Supplementary Appendix for Non-Muscle Invasive Bladder Cancer (NMIBC) Model

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1. Model introduction and overview

1.1 Scope of the model

Bladder cancer is the fifth most common cancer in the United States with an estimated ~65,000 newly diagnosed cases and ~14,000 deaths in the United States annually (ACS 2010). The current bladder cancer model focuses on treatment of non-muscle invasive bladder cancer (NMIBC), which accounts for 70% of all bladder cancer cases. The model tracks recurrence, progression, and survival of NMIBC patients and the interactions between bladder cancer patients and the health care system through medical interventions such as treatment (e.g., intravesical therapies, cystectomy), surveillance (e.g., cytology, cystoscopy), and their complications. The processes underlying the health care system in the model is designed to facilitate implementation of different treatment and surveillance guidelines for NMIBC.

1.2 Motivation

Construction of the Archimedes Bladder Cancer Model was motivated by questions surrounding the clinical and economic outcomes of treating NMIBC patients. The goal of the model-building effort has evolved to the construction of a general non-muscle invasive bladder cancer model that can be used to answer clinical and economic questions around the use of therapeutics and diagnostics, variations in practice guidelines, and differing patient populations.

1.3 Sources of data

The NMIBC model is built from the following major sources of data:

- Surveillance, Epidemiology and End Results Registry (SEER)
- Individual patient data from Urocidin 201 trial
- Published predictive models (e.g., clinical nomograms, risk look-up tables)
- Meta-analyses of clinical trial data

1.4 Model terminology

The terminology used in this model is defined below. There are two categories of terms, those pertaining to patient-level events and those pertaining to specific tumor-level events.

Patient-Level Terminology

- **Disease-free period** refers to the period of time following initial diagnosis and treatment of NMIBC when no additional tumors have yet appeared.
- **Recurrence** refers to the diagnosis of at least one bladder tumor of the same or lower histological grade and T-stage as the primary (initial) tumor after a disease-free period.
- **Progression** refers to the diagnosis of a new tumor within the bladder that is of higher histological grade or T-stage than the primary tumor.
- **Metastatic disease** refers to the diagnosis of metastases in other organs
- **Death** refers to the death of the patient, from either bladder cancer or other causes.

Tumor-Level Terminology

- **Tumor occurrence** refers to the appearance of a new non-muscle invasive tumor (either CIS or papillary) in the bladder.

- **Tumor worsening** refers to changes in stage and/or grade of a specific tumor.
- **Muscle invasive tumor** refers to a local tumor that has evolved to invade bladder muscle tissue.

A patient may have multiple tumors, each with a specific time of occurrence and a specific timeline for tumor worsening. Each new tumor has a different propensity to become muscle invasive.

1.5 Model features

1.5.1 Risk factors

- Gender
- Age at diagnosis
- Tumor stage
- Tumor size
- Tumor grade
- Lymphovascular invasion

1.5.2 Primary health outcomes

- Recurrence-free survival
- Number of recurrences
- Progression-free survival
- Disease-specific survival
- Overall survival

1.5.3 Secondary health outcomes

- Time to cystectomy
- Treatment complications

1.5.4 Treatments

- Transurethral resection of bladder tumor (TURBT)
- Intravesical immunotherapy (Bacillus Calmette-Guérin (BCG))
- Intravesical chemotherapy (mitomycin C (MMC))
- Radical cystectomy (RC)

1.5.5 Testing, screening, and surveillance

- Cystoscopy
- Urinary cytology

1.5.6 Cost and utility outcomes

- Cost of surgery
- Cost of intravesical therapies
- Cost of surveillance

- Total cost of bladder cancer treatment
- Life years
- Quality-adjusted life years (QALYs)
- Cost per QALY saved

1.6 Model structure

The model consists of 4 major components:

- **A patient generation module** which selects individuals with non-muscle invasive bladder cancer from individual case listings in the Surveillance, Epidemiology and End Results (SEER) registry.
- **A natural history component** that models the underlying disease and tracks recurrence, progression, and survival of bladder cancer patients.
- **An intervention component** that describes the effects of bladder cancer treatment and surveillance interventions on risk of recurrence and risk of dying from bladder cancer, as well as complications associated each intervention.
- **A cost component** that tracks the costs of procedures, tests, and medications related to bladder cancer.

Figure 1 a schematic representation of the bladder cancer model.

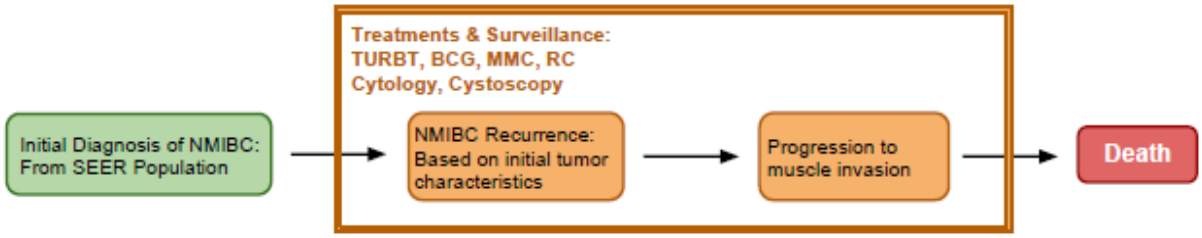


Figure 1. Bladder cancer model schematic.

1.7 Brief description of the natural history model

1. Incidence of new tumor occurrence: A patient diagnosed with non-muscle invasive bladder cancer can develop multiple new tumors in the future. The time to next tumor occurrence is modeled using a survival function derived from a meta-analysis of the published literature and depends upon tumor characteristics (including initial tumor stage, grade, size, and presence of carcinoma in situ (CIS), and number of initial tumors).
2. Tumor worsening: Initially, a tumor can start out as low-grade Ta (TaLG) or as CIS. As time moves forward, the tumor grows in size, becomes more invasive (worsens in T-stage), and acquires more molecular alterations (worsens in grade).
3. Concomitant carcinoma *in situ* (CIS): New tumors may present as concomitant carcinoma in situ tumors. Patients with concomitant CIS are more likely to develop muscle invasive bladder cancer (MIBC).
4. Progression pathways: There are three progression pathways:
    - TaLG → TaHG
    - TaHG → T1→ muscle invasion or spread to regional lymph nodes

- CIS → T1 → muscle invasion or spread to regional lymph nodes

5. Characteristics of muscle invasive tumors: The overall stage of a muscle invasive tumor that progressed from a non-muscle invasive tumor is determined from a distribution based on SEER.
6. Survival following radical cystectomy: Patients with muscle invasive tumors are assumed to undergo cystectomy. Patient survival following radical cystectomy is based on the literature, supplemented with information from SEER.

1.8 Brief description of medical interventions

1. Cystectomy: Cystectomy will eliminate the possibility of local recurrence but not metastatic disease. Survival following cystectomy is derived from SEER and the literature.
2. TURBT: Tumors localized in the bladder can be removed using transurethral resection of bladder tumor (TURBT) and will be restaged at that time. The accuracy of TURBT staging is a function of tumor grade and T-stage.
3. Cystoscopy: New tumor occurrences can be detected using white light cystoscopy. Test specificity and sensitivity are derived from the literature.
4. Cytology: Urinary cytology returns a positive result if tumors are present in the bladder. Specificity and sensitivity of cytology is derived from the literature.
5. Intravesical therapy: We consider only BCG and mitomycin C (MMC) as intravesical agents. Effects of intravesical therapy are represented by hazard ratios, which reduce the rates of tumor occurrence. We model the following intravesical therapy management strategies for bladder cancer: (i) single-instillation chemotherapy; (ii) induction therapy; (iii) maintenance therapy using BCG or MMC; and (iv) salvage therapy for refractory patients.
6. Treatment protocol and surveillance guidelines: Treatment and surveillance protocols are modeled after the National Comprehensive Cancer Network (NCCN) guidelines. Alternative treatment and surveillance regimens may also be used.

2. Natural history of non-muscle invasive bladder cancer

2.1 Overview

2.1.1 Evidence review

Epidemiology of NMIBC

- Bladder cancer is a disease in which the cells lining the urinary bladder lose the ability to regulate their growth, start dividing uncontrollably, and form a tumor.
- Bladder cancers are categorized into two main groups: non-muscle invasive (NMIBC) and muscle invasive (MIBC).
- The most common type of bladder cancer is transitional cell carcinoma (TCC), which accounts for more than 90% of bladder cancers. Other forms of bladder cancer include squamous carcinoma, adenocarcinoma (urachal and non-urachal), small cell carcinoma, sarcoma, and lymphoma.
- NMIBC accounts for 75% of all bladder cancers (Sexton, Wiegand et al. 2010).
- NMIBC is a group of heterogeneous cancers of T-stage Ta, T1, and Tis. Approximately 70% of patients present with Ta, 25% with T1, and 5% with Tis lesions.
- Patients are most likely to experience bladder cancer recurrence within 3-5 years after TURBT. 30-80% of cases will recur and 1-45% of cases will progress to muscle invasion within 5 years.
- Patients with an initial NMIBC diagnosis of Ta will have a high rate of recurrence following TURBT. But the risk of disease progression, particularly for patients having low-grade papillary Ta tumors, remains low at less than 5%.
- Carcinoma *in situ* (CIS) represents a distinct entity defined by flat, high-grade, superficial transitional cell carcinomas. The presence of concomitant CIS with Ta or T1 tumors results in very high rates of disease recurrence and progression. IsolatedCIS tumors are referred to as Tis.

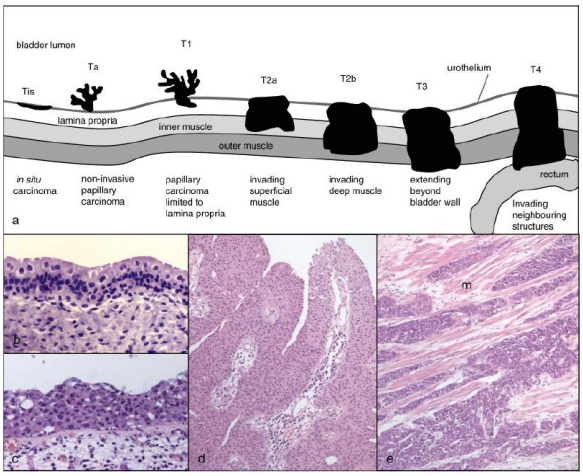


Fig. 1. (a) Staging of UCC. (b–e) Haematoxylin and eosin stained sections. (b) Normal urothelium. Note the large differentiated superficial cells. (c) CIS. Cells are disorganized and show marked nuclear atypia (high-grade). (d) Low-grade superficial papillary tumour. (e) High-grade tumour invading muscle (m).

Figure 2. Staging of bladder cancer (Knowles 2006).

Possible outcomes of NMIBC

There are three possible outcomes associated with NMIBC following initial treatment.

At the patient level, the outcomes are

- Complete response (disease-free) for the remainder of the patient's life.
- Recurrence: Patient is found to have new tumors of the same (or lesser) grade and T-stage as the initial NMIBC diagnosis.
- Progression: Patient is found to have new tumors of increased stage and/or grade compared to the initial diagnosis.
- Progression to MIBC: Patients are diagnosed with MIBC and may die of bladder cancer.

At the tumor level, the outcomes are

- No new tumor occurrences in the bladder.
- A new tumor occurrs, and the tumor worsens in T-stage and grade. The speed with which worsening occurs depends significantly on initial diagnosis. If left unattended, some of the new tumors will invade the muscle, resulting muscle invasive bladder cancer for the patient.

Detection of new tumor occurrences

New tumor occurrences can be detected during surveillance by cytology or cystoscopy or via bladder cancer symptoms. Microscopic or gross hematuria is the most important presenting symptom. Other common symptoms include lower urinary tract symptoms such as urinary frequency, urgency, and dysuria.

Pathways of tumors to muscle invasion

Molecular genetics evidence suggests several pathways of malignancy leading to muscle invasive bladder cancer (Knowles 2008), including

- High grade Ta $\rightarrow$ T1$\rightarrow$T2
- CIS (concomitant or isolated) $\rightarrow$ T1 $\rightarrow$T2

These pathways are also illustrated in Figure 3. All pathways converge on T1 tumors. T1 tumors can arise from either CIS tumors (concomitant or isolated) or from high-grade Ta tumors. As a tumor grows in size, it becomes more invasive (increases in T-stage) and acquires more molecular alterations (increases in grade). It is still unclear whether CIS can lead to high-grade Ta.
Evidence for watchful waiting studies showed that low grade Ta tumors progress to high grade at a very slow rate.

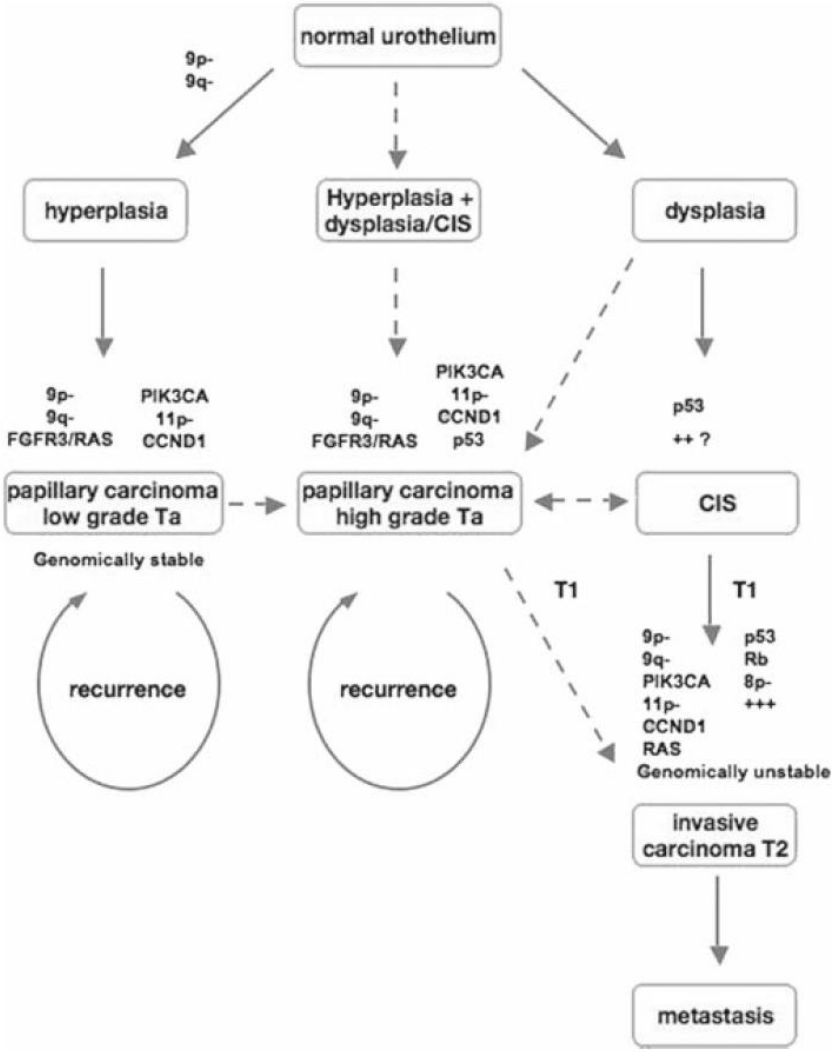


Fig. 1. Model for pathogenesis of bladder cancer based on known histopathology and molecular data. Two major pathways are predicted, leading to the development of low-grade noninvasive tumors (*left*) and muscle-invasive tumors (*right*), respectively. The origin of high-grade papillary Ta tumors is not clear, and these may arise either from flat dysplasia or from an increase in grade of low-grade papillary tumors. Similarly, the route to the development of T1 tumors is not clear, but it may be via the acquisition of invasive capability by high-grade Ta tumors or via carcinoma in situ (*CIS*). Common genetic alterations in the major histopathological groups are indicated; ++? indicates the presence of several additional alterations in CIS; +++ indicates many additional alterations in invasive tumors (see Table 2)

Figure 3. Molecular pathways of tumor genesis (Knowles 2008).

2.1.2 Modeling approach

Assumption 1: Based on literature and inputs from the Advisory Board, we assume that there are three distinct progression pathways for new tumors: one each for TaLG, TaHG and CIS tumors.

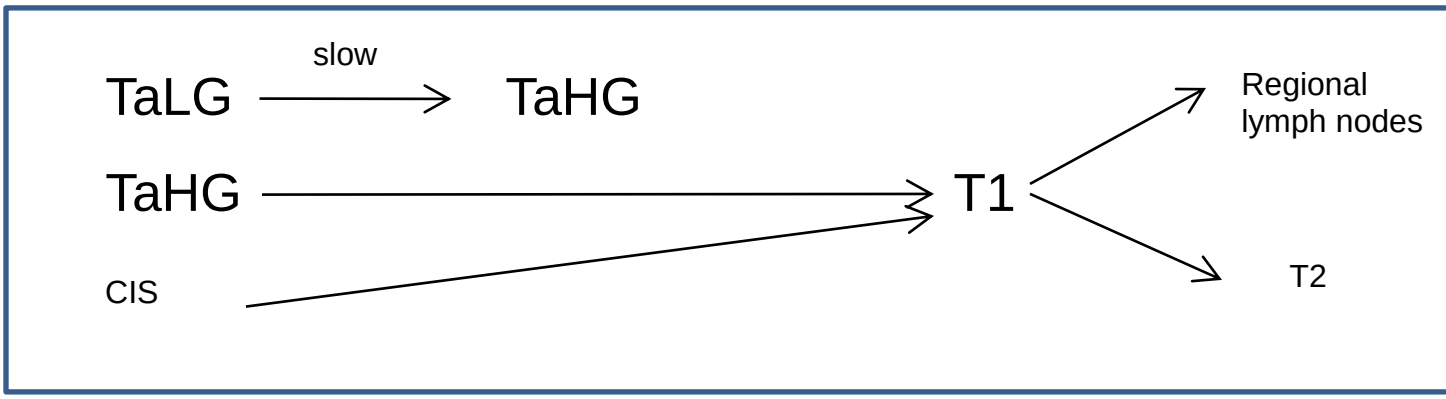


Figure 4. Modeled progression pathways.

- Tumors must invade the lamina propria prior to invading muscle tissue: tumors must become T1 tumors before becoming T2 tumors.
- Rates of TaLG to become TaHG will be very slow.

Justification: The proposed model for progression pathways is based on integrating evidence from molecular, clinical and watchful waiting studies.

2.2 Occurrence of new tumors

2.2.1 Evidence review

Causes of new tumor occurrence

New tumor occurrence can be attributed to:

- New tumor development in other regions of the bladder.
- Cancerous cell implantation resulting from spontaneous perturbations.
- Tumor induction by instrumentation, or incomplete resection of original tumors. (This may account for 50% of early recurrence. Animal models support this theory, confirming the ease of tumor reimplantation onto traumatized urothelial surfaces.)

Risk factors for tumor occurrence

- We reviewed existing predictive models of NMIBC tumor occurrence, worsening, and progression to MIBC. The results are summarized in Table 1.
- The following tumor characteristics and demographic variables have been identified in the literature as predictors of tumor occurrence, worsening, and progression to MIBC:
    - Tumor T-stage
    - Tumor grade
    - Multifocality (single versus multiple tumors)
    - Presence of concomitant CIS
    - Tumor size (>3 cm)

- Past recurrence history (e.g. primary versus recurrence, number of recurrences in first-year)
- Age
- Gender
- Cytology
- NMP22
- Tumor location (bladder neck, trigone, posterior wall, etc.)
- Tumor shape
- Lymphovascular invasion
- New tumor occurrence at 3-month cystoscopy

The most frequently reported and strongest predictors for tumor occurrence are tumor T-stage (Ta, T1, or Tis), grade, presence of concomitant CIS, tumor size, and multiplicity. Similar risk factors were identified by the EORTC model and the meta-analysis conducted by van der Aa (2009).

Reference	Population	Predictor of recurrence	Predictor of progression to MIBC
Millan-Rodriguez (Millan-Rodriguez, Chechile-Toniolo et al. 2000)	A cohort of 1,529 patients with primary superficial transitional cell carcinoma of the bladder treated with transurethral resection and random bladder biopsies	Multiple tumors (OR: 2), tumor greater than 3 cm. (1.65) and carcinoma in situ (1.6)	Grade 3 (OR: 19.9), multiple tumors (1.9), tumor greater than 3 cm (1.7) and carcinoma in situ (2.1) For mortality: Grade 3 disease (OR: 14) and carcinoma in situ (OR: 3)
Shariat (2005) (Shariat, Zippe et al. 2005)	2542 patients with Ta, T1, or CIS transitional cell carcinoma (TCC) from 10 centers	Age (OR: 1.03), gender (OR:1.16, p > 0.1), cytology (OR: 9.78), NMP22 (OR:1.03)	Age (OR: 1.04), gender (OR:0.97, p > 0.1), cytology (OR: 3.63), NMP22 (OR:6.93)
Sylvester et al (Sylvester, van der Meijden et al. 2006)	2596 superficial bladder cancer patients included in seven European Organization for Research and Treatment of Cancer trials	Prior recurrence rate (HR: 1.35), number of tumors: single, 2-7, 8 or more (HR: 1.56), tumor size > 3 cm (HR: 1.54), Ta versus T1 (HR: 1.21), CIS (HR: 1.19), Grade G1,G2, and G3 (1.17)	Primary versus recurrence (1.48), number of tumors, single versus multiple (1.70), tumor size > 3 cm (1.89), Ta versus T1 (HR: 2.19), CIS (HR: 3.41), Grade G3 (2.67)
Yamada et al. (Yamada, Tsuchiya et al. 2010)	800 Japanese non-muscle invasive bladder cancer patients newly diagnosed between 1991 and 2001	Number of tumors (OR: 1.43), tumor size (1.33), tumor shape stalk/broad base (1.59), grade of tumor	Tumor shape stalk/broad base, grade of tumor , T1/a versus Tis (OR: 0.27)
Fernandez-Gomez (Fernandez-Gomez,	1062 patients in 4 CUETO randomized phase 3 studies of	Female gender (HR=1.71), recurrent tumors (HR=1.9) compared to primary	Recurrent tumors (HR=1.62) compared to primary tumors, high-grade tumors (HR=5.64)

Solsona et al. 2008; Fernandez-Gomez, Madero et al. 2009)	intravesical therapies. Most patients received BCG once weekly for 6 consecutive weeks and a short-term BCG maintenance (once every 2 wk 6 times more).	tumors, multiplicity, and presence of associated TIS (HR=1.54).	compared to G1 tumors, T1 tumors (HR=2.15) compared to Ta tumors, and recurrence at 3-mo cystoscopy (HR=4.6)

Table 1. Review of existing predictive models for recurrence and progression to MIBC. OR: Odds ratio. HR: Hazard ratio.

Frequency of tumor occurrence

There is limited data on the frequency of tumor occurrence.

We only found one paper reporting the frequency of tumor occurrence in individual patients. This is a study designed to determine the effects of two treatments (pyridoxine and thiotepa) on future tumor occurrence. A total of 118 participants were randomized to three treatment arms: 48 to placebo, 32 to pyridoxine, and 38 to thiotepa (Byar, 1980). The average follow-up was 31 months, and 189 tumor occurrences were observed in 62 participants, which correspond to an average rate of 2.3 occurrences per year. The numbers of participants who experienced from 1 to the maximum 9 tumor occurrences were 23, 11, 8, 4, 8, 1, 1, 3, and 3, respectively. This dataset has been used extensively by statisticians to demonstrate the applicability of accelerated failure time models (Ghosh 2004; Huang and Peng 2009) for bladder cancer occurrences.

2.2.2 Modeling approach

Assumption 1: Time to occurrence of a new tumor is modeled using a hazard function.
Justification: Time to next occurrence is often reported in terms of a survival curve for time to first event. Effects of various risk factors are often analyzed using a proportional hazards model. This assumption allows us to take advantage of the data available in literature.
Assumption 2: The rate of new tumor occurrence depends on

1) Tumor T-stage
2) Tumor maximum size
3) Tumor grade
4) Multiplicity
5) Presence of concomitant CIS
6) Prior recurrence history
7) Lymphovascular invasion

Justification: This assumption is justified based on our meta-analysis of important risk factors for tumor occurrence.
We used the following requirements to select risk factors for the first version of the model

Requirement 1: The impact of risk factors is reproducible, consistent, and statistically significant across several studies

- Example: The effect of gender varies greatly between studies. A meta-analysis indicates that gender effect is not statistically significant (van der Aa et al, 2009).

Requirement 2: Risk factor should be independent of health care processes.

- Example: The risk factor "positive cytology at month 3" identified by 2 studies is dependent on whether patients have cytology at month 3.

Requirement 3: Risk factors are available from SEER case listings or can be imputed from other datasets.

- Example: While NMP22 was reported to be a strong risk factor for progression, it is not used in clinical settings. There is also insufficient data to correlate NMP22 with tumor characteristics.

Assumption 3: The hazard ratios for the risk factors are obtained by calibrating the model to data provided by the EORTC model, the van der Aa (2009) meta-analysis, and Chade et al. (2010).
Assumption 4: The rate of new tumor occurrence is calibrated to disease-free survival data in a number of studies, including EORTC (Sylvester, van der Meijden et al. 2006) and Chade et al. (Chade, Shariat et al. 2010).

2.3 Concomitant CIS

2.3.1 Evidence review

- Carcinoma *in situ* (CIS) of the urinary bladder is defined as a flat (non-papillary), high grade, non-invasive transitional cell carcinoma. Unlike "*in situ*" designations in other cancers, CIS in bladder cancer is a true malignancy.
- Carcinoma *in situ* tumors correspond to T-stage Tis. However, the majority of Tis cases occur in association with other high-grade nodular tumors (thus referred to in this document as concomitant CIS) and only 3-5% occur as isolated Tis disease (AUA Guidelines 2007, (Hall, Chang et al. 2007)).
- The presence of concomitant CIS signals an increased propensity for progression to muscle invasion (Witjes 2004; Hall, Chang et al. 2007).
- SEER case listings report the most advanced stage of NMIBC tumor (Ta or T1) and neglects the presence of concomitant CIS. Given the significance of CIS on outcomes, the presence of concomitant CIS will be assigned to the NMIBC patient population according to distributions from the literature, and used as a risk factor in determining the risk of recurrence and progression to muscle invasion. The presence of CIS is used in assessing treatment modalities, as described by standard treatment guidelines.
- Isolated Tis accounts for roughly 4% of NMIBC cases in SEER.
- Rates of concomitant CIS vary considerably between different studies (see Table 2). All studies indicate that concomitant CIS is more frequent in patients with T1 tumors.
- According to Hara et al. (Hara, Takahashi et al. 2009), tumor grade and multiplicity are also strong predictors of CIS (see Table 3).

Reference	**Study design**	**Tumor number and types**	**Frequency of concomitant CIS**
Yves et al. (2007)	Fluorescence and white light cytoscopies	196 intermediate and high risk NMIBC	29.6%
Van der Meijden	Random biopsies	376 patients with	4.3% in low-risk patients have abnormalities

(van der Meijden, Oosterlinck et al. 1999)		low-risk cancers, 532 patients with intermediate and high-risk	(interpreted as concomitant CIS) 11.6% in patients with high risk
May et al (May, Treiber et al. 2003)	Random biopsies	1033 consecutive patients presenting with Ta, T1 or Tis	2.7% in patients with Ta tumors 13.6% in patients with T1 tumors
Taguchi et al (Taguchi, Gohji et al. 1998)	Random biopsies	83 patients of all-risk superficial cancer	14.5%
Fujimoto et al. (Fujimoto, Harada et al. 2003)	Multiple biopsies	100 patients with superficial bladder transitional cell carcinoma	Concomittant CIS were found in 5% of patients. five were Tis. All of the five patients with carcinoma in situ (CIS) in their biopsy specimens had multiple papillary broad-base tumors and positive urinary cytology. The detection ratio of CIS in patients with these findings was 17.9% (5/28).
Hara et al. (Hara, Takahashi et al. 2009)	Cytoscopies followed by biopsies	173 primary non-muscle invasive bladder cancer cases	One (12.5%) of eight low-risk, 18 (24.7%) of 73 intermediate-risk and 41 (59.4%) of 69 high-risk cases had CIS in normal-looking sites, respectively

Table 2. Rates of concomitant CIS in superficial bladder cancer.

Table 3 Univariate and multivariate analyses for the existence of concomitant carcinoma *in situ* (CIS) in biopsy specimens according to preoperative and pathological characteristics

Clinical characteristics	Univariate		Multivariate 1		Multivariate 2		*P* value
	OR	95% CI	OR	95% CI	OR	95% CI	
Age: >70, ≤71	1.66	0.90–3.04	–	–	–	–	
Gender: male, female	2.06	0.91–4.67	–	–	–	–	
Tumor number: single, multiple	2.44*	1.32–4.53	1.51	0.69–3.40	1.50	0.71–3.19	0.29
Tumor type: papillary, non-papillary	1.44	0.59–3.52	–	–	–	–	
Tumor type: pedunculated, sessile	1.95*	1.05–3.59	0.72	0.08–6.22	0.63	0.07–5.40	0.68
Tumor type: papillary pedunculated, other types	2.11*	1.14–3.91	1.44	0.16–12.6	1.86	0.22–16.0	0.57
Abnormal dominant cystoscopic appearance: no, yes	3.08*	1.10–8.65	3.48	0.86–14.0	3.48	0.95–12.7	0.06
Dominant cytology: non-positive, positive	15.9*	6.58–38.5	9.39**	2.84–31.0	11.9**	3.74–37.3	<0.01
Dominant cytology: negative, non-negative	10.1*	2.94–34.8	1.17	0.23–6.00	1.39	0.27–7.02	0.69
Main cancer T category: pTa, pT1	2.95*	1.43–6.07	1.67	0.59–4.34	–	–	
Main cancer grade: G1, G2/G3	8.90*	1.12–70.6	3.61	0.36–36.6	–	–	
Main cancer Grade: G1/G2, G3	5.90*	3.03–11.5	1.51	0.59–3.84	–	–	

*Statistically significant (*P value* < 0.05) by univariate analysis. **Statistically significant (*P value* < 0.05) by multivariate analysis. CI, confidence intervals; OR, odds ratios.

Table 3. Univariate and multivariate analysis for presence of CIS from Hara et al 2009.

2.3.2 Modeling approach

Assumption 1: At the time of diagnosis, the presence of concomitant CIS will be randomly assigned to NMIBC patients.

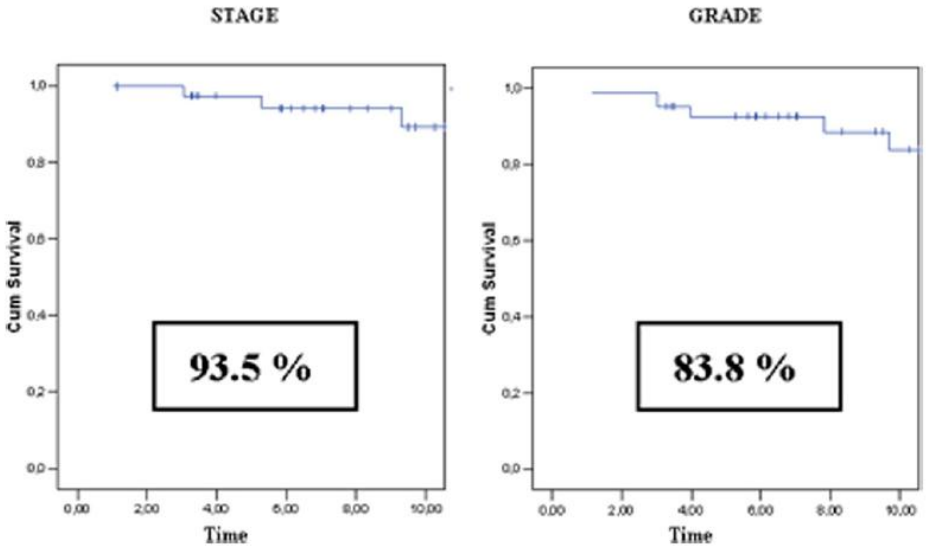
Justification: To our knowledge, SEER does not contain information on concomitant CIS. Given that CIS is an important predictor of new tumor occurrences and progression to MIBC, it is important to model the presence of concomitant CIS at the time of diagnosis for patients with superficial bladder cancer.
Assumption 2: Frequency of concomitant CIS is a function of the T-stage and grade of the initial NMIBC diagnosis.
Justification: Table 2 and Table 3 indicate that T-stage and grade are two important predictors of concomitant CIS. The risk that a NMIBC patient has concomitant CIS is derived from a meta-analysis of studies summarized in Table 2.

2.4 Tumor worsening

2.4.1 Evidence review

Rates of tumor worsening in grade and T-stage of new tumor occurrences

- Rates of tumor worsening in T-stage and grade are reported to be 0-9% of patients in 6-14 months of follow-up (Table 4).
- Soloway et al., (Soloway, Bruck et al. 2003) reported that 3 of 45 (6.7%) patients had tumor worsening from a pre-observation, low grade, noninvasive tumor (TaG1 to TaG2) to a high grade Ta or T1 tumor.
- Hernandez et al. (Hernandez, Alvarez et al. 2009) conducted a prospective cohort study in patients diagnosed with recurrent NMIBC maintained under an active surveillance protocol. The inclusion criteria were papillary tumors with negative cytology findings, previous non-muscle invasive tumors (Stages pTa, pT1a), grades 1-2, size <1 cm, and fewer than 5 tumors. After 10.3 months, 93.5% of the patients had not worsened in T-stage and 83.8% had not worsened in grade



(**Figure 1.** Probability of progression in stage and grade analyzed by Kaplan-Meier method.

- Figure 5). Most interestingly, the rate of worsening in T-stage and grade do not significantly differ from that of the control group, consisting of patients with clinical characteristics similar to those of the patients on active surveillance, but who underwent transurethral resection immediately after the new occurrence was diagnosed. Roughly 4.3% of patients in both groups developed worsening to G3 or presented with associated CIS.

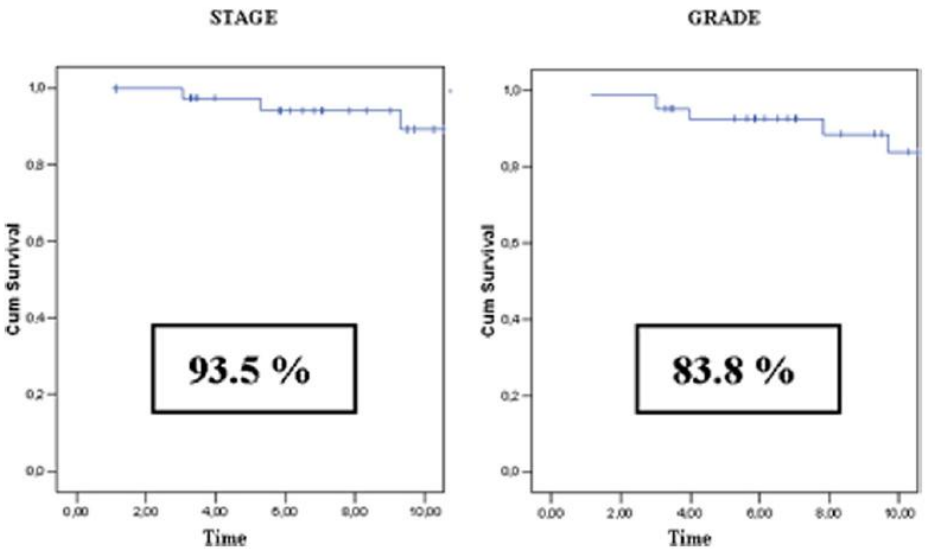


Figure 1. Probability of progression in stage and grade analyzed by Kaplan-Meier method.

Figure 5. Probability of worsening in T-stage and grade (Hernandez, Alvarez et al. 2009). The data is based on 64 patients (70 observation events), with a median follow-up of 10 months. Note that the y-axis label represents cumulative incidence of tumor worsening.

Table 3. Comparison between progression rates in grade and stage for each group

Investigator	n	Median Time in Observation (mo)	Pathologic Findings Before Observation	Progression To High Grade (%)
Soloway et al.,[4] 2003	44	10.09	Ta-T1/G1-G3	6.7
Martinez Caceres et al.,[12] 2005	15	5.76	Ta-T1/G1-G3	6.67
Gofrit et al.,[5] 2006	38	13.5	Ta/G1-G2	0
Pruthi et al.,[13] 2008	22	NA	Ta-T1/G1-G3	9
Present study	70	10.3	Ta-T1a/G1-G2	4.28

NA = not available.

Table 4. Summary of worsening rates in stage and grade in 5 different studies. Present study refers to (Hernandez, Alvarez et al. 2009).

Tumor growth rates

There is very limited data on the growth of non-muscle invasive tumors; only 2 studies have been found thus far.

- Gofrit et al (Gofrit, Pode et al. 2006) followed 28 patients with small, papillary, asymptomatic tumor(s) with negative urinary cytology with previous resection of superficial, low-grade (TaG1) bladder tumors. The mean length of surveillance was 13.5 months. The main reasons for termination of surveillance were the appearance of additional tumors (19 patients) and excessive tumor growth (9 patients). Hematuria indicated tumor removal in only one patient. All resected tumors were stage Ta (23 were grade 1, 7 were grade 2).The rate of tumor growth during the watchful waiting period depended highly on the tumor's largest diameter at the beginning of surveillance. If the initial tumor diameter was smaller than 5 mm (32 cases), the tumor growth

rate was 4+/-5.1 mm^3/mo (mean+/-SD); if the initial tumor diameter was at least 5 mm or larger (6 cases), the tumor growth rate was 870+/-1116 mm^3/mo ($p < 0.05$).

- In 6 cases, initial tumor diameter was >5mm; it was 6 +/- 2 mm(mean +/-SD) at the beginning of follow-up and 28 +/- 13.8mm at the end. Tumor volume growth rate in this group was 870 +/-1116mm^3/mo.
- In 32 cases, the initial tumor diameter was <5 mm; it was 2.5 +/- 0.7 mm at the beginning of follow-up and 4.6 +/- 1.8 mm at the end. Tumor growth rate in this group was 4+/-5.1 mm^3/mo.

- Soloway et al., (Soloway, Bruck et al. 2003) reported on a heterogeneous series of 32 patients with a history of Ta or T1 bladder tumors who developed new tumor occurrences and were not operated on immediately . The authors found that the growth rate of these tumors is slow. Mean tumor growth rate for 37 tumors was 1.77 mm per month (range 0 to 5.8). Only 3 of 45 (6.7%) patients had tumor worsening from a pre-observation, low grade, noninvasive (TaG1 to 2) to a high grade Ta or T1 tumor. The authors did not observe any progression to T2 tumors.

Correlation between tumor size and tumor multiplicity

- Based on SEER data, tumor size tends to decrease with the number of initial tumors. However, the correlation between size and multiplicity is not statistically significant.
- We can extrapolate this data to new tumor occurrences and assume that tumor size is independent of the number of tumors as well as the frequency of tumor occurrence.

Multiplicity	Raw count	% of tumors	Mean tumor size (mm)
1	10046	76.47%	29.89
2	2589	19.71%	28.11
3	418	3.18%	26.38
4	69	0.53%	25.94
5	14	0.11%	21.50
6	52	0.02%	26.50
7	0	0.0%	NA

Table 5. Mean of tumor size as the number of tumors (SEER)

Correlation between tumor size and T-stage

According to SEER data, tumor T-stage appears to be correlated with tumor size. The larger a non-muscle invasive tumor is, the more likely it is a T1 tumor.

- Average tumor sizes for Ta, Tis, and T1 tumors are 27.47, 27.98, and 34.94 mm, respectively.
- Size distributions of Ta and Tis tumors are not significantly different (Table 5)

- To our knowledge, there are no other data available on correlation between T-stage and size besides SEER.

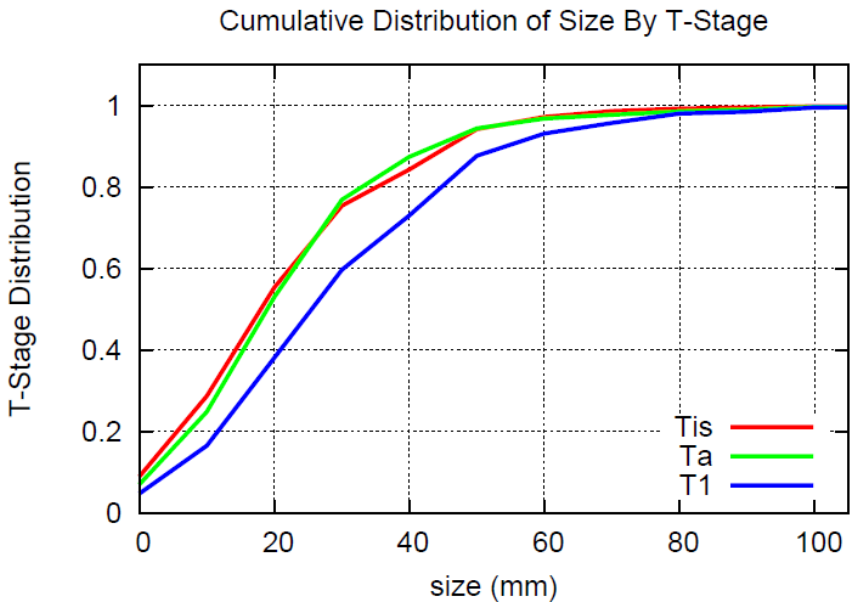


Figure 6. Cumulative distribution of size of original tumors for T1, Ta and Tis tumors (SEER).

Correlation between tumor size and grade

Based on SEER data, tumor grade appears to be correlated with tumor size. The larger a non-muscle invasive tumor is, the more likely it is a high-grade tumor.

- Average tumor sizes for grades 1, 2 and 3 are 27.09, 29.63, and 38.02 mm, respectively.
- Tis tumors tend to be of higher grade as compared with Ta tumors of the same size.
- To our knowledge, no other data are available on the correlation between T-stage and size besides SEER.

2.4.2 Modeling approach

Assumption 1: For the first version of the model, we do not explicitly model growth of bladder tumors; rather we correlate tumor size to T-stage. Once the type and T-stage of a recurrent tumor type is determined, its size can be determined from a distribution derived from SEER data.

Justification:

- There is insufficient robust longitudinal data capturing tumor growth as well as how tumor size is correlated with T-stage and grade.
- SEER data provides some insights into correlations between tumor size and T-stage. It should be noted that the data is cross-sectional and obtained at the time of diagnosis.
- In the future, it may be possible to model tumor growth if we have access to longitudinal data at the individual level.

Assumption 2: Rate of tumor worsening is calibrated to data from Soloway et al., (Soloway, Bruck et al. 2003), Gofrit et al (Gofrit, Pode et al. 2006), Hernandez et al. (Hernandez, Alvarez et al. 2009). Based on input from the Advisory Board, the rate of TaLG becoming TaHG set to be very low (1-3% per year).

2.5 Progression to muscle invasive disease

2.5.1 Evidence review

Risk factors for progression to invasive disease in a patient diagnosed with NMIBC

Review of the literature indicates that the strongest predictors for the progression of NMIBC to muscle invasion are:

1) History of new occurrences
2) T-stage at initial diagnosis
3) Grade at initial diagnosis
4) Presence of CIS at initial diagnosis
5) Largest tumor size at the time of diagnosis

The higher the rate of new occurrences, the more likely progression to MIBC will occur. Tanaka et al. reported a 10-year progression-free survival rate of 58.0% in patients with a new tumor occurrence rate of 1 or more per year and 93.3% for patients with fewer than 1 occurrence in a year (Tanaka, Kikuchi et al. 2011).

Correlation between the size of a given tumor and its risk of muscle invasion

Satoh et al. reported that size, stalk, and configuration of a tumor independently predict the risk that a tumor is muscle invasive (Satoh, Miyao et al. 2002). While bladder tumors smaller than 1 cm have a 0.9% (1/111) likelihood to be muscle invasive, tumors 1 cm and larger have a 28% (45/(87+72)) likelihood to be muscle invasive (Satoh, Miyao et al. 2002) .

2.5.2 Modeling approach

We distinguish between two descriptions of risk of progression:

- **Risk of progression at the tumor-level:** Each new tumor occurrence has a propensity of becoming muscle invasive. The risk of a given tumor becoming muscle invasive depends on characteristics of the original NMIBC diagnosis.
- **Risk of progression to MIBC at the patient-level:** A patient can develop one or more new tumors in the bladder. The risk of progression is the sum of the risks of progression of all new tumors present in the bladder at a given time. The time to progression is the time that the first new tumor in the bladder of the patient progresses to be a muscle invasive tumor.

Assumption 1: Before becoming muscle invasive (T2 and higher), a tumor has to be a stage T1 tumor.

Justification: This assumption is based on our proposed pathway to muscle invasion (see section 2.1) in which all pathways to muscle invasive tumors (T2 and higher) go through T1 tumors. This is consistent with the clinical definition of T-stage.

Assumption 2: The hazard rate for muscle-invasion of individual tumors (tumor-level progression) is calibrated to reproduce the overall risk of progression to muscle invasion at the patient-level. The risk of progression to MIBC at the patient level as function of risk factors is calibrated to data from the EORTC risk model (Sylvester et al., 2006) and Chade et al. (2010).

Justification: Literature review indicates that high grade T1 tumors, CIS tumors, and tumor size at initial diagnosis are the strongest risk factors for progression. While history of new tumor occurrences is a risk factor for progression at the patient-level, it may not be a risk factor for progression at the tumor-level. A history of frequent tumor

occurrences (e.g., more than 1 occurrence/year) increases the likelihood for developing multiple new tumors, and consequently increases the likelihood of progression in at least one of these tumors.

2.6 Survival following progression to muscle invasion

2.6.1 Evidence review

Tumor characteristics at the time of diagnosis with progressive muscle invasive disease

- There is little information on the characteristics of a tumor at the time of progression to muscle invasion.
- In a restrospective non-randomized analysis, Ferreira et al. (2007) studied two groups of patients with MIBC: group 1 included 57 patients with progressive muscle invasive tumors, and group 2 included 185 patients with primary muscle invasive tumors. The differences in tumor characteristics between these groups were not significantly different (Table 6). Roughly 50% of patients presented with T2 and the remainder presented with T3 and T4.
- Turkomelz et al. (Turkolmez, Tokgoz et al. 2007) reported that 55% (25/45) of progressive muscle invasive patients in a sample of 45 patients presented with pT2, as compared to 56% in primary muscle invasive tumors.
- Similarly, in SEER, roughy 51% of MIBC patients presented with T2.

Table 1. Group demography

	Progressive invasive group 1	Primary invasive group 2	p
Patients	57	185	
Median age, years	65.3 ± 8.5	63.7 ± 9.7	0.3687
Smoking habit	42 (73.68%)	139 (75.96%)	0.7279
Sex			
Men	47 (82.46%)	145 (78.38%)	0.5062
Women	10 (21.62%)	40 (17%)	0.5062
TNM			
PT2	29 (50.88%)	105 (56.76%)	0.4349
PT3/4	28 (49.12%)	80 (43.24%)	0.4349
N+	16 (28.07%)	57 (20.81%)	0.6925
M+	14 (24.56%)	35 (18.92%)	0.3540

Table 6. Comparisons between progressive muscle invasive tumors and primary muscle invasive tumors (Ferreira, Matheus et al. 2007).

Survival rate following cystectomy for muscle invasive disease

- de Vries et al. (2010) observed that despite close observation of patients treated for NMIBC, the survival of patients who progress to muscle invasion is not better than the survival of patients presenting with primary muscle invasive cancer (de Vries, Nieuwenhuijzen et al. 2010).
- Ferreira et al. reported the same observation (Ferreira, Matheus et al. 2007): patients with primary muscle invasive cancer and progressive invasive cancer showed a similar 5-year disease-specific survival rate.

- Turkomelz et al (Turkolmez, Tokgoz et al. 2007) also did not find any survival benefit for patients with primary muscle invasive tumors as compared to those with progressive invasive tumors. The 2-, 3-, and 5-year cancer-specific survival rates were 72%, 61%, and 43% for patients with progressive tumors and 75%, 62%, and 54% for patients with primary tumors, respectively (P >0.05).
- However, a number of earlier studies (Schrier, Hollander et al. 2004; Soloway 2005) indicated that patients with progressive muscle invasive tumors have a worse prognosis than those with primary muscle invasive tumors. This conclusion is most likely superseded by recent studies.

2.6.2 Modeling approach

Assumption 1: Tumor characteristics of progressive muscle invasive tumors are similar to those of primary muscle invasive tumors and will be sampled from SEER.

Justification:

- This assumption is supported by Ferreira et al. (2007), Turkomelz et al. (2007), and qualitative agreement between Ferrieira et al. (2007) data and SEER.

Assumption 2: Disease-specific survival following progression to muscle invasion is modeled using SEER survival data for different invasive stages at initial diagnosis. Survival following diagnosis with muscle invasive disease is stratified by gender, stage, and race.

Justification:

- This assumption is based on observations by de Vries et al. (2010), Turkomelz et al. (2007) and Ferreira et al. (2007) that the survival of patients who progress to muscle invasion is not significantly different from the survival of patients presenting with primary muscle invasive cancer.
- Analysis of SEER data shows that gender, race, and stage are strong predictors of survival following diagnosis of MIBC.

3. Diagnostic tests for staging and surveillance

3.1 Transurethral Resection of Bladder Tumors (TURBT)

TURBT is the primary method of diagnosis and treatment for Ta and T1 bladder tumors. The initial TURBT provides pathologic material to determine the tumor's histologic type, grade, and depth of invasion. This information helps to direct additional therapy, dictates the follow-up schedule, and indicates prognosis.

3.1.1 Evidence review

Performance of TURBT

- TURBT removal is incomplete
- 20-76% of second TURBTs performed 4-6 weeks after the first TURBT found residual tumors.
- Residual tumors were found in 31% of third TURBTs (Köhrmann et al., 1994).
- Most residual tumors are due to incomplete removal: 14% of the malignant tissue was at other locations outside the initial tumor resection area (Schwaibold, Sivalingam et al. 2006).
- TURBT performance may depend on tumor T-stage.

Accuracy of TURBT staging

- Inaccuracies in TURBT staging are widely reported. Shariat et al. reported over-staging at the time of radical cystectomy (RC) in 42% of clinically localized cases, and down-staging in 22% of cases (Shariat, Palapattu et al. 2007). Furthermore, 40% of patients with non-muscle invasive clinical stage had muscle invasive pathologic stage.
- Chang et al. reported that, for clinical T1G3 patients, under-staging occurs in up to 46-50% of patients (Chang, Kim et al. 2001; Fritsche, Burger et al. 2010).
- Van Der Meijden et al. (Van Der Meijden, Sylvester et al. 2000) reviewed pathology reports for 1400 patients enrolled in five EORTC trials and reported down-staging of T-stage from T1 to Ta in 53% of cases. There was agreement in only 57% and 50% of TaG1 and T1G3 cases, respectively, of which 10% were reclassified as muscle invasive disease.

3.1.2 Modeling approach

Assumption 1: TURBT will fail to detect some bladder tumors (miss rate: 16%).
Assumption 2: TURBT will incompletely remove some bladder tumors, leaving some of the tumor behind (TURBT incomplete removal rate: 40%).
Assumption 3: Clinical staging using TURBT is inaccurate. Some tumors will be under-staged or over-staged as compared to the true underlying disease.
Assumption 4: The rates of under- and over-staging are derived from comparing pathological staging to clinical staging, assuming that (i) pathological stage corresponds to the true underlying disease, and (ii) the rates of under- and over-staging obtained around the time of cystectomy are applicable to the TURBT performed at an earlier stage of disease evolution.

Assumption 5: Parameters characterizing TURBT performance (e.g., detection rate, performance rate, and rates of under- and over-staging) depend on the T-stage and grade of the tumor at the time the TURBT is performed.
Assumption 6: TURBT performance on one tumor in the bladder is independent of its performance on other, concurrently present, tumors in the bladder.

3.2 Cytology

3.2.1 Evidence review

- On average, cytology has a sensitivity of 48% (with range 16-89%) and a specificity of 96% (with range 81-100%) (Sexton, Wiegand et al. 2010). Performance of urinary cytology depends on tumor grade. Cytology has a high specificity (94%) and a reasonable sensitivity (~60%) for high grade tumors (van Rhijn, van der Poel et al. 2005).

Table 3 – Median sensitivity per grade (G1-3, WHO 1973) and specificity of the urine markers for patients under surveillance (the same studies as reported in Table 2 were considered)

Marker (number of studies)	No. pts./sensitivity			No. pts./specificity
	G 1	G 2	G 3	
BTA stat (7)	228/45	206/60	208/75	972/79
NMP22 Elisa (4)	111/43	139/58	144/82	357/64
NMP22 POC (1)	38/32	16/44	32/75	565/87
uCyt + /ImmunoCyt (3)	172/79	108/86	113/90	1509/72
FISH UroVysion (3)	52/38	28/51	38/82	169/75
Microsatellite (6)	69/61	53/63	40/92	869/77
Cytology (10)	239/17	274/34	201/58	861/95

Pts. = patients; POC = point-of-care.

Table 7. Sensitivity and specificity of urine markers for patients under surveillance (van Rhijn, van der Poel et al. 2005).

TABLE 52 *Summary of pooled estimate results and predictive values for biomarkers and cytology for patient-based detection of bladder cancer*

Test	Number of studies	Number analysed	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)	PPV (%), median (range)	NPV (%), median (range)
FISH	12	2535	76 (65 to 84)	85 (78 to 92)	18 (3 to 32)	78 (27 to 99)	88 (36 to 97)
ImmunoCyt	8	2896	84 (77 to 91)	75 (68 to 83)	16 (6 to 26)	54 (26 to 70)	93 (86 to 100)
NMP22	28	10,119	68 (62 to 74)	79 (74 to 84)	8 (5 to 11)	52 (13 to 94)	82 (44 to 100)
Cytology	36	14,260	44 (38 to 51)	96 (94 to 98)	19 (11 to 27)	80 (27 to 100)	80 (38 to 100)

Table 8. Sensitivity of cytology and urine biomarkers (Mowatt, Zhu et al. 2010)

3.2.2 Modeling approach

Assumption 1: Sensitivity of cytology is a function of tumor grade, based on van Rhijn et al. (2005).

Justification: To our knowledge, van Rhijn et al. (2005) is the only publication reporting sensitivity of cytology as a function of tumor grade. The overall sensitivity reported by van Rhijn et al. (2005) is consistent with existing meta-analyses.

Assumption 2: Specificity of cytology is set to 96% based on Sexton et al. (2010).

Justification: Sexton et al. (2010) is the most recent review on performance of cytology.

3.3 Cystoscopy

3.3.1 Evidence review

Cystoscopy is endoscopy of the urinary bladder and urethra using a cytoscope, a thin tube with a lighted camera. The cystoscope enters via the urethra and advances into the bladder. Surgical instruments may be attached to the cystoscope to allow for stone removal, bladder biopsy, resection of bladder or prostate tumors, and cauterization.

Conventional cystoscopy uses white light. Fluorescence cystoscopy using hexaminolevulinate (HAL) or 5-aminolevulinic acid (5-ALA). 5-ALA is gaining popularity due to its improved rates of identification of CIS tumors and Ta and T1 papillary lesions which fluoresce red under blue illuminated light (Fradet et al 2007, Witjes 2010).

According to a European panel of experts (Witjes, Redorta et al. 2010) the recommended approach is a combination of white light and fluorescence cystoscopies. Their recommendations are to use fluorescence cystoscopy in the following situations

1. Initial suspicion of bladder cancer.
2. Recurrence in patients not staged using conventional cystoscopy.
3. Positive cytology but negative white light cystoscopy.
4. Surveillance of patients with CIS or multifocal tumors.

The rates of detection are given in Table 9.

Tumor Type	**Cystoscopy**	**Detection Rate (%)**
CIS	White light	68
	Fluorescence	92
Papillary Ta	White light	83
	Fluorescence	95
Papillary T1	White light	86
	Fluorescence	95

Table 9. Detection rates of white light and fluorescence cytoscopies for different tumor stages (Fradet, Grossman et al. 2007; Grossman, Gomella et al. 2007).

3.3.2 Modeling approach

Assumption 1: Only white light cytoscopy is modeled in the current version of the model.
Justification:

- Use of fluorescence cystoscopy is not widespread in the US.

Assumption 2: The results of the cystoscopy will be determined by the number of tumors present (either papillary or CIS) and its sensitivity and specificity rates.

Assumption 3: Detection rates of cystoscopies are based on a meta-analysis of the literature and depend on tumor stage.
Justification: See Table 9.

4. Treatment

4.1. Cystectomy

4.1.1 Evidence review

Indications for cystectomy for NMIBC patients

Indications for cystectomy for NMIBC patients include:

- Unfavorable histology (micropapillary,adenocarcinoma, squamous cell carcinoma)
- Lymphovascular invasion in patients with clinical stage T1 tumors
- Incomplete resection of multifocal T1 high grade tumors
- BCG induction failure in patients with high grade T1 tumors or CIS
- Deep prostatic ductal involvement with TCC

Cystectomy is optional for patients with any high-grade Ta or T1 tumors or CIS at initial presentation dependent on the volume of disease, the completeness of resection, and a discussion of the potential risks and benefits associated with intravesical therapy.

Complications of cystectomy

The rates of long- and short-term surgical complications are listed in Table 10 and Table 11.

Long term complications	***Frequency***
Ureteral intestinal obstruction	15%
Renal deterioration	15%
Renal failure	7%
Stoma problems	15%
Intestinal stricture	10%
Bowel obstruction	5%

Table 10. Long term complications of cystectomy and urinary diversion (McDougal, Shipley et al. 2008).

Short term complications	***Frequency***
Acute acidosis requiring therapy	16%
Urine leak	3-16%
Bowel obstruction	5%
Fecal leak	5%

Pyelonephritis	5-15%
Sepsis	5-15%

Table 11. Short-term complications of cystectomy and urinary diversion (McDougal, Shipley et al. 2008)

Rate of post-operative mortality following cystectomy

The rate of postoperative mortality is estimated to be 2.5%, based on data in Table 12.

Reference		**Complications of Cystectomy**		
First Author	**Title**	**Number of patients**	**Number of post-operative complications**	**Number of deaths within 30 days of surgery**
Stein (Stein, Lieskovsky et al. 2001)	Radical Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patients	1054	292	27
Lee	Cystectomy for bladder cancer	262	93	NA
Konety (Konety and Allareddy 2007)	Influence of Post-Cystectomy Complications on Cost and Subsequent Outcome	1869	540	49
Malavaud (Malavaud, Vaessen et al. 2001)	Complications for Radical Cystectomy	161	41	0
Frazier (Frazier, Robertson et al. 1992)	Complications of radical cystectomy and urinary diversion : a retrospective review of 675 cases in 2 decades	675	215	17

Table 12. Rates of complications and mortality for cystectomy.

4.1.2 Modeling approach

Assumption 1: We only model radical cystectomy.

Justification: Segmental cystectomy is infrequently performed and accounts for less than 5-10% of all cystectomies.

Assumption 2: Survival following cystectomy of patients with muscle invasive disease at the time of cystectomy is modeled according to Section 2.6 Survival following progression to muscle invasion.

Assumption 3: The effects of cystectomy complications are captured through the cost model.

4.2 Intravesical therapy

4.2.1 Evidence review

Current intravesical therapies for treating NMIBC

Table 13 summarizes the existing intravesical immunotherapies and chemotherapies.

Table 4. Intravesical Immunotherapy and Chemotherapy

Agent	Mechanism of Action
Immunomodulatory Agents	
Bacillus Calmette-Guérin (BCG)	• Inflammatory host response; release of cytokines • May be combined with interferons[90-94]
Interferons	• Lymphocyte activation; cytokine release; phagocyte stimulation • Antiproliferative actions • Antiangiogenic[31,90]
Chemotherapeutic Agents	
Thiotepa	• Alkylating agent; cross-links nucleic acids[95]
Mitomycin C	• Antibiotic; inhibits DNA synthesis[76-78]
Doxorubicin, epirubicin, valrubicin	• Intercalating agents; inhibits DNA synthesis[75,96-98]
Gemcitabine	• Deoxycytidine analog; inhibits DNA synthesis[99-103]

Table 13. Intravesical immunotherapy and chemotherapy

Use of intravesical therapies

Intravesical therapies are employed at various stages for the management of NMIBC:

- Immediate Post-resection Intravesical Therapy:
  - Single-instillation of intravesical chemotherapy agents (e.g., mitomycin C , thiotepa, and doxorubicin) is designed to reduce the risk of early new tumor occurrences.
  - The most desirable time is 2-6 hours after resection. After 24 hours, intravesical therapy may not have the desired protective effect against new tumor occurrences.
  - Sylvester et al. showed that patients treated with TURBT and a single instillation of mitomycin C within 24 hours of resection are 39% less likely (odds ratio: 0.61) to have recurrence as compared with those treated with TURBT alone (Sylvester, Oosterlinck et al. 2004).
  - The benefit of an immediate instillation occurs early on, mainly during the first 1-2 years, with a possible dilution of the treatment effect with longer follow-up (Solsona, Iborra et al. 1999).

- Induction Intravesical Therapy:
  - Induction therapy is defined as a weekly administration of an intravesical agent for at least 6 consecutive weeks.

- An induction course of either intravesical chemotherapy or BCG should be administered for the treatment of patients with NMIBC that have an increased risk of recurrence but a low risk of progression (e.g., low grade Ta tumors) (Hall, Chang et al. 2007).
- For patients with high-risk tumors (high-grade Ta, high-grade T1, CIS, or a combination thereof), the recommended therapy is BCG induction followed by BCG maintenance, which has been shown to be superior to mitomycin C and maintenance (Hall, Chang et al. 2007).
- In a meta-analysis of 8 clinical trials, Huncharek et al. (Huncharek, McGarry et al. 2001) found that using 1 year recurrence as the outcome measure yielded an odds ratio (ORp) of 0.62, demonstrating a 38% reduction in one year recurrence among patients treated with intravesical chemotherapy versus TURBT alone. Using 2 and 3 year recurrence as the outcome measure yielded ORp's of 0.46 and 0.35 respectively, favoring TURBT + intravesical chemotherapy versus TURBT alone.

- Maintenance Intravesical therapy:
  - Maintenance intravesical therapy is defined as the periodic continued exposure to an intravesical agent following the achievement of complete response to an initial induction course of intravesical therapy.
  - Lamm et al. (Lamm, Blumenstein et al. 2000): The 5-year recurrence-free survival rate was 60% in the BCG maintenance arm compared with 41% in the no-maintenance arm. The 5-year progression-free survival rate was 76% in the maintenance arm compared with 70% in the no-maintenance arm.
  - Risk ratio for TURBT+BCG maintenance versus TURBT+MMC maintenance is 0.68 (Malmstrom, Sylvester et al. 2009).
  - Risk ratio for TURBT+BCG induction only versus TURBT+MMC maintenance is 1.28.(Malmstrom, Sylvester et al. 2009)

- BCG Failures and Salvage Intravesical Therapy
  - The category of BCG-refractory cases includes (i) patients who fail to achieve a disease free state by 6 months after initial BCG therapy with either maintenance or re-treatment at 3 months because of either persistent or rapidly recurrent tumors; and (ii) patients with any progression in T-stage, grade, or extent of disease after the first cycle of BCG.
  - Treatment for BCG-refractory patients includes a second induction course followed by cystectomy if patients continue to not respond to BCG (Hall, Chang et al. 2007).

Complications of intravesical therapies

- Rates of complications of therapies using BCG and MMC are summarized in Table 14.

Table 6. Complications Incidence by Category and Treatment

Treatment	Bladder Contracture			Epid/Prost/ Urethral Infections			Hematuria			LUTS			Fever/Chills/Flu Symptoms			Systemic Infection		
	G/P	Est Rate %	CI*	G/P	Est Rate %	CI*	G/P	Est Rate %	CI*	G/P	Est Rate %	CI*	G/P	Est Rate %	CI*	G/P	Est Rate %	CI*
TURBT alone	1/27									3/3,043								
Minimal overlap (or none)		**1**	(0, 9)								**2**	(0, 5)						
Maximal overlap (if minimal)																		
TURBT + BCG Induct	1/21			2/168			11/527			17/1,584			14/1,233			1/23		
Minimal overlap (or none)		**1**	(0, 11)		**4**	(0, 16)		**29**	(21, 38)		**59**	(42, 74)		**26**	(16, 39)		**1**	(0, 10)
Maximal overlap (if minimal)											**38**	(28, 49)		**19**	(13, 28)			
TURBT + BCG Induct+ BCG Maint	8/949			6/443			17/1,523			22/1,753			20/1,667			4/255		
Minimal overlap (or none)		**3**	(2, 6)		**4**	(2, 6)		**20**	(13, 30)		**71**	(56, 83)		**30**	(22, 41)		**7**	(2, 17)
Maximal overlap (if minimal)											**57**	(44, 69)		**22**	(16, 30)			
TURBT + MMC: Single dose postop										2/209								
Minimal overlap (or none)											**2**	(0, 8)						
Maximal overlap (if minimal)																		
TURBT + MMC Induct							5/418			7/657			3/309					
Minimal overlap (or none)								**16**	(9, 25)		**58**	(32, 81)		**30**	(17, 47)			
Maximal overlap (if minimal)											**24**	(16, 24)		**26**	(13, 43)			
TURBT + MMC Induct + MMC Maint	2/234			1/26			4/544			9/843			2/220					
Minimal overlap (or none)		**5**	(2, 11)		**8**	(2, 22)		**19**	(10, 31)		**31**	(19, 44)		**16**	(11, 23)			
Maximal overlap (if minimal)											**22**	(15, 30)						

*Confidence interval (2.5, 97.5)%

BCG, bacillus Calmette-Guérin; CI, confidence interval; Est Rate, estimated occurrence rate; Epid, epididymitis; G/P, Number of group/Number of patients; Induct, induction; LUTS, lower urinary tract symptoms; Maint, maintenance; MMC, mitomycin C; Prost, prostatitis; TURBT, transurethral resection of bladder tumor

Table 14. Complications of intravesical therapy + TURBT (Hall, Chang et al. 2007).

Effects of intravesical therapies

Table 15 and Table 16 provide an overview of available literature on intravesical therapies.

Table 2c. Progression, Disease-Specific Survival, Overall Survival by Treatment: Randomized Controlled Trials*

Treatment	Progression Overall Overall/Unspecified			Progression High Risk† Overall/Unspecified			Disease-Specific Survival Overall/Unspecified			Overall Survival Overall/Unspecified		
	G/P	Est Rate %	CI (2.5, 97.5)%	G/P	Est Rate %	CI (2.5, 97.5)%	G/P	Est Rate %	CI (2.5, 97.5)%	G/P	Est Rate %	CI (2.5, 97.5)%
TURBT alone	17/917	**12**	(9, 17)	2/48	**17**	(3, 46)	4/383	**94**	(89, 97)	5/505	**84**	(73, 92)
TURBT + MMC Single dose	1/57	**2**	(0, 8)									
TURBT + MMC Induction	3/343	**6**	(2, 12)				1/92	**91**	(84, 96)			
TURBT + MMC + Maintenance	9/928	**11**	(8, 16)	1/63	**10**	(4, 19)	7/740	**93**	(91, 95)	7/914	**81**	(71, 89)
TURBT + BCG Induction	8/546	**10**	(7, 13)	4/260	**14**	(9, 19)	3/325	**89**	(79, 96)	3/335	**73**	(56, 87)
TURBT + BCG + Maintenance	17/1,701	**9**	(7, 12)	5/341	**14**	(8, 22)	10/1,442	**95**	(92, 97)	13/1,557	**84**	(78, 89)

* Please see text for data qualification.

† A subgroup of the first column. High risk included groups that had no Grade 1 patients or were entirely carcinoma in situ and/or T1.

BCG, bacillus Calmette-Guérin; CI, confidence interval; Est Rate, estimated occurrence rate; G/P, Number of groups/Number of patients; MMC, mitomycin C; TURBT, transurethral resection of bladder tumor.

Table 15. Progression and survival for different treatment strategies (Hall, Chang et al. 2007).

Treatment A	Treatment B	Population	Odd ratio on recurrence comparing Treatment A to Treatment B	Study or meta-analysis
TURBT alone	TURBT + Single immediate chemotherapy	cTa low-grade	0.61	(Sylvester, Oosterlinck et al. 2004).
TUBRT alone	TURBT + Induction chemotherapy	8 randomized trials	0.62 for 1 year recurrence 0.46 for 2 year recurrence 0.35 for 3 year recurrence	(Huncharek, McGarry et al. 2001)
TURBT alone	TURBT + BCG	6 randomized trials, 585 Ta and T1 patients	0.30 (CI 0.21, 0.43)	(Shelley, Court et al. 2000)
TURBT + MMC	TURBT + BCG induction	9 randomized trials	1.28	(Malmstrom, Sylvester et al. 2009)
TURBT + MMC	TURBT + BCG maintainance	9 randomized trials	0.68	(Malmstrom, Sylvester et al. 2009)

Table 16. Examples of meta-analyses comparing different treatment regimens for NMIBC.

4.2.2 Modeling approach

We model two intravesical therapies: BCG and mitomycin C (MMC), the two most common therapies for NMIBC. We model 4 management strategies: (i) single-instillation, (ii) induction, and (iii) maintenance.

Assumption 1: The effects of a treatment strategy will be represented by a hazard ratio acting on the hazard rate of tumor occurrence. The values of the hazard ratio can be time dependent to represent the dilution of therapeutic efficacy.

Assumption 2: Treatment efficacy of different regimens is compared with TURBT alone.

Justification: All occurrences of non-muscle invasive bladder tumors are assumed to be removed by TURBT in order to determine treatment effects on the tumors.

Assumption 3: The hazard ratios will be derived from a network meta-analysis utilizing trials comparing

- TURBT alone vs. TURBT + MMC single dose
- TURBT alone vs. TURBT + MMC induction
- TURBT alone vs. TURBT + MMC maintenance
- TURBT alone vs. TURBT + BCG induction
- TURBT alone vs. TURBT + BCG maintenance
- TURBT + BCG induction vs. TURBT + MMC maintenance
- TURBT + BCG maintenance vs. TURBT + MMC maintenance

Justification: Network meta-analysis allows us to take advantage of all existing trials that compare one treatment modality to another. The methodology for network meta-analysis is well-established and can be found elsewhere (Psaty, Lumley et al. 2003).

The table below lists the trials and the systematic reviews used to construct the network meta-analysis.

Treatment A	**Treatment B**	**References (trials and systematic reviews)**
TURBT alone	TURBT + Single immediate chemotherapy	(Sylvester, Oosterlinck et al. 2004) (meta-analysis of 7 trials)
TUBRT alone	TURBT + MMC induction	(Tolley, Parmar et al. 1996) (Niijima, Koiso et al. 1983)
TURBT alone	TURBT + MMC maintenance	(Krege, Giani et al. 1996) (Akaza, Isaka et al. 1987) (Tsushima, Nasu et al. 1992) (Tolley, Parmar et al. 1996)
TUBRT alone	TURBT + BCG induction	(Krege, Giani et al. 1996) (Lamm 1985) (Melekos 1990) (Pinsky, Camacho et al. 1985)
TURBT alone	TURBT + BCG maintenance	(Pagano, Bassi et al. 1991) (Yamamoto, Hagiwara et al. 1990) (Krege, Giani et al. 1996)
TURBT + BCG induction	TUBRT + MMC induction	(Ojea, Nogueira et al. 2007) (Friedrich, Pichlmeier et al. 2007)
TUBRT + BCG induction	TURBT + MMC maintenance	(Witjes, v d Meijden et al. 1998) (Vegt, Witjes et al. 1995) (Friedrich, Pichlmeier et al. 2007)

		Lee et al 1992 DeBruyne et al 1992 See also Bohle, Jocham et al. 2003 (meta-analysis)
TURBT + MMC maintenance	TURBT + BCG maintenance	(Rintala, Jauhiainen et al. 1991), also see (Jarvinen, Kaasinen et al. 2009) (Malmstrom, Wijkstrom et al. 1999) (Lamm, Blumenstein et al. 1995) (Di Stasi, Giannantoni et al. 2003) (Martinez-Pineiro, Jimenez Leon et al. 1990) (Krege, Giani et al. 1996) (Ayed, Ben Hassine et al. 1998) (Millan-Rodriguez, Chechile-Toniolo et al. 2000) (Lundholm, Norlen et al. 1996) See also Bohle, Jocham et al. 2003 (meta-analysis)

Table 17. Trials and studies used to construct the network meta-analysis.

Assumption 4: Complications of intravesical therapies will be captured through cost models.
Justification: At the current stage of development, it is sufficient to capture the effects of treatment complications on an aggregated level through increases in costs.

4.3 Management guidelines for NMIBC

4.3.1 Evidence review

General strategy for management of NMIBC

Patients are typically stratified according to the risk of progression to MIBC. A number of treatment options including TURBT, observation, single immediate post-operative instillation of chemotherapy, induction therapy with either BCG or MMC, and cystectomy will be recommended based on a patient's risk category. Figure 7 provides a summary of the management pathways for bladder cancer.

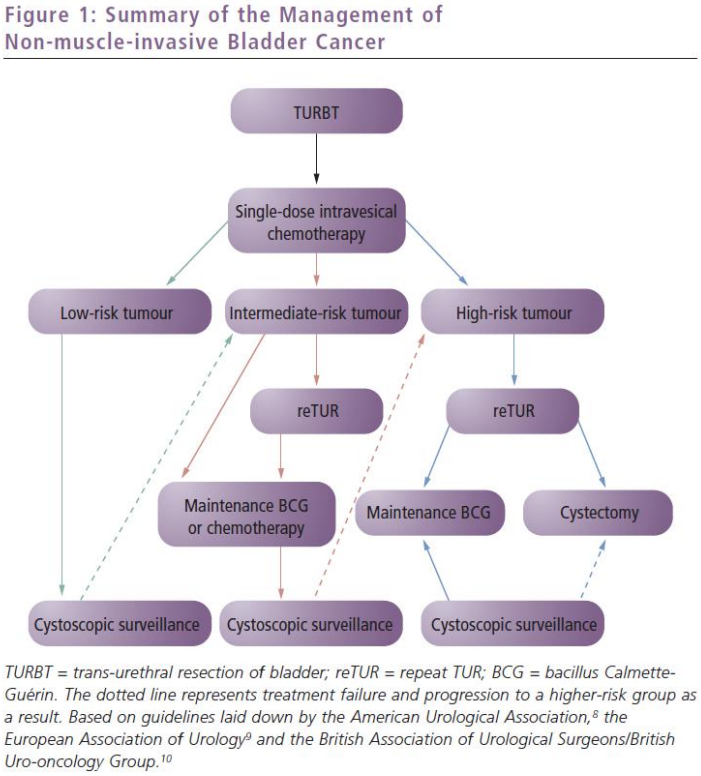


Figure 7. Summary of the management of NMIBC (Ayres and Persad, 2007).

Current guidelines for management of NMIBC

Over the past decade, several guidelines for the management of NMIBC have emerged, including

- European Association of Urology (EAU) Guidelines on Ta, T1 (non-muscle invasive) Bladder Cancer
- First International Consultation on Bladder Tumors (FICBT)
- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Bladder Cancer: 2011 Update
- American Urological Association (AUA) Guidelines for the Management of Non-muscle Invasive Bladder Cancer (Stages Ta,T1, and Tis): 2007 Update
- British Association of Urological Surgeons (BAUS)/British Uro-oncology Group (BUG)

The most prominent guidelines are the EAU, AUA, NCCN and FICBT guidelines.

Differences and similarities between current guidelines for management of NMIBC

There are considerable similarities between existing guidelines. For instance, all guidelines support TURBT for removal of tumor(s) and diagnosis. All guidelines group patients according to three risk categories: low, intermediate, and high; however, the definitions used for risk stratification vary considerably between guidelines. All guidelines recommend single immediate post-operative instillation of chemotherapy for low risk patients. However, the EAU guidelines extend that recommendation to all NMIBC patients, not just low risk patients.

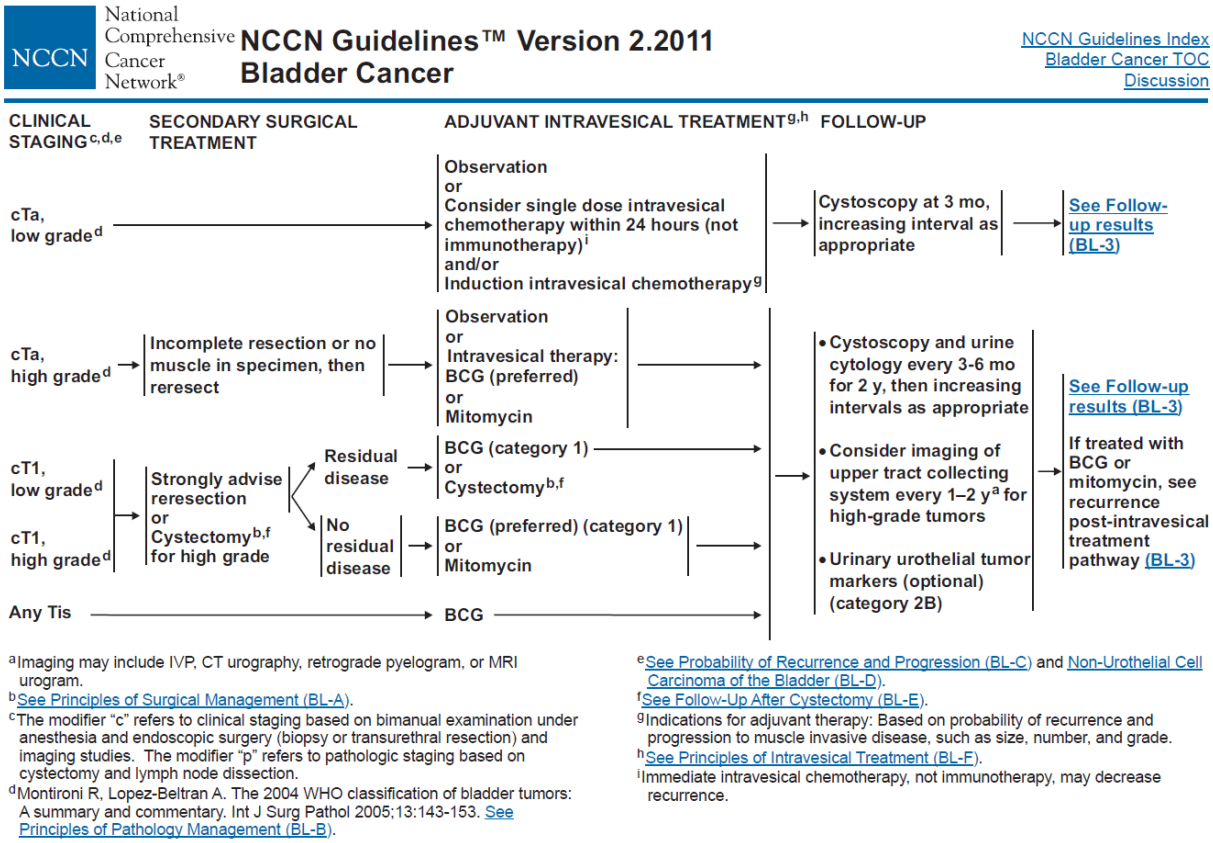


Figure 8. NCCN Guidelines 2011 for bladder cancer.

4.3.2 Modeling approach

The health care processes are designed so that we can implement any guideline of interest. A flexible design of the health care processes relevant to NMIBC will enable implementation of different guidelines for the management of NMIBC.

Assumption 1: For the first version of the model, we will program the NCCN 2011 guidelines.

Justification: The NCCN 2011 guidelines are the most up-to-date and particularly relevant to the US market. It should be noted that NCCN 2011 guidelines use the 2004 WHO classification system of bladder tumors (low grade and high grade versus grades 1, 2 and 3).

5. Patient generation

5.1 Evidence review

5.1.1 Review of SEER data

Variables included in individual SEER case listings:

- Patient demographics:
  - Age at diagnosis
  - Gender
  - Race
- Tumor characteristics:
  - Tumor T, N, and M stages
  - Tumor size (mm)
  - Tumor grade
  - Number of tumors
  - Primary site
  - Histology (transitional cell, squamous cell, or adenoma- carcinoma)

ID	Age at Dx	Ethnicity / Race	Sex	Grade	Tumor Size (mm)	Stage	T Stage	N Stage	M Stage
66663	80	White	Female	I	26	0	Tis	N0	M0
5396208	57	White	Male	I	32	0a	Ta	N0	M0
5347983	72	Black	Male	III	15	I	T1	N0	M0
72819338	56	Asian/Pac. Is.	Male	III	70	0a	Ta	N0	M0
72834793	76	Hispanic	Female	III	10	0a	Ta	N0	M0
55798883	55	White	Male	II	80	0a	Ta	N0	M0

Table 18. Examples of case listings in SEER.

5.1.2 Lymphovascular invasion

- Lymphovascular invasion (LVI) status does not exist in SEER. We must therefore impute this tumor characteristic for our NMIBC population.

- Although there is abundant data on the significance of LVI in radical cystectomy populations, there is limited evidence on LVI at initial diagnosis (~5 studies).

- Only one publication (Cho 2009) conducted a multivariate analysis of LVI.
- LVI rate in T1 patients: 10-28%.
- We have not found any studies reporting positive LVI status in Tis and Ta patients.
- Cho (2009) concluded that LVI correlates with tumor grade, but is not associated with gender, age, tumor size, bladder tumor history, multiplicity, or concomitant CIS.
- Other studies also suggest that the LVI rate is independent of concomitant CIS (Gohji 1999).

Table 3. *Multivariate Cox proportional hazards model of disease recurrence and progression*

	Recurrence		Progression	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Bladder tumor history (yes vs no*)	3.405 (1.738–6.672)	<0.001		
Tumor size (3 or greater vs less than 3 cm*)	1.995 (1.064–3.741)	0.031	2.344 (0.918–5.984)	0.075
No. tumors (4 or greater vs less than 4*)	1.972 (1.021–3.811)	0.043		
LVI (yes vs no*)	2.016 (1.114–3.903)	0.029	3.065 (1.233–7.620)	0.016
Intravesical therapy (no vs yes*)	1.095 (0.483–2.484)	0.828		

* Referent.

Table 19. Effects of lymphovascular invasion on recurrence and progression (Cho 2009).

5.2 Modeling approach

Patients are constructed from sampled individuals from the SEER NMIBC database. This allows us to maintain the correlations between the key variables at the individual patient level.

- Use SEER*Stat software (http://seer.cancer.gov/seerstat/, release April 23, 2010) to download individual case listings for years of diagnosis 2004-2007.
- Exclude individuals with missing data.
- Obtain 13,164 individuals with NMIBC at initial diagnosis with the above listed patient demographics and tumor characteristics.
- Lymphovascular invasion and presence of concomitant CIS are imputed using data from literature.

6. Cost assumptions

Costs are based on Medicare reimbursement rates derived from literature and SEER-Medicare databases (Table 20).

Cost type	Cost item	Cost assumption (Medicare reimbursement rate)	Estimated cost (2011 dollars)
Surveillance	Cytology	• Including both professional and technical components.	• $90 (Kamat, Karam et al. 2011)
	Cytoscopy	• Neglecting cost due to complications	• $241 (Office setting) (Lotan and Svatek 2007; Kamat, Karam et al. 2011)
Surgery	TURBT	• Including hospital, urologist, anaesthetist and pathologist costs. • Outpatient. • CPT codes: codes 52224, 52234, 52235, and 52240	• $2755 (Rao and Stephen Jones 2009; Hemani and Bennett 2010; Kamat, Karam et al. 2011)
	Cystectomy	• Open radical cystectomy. • Including direct costs (surgeon fee, anaesthesia cost, length-of-stay (LOS)) and indirect costs (complications). Independent of clinical stage. • Cost calculated as a lump sum at the time of cystectomy.	• $ 60,405 (Expert opinion and (Avritscher, Cooksley et al. 2006), inflated to 2011 dollars)
Intravesical therapy	Single-instillation chemotherapy	• Outpatient. Treated with MMC • CPT code: 51720 for Prof/Tech and J9291 for Drug (Mutamycin, 40 mg). • Cost of treating side-effects of MMC are negligible	• $241 (Medicare 2011 reimbursement rate)

	BCG Induction	• Outpatient • A weekly administration BCG (TheraCys or Tice) for 6 consecutive weeks for • CPT code: 51720 for Pro/Tech and J9031 for Drug. • $113.85 for drug and $221 for instillation (CPT 51720, average outpatient hospital) • Cost of treating BCG complications is 11% of the total cost of BCG (Uchida et al., 2007, Japanese's system)	• $2305
	BCG Maintenance	• Every week for 3 weeks at 3,6,12,18,24,30, & 36 months (Southwest Oncology Group regimen, Lamm et al) for a total of 21 instillations • Cost of treating BCG complications is 11% of the total cost of BCG (Uchida et al., 2007, Japanese's system)	• $7452
	MMC Induction	• Outpatient • A weekly administration of MMC (40 mg) for 6 consecutive weeks • CPT code: 51720 for Pro/Tech and J9031 for Drug. • $20.57 for drug and $221 for instillation (CPT 51720, average outpatient hospital) • Cost of treating side-effects of MMC are negligible	• $1452 (Medicare 2011)
	MMC Maintenance	• Every other week for 14 week. Every month for 8 months. Every 3 months for 1 year (a total of 19	• $4579 over 2 years

		instillations) • Cost of treating side-effects of MMC are negligible	
Treatment of MIBC	Initial work-up		• $5,759 (Avristcher et al., 2006, inflated to 2011 dollars)
	Initial disease treatment	• Including cystectomy, systemic therapy, radiotherapy	• $54,646 (Avristcher et al., 2006, inflated to 2011 dollars)
	Surveillance		• $12,698 (Avristcher et al., 2006, inflated to 2011 dollars)
	Treatment of recurrences		• $46,931 (Avristcher et al., 2006, inflated to 2011 dollars)
	Terminal care	• For patients died of bladder cancer	• $76,909 (Avristcher et al., 2006, inflated to 2011 dollars)

Table 20. Cost assumptions.

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