kent M, Kluth L, et al. Accuracy of the EORTC risk tables and of the CUETO scoring model to predict outcomes in non-muscle-invasive urothelial carcinoma of the bladder. Br J Cancer 2013;109:1460–1466.
9. Hernandez V, De La Pena E, Martin MD, et al. External validation and applicability of the EORTC risk tables for non-muscle-invasive bladder cancer. World J Urol 2011;29:409–414.
10. Lammers RJ, Palou J, Witjes WP, et al. Comparison of expected treatment outcomes, obtained using risk models and international guidelines, with observed treatment outcomes in a Dutch cohort of patients with non-muscle-invasive bladder cancer treated with intravesical chemotherapy. BJU Int 2014;114:193–201.
11. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–866.
12. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol 2001;19:666–675.
13. Canter D, Long C, Kutikov A, et al. Clinicopathological outcomes after radical cystectomy for clinical T2 urothelial carcinoma: further evidence to support the use of neoadjuvant chemotherapy. BJU Int 2011;107:58–62.
14. Green DA, Rink M, Hansen J, et al. Accurate preoperative prediction of non-organ-confined bladder urothelial carcinoma at cystectomy. BJU Int 2013;111:404–411.
15. Logothetis CJ, Johnson DE, Chong C, et al. Adjuvant cyclophosphamide, doxorubicin, and cisplatin chemotherapy for bladder cancer: an update. J Clin Oncol 1988;6:1590–1596.
16. Culp SH, Dickstein RJ, Grossman HB, et al. Refining patient selection for neoadjuvant chemotherapy before radical cystectomy. J Urol 2014;191:40–47.
17. Clark PE, Spiess PE, Agarwal N, et al. NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 2, 2014. Available at: NCCN.org. Accessed October 9, 2014.
18. Bochner BH, Kattan MW, Vora KC; International Bladder Cancer Nomogram Consortium. Postoperative nomogram predicting risk of recurrence after radical cystectomy for bladder cancer. J Clin Oncol 2006;24:3967–3972.
19. Sternberg CN. Are nomograms better than currently available stage groupings for bladder cancer? J Clin Oncol 2006;24:3819–3820.
20. Karakiewicz PI, Shariat SF, Palapattu GS, et al. Nomogram for predicting disease recurrence after radical cystectomy for transitional cell carcinoma of the bladder. J Urol 2006;176:1354–1361.
21. Shariat SF, Karakiewicz PI, Palapattu GS, et al. Nomograms provide improved accuracy for predicting survival after radical cystectomy. Clin Cancer Res 2006;12:6663–6676.
22. Zaak D, Burger M, Otto W, et al. Predicting individual outcomes after radical cystectomy: an external validation of current nomograms. BJU Int 2010;106:342–348.
23. Al-Daghmin A, English S, Kauffman EC, et al. External validation of preoperative and postoperative nomograms for prediction of cancer-specific survival, overall survival and recurrence after robot-assisted radical cystectomy for urothelial carcinoma of the bladder. BJU Int 2014;114:253–260.
24. Nuhn P, May M, Sun M, et al. External validation of postoperative nomograms for prediction of all-cause mortality, cancer-specific mortality, and recurrence in patients with urothelial carcinoma of the bladder. Eur Urol 2012;61:58–64.
25. Eisenberg MS, Boorjian SA, Cheville JC, et al. The SPARC score: a multifactorial outcome prediction model for patients undergoing radical cystectomy for bladder cancer. J Urol 2013;190:2005–2010.
26. Sonpavde G, Khan MM, Svatek RS, et al. Prognostic risk stratification of pathological stage T3N0 bladder cancer after radical cystectomy. J Urol 2011;185:1216–1221.
27. Sonpavde G, Khan MM, Svatek RS, et al. Prognostic risk stratification of pathological stage T2N0 bladder cancer after radical cystectomy. BJU Int 2011;108:687–692.
28. Leow JJ, Martin-Doyle W, Rajagopal PS, et al. Adjuvant chemotherapy for invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 2014;66:42–54.
29. Fernando SA, Sandler HM. Multimodality bladder preservation therapy for muscle-invasive bladder tumors. Semin Oncol 2007;34:129–134.
30. Coen JJ, Paly JJ, Niemierko A, et al. Nomograms predicting response to therapy and outcomes after bladder-preserving trimodality therapy for muscle-invasive bladder cancer. Int J Radiat Oncol Biol Phys 2013;86:311–316.
31. Isbarn H, Jeldres C, Zini L, et al. A population based assessment of perioperative mortality after cystectomy for bladder cancer. J Urol 2009;182:70–77.
32. Shabsigh A, Korets R, Vora KC, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol 2009;55:164–174.
33. Edwards BK, Howe HL, Ries LA, et al. Annual report to the nation on the status of cancer, 1973-1999, featuring implications of age and aging on U.S. cancer burden. Cancer 2002;94:2766–2792.
34. Morgan TM, Keegan KA, Barocas DA, et al. Predicting the probability of 90-day survival of elderly patients with bladder cancer treated with radical cystectomy. J Urol 2011;186:829–834.
35. Aziz A, May M, Burger M, et al. Prediction of 90-day mortality after radical cystectomy for bladder cancer in a prospective European multicenter cohort. Eur Urol 2014;66:156–163.