Trimodal therapy vs. radical cystectomy for muscle-invasive bladder cancer: A Markov microsimulation model

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Abstract

Introduction: Radical cystectomy (RC) is the historic gold standard treatment for muscle-invasive bladder cancer (MIBC), but trimodal therapy (TMT) has emerged as a valid therapeutic option for selected patients. Given that prospective clinical trials have been difficult to perform in this area, our aim was to compare these two primary treatment strategies using decision analytic methods.

Method: A two-dimensional Markov microsimulation model was constructed using TreeAge Pro to compare RC and TMT for patients with newly diagnosed MIBC. A comprehensive literature search was used to populate model probabilities and utilities. Our primary outcome was quality-adjusted life expectancy (QALE). Secondary outcomes included crude life expectancy (LE) and bladder cancer recurrences. The simulated patient for our model was an adult with MIBC (pT2-4 N0 M0) who was a candidate for either RC or TMT.

Results: A total of 500 000 patients were simulated. TMT resulted in an estimated mean QALE of 7.48 vs. 7.41 for RC. However, the average LE for patients treated with TMT was lower compared with RC (10.20 vs. 10.74 years). A sensitivity analysis evaluating the impact of age showed that younger patients treated with RC had greater QALE and longer LE than those

treated with TMT; inverse findings were observed for elderly patients. Overall, 39.4% of patients treated with TMT experienced a bladder recurrence.
Conclusions: RC results in a longer LE compared to TMT (0.54 years), but with a lower QALE (-0.07 years). The preferred treatment strategy varied with patient age.

Introduction

Bladder cancer represents a significant source of morbidity and mortality worldwide. Nearly 430,000 diagnoses of bladder cancer are made each year leading to approximately 165,000 deaths (1). Radical cystectomy (RC) has historically been accepted as the gold standard treatment for muscle invasive bladder cancer (MIBC) supported by a large body of long-term evidence (2, 3). However, RC is associated with significant risks of post-operative morbidity and even mortality (4). Due to the risks associated with RC and the appeal of bladder preservation, trimodal therapy (TMT) including debulking transurethral resection of the tumour, followed by concurrent radiosensitizing chemotherapy and external beam radiation has emerged as a valid treatment option, albeit in selected patients (5).

Evaluating the two modalities directly has been challenging. Retrospective studies which include the early years of TMT adoption are likely impacted by indication bias making conclusions regarding efficacy difficult to draw. The only randomized clinical trial in this space was closed early due to poor accrual due to issues with perceived lack of equipoise and patient reluctance to randomization (6).

Our group has previously compared the oncologic outcomes between patients treated with RC or TMT using a propensity score matched-cohort analysis and found that TMT yielded survival outcomes similar to those of matched patients who underwent RC (7). However, little literature has been published evaluating the quality of life impact from the two treatment types. Since these interventions and their downstream sequalae are complex, involving both benefits and harms to health, distillation of the relevant information to an overall estimation can contribute to better decision making (8). Decision models are an accepted tool used to guide clinical decision making and models have previously been used in the field of urologic oncology (9, 10). Therefore, the purpose of this study is to directly compare the effectiveness of TMT versus RC for patients with MIBC using decision analytic techniques.

Methods

Model overview

We constructed a two-dimensional Markov microsimulation model with trackers using TreeAge Pro 2019 (TreeAge Software Inc., Williamstown, MA) to compare treatment strategies for patients with newly diagnosed MIBC. A Markov model simulates patients over time and allows for transitions between various health states as disease progresses. Two management strategies

were modelled – TMT versus RC. Our primary outcome was quality adjusted life expectancy (QALE). Secondary outcomes included crude life expectancy, overall survival, distant recurrence rates and bladder cancer diagnoses in the TMT arm over a lifetime time horizon. The Markov cycle length mimicked the clinical experience: every 3 months in active treatment and during the first year of follow-up, then every 6 months for the second and third year and then yearly moving forward if patients had no evidence of recurrence. If evidence of recurrence developed, they returned to a cycle length of 3 months. Within cycle correction with a 1.5% discount rate was used to account for bias arising from discrete-time Markov models (11, 12).

Base case

The base case for our model was an adult patient with MIBC (pT2-4 N0 M0) appropriate for either RC or TMT. Distributions representative of the typical MIBC population were used to simulate real patients seen in clinical practice with individual level sampling for age, gender, and reconstruction type. Distributions for patient level variables are shown in Appendix S1.

Model structure

Figure 1 depicts the Markov state transition diagrams for both strategies. In both arms, patients may be treated with neoadjuvant chemotherapy (NAC), and experience adverse events, progression, or death, impacting their ability to complete chemotherapy.

Patients in the TMT arm (Figure 1A) could have a complete or incomplete response to therapy (requiring salvage cystectomy or systemic treatment). Following TMT, patients entered the surveillance phase where they could develop a local recurrence, treatment-related complication (minor and major, based on CTCAE grading), distant recurrence, or death. The bladder cancer recurrence could be non-muscle invasive (high [HG] or low grade [LG]) or muscle invasive. Patients diagnosed with MIBC or recurrent HG NMIBC (>1 recurrence) underwent a salvage cystectomy. Further details regarding the modelling of complications can be found in Appendix S2.

In the RC arm (Figure 1B) and for patients undergoing salvage cystectomy in the TMT arm, patients could experience peri-operative complications or mortality. Complications were similarly modelled as minor and major (based on Clavien Dindo grading), which increased peri-operative mortality rates (13, 14). Following treatment, patients entered a post-cystectomy surveillance state. With each cycle, each patient had a risk of distant recurrence, short or long term post-operative complications, and death.

If patients in either cohort developed a distant, metastatic recurrence, they could be treated with either first line (cisplatin based) chemotherapy or second line therapy. Eligibility for first line chemotherapy was modelled based on the probability of a simulated patient having adequate renal function for cisplatin (defined as GFR $\geq$ 60mL/min), which decreased with age (15). Patients ineligible for cisplatin were treated with gemcitabine/carboplatin (16). Second line therapy was modelled as pembrolizumab in keeping with the inclusion criteria from the

KEYNOTE-045 trial (17). Patients could also transition into a palliative state (best supportive care). Assumptions made in the development of the model are detailed in the Appendix S3.

Model parameters

Transition probabilities were determined from a comprehensive MEDLINE literature search as of March 1, 2019, supplemented by hand search of references from retrieved studies, review articles, previous decision analyses and expert consultation (Table 1). If there were multiple datapoints obtained for a given probability, we chose the value that was from the publication of the best methodological grade and represented the modelled cohort most accurately. In order to more closely approximate real-life events, equations representing survival and cumulative incidence curves from the published literature were calculated; these were then used to create per cycle probabilities for key transition probabilities (Appendix S4).

Utilities were obtained using the Tufts-New England Medical Center Cost Effectiveness Analysis registry (http://www.tufts-nemc.org/cearegistry/data/default.asp) and using a manual search of published urology decision models (Table 2). In cases where exact probabilities or utilities were not available, our search expanded to include other cancer sites and expert opinion. Transitional penalties to account for the inconvenience of procedures and potential short-term complications (e.g. transurethral resection of bladder tumour, chemotherapy and operative complications) were subtracted from a given health state's baseline utility.

Model calibration

We calibrated the baseline non-cancer mortality rate using two- and ten- year survival in the RC arm to better model overall survival with MIBC. Calibrations in the TMT arm were completed for the probabilities of proceeding to immediate cystectomy following incomplete response to TMT, developing a distant or bladder recurrence. These uncertain probabilities were calibrated against the salvage cystectomy rate and two- and ten- year survival in TMT. Further details are available in Appendix S5.

Model validation

Internal model validity was assured through assessment of results' face validity, placement of internal trackers and ensuring logical model flow through the stages. We assessed external validity by evaluating our model's ability to reproduce overall survival rates, disease specific survival (DSS) rates and absolute benefit derived from NAC in both the TMT and RC arms by comparing model generated estimates with those published that were separate from those used to generate model probabilities.

Sensitivity analyses

Sensitivity analyses are used to assess how the change in one variable affects the overall outcome of the model. Scenario-based sensitivity analyses were utilized to evaluate the impact of neoadjuvant chemotherapy utilization and age on the primary outcome. One-way sensitivity

analyses where the variable of interest can vary across the range of clinically plausible values were completed on the surveillance utility values.

Results

A total of 500,000 patients were simulated. Based on our base case analysis, TMT was the preferred treatment pathway with an estimated QALE of 7.48 versus 7.41 for RC. The non-quality of life adjusted crude life expectancy for patients treated with TMT was 10.20 years versus 10.74 years with RC.

The model's overall survival rates at 1, 5 and 15 years for TMT and RC were 90.2%, 58.8%, 24.1% and 93.5%, 56.9%, and 26.7%, respectively (Table 3).

DSS rates at 5 years were 69.5% in TMT and 65.7% in RC. Our validation cohort had DSS rates of 76.6% for TMT and 73.2% for RC (7).

Secondary outcomes of interest were analyzed. In the TMT arm, 6.3% of patients did not complete therapy. Overall, 39.4% of patients experienced a bladder recurrence, with 66.9% were NMIBC. The overall rate of salvage cystectomy was 26.6%; the 2- and 5-year salvage cystectomy rates were 11.2% and 17.9%, respectively. Over the course of the simulation, 31.8% of patients in the TMT arm had a distant recurrence.

In the RC arm, the perioperative mortality rate was 2.24%. Distant recurrence occurred in 41.3% of patients during the simulation. The overall incidence of complications during surveillance in the TMT arm was 44.3% and 38.9% in the RC arm.

Sensitivity analysis

Impact of neoadjuvant chemotherapy

As the use of NAC prior to TMT or RC is not universal, scenario-based analyses were undertaken to explore the impact of 100% utilization of NAC in both arms. If all patients received NAC in the TMT arm, the 5-year OS was 60.4% compared to 57.9% if none of the patients received it. This represents an absolute OS benefit of 2.5%. In the RC arm, if 100% of patients received NAC the 5-year OS was 59.2% and 55.6% if none of the patients received chemotherapy. The absolute OS benefit was 3.6%. The absolute OS benefit from published meta-analyzed data is 5% (23).

Impact of age

The impact of age on QALE and crude life expectancy was investigated using scenario-based analyses. The starting age distribution was replaced with distinct age thresholds. This analysis showed that younger patients treated with RC had both greater QALE and longer crude survival than those treated with TMT. However, for elderly patients, the inverse was true (Table 4).

Impact of utilities

One-way sensitivity analyses were completed around surveillance utility values for TMT and RC. Decreasing the TMT surveillance state utility from 0.91 to 0.899 results in a change in the preferred pathway; in the RC arm increasing the surveillance state utility for non-neobladder patients to 0.848 from 0.84 results in a change in the preferred treatment modality with respect to QALE (Appendix S6).

Discussion

This Markov microsimulation comparing two treatment modalities for patients with newly diagnosed MIBC revealed that TMT resulted in a net gain of 0.07 quality adjusted life years (QALYs) compared with RC. The quality-unadjusted life years however, reveal that patients treated with TMT have an average life expectancy of 10.20 compared to 10.74 years for those treated with RC (a net benefit for RC of 0.54 years).

As a composite measure, QALYs encompass overall survival and health related quality of life. In oncology decision analyses, the clinical interpretation of a meaningful change in QALYs can be challenging (48). In this setting, where TMT leads to a gain of 1 quality adjusted life month (QALM) in the setting of a 6-month crude life expectancy decrease, the gain in QALM is of questionable clinical significance. Our sensitivity analysis demonstrates that the model is exquisitely sensitive to changes in patient preference for both TMT and RC surveillance states.

In this decision analysis, the impact of age on the ultimate treatment choice was investigated. When patients are younger (≤55 years old), they derive greater QALYs and unadjusted life years from RC than they do from TMT because the impact of a longer follow up results in the need for salvage procedures (i.e. greater oncologic control from RC) and the occurrence of secondary malignancies in the TMT group. Whereas when patients are ≥81 years old, the inverse is true; the elderly have a longer unadjusted life expectancy and experience greater QALYs when treated with TMT, in large part because of the avoidance of post-operative mortality after RC. In the intermediate ranges of age (64-80), the results are mixed. TMT results in greater QALYs but RC leads to more unadjusted life years gained. Therefore, discussions about individual patient priorities are especially important in these age ranges. Since age and comorbidity are often correlated, we would expect similar findings in patients with high and low comorbidity states (i.e.: TMT favoured for highly comorbid patients regardless of age and RC favoured for patients with few comorbidities). As the literature is conflicted with respect to whether octogenarians face an increased risk of peri-operative mortality(49-52), all patients were modelled to have the same peri-operative risk of morbidity and mortality. If the true risks for elderly patients are in fact higher than those in younger age cohorts, our findings would be further reinforced.

It is worth noting that not all patients with MIBC are ideal candidates for TMT and the selection of these eligible patients is of utmost importance. Patients with preserved bladder

function with a unifocal tumour less than 7 cm in size, at maximum unilateral hydronephrosis and the absence of multifocal carcinoma in situ represent the best candidates when comparing oncological outcomes.

External validity of the model was evaluated by comparing our OS results to those from studies not used in the generation of our analysis. Overall, the generated OS results fall within 7% of the literature results; importantly our results follow the appropriate trend within the RC and TMT arms themselves and in relation to each other. Despite level 1 evidence to support the use of NAC in MIBC, there is consistent underutilization (53, 54).

Our model illustrates that when every patient is given NAC prior to definitive management (compared to when 0% receive NAC) an absolute OS benefit is achieved between 2.5-3.6% at 5 years. While this is slightly lower than the estimates of effect generated by the meta-analyzed data, the OS from that meta-analysis was 45-50% which is lower than contemporary data (23). As a result, they have more room for benefit to be derived from NAC and so these estimates of benefit from NAC are in largely in keeping with the meta-analyzed data.

Randomized clinical trials in this setting have been difficult to perform as evidenced by the SPARE trial which closed due to slow accrual (55). Given these circumstances, decision models are an increasingly accepted tool to guide clinical decision making in the field of urologic oncology when trials are not available or possible. Similar models have been developed to guide management in prostate cancer (56) and recurrent HG NMIBC (9).

Our analysis is the most robust evaluation of TMT versus RC for the treatment of muscle invasive bladder cancer to date. Royce and others have previously examined this research question with a decision analysis and demonstrated that TMT resulted in 0.59 more QALYs than RC but with identical unadjusted life years (41). Our analysis however, employs a more detailed modelling approach, necessary to ensure that patient characteristics and treatment options are realistic and reflective of the population and their disease experience. For example, we consider patient level sampling and variability; the potential for complications to develop during the treatment, peri-operative and surveillance phases; and multiple lines of systemic therapy and palliation during the clinical course. These nuances, along with a clinically appropriate cycle length, ensure that the experience is reflective of those from real-world patients. The difference in modelling details helps to explain the difference in QALYs between treatments produced in their paper compared to ours.

Our study demonstrates that the choice between TMT and RC is extremely preference sensitive, with a small shift in preference / utility, changing the recommendation from TMT to RC, or vice versa. As a result, incorporating cost within the model is unlikely to yield further benefit as the resulting incremental cost-effectiveness ratio (ICER) would become very unstable as the difference in effectiveness approaches zero. Given this, we believe the selection of treatment should be based on individual patient factors and their preference in a clinical setting.

Due to the nature of literature comparing the two treatment modalities, our study has some limitations. Stratifying patients by pathological details (presence of CIS, hydronephrosis, clinical tumour stage) would add more granularity to help decide which treatment is best suited for which patient, but insufficient data were available. Moreover, due to the inconsistencies in reporting comorbidities between radiation and surgical papers, the inclusion of comorbidity status was not possible, although age may represent a surrogate. Also, many of our input parameters were obtained from retrospective studies. Although bias is inherent in these studies, we chose values from the highest quality studies where possible. Since much of our current knowledge and clinical practice as it pertains to TMT and RC stems from retrospective studies, our confidence in the model inputs should not be undermined by the retrospective nature of the data.

Conclusions

We demonstrated that in patients with MIBC who are a candidate for either therapy, RC provides slightly longer unadjusted overall survival compared to TMT (0.54 years) but with slightly less quality of life (-0.07 QALYs) of questionable clinical significance. Differences in treatment preference were dependent on age with a larger survival benefit seen in younger patients treated with RC secondary to improved oncologic control. NAC with either TMT or RC provides a meaningful overall survival benefit.

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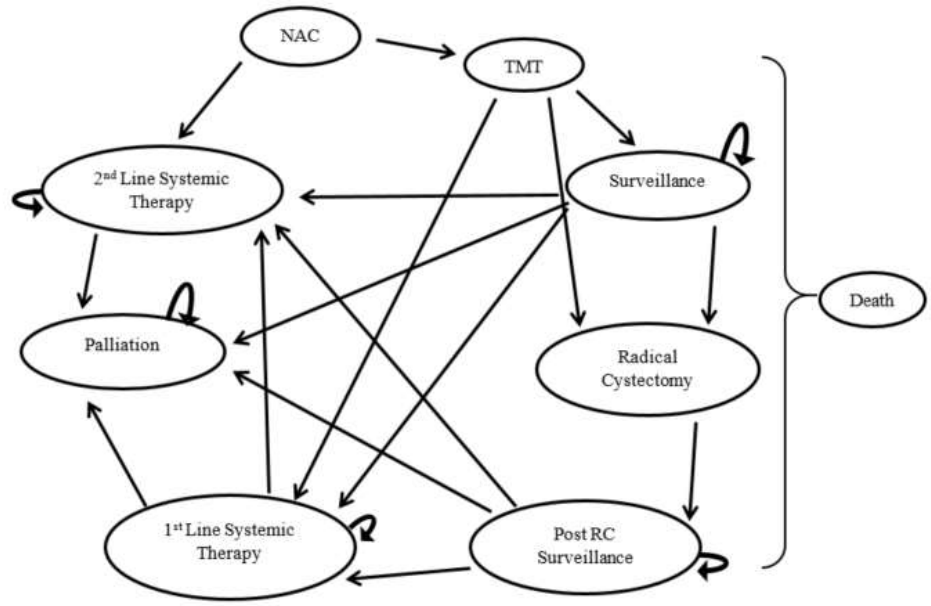
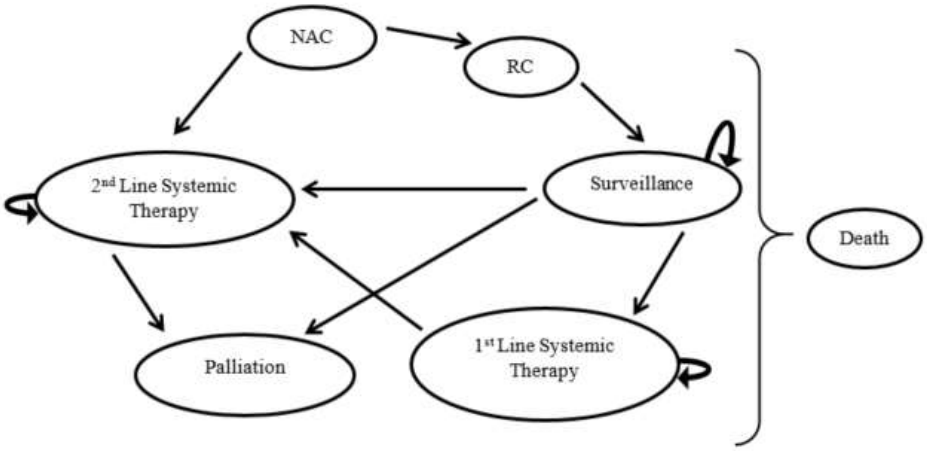
Figures and Tables

Fig. 1. Model schematics depicting state transitions for TMT (A) and RC (B). MIBC: muscle-invasive bladder cancer; NAC: neoadjuvant chemotherapy; RC: radical cystectomy; TMT: trimodal therapy.



A.



B.

Table 1. Model probabilities		
Variable	**Probability**	**Reference**
Neoadjuvant chemotherapy		
Starting proportion of patients in NAC	36%^	Krabbe et al, 2015 (18) Kulkarni et al, 2017 (7)
Death on chemotherapy	1.1%	Winquist et al, 2004 (19)
Completing NAC	90.3%	Zargar et al, 2015 (20)
Adverse event	36.7%	Neidersuss-Beke et al, 2017 (21)
Progression on NAC	3.0%	Galsky et al 2015 (22)
HR for distant recurrence if completed NAC	0.78	ABC meta-analysis Collaboration, 2005 (23)
Radical cystectomy		
Peri-operative mortality	2.4%	Wallace et al, 2018 (24)
Postoperative complication (grade III/IV)	68% (22%)	Parekh et al, 2018 (25)
Complication on surveillance	40% at 2 years*	Shimko et al, 2011 (26)
Composite long-term complication	10% over 1.1 years**	Shimko et al, 2011 (26)
Distant recurrence	38% at 5 years*	Nuhn et al, 2012 (27)
Trimodal therapy		
Complication on treatment (major)	55% (15.5%)	Tunio et al, 2012 (28)
Complete response	75.3%	Fahmy et al, 2018 (29)
Immediate salvage cystectomy	31.8%	Calibrated value
Complication on surveillance	39% over 31 months**	Efstathiou et al, 2009 (30)
Major complication on surveillance	9.58% over 22.1 months**	Efstathiou et al, 2009 (30) and Rodel et al, 2002 (31)
Bladder cancer recurrence	60% over 10 years	Calibrated value
Secondary malignancy	0.7% over 75 months**	Zelefsky et al, 2012 (32)
Distant recurrence on surveillance	28.8% at 5 years	Calibrated value
Complication post salvage cystectomy (grade III/IV)	69% (16%)	Eswara et al, 2012 (33)
Perioperative mortality from salvage cystectomy	2.2%	Eswara et al, 2012 (33)
Composite long-term complication post salvage cystectomy	20% at 1 year*	Knap et al, 2004 (34)

Distant recurrence post-salvage cystectomy		
Immediate salvage cystectomy	22.4% at 2 years*	Eswara et al, 2012 (33)
Delayed salvage cystectomy	16.14% at 2 years*	Eswara et al, 2012 (33)
Systemic therapy		
Eligibility for first line chemotherapy	28% overall – age adjusted	Dash et al, 2006 (15)
Survival on first line cisplatin-based chemotherapy (carboplatin-based)	50% over 14 months** (50% over 9.3 months**)	Von der Maase et al, 2005 (35); De Santis et al, 2012 (16)
Progression on first line cisplatin-based chemotherapy (carboplatin-based)	50% over 7.7 months** (50% over 5.8 months**)	Von der Maase et al, 2005 (35); De Santis et al, 2012 (16)
Receipt of second line systemic therapy after progression on first-line	39.2%	Wang et al, 2017 (36)
Survival on second line systemic therapy:		
Pembrolizumab	50% over 10.3 months**	Bellmunt et al, 2017 (17)
Survival on palliative therapy	50% over 5.3 months**	Smith et al, 2014 (37)
Baseline mortality rates		
Non-bladder specific cancer related mortality	0.7% (adjusted based on gender & age) per year	Calibrated value
HR female	0.78	Williams et al, 2011 (38)
HR age 70–74	1.08	Williams et al, 2011 (38)
HR age 75–79	1.30	Williams et al, 2011 (38)
HR age≥80	1.76	Williams et al, 2011 (38)

*Representative value – created equation from published data (see Appendix). **Time to event probability. ^Average of percentages from Krabbe et al 2015 and Kulkarni et al 2017.

Table 2. Model utilities		
Variable	**(Dis)utility**	**Reference**
Neoadjuvant chemotherapy		
NAC treatment state	0.64	Stevenson et al, 2014 (39)
Adverse Event	-0.17	Stevenson et al, 2014 (39)
Radical cystectomy		
RC postoperative state	0.8	Kulkarni et al, 2007 (9)
Major perioperative complication requiring return to OR	-0.25	Stevenson et al, 2014 (39)
Major perioperative complication	-0.2	Stevenson et al, 2014
Minor perioperative complication	-0.06	Truzzi et al, 2018 (40)
Cystectomy (ileal conduit) surveillance state	0.84	Royce et al, 2018 (41)
Neobladder surveillance state	0.88	Expert opinion
Long-term complication in surveillance state	0.88*	Joshi et al, 2003 (42)
Short-term complication in surveillance state	-0.06	Truzzi et al, 2018 (40)
Trimodal therapy		
TMT treatment state	0.8	Expert opinion
TMT surveillance state	0.91	Royce et al, 2018 (41)
Major treatment complication	-0.274	Tam et al, 2013 (43)
Minor treatment/surveillance complication	-0.06	Truzzi et al, 2018 (40)
BCG	-0.02	Kulkarni et al, 2007 (9)
TURBT	-0.1	Kulkarni et al, 2007 (9)
GI complication requiring OR	0.8*	Expert opinion
Salvage cystectomy utilities	0.8*	
Secondary malignancy	0.84*	Ayvaci et al, 2013 (44)
Progression		
First-line therapy	0.6	Kulkarni et al, 2007 (9)
Second-line therapy	0.5	Aguiar et al, 2017 (45)
Palliative therapy	0.3	Kulkarni et al, 2007 (9)
Death	0	

*Applied as a multiplicative factor to the current state utility.

Table 3. Overall survival (OS) of the simulated results and validation cohorts				
	TMT		**RC**	
Overall survival	**Simulated results**	**External validation**	**Simulated results**	**External validation**
1-year	90.2%	90%[a]	93.5%	90%[a]
3-year	70.7%	70%[a]	69.9%	65%[a]
5-year	58.8%	62%[a]	56.9%	59%[a]
15-year	24.1%	25%[b]	26.7%	30%[c]

[a]Kulkarni et al, 2017(7); [b]Giacalone et al, 2017(46); [c]Zehnder et al. 2011(47).

Table 4. Scenario based analysis varying starting age		
Starting age	**TMT (QALE/LY)**	**RC (QALE/LY)**
45	8.26/11.56	8.45/12.87
55	8.10/11.20	8.13/12.17
65	7.68/10.45	7.57/11.08
75	6.67/8.97	6.41/9.13
80	6.03/8.08	5.69/8.00
85	5.58/7.43	5.19/7.26

LY: life years; QALE: quality adjusted life expectancy.