Comparison of Surveillance Strategies for Low-Risk Bladder Cancer Patients

Yuan Zhang, PhD, Brian T. Denton, PhD, Matthew E. Nielsen, MD, MS

Objective. *Low-grade noninvasive disease comprises approximately half of incident bladder cancer cases. These lesions have exceedingly low rates of progression to aggressive, muscle-invasive bladder cancer, and there is salient discordance with regard to management recommendations for these patients between the principal clinical practice guidelines. In this context, we compare the international guidelines with alternative surveillance strategies for low-risk bladder cancer patients.* ***Methods***. *We used a partially observable Markov model based on states that defined patient risk levels associated with recurrence and progression of bladder cancer. The model also included states defining the effects of treatment, death from bladder cancer, and all other-cause mortality. Simulation was done to estimate quality-adjusted life years (QALYs), expected lifelong progression probability, and lifetime number of cystoscopies.* ***Results***. *We compared current international guidelines and additional proposed surveillance strategies on the basis of QALYs. We conducted a bicriteria analysis to compare expected lifelong progression rate v. the number of cystoscopies. One-way sensitivity analysis was used to evaluate the influence of model parameters, including a patient's disutility associated with cystoscopy, bladder cancer mortality, and all other-cause mortality.* ***Conclusions***. *Age and comorbidity significantly affect the optimal surveillance strategy. Results suggest that younger patients should be screened more intensively than older patients, and patients having comorbidity should be screened less intensively.* ***Key words:*** *bladder cancer; surveillance; partially observable Markov model.* ***(Med Decis Making 2013;33:198–214)***

Carcinoma of the urinary bladder ranks fifth among malignancies, with more than 70,000 new cases estimated in 2011 and over 500,000 survivors in the United States alone.[1] Typical of epithelial malignancies, bladder cancer incidence is highest in the elderly. Therefore, the changing age structure of the US population suggests that the burden of this disease will increase in the future. Clinically, bladder cancer cases are risk-stratified on the basis of stage and grade. The natural history and molecular biology of different risk groups are sufficiently different to suggest the existence of at least 3 discrete phenotypes: high-grade muscle invasive and high- and low-grade non–muscle invasive.[2,3] Muscle-invasive disease (stage T2 or greater) accounts for approximately 25% of incident cases, with high risks of metastasis-related morbidity and disease-specific mortality despite radical surgical therapy and systemic chemotherapy. The overwhelming majority of incident bladder cancer presents at a stage superficial to the muscularis propria, broadly defined as non-muscle-invasive bladder cancer (NMIBC). For these NMIBC cases, standard clinical management includes endoscopic transurethral resection of the bladder tumor (TURBT) and intravesical bacillus Calmette-Guerin (BCG) therapy, followed by frequent, invasive surveillance with cystoscopy.

The proximate outcomes for patients with a history of NMIBC are recurrence of NMIBC or progression, defined as recurrence of a tumor with invasion into

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the muscle. The risks of these distinct outcomes differ starkly between high- and low-grade NMIBC. Low-grade noninvasive tumors account for approximately two-thirds of all incident NMIBC and, given the comparatively indolent natural history of these cases, likely represent the majority of prevalent bladder cancer cases.[4] In this setting, the principal risk (approximately 40%–50% by 5 years[5]) is recurrence of low-grade noninvasive tumors, whereas the long-term risk of progression to muscle-invasive disease is less than 5% and, in some series, less than 1%.[5–7] The long-term progression rates from low-grade noninvasive urothelial carcinoma to invasive cancer, in some respects, parallel those of colorectal adenomata.[8] In contrast, high-grade NMIBC cases have not only higher rates of recurrence, typically of high-grade NMIBC, but, more important, substantially higher risks of progression to muscle-invasive disease, up to 50% to 75% by 5 years.[5,9] Given that low-grade noninvasive bladder cancer accounts for nearly half of the overall incident cases, these differences in phenotype-associated outcomes argue for consideration of a risk-adjusted approach to surveillance.

Cystoscopy is the reference standard for surveillance of patients with a history of NMIBC. In the context of the heterogeneous natural history of NMIBC, there is an interesting and substantial difference between the recommendations of the relevant European and US clinical practice guidelines. The European Association of Urology (EAU 2009)[10] advocates explicit risk stratification and, among low-risk cases, recommends surveillance cystoscopy at 3 months, 9 months, and annually thereafter for patients without recurrence. In contrast, the American Urological Association (AUA) guidelines (e.g., AUA 2007[11]) do not explicitly risk-stratify surveillance recommendations and outline a schedule of cystoscopy every 3 months for 2 years, every 6 months for the next 3 years, and annually thereafter for patients without recurrence, which is consistent with the EAU's schedule for high-grade NMIBC. The AUA guidelines acknowledge the potential appropriateness of less intensive regimens for select patients, but no explicit guidance is given, and a one-size-fits-all, relatively intensive approach would be consistent with the AUA guidelines recommendations.

For NMIBC patients, surveillance policies must trade off the benefit of early detection of recurrence and/or progression against the economic and quality-of-life costs of frequent, invasive surveillance. Cystoscopy can be painful and anxiety provoking for patients.[12,13] Given the variable natural history of NMIBC, these tradeoffs can differ greatly not only in terms of cancer-specific risks but also, with the predominantly elderly demography of the bladder cancer population, in terms of age and associated competing risks to survival.

We developed a partially observable Markov model to compare surveillance strategies for patients with low-grade noninvasive bladder cancer. We evaluated strategies based on quality-adjusted life years (QALYs); we also performed a bicriteria analysis to compare expected lifelong progression rate v. the number of cystoscopies. We found that the best strategy is sensitive to the disutility of cystoscopy, age, and all other-cause mortality. We conclude that the best surveillance strategy is highly dependent on the individual patient. The lower the disutility of cystoscopy, the more frequently cystoscopy should be performed. Older patients and patients with comorbidity should be screened less frequently.

METHODS

The EAU and AUA guidelines represent the reference standard practice guidelines for bladder cancer surveillance in Europe and the United States, respectively, as summarized in Table 1. For low-risk patients, the EAU suggests cystoscopy at 3 months; if negative, then follow-up cystoscopy is advised at 9 months and, subsequently, at yearly intervals for 5 years. The AUA guidelines do not make specific, explicit recommendations for low-risk disease;

Table 1 Published Guidelines for Surveillance of Low-Risk Bladder Cancer Patients

Guidelines	Recommendations for Low-Risk Bladder Cancer Patients
European Association of Urology[10]	Cystoscopy at 3 months
	If negative, next cystoscopy at 9 months
	If negative, cystoscopy yearly for 5 years
American Urological Association[11]	No low-risk stratum-specific schedule is explicitly advocated; the following is mentioned:
	Every 3 months in the first 2 years
	Every 6 months for subsequent 2–3 years
	Annually thereafter

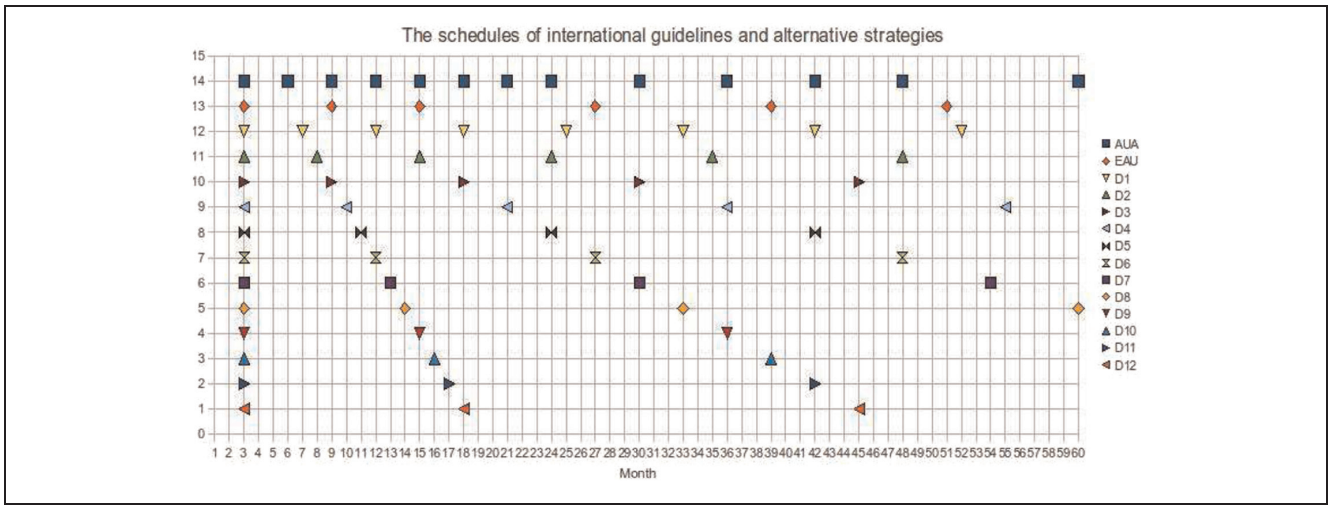

Figure 1 The surveillance month for each dynamic surveillance strategy as well as the European Association of Urology (EAU) and American Urological Association (AUA) guidelines. Each row represents one strategy.

instead, they recommend a more intense surveillance schedule for all patients, regardless of risk stratum. The AUA guidelines do suggest, however, consideration of less intensive regimens (not further specified) based on individual patient factors (also not further specified). In this context, we also considered additional hypothetical dynamic strategies.

We designed a series of dynamic surveillance strategies based on 3 elements: first surveillance interval, subsequent interval increment, and stopping time. Since it is a standard among published guidelines to do the first cystoscopy at 3 months and to stop surveillance for low-risk patients after 5 years, all strategies we evaluated began surveillance at 3 months and stopped within 5 years. The strategies were differentiated on the basis of the subsequent interval increment. The dynamic strategies are denoted by D_i, in which cystoscopies are performed at increasing intervals of $3, 3+i, 3+2i, 3+3i$, up to 5 years if no recurrence occurs. Thus, for example, strategy D_3 involved cystoscopies at months 0, 3, 9, 18, 30, and 45. It is important to note that based on the design of the rules, the policies are not uniform in their surveillance duration. For example, for dynamic strategies D_3, D_7, D_{11}, D_{12}, the last follow-up cystoscopy was in months 45, 54, 42, and 45. The surveillance time for each dynamic strategy is listed in Figure 1.

Partially Observable Markov Model

The patient's health state at any given month, which is defined as a *decision epoch* in this context, is not known with certainty. Observations are obtained as a result of cystoscopy, and a positive observation will trigger treatment. Therefore, frequent cystoscopy will result in a higher probability of diagnosing recurrent tumors prior to progression. On the other hand, more frequent surveillance results in a reduction in expected rewards due to the disutility associated with cystoscopy. To compare how strategies balance these competing factors, we used a Markov model composed of health states that define the natural history of bladder cancer, treatment, and death from bladder cancer and all other causes. The model is illustrated in Figure 2. The model formulation is defined as follows:

Decision epochs. We let $t=1,2,\ldots,T$ index monthly decision epochs over the course of a bladder cancer patient's lifetime, where T represents a reasonable upper limit on a patient's age (e.g., 100 years).

States. The patients' health state at epoch t is indexed by $s_t \in S$, where $S=\{1,,H,H+1\}$. State H represents the state of muscle-invasive bladder cancer, and $H+1$ represents the state of death. States 1 to $H-1$ were developed from the EAU classification of non-muscle-invasive patients, based on prognostic factors including tumor stage, tumor grade, tumor size, and recurrence rate.[10] A descriptive list of states, including the index for each state, is provided in Table 2. The model includes the following 5 health states: low-risk NMIBC, intermediate-risk

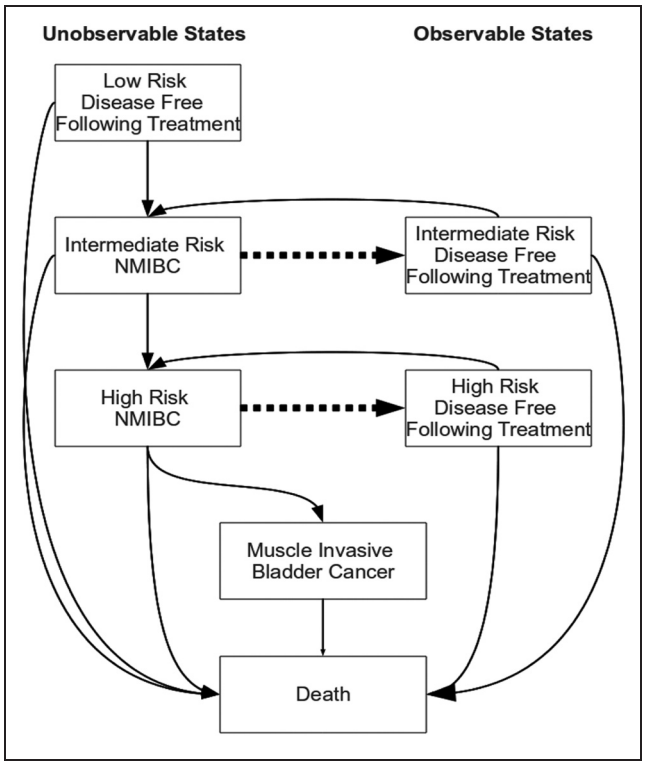

Figure 2 The states and possible transitions between states for a patient with bladder cancer. The solid lines indicate the probabilistic transitions. The dashed lines indicate the transitions resulting from the detection of bladder cancer via cystoscopy. NMIBC, non-muscle-invasive bladder cancer.

NMIBC, high-risk NMIBC, muscle-invasive bladder cancer, and death from bladder cancer and all other causes. Note that the intermediate- and high-risk NMIBC states are assumed to be unobservable as NMIBC is unlikely to be associated with noticeable symptoms and can only be diagnosed with cystoscopy. For high-risk and muscle-invasive disease, cystectomy is a common recommendation.[14] For small, recurrent, low-grade bladder tumors, some studies suggest it may not be necessary to remove tumors promptly at recurrence.[1,15,16] In our model, low-risk patients continue to follow cystoscopic surveillance, and treatment is triggered when the patient progresses to intermediate or high risk. We include the following 2 treatment states: 1) intermediate risk, disease free following treatment and 2) high risk, disease free following treatment. Patients are only low risk until the first occurrence, after which they are intermediate risk (recurrent low-grade Ta) or high risk (high-grade NMIBC recurrence).

Transition probabilities. We let $p_{s_t,s_{t+1}}(t)$ denote the probability that the patient will be in health state s_{t+1} in epoch $t+1$ given that he or she is in state s_t in epoch t. The transition probability matrix, $P(t)$, can be written as follows (blank spaces indicate zeros):

$$P(t)=\begin{bmatrix} p_{1,1}(t) & p_{1,2}(t) & & & & & p_{1,7}(t) \\ & p_{2,2}(t) & & p_{2,4}(t) & & & p_{2,7}(t) \\ & p_{3,2}(t) & p_{3,3}(t) & & & & p_{3,7}(t) \\ & & & p_{4,4}(t) & & p_{4,6}(t) & p_{4,7}(t) \\ & & & p_{5,4}(t) & p_{5,5}(t) & & p_{5,7}(t) \\ & & & & & p_{6,6}(t) & p_{6,7}(t) \\ & & & & & & p_{7,7}(t) \\ & & & & & & \end{bmatrix}. \quad (1)$$

We define parameters for annual rates of bladder cancer mortality, bladder cancer recurrence and progression, and all other-cause mortality in Table 3. At each health state, patients may die from other causes; we assume $p_{1,7}(t)=p_{2,7}(t)=p_{3,7}(t)=p_{4,7}(t)=p_{5,7}(t)=\delta(t)$.

Table 2 Markov States of the Natural History Model and Treatment Model for Bladder Cancer

Index	Natural History States	Description
1	Low risk, disease free (LRDF)	History of small-volume, low-grade Ta
2	Intermediate-risk NMIBC (IRBC)	Recurrent low-grade Ta or multifocal and/or large-volume low-grade Ta
4	High-risk NMIBC (HRBC)	High-grade Ta, T1, and/or CIS
6	Muscle-invasive bladder cancer (MIBC)	T2, T3, T4 tumors
7	Death from other causes (D)	Competing mortality
Index	**Treatment States**	**Description**
3	Intermediate risk, disease free following treatment (IRDF)	Intermediate risk, bladder cancer treated, disease free
5	High risk, disease free following treatment (HRDF)	High risk, bladder cancer treated, disease free

Note that the stratification of low risk, intermediate risk, and high risk is with regard to non-muscle-invasive bladder cancer, and the high-risk state is actually lower risk than the muscle-invasive bladder cancer state. CIS, carcinoma in situ; NMIBC, non-muscle-invasive bladder cancer.

Table 3 Model Parameters and Data Sources for Monthly Mortality, Bladder Cancer Mortality, Bladder Cancer Recurrence, and Progression Rates

Parameter	Description	Value	Data Sources
$\delta(t)$	Mortality rate at age t	Time variant	CDC[26]
δ_{BC}	Bladder cancer mortality	0.01083	Madersbacher and others[23]
φ_C	Sensitivity of cystoscopy	95%	Soloway and others[31]
γ_{IR}	Recurrence rate of intermediate-risk NMIBC after treatment	0.03045	EORTC[35]
γ_{HR}	Recurrence rate of high-risk BC after treatment	0.07547	
τ_{LR}	Probability of transition from LRDF to IRBC	0.002	
τ_{IR}	Probability of transition from IRBC to HRBC	0.008	
τ_{HR}	Probability of transition from HRBC to MIBC	0.07	

BC, bladder cancer; CDC, Centers for Disease Control and Prevention; EORTC, European Organisation for Research and Treatment of Cancer; NMIBC, non-muscle-invasive bladder cancer; LRDF, low risk, disease free; IRBC, intermediate-risk bladder cancer; HRBC, high-risk bladder cancer; MIBC, muscle-invasive bladder cancer.

In the muscle-invasive bladder cancer (MIBC) state, patients may die from bladder cancer (BC) with probability δ_{BC} or other causes with probability $\delta(t)$. Therefore, we assume $p_{6,7}(t)=\delta_{BC}+\delta(t)$. In the low-risk, disease-free (LRDF) state, patients may have recurrent cancer of intermediate risk with probability $p_{1,2}(t)=\tau_{LR}$. In the intermediate-risk bladder cancer (IRBC) state, bladder cancer may progress to the high-risk bladder cancer (HRBC) state with probability τ_{IR}, and thus $p_{2,4}(t)=\tau_{IR}$. In the intermediate-risk, disease-free (IRDF) state, patients may have recurrence with probability γ_{IR}, and thus $p_{3,2}(t)=\gamma_{IR}$. Similarly, in the high-risk, disease-free (HRDF) state, patients may have recurrence with probability γ_{HR}, and thus $p_{5,4}(t)=\gamma_{HR}$. In the HRBC state, patients may progress to the MIBC state with probability τ_{HR}, and thus $p_{4,6}(t)=\tau_{HR}$. Finally, the death state is an absorbing state, with $p_{7,7}(t)=1$.

Decision. The cystoscopy surveillance decision at epoch t is indexed by $a_t \in A_t=\{$Cystoscopy (C), No Cystoscopy (N)$\}$.

Rewards. The rewards for state s_t and decision a_t are denoted by $r(s_t,a_t)$. They are measured in QALYs, by subtracting the disutilities of cystoscopy and treatment associated with decision a_t. Both chemotherapy and BCG immunotherapy are topically applied to the bladder mucosa, after instillation with a catheter, as adjuvant treatment following TURBT if the cystoscopy result is positive. In the model, we assume BCG is the adjuvant therapy of choice and do not separately consider intravesical chemotherapy, as BCG is the current standard intravesical therapy in the United States. Cystoscopy and TURBT are short medical procedures, whereas BCG therapy may last longer than 6 weeks per course. In the model, the utility reductions are measured in life years and are applied to the 3-month period in which the procedure or treatment was initiated. The disutilities are defined in Table 4.

We use $R(a_t)=\{r(s_t,a_t)\}$ to denote the *reward vector*, which can be written as follows:

$$R(N)=\begin{bmatrix} r_{LRDF} \\ r_{IRBC} \\ r_{IRDF} \\ r_{LRBC} \\ r_{HRDF} \\ r_{MIBC} \\ 0 \end{bmatrix},$$

$$R(C)=\begin{bmatrix} r_{LRDF}-\mu_C \\ r_{IRBC}-\mu_C-\mu_T-\mu_{Chemo}-\mu_{BCG} \\ r_{IRDF}-\mu_C \\ r_{HRBC}-\mu_C-\mu_T-\mu_{Chemo}-\mu_{BCG} \\ r_{HRDF}-\mu_C \\ r_{MIBC} \\ 0 \end{bmatrix}.$$

A surveillance strategy defines the sequence of decisions, $\xi=\{a_1,a_2,\ldots,a_T\}$, about whether to perform a cystoscopy at each decision epoch, t. To compare strategies, we estimated the total expected QALYs, $E_\xi[\sum_{t=1}^{T} r(s_t,a_t)]$, over the patient's lifetime. We also estimated expected lifelong progression rate and the expected number of cystoscopies.

Data Sources

Transition probabilities are derived from the European Organisation for Research and Treatment of Cancer (EORTC) risk Table 7, Centers for Disease Control and Prevention (CDC) mortality Table 15, and survival data 31, summarized in Table 3. The

Table 4 Model Parameters and Data Sources for Utilities and Disutilities for Estimating QALYs

Parameter	Description	Value (QALYs)	Source
μ_C	Disutility of cystoscopy	0.025	Kulkarni and others[28]
μ_T	Disutility of TURBT	0.03	
μ_{BCG}	Disutility of BCG	0.09	
r_{LRDF}	Utility in low risk, disease free following treatment	0.98	
r_{IRBC}	Utility in intermediate-risk NMIBC	0.95	
r_{IRDF}	Utility in intermediate risk, disease free following treatment	0.95	
r_{HRBC}	Utility in high-risk NMIBC	0.93	
r_{HRDF}	Utility in high risk, disease free following treatment	0.93	
r_{MIBC}	Utility in high muscle-invasive bladder cancer	0.80	

The base case values are drawn from Kulkarni and others' study.[28] TURBT, transurethral resection of the bladder tumor; BCG, bacillus Calmette-Guerin; NMIBC, non-muscle-invasive bladder cancer; QALY, quality-adjusted life year.

EORTC risk tables were developed from pooled individual patient-level data from 2596 patients with NMIBC enrolled in 7 clinical trials. Annual (1- through 5-year) probability estimates of NMIBC recurrence and progression to muscle-invasive bladder cancer are calculated on the basis of coefficients from clinicopathological variables in multivariate logistic regression models. A recent study[17] of 13 cancers (not including bladder cancer) provides evidence that conditional survival rate increases with time since diagnosis of cancer. To incorporate this into the bladder cancer survival probability, we used a yearly discounting factor, γ, and we assumed the recurrence rate in year t, conditional on remaining disease free, is $p_t = p_1\gamma^{t-1}$. We used 1-year and 5-year recurrence and progression rates from the EORTC table to estimate γ.

We estimated the mortality rate of MIBC from survival data of MIBC patients who underwent radical cystectomy. We performed a PubMed search on the recent published literature on bladder cancer survival from 2000 to 2010 using the following keywords: bladder cancer[Title/Abstract] AND survival[Title] AND radical cystectomy[Title]. We excluded studies that were not based on patient cohort data or clinical trials, leaving 8 studies in total,[18–25] among which the study by Shariat and others[24] had the largest sample size for bladder cancer disease-specific survival. Therefore, we estimated the base case mortality rate, δ_{BC}, from the 5-year disease-specific survival of MIBC patients reported by Shariat and others.[24] The authors reported results based on a multi-institutional database consisting of 888 consecutive patients with bladder transitional cell carcinoma who were treated with radical cystectomy and pelvic lymphadenectomy at 3 academic centers in the United States between 1984 and 2003. Mortality rates from all other causes were estimated from the statistics reports published by the CDC.[26] We transformed yearly rates, denoted by p_y, to corresponding monthly rates, p_m, by the formula $(1-p_m)^{12} = (1-p_y)$. The base case of cystoscopy sensitivity is set to be 0.95.[27]

We used estimates of utilities and disutilities reported by Kulkarni and others.[28] The estimates are summarized in Table 4. The disutility of cystoscopy was taken as the midpoint of the reported plausible range.

Inverse Optimization

It was not possible to estimate the parameters for grade progression, $\tau_{LR}, \tau_{IR}, \tau_{HR}$, directly from the literature. Therefore, we estimated them by comparing the model outputs with published progression rates $\rho_{LR}, \rho_{IR}, \rho_{HR}$. We denote the model output of the 5-year progression rate of HRBC patients starting at age t as $f_{HR}(\tau_{HR})$. Similarly, we denote the model output of the 5-year progression rate of IRBC at age t as $f_{IR}(\tau_{IR}, \tau_{HR})$ and for LRBC as $f_{LR}(\tau_{LR}, \tau_{IR}, \tau_{HR})$. We solved an inverse problem to compute the implied value of these unknown parameters.

Sampled estimates of progression rates were generated by Monte Carlo simulation using the model based on initial parameter estimates. The samples from the model were then compared with the published progression rates. The parameter τ_{HR} was iteratively adjusted to minimize the absolute difference, $|f_{HR}(\tau_{HR}) - \rho_{HR}|$, using a simple search algorithm. Once τ_{HR} was fixed, we proceeded to estimate τ_{IR} and then τ_{LR} as the choices that minimize $|f_{IR}(\tau_{IR}, \tau_{HR}) - \rho_{IR}|$ and $|f_{LR}(\tau_{LR}, \tau_{IR}, \tau_{HR}) - \rho_{LR}|$, respectively. Note that the sequence in which estimates are generated (decreasing order of risk) is important since τ_{HR} is required to estimate τ_{IR}, and both τ_{HR} and τ_{IR} are required to estimate τ_{LR}.

RESULTS

We used our Markov model to compare the EAU, AUA, and dynamic strategies $D_1, D_2, \ldots, D_{12}$. The base case parameter choices are defined in Tables 3 and 4. We performed sensitivity analysis with respect to this base case. The results, if not specified otherwise, are based on the base case scenario. We used C++ to implement the simulation process. For each scenario, we used 1,000,000 samples to estimate the mean and 95% confidence intervals. In all the scenarios presented below, the simulation process was completed within 1 hour on a PC with quad core 2.83 GHz CPU and 8 GB RAM.

Model Validation

We compared our model estimates of survival with those published in the EUROCARE-3 study,[29] which studied patients diagnosed with bladder cancer during 1990 to 1994. The EUROCARE-3 study summarized 1-year, 3-year, and 5-year survival by age at diagnosis for 21 European countries. The age ranges reported are 45 to 54, 55 to 64, 65 to 74, and 75 to 99 years. For our validation results, we assigned the value of each age range to the appropriate range in the EUROCARE-3 study. Most of the bladder cancer patients in the EUROCARE-3 study had muscle-invasive disease, but the proportion varies considerably from one country to another. Therefore, we compared the EUROCARE-3 study results with the computational lower bounds and upper bounds of our model, defined by the survival of MIBC patients and the survival of LRBC patients, respectively. As expected, the 5-year survival results obtained from our model lie between the survival of MIBC patients and that of LRBC patients starting at any age between 50 and 85 years.

Base Case Results

According to Surveillance Epidemiology and End Results (SEER),[30] the median age at diagnosis (2004–2008) for bladder cancer was 73 years; approximately 9.6% were diagnosed younger than age 55 years and 13.2% older than age 85 years. Therefore, we compare the EAU and AUA guidelines, strategies D_1 to D_{12}, and the no-surveillance (NS) strategy for the base case of a 73-year-old male and female patient. Note that the median age for female patients (2004–2008) was 74 years,[30] but we chose to compare male and female patients of the same age to focus on the effect of the covariate of sex (the ranking of strategies is the same for 74-year-old female patients). From Figure 3, the EAU guideline resulted in higher mean QALYs compared with the more intensive AUA guideline (11.05 v. 10.90 QALYs for a 73-year-old man). In the male base case, NS had the highest QALYs (11.13 QALYs), although the confidence interval overlapped with dynamic policies D_{10} to D_{12}. In the female base case, D_{12} was highest but not significantly different from D_5 to D_{11} and NS.

We compared the surveillance strategies on the basis of expected progression rate v. number of cystoscopies. Figure 4 shows the outcome of all strategies for low-risk male patients aged 73 years. The results indicate considerable differences between the EAU and AUA guidelines. For example, the EAU guideline resulted in a higher expected lifelong progression rate but with approximately half the number of cystoscopies over the patient's lifetime. The AUA guideline had an absolute reduction of 0.4% in the lifelong progression rate and an increase of 6.48 cystoscopies on average compared with the EAU guideline. We found that the AUA guideline resulted in an absolute reduction of 4.3% in the expected lifelong progression rate with 14.86 cystoscopies on average compared with the NS strategy. We observed that there were significant differences among strategies in the number of cystoscopies, ranging from 4.13 for strategy D_{12} to 13.76 for the AUA strategy. The differences in the lifelong progression rate in Figure 4 are likely related to the total duration of surveillance. For example, for D_2 to D_5, the durations are 52, 48, 45, 55, and 42 months, respectively. This explains why, for example, D_4 leads to a lower expected progression rate than D_1 to D_3. The results of bicriteria analysis for female patients are similar, shown in Figure A1 in the appendix.

Sensitivity Analysis

We performed a one-way sensitivity analysis on all strategies for model parameters, including disutility of cystoscopy, BC mortality, recurrence and progression rates, and all other-cause mortality. The parameter ranges are presented in Table 5. The lower bound and upper bound of cystoscopy disutility were sourced from the literature.[28] The lower bound and upper bound of cystoscopy sensitivity were chosen as 90% and 100%, respectively, as cystoscopy is the reference standard for detection of bladder cancer.[31] All the other parameters were varied from 50% to 200% of their base case values. In the case of recurrence and progression rates, all parameters

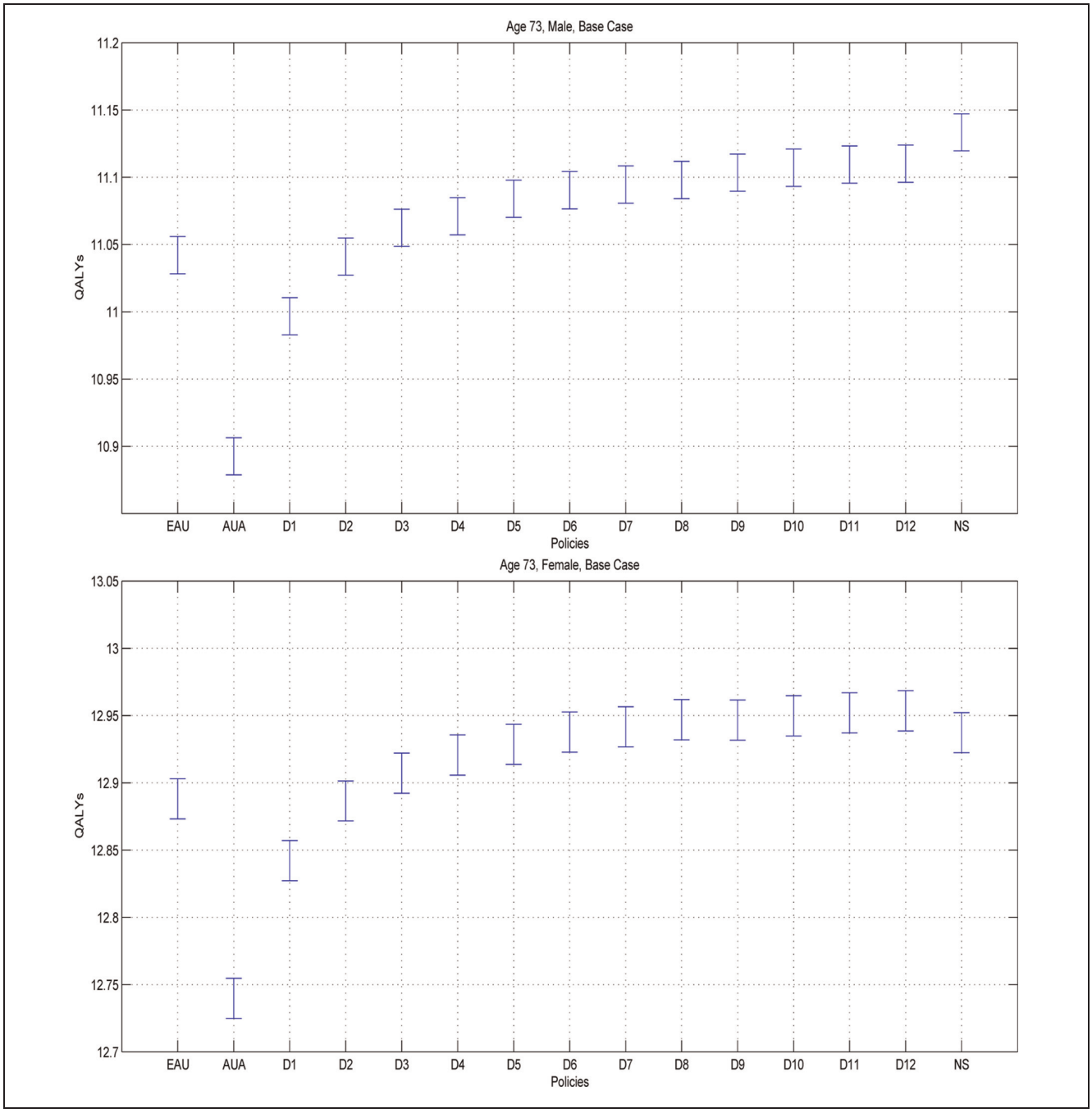

Figure 3 Expected quality-adjusted life years (QALYs) and 95% confidence intervals for all strategies for a 73-year-old male and a female patient in the base case. EAU, European Association of Urology; AUA, American Urological Association; NS, no surveillance.

were varied simultaneously. Table 6 provides the one-way sensitivity analysis for disutility of cystoscopy. In the scenario representing the upper bound of cystoscopy disutility, the best strategy is NS; for the lower bound of cystoscopy disutility, the worst is NS, and the other strategies are not statistically different from each other.

Table 7 provides the one-way sensitivity analysis for other-cause mortality. In the case of the upper bound of other-cause mortality, the optimal strategy

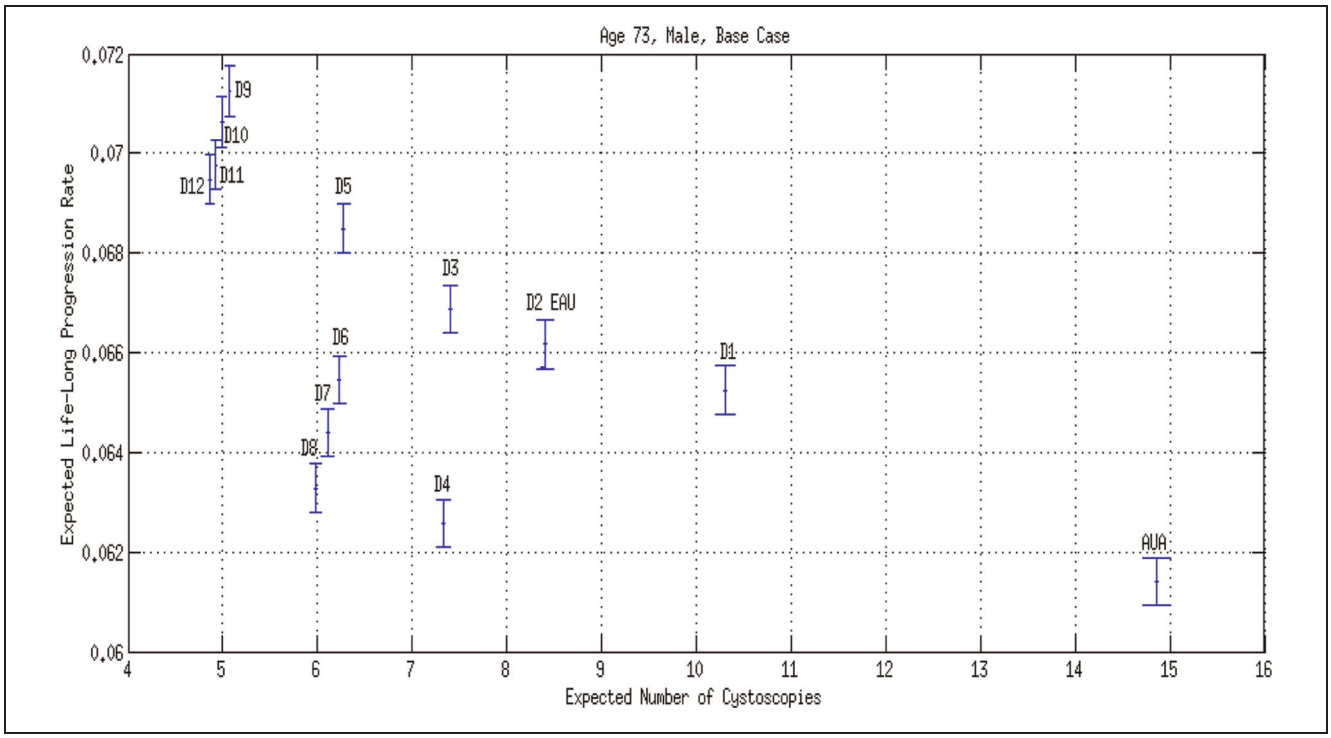

Figure 4 The expected lifelong progression rate to muscle-invasive disease v. number of cystoscopies over a patient's lifetime for a male patient aged 73 years under the base case scenario. The no-surveillance (NS) strategy resulted in an expected lifelong progression rate of 0.1045 (95% confidence interval, 0.1039–0.1051). EAU, European Association of Urology; AUA, American Urological Association.

is NS, whereas for the lower bound of other-cause mortality, the optimal strategy is D_8, which is statistically significantly better than strategy EAU, AUA, D_1, D_2, D_3, D_5, and NS. Hence, these results for all other-cause mortality indicate that elderly bladder cancer patients should have less intensive surveillance as they carry a high burden of competing risks. The sensitivity analysis results with respect to cystoscopy disutility and other-cause mortality for female patients are similar, as shown in Tables A4 and A5 in the appendix. Finally, the ranking of strategies does not change significantly within the range of bladder cancer mortality, recurrence and progression rates, and cystoscopy sensitivity, as shown in Tables A1 to A3 in the appendix. For example, for both cases of upper and lower bounds of cystoscopy sensitivity, as shown in Table A3, the best strategy is NS, which is statistically significantly better than EAU, AUA, D_1, D_2, and D_3 to D_9.

We evaluated the sensitivity of strategies to the starting age of surveillance. We compared the strategies for male patients aged 55 to 85 years, as shown in Table 8. The best strategy for 55-year-old patients is D_8. The best strategy for 85-year-old patients is NS. We also evaluated the base case results for female patients in different age groups, as shown in Table A6 in the appendix.

DISCUSSION AND CONCLUSIONS

Bladder cancer is an increasingly common condition, and low-grade noninvasive disease comprises approximately half of incident cases. There is uncertainty regarding the optimum management of these patients, reflected in the discordant recommendations of clinical practice guidelines. Given this, as well as the invasive nature of standard surveillance procedures and the low risk of progression to potentially life-threatening disease in an elderly population with competing risks, we developed a simulation model to evaluate the tradeoffs of different approaches, with the primary outcome of QALYs.

Our model for bladder cancer is based on recent estimates of the risk of recurrence and progression derived from the EORTC risk Table 7. The most related work to ours is that of Kent and others.[32,33] The authors developed a probabilistic model with 5 health states: free of tumor, with tumor and intact

Table 5 Base Case Values and Ranges for the Parameters That Changed in the One-Way Sensitivity Analysis

Description	Parameter	Base Case Value	Lower Bound	Upper Bound
Disutility of cystoscopy	μ_C	0.025	0.003	0.05
Bladder cancer mortality	δ_{BC}	0.011	0.005	0.016
Other-cause mortality	$\delta(t)$	$\delta(t)$	$0.5\times\delta(t)$	$2\times\delta(t)$
Cystoscopy sensitivity	φ_C	0.95	0.90	1.00
Progression and recurrence rates	γ_{IR}	0.030	0.015	0.060
	γ_{HR}	0.075	0.038	0.150
	τ_{LR}	0.002	0.001	0.004
	τ_{IR}	0.008	0.004	0.016
	τ_{HR}	0.070	0.035	0.140

Note that parameter $\delta(t)$ is dependent on age; progression and recurrence rates were varied by a factor of 0.5 and 2.0.

Table 6 One-Way Sensitivity Analysis with Respect to Disutility of Cystoscopy on Practical and Dynamic Policies for 73-Year-Old Low-Risk Male Patients

Strategies	Disutility of Cystoscopy Lower Bound (QALYs)	Disutility of Cystoscopy Upper Bound (QALYs)
EAU	11.230 (11.216, 11.244)	10.835 (10.821, 10.849)
AUA	11.225 (11.211, 11.239)	10.523 (10.510, 10.537)
D_1	11.227 (11.213, 11.241)	10.741 (10.727, 10.755)
D_2	11.230 (11.216, 11.244)	10.834 (10.820, 10.848)
D_3	11.229 (11.215, 11.243)	10.880 (10.866, 10.894)
D_4	11.236 (11.222, 11.250)	10.892 (10.878, 10.906)
D_5	11.225 (11.211, 11.239)	10.930 (10.917, 10.944)
D_6	11.230 (11.216, 11.244)	10.938 (10.925, 10.952)
D_7	**11.232 (11.218, 11.246)**	10.947 (10.933, 10.960)
D_8	**11.232 (11.218, 11.246)**	10.953 (10.939, 10.967)
D_9	11.218 (11.204, 11.231)	10.980 (10.967, 10.994)
D_{10}	11.219 (11.205, 11.233)	10.987 (10.973, 11.000)
D_{11}	11.219 (11.205, 11.233)	10.990 (10.976, 11.004)
D_{12}	11.219 (11.205, 11.232)	10.993 (10.979, 11.007)
NS	11.133 (11.120, 11.147)	**11.133 (11.120, 11.147)**

The boldfont value in each column indicates the best strategy in the corresponding scenario. AUA, American Urological Association; EAU, European Association of Urology; NS, no surveillance; QALY, quality-adjusted life year.

bladder, postcystectomy and tumor free, postcystectomy with tumor, and death. They compared hypothetical surveillance strategies with an optimal strategy that was calculated using a nonlinear optimization model to minimize expected delay of tumor detection. In contrast, our study uses recent data, including the EORTC risk tables, to define the model. We compared current guidelines specifically for low-risk bladder cancer patients, which are the focus of our study and represent the majority of patients with bladder cancer. We compared strategies on the basis of QALYs and used bicriteria analysis to compare the expected lifelong progression rate v. the expected number of cystoscopies over a patient's lifetime.

Our base case results indicated that the EAU guideline is associated with greater QALYs than the AUA guideline. The best strategy for a 73-year-old male patient was found to be NS. The best strategy for a 73-year-old female patient was found to be D_{12}, which has nearly half the expected number of cystoscopies compared with the EAU guideline over a patient's lifetime. The best strategy is D_8 for a 55-old-male patient and NS for an 85-year-old male patient, suggesting that older patients, or patients with higher all other-cause mortality, should generally undergo less intensive surveillance.

Although the differences among strategies on the basis of QALYs are relatively small, our bicriteria analysis revealed there are significant differences among strategies, particularly in the number of cystoscopies. We observed that the AUA guideline resulted in an absolute reduction of 4.3% in the expected lifelong progression rate, with 14.86

Table 7 One-Way Sensitivity Analysis with Respect to Other-Cause Mortality on Practical and Dynamic Policies for 73-Year-Old Low-Risk Male Patients

Strategies	Other-Cause Mortality Lower Bound (QALYs)	Other-Cause Mortality Upper Bound (QALYs)
EAU	16.757 (16.736, 16.779)	8.626 (8.615, 8.637)
AUA	16.627 (16.605, 16.649)	8.476 (8.465, 8.487)
D_1	16.711 (16.689, 16.732)	8.580 (8.569, 8.591)
D_2	16.752 (16.730, 16.773)	8.624 (8.613, 8.635)
D_3	16.773 (16.752, 16.795)	8.646 (8.635, 8.657)
D_4	16.808 (16.787, 16.830)	8.653 (8.642, 8.664)
D_5	16.789 (16.767, 16.810)	8.670 (8.659, 8.681)
D_6	16.814 (16.793, 16.836)	8.674 (8.663, 8.685)
D_7	16.826 (16.804, 16.847)	8.677 (8.666, 8.688)
D_8	**16.841 (16.819, 16.863)**	8.680 (8.669, 8.691)
D_9	16.798 (16.776, 16.819)	8.694 (8.683, 8.705)
D_{10}	16.802 (16.780, 16.824)	8.697 (8.686, 8.708)
D_{11}	16.813 (16.791, 16.834)	8.698 (8.687, 8.709)
D_{12}	16.818 (16.796, 16.840)	8.700 (8.689, 8.711)
NS	16.636 (16.614, 16.657)	**8.768 (8.757, 8.779)**

The boldfont value in each column indicates the best strategy in the corresponding scenario. AUA, American Urological Association; EAU, European Association of Urology; NS, no surveillance; QALY, quality-adjusted life year.

Table 8 Comparison of Strategies with Respect to Changes in Starting Age of Surveillance for Male Patients

Strategies	55	73	85
AUA	21.713 (21.694, 21.732)	11.045(11.031, 11.059)	5.913 (5.901, 5.924)
EAU	21.605 (21.585, 21.624)	10.896 (10.883, 10.910)	5.792 (5.780, 5.803)
D_1	21.668 (21.649, 21.687)	10.999 (10.986, 11.013)	5.873 (5.862, 5.885)
D_2	21.705 (21.686, 21.724)	11.044 (11.031, 11.058)	5.910 (5.898, 5.921)
D_3	21.722 (21.703, 21.741)	11.066 (11.052, 11.079)	5.929 (5.918, 5.940)
D_4	21.785 (21.766, 21.804)	11.075 (11.061, 11.089)	5.937 (5.926, 5.949)
D_5	21.733 (21.713, 21.752)	11.087 (11.073, 11.101)	5.949 (5.938, 5.961)
D_6	21.774 (21.755, 21.794)	11.094 (11.080, 11.107)	5.955 (5.943, 5.966)
D_7	21.795 (21.776, 21.814)	11.098 (11.084, 11.112)	5.959 (5.948, 5.971)
D_8	**21.813 (21.794, 21.832)**	11.101 (11.087, 11.115)	5.963 (5.952, 5.975)
D_9	21.729 (21.710, 21.749)	11.107 (11.093, 11.120)	5.969 (5.958, 5.981)
D_{10}	21.738 (21.719, 21.757)	11.110 (11.096, 11.124)	5.972 (5.960, 5.983)
D_{11}	21.752 (21.733, 21.772)	11.112 (11.098, 11.126)	5.974 (5.963, 5.985)
D_{12}	21.762 (21.742, 21.781)	11.113 (11.099, 11.127)	5.977 (5.965, 5.988)
NS	21.406 (21.386, 21.425)	**11.133 (11.120, 11.147)**	**6.031 (6.020, 6.043)**

AUA, American Urological Association; EAU, European Association of Urology; NS, no surveillance.

cystoscopies on average compared with the no-surveillance strategy. We also observed that (except for the NS strategy) the number of cystoscopies over a patient's lifetime ranged from 4.86 for strategy D_{12} to 14.86 for the AUA strategy, whereas the expected lifelong progression rate ranged from 6.14% for the AUA strategy to 7.12% for strategy D_9. We observed that the EAU policy resulted in nearly half the number of cystoscopies, with a relative risk increase of 6.5% and an absolute risk increase of 0.43% compared with the AUA strategy. The large variation in the number of cystoscopies with the different surveillance strategies, particularly in the context of the very low background rate of progression to invasive cancer in this population, underscores the importance of understanding the quality-of-life impact of this management practice on patients.

On the basis of the sensitivity analysis, we found that the disutility of cystoscopy affected the selection of the best strategy. Generally speaking, patients should undergo more intensive surveillance as the disutility of cystoscopy is reduced. All other-cause

mortality also affects the selection of the best strategy. Patients with higher all other-cause mortality should undergo less intensive surveillance. Factors that were not associated with significant differences included bladder cancer mortality, sensitivity of cystoscopy, and progression rate. On the basis of these results, we conclude that patient-specific factors such as the presence of comorbidity, or perception of utility loss from cystoscopy, should play an important role in determining the best surveillance strategy.

This article fills a gap in the literature about the degree to which sex, competing risks, and cystoscopy disutility are important for low-risk bladder cancer surveillance and stimulates future study to evaluate these questions in the cancer survivorship/surveillance realm more broadly. Given the fact that low-risk patients make up a large proportion of incident cases (approximately half) and, given the indolent natural history of disease, a presumably larger share of prevalent cases, we believe that the partially observable Markov model employed in this study affords a lens through which to evaluate the comparative effectiveness of the different approaches that raise important clinical and policy questions. We believe these results, particularly the association of the no-surveillance strategy with higher QALYs in the male base case, are hypothesis generating. Although the results do not suggest abandonment of surveillance among this population, these data do suggest that a less aggressive regimen may actually yield benefits from the patients' perspective, given the low risks of progression in this context. Additional work is needed to validate the published progression risk estimates for low-grade noninvasive disease, which has been understudied in the urologic oncology literature, relative to the higher risk phenotypes. In addition, to the extent QALYs are pursued as outcomes for future effectiveness studies in this setting, the disutilities associated with bladder cancer surveillance in general, and cystoscopy in particular, warrant future study.

Our study has some limitations. First, in the absence of estimates from the literature, we calculated the monthly stage progression rates in our natural history model by minimizing the absolute deviations of observed 5-year progression rates from the EORTC risk table with our simulation model. Second, we made several assumptions regarding the timing, adherence, and duration of treatment. We assumed that treatment is immediate and adherence to treatment is perfect; we did not actually include chemotherapy in the model and instead assumed that the default treatment for recurrent non-muscle-invasive bladder cancer is TURBT and BCG immunotherapy. Although chemotherapy is sometimes used as an alternative or adjunctive treatment to BCG, we chose to simplify this parameter to include only BCG, as this is the first-line adjunctive treatment used in the United States. Estimates for the disutility associated with this were drawn from the relevant literature.[28] Finally, the disutilities of cystoscopy and various treatments were drawn from the study by Kulkarni and others,[28] which were in turn drawn from studies of disutility of other invasive procedures, not specifically cystoscopy. Low-risk bladder cancer patients have a very low risk of disease progression and cancer-specific mortality. Finally, we did not include considerations of costs in this model. Given that bladder cancer has been characterized as having the highest cost per patient from diagnosis to death of all cancer sites,[34] future research could consider the economic and quality-of-life impacts of these common practices in a predominantly elderly population.[34]

APPENDIX

Table A1 One-Way Sensitivity Analysis with Respect to Bladder Cancer Mortality on Practical and Dynamic Policies for 73-Year-Old Low-Risk Male Patients

Strategies	Bladder Cancer Mortality Lower Bound (QALYs)	Bladder Cancer Mortality Upper Bound (QALYs)
EAU	11.110 (1.096, 11.124)	11.009 (10.995, 11.023)
AUA	10.956 (10.942, 10.970)	10.863 (10.850, 10.877)
D_1	11.063 (11.049, 11.077)	10.964 (10.950, 10.978)
D_2	11.109 (11.095, 11.123)	11.008 (10.994, 11.021)
D_3	11.132 (11.118, 11.146)	11.028 (11.014, 11.042)
D_4	11.137 (11.123, 11.151)	11.040 (11.026, 11.053)
D_5	11.156 (11.142, 11.170)	11.049 (11.035, 11.063)
D_6	11.160 (11.146, 11.174)	11.056 (11.042, 11.070)
D_7	11.163 (11.149, 11.177)	11.061 (11.047, 11.075)
D_8	11.166 (11.152, 11.180)	11.064 (11.051, 11.078)
D_9	11.180 (11.166, 11.194)	11.066 (11.052, 11.079)
D_{10}	11.183 (11.169, 11.197)	11.070 (11.056, 11.084)
D_{11}	11.184 (11.170, 11.198)	11.072 (11.058, 11.086)
D_{12}	11.186 (11.172, 11.200)	**11.072 (11.059, 11.086)**
NS	**11.250 (11.236, 11.264)**	11.067 (11.053, 11.081)

The boldfont value in each column indicates the best strategy in the corresponding scenario. AUA, American Urological Association; EAU, European Association of Urology; NS, no surveillance; QALY, quality-adjusted life year.

Table A2 One-Way Sensitivity Analysis with Respect to Progression and Recurrence Rates on Practical and Dynamic Policies for 73-Year-Old Low-Risk Male Patients

Strategies	Progression and Recurrence Rates Lower Bound (QALYs)	Progression and Recurrence Rates Upper Bound (QALYs)
EAU	11.289 (11.275, 11.304)	10.406 (10.393, 10.419)
AUA	11.132 (11.117, 11.146)	10.292 (10.280, 10.305)
D_1	11.242 (11.228, 11.257)	10.373 (10.360, 10.386)
D_2	11.289 (11.274, 11.303)	10.405 (10.393, 10.418)
D_3	11.312 (11.297, 11.326)	10.419 (10.406, 10.431)
D_4	11.317 (11.303, 11.332)	10.425 (10.412, 10.437)
D_5	11.336 (11.322, 11.351)	10.429 (10.416, 10.442)
D_6	11.340 (11.326, 11.355)	10.431 (10.419, 10.444)
D_7	11.342 (11.328, 11.357)	10.433 (10.420, 10.445)
D_8	11.346 (11.332, 11.361)	10.432 (10.419, 10.445)
D_9	11.360 (11.346, 11.375)	10.433 (10.421, 10.446)
D_{10}	11.363 (11.348, 11.377)	**10.434 (10.422, 10.447)**
D_{11}	11.364 (11.350, 11.378)	10.433 (10.420, 10.445)
D_{12}	11.365 (11.351, 11.380)	10.432 (10.419, 10.445)
NS	**11.433 (11.418, 11.447)**	10.415 (10.402, 10.427)

The boldfont value in each column indicates the best strategy in the corresponding scenario. AUA, American Urological Association; EAU, European Association of Urology; NS, no surveillance; QALY, quality-adjusted life year.

Table A3 One-Way Sensitivity Analysis with Respect to Sensitivity of Cystoscopy on Practical and Dynamic Policies for 73-Year-Old Low-Risk Male Patients

Strategies	Cystoscopy Sensitivity Lower Bound (QALYs)	Cystoscopy Sensitivity Upper Bound (QALYs)
EAU	11.041 (11.027, 11.055)	11.045 (11.031, 11.059)
AUA	10.891 (10.877, 10.905)	10.896 (10.883, 10.910)
D_1	10.995 (10.981, 11.009)	10.999 (10.986, 11.013)
D_2	11.039 (11.026, 11.053)	11.044 (11.031, 11.058)
D_3	11.061 (11.047, 11.075)	11.066 (11.052, 11.079)
D_4	11.069 (11.055, 11.083)	11.075 (11.061, 11.089)
D_5	11.082 (11.068, 11.095)	11.087 (11.073, 11.101)
D_6	11.089 (11.075, 11.102)	11.094 (11.080, 11.107)
D_7	11.092 (11.079, 11.106)	11.098 (11.084, 11.112)
D_8	11.095 (11.082, 11.109)	11.101 (11.087, 11.115)
D_9	11.101 (11.088, 11.115)	11.120 (11.107, 11.914)
D_{10}	11.105 (11.091, 11.119)	11.110 (11.097, 11.124)
D_{11}	11.107 (11.093, 11.121)	11.112 (11.098, 11.126)
D_{12}	11.108 (11.094, 11.122)	11.113 (11.099, 11.127)
NS	**11.133 (11.120, 11.147)**	**11.133 (11.120, 11.147)**

The boldfont value in each column indicates the best strategy in the corresponding scenario. AUA, American Urological Association; EAU, European Association of Urology; NS, no surveillance; QALY, quality-adjusted life year.

Table A4 One-Way Sensitivity Analysis with Respect to Disutility of Cystoscopy on Practical and Dynamic Policies for 73-Year-Old Low-Risk Female Patients

Strategies	Disutility of Cystoscopy Lower Bound (QALYs)	Disutility of Cystoscopy Upper Bound (QALYs)
EAU	13.102 (13.087, 13.117)	12.666 (12.651, 12.680)
AUA	**13.114 (13.099, 13.129)**	12.350 (12.335, 12.365)
D_1	13.103 (13.088, 13.118)	12.570 (12.555, 12.585)
D_2	13.101 (13.086, 13.116)	12.664 (12.649, 12.679)
D_3	13.097 (13.082, 13.112)	12.710 (12.695, 12.725)
D_4	13.110 (13.095, 13.125)	12.724 (12.709, 12.738)
D_5	13.090 (13.075, 13.105)	12.760 (12.745, 12.775)
D_6	13.099 (13.084, 13.114)	12.770 (12.755, 12.784)
D_7	13.101 (13.086, 13.116)	12.776 (12.761, 12.791)
D_8	13.104 (13.089, 13.119)	12.784 (12.769, 12.799)
D_9	13.078 (13.063, 13.093)	12.810 (12.795, 12.825)
D_{10}	13.079 (13.064,13.094)	12.815 (12.800, 12.83)
D_{11}	13.080 (13.065, 13.095)	12.818 (12.804, 12.833)
D_{12}	13.080 (13.065, 13.095)	12.821 (12.807, 12.836)
NS	12.937 (12.922, 12.952)	**12.937 (12.922, 12.952)**

The boldfont value in each column indicates the best strategy in the corresponding scenario. AUA, American Urological Association; EAU, European Association of Urology; NS, no surveillance; QALY, quality-adjusted life year.

Table A5 One-Way Sensitivity Analysis with Respect to Other-Cause Mortality on Practical and Dynamic Policies for 73-Year-Old Low-Risk Female Patients

Strategies	Other-Cause Mortality Lower Bound (QALYs)	Other-Cause Mortality Upper Bound (QALYs)
EAU	18.885 (18.862, 18.908)	10.310 (10.298, 10.321)
AUA	18.758 (18.735, 18.782)	10.156 (10.145, 10.168)
D_1	18.840 918.816, 18.863)	10.264 (10.252, 10.275)
D_2	18.879 (18.856, 18.902)	10.309 (10.297, 10.320)
D_3	18.900 (18.877, 18.923)	10.330 (10.318, 10.342)
D_4	18.943 (18.920, 18.966)	10.336 (10.324, 10.348)
D_5	18.913 (18.889, 18.936)	10.353 (10.341, 10.365)
D_6	18.945 (18.922, 18.969)	10.358 (10.346, 10.370)
D_7	18.962 (18.938, 18.985)	10.361 (10.349, 10.372)
D_8	**18.982 (18.958, 19.005)**	10.363 (10.351, 10.375)
D_9	18.917 (18.894, 18.940)	10.375 (10.363, 10.387)
D_{10}	18.928 (18.905, 18.951)	10.378 (10.366, 10.390)
D_{11}	18.937 (18.913, 18.960)	10.380 (10.368, 10.392)
D_{12}	18.946 (18.923, 18.969)	10.380 (10.368, 10.392)
NS	18.703 (18.680, 18.726)	**10.431 (10.419, 10.443)**

The boldfont value in each column indicates the best strategy in the corresponding scenario. AUA, American Urological Association; EAU, European Association of Urology; NS, no surveillance; QALY, quality-adjusted life year.

Table A6 Comparison of Strategies with Respect to Changes in Starting Age of Surveillance for Female Patients

Strategies	55	73	85
EAU	24.353 (24.333, 24.373)	12.888 (12.873, 12.903)	6.661 (6.648, 6.673)
AUA	24.251 (24.231, 24.270)	12.740 (12.725, 12.755)	6.536 (6.523, 6.549)
D_1	24.309 (24.290, 24.329)	12.842 (12.827, 12.857)	6.621 (6.608, 6.633)
D_2	24.346 (24.326, 24.366)	12.887 (12.872, 12.902)	6.658 (6.645, 6.671)
D_3	24.361 (24.341, 24.381)	12.907 (12.892, 12.922)	6.677 (6.664, 6.690)
D_4	24.440 (24.421, 24.460)	12.921 (12.906, 12.936)	6.687 (6.674, 6.700)
D_5	24.369 (24.349, 24.389)	12.929 (12.914, 12.944)	6.698 (6.685, 6.711)
D_6	24.421 (24.401, 24.441)	12.938 (12.923, 12.953)	6.704 (6.691, 6.717)
D_7	24.453 (24.434, 24.473)	12.942 (12.927, 12.957)	6.709 (6.696, 6.722)
D_8	**24.478 (24.459, 24.498)**	12.947 (12.932, 12.962)	6.713 (6.700, 6.726)
D_9	24.360 (24.340, 24.380)	12.947 (12.932, 12.962)	6.717 (6.705, 6.730)
D_{10}	24.378 (24.358, 24.398)	12.950 (12.935, 12.965)	6.720 (6.707, 6.733)
D_{11}	24.395 (24.375, 24.415)	12.952 (12.937, 12.967)	6.723 (6.710, 6.736)
D_{12}	24.408 (24.388, 24.428)	**12.954 (12.939, 12.969)**	6.725 (6.713, 6.738)
NS	23.940 (23.920, 23.960)	12.937 (12.922, 12.952)	**6.773 (6.760, 6.786)**

The boldfont value in each column indicates the best strategy in the corresponding scenario. AUA, American Urological Association; EAU, European Association of Urology; NS, no surveillance.

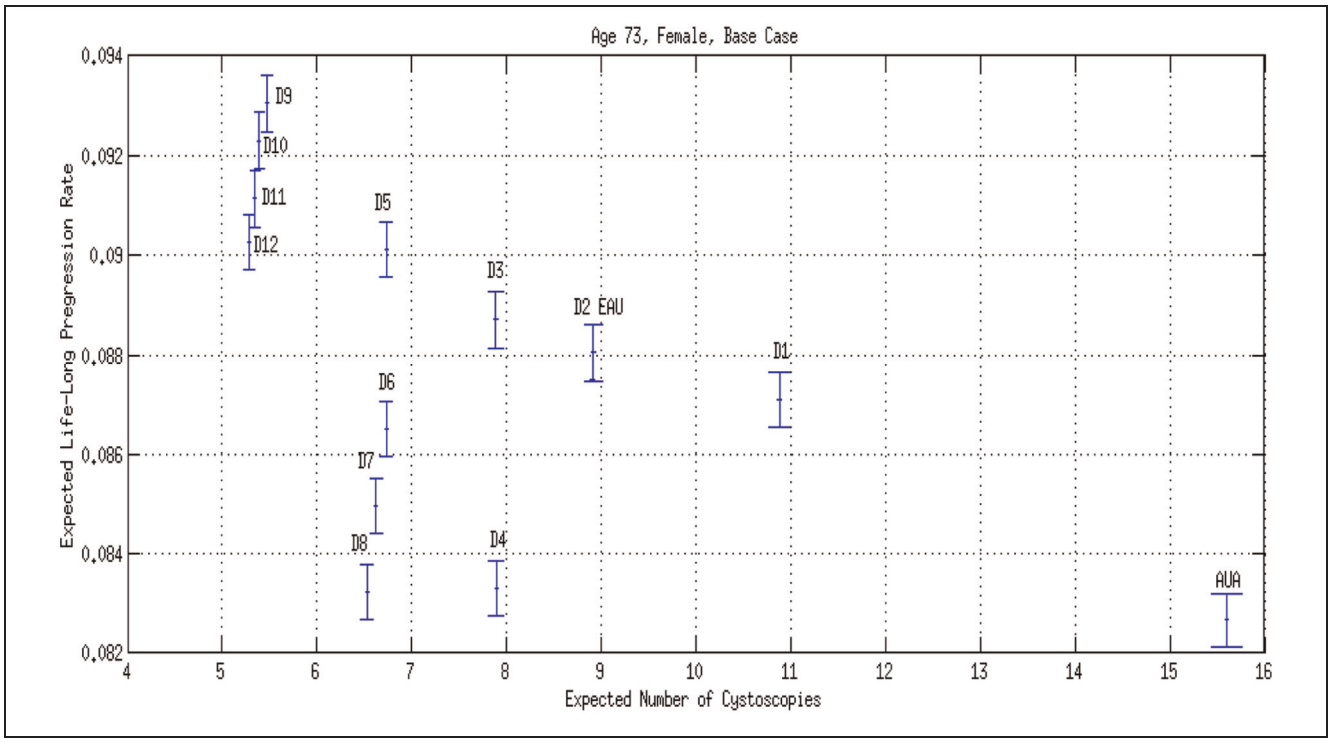

Figure 5 The expected lifelong progression rate to muscle-invasive disease v. number of cystoscopies over a patient's lifetime for a female patient aged 73 years under the base case scenario. The no-surveillance (NS) strategy resulted in an expected lifelong progression rate of 0.1306 (95% confidence interval, 0.1299–0.1313).

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