Trimodal therapy vs. radical cystectomy for muscle-invasive bladder cancer: A Canadian cost-effectiveness analysis

Ronald Kool[*1], *Ivan Yanev*[*1], *Tarek Hijal*[2], *Marie Vanhuyse*[3], *Fabio L. Cury*[1,2], *Luis Souhami*[2], *Wassim Kassouf*[1], *Alice Dragomir*[1]

[1]Division of Urology, McGill University Health Centre, McGill University, Montreal, QC, Canada; [2]Division of Radiation Oncology, McGill University Health Centre, Montreal, QC, Canada; [3]Division of Medical Oncology, McGill University Health Centre, McGill University, Montreal, QC, Canada

[*]*Equal contributors*

Cite as: Kool R, Yanev I, Hijal T, et al. Trimodal therapy vs. radical cystectomy for muscle-invasive bladder cancer: A Canadian cost-effectiveness analysis. *Can Urol Assoc J* 2022;16(6):189-98. http://dx.doi.org/10.5489/cuaj.7430

Published online January 27, 2022

Abstract

Introduction: Trimodal therapy (TMT) is a suitable alternative to neoadjuvant chemotherapy (NAC) and radical cystectomy (RC) for patients with muscle-invasive bladder cancer (MIBC). In this study, we conducted a cost-effectiveness evaluation of RC±NAC vs. TMT for MIBC in the universal and publicly funded Canadian healthcare system.

Methods: We developed a Markov model with Monte-Carlo microsimulations. Rates and probabilities of transitioning within different health states (e.g., cure, locoregional recurrence, distant metastasis, death) were input in the model after a scoped literature review. Two main scenarios were considered: 1) academic center; and 2) populational-level. Results were reported in life-years gained (LYG), quality-adjusted life years (QALY), and incremental cost-effectiveness ratio (ICER). A sensitivity analysis was performed.

Results: A total of 20 000 patients were simulated. For the academic center model, TMT was associated with increased effectiveness (both in LYG and QALY) at a higher cost compared to RC±NAC at five and 10 years. This resulted in an ICER of $19 746/QALY per patient undergoing the TMT strategy at 10 years of followup. For the populational-level model, RC±NAC was associated with higher effectiveness at 10 years, with an ICER of $3319/QALY per patient. This study was limited by heterogeneity within the studies used to build the model.

Conclusions: In this study, TMT performed in academic centers was cost-effective compared to RC±NAC, with higher effectiveness at a higher cost. On the other hand, RC±NAC was considered cost-effective compared to TMT at the populational-level. Further studies are needed to confirm these results.

Introduction

On a per-patient basis from diagnosis to death, bladder cancer is an expensive malignancy to treat, and costs associated with its management have been rising continuously in the last decades.[1] Muscle-invasive bladder cancer (MIBC) is the initial diagnosis in 25% of bladder cancer patients and is associated with higher rates of progression to metastatic disease, which contributes to a significant proportion of the economic burden of the disease.

Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) and pelvic lymph node dissection (PLND) is a current standard of care for MIBC.[2] Trimodal therapy (TMT) consists of a maximal transurethral resection of the bladder tumor (TURBT) followed by curative-intent radiation therapy and concurrent chemotherapy. TMT has emerged as a suitable bladder-sparing alternative for properly selected patients or for those who refuse RC or are deemed non-surgical candidates.[3] While no randomized controlled trials have successfully been performed to compare both approaches, retrospective series of patients treated with TMT at high-volume academic centers have shown oncological outcomes comparable to RC.[4,5] In addition, RC appears to be associated with better long-term survival compared to TMT at the populational level when adjusted for age, comorbidities, and clinical tumor stage.[6,7]

In the light of increasing appeal for bladder preservation, we performed a cost-effectiveness analysis to compare RC±NAC vs. TMT from a healthcare system perspective in Canada regarding oncological outcomes, effectiveness, and costs at both the academic center and the populational level.

Methods

Model design

Two Markov models were built using Monte-Carlo microsimulation for a pre-set maximum period of 10 years, divided into 40 cycles of three months each: the academic center model and the populational-level model. Health states were established to simulate the journey of MIBC patients treated with either RC±NAC (open technique) vs. TMT. Patients experiencing disease relapse transitioned to other health states according to further management ("intravesical therapy," "salvage RC," "first-line chemotherapy," or "second-line immunotherapy") before eventual "palliative care" and "death" from bladder cancer or from other causes. A simplified version of both models is shown (Figure 1).

Treatment response rates and probabilities of transitioning between health states were input in the model after a scoped literature review of MEDLINE through PubMed using the following MeSH terms: "urinary bladder neoplasms," "urothelial cell carcinoma," "cystectomy," "combined modality therapy," "systemic therapy;" and keywords: "muscle-invasive bladder cancer," "radical cystectomy," "neoadjuvant chemotherapy," "trimodality," "trimodal therapy," "chemoradiation," "systemic therapy," "immunotherapy." Relevant studies with confirmatory references were selected (Table 1).

For the academic center model, oncological outcomes for TMT were retrieved from studies performed at high-volume academic institutions. For the populational-level model, probabilities were taken from larger studies that typically included both community and academic centers. Specific parameters not available in population-based studies were kept unchanged in both models.

Modeling assumptions for RC±NAC

To incorporate a survival benefit from NAC, an absolute increase of 5–7% in disease-free survival (DFS) rates at five and 10 years was applied only to a proportion of patients undergoing RC, according to the study by Griffiths et al.[8] Since salvage curative options for locoregional recurrences after RC±NAC (e.g., surgical resection, radiotherapy) are limited, these patients in our model were managed with first-line systemic chemotherapy (or palliative care if not eligible).

Modeling assumptions for TMT

For the TMT strategy, radiation consisted of 50 Gy delivered through intensity-modulated radiation therapy in 20 daily fractions of 2.5 Gy each (hypofractionated protocol). After TMT, residual non-muscle invasive bladder cancer (NMIBC) was managed with TURBT plus adjuvant intravesical bacillus Calmette-Guérin (BCG), with six weekly instillations for six consecutive weeks (induction) followed by three weekly instillations at three, six, and 12 months (maintenance). The one-year BCG maintenance schedule was chosen instead of three years (as per guideline recommendation for high-risk NMIBC) due to the low compliance of patients when recommended for the full protocol (35%), as reported in the literature.[9]

A significant proportion of patients is unfit for salvage RC after TMT failure. As a result, patients with locoregional MIBC (persistent or recurrent) who were deemed non-surgical candidates were managed with systemic first-line chemotherapy or best supportive care.[10]

Modeling assumptions for metastatic disease and palliative care

Local but unresectable disease or distant metastasis in our model was managed with first-line cisplatin- or carboplatin-based chemotherapy.[11] Progression after first-line chemotherapy was managed with second-line immunotherapy.[12] In Canada, pembrolizumab is the main immunotherapy option for patients with metastatic bladder cancer and can

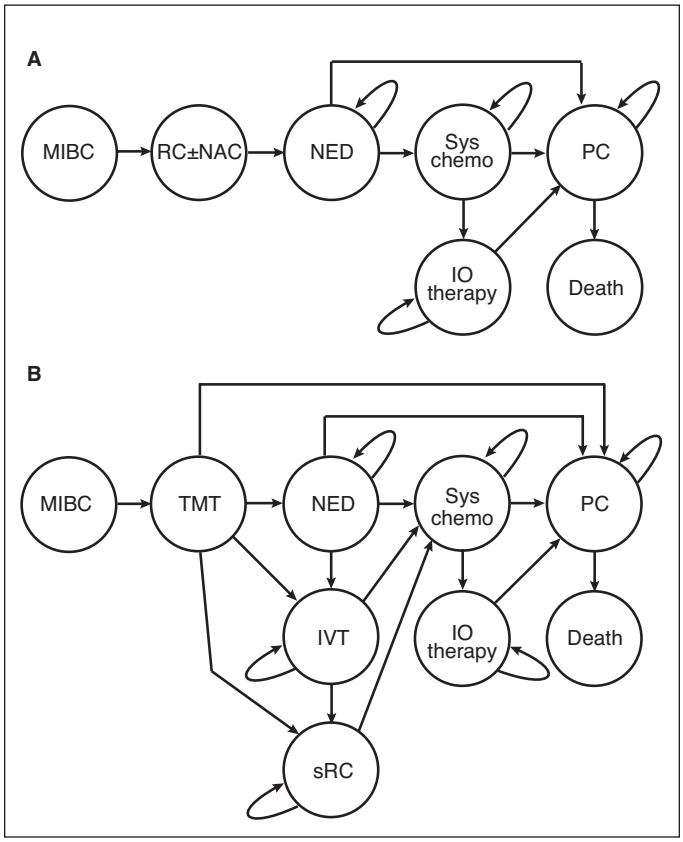

Figure. 1. Simplified Markov models for **(A)** radical cystectomy (RC) ± neoadjuvant chemotherapy (NAC); and **(B)** trimodal therapy (TMT). Arrows represent transitions between health states. Patients can transition from every state to death (arrows were omitted for graphic simplicity). IO: immuno-oncology; IVT: intravesical therapy; MIBC: muscle-invasive bladder cancer; NED: no evidence of disease; PC: palliative care; sRC: salvage radical cystectomy; Sys Chemo: systemic chemotherapy.

Table 1. Rates and probabilities input in the Markov model

Radical cystectomy			
Rates and probabilities	**Base case**	**References**	**Confirmatory base case**
Proportion of patients receiving NAC			
Academic centers	49%	Hermans et al[32]	57%[33]
Population-level	27%	Booth et al[34]	–
NAC regimen			
ddMVAC	39%	Galsky et al[35]	–
Gemcitabine + cisplatin	61%	Galsky et al[35]	–
90-day mortality from RC (±NAC)			
Academic centers	3.2%	Yafi et al[36]	3.7%[8]
Populational-level	7.2%	Waingankar et al[37]	–
RFS after RC±NAC			
5 years	83.6%	Culp et al[23]	69.5%[38]
10 years	79.6%†	Culp et al[23]	65.5%[38]
OS after RC (±NAC)			
Academic centers			
5 years	68.3%	Culp et al[23]	57%[39]
10 years	49.0%	Culp et al[23]	45%[39]
Population-level			
5 years	43.5%	Seisen et al[6]	40.1%[31]
10 years	24.1%	Seisen et al[6]	21.5%[31]
Other-cause mortality after RC			
Academic centers			
5 years	18.4%	Culp et al[23]	13.3
10 years	35.1%	Culp et al[23]	22.5[38]
Population-level			
5 years	19.6%	Williams et al[31]	18.0%[40]
10 years	35.4%	Williams et al[31]	33.3%[40]
Trimodal therapy			
Rates and probabilities	**Base case**	**References**	**Confirmatory references**
Complete response after TMT	75%	Giacalone et al[4]	69–72%[5,10]
Death from TMT	0.24%	Rodel et al[10]	0%[4]
Residual disease after TMT	25%	Giacalone et al[4]	28–31%[5,10]
Residual NMIBC	18.2%	Rodel et al[10]	–
Residual MIBC	81.8%	Rodel et al[10]	–
sRC rates	31%	Giacalone et al[4]	20–21%[10]
90-day mortality from sRC	2.2%	Eswara et al[41]	–
Residual disease post-TMT – no treatment	41.4%	Giacalone et al[4]	54.4%[10]

*Pembrolizumab. †Additional 4% decrease in PFS from 5–10 years was applied using results from Hautmann et al.[38] CHT: chemotherapy; CIS: cisplatin; CR: complete response; GEM: gemcitabine; IVT: intravesical therapy; MIBC: muscle-invasive bladder cancer; NAC: neoadjuvant chemotherapy; NMIBC: non-muscle-invasive bladder cancer; OS: overall survival;PFS: progression-free survival; RC: radical cystectomy; RFS: recurrence-free survival; sRC: salvage radical cystectomy; TMT: trimodal therapy; TURBT: transurethral resection of the bladder tumor.

Table 1 (cont'd). Rates and probabilities input in the Markov model

Trimodal therapy (cont'd)			
Rates and probabilities	**Base case**	**References**	**Confirmatory base case**
Recurrence rates after CR			
NMIBC			
5 years	26%	Giacalone et al[4]	31%[5]
10 years	26%	Giacalone et al[4]	36%[5]
MIBC			
5 years	16%	Giacalone et al[4]	13%[5]
10 years	18%	Giacalone et al[4]	14%[5]
Distant metastasis			
5 years	44%	Giacalone et al[4]	44%[5]
10 years	49%	Giacalone et al[4]	51%[5]
Management of NMIBC recurrence after CR			
RFS after IVT (3y)	59%	Sanchez et al[42]	–
sRC rate post-IVT	70%	Zietman et al[43]	40.9%[42]
Management of MIBC recurrence after CR			
sRC	82.4%	Rodel et al[10]	–
1st-line chemotherapy	17.6%	Rodel et al[10]	–
RFS after immediate sRC			
5 years	58.6%	Eswara et al[41]	51%[4]
10 years	28.2%	Eswara et al[41]	32%[4]
RFS after delayed sRC			
5 years	64.5%	Eswara et al[41]	64%[4]
10 years	61.1%	Eswara et al[41]	64%[4]
OS after TMT			
Academic centers			
5 years	75%	Giacalone et al[4]	57%[5]
10 years	67%	Giacalone et al[4]	36%[5]
Population-level			
5 years	35%	Seisen et al[6]	23.5%[31]
10 years	16%	Seisen et al[6]	7.8%[31]
Other-cause mortality after TMT			
Academic centers			
5 years	9%	Giacalone et al[4]	–
10 years	20%	Giacalone et al[4]	20%[22]
Population-level			
5 years	23.8%	Williams et al[31]	–
10 years	32.9%	Williams et al[31]	–

*Pembrolizumab. †Additional 4% decrease in PFS from 5–10 years was applied using results from Hautmann et al.[38] CHT: chemotherapy; CIS: cisplatin; CR: complete response; GEM: gemcitabine; IVT: intravesical therapy; MIBC: muscle-invasive bladder cancer; NAC: neoadjuvant chemotherapy; NMIBC: non-muscle-invasive bladder cancer; OS: overall survival;PFS: progression-free survival; RC: radical cystectomy; RFS: recurrence-free survival; sRC: salvage radical cystectomy; TMT: trimodal therapy; TURBT: transurethral resection of the bladder tumor.

be delivered for a maximum period of two years if responses are sustained. More recently, switch maintenance therapy with avelumab was approved in Canada for patients with any response or stable disease after first-line chemotherapy, with a significant benefit in both progression-free (PFS) and

Table 1 (cont'd). Rates and probabilities input in the Markov model

Systemic disease			
Rates and probabilities	**Base case**	**References**	**Confirmatory base case**
1st-line CHT	74.3%	Bamias et al[11]	–
Cisplatin-based	62.5%	Bamias et al[11]	72.6[44]
Carboplatin-based	37.5%	Bamias et al[11]	27.4[44]
PFS on 1st-line CHT – 1 year			
GEM/CIS	26.4%	Dogliotti et al[45]	–
GEM/Carboplatin	18.5%	Dogliotti et al[45]	–
OS on 1st—line CHT – 1 year			
GEM/CIS	63.7%	Dogliotti et al[45]	58.4%[46]
GEM/Carboplatin	37.5%	Dogliotti et al[45]	37.0%[47]
PFS on 2nd-line systemic therapy* – 1 year	18.2%	Fradet et al[12]	20.7%[48]
OS on 2nd-line systemic therapy* – 1 year	44.2%	Fradet et al[12]	39.2%[48]
OS on palliative care – 2 years	7%	Bellmunt et al[49]	6%[50]

*Pembrolizumab. †Additional 4% decrease in PFS from 5–10 years was applied using results from Hautmann et al.[38] CHT: chemotherapy; CIS: cisplatin; CR: complete response; GEM: gemcitabine; IVT: intravesical therapy; MIBC: muscle-invasive bladder cancer; NAC: neoadjuvant chemotherapy; NMIBC: non-muscle-invasive bladder cancer; OS: overall survival;PFS: progression-free survival; RC: radical cystectomy; RFS: recurrence-free survival; sRC: salvage radical cystectomy; TMT: trimodal therapy; TURBT: transurethral resection of the bladder tumor.

overall survival (OS).[13] This strategy was integrated in sensitivity analysis (Table 2).

Palliative care consisted of the combination of an interdisciplinary approach (e.g., nutritionist, physiotherapist, psychologist), palliative surgery (e.g., emergency surgeries, endourological procedures), and end-of-life management.[14] In our model, patients experiencing failure of previous lines of treatment or those unfit for further therapies underwent palliative care before death. Patterns, parameters, and costs of palliative care were defined using the Canadian study by de Oliveira et al (Table 3).[14] In this study, costs were based on the median amount spent within the last 12 months of life and were reflective of services, mostly palliative, delivered to this specific population.

Utilities and costs

Utilities of 0.84 and 0.91 were set for patients with no evidence of disease after RC±NAC and TMT, respectively.[15] For the metastatic setting, utilities of 0.64 and 0.62 were used for the first- or second-line (and palliative care) settings, respectively.[16] Costs were retrieved from the *Régie d'Assurance Maladie du Québec* (RAMQ) and reported in 2019 Canadian dollars (CAD).

Model calibration and sensitivity analysis

The Markov model was tested and calibrated on OS and PFS, using the built-in feature of TreeAge Pro Healthcare 2020 (TreeAge Software®, Inc, Williamstown, MA, U.S.). This calibration tool was carried over with the microsimulation analysis using the BOBYQA algorithm to minimize potential errors, using an e^{-10} relative and an e^{-13} absolute optimization threshold.[17] The BOBYQA has the advantage of being less sensitive to local minimums in the optimization process compared to other algorithms.[17]

A sensitivity analysis was performed on key parameters (discounting rates, proportion of patients receiving NAC before RC, absolute benefit of NAC on DFS rates before RC, potential use of NAC before TMT, different NAC regimens, different radiation protocols, use of switch maintenance avelumab after first-line chemotherapy, death rates for patients on palliative care, and palliative care costs) to assess for potential impacts on final model results.

Results

Academic center model

After microsimulation of 20 000 patients, OS was 66% and 44% at five and 10 years for RC±NAC, and 68% and 42% at five and 10 years for TMT at academic centers, respectively. As a result, incremental effectiveness of 0.13 life-years gained (LYG) favoring the TMT approach was reported at 10 years. Regarding effectiveness in terms of quality-adjusted life years (QALY) at five and 10 years, RC±NAC was associated with 3.35 and 5.33, while TMT was associated with 3.63 and 5.68 QALY, respectively. As a result, an increment of 0.35 QALY at 10 years favored the TMT strategy.

Mean costs per patient associated with RC±NAC vs. TMT were $29 992 (95% confidence interval [CI] 29 576–30 408) vs. $30 266 (95% CI 29 806–30 726) at five years and $33 286 (95% CI 32 798–33 774) vs. $40 197 (95% CI 39 571–40 823) at 10 years, respectively. In comparison with RC±NAC, TMT had incremental cost-effectiveness ratios (ICERs) of $979/QALY and $19 746/QALY at five and 10 years, respectively.

Populational-level model

For the populational level, parameters on perioperative mortality, the proportion of patients undergoing NAC in the RC±NAC arm, rates of other-cause mortality, and PFS were modified in the model. In addition, the model was then further calibrated for OS. Mean cost per patient for RC±NAC vs. TMT at five years was of $38 382 (95% CI 37 798–38 966) vs. $39 304 (95% CI 38 678–39 930) at five years and of $47 391 (95% CI 46 673–48 109) vs. $45 541 (95% CI

Table 2. Sensitivity analysis on incremental costs, QALY, and ICERs at 10 years

Variables and variations	Incremental cost†	Incremental QALYS	Favorable strategy	TMT vs. RC ICER
Base case (10y)				
Academic centers	$6911	0.35	TMT	$19 746
Population-level	-$1850	-0.56	RC	$3319
Discount rate				
Academic centers				
0%	$7463	0.15	TMT	$51 469
3%	$5072	0.38	TMT	$13 436
5%	$4589	0.30	TMT	$15 556
Population-level				
0%	-$796	-0.58	RC	$1378
3%	-$411	-0.43	RC	$950
5%	-$1424	-0.42	RC	$3431
% of NAC (RC modality)				
Academic centers				
0%	$8090	0.48	TMT	$16 942
27%	$6821	0.42	TMT	$16 436
57%	$6351	0.33	TMT	$19 245
Population-level				
0%	$1060	-0.39	RC	Dominated
27%	-$1850	-0.56	RC	$3319
57%	-$2923	-0.47	RC	$6219
NAC regimen (RC modality)				
Academic centers				
31% ddMVAC/69% Gem-Cis	$5742	0.43	TMT	$13 353
21% ddMVAC/79% Gem-Cis	$6541	0.37	TMT	$17 560
41% ddMVAC/59% Gem-Cis	$4950	0.40	TMT	$12 375
Population-level				
31% ddMVAC/69% Gem-Cis				
21% ddMVAC/79% Gem-Cis	-$837	-0.45	RC	$1860
41% ddMVAC/59% Gem-Cis	-$772	-0.52	RC	$1485
DFS benefit after NAC				
Academic centers				
3%	$12 927	0.39	TMT	$33 576
5%	$13 036	0.32	TMT	$40 111
NAC included as option before TMT				
Academic centers	$11 634	0.41	TMT	$28 726
Population-level	$2995	-0.43	RC	Dominated
Radiation protocol with 64G (32 fractions)				
Academic centers	$9979	0.39	TMT	$25 919
Population-level	$3743	-0.46	RC	Dominated
Utilities				
Academic centers				
80%	$6569	0.28	TMT	$23 461
90%	$6634	0.35	TMT	$19 091
110%	$5544	0.39	TMT	$14 215
120%	$6724	0.43	TMT	$15 637

Costs in Canadian dollars (CAD); ‡Canadian dollars/QALY per patient; increment = TMT – RC. ddMVAC: dose-dense combination of methotrexate, vinblastine, adriamycin, and cisplatin; DFS: disease-free survival; Gem-Cis: combination of gemcitabine and cisplatin; ICER: incremental cost-effectiveness ratio; NAC: neoadjuvant chemotherapy; QALY: quality-adjusted life years; RC: radical cystectomy; TMT: trimodal therapy.

Table 2 (cont'd). Sensitivity analysis on incremental costs, QALY, and ICERs at 10 years

Variables and variations	Incremental cost[†]	Incremental QALYS	Favorable strategy	TMT vs. RC ICER[‡]
Utilities (cont'd)				
Population -level				
80%	-$321	-0.40	RC	$813
90%	-$533	-0.40	RC	$1333
110%	-$1608	-0.55	RC	$2950
120%	-$1112	-0.84	RC	$1320
Avelumab switch maintenance				
Academic centers	$8262	0.36	TMT	$22 950
Palliative care cost				
Academic centers				
80%	$5561	0.39	TMT	$14 168
90%	$6013	0.35	TMT	$17 058
110%	$6382	0.39	TMT	$16 577
120%	$6038	0.37	TMT	$16 542
Population-level				
80%	-$1551	-0.49	RC	$3165
90%	-$1061	-0.49	RC	$2165
110%	-$477	-0.52	RC	$926
120%	$644	-0.48	RC	Dominated
Palliative care death rate				
Academic centers				
80%	$6180	0.34	TMT	$18 311
90%	$6424	0.31	TMT	$20 557
110%	$5544	0.39	TMT	$14 125
120%	$6724	0.38	TMT	$17 931
Population-level				
80%	-$968	-0.45	RC	$2163
90%	-$780	-0.52	RC	$1493
110%	-$345	-0.43	RC	$812
120%	-$436	-0.44	RC	$985

Costs in Canadian dollars (CAD); [‡]Canadian dollars/QALY per patient; increment = TMT – RC. ddMVAC: dose-dense combination of methotrexate, vinblastine, adriamycin, and cisplatin; DFS: disease-free survival; Gem-Cis: combination of gemcitabine and cisplatin; ICER: incremental cost-effectiveness ratio; NAC: neoadjuvant chemotherapy; QALY: quality-adjusted life years; RC: radical cystectomy; TMT: trimodal therapy.

44 831–46 251) at 10 years, respectively. RC±NAC was the dominant strategy at five years, while associated with ICER of $3319/QALY at 10 years, compared to TMT at the populational level. Results are further detailed in Table 4.

Sensitivity analysis

Sensitivity analysis is reported in Table 2. In summary, higher effectiveness for the TMT strategy at higher costs was consistently demonstrated at academic centers, with ICERs ranging from $12 375/QALY to $51 469/QALY. On the other hand, RC±NAC was associated with higher effectiveness compared to TMT at 10 years, with ICERs ranging from $812 to $6219 at the populational level. Additionally, sensitivity analysis showed that RC±NAC would become the dominant strategy (higher effectiveness and lower costs) in the following scenarios: no NAC for both strategies; if NAC was delivered before TMT; if palliative care costs were increased by 20%; or if conventional fractionation (rather than hypofractionation) was used for the TMT strategy.

Discussion

Using a comprehensive Markov model with microsimulation built with studies performed at academic centers, TMT was cost-effective compared to RC±NAC, with an ICER of $19 746/QALY per patient at 10 years. On the other hand, RC±NAC was associated with increased effectiveness and an ICER of $3 319/QALY at the populational level.

Oncological outcomes and effectiveness

Historically, TMT has been mainly offered to MIBC patients who were deemed non-surgical candidates due to advanced age, limiting comorbidities, and poor performance status.[18] In Canada, this pattern seems to be currently shifting, as an

increasing proportion of surgical candidates are now being referred to medical and radiation oncologists to be considered for bladder preservation.[19] The only study designed to randomize patients to RC vs. TMT (SPARE trial) was prematurely closed due to poor accrual.[20] Therefore, any attempt to compare outcomes for these two approaches is limited by retrospective design, heterogeneity, and selection bias.

In 2017, Kulkarni et al matched 112 patients who underwent RC or TMT in a propensity score analysis using main clinicopathological factors.[21] This study demonstrated comparable OS and disease-specific survival for both strategies.[21] Additionally, a large meta-analysis on retrospective studies (mainly from academic centers) by Fahmy et al supported TMT as a suitable alternative to RC with comparable survival outcomes.[22] Using population-based data, others suggested that long-term survival rates might be inferior for TMT compared with RC±NAC.[6,7]

Our study reinforces the comparable effectiveness of TMT vs. RC±NAC at academic centers, mimicking a scenario where patients are strictly selected. TMT was associated with a slightly improved OS rate at five years, while long-term survival at 10 years favored RC±NAC. The study by Giacalone et al was the main source of parameters input in our TMT model, which resulted in the high effectiveness for TMT.[4] In that study, patients treated in the most recent era (after 2005) were mostly cT2 stage (97%), with 88% achieving a complete response and a five-year OS of 75%. To compare TMT using this cohort of patients with favorable disease with surgery, parameters were mainly extracted from the study by Culp et al, particularly the subset of low-risk MIBC patients who underwent upfront RC without NAC and experienced a five-year OS of 64.8%.[23] Given the results of these two pivotal studies, effectiveness in our model was higher for TMT compared to RC±NAC in the academic setting.

In addition, although a benefit from NAC in DFS was applied to RC patients (7%), NAC was not included in the base case for the TMT strategy in our study, as its systematic use is still under discussion.[24] Nevertheless, sensitivity analysis showed that in a scenario with NAC being given to TMT patients with similar proportions and chemotherapy regimens (drugs, doses, number of cycles) as preceding RC, the difference of costs would be higher for TMT in comparison to RC±NAC at academic centers, with an ICER of $28 726/QALY. Moreover, considering a potential lower effect of NAC in cT2 patients compared to cT3-4a or cN+ patients, sensitivity analysis with a benefit of 3% and 5% in terms of DFS at 10 years showed that TMT would be still cost-effective compared to RC±NAC, with a higher ICER compared to the base case (Table 2).

Perhaps the most appealing benefit of TMT consists of a positive impact on the quality of life of patients who can retain their native bladder. Using a Markov model, Royce et al have shown comparable effectiveness (in LYG) between TMT and RC±NAC, with an increment of up to 1.61 QALY favoring TMT during a predefined period of 33 years, showing the higher quality of life perceived by patients undergoing bladder preservation.[15,25] In our model, an incremental gain of up to 0.35 QALY was reported for TMT at 10 years in the academic centers, while for patients treated at the populational level, a better quality of life for TMT did not compensate for lower OS and effectiveness in LYG. These results suggest the impact in the quality of life for TMT compared to RC±NAC might be optimized in appropriately selected patients with more favorable disease.

Previous RC series have shown lower surgical complication rates and improved oncological outcomes for patients operated at high-volume centers.[26,27] Although there are no such studies on TMT, the main oncological outcomes reported in the academic setting seem to outperform the ones reported at the populational level, similarly to RC.[4,6] Williams et al have shown that TMT was associated with worse OS compared to RC, particularly for patients treated with radiation delivered in less than <27 fractions.[28] Importantly, the definition of curative bladder preservation (TMT) was challenging since doses of chemotherapy and radiotherapy were not available in the

Table 3. Costs associated with MIBC management

Procedure	Unit cost[†]
TURBT	$1872
NAC	
ddMVAC	$3600 (per cycle)
Gemcitabine + Cisplatin	$808 (per cycle)
Radical cystectomy	$19 409 (Santos et al[51])
Radiotherapy	$5558 (per treatment)
Concurrent chemotherapy	
Gemcitabine	$362 (per cycle)
Cisplatin	$534 (per cycle)
5FU + MMC	$993 (per cycle)
Followup	
Consultation	$48
Imaging	$1144
Laboratory	$25
Cystoscopy	$350
Urine cytology	$92
Intravesical therapy	
BCG	$237 (per dose)
Chemotherapy	
Gemcitabine + Cisplatin	$4846 (per treatment)
Gemcitabine + Carboplatin	$2342 (per treatment)
Immunotherapy (pembrolizumab)	$8800 (per dose)
Palliative care (until death)	$10 271 (de Oliveira et al[14])

[†]Costs presented in Canadian dollars (CAD) and retrieved from the "Liste de médicament - Régie d'assurance maladie du Québec (RAMQ)" or the Pharmacy department at the McGill University Health Center, Montreal, QC. BCG: bacillus Calmete-Guérin; ddMVAC: dose-dense methotrexate + vinblastine + adriamycin + cisplatin; MMC: mitomycin; NAC: neoadjuvant chemotherapy; TURBT: transurethral resection of bladder tumor; 5FU: 5-flouracil.

Table 4. Comparison of effectiveness, costs, and oncological outcomes between RC±NAC and TMT

Parameters	Academic center			Population-level		
	RC±NAC	TMT	Increment (TMT – RC±NAC)	RC±NAC	TMT	Increment (TMT – RC±NAC)
LYG						
5 years	4.00	4.15	+0.15	3.43	3.11	-0.32
10 years	6.40	6.53	+0.13	4.88	4.16	-0.72
QALY						
5 years	3.35	3.63	+0.28	2.80	2.60	-0.20
10 years	5.33	5.68	+0.35	4.02	3.46	-0.58
Costs†						
5 years	$29 99	$30 266	$274	$38 382	$39 304	$922
10 years	$33 2862	$40 197	$6911	$47 391	$45 541	-$1850
OS (%)						
5 years	66.0	68.0	+2.0	44.0	34.0	-10.0
10 years	44.0	42.0	-2.0	24.0	17.0	-7.0
PFS (%)						
5 years	62.0	62.0	0.0	36.0	27.0	-9.0
10 years	42.0	39.0	+3.0	22.0	15.0	-7.0

†Costs presented in Canadian dollars (CAD); mean cost per patient. LYG: life-years gained; NAC: neoadjuvant chemotherapy; OS: overall survival; PFS: progression-free survival; QALY: quality-adjusted life-years; RC: radical cystectomy.

Surveillance, Epidemiology, and End Results (SEER) database, leading to a proportion of patients possibly treated with palliative rather than curative-intent radiation-based therapy.[28] Another large populational study by Seisen et al showed that TMT was an independent factor for worse long-term OS compared to RC (hazard ratio [HR] 1.37; p<0.001), although this difference was not significant among older patients.[6] Granular data on baseline predictors of outcomes for TMT was unavailable in this study (e.g., completeness of initial TURBT, use of concurrent chemotherapy), which might have negatively impacted the outcomes for TMT.[6]

Although these comparisons at the populational level were adjusted for main clinicopathological factors (e.g., age, cT stage, comorbidities), important residual confounders were not accounted for, such as completeness of TURBT, presence of lymphovascular invasion/carcinoma in situ, radiation and concurrent chemotherapy protocols, and use of salvage RC. In addition, other confounders may play a role, such as the subjective impression of patients (e.g., frailty, performance status, preferences), physicians' personal beliefs when offering surgery vs. radiation-based therapy, academic vs. community centers' experience, and non-standardized protocols and institutional practices. Although limited by selection bias, our populational model was built on studies published in high-impact journals, and our results were also reflective of the inferior OS and effectiveness for TMT observed at the populational level.

Cost-effectiveness

To the best of our knowledge, this is the first cost-effectiveness study comparing RC±NAC vs. TMT for MIBC outside the U.S. The study by Williams et al was based on SEER, a well-recognized populational data source in the U.S.[28] The authors of that study showed that TMT was associated with a significantly higher cost per patient after one year of diagnosis (additional $136 935) and an estimation of US$468 million in excess for TMT in comparison to RC, considering the total U.S. population treated in the year 2017.[28] While recent studies suggest comparable oncological outcomes of TMT in Canada,[29] the health systems in these countries are different in many ways, and studies have demonstrated that general costs in the U.S. are mainly derived from medication and administrative expenses.[30]

In our study, differences in costs associated with RC±NAC and TMT were significantly lower if compared to the U.S. As a result, when effectiveness was incorporated in the analysis, TMT was found to be cost-effective in Canada at academic centers. At the populational level, surgery was the dominant strategy at five years and slightly more expensive at 10 years. Importantly, the higher mean cost for RC±NAC at 10 years might be explained not only by the initial cost of the surgery (Table 3) but also by significantly higher rates of other-cause mortality and lower OS, which prevented patients from undergoing surveillance and further therapies in the TMT model (e.g., systemic therapy, salvage RC, palliative care) compared to RC±NAC.

Limitations

Our Markov model considered health states from the initial treatment until death, which resulted in significant granularity. Rates and probabilities were retrieved from different studies published in different eras, based on different populations, interventions, and methodologies, ultimately leading

to heterogeneity and selection bias. Moreover, parameters related to TMT were taken from retrospective studies. To minimize the effect of significant and inevitable heterogeneity and optimize the model's precision, we sought to select studies performed at high-volume academic centers and compare these parameters with confirmatory references whenever possible. Moreover, the model was calibrated on main oncological outcomes and a sensitivity analysis, including key variables that could potentially impact our base-case results, was performed.

For the populational-level model, limitations were even more pronounced. Several rates and probabilities, particularly DFS and PFS, were not available from population-based studies, and the model was therefore calibrated only on OS. Despite the potential impact of older age and comorbidities among TMT patients at the populational level, rates were taken from studies in which both populations were balanced. Seisen et al reported lower OS rates for TMT with median age of 69.0 and 68.8 years for TMT and RC patients, respectively (standardized difference=2.1), while Charlson Comorbidity Index was ≥2 in 8.5% and 6.9%, respectively (standardized difference=5.9).[6] In addition, the study by Williams et al reported similar proportion of patients in different age groups (66–69, 70–74, 75–79, and 80) and number of comorbidities among TMT and RC patients.[31]

Conclusions

TMT was found cost-effective compared to RC±NAC when patients are better selected and when performed at academic centers, with an estimated ICER of $19 746/QALY. On the other hand, RC±NAC was cost-effective at the populational level, with an estimated ICER of $3319/QALY at 10 years. These results might contribute to planning bladder cancer management in the future.

Competing interests: Dr. Cury reports conflicts of interest from Abbvie, Bayer, Boston Scientific, Sanofi, and Varian Medical Systems. Dr. Souhami reports conflicts of interest from Abbvie and Varian Medical Systems. The remaining authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

References

1. Yeung C, Dinh T, Lee J. The health economics of bladder cancer: An updated review of the published literature. *Pharmacoeconomics* 2014;32:1093-104. https://doi.org/10.1007/s40273-014-0194-2
2. Kulkarni GS, Black PC, Sridhar SS, et al. Canadian Urological Association guideline: Muscle-invasive bladder cancer. *Can Urol Assoc J* 2019;13:230-8. https://doi.org/10.5489/cuaj.5902
3. El-Achkar A, Souhami L, Kassouf W. Bladder preservation therapy: Review of literature and future directions of trimodal therapy. *Curr Urol Rep* 2018;19:108. https://doi.org/10.1007/s11934-018-0859-z
4. Giacalone NJ, Shipley WU, Clayman RH, et al. Long-term outcomes after bladder-preserving trimodality therapy for patients with muscle-invasive bladder cancer: An updated analysis of the Massachusetts General Hospital experience. *Eur Urol* 2017;71:952-60. https://doi.org/10.1016/j.eururo.2016.12.020
5. Mak RH, Hunt D, Shipley WU, et al. Long-term outcomes in patients with muscle-invasive bladder cancer after selective bladder-preserving combined-modality therapy: A pooled analysis of Radiation Therapy Oncology Group protocols 8802, 8903, 9506, 9706, 9906, and 0233. *J Clin Oncol* 2014;32:3801-9. https://doi.org/10.1200/JCO.2014.57.5548
6. Seisen T, Sun M, Lipsitz SR, et al. Comparative effectiveness of trimodal therapy vs. radical cystectomy for localized muscle-invasive urothelial carcinoma of the bladder. *Eur Urol* 2017;72:483-7. https://doi.org/10.1016/j.eururo.2017.03.038
7. Cahn DB, Handorf EA, Ghiraldi EM, et al. Contemporary use trends and survival outcomes in patients undergoing radical cystectomy or bladder-preservation therapy for muscle-invasive bladder cancer. *Cancer* 2017;123:4337-45. https://doi.org/10.1002/cncr.30900
8. Griffiths G, Hall R, Sylvester R, et al. International, phase 3 trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: Long-term results of the BA06 30894 trial. *J Clin Oncol* 2011;29:2171-7. https://doi.org/10.1200/JCO.2010.32.3139
9. Tapiero S, Helfand A, Kedar D, et al. Patient compliance with maintenance intravesical therapy for non-muscle-invasive bladder cancer. *Urology* 2018;118:107-13. https://doi.org/10.1016/j.urology.2018.04.039
10. Rodel C, Grabenbauer GG, Kuhn R, et al. Combined-modality treatment and selective organ preservation in invasive bladder cancer: Long-term results. *J Clin Oncol* 2002;20:3061-71. https://doi.org/10.1200/JCO.2002.11.027
11. Bamias A, Tzannis K, Harshman LC, et al. Impact of contemporary patterns of chemotherapy utilization on survival in patients with advanced cancer of the urinary tract: A Retrospective International Study of Invasive/Advanced Cancer of the Urothelium (RISC). *Ann Oncol* 2018;29:361-9. https://doi.org/10.1093/annonc/mdx692
12. Fradet Y, Bellmunt J, Vaughn DJ, et al. Randomized, phase 3 KEYNOTE-045 trial of pembrolizumab vs. paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: Results of > 2 years of followup. *Ann Oncol* 2019;30:970-6. https://doi.org/10.1093/annonc/mdz127
13. Powles T, Park SH, Voog E, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. *N Engl J Med* 2020;383:1218-30. https://doi.org/10.1056/NEJMoa2002788
14. de Oliveira C, Pataky R, Bremner KE, et al. Phase-specific and lifetime costs of cancer care in Ontario, Canada. *BMC Cancer* 2016;16:809. https://doi.org/10.1186/s12885-016-2835-7
15. Mak KS, Smith AB, Eidelman A, et al. Quality of life in long-term survivors of muscle-invasive bladder cancer. *Int J of Radiat Oncol Biol Phys* 2016;96:1028-36. https://doi.org/10.1016/j.ijrobp.2016.08.023
16. Stevenson SM, Danzig MR, Ghandour RA, et al. Cost-effectiveness of neoadjuvant chemotherapy before radical cystectomy for muscle-invasive bladder cancer. *Urol Oncol* 2014;32:1172-7. https://doi.org/10.1016/j.urolonc.2014.05.001
17. Powell MJD. "The BOBYQA algorithm for bound constrained optimization without derivatives." Cambridge NA Report NA2009/06, University of Cambridge, Cambridge. 2009.
18. Gray PJ, Fedewa SA, Shipley WU, et al. Use of potentially curative therapies for muscle-invasive bladder cancer in the United States: Results from the National Cancer Data Base. *Eur Urol* 2013;63:823-9. https://doi.org/10.1016/j.eururo.2012.11.015
19. Wei X, Siemens DR, Mackillop WJ, et al. Use of radiotherapy for bladder cancer: A population-based study of evolving referral and practice patterns. *Can Urol Assoc J* 2019;13:92-101. https://doi.org/10.5489/cuaj.5447
20. Huddart RA, Birtle A, Maynard L, et al. Clinical and patient-reported outcomes of SPARE — a randomized feasibility study of selective bladder preservation vs. radical cystectomy. *BJU Int* 2017;120:639-50. https://doi.org/10.1111/bju.13900
21. Kulkarni GS, Hermanns T, Wei Y, 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;35:2299-305. https://doi.org/10.1200/JCO.2016.69.2327
22. Fahmy O, Khairul-Asri MG, Schubert T, et al. A systematic review and meta-analysis on the oncological long-term outcomes after trimodality therapy and radical cystectomy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer. *Urol Oncol* 2018;36:43-53. https://doi.org/10.1016/j.urolonc.2017.10.002
23. Culp SH, Dickstein RJ, Grossman HB, et al. Refining patient selection for neoadjuvant chemotherapy before radical cystectomy. *J Urol* 2014;191:40-7. https://doi.org/10.1016/j.juro.2013.07.061
24. Royce TJ, Liu Y, Milowsky MI, et al. Trimodality therapy with or without neoadjuvant chemotherapy for muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2021;19:362-8 https://doi.org/10.1016/j.clgc.2021.03.007
25. Royce TJ, Feldman AS, Mossanen M, et al. Comparative effectiveness of bladder-preserving tri-modality therapy vs. radical cystectomy for muscle-invasive bladder cancer. *Clin Genitourin Cancer* 2019;17:23-31.e3. https://doi.org/10.1016/j.clgc.2018.09.023

26. Nielsen ME, Mallin K, Weaver MA, et al. Association of hospital volume with conditional 90-day mortality after cystectomy: An analysis of the National Cancer Data Base. *BJU Int* 2014;114:46-55. https://doi.org/10.1111/bju.12566
27. Scarberry K, Berger NG, Scarberry KB, et al. Improved surgical outcomes following radical cystectomy at high-volume centers influence overall survival. *Urol Oncol* 2018;36:308.e11-7. https://doi.org/10.1016/j.urolonc.2018.03.007
28. Williams SB, Shan Y, Ray-Zack MD, et al. Comparison of costs of radical cystectomy vs. trimodal therapy for patients with localized muscle-invasive bladder cancer. *JAMA Surg* 2019;154:e191629. https://doi.org/10.1001/jamasurg.2019.1629
29. Kool R, Marcq G, Busca I, et al. PD60-01 definitive radiation-based therapy for muscle-invasive bladder cancer: The Canadian multicenter experience. *J Urol* 2020;203:e1273. https://doi.org/10.1097/JU.0000000000000977.01
30. Papanicolas I, Woskie LR, Jha AK. Health care spending in the United States and other high-income countries. *JAMA* 2018;319:1024-39. https://doi.org/10.1001/jama.2018.1150
31. Williams SB, Shan Y, Jazzar U, et al. Comparing survival outcomes and costs associated with radical cystectomy and trimodal therapy for older adults with muscle-invasive bladder cancer. *JAMA Surg* 2018;153:881-9. https://doi.org/10.1001/jamasurg.2018.1680
32. Hermans TJN, Fransen van de Putte EE, Horenblas S, et al. Perioperative treatment and radical cystectomy for bladder cancer — a population-based trend analysis of 10 338 patients in the Netherlands. *Eur J Cancer* 2016;54:18-26. https://doi.org/10.1016/j.ejca.2015.11.006
33. El-Gehani F, North S, Ghosh S, et al. Improving the outcome of patients with muscle-invasive urothelial carcinoma of the bladder with neoadjuvant gemcitabine/cisplatin chemotherapy: A single-institution experience. *Can Urol Assoc J* 2014;8:e287-93. https://doi.org/10.5489/cuaj.1643
34. Booth CM, Karim S, Brennan K, et al. Perioperative chemotherapy for bladder cancer in the general population: Are practice patterns finally changing? *Urol Oncol Sem Orig Invest* 2018;36:89.e13-20. https://doi.org/10.1016/j.urolonc.2017.11.015
35. Galsky MD, Pal SK, Chowdhury S, et al. Comparative effectiveness of gemcitabine plus cisplatin vs. methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer. *Cancer* 2015;121:2586-93. https://doi.org/10.1002/cncr.29387
36. Yafi FA, Aprikian AG, Chin JL, et al. Contemporary outcomes of 2287 patients with bladder cancer who were treated with radical cystectomy: A Canadian multicentre experience. *BJU Int* 2011;108:539-45. https://doi.org/10.1111/j.1464-410X.2010.09912.x
37. Waingankar N, Mallin K, Smaldone M, et al. Assessing the relative influence of hospital and surgeon volume on short-term mortality after radical cystectomy. *BJU Int* 2017;120:239-45. https://doi.org/10.1111/bju.13804
38. Hautmann RE, de Petriconi RC, Pfeiffer C, et al. Radical cystectomy for urothelial carcinoma of the bladder without neoadjuvant or adjuvant therapy: Long-term results in 1100 patients. *Eur Urol* 2012;61:1039-47. https://doi.org/10.1016/j.eururo.2012.02.028
39. Grossman HB, Natale RB, Tangen CM, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859-66. https://doi.org/10.1056/NEJMoa022148
40. Bekelman JE, Handorf EA, Guzzo T, et al. Radical cystectomy vs. bladder-preserving therapy for muscle-invasive urothelial carcinoma: Examining confounding and misclassification bias in cancer observational comparative effectiveness research. *Value Health* 2013;16:610-8. https://doi.org/10.1016/j.jval.2013.01.005
41. Eswara JR, Efstathiou JA, Heney NM, et al. Complications and long-term results of salvage cystectomy after failed bladder sparing therapy for muscle-invasive bladder cancer. *J Urol* 2012;187:463-8. https://doi.org/10.1016/j.juro.2011.09.159
42. Sanchez A, Wszolek MF, Niemierko A, et al. Incidence, clinicopathological risk factors, management, and outcomes of non-muscle-invasive recurrence after complete response to trimodality therapy for muscle invasive bladder cancer. *J Urol* 2018;199:407-15. https://doi.org/10.1016/j.juro.2017.08.106
43. Zietman AL, Grocela J, Zehr E, et al. Selective bladder conservation using transurethral resection, chemotherapy, and radiation: Management and consequences of Ta, T1, and Tis recurrence within the retained bladder. *Urology* 2001;58:380-5. https://doi.org/10.1016/S0090-4295(01)01219-5
44. Robinson AG, Wei X, Vera-Badillo FE, et al. Palliative chemotherapy for bladder cancer: Treatment delivery and outcomes in the general population. *Clin Genitourin Cancer* 2017;15:e535-e41. https://doi.org/10.1016/j.clgc.2016.12.025
45. Dogliotti L, Carteni G, Siena S, et al. Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: Results of a randomized phase 2 trial. *Eur Urol* 2007;52:134-41. https://doi.org/10.1016/j.eururo.2006.12.029
46. von der Maase H, Sengelov L, Roberts JT, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. *J Clin Oncol* 2005;23:4602-8. https://doi.org/10.1200/JCO.2005.07.757
47. De Santis M, Bellmunt J, Mead G, et al. Randomized phase 2/3 trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. *J Clin Oncol* 2012;30:191-9. https://doi.org/10.1200/JCO.2011.37.3571
48. Powles T, Duran I, van der Heijden MS, et al. Atezolizumab vs. chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): A multicenter, open-label, phase 3 randomized controlled trial. *Lancet* 2018;391:748-57. https://doi.org/10.1016/S0140-6736(17)33297-X
49. Bellmunt J, Theodore C, Demkov T, et al. Phase 3 trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. *J Clin Oncol* 2009;27:4454-61. https://doi.org/10.1200/JCO.2008.20.5534
50. Flannery K, Cao X, He J, et al. Survival rates and healthcare costs for patients with advanced bladder cancer treated and untreated with chemotherapy. *Clin Genitourin Cancer* 2018;16:e909-17. https://doi.org/10.1016/j.clgc.2018.03.002
51. Santos F, Dragomir A, Zakaria AS, et al. Predictors of costs associated with radical cystectomy for bladder cancer: A population-based retrospective cohort study in the province of Quebec, Canada. *J Surg Oncol* 2016;113:223-8. https://doi.org/10.1002/jso.24132

Correspondence: Dr. Wassim Kassouf, Division of Urology, McGill University Health Centre, Montreal, QC, Canada; wassim.kassouf.med@ssss.gouv.qc.ca