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APPENDIX

S1.

Supplementary Table 1. Distributions used for sampling patient level characteristics (all 1st order)				
Variable	**Distribution type**	***Mean***	***SD***	***Reference***
Age	Gamma	68.8	10.6	Seisen et al 2017[1]
Gender (male threshold 0.75)	Uniform	0 (LB)	1 (UB)	Cahn et al 2017[2]
Age-related probability of neobladder				
Age<60	Triangular	0.4	±20%	Expert opinion
Age>60	Triangular	0.15	±20%	Expert opinion
Length of major TMT complication	Normal distribution capped at a minimum of 5 days	7.1	4.833	Efstathiou et al 2011[3]

LB: lower bound; SD: standard deviation; UB: upper bound.

S2. Modelling of complications

Complications arising from the treatment of MIBC with either TMT or RC were accounted for in the model.

In the TMT arm, the development of radiation-induced complications, either minor or major (including secondary malignancy[4]), were modelled using representative complications. Severity (major and minor as per Common Terminology Criteria for Adverse Events grading), and systems (GI/GU)-based were considered. Minor complications were modelled using cystitis as the representative condition.[5] Grade 3 complications were modelled as severe lower urinary tract symptoms. Grade 4 complications were either genitourinary (GU) or gastrointestinal (GI) in nature. Patients with a GU complication underwent a salvage cystectomy. Patients with a GI complication were assumed to undergo a laparotomy for small bowel obstruction.[3,6]

In the RC arm, probabilities of perioperative and long-term complications[7-9] were modified based on type of reconstruction (ileal conduit vs. neobladder). Short-term complications in the surveillance arm following RC were a composite measure of pyelonephritis, upper tract stones, and bowel obstruction.[7,10] Long-term complications were modelled using ureteric stricture as the representative complication.[7,10]

S3. Assumptions

Several assumptions were made in the creation of this decision analysis. The completion of neoadjuvant chemotherapy (NAC) was defined as receiving at least three of four cycles. We assumed that patients who did not complete NAC did not modify their risk of distant recurrence. Patients who did not complete their NAC and did not go on to have definitive management (TMT or RC) were assumed to have disease progression.[11] No increase in perioperative complications was modelled for patients who received NAC, as this is not supported in the literature.[12] Ureteric strictures were selected as the representative, long-term complication in the post-cystectomy state. Strictures represent a chronic condition requiring frequent intervention (stent/nephrostomy tube changes) and are affected by both primary and salvage cystectomy, as well as reconstruction choice.[7,9] Only ileal conduits were constructed in the case of a salvage cystectomy. All patients requiring a salvage cystectomy in the TMT arm were assumed to still be candidates for surgical intervention. All cystectomies were assumed to be open, rather than laparoscopic or robotic. Response to systemic therapies (first- and second-line) were the same regardless of primary treatment. Secondary malignancy risk after TMT was modelled only as colon cancer (rather than cervical cancer or sarcoma) based on prostate cancer studies since secondary malignancy risk following TMT has not been explored in the literature.[4]

S4. Derivation of probabilities

Recurrence-free survival (RFS) does not decrease in a linear fashion, as would be modelled using the standard rate to probability conversion functions in TreeAge. Therefore, we elected to use a Weibull function to more appropriately mimic the Kaplan-Meier curves for RFS following RC (lambda: 0.226, gamma: 0.333) and following immediate salvage cystectomy (lambda: 0.074, gamma: 0.794), as depicted from the published data.[13,14]

To create transition probabilities that appropriately represented the cumulative events curve of complications following cystectomy,[7] and the cumulative recurrence probability following delayed salvage cystectomy,[14] the data from the Kaplan-Meier curves in the original papers were graphed in Excel. Using those data points, a line of best fit was created (Supplementary Figs. 1, 2), which demonstrated a logarithmic function. This formula was then used to create the transition probability for each Markov cycle. This table was then imported into TreeAge and referenced at the appropriate point in the tree.

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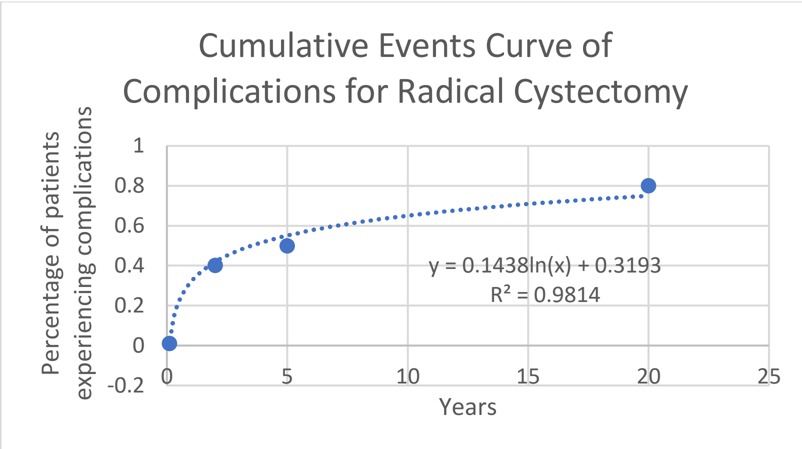
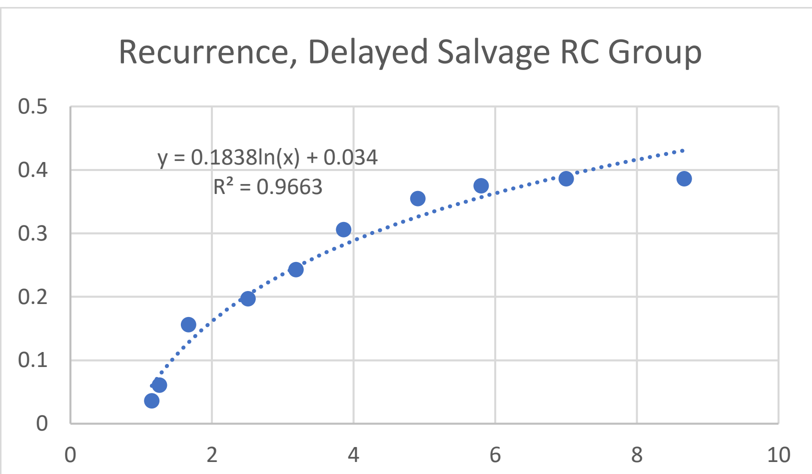
Supplementary Fig. 1. Cumulative events curve of overall complications following RC. Equation for line of best fit and R^2 value displayed.



Supplementary Fig. 2. Cumulative recurrence probability over time following delayed salvage cystectomy. Equation for line of best fit and R^2 value displayed.



S5. Calibration

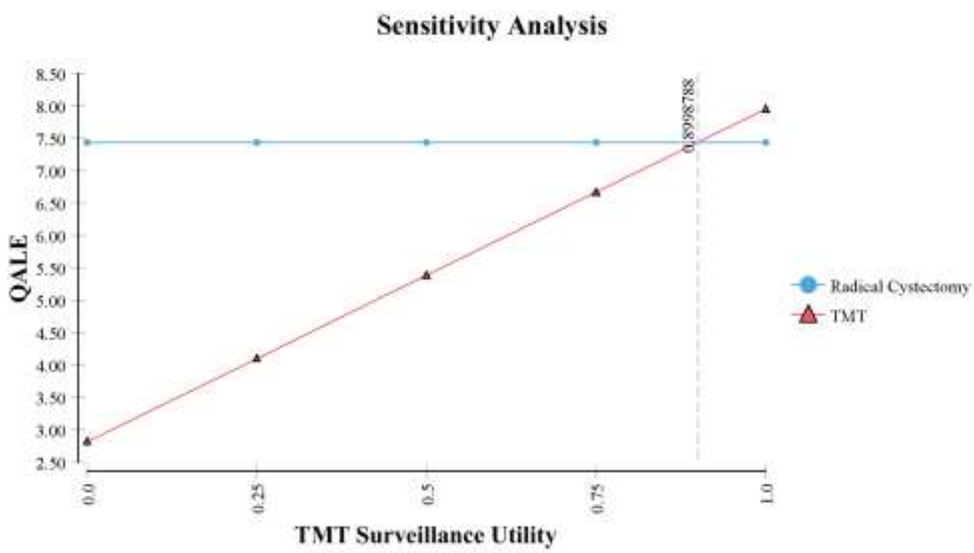
Model calibration is the systematic adjustment of model inputs such that the resulting model better reflects setting specific observed disease outcomes. Model calibration is especially useful when there are limited or non-existent data on transition probabilities within a certain clinical context, but disease endpoint data are available.[15] Calibration requires identifying the model inputs to be calibrated, the target that the model is aiming for, implementing an appropriate parameter search strategy, and assessing for the goodness of fit of the calibrated values.

The background non-bladder cancer mortality rate was calibrated using the two- and 10-year overall survival (OS) as targets. In the TMT arm, probability of proceeding to immediate salvage cystectomy following incomplete TMT response, probability of developing a distant recurrence on surveillance, and probability of developing a non-muscle-invasive bladder cancer were similarly calibrated using the salvage cystectomy rate and two- and 10-year OS as targets. Latin hypercube sampling was used as the search method for calibration values. Euclidian distance calculations were then used to develop a goodness of fit (GOF) score. The lowest GOF score, that corresponded to clinically plausible values, was used to determine the final set of calibrated values to be used as transition probabilities.

S6. Sensitivity analyses

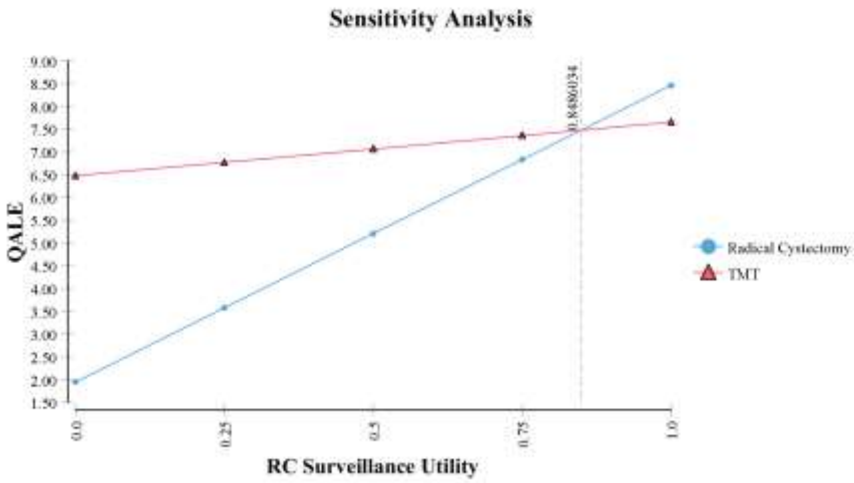
Several sensitivity analyses were conducted to determine the impact of certain key inputs on the preferred base case results. In Supplementary Fig. 3, the influence of the TMT surveillance utility value in the was evaluated in a deterministic, one-way sensitivity analysis.

Supplementary Fig. 3. One-way sensitivity analysis evaluating TMT surveillance utility. Threshold at 0.899, below which RC offers improved quality-adjusted life expectancy. Current base case TMT surveillance utility is 0.91.



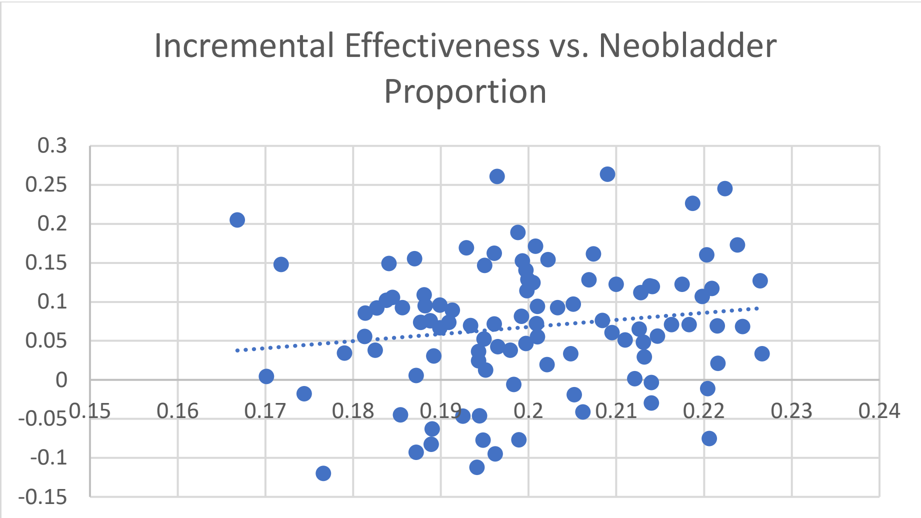
Sensitivity analyses were conducted also to determine if the use of neobladders in the RC could impact the effectiveness of the model. At first, a one-way sensitivity analysis was conducted on the utility values in the RC arm. The RC arm became the preferred arm when the surveillance utilities in the RC surpassed 0.848 (base case ileal conduit utility of 0.84 and neobladder utility of 0.88) (Supplementary Fig. 4).

Supplementary Fig. 4. One-way sensitivity analysis evaluating RC surveillance utility. Threshold at 0.848, below which RC offers worse quality-adjusted life expectancy. Current base case RC with ileal conduit is 0.84 and with neobladder is 0.88.



Therefore, a further analysis was completed to determine the impact of neobladder use on effectiveness. A scatterplot was created to investigating how incremental effectiveness changes when the proportion of neobladders was increased within clinically plausible ranges. The results of the graph show that while the slope of the line is shallow, the change in incremental effectiveness is quite meaningful, compared to the QALE outputs from the model. This graph indicates that increasing use of neobladders improves effectiveness scores, which is in keeping with the findings from the one-way sensitivity analysis above. The large variability seen within the incremental effectiveness is due to the other contributing variables within the model, illustrating that while neobladder use plays a role in improving quality of life, quality of life remains an extremely preference-sensitive decision for each individual.

Supplementary Fig. 5. Incremental effectiveness versus proportion of patients receiving a neobladder.



S6. Modelling of complications and supplementary results

Complications arising from the treatment of MIBC with either TMT or RC were accounted for in the model.

In the TMT arm, the development of radiation-induced complications, either minor or major (including secondary malignancy[4]), were modelled using representative complications. Severity (major and minor as per Common Terminology Criteria for Adverse Events grading), and systems (GI/GU)-based were considered. Minor complications were modelled using cystitis as the representative condition.[5] Grade 3 complications were modelled as severe lower urinary tract symptoms. Grade 4 complications were either genitourinary (GU) or gastrointestinal (GI) in nature. Patients with a GU complication underwent a salvage cystectomy. Patients with a GI complication were assumed to undergo a laparotomy for small bowel obstruction.[3,6]

In the RC arm, probabilities of perioperative and long-term complications[7-9] were modified based on type of reconstruction (ileal conduit vs. neobladder). Short-term complications in the surveillance arm following RC were a composite measure of pyelonephritis, upper tract stones, and bowel obstruction.[7,10] Long-term complications were modelled using ureteric stricture was the representative complication.[7,10]

The overall incidence of complications during surveillance in the TMT arm was 44.3% and 38.9% in the RC arm.

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