Trimodal Therapy vs. Radical Cystectomy for Muscle Invasive Bladder Cancer
A Markov Microsimulation Model

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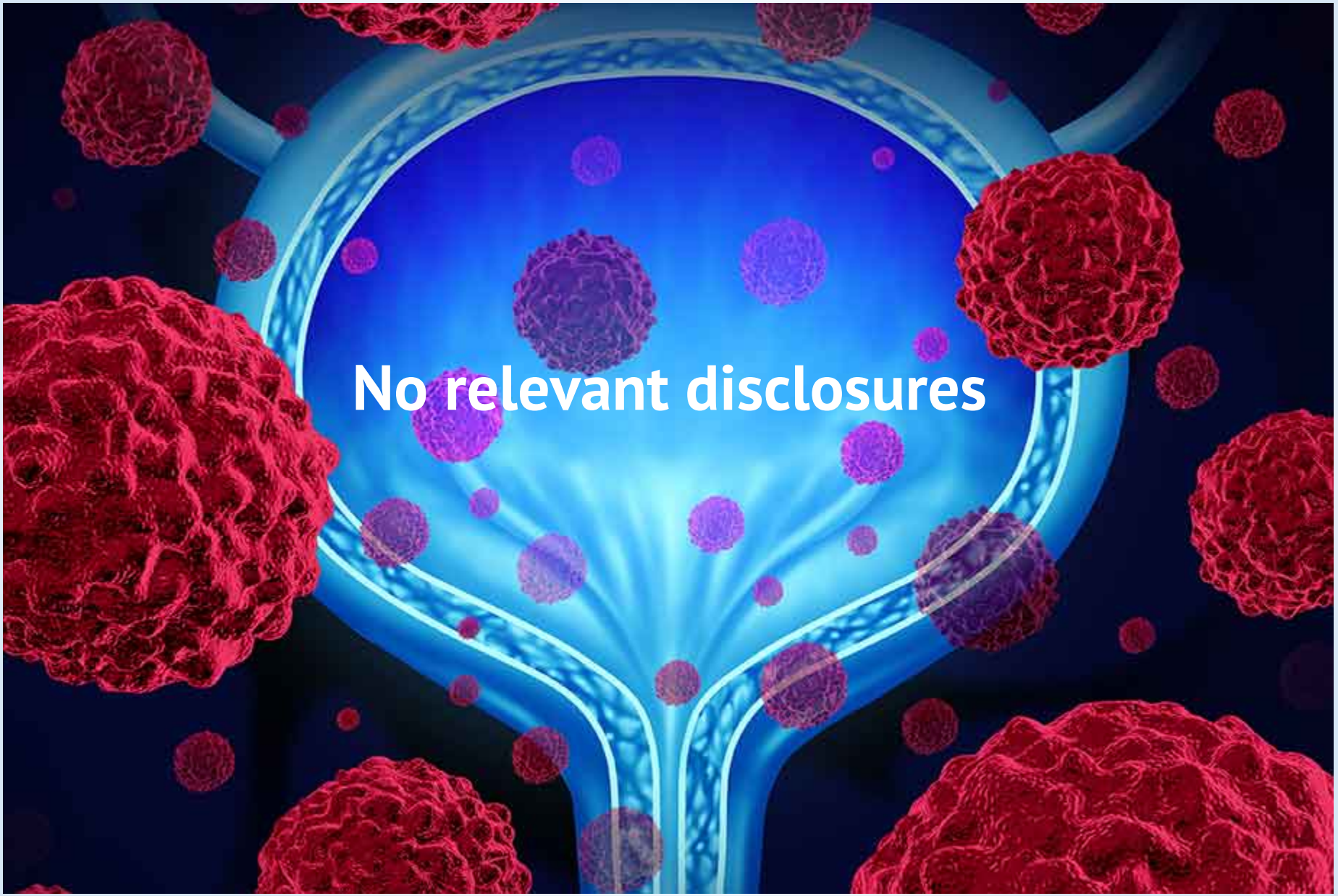

No relevant disclosures

Background

- Radical cystectomy (RC) remains widely accepted as the gold standard treatment for muscle invasive bladder cancer (MIBC)
- This surgery however, is highly invasive and may lead to significant morbidity and deterioration in quality of life
- Bladder sparing strategies have therefore emerged as an option for appropriately selected patients
- Trimodal therapy (TMT) entails a debulking resection of the tumour, chemotherapy for radiation sensitization and external beam radiation therapy
  - This allows patients to keep their native bladder but to treat the primary tumour

Background

- Head to head trials in this setting are difficult to complete, as evidenced by a failed randomized controlled trial
- Therefore, we elected to perform a decision analysis investigating TMT vs. RC

Research Question

Among appropriately selected patients with MIBC, does treatment with TMT result in similar oncological outcomes with improved quality of life?

Study Design

- Microsimulation Markov Model created using TreeAge Pro
- Comparators: TMT vs. RC
- Outcomes: QALYs, Overall Survival (OS)
- Dynamic Cycle Length: Varying from 3-12 months
- Time Horizon: Lifetime
- Discount Rate: 1.5% within cycle correction

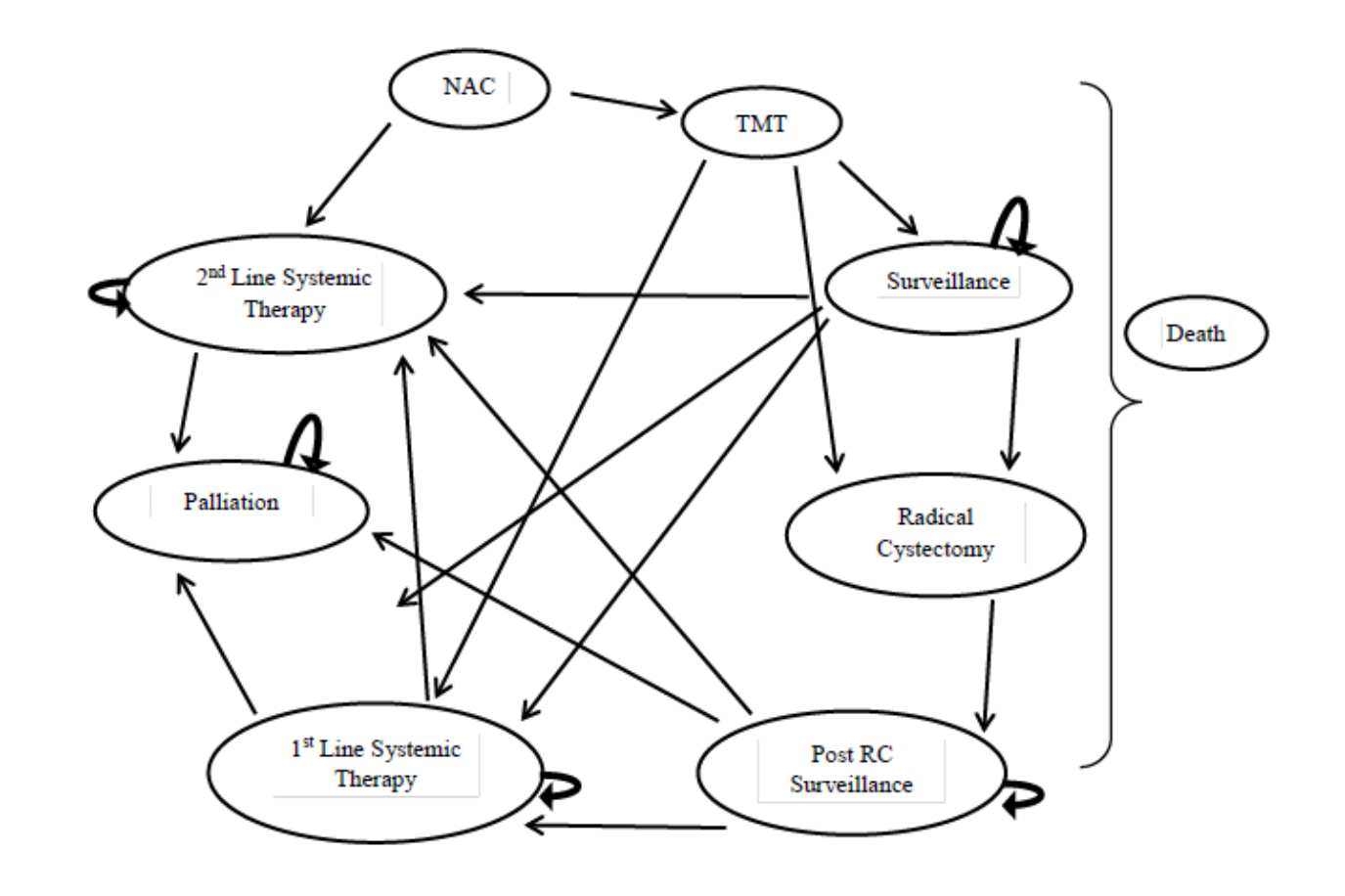
Base Case

- Adult patient with MIBC appropriate for either RC or TMT (pT2-4 N0 M0)
- Individual level sampling completed for:

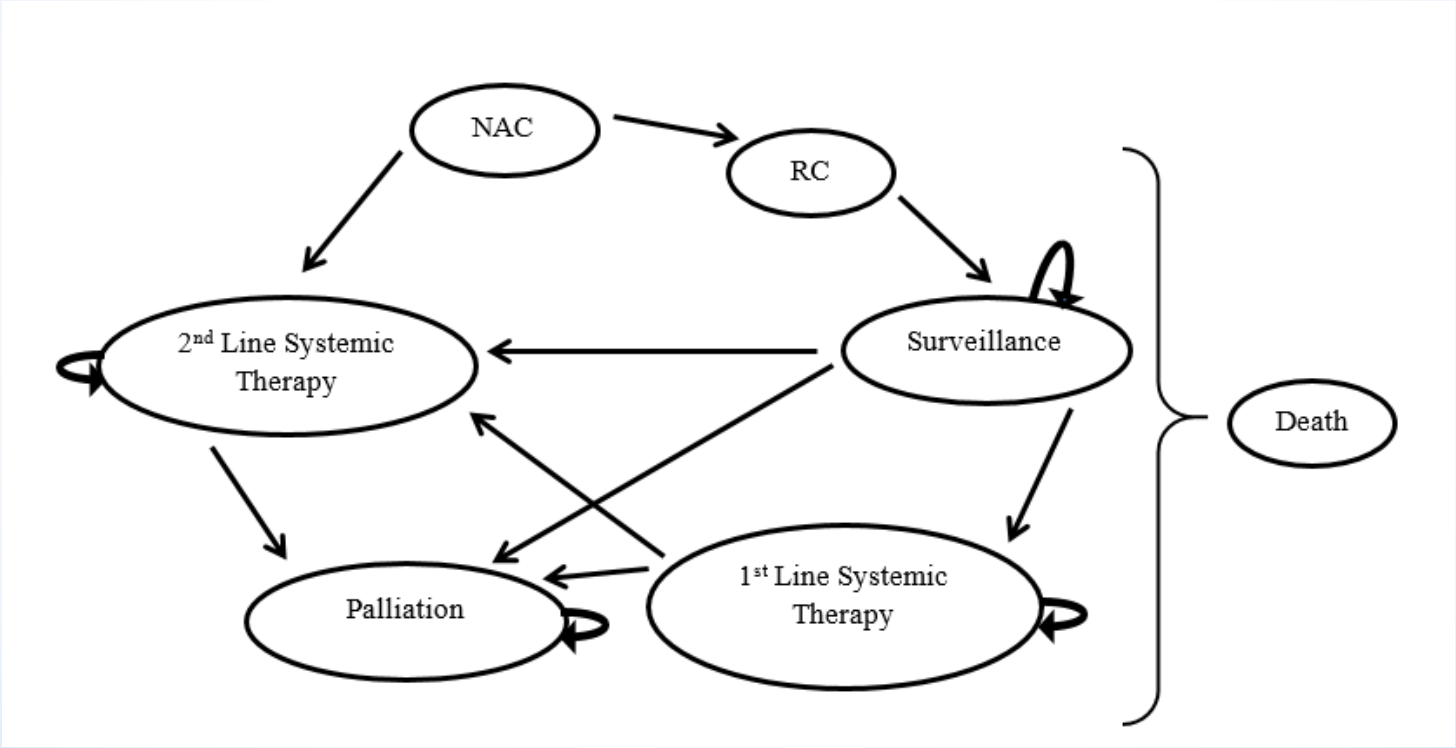
Variable	Distribution Type	Mean or LB	SD or UB	Reference
Age	Gamma	68.8	10.6	Seisen et al 2017
Gender (% Male)	Uniform	0	0.75	Cahn et al 2017
Age related probability of neobladder				
Age<60	Triangular	0.4	±20%	Expert Opinion
Age>60	Triangular	0.15	±20%	Expert Opinion
Length of major TMT complication	Normal with minimum at 5	7.1	4.833	Efstathiou et al 2011

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

Model Schematic – TMT



Model Schematic – RC



Methods

- Transition probabilities were determined from a MEDLINE literature search as of March 1, 2019, supplemented with a hand search and expert consultation
- Utilities were obtained using the Tufts-New England Medical Center Cost Effectiveness Analysis registry and using a manual search of published urology decision models

Data Inputs

Probabilities	Modifications
Baseline Mortality Rate	Modified by gender and age
Probability of Peri-Operative Morality	Modified by age
Probability of Long Term Post Cystectomy Complications	Modified by presence of neobladder, primary or salvage cystectomy
Probability of Distant Recurrence (both TMT and RC)	Modified by completion of NAC
Probability of Distant Recurrence Post Salvage Cystectomy	Modified by whether RC was immediate (due to incomplete TMT response) or delayed
Probability of receiving 1st line systemic therapy	Influenced by age which influenced the likelihood of having renal function appropriate for cisplatin based therapy

Calibration and Validation

- Latin Hypercube Sampling completed and GOF scores calculated using Euclidian distances
- Internal model validity assessed by checking face validity of results and placement of internal trackers
- External validity assessed by evaluating the model's ability to reproduce overall survival rates, disease specific survival and absolute benefit derived from NAC

Results

- 50,000 inner loop samples with 10 outer loop samples were run
- Base case results:
  - TMT was the preferred modality with a mean quality-adjusted life expectancy of 7.49 (95% CI: 6.89-7.86) versus 7.41 (95% CI: 6.95-7.86) for RC
  - However, life expectancy for patients treated with TMT was lower (10.21 years, 95% CI: 9.3-10.7) compared to RC (10.74 years, 95% CI: 10.0-11.4).

Base Case Results and Validation

Overall Survival	TMT Model Cohort	TMT Validation Cohort	RC Model Cohort	RC Validation Cohort
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, G.S., et al., *Propensity Score Analysis of Radical Cystectomy Versus Bladder-Sparing Trimodal Therapy in the Setting of a Multidisciplinary Bladder Cancer Clinic.* J Clin Oncol, 2017. **35**(20): p. 2299-2305. b. Giacalone, N.J., et al., *Long-term Outcomes After Bladder-preserving Tri-modality Therapy for Patients with Muscle-invasive Bladder Cancer: An Updated Analysis of the Massachusetts General Hospital Experience.* Eur Urol, 2017. **71**(6): p. 952-960. c. Zehnder, P., et al., *Super extended versus extended pelvic lymph node dissection in patients undergoing radical cystectomy for bladder cancer: a comparative study.* J Urol, 2011. **186**(4): p. 1261-8.

Scenario Based Analysis

Overall Survival (OS)	OS with NAC	OS without NAC	Absolute OS Benefit
Trimodal Therapy			
5 Year	60.4%	57.9%	2.5%
Radical Cystectomy			
5 Year	59.2%	55.6%	3.6%
5 year absolute OS from published meta-analyzed data is 5%[a]			

a. Advanced Bladder Cancer Meta-analysis, C., *Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration.* Eur Urol, 2005. **48**(2): p. 202-5; discussion 205-6.

Scenario Based Analysis

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

QALE: quality adjusted life expectancy; LY: life years

Conclusion

- RC provides slightly better overall survival however, the average quality of life associated with each life year is lower for those patients
- The younger patients are, the more likely they are to benefit from the oncological control derived from RC
- NAC in either RC or TMT provides a meaningful OS benefit

Questions?

Key Assumptions

- Completion of NAC defined as receiving at least 3 of 4 cycles
- Response to systemic therapies (first and second line) was the same regardless of primary treatment
- First line systemic therapy was modelled as cisplatin – eligibility for this was modelled based on GFR
- Pembrolizumab was modelled as second line therapy for patients who met inclusion criteria
  - Otherwise, for patients who were ineligible for pembrolizumab modelled as gemcitabine/carboplatin