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TOPIC PAPER

Evaluating the cost of surveillance for non-muscle-invasive bladder cancer: an analysis based on risk categories

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Abstract

Introduction Non-muscle-invasive bladder cancer (NMIBC) is a biologically heterogeneous disease and is one of the most expensive malignancies to treat on a per patient basis. In part, this high cost is attributed to the need for long-term surveillance. We sought to perform an economic analysis of surveillance strategies to elucidate cumulative costs for the management of NMIBC.

Methods A Markov model was constructed to determine the average 5-year costs for the surveillance of patients with NMIBC. Patients were stratified into low, intermediate, and high-risk groups based on the EORTC risk calculator to determine recurrence and progression rates according to each category. The index patient was a compliant 65-year-old male. A total of four health states were utilized in the Markov model: no evidence of disease, recurrence, progression and cystectomy, and death.

Results Cumulative costs of care over a 5-year period were $52,125 for low-risk, $146,250 for intermediate-risk, and $366,143 for high-risk NMIBC. The primary driver of cost was progression to muscle-invasive disease requiring definitive therapy, contributing to 81% and 92% of overall cost for intermediate- and high-risk disease. Although low-risk tumors have a high likelihood of 5-year recurrence, the overall cost contribution of recurrence was 8%, whereas disease progression accounted for 71%.

Conclusion Although protracted surveillance cystoscopy contributes to the expenditures associated with NMIBC, progression increases the overall cost of care across all three patient risk groups and most notably for intermediate- and high-risk disease patients.

Keywords Bladder cancer · Non-muscle invasive · Costs · Markov model · Surveillance

Introduction

Non-muscle-invasive bladder cancer (NMIBC) is a complex disease. The high propensity for recurrent and progressive disease compels a rigorous surveillance protocol which is associated with a significant healthcare cost. In fact, the costly nature of surveillance accounts for the reason behind bladder cancer being described as one the most expensive cancers to manage on a per patient basis [1, 2]. Beyond straining an already overwhelmed healthcare system, rising healthcare costs may impact patients with bladder cancer via financial toxicity [3] which is linked to poorer patient well-being and outcomes [4]. Moreover, bladder cancer care also entails a significant indirect burden attributable to factors beyond the quantifiable financial toll through detriments in psychological health, societal productivity, or quality of life [5]. Balancing between clinical consequences and healthcare costs of bladder cancer presents a financial challenge for providers as they manage these patients.

An economic analysis of surveillance strategy and its respective costs may be a valuable method to elucidate

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trends and sources of cost. Data from iterative modeling can inform strategies to improve quality of bladder cancer care and reduce costs by reducing superfluous elements. Examining the contributing medical expenditures over a given time period and accounting for a multitude of clinical scenarios can be accomplished using Markov modeling [6]. Previous studies have used modeling in the bladder cancer space to compare surveillance strategies for low-risk disease [7], examine the optimal management of high-risk disease [8], or determine lifetime costs [9]. In this study, we utilized mathematical modeling to specifically compare costs across risk categories for NMIBC. Here, we perform an evaluation of the financial burden due to the management of low-, intermediate-, and high-risk NMIBC. We hypothesized that costs would vary across risk levels and medical expenditure would be driven primarily by the need for frequent and costly cystoscopic surveillance.

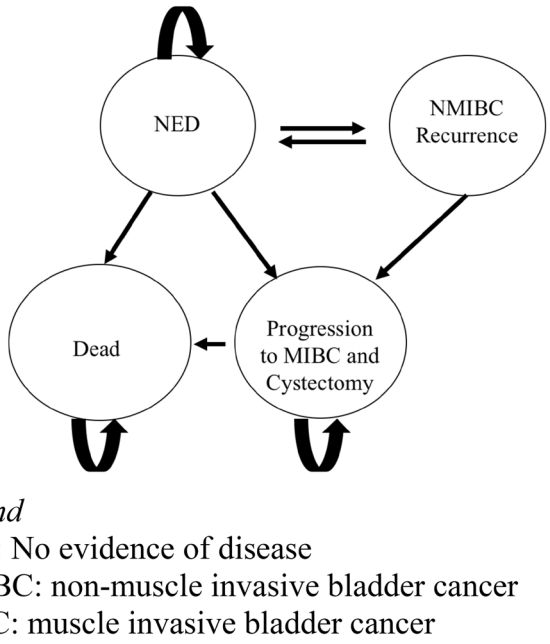

Fig. 1 Markov model of health states during surveillance for NMIBC. *NED* no evidence of disease, *NMIBC* non-muscle-invasive bladder cancer, *MIBC* muscle-invasive bladder cancer

Methods

Model design

We constructed a Markov model with a 3-month cycle length to perform an economic evaluation of the surveillance of NMIBC. To provide better estimates of disease progression and recurrence, risk stratification into low-, intermediate-, and high-risk categories may be used to predict clinical outcomes, counsel patients, and guide management [10]. The biological heterogeneity of NMIBC is supported by the fact that low-grade tumors have a significant likelihood of recurrence that varies, but can be as high as 40–80%, whereas high-risk tumors have a significant concern for progression (as high as 45%) [10, 11]. TreeAge Pro (TreeAge Software, Inc., Williamstown, Massachusetts, 2017) was used for model construction. Patients were stratified into (1) low-, (2) intermediate-, or (3) high-risk categories according to previously established data from the European Organization for Research and Treatment Center (EORTC) risk tables which is based on 2596 patients from seven randomized trials [10].

A total of four disease states were utilized including no evidence of disease, recurrence, progression and cystectomy, and death. Recurrence was defined as evidence of disease that is the same or lower stage of disease. Progression was defined as increase in stage to muscle-invasive disease (Stage II). A patient with NED could stay in that health state or move from NMIBC back to NED. Any patient that entered the health state of MIBC or death would remain in that state. The primary outcome evaluated was cost of care which was determined by calculating the cumulative 5-year costs for each health state.

Base case

The base case was a 65-year-old male compliant patient with NMIBC. In this scenario, the base case had an overall functional and renal status that made them capable of receiving all available management options.

Model assumptions

We used the EORTC risk calculator to determine recurrence and progression rates according to each category [10]. Available professional organization guidelines from the American Urological Association, European Association of Urology, and National Comprehensive Cancer Network, National Institute for Health and Care Excellence were reviewed and a composition was used that encompassed the core aspects of these strategies [12]. Surveillance regimens were as follows, low-risk: 3 months after TURBT, then at 9 months, then annually until 5 years with imaging biennially; and for intermediate/high: 3 months after TURBT, then every 3 months for 2 years, then every 6 months until 5 years with imaging annually. If a patient with intermediate- or high-risk NMIBC had three recurrences the model, then sent that patient to the progression pathway which proceeded to cystectomy.

Table 1 Estimated cumulative probabilities for recurrence, progression, and death for NMIBC stratified by risk categories

	Probability of NED		Probability of recurrence		Probability of progression		Probability of death due to bladder cancer	
Risk category	1 year	5 years	1 year	5 years	1 year	5 years	1 year	5 years
Low	0.918	0.853	0.244	0.460	0.010	0.061	0.013	0.070
Intermediate	0.845	0.733	0.380	0.618	0.050	0.172	0.015	0.074
High	0.661	0.392	0.613	0.782	0.169	0.454	0.04	0.139

Recurrence signifies development of the same or lower stage of disease. Progression signifies development of muscle-invasive bladder cancer. Estimated values for probability of disease recurrence and progression based on EORTC risk tables [10]

NMIBC non-muscle-invasive bladder cancer, *NED* no evidence of disease

Model inputs

To model the natural history of this disease, we established nonlinear rates for recurrence and progression based on 1- and 5-year probabilities for these events among patients with NMIBC calibrated based on values provided by the EORTC risk calculator [10] (Table 1). The probability of cancer-specific mortality for NMIBC was obtained from previously established literature with morality estimates for superficial bladder cancer [13]. Probability of non-event deaths was obtained from the United States Life Table in 2014 [14].

The model was constructed using direct medical costs derived from the literature (Table 2). The annual cost of surveillance for non-invasive disease was $3297 and $1649 for the first and subsequent years of low-risk disease. The annual cost of surveillance was $6594 for the first 2 years and $3297 for subsequent years for intermediate- and high-risk disease. The costs of treatment for recurrence and progression were $9328 and $61,257, respectively [9]. The last year of life cost was $20,116, and this was derived from Medicare spending data involving the delivery of medical care in last year of life [15, 16] (Table 3). Costs were discounted by 3% and inflated to 2017 US dollars using the Consumer Price Index for medical care [17].

Results

Base case

The cumulative 1- and 5-year costs for low, intermediate, and high-risk NMIBC were $6003 and $52,125, $16,892 and $146,250, and $37,427 and $366,143, respectively (Fig. 1). Across each risk category, the sources of costs were examined over a 5-year time frame (Fig. 2). For each category progression to MIBC represented the largest source of expenditures. In low, intermediate, and high-risk diseases, this cost was approximately 71%, 81%, and 92% of the total expenditures.

Discussion

In this study, we demonstrate that NMIBC is a complex and costly disease. We examined the economic burden of surveillance for differing risk categories. Our economic analysis supported the hypothesis that there is a differential financial toll according to the risk level of NMIBC being managed. During a 5-year period following diagnosis, the cumulative costs of care were approximately $52,000 for low risk, $146,000 for intermediate risk, and $366,000 for high-risk NMIBC. However, interestingly, at the patient level, the primary driver of this cost was not the frequent cystoscopic surveillance, but the disease progression to muscle-invasive disease leading to definitive therapy. NMIBC disease progression entailed a substantial proportion of the overall cost associated with surveillance contributing to over 80% and 90% for intermediate- and high-risk disease, respectively. These results underscore the importance of continuing to examine NMIBC care to optimize both quality of care and healthcare costs during surveillance.

Bladder cancer has been well-recognized as one of the most expensive malignancies to treat on a per patient basis [18], and the financial burden has been attributed to the need for long-term surveillance. Our analysis modifies this traditional viewpoint. Although protracted cystoscopy certainly contributes to substantial costs, we found that disease progression to MIBC disproportionately increased the overall cost of care. In comparison with surveillance cystoscopy, a cystectomy—the standard of care for MIBC—is a costly procedure at baseline and is associated with complications and readmissions which further aggravate the financial toll imposed by the disease. After cystectomy, a complication during the index hospitalization may extend length of stay by 4 days and increase hospital costs by $9000, while a readmission complication may increase costs by over $20,000 [19]. Furthermore, bladder cancer treatment also entails an indirect burden on society resulting from declines in sexual function, detriments to quality of life, and decreases in societal productivity.

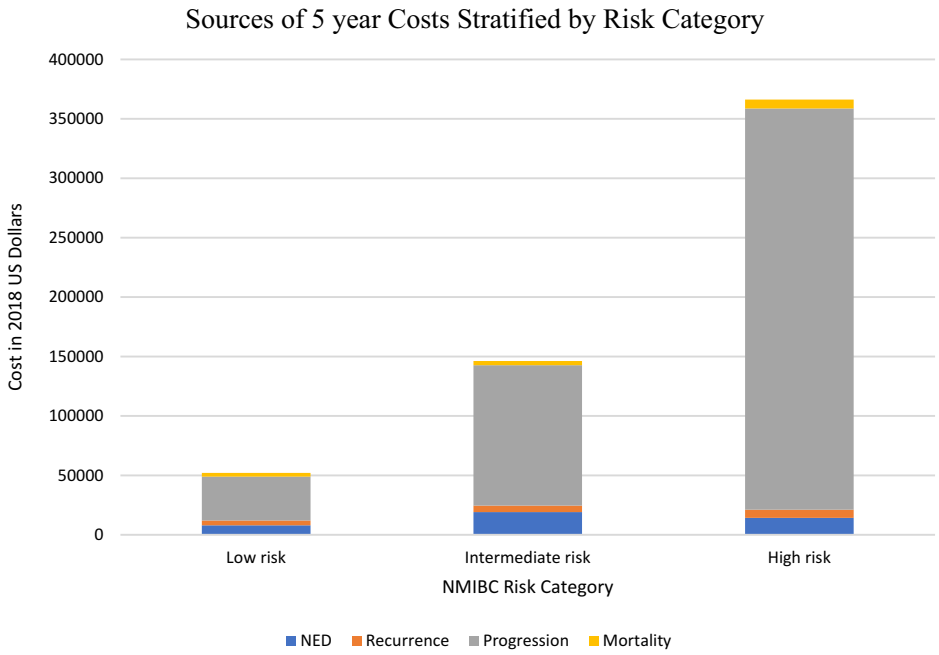

Fig. 2 Sources of 5-year total costs during NMIBC surveillance stratified by risk category

Risk Category	Low		Intermediate		High	
NED	7969	15%	19141	13%	14266	4%
Recurrence	4042	8%	5417	4%	6881	2%
Progression	36902	71%	118185	81%	337529	92%
Mortality	3213	6%	3507	2%	7467	2%
Total Cost	52125		146250		366143	

Table 2 Projected cumulative costs for NMIBC at 1- and 5-year stratified by risk category

	Cost for NED		Cost of recurrence		Cost of progression		Cost of mortality		Total cost	
Risk	1 year	5 years	1 year	5 years	1 year	5 years	1 year	5 years	1 year	5 years
Low	2094	7969	2234	4042	1520	36 902	155	3213	6003	52 125
Int.	5595	19 141	3474	5417	7642	118 185	180	3507	16 892	146 250
High	4615	14 266	5556	6881	26 779	337 529	476	7467	37 427	366 143

Values are in 2017 United States Dollars. Recurrence signifies development of the same or lower stage of disease. Progression signifies development of muscle-invasive bladder cancer. Estimated values for probability of disease recurrence and progression based on EORTC risk tables [10]

Int. intermediate, *NMIBC* non-muscle-invasive bladder cancer, *NED* no evidence of disease

One unique challenge of examining NMIBC is the heterogeneous nature of the disease. Within this disease, the 5-year probabilities of recurrence (31–78%) and progression (1–45%) vary widely, and therefore, the accumulation of costs over time is quite heterogeneous among patients with NMIBC [10, 11]. The strength of the current study is that we capitalized on the flexibility of Markov modeling to stratify the analysis into low-, intermediate-, and high-risk patients to compare and contrast the differing biological nature and natural history of these disease states rather than study only one in isolation. In addition, we utilized contemporary guideline recommendations making the analysis more relevant to current healthcare practice. Finally, we used modern cost estimates to elucidate the economic impact surveillance entails in each category and placed this cost in the context of the overall cost of care for a patient with bladder cancer (Fig. 3).

Our analysis demonstrates that low-risk NMIBC has a high recurrence rate and is relatively unlikely to progress to MIBC [11]. Consequently, among these patients,

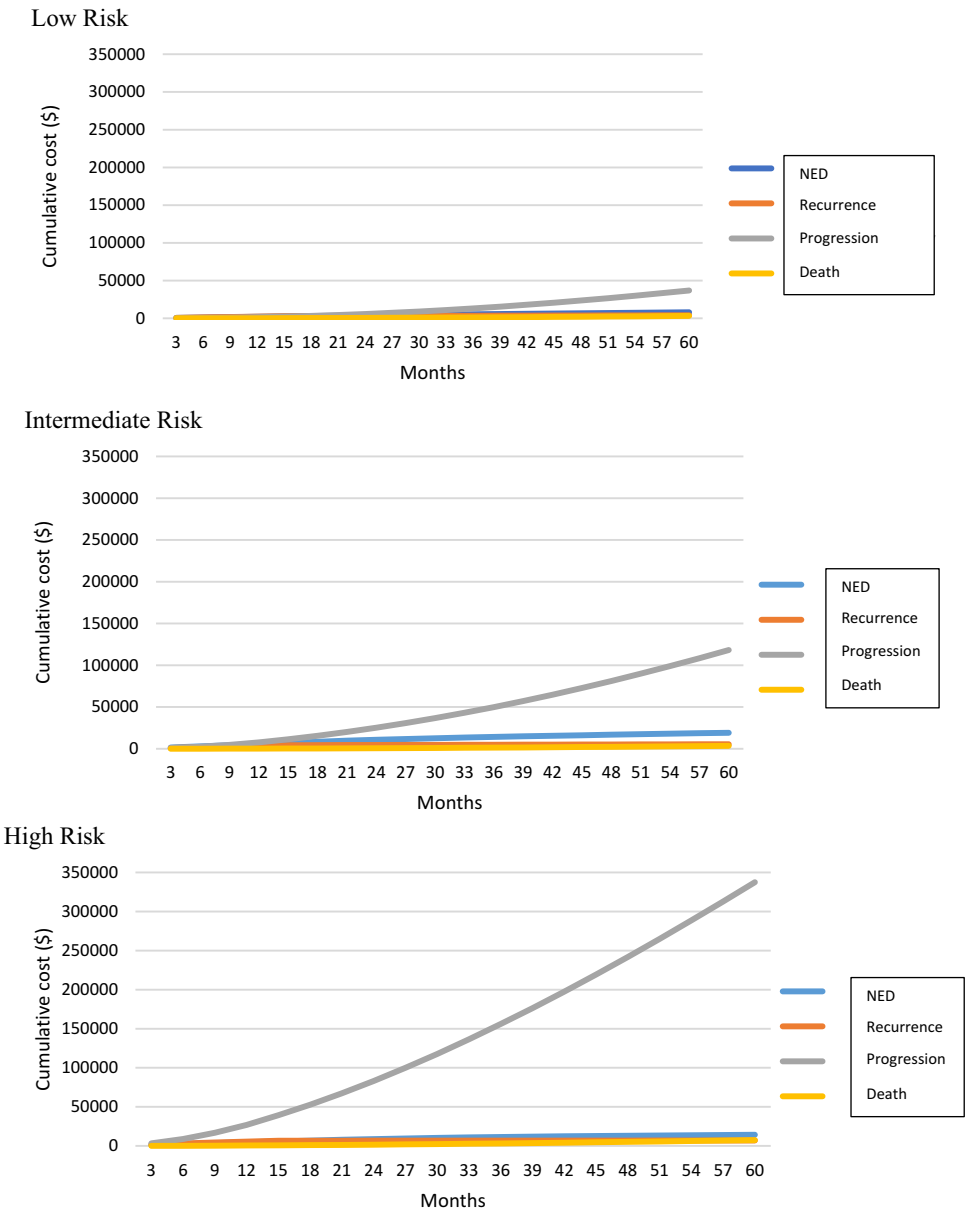

Fig. 3 Trends in 5-year total costs of surveillance for low, intermediate and high-risk disease

non-oncologic mortality is higher than the risk of bladder cancer-specific mortality. Emphasis on overall patient well-being is essential when managing bladder cancer patients [20]. Nearly, 20% of patients are active smokers at the time of bladder cancer diagnosis [21] and smoking accounts for over 50% of all new bladder cancer cases [22]. Urologists that manage patients with NMIBC have the unique opportunity to recommend lifestyle interventions during each visit which can improve overall and urologic health. Interestingly, smokers with a new diagnosis of bladder cancer are much more likely to quit than the general population (10% vs. 48%, $p < 0.001$), and in fact, the diagnosis and urologist's advice are the most common reported reasons behind cessation [23]. Over 10 studies indicate active smoking and high lifetime exposure significantly increases the risk of recurrence in NMIBC [24]. While retrospective and subject to confounders, such data only support the idea that smoking cessation can be an effective way to impact patient health. Promotion of smoking cessation may be one component of a holistic approach to improve patient health. Improved nutrition, fitness, and education may work synergistically to help make patients more resilient through efforts known as prehabilitation that can be done at the time of diagnosis or prior to surgery [25].

In contrast, among patients with intermediate- and high-risk NMIBC, there is a considerable risk of progression of approximately 45% [11], which represents the major driver of the financial burden of disease. Innovations in evaluation and management may help detect patients earlier on their course or even reduce the chance

Table 3 Sources of cost for Markov model inputs

Cost		References
NED (per cycle)		[9]
Low risk		
1–3 months	$1648	
4–12 months	$549	
After 12 months	$412	
Intermediate/high risk		
1–24 months	$1648	
After 24 months	$824	
Recurrence (one time)	$9328	[9]
MIBC (one time)	$61257	[9]
Last-year cost (per cycle)	$5029	[15, 16]

of disease progression. Urinary biomarkers, cytology and immunostaining, urine protein markers, and especially genomic profiles [26] may change approaches to diagnosis, management, and surveillance [27]. In addition, as new intravesical or immunotherapy protocols emerge in the NMIBC space, paradigms will evolve. Leveraging innovations in technology should be done with attention to price to ensure future scalability and investigating the cost of those changes.

This work has several limitations. First, models can only be as robust as the data used. Therefore, part of this data is based on retrospective data and expert opinion thus introducing the potential for confounding and bias. However, the data utilized in this model are derived from the EORTC trials which is a series of seven randomized trials, thereby strengthening the quality of the data, and thus, the constructed model. In addition, these data on which the model is based on clinical that may not have included routine use of repeat TURBT with BCG therapy. Second, the rates of recurrence and progression can vary more widely than what we included in our model, which may cause inaccuracies in our estimations. However, the assumptions are used as a tool to help illustrate overarching themes in bladder cancer care. Third, healthcare costs vary across healthcare contexts and over time which may limit the generalizability of the findings. Fourth, the model does not capture the impact of quality of life which is an important element of patient centered cancer care. Fifth, this model does not include detailed analysis of intravesical therapy, or blue light cystoscopy. There is a large body of emerging evidence on the utility of intravesical therapy for patients with NMIBC and future models should examine the value of such therapies. Future model constructions can incorporate new data and update the cost of care for NMIBC as it continues to advance.

Conclusion

We demonstrate a differential financial cost of surveillance stratified by risk disease state for patients with NMIBC. The primary driver of costs is the progression to MIBC rather than frequent surveillance cystoscopy. As healthcare costs continue to risk, considering cost and consequences are important determinants of overall sustainability. These results emphasize the importance of future work to detect intermediate or high-risk disease before it progresses may improve clinical and economic outcomes. Multidisciplinary approaches and analyses that account for economic dimensions of care will be vital. Future work should focus on optimizing clinical outcomes while limiting healthcare costs to improve quality of care for patients with bladder cancer.

Author contribution MM: project development, data analysis, and manuscript writing and editing. YW: data analysis, data management, and manuscript writing and editing. JS: data analysis and manuscript writing and editing. WST: data analysis and manuscript writing and editing. MJH: manuscript review and editing. MAP: manuscript review and editing. Q-DT: manuscript review and editing. GS: manuscript review and editing. ASK: manuscript review and editing. SLC: project development, data analysis, and manuscript writing and editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement Dr. Sonpavde has the following disclosures: Consultant for Bayer, Sanofi, Pfizer, Novartis, Eisai, Janssen, Amgen, Astrazeneca, Merck, Genentech, EMD Serono, Agensys/Astellas; Research support to institution from Bayer, Celgene, Boehringer-Ingelheim, Merck, Pfizer, Sanofi, Janssen; Author for Uptodate; Speaker fees from Clinical Care Options, Physicians Education Resource (PER), Research to Practice (RTP), Onclive. This research did not involve human participants or animals.

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