An Outcomes Model for High-Risk Non–Muscle-Invasive Bladder Cancer Treatment Options

Varun Ramamohan,[1] Deirdre M Mladsi,[1] Wylinn Boey,[2] Raffaella Pozzi,[2] James A Kaye[1]

[1]RTI Health Solutions, Research Triangle Park, NC, United States; [2]Telormedix SA, Bioggio, Switzerland

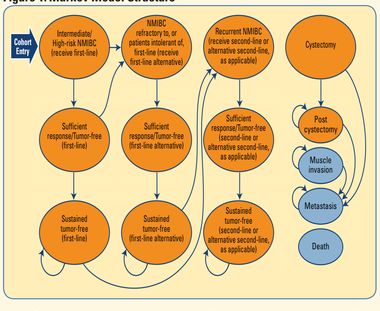
BACKGROUND AND OBJECTIVE

- The European Association of Urology offers treatment guidelines for non–muscle-invasive bladder cancer (NMIBC), which includes carcinoma in situ (Cis) and Ta and T1 tumors.[1] The guidelines define high-risk (HR) NMIBC to include the following: Cis; T1 tumors; and a subset of Ta tumors (described as "HR Ta")—specifically, those that are grade 3 (G3) or are multiple, recurrent, large (> 3 cm) G1 and/or G2 tumors. This heterogeneous presentation results in patient subpopulations with diverse treatment requirements.
- Current health economic models for NMIBC have the following limitations: (1) they focus only on a single NMIBC subpopulation[2,3]; (2) they do not cover all relevant treatment options[2-4]; and/or (3) they are not specific to HR NMIBC.[3,4]
- The objective of this study was to develop a comprehensive model to estimate costs and health outcomes with various HR NMIBC treatment strategies for a variety of patient subpopulations.

METHODS

- In Microsoft Excel, we programmed a Markov model (Figure 1) to estimate the costs and health outcomes associated with the treatment of patients with HR NMIBC based on published European and United States (US) treatment guidelines.[1,5] The model, which employs a 3-month cycle and runs over a lifetime time horizon, takes a United Kingdom (UK) payer perspective.
- The model considers three patient populations according to tumor type: Cis, HR Ta/T1, and concomitant Cis + Ta/T1 NMIBC.
- In addition to trans-urethral resection of the bladder tumor (TURBT), applicable for Ta and T1 tumors, the model considers intravesical therapy with bacillus Calmette-Guerin (BCG) and mitomycin C (MMC) as first- and/or second-line or as alternative treatments for patients refractory to or intolerant of first- and/or second-line treatment.
  - Valrubicin, although not approved for use in the UK, was included in the model for use in BCG-refractory patients with Cis, according to its package insert in the US.[6]
- The goals of intravesical therapy include delaying or avoiding recurrence of NMIBC.
- A cohort of patients enters the model upon diagnosis of HR NMIBC and receives a first-line intravesical therapy (adjunctive to TURBT or as monotherapy, as applicable). If the tumor is refractory to or the patient is intolerant of the first-line intravesical therapy (established within the first 6 months [2 cycles] of use), the patient receives the alternative first-line therapy if an alternative therapy has been selected. Otherwise, the patient moves directly to cystectomy.
  - In the case of refractoriness to/intolerance of an alternative therapy, the patient moves directly to cystectomy.
- Patients who move into the "Sustained tumor free (first-line)" health state but who eventually experience a recurrence receive second-line therapy (which may be the same or different from the first-line therapy) if a second-line has been selected. Otherwise, the patient moves directly to cystectomy.
  - In the case of refractoriness to/intolerance of second-line therapy, the patient moves directly to cystectomy.
  - Patients who move into the "Sustained tumor free (second-line)" health state but who eventually experience a recurrence move directly to cystectomy.
- Transition probabilities (based on response rates and recurrence rates among responders for Cis, and based on recurrence rates for HR Ta/T1), adverse event rates, resource use, unit costs, and utilities were estimated based on published literature and/or publicly available data.
- The model was validated against published epidemiology and cost data.

Figure 1. Markov Model Structure



Note: Patients move to cystectomy if refractory to, if intolerant of, or upon recurrence following their last line of therapy. Cystectomy is assumed to occur in the case of muscle invasion. Patients are at risk of muscle invasion from all states except cystectomy, postcystectomy, metastasis, and death. Patients are at risk of death from any health state.

Key Model Assumptions

- The efficacy of an intravesical treatment in preventing muscle invasion is linked to its efficacy at preventing recurrence.
- With the exception of muscle invasion, recurrence is of the same grade and stage as at model entry.

Key Model Inputs

Intravesical Therapy Administration and Safety/Tolerability

- Table 1 presents the intravesical therapy induction and maintenance regimens.

Table 1. Induction and Maintenance Regimens for Intravesical Therapy

Intravesical Therapy	Induction	Maintenance
BCG[a]	75 mg BCG Connaught; 6 weekly instillations	75 mg BCG Connaught; 3 weekly instillations at 3, 6, 12, 18, 24, 30, and 36 months
MMC[b]	20 mg; 6 weekly instillations	20 mg; 1 instillation every month up to 12 months
Valrubicin[c]	6 weekly instillations	every 3 months up to 6 months

[a] Sylvester et al.[7]
[b] Lamm et al.[8]
[c] Dinney et al.[9]

- Adverse event rates and rates of discontinuation due to intolerance to intravesical treatment were obtained from Bohle et al.[10] The adverse event rates were distributed by grade for BCG and MMC, based on Lamm et al.[8] The valrubicin adverse event rates were distributed by grade according to the MMC proportions.

Intravesical Therapy Efficacy

- For each intravesical therapy when used at each line, the rates of insufficient response (for patients with Cis [Table 2]) and recurrence (among responders with Cis [Table 3] and among patients with HR Ta/T1 [Table 4]) were standardized to a follow-up period of 6 months (insufficient response) or 2 years (recurrence) and then converted into cycle-specific transition probabilities by fitting a geometric distribution to the standardized insufficient response and/or recurrence rates.
- Efficacies in patients with concomitant Cis + Ta/T1 are assumed equal to efficacies in patients with Cis.

Table 2. Rates of Insufficient Response Among Patients With Cis

Treatment Line	Percentage of Patients With Cis With Insufficient Response at 6 Months		
	BCG	MMC	Valrubicin
First-line	31.90[a]	44.02[a]	N/A
Second-line	40.13[b]	55.38[b]	N/A
Alternative first-line	40.13[b]	55.38[b]	78.00[c]
Alternative second-line	50.48[b]	69.66[b]	98.12[c]

N/A = not applicable.
[a] Sylvester et al.[11]
[b] Estimated using Table 6 in Babjuk et al.[1]
[c] Dinney et al.[9]

Table 3. Recurrence Rates (Following Response) Among Patients with Cis

Treatment Line	Recurrence Rate		
	BCG	MMC	Valrubicin
First-line	34.00% over 3.6 years[a]	46.92% over 3.6 years[a]	N/A
Second-line	42.77% over 3.6 years[b]	59.02% over 3.6 years[b]	N/A
Alternative first-line	42.77% over 3.6 years[b]	59.02% over 3.6 years[b]	81.82% over 2 years[c]
Alternative second-line	53.81% over 3.6 years[b]	74.25% over 3.6 years[b]	100.00% over 2 years[c]

[a] Sylvester et al.[11]
[b] Estimated using Table 6 in Babjuk et al.[1]
[c] Dinney et al.[9]

Table 4. Recurrence Rates Among Patients With HR Ta/T1

Treatment Line	Recurrence Rate	
	BCG	MMC
First-line[a]	34% over 5 years	62% over 5 years
Second-line[b]	35.63% over 5 years	64.98% over 5 years
Alternative first-line[b]	42.77% over 5 years	78% over 5 years
Alternative second-line[b]	44.83% over 5 years	81.74% over 5 years

[a] Estimated from the American treatment guidelines.[5]
[b] Estimated using Table 6 in Babjuk et al.[1]

Risks of Metastasis and Death

- The model assumed an average cohort age of 60 years, 77.6% male.[12] Average life expectancy of males and females in England and Wales at 60 years was estimated as 79.90 years and 83.32 years, respectively, from the UK Office for National Statistics.[13] Risk of death was adjusted to reflect acute postoperative (cystectomy) risk and in the case of muscle-invasion and metastasis (Table 5).

Table 5. Risks of Metastasis and Death

Input Parameter	Percentage	Follow-up Period (Years)
Postoperative (cystectomy) acute mortality	2.60%	0.25
Survival postcystectomy for muscle invasion	81.69%	5.00
Progression to metastasis postcystectomy	12.21%	3.57
Mortality from metastasis	88.85%	5.00

Source: Ghoneim et al.[14]

Costs and Utilities

- TURBT plus one follow-up physician visit post-TURBT was assumed for patients with HR Ta/T1 or concomitant Cis + Ta/T1. The unit costs for a TURBT and a follow-up visit were £1,745.00 and £94.00.[15] Table 6 presents costs of intravesical therapy.
- Resources assumed to be used to treat adverse events were reviewed with a clinical advisor. Unit costs associated with resources used to treat adverse events were obtained from the UK's Personal Social Services Research Unit (PSSRU) for 2013.[15]

Table 6. Costs of Intravesical Therapy (2013)

Resource	BCG	MMC	Valrubicin	Source
Cost per administration	£203.00	£165.00	£165.00	Intravesical administration costs for BCG and MMC were obtained from PSSRU,[15] with the assumption that BCG administration required a more complex administration than MMC. Cost for valrubicin assumed equal to MMC.
Cost per dose	£73.36	£39.94	£3,011.88	Cost per dose for BCG (ImmuCyst, Sanofi) and MMC (Mitomycin C, Kyowa) obtained from PSSRU.[15] Cost of valrubicin (Valstar, Endo Pharmaceuticals, Inc.) obtained from Redbook[16] in 2013 US dollars and converted to British pounds.

- Baseline utility (from which are deducted disutilities for treatment and treatment-related adverse events, as applicable) is assumed to be 1; utility of death is assumed to be 0.
- Disutility from TURBT, –0.10, is from Kulkarni et al.[2] and is applied for 1 day.
- Intravesical therapy disutilities for MMC and valrubicin are assumed to be the same as BCG, –0.02, from Kulkarni et al.[17] Intravesical therapy disutilities are applied for one day for each day of intravesical administration.
- Table 7 presents health state costs and utilities associated with cystectomy, postcystectomy, muscle-invasion, and metastasis.

Table 7. Health State Costs and Utilities Associated With Cystectomy, Postcystectomy, Muscle-Invasion, and Metastasis

Health State	Health State Cost (2013)	Utility
Cystectomy	£13,631.76[a]	0.8[c]
Postcystectomy	£365.33[b]	0.87[d]
Muscle invasion (assumes cystectomy)	£13,631.76[a]	0.8
Metastasis	£1,568.23[b]	0.62[c]

[a] Includes cost of cystectomy,[15] expected costs of complications postcystectomy, and follow-up costs (both from Kulkarni et al., 2009, inflated to 2013 and converted to British pounds).
[b] Follow-up costs from Kulkarni et al.,[2] inflated to 2013 and converted to British pounds.
[c] Kulkarni et al.[17]
[d] Estimated based on Kulkarni et al.[17]

RESULTS

- We present results from some key scenario analyses (Table 8).

Table 8. Economic and Health Outcomes from Key Scenario Analyses

Outcomes	Cis; BCG first- and second-line, BCG-refractory/intolerant patients		HR Ta/T1; BCG as first- and second-line, with no alternative therapy	HR Ta/T1; MMC as first- and second-line, with no alternative therapy	Concomitant Cis + Ta/T1; BCG as first- and second-line, with no alternative therapy
	Treated with valrubicin	Undergoing immediate cystectomy			
Economic outcomes (per person, £)					
TURBT (Ta/T1 only)	—	—	2,321	2,690	2,154
Intravesical therapy	18,401	8,572	13,416	4,379	8,572
Acquisition	10,508	1,274	1,892	765	1,274
Administration	4,032	3,526	5,235	2,249	3,526
Adverse events	3,861	3,772	6,289	1,365	3,772
Follow-up	7,826	7,220	8,359	7,384	7,220
Cystectomy (for treatment failure or muscle-invasion), including postcystectomy care	18,193	18,474	10,681	14,182	18,474
Metastatic disease	2,700	2,745	1,572	2,096	2,745
Total	47,120	37,011	36,349	30,731	39,165
Health outcomes (per person)					
Life-years	8.99	8.91	11.11	10.20	8.91
QALYs	7.96	7.88	10.34	9.48	7.88

- The total cost of treating BCG-refractory patients with Cis with valrubicin is approximately 27% higher than treating them with cystectomy. (Note: This estimate differs from the 45% value reported in the abstract due to updates performed on the model since the time of abstract submission.)
- Adverse event costs are estimated to be 4.4% of total costs for patients with HR Ta/T1 treated with MMC (updated from 5% for general HR NMIBC in the abstract) compared to 17% for patients treated with BCG, reflecting the significant toxicity associated with use of BCG.
- Further, the model estimates that approximately 33% of patients with HR Ta/T1 treated with BCG undergo cystectomy (updated from 40% for general HR NMIBC in the abstract), and 22% (15% in the abstract) experience muscle invasion.

Model Validation

- We compared this model's result to results from Kulkarni et al.,[2] which was the only other health economic model published in HR NMIBC that considered use of a full regimen (i.e., induction and maintenance) of intravesical therapy. The Kulkarni et al.[2] model had been previously described and validated.[17] We compared the current model's results also to epidemiology studies identified by Kulkarni et al.[17]
- The lifetime cost per person of treating patients with HR Ta/T1 with BCG used first-line and second-line (£36,349) was 27% higher (20% in the abstract) than comparable costs (£28,710 [CAN$42,400, 2005, inflated to 2013, and converted to British pounds using a factor of 0.59.]) estimated by Kulkarni et al.,[2] who also used a similar treatment pathway. This difference is due to the inclusion of costs of managing 15 adverse events (£6,289) in the present model.
- The model estimates of survival and quality-adjusted survival per person with HR Ta/T1 treated with BCG (11.1 years and 10.3 quality-adjusted life-years [QALYs]) were within 5% and 10% of that reported in Kulkarni et al.[2] (10.6 years and 9.39 QALYs).
- The model estimates a 5-year overall survival rate of approximately 80% for patients with HR Ta/T1 treated with BCG, and this is comparable to the 83% 5-year overall survival rate reported in Lamm et al.[18] The model estimates a 44% overall survival rate at 15 years, which is somewhat higher than the 37% overall survival rate reported in Cookson et al.[19] Kulkarni et al.[17] also compared their estimates of overall survival against these studies.

CONCLUSION

- This model can be used to estimate costs and health outcomes associated with existing treatment strategies as well as the cost-effectiveness of novel intravesical therapies.

REFERENCES

Please see handout for complete reference list.

FUNDING

This work was funded in part by Telormedix.

CONTACT INFORMATION

Varun Ramamohan, PhD
Research Health Economist

RTI Health Solutions
Phone: +1.919.541.6162
E-mail: ramamohan@rti.org

ISPOR 19th Annual International Meeting
May 31-June 4, 2014
Montreal, Quebec, Canada