Molecular Subtyping to Stratify the Treatment of Muscle-Invasive Bladder Cancer: A Cost-Effectiveness Analysis

by

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Institute of Health Policy, Management and Evaluation
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ABSTRACT:
Introduction: The standard treatment for muscle invasive bladder cancer (MIBC) is neoadjuvant chemotherapy (NAC) followed by radical cystectomy but response to NAC is unpredictable. Molecular subtypes allow for an improved ability to select a tailored treatment course. Our study aims to assess the cost-effectiveness of molecular subtyping.

Methods: A Markov microsimulation model was developed comparing three strategies: NAC at current usage rates, universal NAC usage, and molecular subtype-directed care. Primary outcomes were quality-adjusted life years (QALYs), cost, and the incremental cost-effectiveness ratio (ICER).

Results: The predicted QALYs were 8.34, 8.73, and 9.14 with costs of $62,478, $76,962, and $62,579 for NAC at current usage rates, universal NAC usage, and subtype-directed care. When comparing subtype-directed care to current rates of NAC usage the ICER was $127/QALY.

Conclusion: In patients with MIBC a subtype-directed approach to the administration of NAC can result in greater QALYs and be cost-effective.

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TABLE OF CONTENTS:

LIST OF FIGURES:

LIST OF TABLES:

1. INTRODUCTION

1.1 Statement of the Problem:

Bladder cancer is the fifth most common cancer in Canada (1). The current management of bladder cancer is stratified based on its presentation either as non-muscle invasive, which represents approximately 70-85% of all new cases, or as muscle invasive (2). In non-muscle invasive bladder cancer (NMIBC) the goal of therapy, through the use of transurethral bladder tumour resections (TURBTs) and intravesical instillations, is to prevent progression to the invasive form which is life threatening (3).

In the muscle invasive setting (MIBC) radical cystectomy (RC) is the gold standard treatment modality for patients with non-metastatic disease (4). Unfortunately, cancer specific survival with cystectomy alone remains fairly low ranging from 25% to 72% 5 years post-operatively (5, 6). In patients with more locally invasive disease (tumour stage T2b-T4a) almost 50% develop metastases within 2 years of RC implying that micro-metastatic disease may be present at the time of surgery (5, 6).

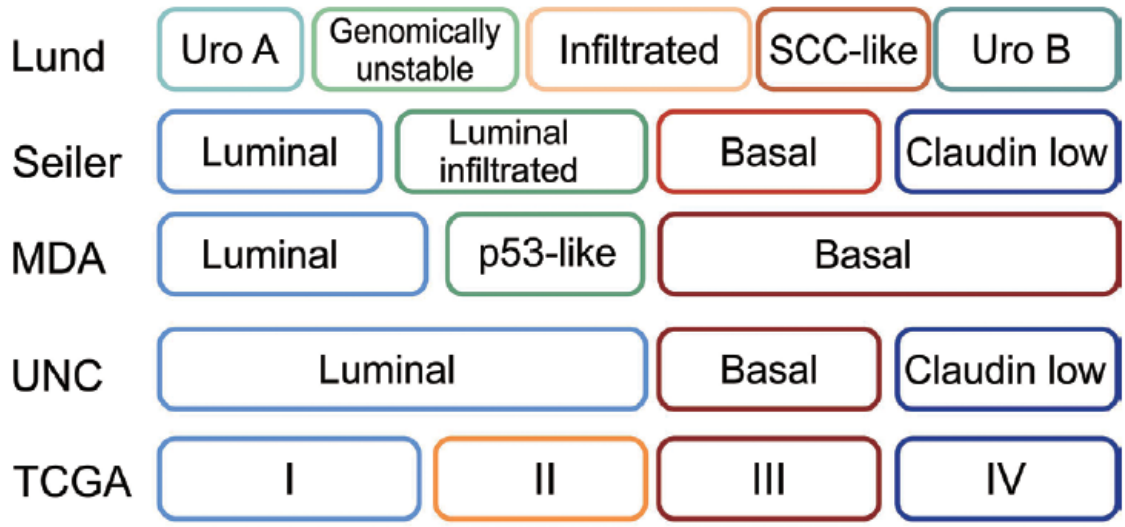
Therefore, focus has been placed on the utility of neoadjuvant chemotherapy (NAC) to reduce recurrence and improve survival. The results of two large, randomized trials and two meta-analyses demonstrated a survival benefit for NAC compared to surgery alone in patients with MIBC (7-10). Overall, the use of NAC leads to a 5-10% increase in 5-year cancer specific survival in MIBC compared to surgery alone (7-10). Despite this evidence there is reluctance regarding the utilization of NAC due to concerns surrounding delaying surgery, NAC's potential toxicity and most importantly the inability to predict response and therefore know who will benefit.

A subset of patients with MIBC will respond to NAC and have improved cancer specific survival. However, there is no reliable method of identifying those patients, leading to the overtreatment of non-responders, exposing them to undue toxicity and delaying time to RC. Therefore, identifying patients who are more likely to be NAC responders would be helpful in the treatment of MIBC.

In recent years there have been advances in the field of molecular subtyping through the use of whole transcriptome profiling with ribonucleic acid (RNA) sequencing, leading to the identification of distinct bladder cancer subtypes. This method of evaluating distinct entities has been previously established and used to guide oncological treatment decisions (11). Overall, within urothelial bladder cancer, multiple groups have completed subtype classifications each developing slightly different molecular subtypes. While the published subtype classifications are not universal, overwhelming overlap exists between the groups with regards to molecular characteristics, prognosis and response to therapy (12).

All studies found that urothelial bladder cancer can be divided into basal and luminal subtypes, similar to classifications with breast cancer (13). The remaining subtypes have significant commonalities and represent a subdivision of the basal and luminal subgroups. The University of North Carolina initially distinguished three subtypes – luminal, basal-like, and claudin-low (14). Research from MD Anderson also identified three subgroups, albeit with slightly different terminology – basal, p53-like and luminal (12). The Cancer Genome Atlas (TCGA) characterized MIBC initially into four groups, category I-IV (15) while Seiler et. al. published their stratification including four subgroups naming them luminal, luminal infiltrated, basal and claudin-low (16). Figure 1 demonstrates an overview of the subtyping systems and their interrelationship.

Figure 1: Overview of current taxonomy of molecular subtypes and their overlap



MDA: MD Anderson; UNC: University of North Carolina; TCGA: The Cancer Genome Atlas

Each of these subtypes, regardless of differing names, have distinct characteristics leading to differing prognoses and treatment susceptibilities. Basal or equivalent subtypes of MIBC are aggressive and are associated with shorter disease specific and overall survival compared to the luminal subtypes. However, they are the most susceptible subtype to NAC and the greatest improvement in overall survival is seen in these patients with the use of cisplatin-based NAC (16). This subgroup has also been shown to have the greatest response to nivolumab, a novel immune checkpoint inhibitor (17). The benefit from NAC, however, is not seen in the basal subset, claudin low or TCGA's original category IV. These patients have the worst prognosis irrespective of treatment modality (16). There is some evidence that luminal infiltrated/TCGA category II responds to immunotherapy despite being resistant to chemotherapy (18) but other research has questioned its sensitivity to immunotherapy agents leaving the treatment recommendation for this subgroup uncertain (19). Patients with luminal or category I respond to neither chemotherapy nor immunotherapy but have the best overall

survival, suggesting that neoadjuvant treatment may not be necessary in this subset of patients (16).

With the development of the molecular subtypes of MIBC, we have a greater understanding of the heterogeneity of the disease and therefore, an increased ability to select an appropriate course of treatment. However, the implications of this new development have yet to be examined from a policy perspective. Health Technology Assessment (HTA) aims to summarize information about the broader impact (i.e.: medical, economic, ethical, legal and social impact) of a health technology to inform policy decisions such that they are patient focused and achieve the best value (20). The development of molecular subtyping and its impact on the treatment of MIBC lends itself to be studied in a systematic manner from an HTA perspective as a tailored application of neoadjuvant systemic therapy (NAC, immunotherapy or no neoadjuvant therapy) has the potential to maximize survival outcomes while optimizing quality of life. Understanding the impact of molecular subtyping on the care of MIBC patients and the associated economic realities of adopting this technology are necessary to informing well-grounded healthcare and policy decisions.

1.2 Purpose of the Study

Our study aims to create a treatment algorithm and respective cost-effectiveness analysis to inform MIBC management. We hypothesize that such a strategy will improve outcomes, improve quality of life and potentially yield cost-savings.

Objectives:

1) To determine whether a precision medicine treatment strategy based on molecular subtyping of MIBC yields **greater efficacy** (unadjusted and quality adjusted years gained) compared to

standard approaches of cystectomy with undirected neoadjuvant systemic therapy (chemotherapy or immunotherapy).

2) To determine whether a precision medicine treatment strategy based on molecular subtyping of MIBC is **cost effective** compared to standard approaches of cystectomy with neoadjuvant systemic therapy (chemotherapy or immunotherapy).
3) To determine the **maximum cost** at which a molecular subtyping test would be cost-effective from the Ontario healthcare payer perspective.

2. BACKGROUND

2.1 Bladder Cancer Epidemiology

Bladder cancer is the second most prevalent urological malignancy and the fifth most commonly diagnosed cancer in Canada, with over 11,000 incident cases and 2,500 deaths reported in 2019 (1). Worldwide, nearly 430,000 diagnoses of bladder cancer are made each year leading to 165,000 deaths (21). Bladder cancer is stratified into two main groups – NIMBC and MIBC. NIMBC is diagnosed in the majority of patients and is characterized by frequent recurrences but with a low tendency to progress. MIBC however, has a high rate of metastasis and a 5-year survival of approximately 60%. Urothelial carcinoma is the predominant histological type (95% of cases), with less frequent histological variants including squamous, neuroendocrine, micropapillary and sarcomatoid (22). As urothelial is the predominant pathology, this thesis will focus on treatments specifically addressing urothelial bladder cancer rather than other bladder pathologies.

2.2 Current Management of MIBC

The gold standard definitive management option for MIBC is RC (4). However, the risk of recurrence remains high if localized bladder cancer is treated with RC alone. The majority of patients who develop recurrences have distant failures, illustrating that a potential cause is occult micrometastatic disease present at the time of RC (23). To mitigate this risk, NAC was investigated as a mechanism to improve survival (9, 24, 25). In the landmark randomized controlled trial comparing neoadjuvant cisplatin-based chemotherapy followed by RC versus RC alone Grossman et al. found a prolonged median survival of 77 months with NAC compared to 46 months with RC alone ($p=0.05$). Furthermore, updated results from the largest randomized controlled trial (976 patients) investigating NAC followed by RC revealed that the administration

of cisplatin-based chemotherapy prior to definitive treatment resulted in a 16% reduction in the risk of death; treatment with NAC led to an increase in the 3-year survival from 50% to 56%, 10-year survival from 30% to 36% and a median survival improvement of 7 months (37 to 44 months) (10). A subsequent meta-analysis using patient level data from over 3000 individuals and based on 11 trials found a significant survival benefit associated with the use of platinum-based combination NAC (HR=0.86, 95%CI: 0.77-0.95, p=0.003) (7). This translated to a 5% absolute improvement in survival at 5 years. Following these studies, all urologic professional organizations (European Association of Urology, American Urologic Association and the Canadian Urologic Association) recommended NAC prior to definitive management of MIBC in eligible patients (3, 4, 26).

However, there are limitations to the administration of NAC. Cisplatin toxicities include diminished renal and cardiac function, neurotoxicity and hearing loss (27). In part due to the significant adverse events associated with cisplatin-based chemotherapy NAC has not seen the widespread uptake that would have been anticipated. Other reasons for poor uptake include patient refusal, concerns regarding delaying time for surgery and most importantly the inability to predict which patients will benefit from NAC leading to a rate of 20-36% usage in eligible patients (28, 29). The survival benefit from NAC has been largely attributed to patients who achieve a complete pathological response which occurs in approximately 20-38% of patients (30). Furthermore, Bhindi et al. demonstrated that patients with residual disease at RC following NAC, particularly those with residual muscle invasive or nodal metastatic disease, have worse oncologic outcomes compared to pathologically stage matched patients who underwent RC alone (31) which further highlights the concern regarding a universal administration of NAC.

The introduction of immune based therapy has revolutionized the therapeutic landscape of MIBC and introduced an alterative option for patients with bladder cancer. Immunotherapy is better tolerated than cisplatin-based chemotherapy with fewer associated adverse events and wider eligibility criteria thus lending itself to exploratory use in the neoadjuvant space. The PURE-01 study evaluated the use of neoadjuvant immune checkpoint inhibition using three cycles of pembrolizumab in patients with MIBC prior to RC (32). This phase II trial demonstrated a complete pathological response in 42% of patients who received pembrolizumab. Moreover, these results were achieved with fewer adverse events than seen with traditional cisplatin-based chemotherapeutic regimens. The benefit of immunotherapy was further supported by the results of the phase II ABACUS trial which demonstrated safety and efficacy from two cycles of neoadjuvant atezolizumab (immune checkpoint inhibitor) in cisplatin-ineligible patients (33). Pathologic complete response occurred in 29% of patients which enriched to 40% in a certain subset of patients. The use of immunotherapy as a neoadjuvant treatment is novel and exploratory in the field of bladder cancer as trials continue to pass through phase II studies.

Both NAC and immune-based therapy demonstrate a variable efficacy. Therefore, identifying which specific subset of patients would derive the most benefit from these therapies is important as it would prevent unnecessary exposure to potentially toxic therapies, and unproductive delays in time to RC.

2.3 Molecular Subtyping

New technology, in the form of next-generation sequencing (NGS) has opened the gateway to large-scale analyses to explore the genomic landscape of MIBC (34). By harnessing the advantages of “big data” these recent advances, specifically the use of RNA expression profiling, allow for a greater understanding into the various subtypes of MIBC. The discovery

and recognition of different molecular subtypes of MIBC has allowed for better understanding of variable prognoses and variable treatment responses. The standard method to derive these subtypes is to complete RNA sequencing of the tumours of a cohort of patients, and then use unsupervised clustering (i.e.: all results are available for cohort of patients and then based on over/under expression of genes, patients are placed into “like” or “similar” groups based on expression).

Multiple different research teams over the last several years have offered increasingly refined approaches to the molecular subtyping of MIBC. While each study varies slightly in its interpretation, there are consistent patterns in their classifications. The first major classification, from which the others have evolved, identified three major subtypes, termed luminal, basal-like, claudin-low (14). This initial study from the University of North Carolina created a meta-dataset of 262 high-grade muscle invasive tumours and used an independent dataset of 49 high-grade tumours from Memorial Sloan Kettering Cancer Center (MSKCC) as a validation set. They defined a minimal set of genes that could accurately classify tumours and developed a 47-gene signature which proved to be correlated between the meta-dataset and the MSKCC dataset. From these analyses they were able to determine that basal-like tumours had significantly decreased overall survival (median survival approximately 22 months versus 40 months, $p=0.0081$) compared to their luminal counterparts.

Choi and colleagues evaluated 73 muscle-invasive bladder tumours through whole genome micro-RNA expression profiling (35). Their analysis yielded the luminal and basal subtypes similar to previous research but also revealed a slightly different third classification: a p-53 subtype based on a distinct expression signature. Results of the group from MD Anderson echoed earlier research in that basal subtypes had the shortest disease-specific and overall

survival time compared to both p-53 and luminal subtypes. However, basal tumours had the best prognosis after NAC administration, illustrating remarkable cisplatin sensitivity compared to luminal and p-53 subtypes.

Developing from MD Anderson's work The Cancer Genome Atlas (TCGA) project identified four distinct expression subtypes from the mRNA sequencing of 131 high-grade muscle invasive urothelial bladder tumours (15). They termed their subtypes clusters I-IV. Cluster I closely resembles the luminal subtype from the MD Anderson group while cluster II overlaps with the p-53 subtype. The basal subgroup was split into two classifications – cluster III and IV. The Lund group further extended the classifications into five subtypes using a meta-dataset of 308 urothelial bladder tumours with validation in three independent datasets (36). The five major molecular subtypes under their classification include: urobasal A, genomically unstable, urobasal B, SCC-like and a heterogeneous infiltrated class of tumours. Their overall analysis included both muscle invasive and non-muscle invasive tumours and illustrated that their proposed classification was independent from pathological stratification. In survival analyses including only high-grade tumours urobasal A tumours (similar to luminal/cluster I) had the best disease specific survival whereas those in the urobasal B subgroup (similar to cluster IV) had the worst.

Seiler et al. expanded upon the work of the four teams, using a novel sequencing technique to further demonstrate that molecular subtypes could be used to guide selection of optimal therapy (16). The authors pioneered a novel method of determining molecular subtypes using a single sample genomic subtyping classifier (GSC) compared to previous studies which used large tissue databases to explore molecular classifications. Using this new approach, they developed a four-category classification system with strong similarities to the TCGA system.

Their categories include luminal, luminal-infiltrated, basal and claudin-low. The interplay between subtype systems is depicted in Figure 1.

Using these classifications, they assessed survival and NAC treatment responses. In the absence of NAC, luminal subtypes fared the best with a 3-year OS of 76.6% which did not change with the administration of NAC suggesting that these patients would do best with immediate RC. However, basal subtypes, whose 3-year OS without NAC was 49.3%, improved to 77.8% upon receipt of NAC. In multivariable analysis adjusting for clinical tumour stage, age, and gender in the non-NAC cohort, patients with a basal subtype had a HR of 2.22 for OS compared with the luminal subtype. However, in the NAC cohort, basal subtype OS was not statistically different, illustrating the beneficial impact that NAC has on OS for basal subtypes. Luminal-infiltrated subtypes (corresponding to TCGA cluster II or genomic unstable in the Lund classification) show evidence of chemoresistance (37). There are mixed reports in the literature regarding the luminal-infiltrated subtype's susceptibility to immunotherapy. The IMvigor210 trial, which evaluated the use of atezolizumab in second-line metastatic MIBC indicated it was responsive to the agent (18, 38). Preliminary evidence of this particular subtype's susceptibility to immunotherapy was also demonstrated by the CheckMate 275 trial in which patients with metastatic MIBC were treated with nivolumab, another immune based systemic therapy (17). However, in the ABACUS trial evaluating the use of atezolizumab in the neoadjuvant setting, this subtype did not correlate with outcome (33).

Patients with claudin-low (corresponding to cluster IV, urobasal B) subtypes were found to have the worst prognosis overall, with little to no evidence of improvement after receipt of NAC on multivariable analysis (OS HR non-NAC: 3.06, 95%CI: 1.71-5.47; OS HR NAC set:

2.16, 95%CI: 1.22-3.81). Moreover, the benefit of immunotherapy was limited in this subtype in the IMvigor 210 and CheckMate 275 trials (17, 38).

More recent studies have published further iterations of the molecular subtyping system and within the bladder cancer community a consensus definition was recently published to unify the multiple definitions (22, 39, 40). However, the more detailed classifications systems, while potentially more nuanced from a gene expression perspective, are not accompanied, at this point in time, with granular information regarding treatment susceptibility. Furthermore, the GSC, as developed by Seiler and colleagues, is the only feasible mechanism for testing patients at an individual level as other methods of determining molecular subtypes require classification of an entire patient cohort using large datasets.

2.4 Test Parameters

Understanding that no diagnostic test possesses perfect accuracy, the GSC test parameters were evaluated during its development using a validation cohort in Seiler and colleagues' original paper (16). The GSC subtype outcome was compared to a subtype classification based on traditional methods of subtyping (i.e. using a large patient datasets). When compared to the standard methods the test accuracy was found to be 76% overall. The reported area under the curves for each respective subtype were 0.97 (luminal), 0.9 (luminal-infiltrated), 0.89 (basal) and 0.96 (claudin-low).

2.5 Overview of Bladder Cancer Management Costs

Bladder cancer is the most expensive diagnosis per patient lifetime among all cancers (41, 42), with a total cost of $3.98 billion annually in the United States in 2010 (43). Despite the fact that NMIBC represents the more prevalent condition, MIBC's annual treatment cost is four

times greater than NMIBC (44). Previous studies have shown that a significant economic burden of MIBC is derived from the RC itself which is further exacerbated by peri-operative complications (45). Therefore, as this disease is already expensive to treat, it is of paramount importance to understand how to provide care for MIBC patients in the most cost-effective manner, especially considering the steady increase in health costs over time due to the development of new technologies and advanced pharmaceuticals (43).

Unfortunately, a large proportion of the bladder cancer cost literature has methodological limitations. Two recent studies evaluated the 6-month and 1-year cost of MIBC from the time of diagnosis using large, American administrative datasets (46, 47). They found a median cost of $107,017 at 6-months and $148,757 at 1-year. These studies' results, however, are difficult to interpret as they did not estimate attributable costs. As well, as the cohort was derived from an administrative dataset it is impossible to determine the indication for the RC (i.e. curative versus palliative) and therefore the results may be skewed by indication bias. Furthermore, their costs are difficult to apply to a decision analytic model since time-based costs were reported rather than phase-specific costs.

A prior retrospective, single-centre study investigated cost-effectiveness of NAC in the setting of MIBC. Stevenson et al, demonstrated that NAC was cost-effective with an incremental cost-effectiveness ratio (ICER) of $6,187/QALY gained (48). However, in this study a significant portion of patients did not go on to RC following the receipt of NAC. Therefore, they likely underestimated the cost of care in the NAC arm thereby artificially lowering the ICER as not all patients would have accrued the downstream cost of cystectomy or its associated complications.

A previously completed cohort study using administrative data from Ontario, evaluated the phase of care costs for bladder cancer over a 10-year period between 1997 and 2007 (49). These data illustrate that the greatest cost of care stems from the initial treatment phase (first 6 months) and from the terminal phase of care (last 12 months). Unfortunately, this paper did not distinguish between NMIBC and MIBC in their analysis and therefore, the treatment costs are not translatable to our study. Moreover, with respect to their terminal phase costs, this study was completed in an era prior to the advent and approval of immunotherapeutic agents which have increased the cost of care significantly; as a result, the costs reported may not represent the current burden with all of the modern therapeutic options.

As a result of the challenges associated with obtaining accurate MIBC cost data a retrospective, single centre, chart review evaluating phase-specific and cancer-specific costs for patients treated for MIBC was integral to the completion of this thesis.

2.6 Modelling Approaches and Economic Evaluation

As the knowledge of MIBC evolves, an assessment of how to use novel technology to improve care for this disease becomes increasingly relevant. HTA seeks to systematically evaluate the practical application of health care technology to improve or maintain individual or population health with the aim of informing policymakers and guidelines (50). Achieving optimal health requires investment in medical care but in a limited resource environment, decisions must be made regarding how to prioritize those resources; HTA facilitates prioritizing those needs. HTAs can be performed from three basic orientations, which overlap and complement one another (20). The technology-oriented assessment seeks to determine the impact (i.e.; clinical, economic, social) of a technology while the problem-oriented assessment works to evaluate strategies for managing a specific disease and inform the development of clinical

guidelines (20). The project-oriented assessment focuses on the local use of a technology within a certain setting (i.e.; institution, program, project) considering supporting and competing factors. In this setting, each perspective helps to inform the HTA of molecular subtyping of MIBC in the province of Ontario as it reflects a novel technology, addressing the treatment of a specific disease within a setting dictated by finite financial resources and logistical constraints. The Ontario Health Technology Advisory Committee provides a framework for the evaluation of a health technology development through the assessment of its safety, effectiveness, economic impact and ethical, legal and social implications (51).

Health policymakers, physicians and other stakeholders aim to maximize the well-being of society. HTA allows for systematic assessments of specific interventions and technologies to determine the benefit derived from evaluated technologies. However, benefit can be assessed from different perspectives within the health economic literature: the welfarist and extra-welfarist viewpoint. Traditional cost-effectiveness analysis is supported by the extra-welfarist perspective where healthcare preferences (i.e.; utilities) are the same for all patients with the same health state, rather than varied based on how each individual experiences a common health state, as in the welfarist perspective (52). Moreover, in the extra-welfarist paradigm utilities are defined against their contribution to health itself, rather than in comparison to health and other goods (52). While a welfarist perspective offers a more nuanced view of patient utilities since it accounts for the individualized experience of a health condition, the extra-welfare perspective is more pragmatic and applicable within the confines of a health economic assessment (53). As the welfarist approach asserts that individuals are the best judges of their own welfare, this approach lends support for the willingness-to-pay methodology of assessment (i.e.; how much is an

individual willing to pay to prevent or treat disease) as it goes beyond the actual cost of a treatment and incorporates the importance of overall wellness compared to other goods.

Cost-effectiveness analysis represents a type of economic evaluation that assesses health outcomes and the costs of interventions designed to improve health. They have been used extensively in the field of oncology and have been completed within urologic oncology as well (54-56). Cost-effectiveness analyses show the relationship between net resources (costs) and net health benefits (effects) for a specific intervention compared to a specific alterative. As these analyses involve comparisons, the additional cost per additional unit of effectiveness ($\Delta C/\Delta E$) ratio reflects the difference in an intervention's costs divided by the difference in its health outcomes. This cost-effectiveness ratio includes all downstream costs resulting from the specific management decision, not just the cost of the intervention. If the ratios are expressed in the same unit across different interventions and disease areas, they can be compared to determine the most efficient way to improve overall health. The widely recommended approach is to use quality adjusted life years (QALYs) in the calculation of cost-effectiveness as it is readily translatable across diverse medical interventions and incorporates both prolongation and improvement in quality of life (57, 58). By estimating the magnitude of health outcomes and cost of interventions, cost-effectiveness analyses can make important contributions to informing decisions about resource allocation (51). As many interventions are complex, involving both benefits and harms to health, in addition to costs, distillation of the relevant information to an overall estimation can contribute to better decision making. For many situations in HTA, no one study exists which definitively answers the broader clinical or economic questions. Therefore, integrative methods (or synthesis methods) must be used to combine data from existing sources to generate an answer. One method of integrating evidence is through the use of decision-

analytic modelling which simulate health care processes under conditions of uncertainty. For example, decision models can be used to compare two treatment modalities that have not been directly compared in a randomized clinical trial setting and make informed projections regarding treatment and downstream costs that may not be present in primary data. In the creation of any model, assumptions are made, and data sources and techniques are chosen; the findings of any decision model are conditional upon these components and they should be made clear to consumers of the information (59). The use of decision modelling has expanded in recent years and accordingly standards for reporting have followed (60, 61).

Markov decision models are especially useful for representing patient experiences when health problems involve risks that are continuous over time and when some or all of the health states may recur (62). Decision models use a number of health states, each of which is associated with a cost and quality of life weight called a utility. Patients move through the states as time progresses in the model, with movement dictated by the probabilities of events occurring (62). Time spent in a health state multiplied by the utility of that health state yields the QALY. The advantage of QALYs is that they capture in a single measure gains from both reduced morbidity and mortality, and incorporate the value or preferences people have for different outcomes (63). Those following the extra-welfarist approach feel that maximizing QALYs is an appropriate goal (64). Costs and QALYs accrue with time and are used to determine the cost-effectiveness of a proposed intervention/treatment. Cost-effectiveness is one of the factors used by health decision makers to determine whether a health technology should be adopted (65, 66).

Decision models are an accepted tool used to guide clinical decision making and models have been developed to assess the use of novel developments and guide management in prostate cancer (67) and recurrent high grade NMIBC (54, 68). This decision model evaluating the impact

of precision medicine using the molecular subtyping of MIBC lends itself to study through the lens of HTA as it will provide evidence with respect to health outcomes (patient quality of life, survival), cost, and cost-effectiveness (cost of healthcare delivery) of the strategy.

3. COST OF MUSCLE INVASIVE BLADDER CANCER TREATMENT

3.1 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 (21). Within the context of healthcare spending it is a costly diagnosis and has been reported as the most expensive diagnosis per patient lifetime among all cancers (41, 42), with a total cost of almost $4 billion annually in the United States in 2010 (44). Previous studies have shown that radical cystectomy (RC) accounts for the largest proportion of costs associated with bladder cancer care (69); however, few studies have evaluated the cost of trimodal therapy (TMT). TMT has progressively been accepted as a viable treatment option for the treatment of muscle-invasive bladder cancer (MIBC) (3, 4, 29) and therefore the implications from a health economic perspective have become increasingly important to consider. The objective of this study was to determine and compare the cost of MIBC treatment with RC and TMT in Ontario, Canada.

3.2 METHODS

3.2a Study Design

A retrospective chart review of all incident MIBC patients treated with definitive management in the form of RC or TMT at the University Health Network (UHN), a tertiary cancer-specific care centre in Toronto, Canada, between January 1, 2008 and December 31, 2012 was completed. Two separate reviewers read charts and abstracted the data. All non-urothelial subtypes of bladder cancer were excluded. We excluded patients who underwent robotic radical cystectomies due to its rarity and those with concomitant active malignancies requiring treatment as it was difficult to ascribe costs to each individual malignancy. Patients were followed until

December 31, 2012 to help minimize loss to follow up over longer follow-up periods and from a pragmatic perspective to limit the burden of chart reviews.

Patients were identified using pre-existing cystectomy and radiation databases maintained at UHN. The retrieved records were then cross-referenced with pathology reports to ensure that all patients had muscle invasive urothelial bladder cancer. Phases of care evaluated included diagnosis, neoadjuvant treatment, primary therapy (RC or TMT), adjuvant treatment, follow up and recurrence.

The diagnosis period incorporated the time from the identification of a bladder tumour or positive cytology result which initiated the definitive management treatment decision until active treatment began (either neoadjuvant chemotherapy or primary therapy (RC or TMT)); the diagnosis period encompassed cystoscopy, imaging and TURBT. The neoadjuvant time period was defined from the beginning of chemotherapy treatment until the start of primary therapy, either RC or TMT. Primary treatment phase was defined from the first day of definitive management (cystectomy or chemoradiation) to 90 days afterwards or the initiation of adjuvant therapy. Adjuvant treatment period was defined from the start of adjuvant therapy to 90 days afterwards. The follow up phase began immediately after primary treatment or adjuvant therapy and terminated at the time of documented recurrence, patient death or end of study period.

Direct costs associated with each phase of a patient's clinical course were collected from the hospital's financial department. At UHN, all inpatient and outpatient visits with physicians are captured by the hospital financial department. Cost information provided from the financial department included the cost of allied health staff, medications, imaging, laboratory investigations and equipment use. Radiation treatment costs were derived from previously published literature from UHN which incorporated the cost of equipment, allied health staff and

supporting infrastructure (70). Physician costs were assigned based on the Ontario schedule of benefits. Physician costs were calculated based on the type of visit and intervention required (i.e.: follow up visit, cystoscopy, radical cystectomy); physician costs during inpatient visits were determined by reviewing the number and type of specialty consultations required and then applying the appropriate fee code.

Costs attributable to bladder cancer and its care were captured in this study. Any readmission or clinic visit that occurred within the 90-day peri-operative period was considered an attributable cost. The chief complaint for these presentations were most commonly for urinary tract infections, hydronephrosis, stomal complications/medical device problems, and abdominal pain. After the immediate peri-operative period, admissions and interventions were assessed on an individual basis to determine if the were attributable to bladder cancer or to previous treatments. Examples of presenting complaints that were deemed attributable to MIBC included urosepsis, hydronephrosis, and incisional hernias. Examples of costs not attributable to bladder cancer were myocardial infarction, pneumonia, COPD exacerbation, etc. These were not considered attributable costs and thus not included in costing estimates and calculations.

All costs were inflated to 2019 Canadian dollars using the Canadian Price Index (71). Study perspective was completed from the institutional payer perspective. This study was approved by the Research Ethics Board at UHN.

3.2b Outcomes

Our primary outcome was the phase specific cost of treatment of MIBC by primary treatment modality (RC vs. TMT). Descriptive statistics were performed on all demographic variables. Continuous variables were compared using the Wilcoxon Rank sum test and categorical variables were compared using the Chi square test. A sub-group analysis was

conducted to determine if tumour stage had an impact on the cost of care and so the costs were re-analyzed using only those patients with non-locally advanced tumours (cT2).

3.3 RESULTS

A total of 4,175 unique encounters were identified across 137 patients. Patients were predominantly male (76%), with a mean (SD) age of 68.7 (12.2) years (Table 1). Overall, 89 patients (64.9%) underwent radical cystectomy and 48 (35.1%) received trimodal therapy (TMT) for muscle-invasive bladder cancer (MIBC). Patients who received RC were on average younger than their TMT counterparts (66.4 (12) versus 72.8 (11.6), $p=0.0095$). Patients who underwent RC also had higher stage disease at the time of intervention (58% cT3/T4) versus 26% in the TMT group ($p<0.001$). Moreover, they had greater comorbidity indices (ASA and Charlson Comorbidity Index) compared to the TMT cohort.

Table 1: Patient demographics and clinical characteristics

Covariate	Full Sample (n=137)	RC (n=89)	TMT (n=48)	p-value
Age at time of Bladder Ca Dx				0.0095
Mean (sd)	69 (12)	66 (12)	73 (12)	
Median (Q1,Q3)	69 (62,78)	68 (58,75)	71 (64,83)	
Sex				0.68
F	24% (33)	23% (20)	27% (13)	
M	76% (103)	77% (68)	73% (35)	
ASA score				0.0012
<=2	33% (45)	23% (21)	50% (24)	
>2	67% (91)	77% (67)	50% (24)	
CCI				0.058
<=3	7% (9)	7 (6)	7% (3)	
4-6	52% (65)	45% (38)	66% (27)	
>=7	41% (52)	48% (41)	27% (11)	
cT stage				<0.001
T2	52% (72)	42% (37)	73% (35)	
T3	41% (56)	53% (47)	18% (9)	
T4	6% (8)	5% (4)	8% (4)	

ASA: American Society of Anesthesiologists; CCI: Charlson Comorbidity Index

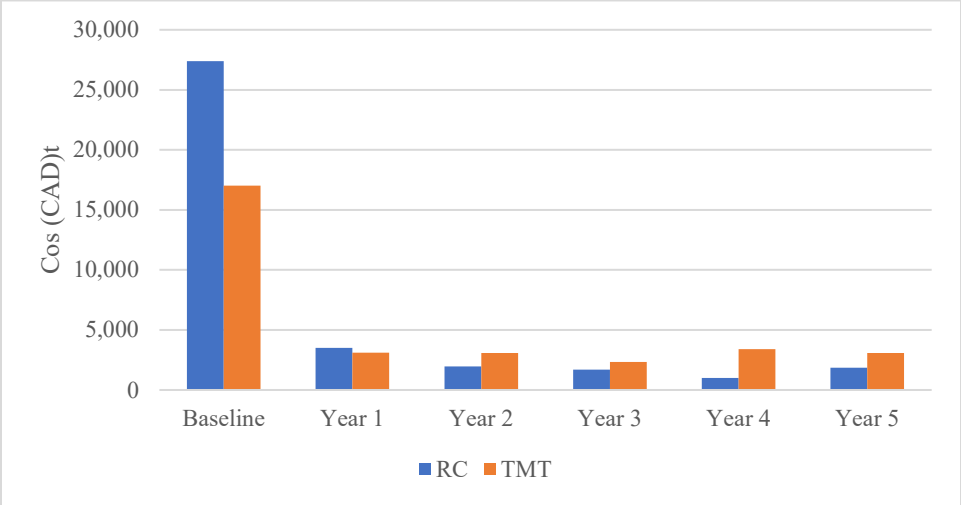
The cost of diagnostic work-up was similar for RC (median: $1,973 IQR: $996-6,239) and TMT (median: $2,627 IQR: $2,187-6,364; p=0.23). Initial treatment costs were significantly higher for RC patients (median: $27,394 IQR: $21,433-34,816) versus those treated with TMT (median: $17,014 IQR: $15,483-21,084; (p<0.001) (Table 2). In the first-year post-treatment, the cost of follow-up in the RC group remained higher than in the TMT group. However, after the first-year stage-specific costs for ongoing follow-up care (clinic visits, imaging and cystoscopy) stabilized in both groups, though they remained persistently higher for patients undergoing TMT compared to RC ($2,776/year vs $1,770/year, p=0.09) (Figure 2).

Table 2: Direct costs of bladder cancer treatment by treatment modality

Radical Cystectomy									
Phases of Care				Ongoing Follow-Up Excluding Terminal Care*					
	Diagnosis / Pre-Treatment Consultation	Neoadjuvant Chemotherapy	RC and Early Post-Operative (Day 0-90) Care	Day 91-365	Year 2	Year 3	Year 4	Year 5 and Beyond	Aggregate over Total Follow-Up After First Year
Number of Unique Visits (Number/Pt)	389 (4.4)	173 (15.7)	N/A	580 (8.7)	405 (10.4)	93 (4.7)	42 (3.5)	35 (5.0)	575 (14.4)
Number of Patients with a Visit/Event	89	11	89	67	39	20	12	7	40
Phase Median Cost (IQR)	$1,973 (996-6,239)	$6,240 ($5,287-7,786)	$27,394 (21,433-34,816)	$3,497 (1,210-9,153)	$1,966 (1,451-9,972)	$1,707 (1,194-3,565)	$992 (659-2,237)	$1,866 / year (567-5,658)	$1,770 / year (1,025-8,382)
*Day 0 was assigned to date of radical cystectomy									
Trimodal Therapy									
Phases of Care				Ongoing Follow-Up Excluding Terminal Care[#]					
	Diagnosis / Pre-Treatment Consultation	Neoadjuvant Chemotherapy	TMT	Day 91-365	Year 2	Year 3	Year 4	Year 5 and Beyond	Aggregate over Total Follow-Up After First Year
Number of Unique Visits (Number/Pt)	314 (6.5)	209 (26.1)	N/A	345 (7.5)	157 (5.6)	73 (4.6)	32 (4.0)	2 (2.0)	264 (9.4)
Number of Patients with a Visit/Event	48	8	48	46	28	16	8	1	28
Phase Median Cost (IQR)	$2,627 (2,187-6,364)	$10,803 ($8,457-13,244)	$17,014 (15,483-21,084)	$3,098 (2,163-5,830)	$3,072 (2,262-4,748)	$2,347 (2,052-5,638)	$3,409 (1,446-8,039)	$3,092 (/ year	$2,776 / year (1,902-5,885)
[#]Day 0 was assigned to the initiation of trimodal therapy.									

**Adjuvant costs were excluded from table as no patients in the TMT group received adjuvant chemotherapy*

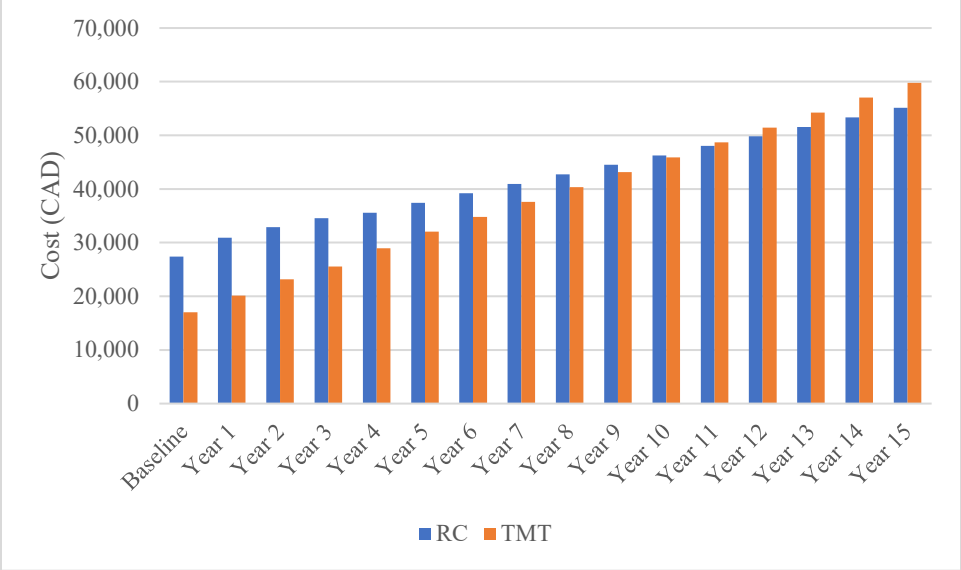
Figure 2:Follow-up cost by strategy



RC: radical cystectomy; TMT: trimodal therapy

While RC has higher initial treatment cost compared to TMT, RC costs were lower after 10.35 years (Figure 3).

Figure 3: Lifetime accumulated cost per strategy



RC: radical cystectomy; TMT: trimodal therapy

Neoadjuvant chemotherapy was used in 12.5% (11) of patients who were treated with RC and 16.3% (8) patients who received TMT. The cost of neoadjuvant chemotherapy and

management of associated complications during treatment was $6,240 (IQR: $5,287-7,786) for those receiving RC versus $10,803 (IQR: $8,457-13,244) in the TMT group (p=0.02). Only patients who underwent RC (15.9%, 14) received adjuvant chemotherapy for a median (IQR) cost of $7,662 ($5,650-10,165). Within the study years, 22.77% (20) of patients recurred in the RC group and 28.5% (14) in the TMT group. Two patients who were originally treated with TMT underwent a salvage cystectomy for local recurrence.

A subgroup analysis was completed to evaluate costs in the clinical tumour stage 2 (cT2) group to determine if a significant difference in treatment cost would remain between the groups if the analysis was controlled for tumour stage. Baseline demographic values remained unchanged with RC patients being younger, but with higher scores on comorbidity indices (ASA and CCI). The cost of RC was $24,096 ($21,136-31,902) versus $16,840 ($16,327-17,716) for those receiving TMT (p<0.001). While the overall cost of treatment was lower in the cT2 group for both treatments, RC remained significantly more expensive in comparison to TMT.

There was no evidence of a relationship between ASA and cost of care in either treatment modality (Table 3 and 4). In the RC arm, the median cost of care was highest in patients 80 and over ($30,103); however, the cost in the youngest group (those <60 years of age) was similar at $27,977). In the TMT group, the cost of treatment was stable across the age intervals. There was no difference in cost of RC based on sex in the use of either modality.

Table 3: Direct costs of radical cystectomy stratified by ASA, age and sex

Radical Cystectomy - Treatment and Early Post-Operative (Day 0-90) Care*									
	Base Model	**Stratification Analyses**							
		ASA <=2[#] (1 missing)	**ASA >=3[#] (1 missing)**	**Age at Dx <60**	**Age at Dx 60-69**	**Age at Dx 70-79**	**Age at Dx 80+**	**Sex = 0 (Female)**	**Sex = 1 (Male)**
Number of Patients	89	21	67	24	23	33	9	20	69
Phase Median Cost (IQR)	$27,394 (21,433-34,816)	$26,373 (22,587-29,235)	$27,853 (21,278-36,322)	$27,977 (21,808-33,831)	$24,140 (20,205-31,143)	$27,733 (22,714-36,031)	$30,103 (22,466-37,596)	$26,800 (21,815-29,316)	$27,733 (21,433-36,322)
*Day 0 was assigned to date of radical cystectomy									

Table 4: Direct costs of trimodal therapy stratified by ASA, age and sex

Trimodal Therapy - Treatment (Day 0-90) Care*									
	Base Model	**Stratification Analyses**							
		ASA <=2	**ASA >=3**	**Age at Dx <60**	**Age at Dx 60-69**	**Age at Dx 70-79**	**Age at Dx 80+**	**Sex = 0 (Female)**	**Sex = 1 (Male)**
Number of Patients	48	24	24	4	19	7	18	13	35
Phase Median Cost (IQR)	$17,014 (15,483-21,084)	$17,209 (15,632-20,505)	$16,846 (15,104-21,123)	$15,464 (14,782-15,640)	$17,564 (15,490-23,152)	$16,748 (16,354-23,646)	$17,098 (13,195-26,992)	$16,834 (15,583-17,490)	$17,334 (15,285-23,231)
*Day 0 was assigned to the initiation of trimodal therapy									

3.4 DISCUSSION

In this retrospective cohort study, which reviewed over 4000 individual patient entries, we identified the phase-specific costs for patients treated between 2008 and 2012. RC is the standard surgical therapy for MIBC with established, long term oncologic outcome data (72). However, it is accompanied with significant upfront risk of morbidity and mortality (72-74). TMT offers patients an opportunity for bladder preservation and provides a treatment option for patients who generally would otherwise be poor surgical candidates as it is associated with less frontloaded risk (75). Therefore, TMT has increased in its utilization in selected patients (76, 77).

However, the oncological control derived from its use has been debated and likely is less durable long-term (76). Within a universal healthcare payer system, information about the cost of therapy is an important consideration and little has been published on the differential costs of the two treatments, and data are completely absent in the Canadian context.

To our knowledge this is the first study comparing the costs of RC and TMT in Canada. The main finding of our study is that the two treatment modalities exhibit differing cost characteristics with RC being more expensive upfront, but with this being mitigated over time by the increased cost of ongoing follow-up in the TMT cohort. The increased cost of RC compared to TMT in the treatment phase remained even when controlling for clinical tumour stage indicating that the difference in cost was not driven by the greater burden of disease. Moreover, increased ASA class nor older age were reliable predictors of increased cost of care. However, in our analysis it was apparent that considerable variability exists within the RC treatment costs due to the inherent heterogeneity of the recovery path for patients peri-operatively. The majority of patients, up to 68%, experience a complication within 90 days of a RC (78) and this extra care has a profound impact on the cost of care of RC. Santos et al, in a retrospective administrative study from Quebec demonstrated that post-operative complications and peri-operative mortality have previously been shown to be predictive factors of high costs in the surgical treatment of MIBC (45). This finding corroborated earlier findings from the US that demonstrated that one third of total costs in the treatment of MIBC were attributed to the management of post-operative complications (79).

We also noted that with increasing follow-up time after primary treatment, the cost difference between modalities is mitigated by the increased cost of surveillance in the TMT cohort. The larger follow-up costs in the TMT arm can be explained by the ongoing need for

surveillance of the intact bladder with cystoscopy and urine cytology in addition to the standard imaging and follow-up visits (3). Neoadjuvant chemotherapy was also found to be more costly in the TMT group. This was driven largely by two patients in the TMT group who were admitted during their chemotherapy treatments leading to markedly increased costs and necessitating increased follow-up after discharge, thereby contributing to the increased number of average visits seen in the TMT group (26.1/patient) compared to the RC group (15.7/patient) in this phase care. Given the current healthcare climate and growing emphasis on value-based cancer care, our findings demonstrate that both strategies have merit from a cost perspective, especially when taken in the context of the potential survival differences derived from the two modalities.

Williams et al previously evaluated the costs of MIBC therapy in the US using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database (80). They found that TMT was associated with increased costs compared to RC over the 1-year time horizon. At 90 days, total TMT costs were $83,754 (IQR: 50,754-129,299) versus $68,692 (IQR: $44,912-98,871) for RC. The cost discrepancy continued to widen such that by 1-year the median cost for patients treated with TMT was $289,142 (IQR: $197,649-409,655) versus $148,757 (IQR: $87,282-252,518) for those who received RC. The discrepancies in costs obtained from this paper and ours can be ascribed to differences in the methodologies employed. While the use of administrative datasets allows for much larger sample sizes, their study is subject to indication bias and the use of all-cause billings limiting the assessment of attributable costs to bladder specific causes. Ideal candidates for TMT should meet strict criteria including small, solitary muscle-invasive tumours with no significant carcinoma-in-situ, and who have undergone a complete TURBT without visible evidence of residual disease (81). However, using the SEER database it is difficult to determine if the patients who received TMT met these

exacting inclusion criteria. Complete resection of the tumour is a strong predictor of TMT success, but it is impossible to determine quality of resection from population-level data (82). Second, the quality of the chemotherapy regimens is unknown. Ideally, chemotherapy for TMT should be cisplatin-based and administered concomitantly with radiation therapy (81). However, the type and timing of chemotherapy was not discussed and therefore it is difficult to determine whether the TMT was in fact, complete. If complete TURBTs were not done or appropriate chemotherapy regimens not received or completed this would certainly bias the results towards poorer outcomes and higher costs due to treatment failures. It also remains entirely possible that some of the TMT patients received sequential radiation followed by chemotherapy with palliative rather than curative intent based on tumour and patient characteristics. This is especially true considering the era the paper studied as TMT was rarely used as primary therapy and was not well accepted; thus, the patients receiving TMT may not represent those who received TMT with true curative intent. Given that the costs of palliation and death from cancer are extraordinarily high (49), this possibility would introduce significant cost bias against the TMT group.

Our paper avoids these limitations by using the chart review methodology to ensure that each patient included in the study received treatment for curative intent and that the phases of care were specifically identified. Moreover, by using the chart review methodology, we were able to ensure that costs captured were related to the disease or sequalae of its treatment and not those associated with comorbidities. This allows for better understanding of how these two treatment modalities compare with respect to costs, rather than the costs of treating different patient populations.

Our findings though, must be interpreted within the context of the study design. This was a single centre study completed at an academic institution. Previous literature has demonstrated that having a RC performed in an academic centre is associated with lower RC costs from a healthcare system perspective (45). The academic institution impact likely has less impact on the TMT costs as they are largely fixed in nature whereas there is a well documented relationship between volume and quality of care in the operative management of MIBC (83, 84) that may impact the cost of surgical care of this disease. This may make our estimate of the treatment cost per phase for RC less generalizable to a wider system level and in other jurisdictions. However, there is limited data within this field and our study contributes to a greater understanding of the cost of treatment through a methodology not previously used. A limitation of these cost data is the imperfect capture of patient events that occur outside our institution. For example, patients may seek care for acute illnesses at local hospitals rather than returning to our tertiary care centre. However, manual abstraction of the data revealed that this occurred in less than 10% of the patients as it is routine clinical practice to document the development of interim complications at the next clinical visit. Out of pocket costs would not have been captured with this study methodology but they would represent a small fraction of the total cost (as they would only represent cost of stoma appliances and prescriptions (excluding chemotherapy) and therefore would be unlikely to meaningfully impact the conclusions of the study. Finally, as this study was completed from a healthcare institutional perspective this analysis does not recognize the nonmedical costs associated with bladder cancer care, which take into consideration contributions such as lost productivity from time spent in and recovering from treatment, which in the US account for over $100 million annually (85). This is an area for future research efforts to more fully understand the wider burden of MIBC treatment on patients and their families.

3.5 CONCLUSION

RC and TMT are appropriate options for the treatment of MIBC, although they exhibit differing cost characteristics. RC is more expensive upfront and exhibits much more varied costs reflective of the heterogeneity experienced in the perioperative phase. With increasing follow-up time after primary treatment, the cost difference between modalities is mitigated by the increased costs of ongoing surveillance in the TMT cohort.

4. DECISION MODEL

4.1 METHODS

4.1.a Model Overview

To assess the cost-effectiveness of MIBC management we completed a model-based economic evaluation of treatment strategies. Our analysis included three strategies in the primary analysis: NAC at current usage rates (36%), 100% utilization of NAC prior to RC, and molecular subtype-directed care for MIBC patients. An exploratory analysis using non-subtyped directed use of neoadjuvant immunotherapy was completed as well (i.e. all patients receive neoadjuvant immunotherapy). The model utilized a lifetime time horizon and cost-effectiveness is assessed from a healthcare payer perspective. Within cycle correction with a 1.5% discount rate was used to account for bias arising from discrete-time Markov models (11, 12).

We developed a two-dimensional Markov microsimulation to model the management of MIBC in TreeAge Pro 2019 (TreeAge Software Inc., Williamstown, MA). A Markov model simulates patients over time and allows for transitions between various health states as disease progresses. The primary outcomes were unadjusted survival and QALYs to determine effectiveness of the modelled strategies (objective 1), cost, and the incremental cost-effectiveness ratio (ICER) (objective 2). The ICER was assessed against a cost-effectiveness threshold of $50,000 Canadian dollars per QALY gained. As the current cost of the molecular subtyping test is unavailable, the maximum cost at which the molecular subtyping test would be cost-effective was evaluated (objective 3).

The Markov cycle length mimicked the clinical experience. Cycle length was three months long during the neoadjuvant chemotherapy, radical cystectomy and surveillance phases. During the recurrence phases (first- and second-line systemic therapy and palliative care) the cycle length was one month.

4.1.b Base Case

The base case for our model was an adult patient with MIBC (pT2-4 N0 M0) appropriate for NAC, immunotherapy and RC. Distributions representative of the typical MIBC population were used to simulate patients seen in clinical practice with individual level sampling for age and gender (Table 5).

Table 5: Distributions used for sampling patient level characteristics (all 1st order)

Variable	*Distribution Type*	*Distribution Parameters*	*Reference*
Age	Gamma	Mean: 68.8; SD: 10.6	Seisen et al 2017 (86)
Gender	Beta	Male: 0.75 Alpha: 17,055; Beta: 5,625 (modelled against uniform distribution)	Cahn et al 2017(77)

In each of the modelled strategies, regardless of whether patients were in the subtyped group, the model was structured such that patients were assigned their true molecular subtype identity. Only in the upfront subtyping arm were treatment decisions made based on this information. Table 6 presents the breakdown of the subtypes by prevalence (37). The model was built by modelling the underlying biology to ensure structural symmetry even in the non-subtyped arms.

Table 6: Muscle-invasive bladder cancer subtype prevalence

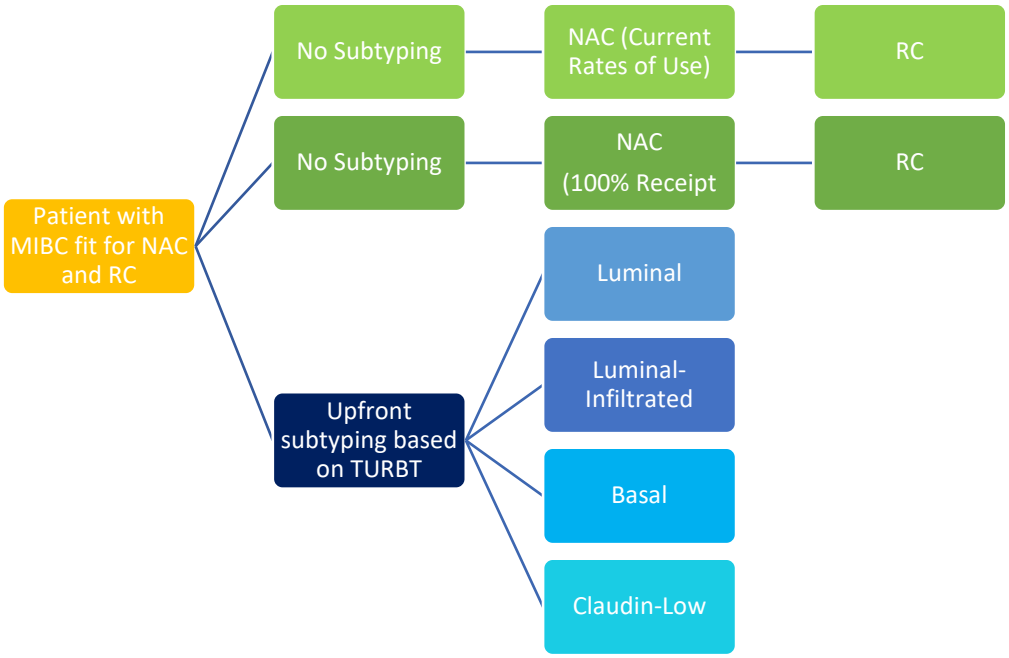
MIBC Subtype	Prevalence %
Luminal	41.6%
Luminal Infiltrated	12.7%
Basal	25.6%
Claudin-Low	20.1%

MIBC: muscle-invasive bladder cancer

4.1.c Model Structure

Figure 4 gives an overview of the model structure. The three strategies for primary analysis are depicted: current rates of use of NAC, universal use of NAC, and subtype directed care.

Figure 4: Overall model structure



NAC: neoadjuvant chemotherapy; MIBC: muscle-invasive bladder cancer; RC: radical cystectomy; TURBT: transurethral resection of bladder tumour

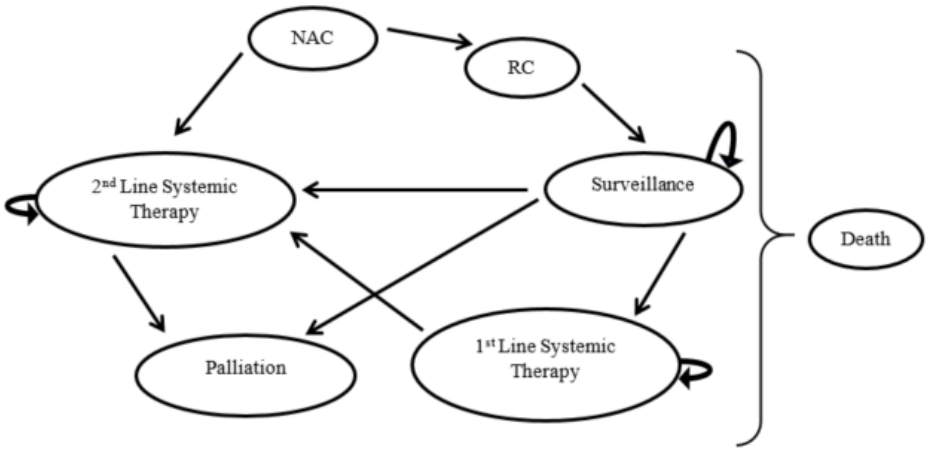
Figure 5 depicts the Markov state transition diagrams for the three arms. Patients could start either in the NAC or RC state. NAC consisted of four cycles of gemcitabine/cisplatin and during this state patients could experience adverse events that could impact their ability to complete chemotherapy and affect their downstream risk of disease recurrence. They also had a small risk of disease progression during treatment or death in this state. If disease progression occurred, patients moved to further systemic therapy, rather than RC.

Following NAC (if applicable), patients were treated with a RC for definitive management of their MIBC. They could experience peri-operative complications or mortality.

Complications were stratified into minor and major (based on Clavien Dindo grading) (87). The development of a major complication impacted peri-operative morality rates (88, 89). Following treatment, patients entered a post-cystectomy surveillance state. With each cycle, each patient had a risk of developing a complication (i.e. ureteric obstruction, parastomal hernia,), distant recurrence, and death.

If patients developed a distant, metastatic recurrence, they could be treated with either first line (platinum-based chemotherapy) or second line therapy. Patients received second line therapy if they had recurred within 12 months of receiving NAC. Eligibility for first line chemotherapy was based on the probability of a simulated patient having adequate renal function for cisplatin (defined as GFR $\geq$ 60mL/min), which decreased with age (90). Patients ineligible for cisplatin were treated with carboplatin (91). In the first line chemotherapy setting patients who received either cisplatin or carboplatin also received gemcitabine, in keeping with standard of care (92). Second line therapy was modelled as pembrolizumab in keeping with the inclusion criteria from the KEYNOTE-045 trial (93). Patients could also transition into a palliative state (best supportive care) if too ill for additional systemic therapy.

Figure 5: Markov state transition diagram



NAC: neoadjuvant chemotherapy; RC: radical cystectomy; MIBC: muscle invasive bladder cancer
NAC used as a representative state for any neoadjuvant therapy used in the corresponding arm

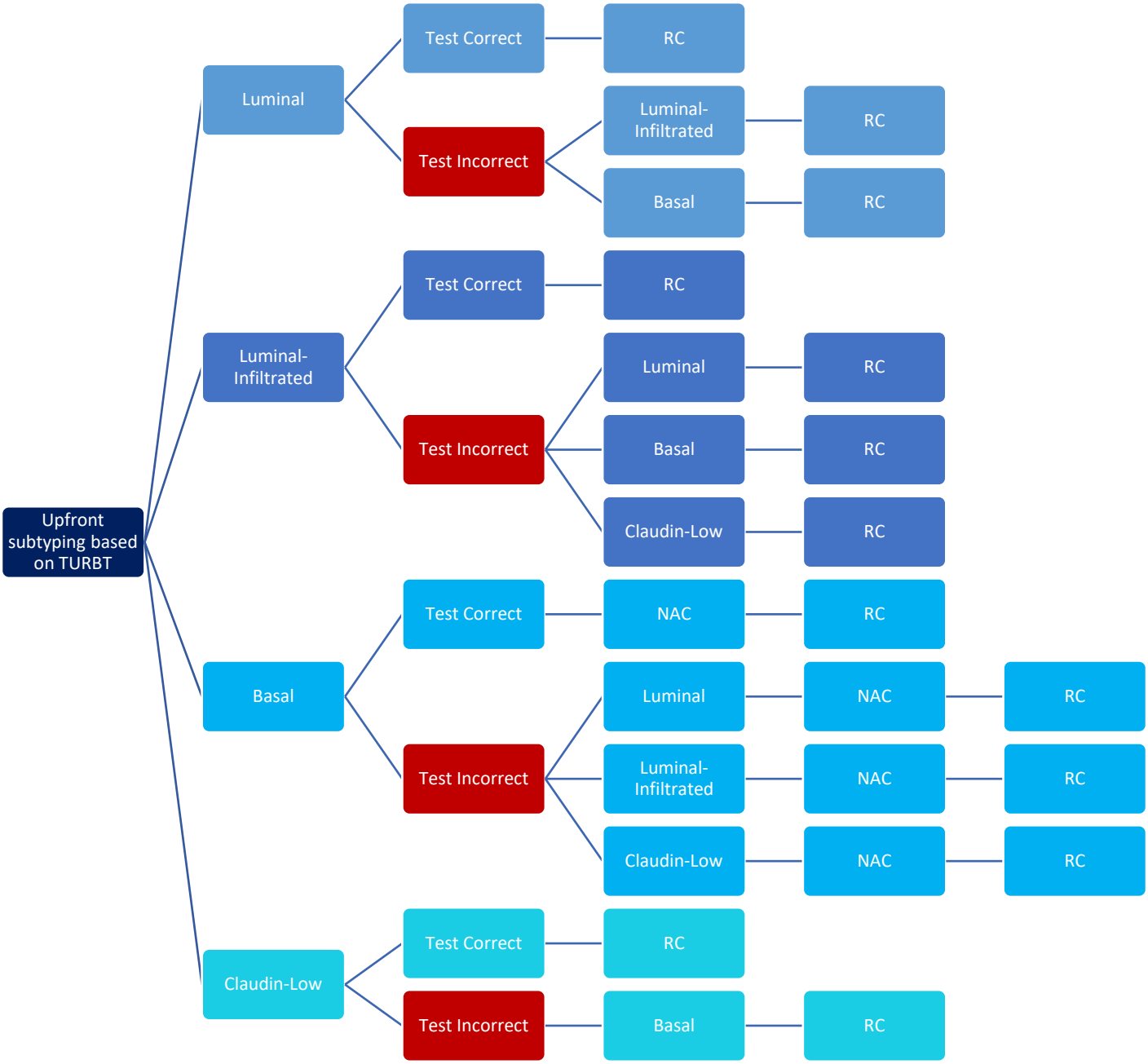
Test performance characteristics of the GSC were built into the structure of the model. For each of the individual subtypes, patients could in fact be the subtype that they tested as, or one of the other 3 subtypes. Their response to treatment, regardless of the test result, was based on their true identity but in the subtype directed arm, but they received treatment based on their GSC test result, not on their true subtype. The details of the test parameters are shown in Table 7.

Table 7: Test parameters of the genomic subtyping classifier (GSC)

GSC Test Subtype	**Luminal**	**Luminal Infiltrated**	**Basal**	**Claudin-Low**
Actual Subtype				
Luminal	**104 (82%)**	4 (10%)	5 (6%)	0
Luminal Infiltrated	19 (15%)	**23 (59%)**	6 (8%)	0
Basal	4 (3%)	11 (28%)	**55 (71%)**	15 (25%)
Claudin-Low	0	1 (3%)	12 (15%)	**46 (75%)**
Totals	127	39	78	61

Figure 6 is a schematic of the subtype-directed arm illustrating the treatments used in each of the different subtypes. Luminal, luminal infiltrated and claudin-low in the base case analysis all receive upfront cystectomy while basal subtypes receive NAC. While it appears that claudin-low may benefit from NAC based on the 3-year OS results (Table 9), longer term results demonstrate little to no benefit from the use of the therapy and thus the decision was made to model claudin-low proceeding to RC for the base-case analysis.

Figure 6: Structure of the subtype directed arm



NAC: neoadjuvant chemotherapy; RC: radical cystectomy; MIBC: muscle invasive bladder cancer

4.1.d Model Inputs

4.1.d.i Health State Transition Probabilities

A comprehensive search of MEDLINE and PubMed electronic databases was completed using MeSH and common language terminology:

"urinary bladder neoplasms" AND one or more of the following:

"antineoplastic agents" AND "neoadjuvant therapy"

"cystectomy"

"molecular subtype" OR "response prediction"

"pembrolizumab" OR "atezolizumab" OR "nivolumab" OR "immunotherapy"

"cost" OR "cost-effectiveness" OR "decision-analysis" OR "cost-benefit analysis" from initiation of the databases through January 30, 2020. This was supplemented by a hand search of references from retrieved studies, review articles, previous decision analyses and expert consultation. The published article that was most relevant to the research question, of the highest quality (i.e. randomized control trial, high quality cohort study) and suited the requirements of the model was used to inform parameter values for the model. A summary of the model probabilities is shown in Table 8.

Table 8: Probability estimates from the literature

Transition Probability	Value	Distribution Type	Source
Neoadjuvant Chemotherapy			
Probability of AE (Grade 3 or 4)	0.367	Beta	Neidersuss-Beke et al 2017 (94)
Completion of NAC	0.952	Beta	Neidersuss-Beke et al 2017 (94)
Current rates of NAC use	0.351	--	Krabbe et al 2015 (95)
Radical Cystectomy			
Any post-operative complication	0.68	Beta	Parekh et al 2018 (78)
Probability of major	0.22	Beta	Parekh et al 2018 (78)

complication (Clavien Dindo Grade 3 or 4)			
Surveillance			
Probability of complication	0.5 at 3 years	Weibull	Shimko et al 2011(96)
Probability of Recurrence	Dependent upon baseline subtype and treatment received (see Table 5)	Weibull	Seiler et al 2017 (37)
Probability of receiving first line systemic therapy	0.74	Beta	Bamias et al 2018(97)
Probability of being cisplatin ineligible	0.28 overall – age adjusted*	Beta	Dash et al 2006 (90)
First Line Systemic Therapy (Platinum Based)			
Probability of survival on cisplatin	0.50 at 14 months	Weibull	Von der Maase et al 2005 (98)
Probability of progression on cisplatin	0.50 at 7.7 months	Weibull	Von der Maase et al 2005 (98)
Probability of survival on carboplatin	0.50 at 9.3 months	Weibull	De Santis et al 2012 (91)
Probability of progression on carboplatin	0.50 at 4.9 months	Weibull	Linardou et al 2004 (99)

Probability of progression to second line therapy	0.38	Beta	Simeone et al 2019 (100)
Second Line Systemic Therapy (Pembrolizumab)			
Probability of survival	0.50 at 10.3 months	Weibull	Bellmunt et al 2017(93)
Probability of progression	0.50 at 2.1 months	Weibull	Bellmunt et al 2017(93)
Palliative Care			
Probability of survival	0.50 at 5.3 months	Weibull	Smith et al 2014 (101)
Baseline Probabilities			
Baseline non-cancer mortality	0.0021	Modified by age and gender	Calibration
Neoadjuvant Immunotherapy (exploratory analysis)			
Probability of AE (Grade ¾)	0.105	Beta	Powles et al 2019 (33)
Completion of IO	0.789	Beta	Powles et al 2019 (33)

*Probability of eligibility based on age as per Table 10

Table 9 depicts the overall survival results for the individual subtypes with and without NAC at the 3-year timepoint. Further information about modelling recurrence in this decision analysis is found in the discussion in Section 4.1.f.

Table 9: Probability of survival for each subtype with and without receipt of NAC prior to RC at 3-years

MIBC Subtype	3 Year OS (No NAC)	3 Year OS (Cisplatin-Based NAC)
Luminal	76.6%	74.7%
Luminal Infiltrated	59.4%	50.6%
Basal	49.2%	77.8%
Claudin-Low	43.1%	57.9%

OS: overall survival; MIBC: muscle-invasive bladder cancer; NAC: neoadjuvant chemotherapy

Table 10 shows cisplatin eligibility by age as a surrogate for the likelihood of having a creatinine clearance high enough to receive cisplatin as first line systemic therapy (90). The values shown in the table were used to create individual beta distributions for each simulated patient.

Table 10: Probability of cisplatin eligibility by age bracket

Age Bracket	Event (Ineligible)	Non-Event (Eligible)	Total Number	Percent Ineligible
<60	7	97	104	6.7%
61-70	26	136	162	16.0%
71-80	65	115	180	36.1%
>80	42	20	62	67.7%

4.1.d.ii Health State Utilities:

A search for utility values was completed using the Canadian Agency for Drugs and Technologies in Health (CADTH) search strategy (102). If available, primary utility data was used to populate appropriate states in the model. However, there is a paucity of primary data on utility values for bladder cancer in the literature. This limitation was handled in three main ways (detailed below): 1) conversion of primary health-related quality of life data (namely EORTC-QLQ-30 and EQ-5D to utility data); 2) literature search for primary utility data in other disease sites which share similar severity; 3) use of wide distributions for utilities in the model where there was uncertainty surrounding a point estimate (non-primary data) found in the literature. A summary of the utility values is shown in Table 11.

Table 11: Utility values from the literature

(shaded values indicate the utility value selected for the base case in the model)

Markov State	***Types of Patients***	***Description***	***Estimate***	***Method of Elicitation***	***Source***
Neoadjuvant Chemotherapy					
	Ovarian cancer	Advanced ovarian cancer	0.79	EORTC-QLQ-30	Chan et al 2003 (103)

		(stage III or IV) patients; QoL measured at 3-month mark during NAC			
	Esophageal cancer	QoL measured at completion of NAC	0.87	EORTC-QLQ-30	Sunde et al 2019 (104)
	MIBC		0.64	Expert opinion	Stevenson et al 2014 (48)
Neoadjuvant Chemotherapy AE					
	MIBC	Neutropenia	0.64	Expert opinion	Stevenson et al 2014 (48)
Radical Cystectomy Post-Operative State					
	MIBC	Derived from utilities associated with abdominal hysterectomy, colostomy creation and radical prostatectomy	0.8	Expert opinion	Kulkarni et al 2007 (68)
	MIBC		0.8	Expert opinion	Stevenson et al 2014 (48)
Radical Cystectomy Major Complication					
	MIBC	Small bowel obstruction requiring surgical intervention	0.55	Expert opinion	Stevenson et al 2014 (48)
	MIBC	Pulmonary embolus	0.62	Expert opinion	Stevenson et al 2014 (48)
	MIBC	Abscess with conservative management	0.64	Expert opinion	Stevenson et al 2014 (48)
Cystectomy Minor Complication					
	MIBC	Acute illness (cellulitis, line infection and wound infection)	0.64	Expert opinion	Stevenson et al 2014 (48)
	MIBC	Urinary tract infection	0.73	Expert opinion	Stevenson et al 2014 (48)

	MIBC	Deep vein thrombosis	0.67	Expert opinion	Stevenson et al 2014 (48)
Cystectomy Surveillance State					
	MIBC	Standard gamble completed with urologists and urology trainees	0.96	Standard Gamble	Kulkarni et al 2007 (68)
	MIBC	Best case and worst-case scenarios taken from EQ-5D data	0.754-1	EQ-5D	Tejido-Sanchez et al 2014 (105)
	MIBC	QoL measured at a mean of 3.5 years post RC	0.89409 (range: 0.802501-0.985679)	EORTC-QLQ-30	Sogni et al 2008 (106)
	MIBC	QoL data measured >2 years after RC	0.88372 (range: 0.75415-1)	EORTC-QLQ-30	Mak et al 2016 (107)
Complication in the Cystectomy Surveillance State					
	MIBC	Nephrostomy tube	0.75	Expert opinion	Stevenson et al 2014 (48)
	MIBC	Urinary tract infection	0.73	Expert opinion	Stevenson et al 2014 (48)
	MIBC	Fistula	0.68	Expert opinion	Stevenson et al 2014 (48)
First Line Systemic Therapy (Platinum-Based Chemotherapy)					
	MIBC	Derived from breast cancer literature originally	0.62	Expert opinion	Kulkarni et al 2007 (68)
	MIBC	Composite outcome of progression-free and progression utilities	0.69	Expert Opinion	Criss et al 2019 (108)
	MIBC	Pts with locally advanced or metastatic MIBC; baseline scores prior to	0.83	EORTC-QLQ-30	Roychowdhury et al 2003 (109)

		initiation of chemotherapy			
Second Line Systemic Therapy (Pembrolizumab)					
	MIBC	Patients without progression from KEYNOTE-052 study	0.842	EQ-5D	Patterson et al 2019 (110)
	MIBC	Patients with progression from KEYNOTE-052 study	0.800	EQ-5D	Patterson et al 2019 (110)
	MIBC	Progression and progression-free survival from KEYNOTE-045	0.61	EORTC-QLQ-C30	Sarfaty et al 2018 (111)
Palliative Care					
	MIBC	Derived from breast cancer literature originally	0.3	Expert opinion	Kulkarni et al 2007 (68)
Neoadjuvant Immunotherapy (exploratory analysis)					
	MIBC	Pembrolizumab in second line	0.865	EORTC-QLQ-30	Srivastava et al 2018 (112)
Neoadjuvant Immunotherapy AE					
	MIBC	Progression free survival with an AE	0.8	EORTC-QLQ-30	Srivastava et al 2018 (112)

The utility values from the literature were recorded in Table 11 and grouped according to the appropriate health state. As a consistent source was not available to use for the population of the utility values, it was important to ensure that health state utility values were appropriate in the context of other health states. In order to determine which set of utilities were the most appropriate for the current model, the Markov states were ranked in order from highest to lowest utility values, based on clinical considerations (Table 12).

Table 12: Ordering of states by utility (from best to worst)

Health State
Perfect Health
Post-Cystectomy Surveillance
Neoadjuvant Immunotherapy State (exploratory analysis)
Post-operative Cystectomy State
Neoadjuvant Chemotherapy State
First Line Systemic Therapy (Platinum Based Chemotherapy)
Second Line Systemic Therapy (Pembrolizumab)
Palliative Care
Death

Using previously established mapping algorithms existing quality of life data were converted to utility data. Results from the EQ-5D questionnaires were converted to time trade-off (TTO) utility data to be applied to the model using an algorithm created by van Hout et al modified for the Canadian experience using the accompanying R package (R Foundation for Statistical Computing, Vienna, Austria – eq5d package) (113). Transformation of EORTC-QLQ-30 data to utilities was completed using the algorithm derived by Kim et al (114).

In situations where no quality of life data or utility data were available in the bladder cancer setting, other disease sites were used as a surrogate. There was no literature regarding the quality of life of patients receiving neoadjuvant chemotherapy in MIBC (115) and therefore these data points were derived from alternate disease sites. Two different malignancies were evaluated (ovarian and esophageal) as they use chemotherapy agents from the same classes and affect patients in a similar age distribution.

In some cases, when converting quality of life data (EORTC-QLQ-30 and EQ-5D), no ranges or standard deviations were available from the primary literature and only point estimates could be converted to utility data. Therefore, when a standard deviation was not provided, it was

calculated using standard frequentist methods that assume a normal sampling distribution (according to the formula, [p(1-p)/N^1/2])(116). This method was also used to generate the distribution for point estimates obtained from the literature, if possible. If this could not be calculated due to the absence of a sample size from the original study, then a variance of ± 20% was assumed.

Utilities were chosen based on:

1. Their fit with respect to other states (ordering of utility scores had to match the order shown in Table 12)
2. The population source (wherever possible, utilities derived from the community were used, as this has been considered the ideal manner to articulate society's preferences for particular health states (117).
3. The elicitation method (where possible, either standard gamble or time-trade off approaches were prioritized over visual analogue scales or expert opinion).
4. Specificity to muscle-invasive bladder cancer whenever possible, otherwise, utilities derived for states that were specific to colon cancer were used. In some cases (such as for NAC), this was not possible, and utilities derived from other types of cancer were used.
5. Sample size: utility values derived from large sample sizes were preferred over small sample sizes.

In the case of adverse events post-operatively (minor and major) as well as during surveillance, the identified adverse event utility scores were averaged to create a composite utility value for the base case. The variance of 20% was used to create the normal distribution around the value for the probabilistic sensitivity analysis. This utility value was then was then applied in the model for remainder of that cycle.

Parameter estimates, standard deviations and data sources for the base case utilities are shown in Table 13

Table 13: Utility weights assigned to each state

Health State	***Mean Value***	***Std Dev***	***Distribution Type***	***Source***
Neoadjuvant Chemotherapy	0.79	0.040	Normal	Chan et al 2002 (103)
Neoadjuvant Chemotherapy AE	0.64	0.01	Normal	Stevenson et al 2014 (48)
Cystectomy Post-Operative State	0.8	0.053	Normal	Kulkarni et al 2007 (68)
Minor Post-Operative Complication	0.68	0.008	Normal	Stevenson et al 2014 (48)
Major Post-Operative Complication	0.61	0.012	Normal	Stevenson et al 2014 (48)
Post-Cystectomy Surveillance State	0.96	0.00768	Normal	Kulkarni et al 2007 (68)
Post-Cystectomy Complication during Surveillance	0.72	0.016	Normal	Stevenson et al 2014 (48)
First Line Systemic Therapy	0.69	0.046	Normal	Criss et al 2019 (108)
Second Line Systemic Therapy	0.61	0.041	Normal	Sarfaty et al 2018 (111)
Palliative Care	0.3	0.02	Normal	Kulkarni et al 2007 (68)
Neoadjuvant Immunotherapy	0.865	0.0028	Normal	Srivastava et al 2018 (112)

Neoadjuvant Immunotherapy AE	0.798 (-0.067)	0.0056	Normal	Srivastava et al 2018 (112)

AE: adverse event

4.1.d.iii Health State Costs:

Costs from our single-centre retrospective study were applied where appropriate to the Markov states in this model. States populated by the primary costing study were cystectomy and ongoing follow-up costs. These values incorporate the cost of cystectomy, peri-operative complications, surveillance, and the cost of managing complications in the surveillance health state. Recurrence cost data, due to the narrow follow up window of the primary costing study, likely did not capture the entirety of costs for patients with recurrence. Moreover, no immunotherapy agents were approved for use in urothelial cancer in the era of the primary costing study and therefore would not represent the costs of their use.

Costs available from the literature were used to supplement our study to populate the model. The individual components required to develop a cost estimate for various health states are shown in Table 14. For patients receiving systemic therapy (either neoadjuvantly or in the metastatic setting) the following cost components were accounted for the in the cost per cycle: drug acquisition, hospital administration, laboratory testing, physician assessment and physician oversight during infusion. In cases where no standard deviation or range was available, a variance of ±20% was assumed and used in the creation of the base case distribution. Neoadjuvant chemotherapy costs were not used from the primary costing study as, due to the sample size, there were minimal complications and therefore, we were unable to ascertain with high reliability the cost of therapy with, and without, treatment of complications.

All costs were inflated to 2019 Canadian dollars using the Consumer Price Index (CPI) (51, 71). As there is no healthcare CPI that incorporates physician and hospital services, it is

appropriate to use the general CPI for all goods and services (118). Parameters estimates, standard deviations, distribution types and sources for the costs used in the model are shown in Table 15.

Table 14: Individual cost components

Parameter	Cost	Volume (Units)	Source
Gemcitabine Drug Cost	$216	28-day cycle	pCODR 2019 (119)
Cisplatin Drug Cost	$467.88	28-day cycle	pCODR 2020 (120)
Carboplatin Drug Cost	$1037.96	28-day cycle	pCODR 2020 (120)
Initial Medical Oncology Assessment (A135)	$157	1 initial value for NAC and systemic recurrence	Ontario Physician Fee Schedule (121)
Medical Oncology Follow Up (A138)	$38.05	1 per cycle of chemotherapy/immunotherapy	Ontario Physician Fee Schedule (121)
Physician Chemotherapy Administration Fee (G345)	$75	2 per chemotherapy cycle; 1 per immunotherapy cycle	Ontario Physician Fee Schedule (121)
Hospital Chemotherapy Administration Cost	$359	2 per chemotherapy cycle; 1 per immunotherapy cycle	Ontario Ministry of Health (122)
Lab Fee	$13.13	1 per chemotherapy cycle	Schedule of Benefits for Laboratory Services (123)
Chemotherapy Adverse Event (Hospitalization)	$6,300		CIHI 2018 (124)
Pembrolizumab Drug Cost	$11,733	200mg dose/cycle	pCODR 2019 (119)

Atezolizumab Drug Cost– neoadjuvant immunotherapy (exploratory analysis	$6,776	1200mg dose/cycle	pCODR 2018 (125)

Table 15: Cost estimates

Markov Health State	***Value***	***Std Dev***	***Distribution***	***Source***
Neoadjuvant Chemotherapy	$7,395.19/3 months	$493	Normal	Composite of above costs (Table 14)
NAC Adverse Event	$6,300	$420	Normal	CIHI 2018 (124)
Cystectomy	$30,477.79	$2,300	Normal	Retrospective UHN study
Surveillance Year 1	$3,890.66/year	$910	Gamma	Retrospective UHN study
Surveillance Year 2	$2,187.32/year	$1200	Gamma*	Retrospective UHN study
Surveillance Year 3	$1,899.16/year	$500	Gamma**	Retrospective UHN study
Surveillance Year 4	$1,103.67/year	$300	Gamma†	Retrospective UHN study
Surveillance Year 5	$2,076.06/year	$1000	Gamma‡	Retrospective UHN study
First Line Systemic Therapy (Cisplatin)	$1,819.06/month	$120	Gamma	Composite of above costs (Table 14)
First Line Systemic Therapy (Carboplatin)	$2,389.14/month	$160	Gamma	Composite of above costs (Table 14)
Second Line Systemic Therapy (Pembrolizumab)	$12,218.18/month	$815	Gamma	Composite of above costs (Table 14)
Palliative Care	$847.21/month	$56	Gamma	Criss et al 2019 (126)
Death	$8,833.09	$588.86	Normal	CIHI 2018 (124)
Molecular Subtype Test	$2,600	$175	Normal	Lotan et al 2018 (127)
Neoadjuvant Immunotherapy (Atezolizumab) – exploratory analysis	14,522.36/3 months	$968.16	Normal	pCODR 2018 (125)

**modified such that minimum is $1600; **modified such that minimum is $1200; † modified such that minimum is $800; ‡modified such that minimum is $600. Distribution lower limits modified such that bounds of the distribution did not surpass the absolute minimum values seen in the retrospective study.*

4.1.e Model Assumptions

Several assumptions were made in the development of this model. The assumption, the rationale for it and the potential effect on the model are laid out in Table 16.

Table 16: Model assumptions

Assumption	***Rationale***	***Effect***
Structural Assumptions		
Patients must progress by entering the recurrence state (i.e. first- or second-line systemic therapy or palliative care).	This is because death from urothelial cancer usually occurs after metastatic spread, rather than from localized disease (92).	May slightly increase survival, but at most by 3 months.
Patients have one true molecular subtype rather than exhibiting tumour heterogeneity.	While it is understood that most tumours likely have internal heterogeneity along a gradient, it is unclear what the impact of this is clinically (128). Cases with their misclassification are nested within the studied cohorts and therefore individual response/non-response is aggregated in the larger assessment of accuracy and response prediction(129); the imprecision is thereby built into the model.	This may lead, in clinical practice, to non-differential misclassification bias; from a modelling perspective it may over-simplify the treatment decisions stemming from this model for individual patients.
Transition Probability Assumptions		
Risk of progression and death while receiving systemic therapy for metastatic disease is independent of the molecular subtype or previous receipt of NAC.	There is evidence of post-chemotherapy molecular changes, however evidence of differential response to chemotherapy in the metastatic setting has not be demonstrated (130).	This may lead to an under or overestimation of survival, but these cases would have been nested within the data used to populate the model. It does, however, prevent the use molecular subtypes to inform patients about survival or progression rates based on

		underlying subtypes in the metastatic setting.
The receipt of NAC (or neoadjuvant immunotherapy) did not impact the risk of peri-operative complications.	The receipt of NAC or neoadjuvant immunotherapy has not been shown to alter the risk of peri-operative complications (32, 33, 131).	This may underestimate the incidence of complications and therefore the short-term disutility experienced by patients.
Patients were required to receive 3 out of 4 cycles of NAC to modify their risk of recurrence.	Completion of 3 out of 4 cycles of chemotherapy is clinically accepted as a benchmark for completion of chemotherapy.	May underestimate the effect of NAC/neoadjuvant immunotherapy if fewer doses do indeed have an impact on the disease trajectory.
Cisplatin eligibility was defined as the likelihood of having a GFR ≥ 60mL/min based on age.	There is strong evidence of renal decline being correlated with increasing age (90).	May overestimate the number of patients eligible for cisplatin as there are other, non-renal function factors, that can impact eligibility (ECOG status, heart failure, neuropathy/hearing loss)(27). This may bias survival results as patients who receive cisplatin have longer survival than those who receive carboplatin, comparatively (3). However, the bias would be applied essentially equally across all arms of the model in the metastatic setting.
Outcome Assumptions		
All RC were assumed to be open, rather than with minimally invasive surgical approaches (laparoscopic or robotic).	No difference QoL has been reported between open and MIS cystectomies (78). Moreover, no difference in risk of recurrence or survival has been noted for MIS or open RC (132).	May underestimate overall costs as robotic RC is more expensive due to the extra equipment.
Patients required one routine out-patient appointment with a medical oncologist per treatment cycle.	This is guided by common clinical practice.	May either over- or under-estimate costs, depending on actual number of visits with a medical oncologist.
It was assumed that resource use for treating adverse events was the same for patients receiving NAC or neoadjuvant immunotherapy.	Most patients with a Grade 3+ complication require hospital admission for management of the event	This may overestimate the costs since not all Grade 3+ events may require a hospital admission. The impact of this

	regardless of the etiology of the event.	was evaluated through a sensitivity analysis.

4.1.f Modelling Recurrence

For each of the four subtypes, simulated patients had a risk of recurrence based on their underlying subtype and the type of treatment they received (either upfront RC or NAC prior to RC). In their paper, Seiler et al, reported overall survival (OS) curves for each subtype with and without the receipt of NAC prior to RC. In order to appropriately account for the benefit (or harm) and associated costs of downstream events following the administration of NAC or the receipt of a RC the structure of the model was built on progression, rather than OS. As a result, calibration was necessary to determine a progression function for the model which would allow progression to vary based on time (rather than being a constant variable).

In order to determine the appropriate function, the original OS curves from the published manuscript were digitized using DigitizeIt (DigitizeIt Inc, Braunschweig, Germany). Using a simulated annealing Excel program, the digitized curves were converted to a Weibull curve. Goodness of fit was assessed using Euclidian distance. Multiple runs of the simulated annealing program were completed for each curve to ensure that the true minimum was reached rather than a local minimum. Since the OS curves had excellent comparability to the Weibull functions, and from clinical knowledge of how progression-free survival correlates to OS, a Weibull function was chosen as the target function.

The digitized data from the original OS curves were then used as targets for the calibration of the Weibull distribution parameters (lambda and shape). The DistTransProb function (built into TreeAge) was used to calculate the transition probability for every cycle based on the underlying Weibull distribution. (133).

4.1.g Calibration

Calibration of several parameters was necessary in the development of this model due to lack of data in the literature for some transition probability parameters. Model calibration involves an iterative process of adjusting key model parameters in order to tune the decision model so that its output matches observed data (134). Weibull function parameters defining the progression curves for the individual subtypes with and without NAC were calibrated as well as the baseline non-cancer mortality risk. We felt that population lifetable could not be used for the baseline mortality risk since they represent an otherwise healthy population and therefore were not applicable to patients with a prior MIBC diagnosis.

For the individual subtype progression curves, the Weibull parameters were calibrated against the 1-, 3- and 5- year OS results for each respective subtype reported by Seiler et al (37). The first calibration to be completed was the luminal subtype without NAC; this was done simultaneously with the calibration for baseline mortality (and its associated modifying covariates: age, gender). Luminal without NAC was chosen as the optimal parameter to calibrate baseline mortality with since it has the best overall survival of all subtypes and therefore would not lead us to overestimate the baseline mortality to account for the poor survival in the other arms. Latin hypercube sampling was used as the parameter search strategy (135) and goodness of fit (GOF) was assessed by calculating unweighted Euclidian distances.

$$GOF = \left[\sum_{i}^{T} (obs_i - pred_i)^2 \right]^{1/2}$$

The lowest GOF score that was derived from the combination of parameters (for the Weibull parameters – lambda and shape) that fell within 10% of the target values was used to guide the termination of calibration after at least three separate calibration runs.

4.1.h Validation

We assessed internal model validity by assessing for face validity of results, placement of internal trackers and ensuring the model flowed logically through the stages. We assessed external validity by evaluating our model's ability to reproduce overall survival rates in the absence of NAC and current rates of NAC when compared to data not used in the development or parameterization of the model. We also assessed external validity by determining the absolute benefit derived from NAC (comparing 0% usage to 100% usage) compared to that which has historically been reported.

4.1.i Sensitivity Analyses

The cost-effectiveness of each strategy was estimated through a probabilistic sensitivity analysis (PSA) as per CADTH guidelines as it provides a less biased estimate of costs and outcomes than deterministic analyses (58). A cost-effectiveness threshold of $50,000 per QALY gained was used as this is the most common threshold and the most conservative measure of cost-effectiveness (51).

In addition to the PSA, a deterministic sensitivity analysis was conducted to evaluate the impact of varying the cost of the molecular subtype test. Further, a range of scenario analyses were conducted whereby the prevalence of each subtype was altered to reflect the respective prevalence seen in other papers (Table 17).

Table 17: Alternate subtype prevalence values

Molecular Subtype	Rosenberg et al 2016 *(18)*	Sharma et al 2017 *(17)*	Seiler et al 2017 *(37)*(Base Case)
Luminal	37.0%	35.9%	41.6%
Luminal Infiltrated	25.6%	29.9%	12.7%
Basal	19.5%	16.3%	25.6%
Claudin-Low	17.9%	17.9%	20.1%

The cost of a NAC associated adverse event was also assessed through the use of sensitivity analyses. In the base case model, all patients with an NAC associated adverse event were assumed to be admitted for treatment. In the sensitivity analysis, the cost of the adverse event was adjusted such that 10% of events required a hospital admission (and the corresponding cost - $6,300), whereas the other 90% required only the cost of a medical oncology appointment (125).

4.1.j Exploratory Analysis

An exploratory analysis was completed evaluating the use of neoadjuvant immunotherapy prior to RC. This analysis is hypothesis generating only because the literature does not yet exist demonstrating how neoadjuvant immunotherapy impacts progression and survival for each subtype. In this analysis, all patients are assumed to receive the neoadjuvant atezolizumab based on the results from the ABACUS trial (33). However, as there is no actionable subtyping data provided in this paper, or in the PURE-01 trial (evaluating neoadjuvant pembrolizumab) the benefit was applied non-differentially (32). It was assumed that patients needed to receive both cycles of atezolizumab in order to derive benefit from the therapy, which may bias results towards seeing a decreased effect from neoadjuvant immunotherapy.

This analysis can only be hypothesis generating as it lacks structural symmetry with the underpinnings of the other arms (i.e. response to treatment predicated on the underlying subtype). This analysis did allow us to gain insight into the relative frequency of adverse events anticipated by universal use of immunotherapy in this setting and the anticipated costs associated with its use.

4.1.k Sample Size Calculation

First-order Monte Carlo simulation models patient-level stochasticity, whereas second-order Monte Carlo simulation models parameter uncertainty. The sample sizes necessary to achieve model stability were determined in a two-step process. In the first step, the number of first-order iterations were determined. Sequentially higher numbers of iterations were run and then plotted to allow for graphic assessment of stability (Figure 7). First order stability was reached at 15,000 trials. After determination of the lowest number of first order trials necessary for stability, sequential runs were completed with increasing numbers of second order samples. The results were plotted for graphical assessment. Second order stability was reached at 1000 samples (Figure 8).

Figure 7: First-order sample size determination

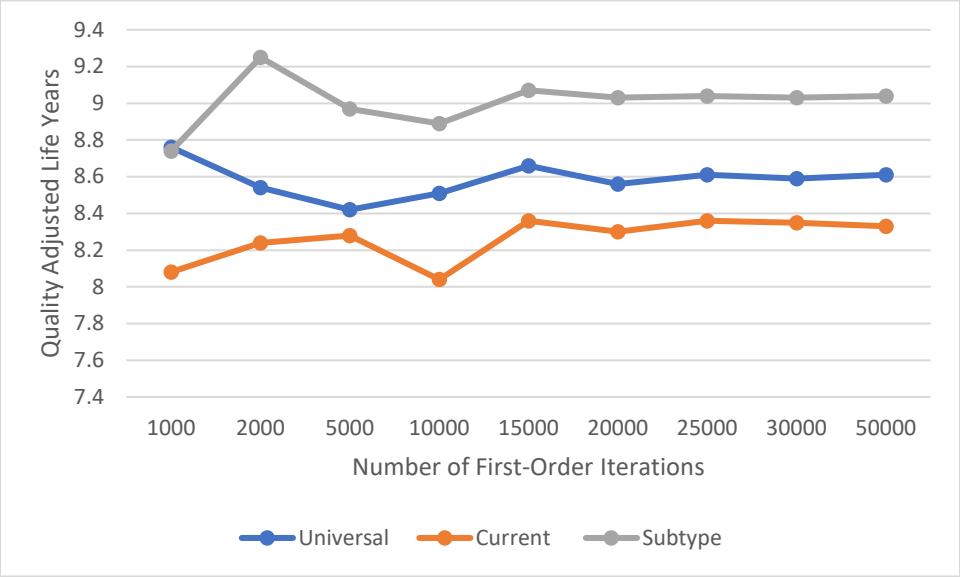
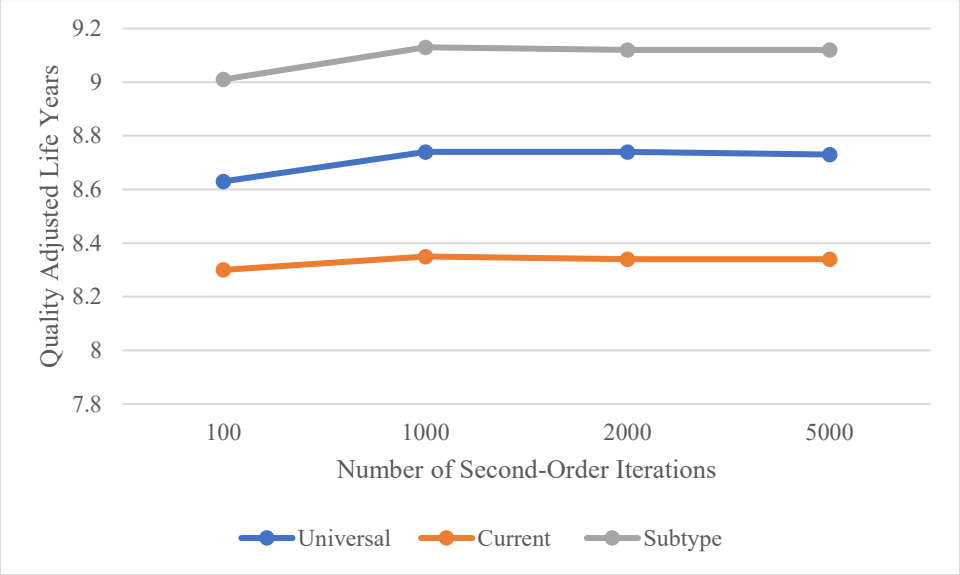


Figure 8: Second-order sample size determination



4.2 VALIDATION

4.2.a Internal Validity

Face validity was completed and agreed upon with urologic oncology content experts. No further modifications were suggested. Sensitivity analyses and internal trackers which were used

to assess for plausibility of variable relationships and logical consistency of the model structure demonstrated internal agreement.

Internal validity was assessed by comparing the accuracy of the individual components of the model outputs against reference literature outcomes. For internal validation, we used the published three-year OS results of each molecular subtype with and without NAC. Our model was able to predict outcomes to within 3.5% of the published values and most values were within 2-4% of the published value (Table 18). These were calibrated Weibull curves and demonstrate the validity of the LHS calibration method.

Table 18: Comparison of simulated cohort against reference literature outcomes for assessment of model internal validity (37)

MIBC Subtype	***Published Results (No NAC)***	***Simulated Cohort Results (No NAC)***	***Absolute Difference***	***Published Results (NAC)***	***Simulated Cohort Results (NAC)***	***Absolute Difference***
	3-Year OS Results					
Luminal	76.6%	76.0%	-0.6%	74.7%	72.0%	-2.7%
Luminal Infiltrated	59.4%	57.5%	-1.9%	50.6%	52.0%	+1.4%
Basal	49.2%	49.2%	0%	77.8%	78.9%	+1.1%
Claudin-Low	43.1%	42.2%	-0.9%	57.9%	54.4%	-3.5%

4.2.b External Validity

The OS rates at 1-, 3-, and 5- years from the simulated cohort who did not receive NAC were compared to published literature not used in the development of the model. Our results at 1-, 3-, and 5-years fall well within the bounds of the published literature rates (Table 19).

Table 19: Comparison of simulated cohort who did not receive NAC against historical published cohorts

Overall Survival	*Simulated Cohort (No NAC)*	*Madersbacher et al 2003 (136)*	*Hautmann et al 2012 (137)*	*Advanced Bladder Cancer Meta-Analysis 2005 (7)*
1 Year	81.8%	83.8%	76.7%	77.4%
3 Year	59.4%	64.7%	54.7%	52.1%
5 Year	51.2%	58.6%	44.2%	43.3%

We also assessed external validity of our model by comparing our simulated universal NAC usage arm to published literature not used in the model development. Our results fall within the bounds of the published literature at 1- and 5-years and within 5% of the published results at 3-years indicating acceptability of our results (Table 20).

Table 20: Comparison of simulated universal NAC cohort against published results

Overall Survival	*Simulated Cohort (Universal NAC)*	*Niedersuss-Beke et al 2017 (94)*	*Advanced Bladder Cancer Meta-Analysis 2005 (7)*
1 Year	84.8%	88.2%	82.4%
3 Year	66.6%	63.7%	56.8%
5 Year	56.7%	61.1%	48.6%

4.3 RESULTS

4.3.a Model Outputs

For the base case, the overall survival results at 1-, 3-, 5- and 10-years are shown in Table 21.

Table 21: Overall survival results

Overall Survival	*Current NAC Usage*	*Universal NAC Usage*	*Subtype Directed Care*
1 Year	82.8%	84.8%	84.0%
3 Year	62.0%	66.6%	64.7%
5 Year	53.1%	56.7%	56.5%
10 Year	39.2%	40.8%	42.8%

The predicted discounted quality adjusted life years (QALY) were 8.34, 8.73, and 9.14 for NAC at current usage rates, universal NAC usage, and subtype directed care, respectively.

The average cost was $62,478, $76,962, and $62,579 for NAC at current usage rates, universal NAC usage, and subtype directed care, respectively. When comparing subtype directed care to current rates of NAC usage the ICER was $127/QALY. Subtype directed care dominates universal NAC usage.

Overall, 94.2% of patients completed NAC in the universal use arm versus 33.9% in the current rate arm and 24.1% in the subtype directed arm. Patients in the universal NAC arm experienced a greater number of CTCAE grade 3 or higher chemotherapy adverse events (36.9%) compared with the current rates of use arm (13.3%) and the subtype directed arm (9.4%).

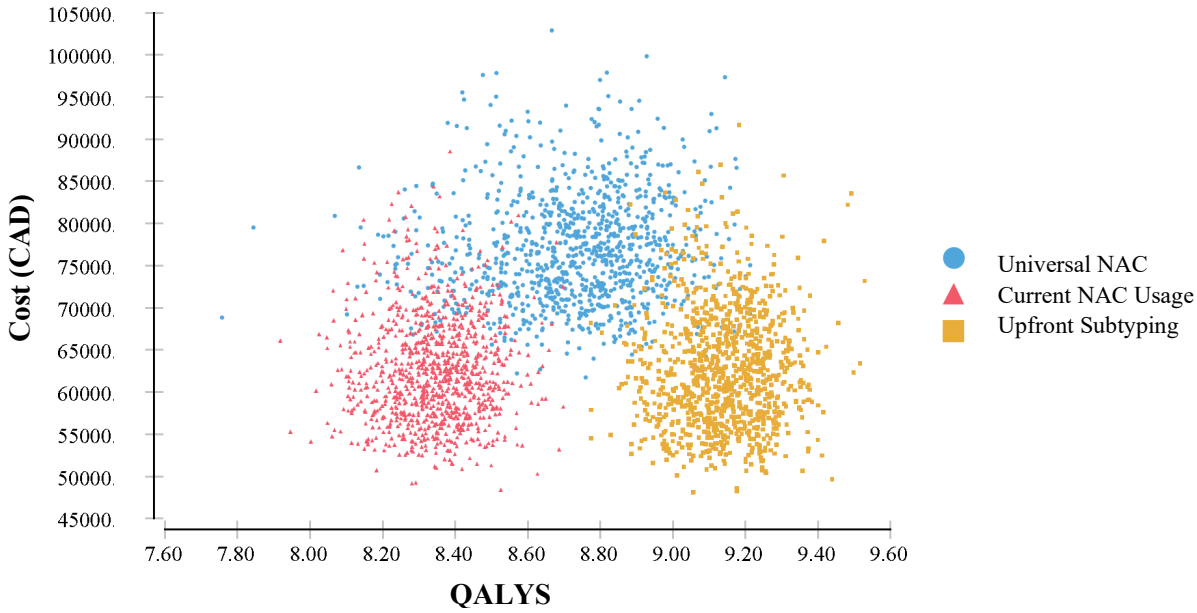
As the ICER for subtype directed care compared with current rates of NAC usage is so low ($127/QALY), subtype directed treatment remains cost-effective at a cost-effectiveness threshold of $50,000/QALY even if the cost of the molecular subtyping test is high.

4.3.b Sensitivity Analysis

4.3.b.i Probabilistic Sensitivity Analysis

The cost-effectiveness of the three strategies was assessed by running 1,000 samples of 15,000 patients each and is depicted graphically in Figure 9. Universal NAC usage is consistently the most expensive therapy with the widest variability in efficacy compared to NAC at the current rates of use strategy which, while consistently the least expensive, also leads to the lowest QALYs. Subtype directed care, on average, provides the greatest number of QALYs at consistently lower costs than universal NAC use and similar costs to the current NAC usage rate strategy.

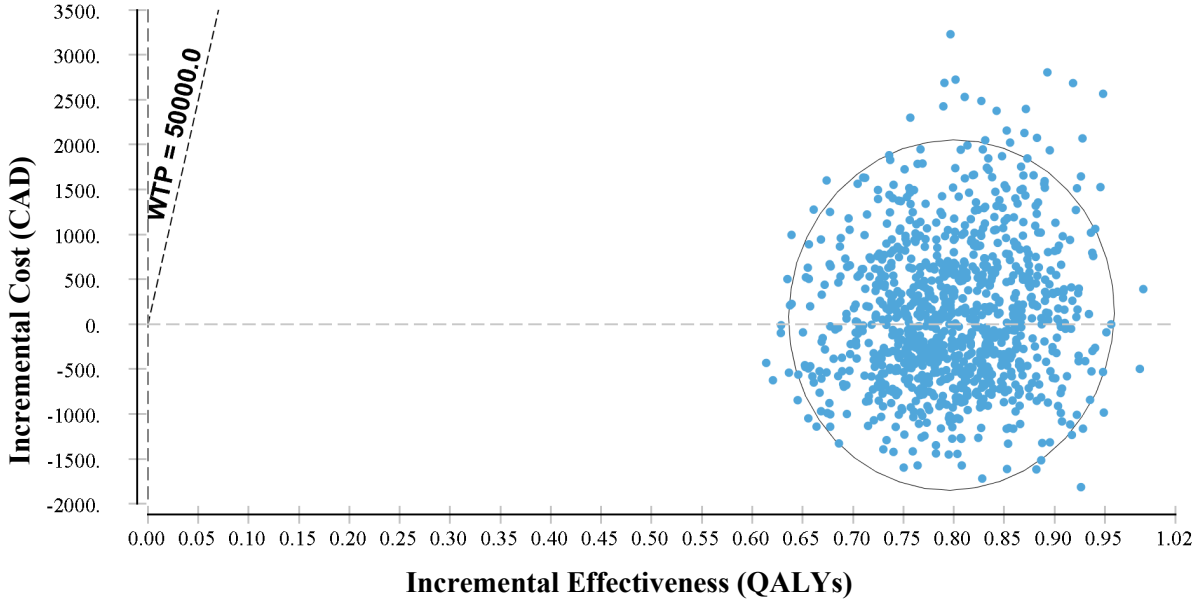
Figure 9: Cost-effectiveness scatterplot comparing the three primary strategies



Across 1,000 samples of 15,000 patients each, subtype directed care resulted in greater QALYs in all cases when compared with current rates of NAC use (Figure 10). The 95% confidence ellipse demonstrates variability between an increased QALY gain for the subtype directed strategy of approximately 0.64 to 0.96 at a cost of -$2000 to +$2000. In approximately 50% of cases, the cost of subtype directed care was the same cost or less than undirected use of

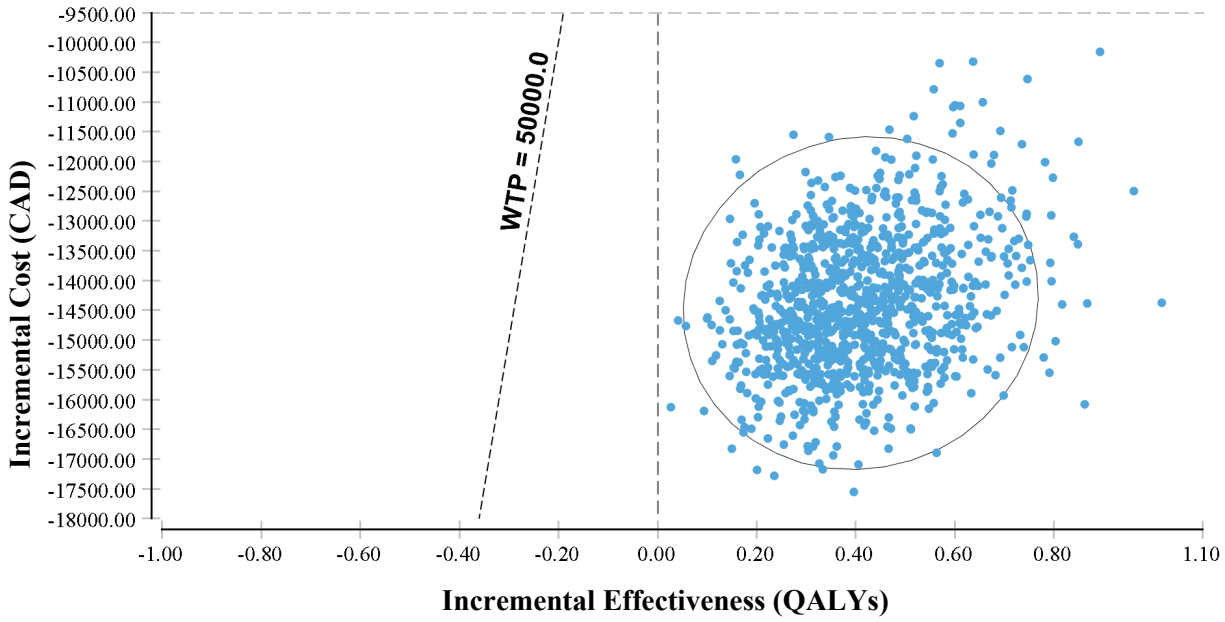
NAC at the current rates of use. The entirety of the 95% confidence ellipse and the remaining iterations outside its boundaries fell well below the pre-established $50,000 cost-effectiveness threshold. (Figure 10).

Figure 10: Incremental cost-effectiveness plot comparing upfront subtyping versus current rates of NAC usage with cost-effectiveness threshold (WTP) ($50,000) depicted



The incremental cost-effectiveness plot for subtype directed care versus universal NAC usage is shown in Figure 11. In all scenarios across 1,000 samples of 15,000 patients each, universal NAC usage was dominated by subtype directed care as universal NAC was more expensive and led to fewer QALYs gained. The 95% confidence ellipse demonstrated variability between an increased QALY gain for the subtype directed strategy of approximately 0.05 to 0.75 at a cost of -$12,000 to -$17,000. The cost-effectiveness threshold of $50,000 is also depicted.

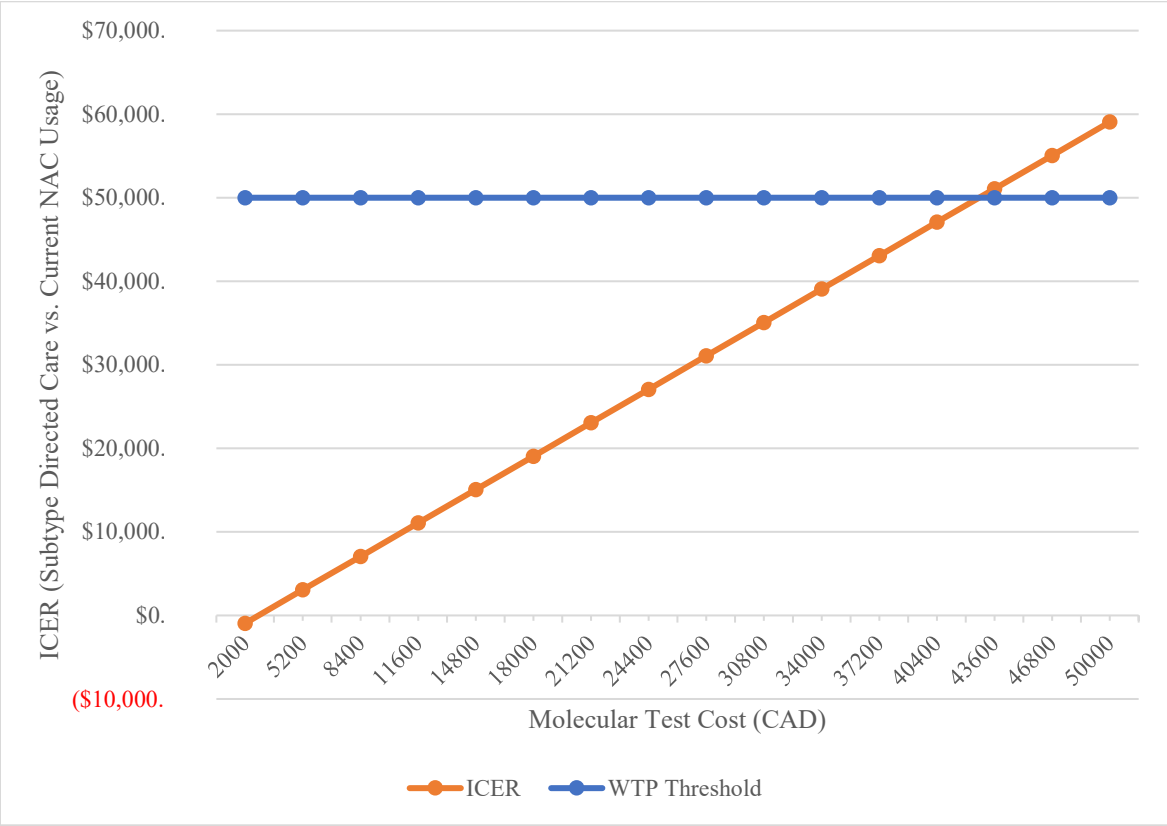
Figure 11: Incremental cost-effectiveness plot comparing upfront subtyping versus universal use of NAC with cost-effectiveness threshold (WTP)($50,000) depicted



4.3.b.ii Molecular Test Cost Analysis

The cost of the molecular subtyping test was altered sequentially from $2,000 to $50,0000 to evaluate the theoretical maximum cost for the molecular test while remaining cost-effective (defined by the $50,000 cost effectiveness threshold). At a test cost of approximately $40,000 the ICER of subtype directed care versus current NAC usage rates exceeds the threshold as seen in Figure 12.

Figure 12: Impact of molecular subtyping test cost on ICER when comparing subtype directed care to current rates of NAC usage



4.3.b.iii Impact of Changing Subtype Prevalence

The impact of changing the underlying prevalence of the individual subtypes was investigated by using the reported values from subtyping papers in the literature. The results are summarized in Table 22. If the proportion of luminal and basal subtypes decreases in the sampled population the overall QALY benefit derived from the subtype directed care arm diminishes and the incremental QALY gain between subtype directed care and universal NAC usage decreases.

Table 22: Outcome of changing the underlying proportion of subtypes the modelled population

	Current NAC Usage	Universal NAC	Subtype Directed Care
Base Case Proportions (Seiler)			
QALY	8.34	8.73	9.14
Cost	$62,478	$76,962	$62,579
Rosenberg Proportions			
QALY	8.13	8.50	8.69
Cost	$62,823	$76,964	$61,886
Sharma Proportions			
QALY	8.05	8.39	8.51
Cost	$63,292	$77,416	$61,783

4.2.c.iv Impact of Changing Cost of Neoadjuvant Chemotherapy Adverse Event

When the cost of adverse events experienced during NAC is, on average, lowered compared to the base case value of $6,300 to $771.30 the cost of all three strategies drops. The largest drop is seen in the universal NAC arm (Table 23). As a result, the ICER for universal NAC compared to current NAC usage decreases and the subtype directed care versus current NAC usage ICER increases due to the relative change in the cost of the NAC state.

Table 23: Outcome of changing the cost of NAC adverse events

Outcome	*Current NAC Usage*	*Universal NAC*	*Subtype Directed Care*
Base Case Cost	$62,478.17	$76,962	$62,579.90
*Base Case ICER**		$37,139/QALY	$127/QALY
Sensitivity Analysis Cost	$60,575	$71,521	$61,301
*Sensitivity Analysis ICER**		28,065/QALY	$907/QALY

**ICER compared to current NAC usage for both universal NAC and subtype directed care*
ICER: incremental cost-effectiveness ratio; NAC: neoadjuvant chemotherapy

4.2.c Exploratory Analysis

For our exploratory analysis where all patients received neoadjuvant immunotherapy and its effectiveness was applied in a non-differential fashion (i.e. patients with different underlying subtypes did not respond in varied ways to the immunotherapy) the predicted QALYs were greatest for those who received neoadjuvant immunotherapy compared to the other modeled strategies. This did however, come at a significantly higher cost compared to the other strategies (Table 24).

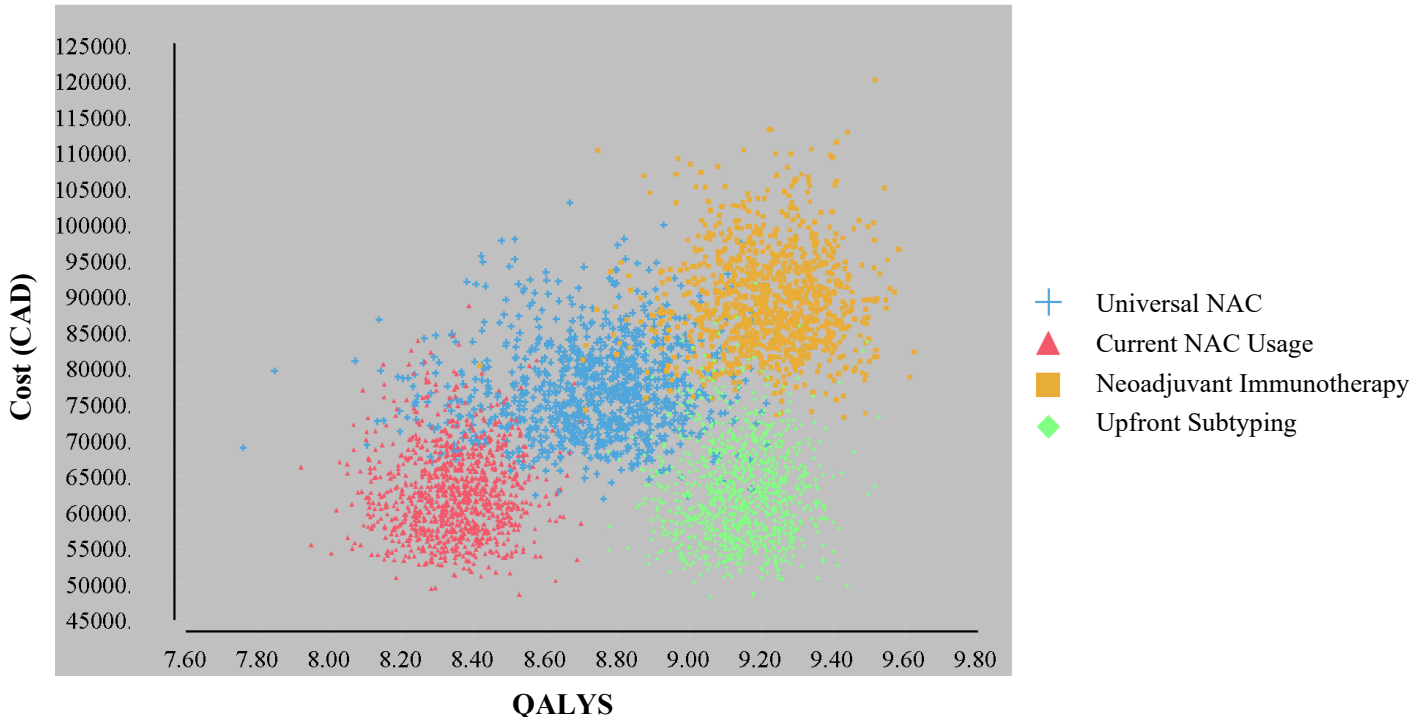
Table 24: Outcomes of neoadjuvant immunotherapy compared with primary strategies

Outcome	*Current NAC Usage*	*Universal NAC*	*Subtype Directed Care*	*Universal Neoadjuvant Immunotherapy*
QALY	8.34	8.73	9.14	9.22
Cost	$62,478	$76,962	$62,579	$89,263

The ICER of neoadjuvant immunotherapy compared to current NAC usage was $18,265.27/QALY and $25,104.08/QALY when compared to universal NAC. The ICER of universal immunotherapy compared to subtype directed care was $333,540.37/QALY.

Figure 13 illustrates the cost-effectiveness scatterplot with all four strategies depicted. Neoadjuvant immunotherapy is generally more effective but at a greater cost than the other three strategies modelled.

Figure 13: Cost-effectiveness scatterplot depicting all four strategies modelled



4.4 DISCUSSION

4.4.a Main Findings

This is the first study to demonstrate that a currently accessible molecular subtyping test could lead to improved survival for patients with MIBC. Our analysis evaluating NAC in patients with MIBC demonstrated that molecular subtype directed care resulted in a net gain of 0.80 QALYs compared to the current patterns of NAC usage and 0.41 in a setting of universal receipt of NAC. Moreover, we were also able to demonstrate that the use of molecular subtype directed care would be a cost-effective treatment within the context of the Canadian single payer healthcare environment. Subtype directed care resulted in an ICER of $127/QALY compared to the current use of NAC and dominated the use of universal NAC. This ICER falls well below the classically cited $50,000 cost-effectiveness threshold (51) and even further below more recent cost-effectiveness threshold estimates (double the per capita annual income (138); $200,000/QALY based on trends in healthcare spending and population health gains (139)). The PSA demonstrates stability of the cost-effectiveness results.

Despite level 1 evidence demonstrating a survival benefit for patients with MIBC who receive NAC (7), multiple studies have shown low utilization rates. Studies have routinely identified barriers to use that included concerns about toxicity of therapy, delay in receiving RC and difficulty in predicting who would benefit from NAC (28). However, this decision analysis illustrates that molecular subtyping has the potential to identify patients who are most likely to benefit from NAC and therefore spare those unlikely to gain any added advantage from the toxic therapy.

Morera et al previously questioned the utility of molecular subtypes in their paper which demonstrated that clinical parameters were better predictors of bladder cancer outcomes (140). In

their paper, which reanalyzed retrospective pathology and bladder cancer outcome data, tumour, nodal and metastasis stage were strong predictors of cancer specific and overall survival. This paper highlighted that tumour characteristics (stage, nodes, and presence of metastasis) are perpetually stalwart predictors of outcome for patients with MIBC; however, what the authors failed to address is the power that subtypes hold in their ability to guide treatment decision making which can affect outcomes by changing management. Moreover, their results differ from the vast majority of literature as numerous other groups have shown the ability of subtypes to predict outcomes (12, 37, 39, 40). Furthermore, in a previous decision analysis by Lotan et al, the authors demonstrated that a biomarker-based strategy (using DNA repair genes) led to prolonged survival compared to traditional approaches illustrating the impact that directed approaches can have on improving survival for MIBC patients (127).

Our model's results were robust on internal and external validity assessments and demonstrated that our model is appropriately representing the disease condition and treatment modalities represented. The majority of the individual 3-year OS values for each subtype fall within 3% of the target value illustrating the accuracy of the model structure and calibration techniques. Comparison of our results with literature not used in the development of our model demonstrates that a cohort treated with RC alone and the group treated with NAC and RC both had results that fell within the threshold of accepted values. Furthermore, our model illustrates that when every patient is given NAC prior to definitive management (compared to when 0% receive NAC) a 4.5% absolute OS benefit is achieved at 5 years. This is line with the anticipated 5% absolute OS benefit seen from meta-analysis data (7), further illustrating the external validity of our model.

The cost and efficacy of the strategies were sensitive to the underlying proportions of each subtype. Both scenario-based sensitivity analyses had lower proportions of basal and luminal subtypes than the base case. As the proportion of the basal subtypes within a sampled population decreases, the net gain in effectiveness derived from the subtype directed care diminishes compared to the other strategies since basal is the only subtype that derives benefit from NAC. However, this does not change the relationship between the strategies and subtype directed care remains cost-effective in in these scenario analyses.

While we found that while the cost of the molecular test itself would have an impact on the ICER, the test would have to become unrealistically expensive to force the ICER to cross the cost-effectiveness threshold. Currently, the GSC test is available in the United States for clinical use but is not yet available in the Canadian marketplace. Therefore, there is uncertainty about the Canadian market price of the test. However, on sensitivity analysis no reasonable price would jeopardize the cost-effectiveness as determined by the cost-effectiveness threshold.

We also noted that if the cost of adverse events experienced during NAC was reduced such that not every patient experiencing a grade 3 or higher adverse event required hospital admission the ICER for subtype directed care relative to current NAC usage and universal NAC usage was increased. While the results were sensitive to these costs, they do not change the ultimate conclusions drawn by this model.

As a composite measure, QALYs encompass overall survival and health related quality of life and form a generic measure of health improvement. In oncology decision analyses, the clinical interpretation of QALYs can be challenging (141); however, a gain of 9.6 quality adjusted life months with a single intervention, as derived with subtype directed care has been established as clinically meaningful (142). Clinical trials demonstrating similar gains in QALYs

have resulted in a change in practice in pancreatic and breast cancer (143, 144) and therefore this model points to potentially clinically meaningful results.

Exploratory Analysis

We completed an exploratory analysis evaluating the use of neoadjuvant atezolizumab modelled off the ABACUS trial (33). This component of the study was hypothesis generating as the benefit of the therapy was applied equally regardless of the underlying subtype. While preliminary data were reported about varying susceptibilities of the subtypes to neoadjuvant atezolizumab, the data presented in these early publications was not detailed enough for application to the model but did signal that not all subtypes are responders. The mixed response to immunotherapy is highlighted by the molecular subtype data that was produced by the IMvigor210 study which demonstrated greater response in the TCGA type II subgroup (luminal-infiltrated equivalent) compared to the other subtypes (38). However, caution should be taken when trying to extrapolate the findings from the metastatic setting as changes to tumour biology have been noted that prevent generalization of response between disease states (145).

Our model demonstrates however, that based on the clinical efficacy and safety data (when applied in an unsubtyped manner) neoadjuvant atezolizumab could be promising as a treatment modality. We were able to show that universal atezolizumab use results in a net gain of 0.08 QALYs compared to subtype directed care and 0.49 compared to universal NAC. However, the gain in QALYs compared to subtype directed care using NAC comes at a significant cost, as the ICER is $333,540/QALY. This further highlights the need to determine how best to use costly cancer medications moving forward.

Phase 3 trials are currently underway evaluating the use of neoadjuvant immunotherapy to determine its efficacy in comparison to standard of care chemotherapy (146-148); results

stratified by molecular subtype will lend further guidance on how best this therapy fits into the treatment algorithm for MIBC patients as currently there exists a treatment gap for certain subtypes. With further evidence from these trials and validation of the molecular subtyping tests, a landscape could be imagined where RC alone would be prioritized for some patients, NAC followed by RC for others, and immunotherapy and RC for some.

4.4.b Limitations

Due to the nature of the question being examined there are limitations of the study. The literature surrounding molecular subtyping in MIBC continues to rapidly evolve and mature. The consensus classifications were just published and will allow all further research to use one uniform system of subtype identification; this will improve the translatability of the results. At present, the subtypes as defined by the Seiler et al paper and the GSC molecular test have differing survival and susceptibility characteristics. These have been modelled as accurately as possible; however, there are remaining uncertainties about treatment recommendations for luminal-infiltrated and claudin-low subtypes. With further maturation of the literature and examination of the place that neoadjuvant immunotherapy has in the treatment of MIBC, the answers to these questions are likely to become clearer.

A limitation inherent to molecular subtyping is that bladder tumours exhibit intra-tumoral heterogeneity, which is beneficial to a tumour, as it allows for the development of clones that may be more aggressive or better able to withstand chemotherapy. Any personalized treatment or prognostic indicator requires a test to distinguish patients who will benefit from those who will not. But regardless of the test, only a portion of the tumour is sampled, and therefore, the molecular subtype is assigned only to the portion assessed (149). This heterogeneity might affect treatment efficacy of neoadjuvant chemotherapy or immunotherapy, for example, if actionable

mutations occur only in a fraction of the tumour. Biomarker driven approaches (of all types – not just molecular subtypes) in the precision treatment of MIBC are susceptible to challenges in their validity due to heterogeneity. However, the data incorporated in this model reflects the entirety of the patient response with both responders and non-responders incorporated into our estimates of response to NAC. More accurate treatment guidance may be possible in the future on the basis of intra-tumoral heterogeneity as the literature develops (128) but at present our model incorporates its impact in an aggregate manner.

The use of adjuvant chemotherapy was not modelled in this study as there is no data available that demonstrates how the respective subtypes respond to the receipt of adjuvant chemotherapy. Moreover, since certain subtypes are more likely to be of advanced tumour or nodal stages compared to others (150), the probability of receiving adjuvant chemotherapy could not be universally applied as some patients may have been more likely to receive peri-operative chemotherapy in clinical practice. The absence of adjuvant chemotherapy use does, however, likely increase the ICER for subtype directed care when compared to current NAC rates, as some patients would have received adjuvant chemotherapy if they did not receive NAC. The ICER demonstrated in this model though had no threat of crossing the cost-effectiveness threshold and therefore, the addition of adjuvant chemotherapy would be unlikely to change the overall conclusion of this model.

As was seen in a review of the literature, different utility values were obtained by using different elicitation methods. In a decision-making context, this makes it difficult to compare QALYs across drugs/technologies (151). While this study has contributed to further building an understanding of the utility values in the MIBC literature through the conversion of quality of

life data to that which can be directly used in decision analyses, there is a great need for a more comprehensive utility dataset derived from the same methodology (152).

4.4.c Future Directions:

Future work will need to be completed on the clinical validation of these results. A study design could be envisioned where patients with luminal tumours are treated with cystectomy alone, those with basal tumours are treated with neoadjuvant chemotherapy followed by cystectomy and those with claudin-low and luminal-infiltrated tumours are randomized to received neoadjuvant therapy (either immunotherapy, in the case of luminal infiltrated, or chemotherapy, for claudin-low). A study like this would provide the level I evidence required to establish the clinical validity and utility in this setting in the same way the TAILORx study was used in the breast cancer space (153).

4.5 POLICY IMPLICATIONS

Canadians have recognized the principle of resource stewardship as a key value of Canada's healthcare system and have it enshrined in health legislation (Excellent Care for All Act (2010); Ontario Pub Law No 46). As medicine advances and greater importance is placed on developing personalized approaches to care, the general trend has been towards increasing costs of care. This approach of molecular subtyping offers a unique opportunity to introduce a relatively inexpensive, and feasibly deployed test to better utilize already existing therapy options.

The Ontario Health Technology Advisory Committee framework for the evaluation of healthcare technologies considers evidence on four criteria: overall clinical benefit, consistency with societal and ethical values, value for money and feasibility of adoption into the health system (51). Evaluation of this test through the lens of this framework illustrates that it would

satisfy these four criteria. The use of the GSC molecular subtype test could lead to improved survival for patients with MIBC and reduce the incidence of unnecessary adverse events in patients whose clinical course would be unchanged secondary to NAC use. The push towards improvement in healthcare at a cost which the healthcare system can bear aligns with the ethical tenets of beneficence and justice (along with the Canada Health Act principle of accessibility). Moreover, a recent investigation evaluating the bladder cancer research priorities of patients and healthcare professionals revealed that the use of molecular profiling and its ability to stratify patients for treatments was one of the most important and consistent priorities of the group (154); this illustrates that at present there is stakeholder interest in the further development and utilization of molecular subtypes in the treatment of MIBC further confirming its alignment with societal values. We have demonstrated the cost-effectiveness of subtype directed therapy for the treatment of MIBC patients and therefore satisfy the value for money component of an evaluation. Finally, the implementation of this testing would be feasible as this test is already commercially available in other jurisdictions and can be performed in standard certified laboratories (155).

The potential implications of the present study are substantial. The use of subtype directed strategies to enrich a population for responders is cost-effective. While further work needs to be completed to elucidate the best treatment for each subtype, this type of modelling shows that even an imperfect strategy can substantially improve survival and cost-effectiveness over unselected use of NAC. Furthermore, it is known that many eligible patients are not receiving NAC and that subtype driven care may improve utilisation by selecting patients most likely to respond. This aspect has relevance for physicians working with patients with respect to clinical decision making and leaders within the field as they form guidelines and identify areas of

targeted research interest. The findings of the model are also relevant to policy makers as they evaluate the many factors involved in resource allocation, but it demonstrates that personalized medicine is feasible within a resource constrained environment and it can be made accessible to all patients which is a unique consideration in the field of oncology.

4.6 CONCLUSION

We demonstrated that in patients with MIBC a molecular subtype directed approach to the administration of NAC can result in improved overall survival, greater QALYs and be cost-effective within a single payer healthcare system. A push to the universal use of NAC will result in improved survival compared with what our current rates of use achieve but is likely not the best approach considering the drawbacks of chemotherapy including toxicity and unequal response. This model is built upon the available literature and requires further validation prior to clinical implementation but it demonstrates that personalized medicine is a feasible option.

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