BLUE LIGHT CYSTOSCOPY FOR NON-MUSCLE INVASIVE BLADDER CANCER

Effectiveness, cost-effectiveness and budget impact of blue light cystoscopy (BLC) with hexaminolevulinate hydrochloride for non-muscle invasive bladder cancer in British Columbia.

HEALTH TECHNOLOGY ASSESSMENT REPORT

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List of Abbreviations

5-ALA	5-aminolevulinic acid
AHRQ	Agency for Healthcare Research and Quality
AUA	American Urological Association
BC	British Columbia
BCG	Bacillus Calmette–Guérin
BLC	Blue light cystoscopy
CADTH	Canadian Agency for Drugs and Technologies in Health
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CUETO	Club Urologico Espanol de Tratamiento Oncologico
EAU	European Association of Urology
EORTC	European Organisation for Research and Treatment of Cancer
HAL	hexaminolevulinate hydrochloride
HQO	Health Quality Ontario
HTA	health technology assessment
HTAC	Health Technology assessment committee
ICER	incremental cost-effectiveness ratio
IHE	Institute of Health Economics
INAHTA	International Network of Agencies for Health Technology
INESS	Institut national d'excellence en santé et en services sociaux
MIBC	muscle invasive bladder cancer
NBI	narrow band imaging
NICE	National Institute for Health and Care Excellence
NMIBC	non-muscle invasive bladder cancer
NNT	number needed to treat
OR	operating room
OR	Odds ratio
PPE	Personal protective equipment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALYs	quality-adjusted life years
RCT	Randomized controlled trial
RD	Risk difference
RR	risk ratio
TRIP	Turning Research into Practice
TURBT	transurethral resection of bladder tumor
VGH	Vancouver General Hospital
WL	White light
WLC	White light cystoscopy

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Chapter 1 Background and Problem

1.1 Purpose of this health technology assessment (HTA)

The objective of this health technology assessment is to determine the clinical effectiveness, cost-effectiveness and budget impact of hexaminolevulinate hydrochloride (HAL) used as an adjunct to white light cystoscopy (WLC) [from here on referred to as Blue light cystoscopy (BLC)] compared with WLC alone, in transurethral resection to treat patients with non-muscle invasive bladder cancer (NMIBC) in British Columbia (BC).

1.2 Primary policy questions

1. What is the clinical and cost effectiveness of BLC in the treatment of patients with NMIBC in BC?
2. What is the budget impact of introducing BLC across BC in the treatment of patients with NMIBC?

1.3 Natural history of non-muscle invasive bladder cancer

Bladder cancer is a fatal disease that is estimated to claim 2,600 Canadian lives in 2020.[1] Bladder cancer is a malignant growth in the urinary bladder. Depending on the stage, it has two distinct types: NMIBC and muscle invasive bladder cancer (MIBC). NMIBC refers to the earlier stage of bladder cancer that is confined to the urothelium and lamina propria, which are the first two layers of tissue that line the lumen of the urinary tract.[2, 3] NMIBC is the most common type of bladder cancer and makes up approximately 75% to 80% of all incident bladder cancer cases.[2] Tumors that are classified as NMIBC included Tis, Ta, T1 tumors (Figure 1.1). Among all NMIBC, the average proportion of Ta, Tis and T1 tumors are 60%, 30%, and 10% respectively.[4] Risk factors for bladder cancer include smoking, exposure to aromatic compounds, radiation

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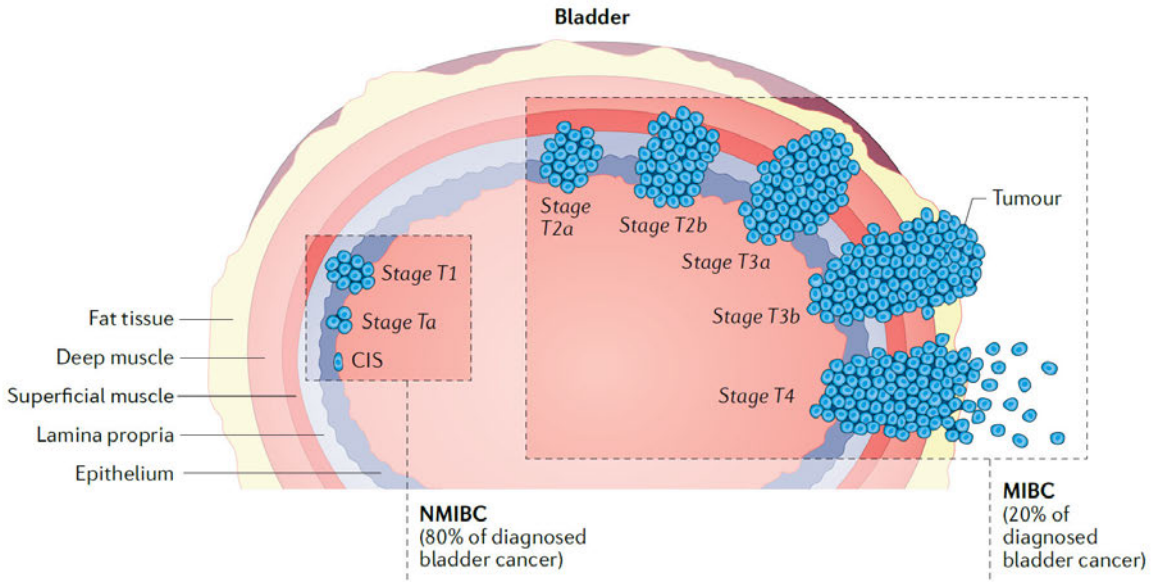
and chemotherapy.[5]

Figure 1.1. Stage of bladder cancer.[3]



Initial symptoms of bladder cancer usually involved blood in the urine. Urine testing typically include macroscopic dipstick, microscopy, culture and sensitivity and cytology. Urine testing would confirm the presence of blood or cancer cells in urine then cystoscopy using flexible scope can be performed to identify the presence of a visible tumor in the bladder and assess the size, number, location, and configuration of tumor. Evaluation of the upper urinary tract is also warranted. When non-muscle invasive bladder cancer is suspected, transurethral resection of bladder tumor (TURBT) can be performed to remove the tumor and perform pathological analysis to confirm the diagnosis of cancer. Recurrence risk stratification can be determined according to size, depth, and the type of tumor cells identified during pathological analysis.

When NMIBC is confirmed, the primary treatment for NMIBC is surgical removal of the tumor and recurrence prevention. Intravesical therapy or chemotherapy can be given after

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TURBT in patients with intermediate to high risk of recurrence. Details regarding risk stratification can be found in section 1.3.1.

After the initial tumor removal, tumors can recur or, recur and progress (invade into the muscle layer). Patients with high risk NMIBC, such as Tis tumor, high grade Ta tumor, and any T1 tumor, have a similar rate of recurrence, progression and all-cause mortality. More specifically, the 2-year rate of progression, recurrence, and mortality is 61.1%, 12.8%, and 6.5% respectively.[6] Low risk tumor, such as low grade Ta tumor, rarely progresses to MIBC (2%) but has a high rate of recurrence (70%).[7]

1.3.1 Risk stratification

Risk stratification is an important part of care in NMIBC. The level of risk of recurrence is an important factor that helps to determine the course of treatment after the surgical procedure. Risk stratification occurs after each TURBT during the index event or recurrent event. Multiple methods of risk stratification have been developed. The European Organisation for Research and Treatment of Cancer (EORTC) and Club Urologico Espanol de Tratamiento Oncologico (CUETO) developed a scoring system that allow clinicians to enter the risk factors of patients which produce a score.[9, 10] According to the score, then patients are stratified to four risk categories. However, the system can be complex in application as the stratification is directly related to the score but not the pathology of the tumor. The European Association of Urology (EAU) and American Urological Association (AUA) developed a guideline that uses the pathological characteristics of the tumor to stratify risk into three or four categories.[11, 12] The Canadian Urological Association (CUA) recently published a guideline that recommended similar risk stratification strategy.[13]

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The stratification system that BC uses is closer to the CUA, EAU, and AUA stratification.[11-13] In general, risk of recurrence is stratified into low, intermediate, and high risk in BC. The stratification system that is commonly used in BC depends on multiple factors that determine the level of risk of recurrence. An overview of the stratification system used in BC is provided in Table 1.1.

The risk of progression to MIBC also depends on NMIBC risk groups which are defined by several well-defined risk criteria including tumor size, prior recurrence history, grade, stage and focality. The average one-year progression risk of low, intermediate, and high-risk tumor are 0.2%, 1% and 5% respectively.[8] Some very high-risk tumor can have risk of progression at 17%.[8]

Table 1.1. Risk stratification of NMIBC.

Risk strata	Criteria
Low	Low grade Ta < 3 cm, solitary first-time tumor
Intermediate	Low grade Ta > 3 cm, or multifocal, or any recurrent tumor (If all three factors present, classify as high risk)
High	Any high-grade Ta, Tis, any T1

NMIBC = non-muscle invasive bladder cancer

1.4 Burden of illness

Bladder cancer is the 5th most common cancer in Canada. It is more prevalent in men than women.[14] According to the BC cancer agency, 1,515 patients were diagnosed with any stage of bladder cancer in 2018.[14] The incidence cases of bladder cancer has been steadily rising from 2009-2015 mostly attributed to rising in cases in males; the incidence cases had plateaued since 2015 (Figure 1.2).[14] These cancer statistics included both NMIBC and MIBC. In the U.S., 0.222% of the U.S. population were living with bladder cancer in 2018.[15] Calculating from the

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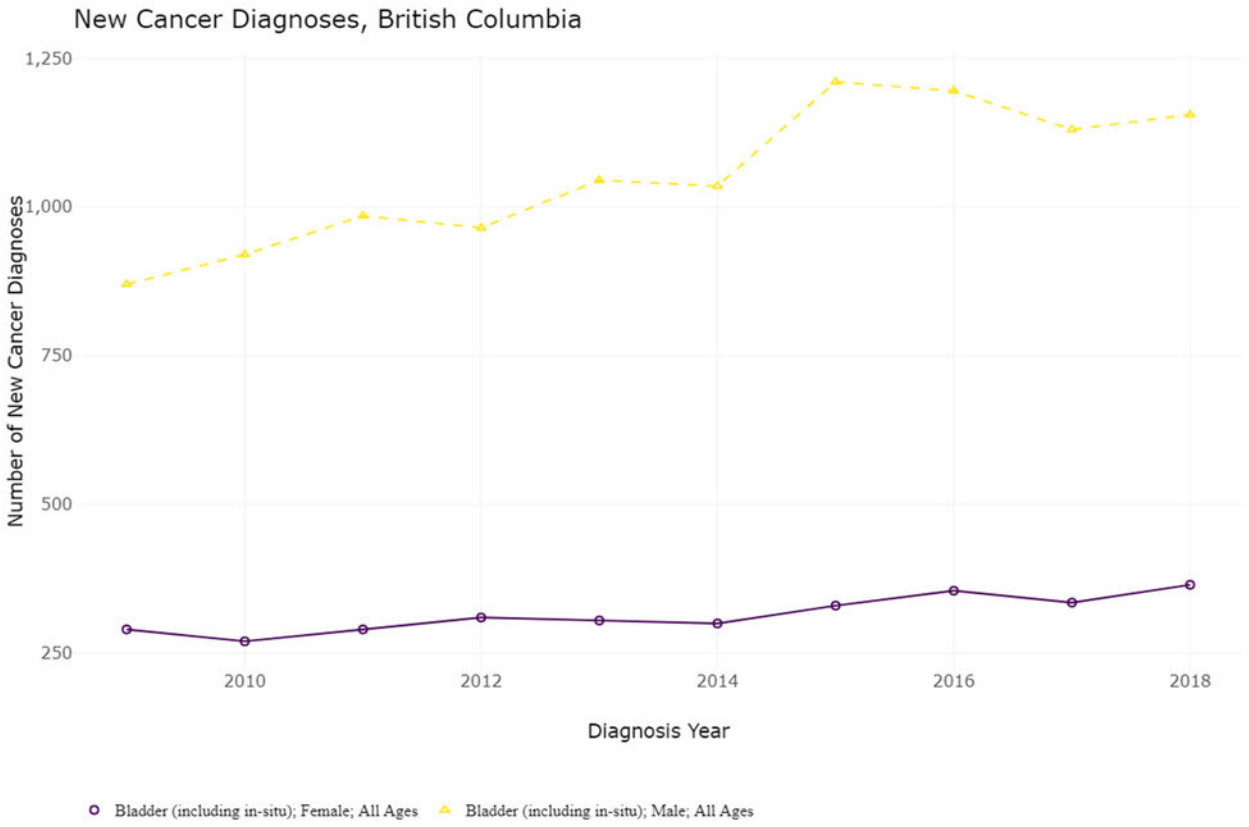
statistics, more than 10,000 people in BC would have been living with bladder cancer in 2018. The median overall survival was 132 months since first BCG treatment.[16]

Figure 1.2. Incidence cases of bladder cancer in BC.[14]



A systematic review that assessed the impact of bladder cancer on the quality of life of patients found that NMIBC reduced quality of life in all domains for function and symptoms when compared with general population.[17] After adjusting for age, patients with NMIBC still reported a lower quality of life in terms of fatigue, social function and role function.[17] Repeated TURBT and intravesical therapy, which are the result of recurrence, lower physical function, cause pain, bowel and urinary problem when compared with a single treatment.[17] Because of the high recurrence rate in NMIBC, treatments that reduce recurrence could potentially have a positive impact on the quality of life of patients.

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1.5 Treatment options

Prevention of recurrence is the main goal of the treatment for NMIBC. TURBT is the standard first-line treatment for all NMIBC. The procedure of TURBT is described below. Depended on the risk of recurrence patients may receive other follow-up therapy (e.g. intravesical therapy). Surveillance is also an important part of the care plan as the early identification of recurrent tumor is crucial in preventing progression. Standard surveillance of NMIBC involves periodic cystoscopy and cytology. Depending on the risk stratification, patients would be enrolled into different surveillance program, some will be enrolled for life.

Intravesical therapy is the instillation of anticancer chemical into the bladder which produce anticancer effect locally within the bladder. The most common intravesical chemo-medication are Bacillus Calmette–Guérin (BCG). The medication is inserted into the bladder and remains in the bladder for around two hours. The procedure is repeated weekly for six weeks as induction. During the maintenance period, the regimen is repeated weekly for three weeks at 3, 6, and 12 months for intermediate risk NMIBC and additionally at 18, 24, 30 and 36 months for high risk NMIBC. Patients in the low risk category will receive a single intravesical therapy after the initial TURBT and be monitored for recurrence for five or more years.[18] Patients in the intermediate risk category may receive one-year of intravesical chemotherapy instead of BCG. Patients with intermediate and high risk NMIBC require lifetime surveillance. For each recurrence event, the patients receive a TURBT and are risk stratified again according to the most current pathological assessment. Other intravesical therapies have other schedule that can be very different than the BCG therapy.

For patients with a very high risk of recurrence or unresponsive to intravesical therapy,

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radical cystectomy should be considered. Radical cystectomy is the removal of bladder and some other pelvic structure such as pelvic lymph nodes, urethra, prostate in male, and uterus in female. The surgeon will also have to use the bowel to divert the urine in the form of a stoma (urostomy), a bladder substitute (neobladder) or a catheterizable pouch. Radical cystectomy is a life style changing surgery, therefore it is not the first line of treatment for most NMIBC. However, for tumors that have the highest risk of progression, earlier cystectomy has shown to improve progression and survival in case series.[19]

1.6 Transurethral Resection of Bladder Tumor and Blue Light Cystoscopy

TURBT is a surgical procedure that utilizes a cystoscope introduced into the bladder through the urethra. A cystoscope is a thin, lighted viewing tool. Other very small instruments can be passed through the cystoscope to perform procedures. A tool called a resectoscope is used to remove the cancer, to acquire tissue to establish the pathologic diagnosis, and to burn away any remaining cancer cells. A white light is used inside the bladder enabling visualization of the bladder structures.

The BLC technology (e.g. Cysview) allows better visualization of the tumor, and therefore, potentially leads to a more thorough removal of cancerous tissue. Cysview with a rigid cystoscope, manufactured by Photocure, was approved by Health Canada in November 2015. A fluorescent agent, hexaminolevulinate HCL (HAL, branded as Cysview) is inserted into the patient's bladder prior to the rigid cystoscopy. The agent preferentially accumulates in cancerous tissue. Under a blue light (360-450 nm) the cancerous tissue fluoresces bright pink whereas healthy tissue appears blue, thus enhancing visualization of tumors. During BLC, the surgeon will first observe and map the bladder under white light and then under blue light to

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optimally detect bladder tumors. Once identified, tumors are resected under white light. The surgeon will switch back and forth between blue light and white light as often as needed, to observe any remaining unresected tumor under blue light and then complete the resection under white light. The improved detection of tumors enables an optimal resection with a complete resection at the tumor margins as well as resection of small, difficult to see tumors.

1.7 Research questions

1. What is the current standard of care for patients with NMIBC in BC (e.g., status quo clinical care pathway)?
    - How is BLC incorporated into the current standard of care (e.g., intervention (BLC) clinical care pathway)
2. What are the guidelines in BC for the treatment of NMIBC?
3. Which provinces and territories currently use BLC and how is BLC funded?
    - How widely available is BLC within the province/territory?
    - What are the experiences with BLC within the province/territory?
4. Have other jurisdictions undertaken an HTA of BLC in transurethral resection to treat patient with NMIBC?
    - If so, what were their findings?
5. What are patient perspectives and experiences with BLC and WLC in BC?
6. What is the stakeholder/clinician perspectives and experiences with BLC and WLC in BC?
7. What is the comparative clinical effectiveness of BLC compared to WLC?
8. What is the cost-effectiveness of BLC compared to WLC?
9. What is the budget impact of introducing BLC in BC for the treatment of patients with NMIBC?

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Chapter 2 Care pathway and jurisdictional Scan

2.1 Care pathway

The care pathway was developed based on CUA, AUA, and EAU guidelines and Canadian clinical expert consultations.[11-13] The care pathway for the treatment of non-muscle invasive bladder cancer (NMIBC) is complex. However, not all of the care pathway involves transurethral resection of bladder tumor (TURBT) that would utilize hexaminolevulinate hydrochloride (HAL) blue-light cystoscopy. Therefore, the care pathway presented in this section has been simplified to reflect only parts that involve TURBT. The primary goal of treating NMIBC is to prevent recurrence and progression to muscle invasive bladder cancer (MIBC). During each occurrence of bladder tumors, including the index event and recurrent event, TURBT is the initial treatment. TURBT serves to remove the tumor and obtain samples for pathological analysis. HAL BLC can be used in any TURBT. The pathological analysis helps determine the type of tumor and risk category. The risk category and the history of patients lead to different follow-up treatments. The care pathways end at progression to MIBC or cystectomy.

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Figure 2.1. Care pathway (a)

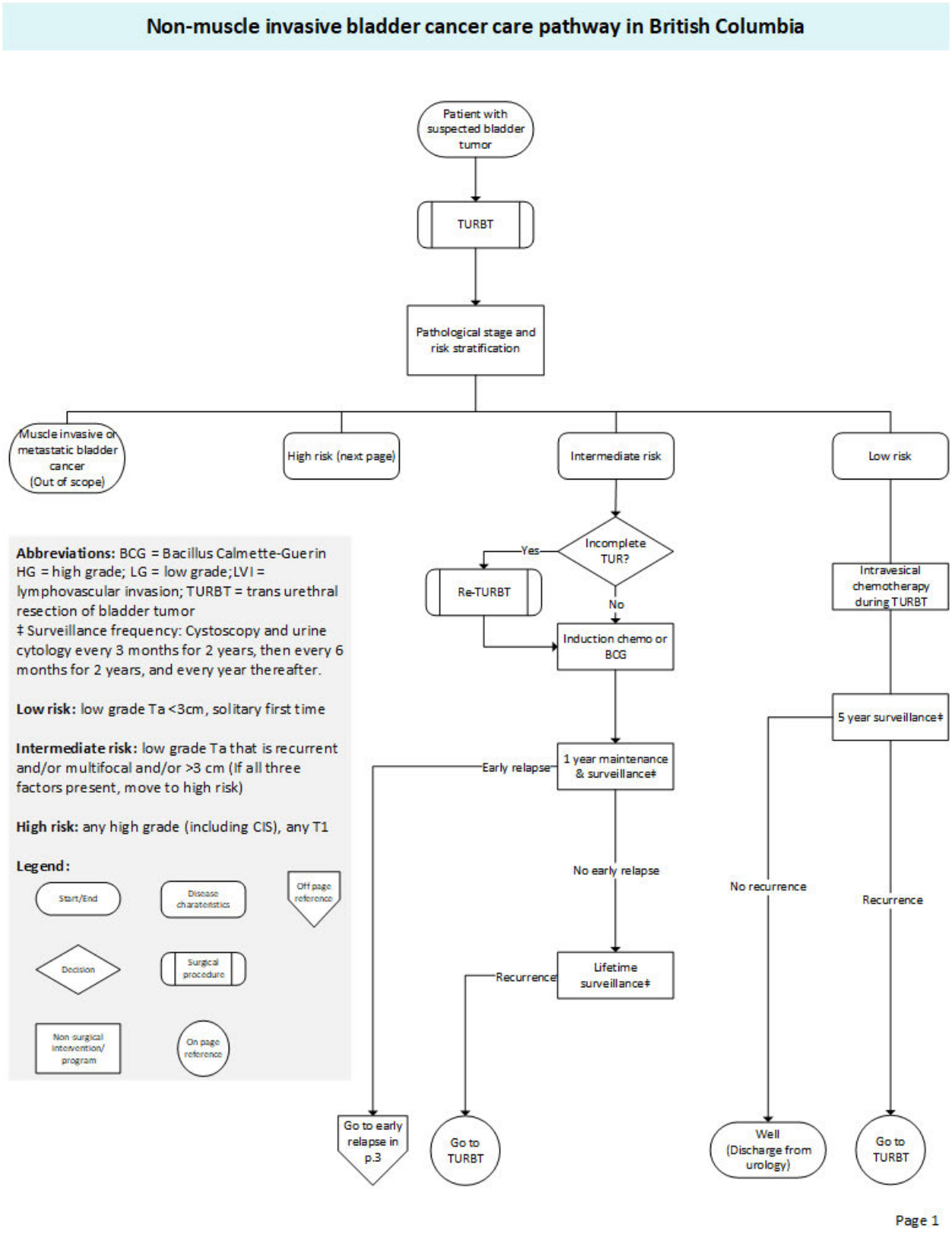

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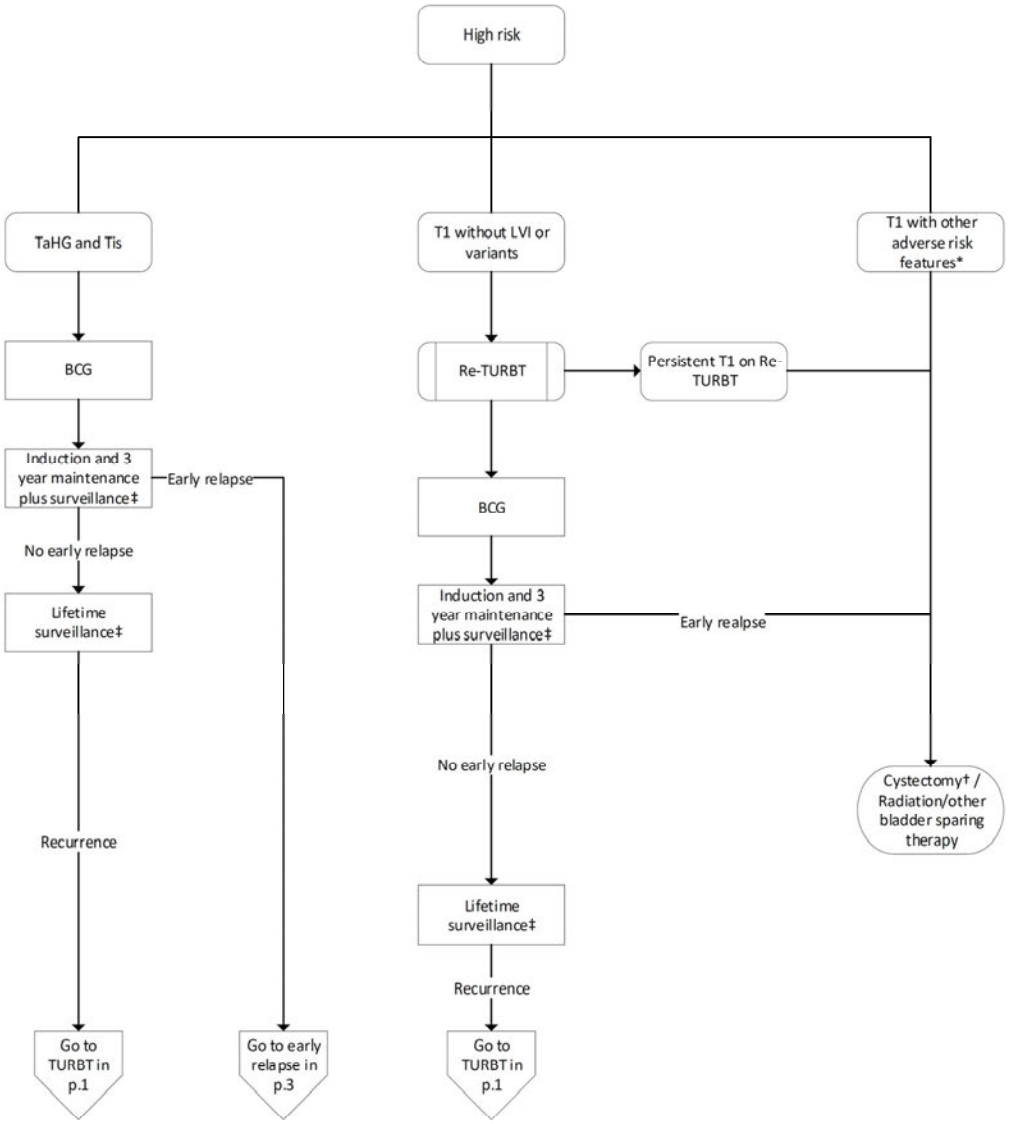
Figure 2.2. Care pathway (b)



Abbreviations:
BCG = Bacillus Calmette-Gueri;n HG = high grade;LG = low grade; LVI = lymphovascular invasion; TURBT = trans urethral resection of bladder tumor
* Adverse risk features include concomitant CIS, LVI, variant histology, multifocality, size>3cm, extensive lamina propria invasion.
† cystectomy for medically fit. Consider radiation therapy or further intravesical therapy for non-cystectomy candidates.
‡ Surveillance frequency: Cystoscopy and urine cytology every 3 months for 2 years, then every 6 months for 2 years, and every year thereafter.

Legend:
Decision | Surgical procedure | Non-surgical intervention/ program | On page reference | Start/End | Disease charateristics | Off page reference

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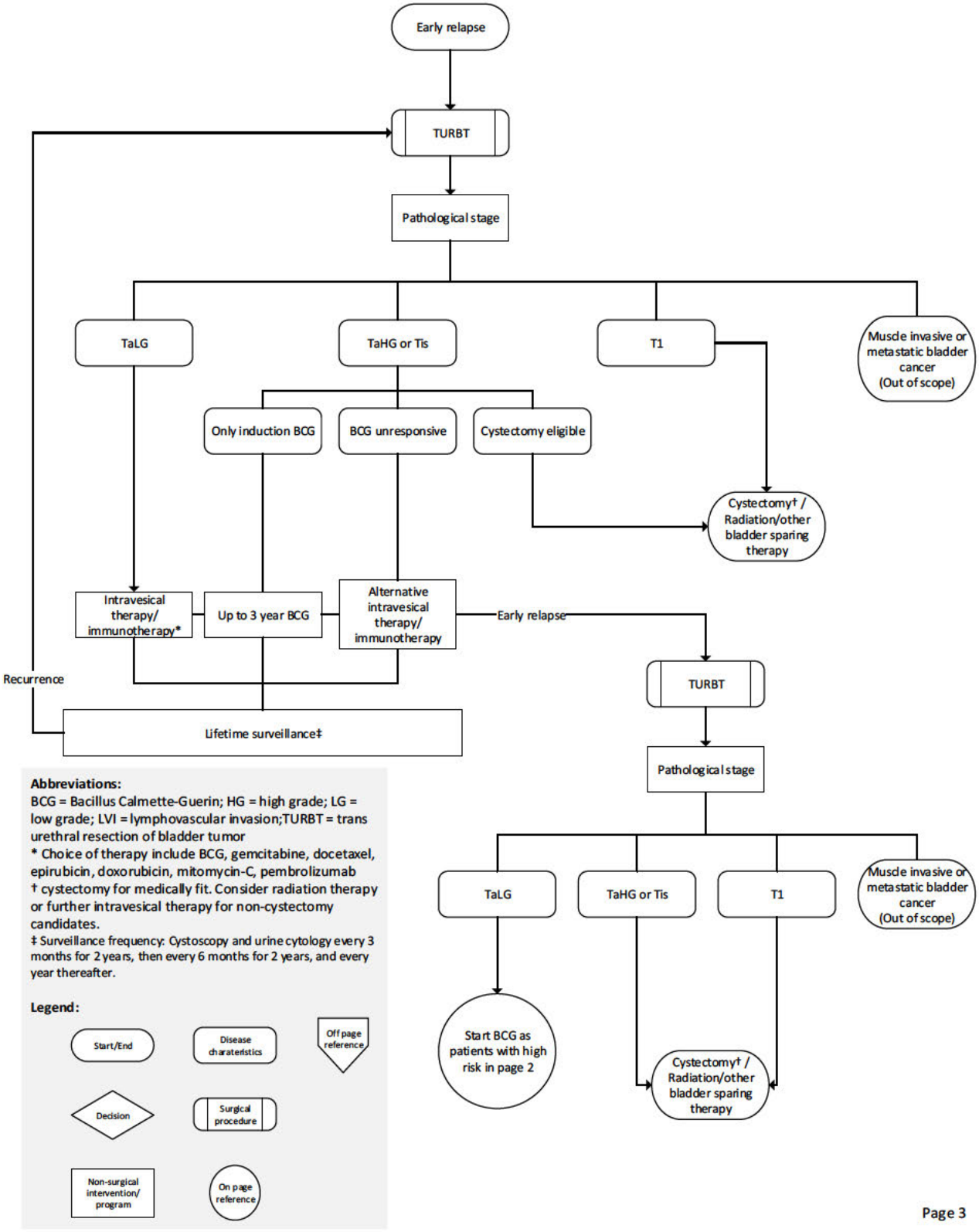
Figure 2.3. Care pathway (c)



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2.2 Health Technology Assessment jurisdictional scan

HTA reports were searched on relevant databases in Canada [e.g., Canadian Agency for Drugs and Technologies in Health (CADTH) (national), Health Quality Ontario (HQO) (Ontario), Institute of Health Economics (IHE) (Alberta), Institut national d'excellence en santé et en services sociaux (INESSS) (Quebec)] and internationally [e.g., the International Network of Agencies for Health Technology (INAHTA), TRIP, the UK's National Institute for Health and Care Excellence (NICE), Scotland, and Australia]. The following keywords were used: "*non-muscle invasive bladder cancer*," "*hexaminolevulinate*," "*BLC*," "*cysview*," "*hexvix*," and "*transurethral resection of bladder tumour*." In total, four HTA reports were identified from the CADTH and TRIP databases.

The objective of the CADTH 2017 report was to assess the clinical utility of BLC in patients with suspected NMIBC undergoing TURBT.[20] The results included a significantly reduced risk of bladder cancer recurrence compared to WLC at short-term and long-term follow-up; no difference in the risk of progression to muscle invasive bladder cancer, mortality, and local adverse events such as hematuria, dysuria, urinary frequency or urgency and bladder spasms was found.

The objective of the 2018 CADTH report was to assess the clinical utility and cost-effectiveness of BLC for patients with suspected NMIBC undergoing TURBT.[21] The results of this report build on the 2017 CADTH report and includes the cost-effectiveness of BLC. This report updated the list of included studies but did not meta-analyze the data.

The objective of the HQO report was to evaluate HAL as an adjunct to WLC during first TURBT for patients with suspected NMIBC.[22] The clinical evidence suggests that HAL-guided

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TURBT likely reduces the rate of recurrence at 12 months and four years, while increasing 5-year recurrence-free survival, when compared with TURBT guided by WLC alone. In terms of cost-effectiveness, over the 15- year time horizon considered, HAL-guided TURBT was found to have a higher cost ($549) and quality-adjusted life years (QALYs) (0.044) per patient, compared to TURBT with white light alone. Further, the probabilistic analysis showed that HAL- guided TURBT had a 69.19% probability of being cost-effective at a willingness to pay threshold of $50,000 per QALY. Model results were sensitive to the model's time horizon, but HAL-guided TURBT remained cost-effective (ICER: $37,689 per QALY) over a 5-year time horizon.

The objective of the report identified from Australia was also to compare BLC with HAL, as an adjunct to standard WLC, for the diagnosis, treatment, and management of NMIBC.[23] Clinical evidence suggests BLC with HAL as an adjunct to WLC will result in improved detection, more complete resection of bladder lesions, more accurate risk stratification, more appropriate treatment and management post-operatively, as well as reduced rates of recurrence, longer times to recurrence, reduced rates of progression and longer times to progression to muscle invasive disease. In addition, surgery may be avoided due to more accurate diagnosis and more complete resection. Regarding the economic impacts, the report found that the base-case incremental cost-effectiveness ratio (ICER) was dominant (incremental cost, -$4153; incremental effectiveness, 0.12 quality adjusted life years). The report noted that incremental effectiveness and cost savings were maintained in a number of sensitivity analyses with the exception of risk of recurrence.

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2.3 Canadian jurisdictional scan

The BC Ministry of Health, using the intergovernmental relations network, distributed a standardized list of questions (Appendix B) to provincial Ministries of Health across Canada. If the email recipient felt that they did not have the necessary expertise to respond, they were asked to forward the request to a knowledgeable colleague. A snowball sampling scheme was used to refer the team to any other stakeholders other than those previously recommended.

2.3.1 Results

[redacted]

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[redacted]

2.3.2 Conclusion

[redacted]

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Chapter 3 British Columbia context and other stakeholder perspectives

3.1 Objective

To understand the context and experience of stakeholders in British Columbia (BC) with therapies available for patients with non-muscle invasive bladder cancer (NMIBC), and determine patterns of care and capacity in BC as it relates to the management of patients with NMIBC.

3.2 Methods

During September and October 2021, phone interviews were conducted with three key stakeholders identified to provide their perspective on the policy question. The participants were all urologists recruited via snowball sampling, working at Vancouver Coastal and Island Health Authorities.

A semi structured interview guide was developed to guide the interviews. This guide was developed to address the criteria considered in the Health Technology Assessment Committee's (HTAC) review process. Specific criteria that were relevant to the technology under evaluation were selected and discussed.

3.3 Findings

3.3.1 Population, cultural & socioeconomic impacts

3.3.1.1 Impact on caregivers

According to the urologists interviewed, NMIBC is associated with the highest number of hospital visits and appointments of all cancers. The cancer is an expensive condition to treat with a high frequency of physician and urologist visits, often burdening caregivers. There are

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logistic difficulties for the caregivers to manage (e.g., accompanying the patient for the visit, finding parking, travel time, etc.). In addition, caregivers heavily emphasize the anxieties surrounding post-treatment complications. Following the treatment procedure, the risk of recurrence is a major concern for caregivers. Further, approximately 5% of patients return to the hospital after a TURBT due to presence of blood in urine. There is further burden placed on the caregiver by the in-person follow-up visits required as part of the patient's surveillance, around every three months.

3.3.1.2 Indirect impact on other populations

The main factors that may lead to one patient population being disproportionately affected are distance and geographical access. These concerns may be relevant to rural and/or Indigenous populations across the province. Stakeholders indicated that approximately 5% of patients in their practice have difficulties accessing hospitals due to distance.

3.3.1.3 Impact on existing inequities

The procedure is expected to alleviate existing inequities. The aim of this technology is to decrease the number of procedures, and instead focus on the quality of each procedure to avoid complications and reduce recurrence rates. However, there are concerns that BLC will not be offered by all urologists but instead only at bigger centres, which would disadvantage rural populations in terms of access to the procedure, and therefore worsen inequity.

3.3.2 Environmental impact

3.3.2.1 Carbon footprint

Blue light cystoscopy (BLC), which is designed to reduce recurrence rates, would reduce the frequency of TURBTs and thus, the need to receive care in the operating room (OR) (i.e., for

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repeat TURBTs). This would decrease the carbon footprint associated with travel and waste associated with the procedure. However, specifically for this patient population, follow-up visits required for patient surveillance in between TURBTs would continue to occur in person and the frequency of in-person versus virtual appointments would not change for patients with NMIBC. However, patients would require more frequent visit for a period of time after recurrence, so reduced recurrence rate could translate into fewer visits.

3.3.2.2 Waste

There is a considerable amount of waste, including the catheter, the catheter package, bottle syringe, packaging of the blue light, the nurse's Personal protective equipment (PPE), and cleaning supplies to clean the patient. However, this waste can be balanced with the potential reductions in repeat surgeries for patients. There is the upfront waste associated with instilling the chemical (i.e. HAL) in the patient's bladder, but there is no additional waste during the procedure itself.

3.3.2.3 Reusables

The blue light technology does not use any more resources than the standard white light assisted TURBT, but none of the chemical components of the chemical (i.e. HAL) are reusable. Meanwhile, interviewed urologists indicate that the system itself will likely need to be replaced every 10-15 years.

3.3.3 Implementation considerations

3.3.3.1 - Status quo

The inter viewed urologists indicate that the use of BLC is determined by whether the hospital funds the procedure (i.e. the HAL solution and instillation of solution in the patient's

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bladder). While every OR has a set of scopes and cameras required for TURBT, there are questions of whether they have a system compatible with blue light procedures. At the moment, at centers where BLC is provided physicians are responsible for sourcing funding through donations for the equipment, before the hospital covers the cost of the procedure and the BLC chemical. In short, hospitals fund the procedure but not the equipment purchases.

On Vancouver Island, physicians do not have access to the intervention (BLC (HAL)) so instead, patients with NMIBC are managed with white light assisted TURBT.

In terms of the human resources required, white light assisted TURBT requires two nurses, one anesthesiologist, and the surgeon intraoperatively. Implementation of BLC will not require additional training for nurses but will require additional perioperative resources, as nurses will need extra time to instill the compound before surgery (i.e., 15 minutes per case). The nursing and support staff would be the same as a regular TURBT. There are no extra equipment or safety measures needed, other than a different camera and monitor for the procedure.

Some current challenges include the access to resources. This is a concern pertaining to patient treatment timelines in general independent of consideration of BLC. The system works well as a whole, since it meets the standards. However, there are major delays in perioperative care, which seems to be the general case in BC.

Other challenges include timing issues, that is at which point in the patient's care pathway BLC should be used. Decisions are made on a case-by-case basis. In theory, it is advantageous to use BLC for every TURBT if the patient is suspected to have NMIBC. If it is an invasive tumour that needs cystectomy, then BLC will likely not be useful. BLC should not be

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used within 12 weeks of the last dose of BCG (as this may cause inflammation and produce false positives with the blue light).

The stakeholders do not believe a separate fee code for HAL-assisted TURBT is required. A separate billing code is only needed if the physicians need to prepare the patient with the catheter preoperatively.

3.3.3.2 Human resources

Expansion of BLC will likely not affect other services. The relevant expertise already exists at a provincial level, as it is essentially the same practice as the current procedure. Additional nursing time may be needed to place the catheter. In general, nurses should already be trained for this procedure but may require some training. The only additional resources required would be for the increased nursing time for perioperative instillation of the chemical. Intraoperatively, the procedure is identical to WLC with the only difference being a pedal for the surgeon to flip between white and blue light. However, the addition of BLC the procedure takes long as the surgeon surveys the bladder using white light first and then with blue light.

3.3.3.3 Stakeholders

No risks identified by stakeholders.

3.3.3.4 Financial

In centers where white light assisted TURBT is routinely practiced, (i.e. as the main equipment is already in place) there are no additional anticipated capital costs. Although, there are addition costs associated with consumables (i.e. HAL solution) for provision of BLC, stakeholders indicated that the downstream utilization costs can also include savings with avoided recurrence. Stakeholders suggest that the public coverage of BLC would improve the

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overall quality of disease care, without impacting the overall system, depending on how many people can access BLC in certain locations that may affect referral patterns. Recommendations include expansion for locations with three or more urologists, especially for higher volume areas.

3.3.3.5 Infrastructure

Infrastructure needed for expansion includes the tower, light source, monitor, camera, and dedicated scopes. However, the system (i.e. the device) can be used to perform WLC alone too. Further, a relevant consideration in implementation of this technology is the potential overlap or cross-compatibility of the equipment infrastructure to perform other relevant procedures (e.g. diagnostic cystoscopies).

3.3.3.6 Other

The monitoring of patients will not change with the implementation of BLC. Currently, there is no registry. At Vancouver General Hospital (VGH), results are tracked, although not specifically for blue light.

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Chapter 4 Patient Experience

4.1 Objective

To gain an understanding of the outcomes important to patients, in order to guide the evaluation of the clinical literature and health policy.

4.2 Patient experience from literature

The current status quo for the treatment of non-muscle invasive bladder cancer (NMIBC) is transurethral resection of bladder tumour (TURBT), via rigid cystoscopy, using white light. The addition of blue light to this procedure may result in improved tumour detection, allowing optimal excision of cancerous cells, and thus potentially better patient outcomes.

A review of qualitative patient experience literature commissioned for this health technology assessment (HTA), conducted by Canadian Agency for Drugs and Technologies in Health (CADTH), identified no published articles which addressed patient perspectives related to cystoscopy (either white or blue light) for TURBT in NMIBC. In fact, overall, "exceedingly few qualitative studies pertaining to NMIBC exist".[24] In order to provide some background on patient experience, we expanded our scope to literature on bladder cancer, taken broadly (which may or may not be NMIBC), and conducted our own assessment of 4 systematic reviews and 3 original primary qualitative studies which address patient experiences, published since 2014, in order to identify relevant treatment outcomes identified by patients themselves. Details of the findings are in Table 4.1 below.

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Table 4.1 Highlights of studies on patient experiences with bladder cancer, from the literature.

Studies	Includes qualitative component	Specific to cystoscopy	#patients enrolled	#NMIBC patients	Patient-identified treatment preferences and outcomes of importance
Original Primary Studies					
Garg et al, 2014[24]	Yes	No	20	100% of sample	Bladder problems Fatigue Emotional issues; worry Family support Avoiding surgery Willing to travel
Barry et al, 2015[25]	Yes	No	60	28% of sample	
Tan et al, 2020[26]	Yes	No	20 interviews (out of 213 who completed a brief questionnaire)	63% of sample	
Systematic reviews					
Edmondson et al, 2017[27]	Yes=14 studies [100%]	No	270	2 of 14 studies	Fatigue, sleep disruption, and nausea Physical and role functioning Urination difficulties, incontinence Sexual issues Pain Reduced social participation Anxiety and depression
Jung et al, 2018[17]	Yes=1 mixed method study out of 15 included [7%]	No	3415	74% of total (in 11 studies specific to NMIBC and 4 mixed)	
Rutherford et al, 2021[28]	Yes=1 qual study, 4 mixed methods out of 29	No	5442	Unclear	

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Studies	Includes qualitative component	Specific to cystoscopy	#patients enrolled	#NMIBC patients	Patient-identified treatment preferences and outcomes of importance
	included [17%]				
Lee et al, 2020[29]	No	No	Not reported	Unclear	

To summarize the findings from these papers, patients present normally with relatively low levels of impairment at diagnosis, but decline in quality of life over time. Similar issues from the patient perspective arise in both the qualitative studies and the systematic reviews: patient outcomes for quality of life appear to revolve around pain, fatigue, urination difficulties, sexual function, reduced participation in social activities, and psycho-emotional issues. The primary studies also identified benefits in terms of reduced worry/improved quality of life, and a desire to avoid surgeries where possible, which should include reduced recurrence where that results from treatment with BLC particularly. Patients appear to recognize and accept travel costs to access centres of excellence, which may include treatments not available to them locally, and the need for regular on-going follow-up.

Most of the available evidence is from muscle invasive bladder cancer (MIBC) patients receiving surgical treatment; there is extremely limited reference to cystoscopy in general, and nothing at all on blue light cystoscopy particularly. The direct relevance of these findings to those who will be treated with blue light cystoscopy cannot necessarily be assumed. However, Health Quality Ontario investigated blue light cystoscopy as a health care intervention [an HTA in progress]. In that province, a patient-partner-led needs assessment “determined that lived-

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experience information related to patient preferences and values would not be needed to evaluate this technology" (p. 80). The rationale is that

- The clinical outcomes are relevant to patients and likely fully inclusive.
- Patient preferences would be unlikely to affect decisions to use the technology.
- Patients don't have to interact with or manage the technology.

4.3 Patient input

C2E2's HTA team, in consultation with our own patient partner representative, independently reached the same conclusion as Health Quality Ontario[30], on the same basis; the patient partner re-confirmed this decision following consideration of the Ontario documentation and other literature. Past experience suggests that it would have been difficult to recruit patients in BC able to speak specifically to this technology through our usual channels such as the Patient Voices Network. While it may have been possible to consult with patients about their experiences with bladder cancer more generally, there is little reason to presume BC patients differ from others in this respect or would identify different outcomes than summarized in Table 4.1 above.

4.3.1 Conclusions

We conclude that existing clinical measures ought to adequately encompass the outcomes which patients would find important when receiving diagnosis and treatment for NMIBC using blue light cystoscopy.

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Chapter 5 Assessment of Evidence

5.1 Objectives

To evaluate the clinical effectiveness of Blue light cystoscopy (BLC) in patients with non-muscle invasive bladder cancer (NMIBC) and to summarize previously published evidence on the cost-effectiveness of BLC in patients with NMIBC.

5.2 Methods

5.2.1 Inclusion criteria

The inclusion criteria can be found in Table 5.1.

Table 5.1. Inclusion criteria.

PICO criteria	
Population	Adults aged ≥18 years diagnosed with non-muscle invasive bladder cancer (multifocal and recurring tumors)
Intervention	Transurethral resection using BLC with hexaminolevulinate hydrochloride
Comparators	Transurethral resection using only WLC
Outcomes	Clinical outcomes: recurrence rate, progression rate (to muscle-invasive disease or from low to high grade NMIBC), quality of life, percentage visible under white vs blue light, percentage malignant resected under blue light, proportion of patients for whom treatment decision changed Cost-effectiveness outcomes (e.g., ICER, ICUR)

Note: ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; NMIBC = non-muscle invasive bladder cancer; QALY = quality-adjusted life year.

Study design

For this project, the hierarchy of evidence published in 2011 by the Centre for Evidence-based Medicine at the University of Oxford was applied.[31] Systematic reviews were first searched for relevant randomized controlled trials (RCTs). The available evidence from the systematic review was used as a guide for the decision to update or start a new review, as well as a cross-reference. The primary sources of data for this review were RCTs. If the amount of evidence was deemed insufficient at the RCT level, nonrandomized studies would be searched.

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Lower levels of evidence, such as single-arm studies, were considered hypothesis-generating and determined to be insufficient for policy decision-making.

In this review, only studies that conducted a full economic evaluation were included; this refers to studies that conducted a comparative analysis of the differences in both costs and benefits across treatment groups.

5.2.2 Exclusion criteria

- Non-English-language publications
- Abstract/conference proceedings
- Letters and commentaries
- Studies without an appropriate comparator arm

5.2.3 Literature search overview

Canadian Agency for Drugs and Technologies in Health (CADTH) published a rapid response report on the same topic in 2017 and found two systematic reviews on the topic.[20] Using the search finding as a base, an update search was performed. The search strategies were developed by an information specialist, with input from the reviewers. The strategies were designed to capture generic terms for NMIBC and hexaminolevulinate hydrochloride (HAL) BLC to capture both clinical and economic studies. Published articles were identified in MEDLINE, Embase, and CENTRAL via Ovid. Since CADTH searched in MEDLINE and CENTRAL up to 2015, the update search was performed for MEDLINE from 2015 to 2021, Embase from 2012 to 2021, and CENTRAL from 2015 to 2021. Search results were imported into Endnote and Microsoft Excel for screening. The search is considered up to date as of January 27th, 2021 for all databases.

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A modified search strategy was developed for economic studies and searched for economic studies was performed on January 27th, 2021. Please see Appendix A for the search strategy.

5.2.4 Study selection

One reviewer screened titles and abstracts and then full texts according to the inclusion and exclusion criteria set in the PICOS question. The study flow was summarized using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.[32]

One reviewer extracted all the data for clinical outcomes, while a second reviewer extracted all the data from economic analyses. Data were cross-checked for errors by the two reviewers. Any discrepancy was resolved by discussion when needed.

5.2.5 Quality assessment

The risk of bias of included RCTs was assessed using the Cochrane Collaboration risk of bias tool.[33] Systematic reviews were assessed using

The International Society for Pharmacoeconomics and Outcomes Research Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[34] was applied to assess the quality of reporting among all included comparative economic studies. The results of this activity are summarized in Appendix C.2.

5.2.6 Data synthesis

For the clinical review, when appropriate, dichotomous outcomes were analyzed by using risk ratio (RR) or odds ratio (OR). When we found a statistically significant RR or OR we also calculated the risk difference (RD) and number needed to treat (NNT) for the outcome when possible. If meta-analysis was not possible, the clinical data would be summarized.

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The following data were extracted from economic studies when appropriate: country of origin, study type, model type, reported outcomes, source of funding, currency, time horizon, discount rate, interventions, costs, quality-adjusted life-years (QALYs), incremental effects, incremental cost-effectiveness ratio (ICERs), incremental cost-utility ratio (ICUR), main assumptions, perspective, and cost and resource utilization and modelling of effectiveness. Data were qualitatively summarized.

5.2.7 Subgroup analysis

No subgroup analysis was performed.

5.3 Search result

A total of 342 records were screened for clinical review, of which 53 records were retrieved for full text review. No new systematic review or RCT was identified. Therefore, the systematic reviews identified in the CADTH 2017 rapid respond report were the most up-to-date evidence. Since the CADTH report was a rapid response report, only a summary of results was included in the report. This review aimed to provide a detailed description of the two systematic reviews included in the CADTH report.

A total of 51 abstracts were screened for the economic review, and 9 studies were retrieved for a full text review. Among the nine studies identified for a full text review, one study was included for data extraction[35], and an additional study was identified through the HTA jurisdictional scan[22], the results of which were included as a part of the cost-effectiveness review (Section 5.5).

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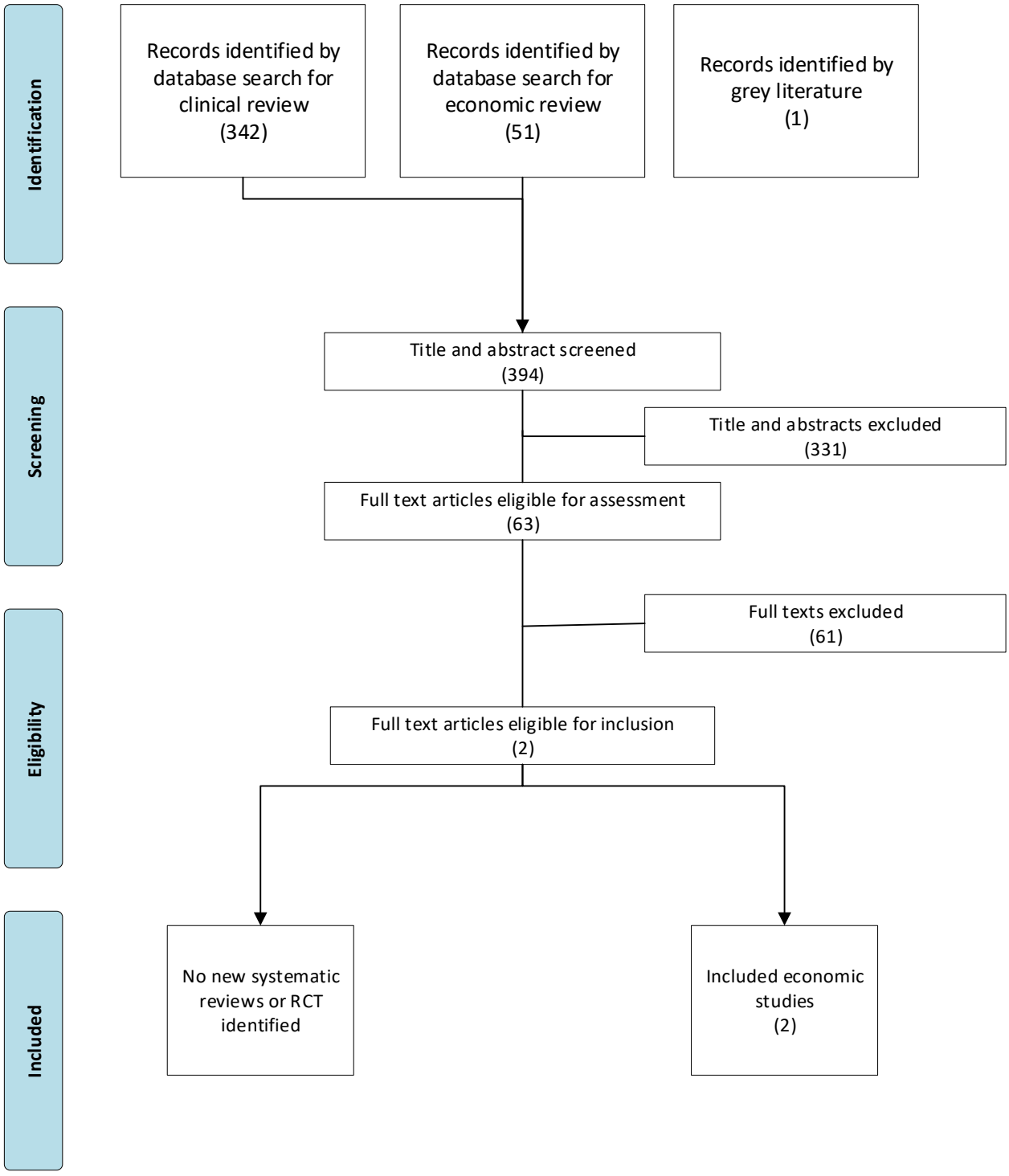
Figure 5.1. PRISMA diagram.



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5.4 Clinical effectiveness review

5.4.1 Description of included studies

The two included systematic review were also included in the CADTH 2017 report.[20] Since no new RCT was found, the results from these two systematic reviews were the most up to date.

Chou 2017 was a systematic review commissioned by Agency for Healthcare Research and Quality (AHRQ) in the U.S. The review compared fluorescent cystoscopy and white light cystoscopy (WLC). The agents include HAL and 5-aminolevulinic acid (5-ALA). The 5-ALA agent was not a part of this review therefore, studies included in Chou 2017 that examined 5-ALA agent were excluded from our review. Only the results from HAL studies was presented in this review. Chou 2017 performed the search in MEDLINE, CENTRAL in September 2015 and included nine RCTs that compared HAL with WLC. The included RCTs randomized 918 patients to HAL and 938 patients to WLC. The follow-up duration ranged from six weeks to 55 months. Recurrence and progression were the two main outcomes reported; mortality and adverse events were also reported in the review.

Gakis 2016 was a systematic review that compared HAL blue-light cystoscopy and WLC.[36] Gakis 2016 performed search in Pubmed between 2000 to 2016. Overall, four RCTs and one retrospective observational study were included in the analysis. A total of 644 patients were enrolled in the HAL blue-light group; 657 patients were enrolled in the white light group. The median follow-up duration was 28 months. Progression to MIBC was the only outcome reported in the review. All four RCTs were also included in Chou 2017. Since Gakis 2016 mixed

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RCT and observational study in their meta-analysis, the result was only presented in this report as a comparison to the Chou 2017 report.

5.4.2 Results

5.4.2.1 Recurrence

The risk ratio of recurrence can be found in (Table 5.2). HAL BLC reduced the risk of recurrence in medium-term (3-12 months) and long-term (>12 months) follow-up when compared with WLC.[37] The short-term recurrence rate also favored HAL BLC but did not achieve statistical significance.[37]

Table 5.2. Recurrence risk ratio

Follow-up period	Risk ratio [95% CI]
Short-term (<3 months)	0.62 [0.38 – 1.00]
Medium-term (3-12 months)	0.76 [0.62 – 0.93]
Long term (>12 months)	0.75 [0.62 – 0.92]

5.4.2.2 Progression

Chou 2017 found that patients who received HAL blue-light cystoscopy had a lower risk of progression to muscle invasive bladder cancer (MIBC) (risk ratio 0.51 [95% CI 0.28-0.98]).[37] Gakis 2016 also found the same result (risk ratio 0.61 [95% CI 0.41-0.91]).[36] Gakis 2016 included the observational study into the meta-analysis which showed no effect on progression. However, mixing observational studies with a different risk of bias profile and uncontrolled confounding factors might not be appropriate. The estimate from Chou 2017 which only included RCTs, was based on higher quality evidence.

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5.4.2.3 Other outcomes

Chou 2017 did not find significant differences between the HAL blue-light and white light groups in either mortality or local adverse events.

5.4.3 Critical appraisal

Critical appraisal of the systematic review was carried out using the AMSTAR-2 tool.[38] Chou 2017 was assessed to be high quality systematic review with robust methodology that provided an accurate summary of the result. One minor concern is that search was not performed in Embase. However, our own updated search which included Embase did not identify any additional RCTs, therefore Chou 2017 did not miss any RCTs due to excluding Embase.

On the other hand, Gakis 2016 was a low-quality review that provided no information on multiple critical domains. It was not clear if multiple reviewers screened the abstracts and full texts; the search was only conducted in one database; combining non-RCT with RCT in a meta-analysis was also problematic. The result of Gakis 2016 was suitable to served only as a comparison to Chou 2017.

5.5 Cost-effectiveness review

Two studies[22, 35] met the inclusion criteria and an overview of the characteristics and results of the included studies is provided below (sections 5.5.1 and 5.5.2).

5.5.1 Description of included studies

An overview of the included economic studies is provided in Appendix C C.1.

The study by Klaassen et al.[35] was funded by BioSyent Pharma Inc. and the target population included patients with suspected new or recurrent NMIBC. The evaluation was

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conducted from the Canadian public payer perspective, assessing the cost-effectiveness of BLC with HAL-assisted versus WL-assisted TURBT. The decision model used to conduct the evaluation reported by Klaassen et al. was adapted from a previously published model. The economic evaluation took the form of a cost-consequence analysis, where the overall cost of the procedure (i.e. initial cost, follow-up cost, and five-year amortized cost), number of recurrences avoided and bed days saved were estimated for incident cases of NMIBC in 3 Canadian provinces; British Columbia, Ontario and Quebec. The clinical evidence used to inform the sensitivity and specificity input data used in the decision model were based on a meta-analysis of 10 RCTs (studies evaluating BLC with HAL vs. WLC) identified from a systematic review performed by the authors. Further, in this study treatment effect (defined as rate of recurrence) was informed by a previously published meta-analysis of recurrence relative risk for BLC with HAL vs. WLC.[39]

The primary economic evaluation conducted by Health Quality Ontario (HQO) was publicly funded, with the target population including people with suspected NMIBC undergoing their first transurethral resection of bladder tumor (TURBT). The evaluation was conducted from the Ontario Ministry of Health perspective, to assess the cost-effectiveness of HAL or narrow band imaging (NBI) as an adjunct to white light during first TURBT, compared with TURBT using white light alone. To address these research questions, a *de novo* eight health state Markov microsimulation model was built in TreeAge Pro 2020. The economic evaluation took the form of a sequential cost-utility analysis, where the sequential ICER of all treatments considered (i.e. TURBT guided by HAL or NBI vs. TURBT guided by white light along) were estimated and assessed for dominance or extended dominance. Lastly, the clinical evidence

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used to inform treatment effect (defined as rate of cancer recurrence) in the model was based on a systematic review and metanalysis of identified evidence.

5.5.2 Results

The results as reported in each included study are summarized in Table 5.3.

Klassen et al. considered a five-year time horizon in the base case, although no discount rate was reported. A micro-costing approach was used to estimate the cost associated with each Canadian province (i.e. ON, BC, Quebec). The base case results indicated that the average cost of HAL guided TURBT was higher than TURBT guided by white light alone (see Table 5.3). Specifically, in BC the average cost per person over the five-year time horizon was estimated $9,421 for HAL guided TURBT vs. $8,126 for TURBT with White light alone. A similar trend was observed in the model outcomes. Over the five-year time horizon, the average number of recurrences (HAL guided: 0.38 vs. White light alone: 0.48) and bed days (HAL guided: 2.03 vs. white light alone: 2.33) associated with HAL guided TURBT was lower than WL-assisted TURBT alone. In reporting the cost-effectiveness, the authors reported the cost per recurrences avoided only using the initial costs (i.e. not including follow-up costs), which corresponded to $23,724 per recurrence avoided in BC. Lastly, the results from the sensitivity analysis indicated that the model was most sensitive to improving NMIBC progression rate, which was assumed to be zero in the base case in the absence of sufficient evidence.

In the primary economic evaluation conducted by HQO, a 15-year time horizon was considered in the base case with an annual discount rate of 1.5% applied to both costs and QALYS. Over the 15- year time horizon considered, HAL-guided TURBT was found to have a higher cost ($549) and QALYs (0.044) per patient, compared to TURBT with white light alone

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(see Table 5.3). Further, the probabilistic analysis showed that HAL- guided TURBT had a 69.19% probability of being cost-effective at a willingness to pay threshold of $50,000 per QALY. Model results were sensitive to the model's time horizon, but HAL-guided TURBT remained cost-effective (ICER: $37,689 per QALY) over a 5-year time horizon.

Table 5.3 Summary of result from the identified economic studies

	Klaassen et al. (2017)[35]			HQO (2020)[22]
Results (Per patient)	**Ontario**	**British Columbia**	**Quebec**	**Ontario**
Currency (Year)		CAD (NR)		CAD (2020)
Total Costs-BLC with HAL	$11,555	$9,421	$7,306	$20,262
Total Costs-WLC	$10,183	$8,126	$6,070	$19,762
Incremental Cost	$1,372	$1,295	$1,236	$500
Total Outcomes-BLC with HAL				
QALY	-	-	-	6.071
Bed days	2.03	2.03	2.03	-
Recurrences	0.38	0.38	0.38	-
Total Outcomes-WLC				
QALY				6.019
Bed days	2.33	2.33	2.33	-
Recurrences	0.48	0.48	0.48	-
Incremental Outcomes				
QALY	-	-	-	0.052
Bed days avoided	0.30	0.30	0.30	-
Recurrences avoided	0.10	0.10	0.10	-
Incremental cost per bed day avoided*	$4,574	$4,315	$4,121	-
Incremental cost per recurrence avoided*	$13,722	$12,945	$12,363	-
Incremental cost per QALY	-	-	-	$9,615

5.6 Summary of findings

Clinical review

- Two systematic reviews reported that HAL BLC lowered the risk of progression to MIBC when compared with WLC.

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- A good quality systematic review included RCT that enrolled 1,856 patients reported HAL BLC lowered the risk of recurrence of NMIBC in medium-term (3-12 months) to long-term (>12 months) when compared with WLC.
- The two systematic reviews differed greatly in terms of quality. Chou 2017 was a better-quality review than Gakis 2016. However, both systematic reviews found comparable results.
- Overall, the best available evidence from two systematic reviews suggested that HAL BLC reduced the risk of medium to long term recurrence and progression to MIBC when compared with WLC.
- The quality of evidence was evaluated as low according to AHRQ methods guide due to inconsistency and susceptibility to performance bias and publication bias. A low quality of evidence suggests that the estimates might change significantly should better quality RCT is available in the future.

Economic review

- Both studies identified in the economic review [22, 35], assessed the cost-effectiveness of HAL-guided TURBT as an adjunct to WL TURBT versus WL-guided TURBT alone within the Canadian setting.
- In both studies HAL was found to be the more costly and more effective intervention. In the primary economic evaluation conducted by HQO, HAL was found to be cost-effective at a willingness to pay threshold of $50,000 per QALY.
- Klassen et al.[35] conducted a cost-consequence analysis, which lacked the key

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common outcome (i.e. QALYs) required for decision makers.

- Both studies assumed BLC with HAL is used only for the initial TURBT, which is not entirely in line with expected clinical practice.
- In line with the BC context both studies evaluated HAL as a therapeutic procedure and not a diagnostic procedure
- The care pathway patients followed in the simulation model developed in the primary economic by HQO did not include patients in the early relapse phase, which was indicated for the BC context (See section 2.1)
- Although the identified studies are conducted within the Canadian setting, as both only the use of BLC guided TURBT to occur for the patient's initial procedure and as some of the modelling assumptions (e.g. change in patients risk categorization upon recurrence) did not align with the expected BC care pathway, a primary economic evaluation was conducted.

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Chapter 6 Primary Economic Analysis for British Columbia

6.1 Objectives

The objective of this analysis was to evaluate the cost-effectiveness of hexaminolevulinate hydrochloride (HAL) used as an adjunct to white light cystoscopy (WLC) [from here on referred to as Blue light cystoscopy (BLC)] compared with WLC alone, in transurethral resection to treat patients with non-muscle invasive bladder cancer (NMIBC) in British Columbia (BC).

6.2 Methods

6.2.1 Type of analysis

The reference case analysis was in the form of a cost-utility analysis (CUA), where health outcomes were expressed as quality adjusted life years (QALYs). In this evaluation a cost-effectiveness analysis (CEA) was also conducted, where health outcomes were expressed as recurrences avoided. Overall, the outcomes reported include the total cost, total recurrences, and total QALYs for the intervention and comparator under evaluation, and the incremental cost per QALY gained and recurrence avoided (see section 6.3.1).

Where appropriate, the reference case definition and sensitivity analyses followed the Canadian Agency for Drugs and Technologies in Health (CADTH) for the Economic Evaluation of Health Technologies.[40]

6.2.2 Target population

The target population for the analysis included people with NMIBC undergoing a TURBT. This analysis was restricted to the therapeutic application of BLC with TURBT. Thus, BLC used

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for routine cystoscopy (i.e. flexible cystoscopy) in the context of surveillance or diagnostic procedures was considered out of scope and not evaluated in this analysis. Further, the patient population was assumed to include patients where the possibility of muscle invasive disease (i.e. MIBC) was already ruled out upon entering the model, although patients could progress to MIBC over the model time horizon.

Patients with NMIBC were classified according to their risk of recurrence based on the stratification system used in BC (See Table 1.1). In this context the risk categories refer to the patient's risk of recurrence, and the categories are defined based on tumor histology, size, number, and whether it is a primary tumor (i.e. first one). The baseline age at model entry was 70 years old, reflecting the median age of the patient population used to inform the clinical inputs of the model (see section 6.2.8.2).

6.2.3 Intervention and comparator

The following interventions were compared in this analysis:

- White light-guided TURBT: This is the *status quo* in BC for people with NMIBC undergoing their initial TURBT and all subsequent TURBTs among patients who experience a recurrence.
- HAL-guided TURBT: This is the health technology under evaluation to be used as an adjunct to WLC, for people with NMIBC undergoing their initial TURBT and *all subsequent* TURBTs among patients who experience a recurrence.

6.2.4 Perspective

In this analysis a publicly funded health-care payer perspective was adopted. Therefore, costs and outcomes considered in this evaluation were restricted to those relevant to the

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publicly funded health-care payer in BC. Out-of-pocket expenses and productivity loss were not considered.

6.2.5 Time horizon and discounting

A 10-year time horizon was used in the reference case, as it aligned with the data available to inform the risk of recurrence for the target population, and it was deemed long enough to capture the clinical progression of patients beyond NMIBC.

In line with the CADTH guideline for the Economic Evaluation of Health Technologies[40], a 1.5% annual discount rate was applied to both costs and outcomes for the reference case.

Alternative time horizons and discount rates were explored in sensitivity analyses (Appendix E).

6.2.6 Model overview

A 14-health state Markov model, with 3-month cycles, was designed to assess the costs and health outcomes associated with BLC versus WLC. In this analysis, treatment effect of BLC vs. WLC was modeled in terms of *a reduction in the risk of recurrence* in patients with NMIBC.

An overview of the model structure is provided in Figure 6.1.

The model structure was designed to reflect the natural history of NMIBC and the clinical care pathway for patients in BC (see Section 2.1). Within the model, a cohort of patients aged 70 enter the model following a TURBT and pathological assessment of the tumor, in one of the three risk categories for NMIBC: Low Risk, Intermediate Risk, or High Risk (See Table 1.1 for clinical definitions). From there, patients can remain under surveillance or have a recurrence and enter the corresponding *recurrence* health state (for example patients from the “Low risk” health state will move to the “Low risk recurrence” health state), where they receive another

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TURBT and pathological assessment of the tumor. After experiencing a recurrence and entering a recurrence health state, depending on their tumor pathology patients can either go to the Intermediate risk health state, High-risk health state, or move to the "progressed" health state.

Overall, each time a patient has a recurrence event, the patient's risk stratification *can* change, based on the pathology of the tumor that is reassessed following their TURBT. Further, after each recurrence, patients in the Intermediate or High-Risk health states can only stay in the same risk category or move to a more severe risk category. However, patients in the "Low Risk" health state can only move to more severe risk categories after a recurrence, while Low risk patients that do not experience any recurrences after 5 years of surveillance are discharged from urology.

In the model patients in the "Intermediate risk" and "High risk" health states that experience a recurrence within the first 6 months of the model time horizon (i.e. have a recurrence while receiving treatment) are assumed to have an early relapse and follow an *Early Relapse* pathway in the model. Upon experiencing an early relapse, patients receive another TURBT, and the pathology of their tumor is reassessed. In the model patients that experience an early relapse have a different rate of disease progression, cystectomy, and receive different treatment combinations than patients who do not experience an early relapse. In general, after experiencing an early relapse patient can have a cystectomy, progress or enter an early relapse surveillance state, where they would be managed medically and remain under surveillance. Patients that enter early relapse surveillance state can experience another early relapse, and from there they receive another TURBT, and if their disease has not progressed enter the Sparing treatment state.

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Lastly, in each cycle all model health states have a probability of transitioning to the "Death" health state.

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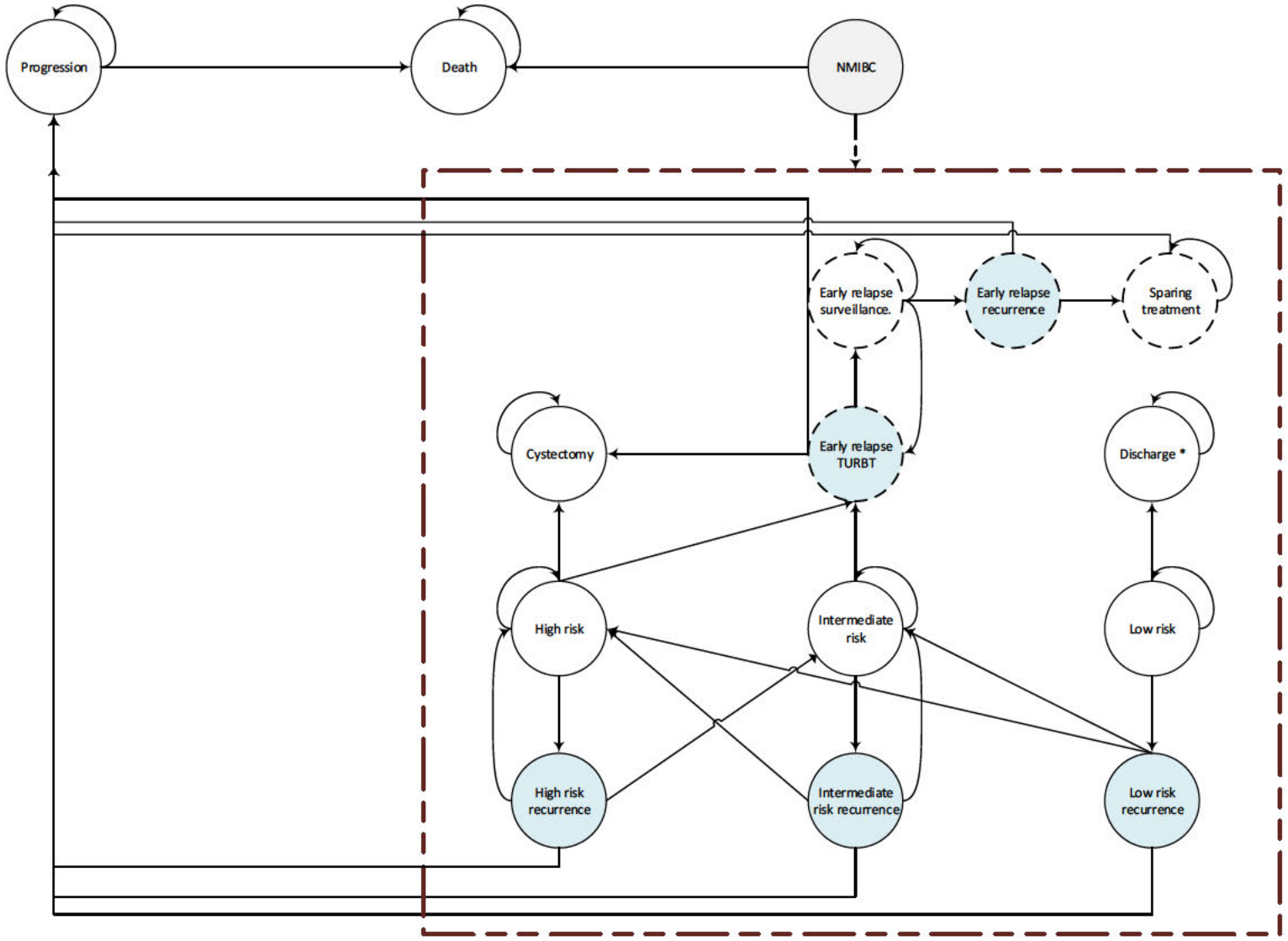
Figure 6.1 Model Schematic



Blue health states reflect states where patients receive repeat TURBTs; Health states with the dashed border reflect the *early relapse* path in the model; All health states within the red dashed box have a probability of transitioning to the "Death" state each model cycle; *Low risk patients that have not had a recurrence after 5 years of surveillance are discharged from urology

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6.2.7 Model assumptions

The main model assumptions include:

- Patients can only progress once they have experienced a recurrence event.
- The same treatment effect (i.e. reduction in the risk of recurrence) was applied to all risk categories, as the estimates of relative risk were not reported by risk categories(Table 5.2).[37] However, the baseline risk of recurrence was informed using separate Kaplan-Meier curves for low, intermediate and high-risk patients (Figure 6.2).[41]
- In the intervention arm; every instance where a patient experiences a recurrence and receives a TURBT it is assumed that BLC will be used.
- Only patients with NMIBC can enter the model, and from there their disease can progress.
- Early relapse is defined as patients in the intermediate or high-risk health states who have a recurrence within the first two model cycles (i.e. six months). The same data (Kaplan-Meier curves; Figure 6.2) was used to inform probability of recurrence to early relapse or one of three recurrence health states, where the only distinguishing factor was the timing of recurrence. Thus, starting in cycle 3, patients in the intermediate and high-risk state no longer entered the early relapse path of the model.
- Low risk patients that did not experience a recurrence within the first 5 years (i.e., 60 model cycles) are discharged from urology and assumed to have no risk of recurrence until the end of the model time horizon.

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- Following a recurrence, patients that originated form the low-risk health state can only move to higher risk categories (i.e. intermediate or high risk).

6.2.8 Model inputs

6.2.8.1 Effectiveness (Treatment effect)

The evidence used to inform the clinical effectiveness of BLC versus WLC in patient with NMIBC was obtained through a systematic review of the literature (see Chapter 5).

In the model the relative effectiveness of BLC versus WLC, defined as a reduction in the risk of recurrence, was obtained from a systematic review commissioned by the Agency for Healthcare Research and Quality (AHRQ) in the U.S.[37] Result from the review identified nine RCTs that compared BLC (i.e. HAL) with WLC. Data from the included RCTs were used to conduct a meta-analysis and estimate the relative risk of recurrence. The results were stratified according to the duration of follow-up after their first procedure as short term (<3months), Medium-term (3-12 months) and long term (> 12 months); (Table 5.2). However, in this review the results were not stratified according to the patient's baseline risk category. Therefore, in this model the same treatment effect (on the relative scale) was applied to all patients regardless of the risk category from which they experienced a recurrence. Other clinical parameters

6.2.8.2 Other clinical inputs

Risk of recurrence

In this analysis, the baseline risk of recurrence was modelled separately for each risk stratification group (Table 1.1). Thus, in the model, the probability of experiencing a recurrence in each model cycle was informed separately for each risk stratification using data obtained

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from an observational study of 5,122 patients with NMIBC for 11 years.[41] Briefly, in the study by Rieken et al all included patients had undergone a TURBT and pathological assessment of their tumor. In the first two years, patients were followed every 3-6 months, then biannually up to five years, and annually after that. Patient follow-up included assessment of patient history, physical examination, urine cytology, WLC, and biopsy of suspicious tumors. In addition, in this study .[41], patients were stratified in each risk category following the European Association of Urology (EAU) guideline[42] definition, which uses the pathological characteristics of the tumor to stratify risk into three categories. As the risk classification system used in BC is closely aligned with the EAU definitions, the patient population used in this study was deemed to be a close representation of the patient population in BC. For further details regarding the risk stratification of patients with NMIBC refer to section 1.3.1.

Kaplan-Meier curves depicting recurrence free survival were digitized and used to inform the time-dependent probability of recurrence in each model cycle (i.e. 3 months) according to low, intermediate and high risk. The digitized curves, depicting the cumulative recurrence-free survival by each risk category which were used in the model are presented in Figure 6.2. Lastly, in the model the same Kaplan-Meier curves were used to inform transitions from each risk category to Early relapse. As noted previously, in the reference case, patients stratified in the intermediate or high-risk category that experienced a recurrence within the first 6 months of the model time horizon were assumed to experience an early relapse and followed a separate path in the model (Figure 6.1).

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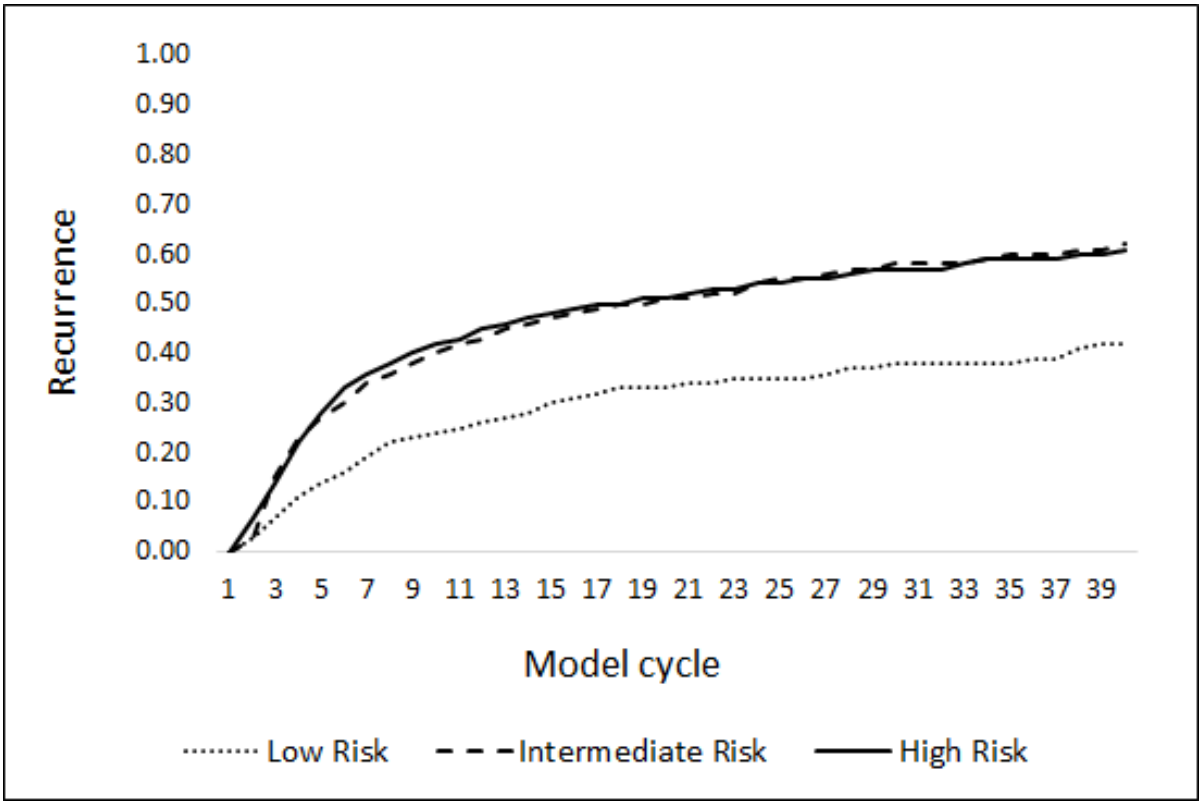
Figure 6.2 Observed 10-year recurrence free survival in patients with NMIBC by risk category



NMIBC: Non-muscle invasive bladder cancer
Source: Rieken et al. 2018[41]

Mortality

Transitions that informed the proportion of patients entering the "Death" health state in each model cycle was based on *all-cause* mortality data, which reflects both background mortality and disease-related mortality in this patient population. More specifically, depending on the stage of disease (e.g. cystectomy or NMIBC etc.), separate estimates of all-cause mortality were used to reflect the rate of death in each model cycles from each health state. With the exception of the "discharge" health state where population background mortality rates were used[43], all other estimates of all-cause mortality were based on Kaplan-Meier data

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(separately for each state) from four different long-term observational studies with 12 to 16 years of follow-up data available.[16, 44-46]

In the model, all Kaplan-Meier curves depicting overall survival were digitized and used to inform a separate probability of death depending on the disease health states in each model cycle (i.e. 3 months). More specifically, application of different all-cause mortality curves in the model was as follows (see Figure 6.1);

- NMIBC all-cause mortality was applied to the following health states:
    - "High risk", "Intermediate risk", "Low risk", "High risk recurrence", "Intermediate risk recurrence", "Low risk recurrence"
- Early relapse all-cause mortality was applied to the following health states:
    - "Early relapse TURBT", "Early relapse surveillance", "Early relapse recurrence", "Sparing Treatment"
- Cystectomy all-cause mortality was applied to the "cystectomy" health state
- MIBC all-cause mortality was applied to the "Progress" health state
- Population background mortality was applied to the "Discharge" health state

The digitized curves used in the model, depicting the cumulative rate of all-cause mortality for patients with NMIBC, cystectomy, early relapse, MIBC, and those who are discharged from urology, are presented in Figure 6.3.

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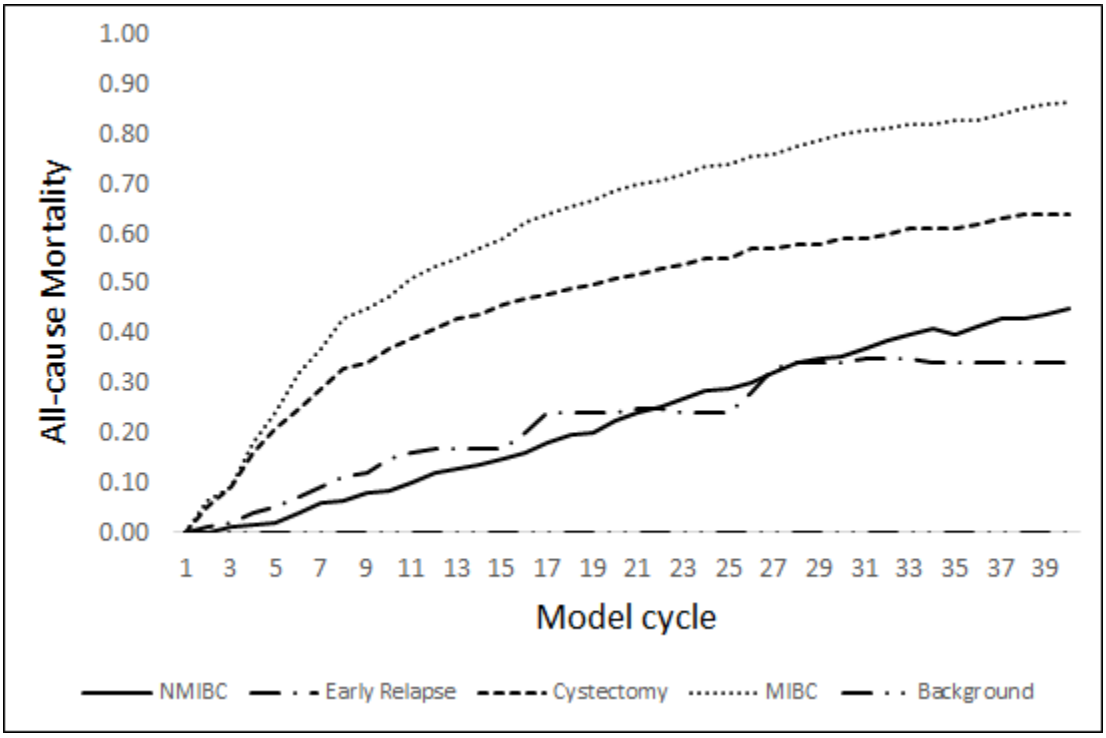
Figure 6.3 Cumulative 10-year all-cause mortality by disease stage



NMIBC= Non-muscle invasive bladder cancer; MIBC= Muscle invasive bladder cancer
Sources: NMIBC (Wiliams et al. 2021)[45]; MIBC (Fischer-Valuck et al. 2021)[45]; Early Relapse (Iida et al. 2021)[44]; Cystectomy (Gschwend et al. 2002)[46]; Background mortality (Statistics Canada; Table 13-10-0114-01)[43]

Progression

In the model, patients that experienced a recurrence were at risk of disease progression (e.g. metastatic disease). Therefore, upon entering a risk recurrence health state (i.e. "low risk recurrence", "intermediate risk recurrence", "high risk recurrence"; Figure 6.1) a separate rate of progression was applied according to each risk category. The data used to inform probability of progression from each risk recurrence health state was also obtained from Rieken et al. 2018[41], where Kaplan-Meier curves depicting progression free survival were digitized and used to inform the probability of disease progression in each model cycle (i.e. 3 months) according to low, intermediate and high risk. However, in the model the rate of progression by each risk

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category was applied as a fixed rate (Table 6.1), calculated as a function of the recurrence-free survival curves (see Figure 6.2) and progression curves (see Figure 6.4) to determine the rate of progression among patients that experienced a recurrence. This step was taken as the Kaplan-Meier curves informing rates of progression obtained from Rieken et al.[41] provided estimates of risk progression among patients who are only *at risk* of experiencing a recurrence and not those who had a recurrence. However, since in this model only patients who experience a recurrence can have a disease progression (Figure 6.1), the application of observed estimates from Kaplan-Meier curves would have underestimated the rate of disease progression.

In the model, patients that had experienced an early relapse (i.e. experience a recurrence within the first 6 months), entering the "early relapse" path of the model, were also at risk of progression, but at a higher rate. However, as disease progression from the early relapse health states did not have the same limitations noted above, observed data obtained from Kaplan-Meier curves from Iida et al.[44] (Figure 6.4) were used to inform transition probabilities to progressed disease among patients who had experienced an early relapse.

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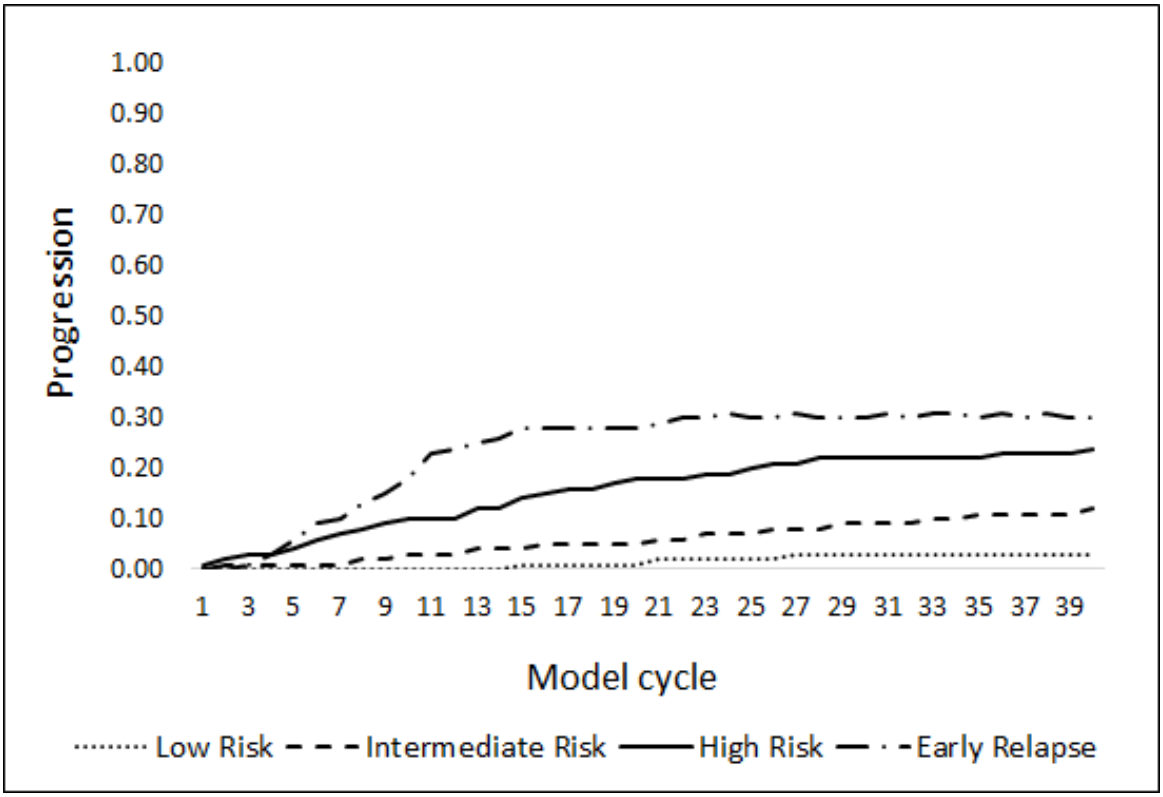
Figure 6.4 Cumulative 10-year rate of progression by risk stratification and early relapse



Source: low, intermediated, high risk of progression (Rieken et al. 2018)[41]; Early Relapse risk of progression (Iida et al. 2021)[44]

6.2.8.3 Calibration of clinical inputs informing transition probabilities

As several different data sources (i.e. different populations) were used to inform the probability of a patient moving between one health state to another, steps were taken to calibrate the clinical inputs informing these transitions. These steps were taken to ensure that in each model cycle all transitions *out* of each health state added to one (this includes the probability of remaining in the health state); in other words, in the cohort simulation each patient staring in the model has to be tracked to one health state or another. Thus, the following steps were taken:

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- The inputs informing transitions out of each health state were first adjusted against the probability of death from each state (i.e. mortality; Figure 6.3);
- Next, all remaining transition probabilities (i.e. exit probabilities) inputs were redistributed and calculated conditioned on the probability of surviving (i.e. staying alive) in each model cycle. This was done separately for each health state;
- In health states where patients could also have a disease progression or return to surveillance health states (i.e. intermediate or high-risk health states), first the probability of disease progression was calibrated conditional on the probability of survival, then among those who did not die or progress, an adjusted probability of returning to either the intermediate or high-risk health states was estimated for each model cycle and applied in the model;
- Similarly, in health states where patients were at risk of having a cystectomy, the probability of cystectomy was calibrated conditional on probability of survival, then the probability of having a recurrence was re-calculated for each model cycle, among those who survived and did not have a cystectomy;
- Where appropriate, the same methodology was applied to all transition probabilities in the model.

6.2.8.4 Utility parameters

An overview of utility estimates applied in the model is provided in Table 6.1.

In this evaluation the quality adjusted life years (QALYs) was the main outcome of interest as it captures both length and quality of life associated with the BLC and WLC group. As a secondary outcome, the number of recurrences avoided was also estimated.

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To quantify QALYs associated with each study group, each health state was assigned a specific utility weight (Table 6.1). The study informing health state utility values was identified through a targeted search of the literature[47], and utility estimates were based on patient-level data from a Randomized Controlled Trial (RCT) (BOXIT trial).[48] In this study health-related quality of life (HRQoL) was measured via the EQ-5D-3L with a 36-month follow-up and values were generated using UK preference tariffs. Overall, the results indicate that in patients with NMIBC deterioration in QoL is driven by recurrence events experienced, and observed at specific points. Thus, a lower utility was applied to recurrence health states (see Figure 6.1) accounting for the utility decrement associated with the recurrences event and the TURBT received by the patients.

In this analysis, the same utility values were used in the intervention and comparator arms (thus assuming that the intervention per se does not change quality of life). This means the difference in QALYs between the two strategies will be due to the differences in rates of transitions between over the model time horizon.

In both groups, patients were assumed to have received a TURBT upon entering the model and thus a utility decrement was applied to account for this. As the addition of BLC to TURBT does not change the experience of the patient during the procedure, the same disutility (i.e. utility decrement) was applied to the treatment and comparator arms of the model. Further, a one-time health utility decrements was applied to the proportion of patients that had a cystectomy upon entering the “cystectomy” health state.

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Table 6.1 Clinical model inputs

Model Parameters	Reference Case		Source
	BLC	WLC	
Baseline Distribution Across Risk Groups			
Low Risk	12%		
Intermediate Risk	45%		Rieken et al. 2018[41]
High Risk	43%		
Risk of Recurrence			
Low Risk			
Intermediate Risk	See Figure 6.2		Rieken et al. 2018[41]
High Risk			
Mortality			
NMIBC			Wiliams et al. 2021[16]
MIBC			Fischer-Valuck et al. 2021[45]
Early Relapse	See Figure 6.3		Iida et al. 2021[44]
Cystectomy			Gschwend et al. 2002[46]
Background mortality			Statistics Canada; Table 13-10-0114-01
Recurrence Redistribution			
Intermediate Risk	44%		Wiliams et al. 2021[16]
High Risk	56%		
Transition probabilities (per model cycle)			
P (LRR-->PROG) *	7%		
P (IRR->PROG) *	19%		Rieken et al. 2018[41]
P (HRR->PROG) *	39%		
P (ER. Survei. -> ER. Recurr)	5%		
P(ER. Survei. -> ER. TURBT)	2%		Iida et al. 2021[44]
P (ER. TURBT-->Cystectomy)	33%		
P(HR-->Cystectomy)	33%		Assumption**
Treatment effect (Risk Ratio)	BLC vs. WLC		
Short-term (<3 months)	0.62		
Medium-term (3-12 months)	0.76		Chou et al. 2017[37]
Long term (>12 months)	0.75		
Health utilities			
Utility (surveillance states)	0.85		
Utility (recurrence states); also cycle 0	0.76		Cox et al. 2020[47]
Utility (Progressed)	0.75		
Utility reduction for radical cystectomy	-0.17		

*Estimates are a function of the recurrence free survival curves (see Figure 6.2) and progression curves (see Figure 6.4) to determine the rate of progression among patients that experienced a recurrence; **Calibrated, to achieve 1/3 of high risk patients in the cystectomy health state at year 10

BLC=Blue light cystoscopy (intervention); WLC=White light cystoscopy (comparator); LRR=Low risk recurrence; IRR=Intermediate risk recurrence; HRR=High risk recurrence; PROG= progression; ER. Survei= Early relapse surveillance; ER. Recurr= Early relapse recurrence; TURBT= Transurethral resection of bladder tumor; ER. TURBT=Early relapse TURBT.

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6.2.8.5 Cost parameters

Cost inputs as applied in the model are summarized in Table 6.2. Costs were primarily obtained from BC specific sources and supplemented with the published literature where appropriate. A detailed overview of how each cost input was estimated is provided in Appendix D. Briefly, in estimation of costs associated with management of patients with NMIBC the following cost categories were considered: medications, professional fees, hospital and procedural fees, equipment, consumables and laboratory fees. Costs associated with professional fees (i.e. consultations, procedural fees) were obtained from BC's Medical services commission (MSC) payment schedule.[49] Laboratory fees were determined from Schedule of fees for the laboratory services outpatient payment schedules for BC. Lastly, hospitalization costs, including inpatient and day surgery procedures, were estimated from the administrative health data in BC.[15] All costs are reported are in 2020 Canadian dollar (CAD).

An overview of how cost estimates presented in Table 6.2 were applied in the model is provided below.

6.2.8.5.1 TURBT costs

In the model every time a patient had a recurrence it was assumed they also received a TURBT. Thus, this cost was applied to all the recurrence health states, which captured all patients with a recurrence, these included the following five health states (see Figure 6.1); "Low risk recurrence", "Intermediate risk recurrence", "High risk recurrence", "Early relapse TURBT", "Early relapse recurrence". However, upon entering the model it was assumed that all patient received a TURBT. Therefore, the cost of TURBT was applied in the "Low risk", "Intermediate risk", and "High risk" health state for the first model cycle only.

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In the BLC arm (i.e. intervention group) it was assumed that for *all* TURBTs BLC was used, and thus the cost of $3,363.74 was applied in all instances where a patient was eligible to receive TURBT. In estimation of the cost of TURBT for BLC, it was assumed that the entire system had to be purchased; this includes the electronic or "tower' as its commonly referred to (each site requires one) and the instrument set that is sterilized for patient use. Thus, the equivalent capital cost of the device was estimated and included as part of the BLC TURBT cost (Appendix D.1).

6.2.8.5.2 Surveillance costs

Surveillance costs were applied per model cycle (i.e. cost per 3 months) to reflect the average cost associated with management of patients who are at risk of experiencing a recurrence. This cost was applied to the following health states (see Figure 6.1): "Low risk", "Intermediate risk", "High risk", "Early relapse surveillance", "Sparing Tx".

The cost of surveillance was estimated to reflect patient management in BC (see section 2.1). Briefly, in the first two years, patient receive a Cystoscopy and urine cytology every 3 months, then in year 3 and 4 the frequency is reduced to every 6 months, and annually thereafter. The average cost per cycle was calculated to account for the change in the frequency of surveillance over the model time horizon, and applied in the model accordingly.

6.2.8.5.3 Treatment costs

In the model, it was assumed that patients received treatment upon experiencing a recurrence. Therefore, treatment costs were applied as a one-time cost in the recurrence health states along with the cost of TURBTs (see section 6.2.8.5.1). The type of treatments received varied depending on the patient's risk category and disease stage. More specifically, upon experiencing a recurrence, treatment options for patients in the low and intermediate risk

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stratification included chemotherapy (i.e. induction) or BCG, while patients in the high-risk stratification were assumed to only receive BCG after first occurrence. It is expected that patients who experience an early relapse and enter the “early relapse surveillance” state are unresponsive to BCG. Thus, for these patients an average cost of maintenance chemotherapy along side the high-risk BCG regimen was applied as a one-time cost for patients entering this health state. Lastly, patients that entered the “Sparing Treatment” health state were assumed to be unresponsive to BCG, and only the cost of maintenance chemotherapy was applied; this was applied as a one-time cost for patients entering the health state.

A detailed overview of specific chemotherapy drugs, dose and schedule for treatment administration of BCG and Chemotherapy, used to estimate the cost of treatment applied in the model is provided in Appendix D.3.

6.2.8.5.4 Other costs

Additional cost inputs applied in the model included costs associated with management of patients who receive a cystectomy or have progressed disease. For patients who received a radical cystectomy, upon entering that health state a one-time cost ($29,260.08) for the procedure was applied, and from there on an average cost of management was applied for patients that remained in the health states (Table 6.1). Similarly, for patient that had a disease progression, an average cost of maintenance was applied per cycle ($2,293.56), and then the cost of palliative care ($56,498.78) was applied to the proportion of patients that died in each cycle. This approach was taken as the cost associated with management of patients in the last year of life is high, and thus incorporating that in the average cost of maintenance per cycle would artificially inflate the cost of management for patients with progressed disease.

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Table 6.2 Cost inputs applied in the model

Resource Category	Cost (2020 CAD)		Source
	BLC	WLC	
TURBT procedure*	$3,298.27	$2,547.36	Appendix D.1
Surveillance (per cycle)			
Year 1, 2	$568.15		
Year 3, 4	$284.08		
Year 5-10	$47.35		Appendix D.2
Chemotherapy			
Intra-operative (single-dose):	$514.18		
Induction	$3,173.42		
Maintenance	$5,289.04		Appendix D.3
BCG			
Intermediate risk	$1,448.68		
High risk	$3,038.18		Appendix D.3
Progressed			
Palliative care*	$56,498.78		
Maintenance cost (per cycle)	$2,293.56		Oliveira et al. 2017[50]
Cystectomy			
Radical cystectomy*	$29,260.08		Appendix D.4
Post-cystectomy care (per cycle)			
Year 1-3	$335.35		
years 4,5	$158.10		AppendixD.4; Kulkarni et al. 2009[51]
Year 6-10	$113.02		

BLC=Blue light assisted cystoscopy; WLC=White light assisted cystoscopy; TURBT=Transurethral removal of bladder tumor; BCG= Bacillus Calmette–Guérin

Note: In the reference case the cost of the tower and instrument sets was included in the estimation of TURBT cost in the BLC group.

*Costs applied as a one-time cost in the model upon occurrence of an event

6.2.9 Analysis

A list of key analysis parameters adopted in the reference case is summarized in Table 6.3 . Reference case results were calculated from a deterministic analysis (using point estimates of parameter values).

Final model outputs from this analysis include total costs, QALYs and recurrences avoided in each study group and the incremental costs per QALY, and incremental costs per recurrence avoided over the model time horizon. Cost outputs were also estimated by specific

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cost components including, cost of recurrence, surveillances and TURBT.

Table 6.3 Summary of model settings in the reference case.

Parameter	Reference case
Time horizon	10 years
Discounting	
Costs	1.50%
Health outcomes	1.50%
Early relapse cutoff	6 months
Discharge from urology	5 years
Cost of device*	Included
Service life of device*	10 years

***Intervention arm only; device cost includes the cost of the tower plus interment sets

6.2.10 Uncertainty

A series of deterministic sensitivity analyses were conducted to assess the impact of alternative model assumptions. More specifically, specific parameters were varied in a one-way sensitivity analysis to account for methodological uncertainty associated with assumptions made in the reference case (Table 6.3). In assessing deviations from the reference case assumptions, the incremental cost-effectiveness ration (ICER) was compared against the traditionally accepted willingness-to-pay (WTP) threshold of $50,000 per QALY gained.

An overview of the model parameters varied in the one-way sensitivity analysis is summarized in Appendix E .

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6.3 Results

6.3.1 Reference case

The reference case results over a 10-year time horizon, are summarized in Table 6.4. Overall, the BLC group resulted in higher discounted total QALYs and recurrences avoided, and lower costs, making it the **dominant** option over WLC. When compared to WLC, BLC led to 0.03 QALY gains, 0.10 recurrences avoided, and avoided on average $1,1059 per person over 10 years, offsetting the costs of addition of BLC and producing overall cost savings.

Over the model time horizon (10 years), the *BLC group* accrued a total cost of **$26,590** per patient. This includes $1,906 for management of recurrences (this includes the cost of TURBTs), $1,141 for TURBTs alone, $11,560 for surveillance, and $13,123 for other costs (i.e. cystectomy and disease progression). These patients experienced 0.35 recurrences and accrued a total QALY of 6.52 over 10 years. *Relative to WLC*, over 10 years patients that received BLC incurred less cost of recurrence (-$219) and other costs (-$1,676), while incurring additional cost of surveillance ($836). Patients in the BLC group also produced an additional 0.03 QALYs and avoided 0.10 recurrences, compared to WLC.

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Table 6.4 Reference case results (per person): 10-year time horizon and 1.5% discount rate

	BLC	WLC	Incremental
Outcomes			
Total QALYs	**6.52**	**6.49**	**0.03**
Total Recurrence	**0.35**	**0.45**	**-0.10**
Costs			
Cost of recurrence*	$1,906	$2,125	-$219
Cost of surveillance	$11,560	$10,725	$836
Cost of TURBT	$1,141	$1,139	$2
Other costs**	$13,123	$14,800	-$1,676
Total Costs	**$26,590**	**$27,649**	**-$1,059**
	BLC vs. WLC		
Incremental cost per QALY	**Dominant**		
Incremental cost per recurrence avoided	**Dominant**		

BLC=Blue light assisted cystoscopy (intervention); WLC=White light assisted cystoscopy (comparator); QALY=Quality adjusted life year

*Note: The cost of recurrence also includes the cost of TURBT. Therefore, the component costs presented in the table do not add up to the total costs

** Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

6.3.2 Sensitivity analysis

An overview of the range of variables evaluated in one-way sensitivity analysis is provided in Appendix E.

Overall, the model results were most sensitive to the reduction in the time horizon considered in the analysis.

Consideration of a 5-year time horizon reduced the cost savings from $1,059 to $249 per patient, but BLC remained the dominant option when compared to WLC. When the time horizon was reduced to 3 years, BLC was no longer cost saving but still cost-effective (Cost/QALY of $19,299), with an incremental cost per QALY below the WTP threshold of $50,000. Reduction of the time horizon to one year resulted in an incremental cost per QALY (Cost/QALY of $327,431) above the $50,000 WTP threshold; this is because although costs are

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incurred upon entering the model (i.e. TURBTs), with a one-year time horizon, enough time has not passed for the QALYs to accrue.

The overall cost-effectiveness results remained robust (i.e. BLC remained dominant) when the cost of surveillance, medications were doubled. Similar trends were observed, when the life of the additional equipment required for BLC was reduced from 10 to 5 years. Lastly, when the cost of the HAL solution required for BLC was doubled (from $707 to $ 1,414), BLC remained the cost saving option.

6.4 Discussion

Based on the best and longest clinical evidence available, in the reference case (Table 6.4), results from the simulation model indicate that as the dominant option (i.e., less costly and more effective compared to WLC), BLC is cost-saving to the health care system. Compared to WLC, BLC saves $1,059 and produces an additional 0.03 QALYs per patient over 10 years. The observed results are largely driven by reducing the number of recurrences (-0.10) experienced by patients, therefore, reducing the downstream costs associated with management of patients experiencing more recurrences (-$219), cystectomy and disease progression (-$1,676).

Given the nature of the disease, while recurrence is an important consideration regarding the patient's experience, the patient's quality of life does not change significantly as the health effects of a recurrence are not sustained, and thus, the incremental gains in QALYs observed in the reference case are small (0.03) over 10 years. This is true for both QALYs (0.03) and recurrences avoided (0.10). Therefore, there is some uncertainty about whether important health gains are achieved for the patient with the addition of BLC. However, these benefits are positive (i.e. there is an incremental gain), demonstrating an increase in recurrences avoided.

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Further, no health losses were observed when assumptions were varied in the sensitivity analysis (Appendix E).

The small difference observed in QALYs across the study arm is in part explained by nature of NIMBC. More specifically, the quality of life of NMIBC patients is relatively high in between recurrences (i.e. when the patient is under surveillance), which is majority of the time in both study arms. The patients experience a decrement in their health utility when they have recurrence, but as they return to surveillance states they adjust back. So, overall given the nature of the disease, the quality of life of the patients does not change significantly when they experience a recurrence, as the effect is not sustained. But, with each recurrence there is a substantial cost to the system (i.e. additional TURBTs and downstream utilization costs for patients that progress to more severe disease states). Therefore, the main "benefit" of BLC is in its cost savings it allows to the system.Thus, the key driver informing policy change for management of patients with NMIBC are the cost savings incurred due to adoption of BLC.

The model results remained robust when most assumptions were varied in a one-way sensitivity analysis (Appendix E). However, the results were sensitive to a change in time horizon. When the time horizon was reduced to 5 years, BLC remained cost saving (-$249) producing an additional 0.016 QALYs. By further reducing the time horizon to 3 years, BLC was cost-effective (Cost/QALY $19,299) but was no longer cost-saving. BLC was not cost-effective within a one-year time horizon (Cost/QALY $327,431); this is compared against the traditionally accepted WTP threshold of $50,000 per QALY gained. In this scenario, although the incremental costs remained low, the small gains in QALYs (0.002) drives the high ICER observed in the one-year time horizon.

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The main strengths of this analysis include, 1) the use of observed clinical data to inform patient transition through the model over 10 years, thus reducing uncertainty, and 2) the consideration of the patient's full trajectory through the care pathway allowing for estimation of downstream costs and associated benefits.

However, as observed in the care pathway (Section 2.1) management of patients with NMIBC can be complex; where the patient's disease status (and therefore their care pathway) can change several times throughout the course of the disease. Therefore, one of the main challenges in this analysis was to design a model structure, which allows for the progression of patients through different potential care pathway options within the confines of a Markov model; referring to the Markov assumption, where the probability of transitioning between health states in the model in independent of where the patient comes from and the timing of earlier transitions (i.e. memory-less). To account for the memory-less feature of a Markov model, the model structure was specifically designed to include health states where the patient transitions through key parts of the care pathway can be captured, allowing for estimation of associated costs and benefits. Nevertheless, as some assumptions had to be made the following limitations should be noted in consideration of the results of this economic analysis.

First, due to the memory-less feature of Markov models, definition of early relapse for this analysis was restricted to patients that had a recurrence within the 6 months of the model simulation. However, in reality patients could potentially fall under the early relapse definition further down in their disease trajectory. This feature could have only been addressed with a microsimulation design that would allow building of patient memory into the model. As this was not within scope for this evaluation we may be underestimating the overall proportion of

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people who will eventually have an early relapse within the 10-year time horizon considered in this model. However, as the expected proportion of patients experiencing an early relapse is quite small in practice[52] this is unlikely to impact the overall cost-effectiveness results. Further, increasing the cutoff time to 36 months for patients to enter the early relapse path in the model in a one-way sensitivity analysis, did not impact the overall result of the model.

Second, as a function of the Markov model design, in each health state all patients are assumed to be the same regardless of their disease history (which health state they came from). In this analysis, in order to allow for different risk of recurrence by the patient's risk stratification (e.g. low/intermediate/high), and to capture the cost of TURBT and associated treatments, "recurrence health states" were added where patients enter every time they had a recurrence and all patients left by the end of the cycle by either, progressing, dying or being redistributed back to the surveillance states (Figure 6.1). Therefore, under this structure patients could have only progressed from the recurrence health states. This meant that in each model cycle as only a small proportion of patients were eligible to progress, their time under *risk of progression* was artificially reduced. To assess the impact of this limitation on the overall cost-effectiveness results, we artificially inflated the rate of disease progression to make up for the lack of time under risk, and found that the model results remained robust (i.e. BLC remained cost saving).

Overall, the results from this analysis tailored for the BC health care system indicate that despite the small incremental gains in QALYs, relative to WLC, BLC remains cost-saving to the health care system.

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Chapter 7 Budget Impact

7.1 Objectives

The objective of this analysis was to evaluate the budget impact of expanding access to hexaminolevulinate hydrochloride (HAL), from here on referred to as Blue Light Cystoscopy (BLC)) used as an adjunct to white light cystoscopy (WLC) in transurethral resection of bladder tumors (TURBT) to treat patients with non-muscle invasive bladder cancer (NMIBC) in British Columbia (BC).

7.2 Methods

An overview of the target population definition and budget impact modelling approach along with scenarios considered is presented in Figure 7.1.

7.2.1 Target population definition

In this analysis the starting population includes the population within BC in 2021[43], where the application of the prevalence of bladder cancer among individuals over the age of 65 with NMIBC results in 9,213 individuals.[2, 15] Further refinement of this population to patients within the 70-79 age group,[43] which is in line with the target population simulated within the cost-effectiveness model (see section 6.2.2), results in 4,119 individuals as the annual prevalent patients who are eligible for BLC in BC (Figure 7.1).

7.2.2 Budget impact and modelling approach

The Markov model utilized in the economic evaluation (Figure 6.1) was also used for the budget impact analysis to simulate a dynamic population level impact over 10 years (2021 to 2030). The model was configured to simulate a dynamic population based on a staggered entry of a new cohort of eligible patients every calendar year. The dynamic population reflects the

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change in the population size over time due to population growth (i.e. arrival of new individuals into the target cohort), as well as departures (i.e. death). Therefore, at any point beyond 2021, multiple cohorts exist within the simulation, where the population is adjusted by rates of death and projected population growth.

As a result of the dynamic population simulation, model outputs in each calendar year are cumulative, reflecting the health and budget impact of the surviving population from the previous calendar year(s), in addition to the new cohort that enters the model each year. For example, in the year 2024, the model outputs for 2024 are estimated for the new cohort of patients entering the model in that year in addition to the individuals who have entered the model in previous years and survived.

Further, as noted above, the budget impact analysis was conducted for the 70-79 age group and incidence of NMIBC was assumed to remain constant in the BC population. Every year, a new cohort of patients enter the model as eligible patients for BLC, and thus, model outputs were calculated cumulatively (starting from 2021).

In line with current best practice guidelines[53], in a BIA discounting financial flows to net present value is not recommended. Therefore, discounting was not applied in the BIA and thus the results reflect the budget impact that is expected at each point in time. Further, no changes in price units were assumed during the considered analysis period (e.g. The cost of the HAL solution required for BLC was assumed to remain at $707 per TURBT).

As presented in Figure 7.1, four adoption scenarios (scenarios B and D were recommended by clinical advisors) were considered to assess the budget impact in BC. An overview of each adoption scenario is described below.

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- **Scenario A**: This reflects the *reference scenario* in this analysis, where it is assumed 100% of eligible patients are managed with WLC only. Although, BLC is currently offered in BC in some centers, this scenario was chosen as use of BLC is currently dependent on whether the hospitals fund the consumables (i.e. HAL solution, catheters etc.) for the procedure. Further, at centers where BLC is provided, there is no dedicated funding available for purchasing the equipment, and funding for equipment is typically secured by physicians through donations.
- **Scenario B:** This scenario reflects complete adoption of BLC in BC, where 100% of TURBT procedures are guided with blue-light in addition to white-light.
- **Scenario C:** This scenario was included to demonstrate the budget impact when the technology is adopted more gradually. Therefore, in this scenario the budget impact is estimated to demonstrate an alternative adoption strategy outside the two extreme scenarios of adoption (i.e 100% WLC vs. 100% BLC). In this context Scenario C was defined as follows: 75% of the eligible patient population is managed with WLC alone and 25% receives BLC.
- **Scenario D:** This scenario was informed through stakeholder feedback and reflects the level of adoption within hospitals where BLC is available. Under this scenario, provision of BLC can be decided on a case-by-case basis, based on clinical judgment. This scenario was included in the analysis to demonstrate the impact where not all patients may receive BLC due to specific clinical judgements of the clinicians (e.g. Following treatment with BCG, the decision to use BLC is

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made on a patient-by-patient basis). In this context Scenario D was defined as follows: 25% of the eligible patient population is managed with WLC alone and 75% receives BLC.

Lastly, to estimate the overall budget and health impact, adoption scenario B and C were considered relative to the reference scenario (Scenario A).

- **Scenario B vs. A (reference scenario):** This comparison estimates the impact on the health care budget if 100% of eligible patients in BC receive BLC.
- **Scenario C vs. A (reference scenario):** This comparison estimates the impact on the health care budget if 25% of eligible patients in BC receive BLC.
- **Scenario D vs. A (reference scenario):** This comparison estimates the impact on the health care budget if 75% of eligible patients in BC receive BLC.

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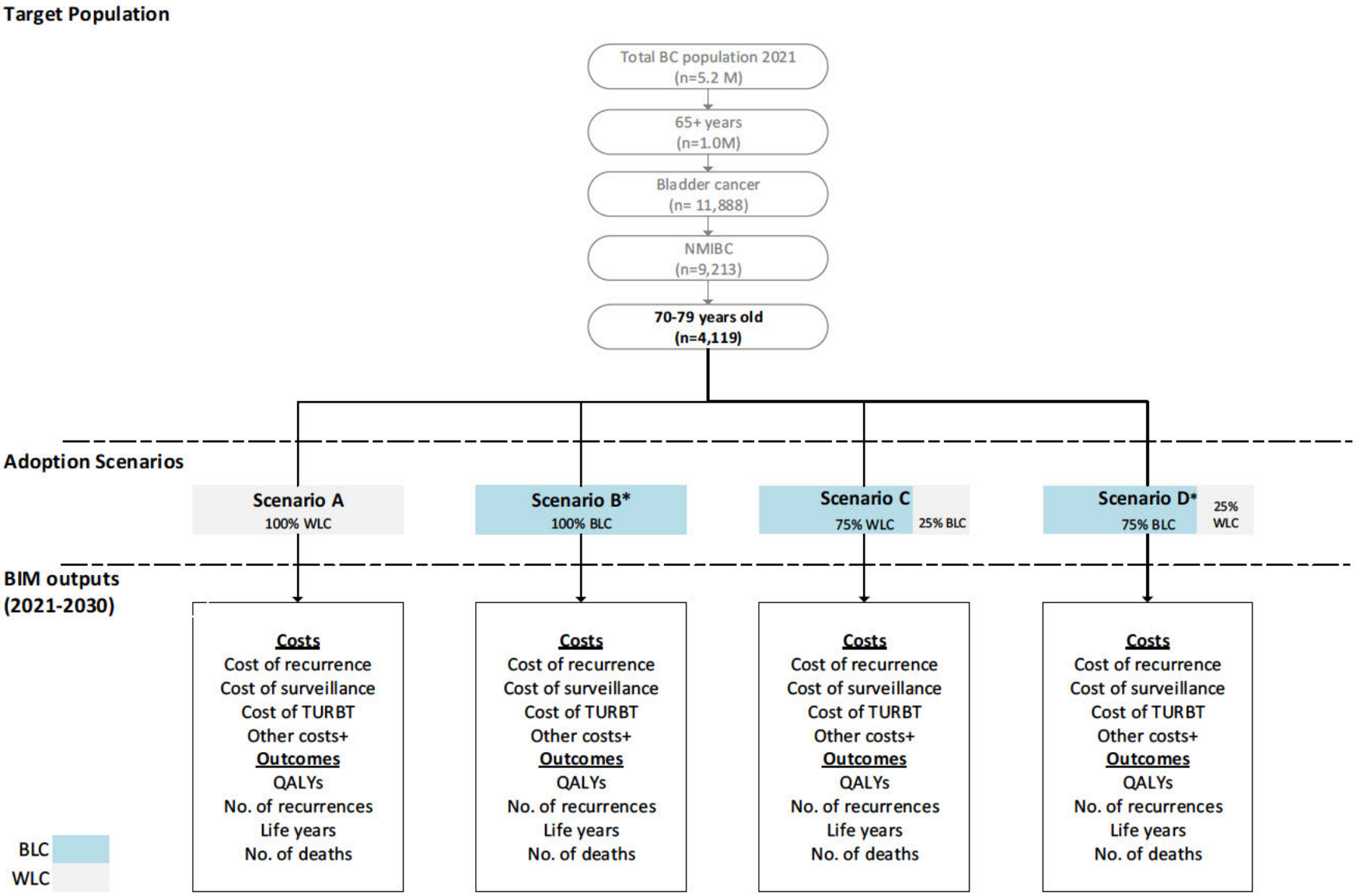
Figure 7.1 Schematic of the budget impact modelling approach and scenarios considered



BIM=Budget impact model; BC=British Columbia; WLC=White light cystoscopy; BLC=Blue light cystoscopy; NMIBC=None-muscle invasive bladder cancer No.= Number; QALYs= Quality adjusted life year; *Scenarios recommended by clinicians; + Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

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7.3 Results

7.3.1 Scenario A- 100% WLC

The estimated annual and cumulative costs and health outcomes associated with Scenario A between 2021 to 2030 is summarized in Table 7.1. Assuming 100% of eligible patients are managed with WLC, the estimated total cumulative cost over ten years is $1,029.8 million. The annual total costs in this scenario are predicted to increase from $29.3 million in 2021 to $164.1 million in 2030. Of the total cumulative cost of $1,029.8 million estimated for this scenario over 10 years, 8% was attributed to cost of managing tumor recurrences (which includes cost of TURBT), 47% to cost of surveillance in between recurrences, 5% to cost of the TURBT procedure alone and 44% to other costs, which includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress.

Other outcomes considered in Scenario A include the annual and 10-year cumulative QALYs, life years, deaths and number of recurrences (Table 7.1). Overall, assuming 100% of eligible patients are managed with WLC, between 2021 to 2030 there is an expected 193,782 QALYs, 235,813 life years, 10,577 deaths, and 18,372 recurrences.

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Table 7.1 Scenario A- Estimated annual and cumulative undiscounted costs and health outcomes between 2021 to 2030

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2021-2030
Outcomes											
QALY	2,055	5,593	9,234	12,991	16,889	20,898	25,025	29,281	33,651	38,165	193,782
Recurrence	178	1,043	1,468	1,738	1,944	2,096	2,264	2,417	2,544	2,677	18,372
Life years	2,571	6,883	11,301	15,857	20,581	25,436	30,430	35,579	40,860	46,314	235,813
Death	12	183	450	702	947	1,208	1,436	1,674	1,885	2,081	10,577
Costs											
Cost of recurrence*	$685.9K	$4.8M	$7.0M	$8.3M	$9.3M	$10.0M	$10.8M	$11.5M	$12.1M	$12.7M	$87.1M
Cost of Surveillance	$26.0M	$35.1M	$41.2M	$46.5M	$49.6M	$52.2M	$54.8M	$57.5M	$60.1M	$62.7M	$485.9M
Cost of TURBT	$454.1K	$2.7M	$3.7M	$4.4M	$5.0M	$5.3M	$5.8M	$6.2M	$6.5M	$6.8M	$46.8M
Other costs**	$2.5M	$11.7M	$21.7M	$31.4M	$41.3M	$50.7M	$60.0M	$69.7M	$79.1M	$88.7M	$456.9M
Total Costs	**$29.3M**	**$51.7M**	**$69.9M**	**$86.2M**	**$100.1M**	**$112.9M**	**$125.6M**	**$138.6M**	**$151.3M**	**$164.1M**	**$1,029.8M**

M=Million; K=Thousand; WLC=White-light cystoscopy; TURBT=Transurethral resection of bladder tumors; QALY=Quality adjusted life year

*Note: The cost of recurrence also includes the cost of TURBT. Therefore, the component costs presented in the table do not add up to the total costs

** Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

Scenario A: 100% WLC

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7.3.2 Scenario B- 100% BLC

The estimated annual and cumulative costs and health outcomes associated with Scenario B between 2021 to 2030 are summarized in Table 7.2. Assuming 100% of eligible patients are managed with BLC, the estimated total cumulative cost over ten years is $1,015.0 million. The annual total costs in this scenario are predicted to increase from $32.2 million in 2021 to $158.0 million in 2030. Of the total cumulative cost of $1,015.0 million estimated for this scenario over 10 years, 8% was attributed to the cost of managing tumor recurrences (which includes cost of TURBT), 52% to cost of surveillance in between recurrences, 5% to cost of the TURBT procedure alone and 40% to other costs, which includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress.

Other outcomes considered in Scenario B include the annual and 10-year cumulative QALYs, life years, deaths and number of recurrences (Table 7.2). Overall, assuming 100% of eligible patients are managed with BLC, between 2021 to 2030 there is an expected 194,664 QALYs, 236,376 life years, 10,460 deaths, and 14,208 recurrences.

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Table 7.2 Scenario B- Estimated annual and cumulative undiscounted costs and health outcomes between 2021 to 2030

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2021-2030
Outcomes											
QALY	2,057	5,606	9,261	13,037	16,958	20,992	25,143	29,426	33,822	38,361	194,664
Recurrence	136	806	1,135	1,344	1,504	1,621	1,752	1,870	1,969	2,072	14,208
Life years	2,571	6,885	11,312	15,882	20,623	25,497	30,508	35,676	40,976	46,446	236,376
Death	12	179	438	689	930	1,192	1,420	1,658	1,871	2,070	10,460
Costs											
Cost of recurrence*	$627.1K	$4.4M	$6.2M	$7.4M	$8.3M	$8.9M	$9.7M	$10.3M	$10.8M	$11.4M	$78.1M
Cost of Surveillance	$29.2M	$38.6M	$45.0M	$50.5M	$53.9M	$56.7M	$59.5M	$62.4M	$65.2M	$68.1M	$529.2M
Cost of TURBT	$449.1K	$2.7M	$3.7M	$4.4M	$5.0M	$5.3M	$5.8M	$6.2M	$6.5M	$6.8M	$46.9M
Other costs**	$2.4M	$10.7M	$19.7M	$28.3M	$37.0M	$45.4M	$53.6M	$62.0M	$70.2M	$78.5M	$407.7M
Total Costs	**$32.2M**	**$53.7M**	**$70.9M**	**$86.3M**	**$99.2M**	**$111.0M**	**$122.8M**	**$134.7M**	**$146.2M**	**$158.0M**	**$1,015.0M**

M=Million; K=Thousand; BLC=Blue-light cystoscopy; TURBT=Transurethral resection of bladder tumors; QALY=Quality adjusted life year

*Note: The cost of recurrence also includes the cost of TURBT. Therefore, the component costs presented in the table do not add up to the total costs

** Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

Scenario B: 100% BLC; This scenario was recommended by clinical advisors

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7.3.3 Scenario C- 25% BLC, 75% WLC

The estimated annual and cumulative costs and health outcomes associated with Scenario C between 2021 to 2030 are summarized in Table 7.3. Assuming 75% of eligible patients are managed with WLC and 25% with BLC, the estimated total cumulative cost over ten years is $1,026.1 million. The annual total costs in this scenario are predicted to increase from $30.0 million in 2021 to $162.6 million in 2030. Of the total cumulative cost of $1.03 billion estimated for this scenario over 10 years, 8% was attributed to cost of managing tumor recurrences (which includes cost of TURBT), 49% to cost of surveillance in between recurrences, 5% to cost of the TURBT procedure alone and 43% to other costs, which includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress.

Other outcomes considered in Scenario C include the annual and 10-year cumulative QALYs, life years, deaths and number of recurrences (Table 7.3). Overall, assuming 75% of eligible patients are managed with WLC and 25% with BLC, between 2021 to 2030 there is an expected 194,003 QALYs, 235,954 life years, 10,548 deaths, and 10,548 recurrences.

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Table 7.3 Scenario C- Estimated annual and cumulative undiscounted costs and health outcomes between 2021 to 2030

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2021-2030
Outcomes											
QALY	2,056	5,596	9,241	13,003	16,906	20,922	25,054	29,318	33,694	38,214	194,003
Recurrence	168	984	1,385	1,640	1,834	1,977	2,136	2,280	2,401	2,526	17,331
Life years	2,571	6,883	11,304	15,864	20,592	25,451	30,450	35,603	40,889	46,347	235,954
Death	12	182	447	699	943	1,204	1,432	1,670	1,881	2,078	10,548
Costs											
Cost of recurrence*	$671.2K	$4.7M	$6.8M	$8.1M	$9.0M	$9.7M	$10.5M	$11.2M	$11.8M	$12.4M	$84.8M
Cost of Surveillance	$26.8M	$36.0M	$42.2M	$47.5M	$50.7M	$53.4M	$56.0M	$58.7M	$61.4M	$64.1M	$496.7M
Cost of TURBT	$452.8K	$2.7M	$3.7M	$4.4M	$5.0M	$5.3M	$5.8M	$6.2M	$6.5M	$6.8M	$46.8M
Other costs**	$2.5M	$11.5M	$21.2M	$30.7M	$40.2M	$49.4M	$58.4M	$67.7M	$76.8M	$86.1M	$444.6M
Total Costs	**$30.0M**	**$52.2M**	**$70.2M**	**$86.2M**	**$99.9M**	**$112.5M**	**$124.9M**	**$137.6M**	**$150.0M**	**$162.6M**	**$1,026.1M**

M=Million; K=Thousand; BLC=Blue-light cystoscopy; WLC=White-light cystoscopy; TURBT=Transurethral resection of bladder tumors; QALY=Quality adjusted life year

*Note: The cost of recurrence also includes the cost of TURBT. Therefore, the component costs presented in the table do not add up to the total costs

** Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

Scenario C: 75% WLC, 25% BLC

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7.3.4 Scenario D- 75% BLC, 25% WLC

The estimated annual and cumulative costs and health outcomes associated with Scenario C between 2021 to 2030 are summarized in Table 7.4. Assuming 25% of eligible patients are managed with WLC and 75% with BLC, the estimated total cumulative cost over ten years is $1,018.7 million. The annual total costs in this scenario are predicted to increase from $31.5 million in 2021 to $159.5 million in 2030. Of the total cumulative cost of $1,018.7 million estimated for this scenario over 10 years, 8% was attributed to cost of managing tumor recurrences (which includes cost of TURBT), 51% to cost of surveillance in between recurrences, 5% to cost of the TURBT procedure alone and 41% to other costs, which includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress.

Other outcomes considered in Scenario D include the annual and 10-year cumulative QALYs, life years, deaths and number of recurrences (Table 7.4). Overall, assuming 75% of eligible patients are managed with WLC and 25% with BLC, between 2021 to 2030 there is an expected 194,443 QALYs, 236,235 life years, 10,489 deaths, and 15,249 recurrences.

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Table 7.4 Scenario D- Estimated annual and cumulative undiscounted costs and health outcomes between 2021 to 2030

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2021-2030
Outcomes											
QALY	2,057	5,603	9,255	13,026	16,940	20,968	25,113	29,390	33,779	38,312	194,443
Recurrence	147	865	1,218	1,442	1,614	1,740	1,880	2,007	2,113	2,223	15,249
Life years	2,571	6,884	11,309	15,876	20,613	25,481	30,489	35,651	40,947	46,413	236,235
Death	12	180	441	692	935	1,196	1,424	1,662	1,874	2,072	10,489
Costs											
Cost of recurrence*	$641.8K	$4.5M	$6.4M	$7.6M	$8.5M	$9.2M	$9.9M	$10.6M	$11.2M	$11.7M	$80.3M
Cost of Surveillance	$28.4M	$37.7M	$44.1M	$49.5M	$52.9M	$55.6M	$58.4M	$61.2M	$63.9M	$66.7M	$518.4M
Cost of TURBT	$450.4K	$2.7M	$3.7M	$4.4M	$5.0M	$5.3M	$5.8M	$6.2M	$6.5M	$6.8M	$46.8M
Other costs**	$2.4M	$11.0M	$20.2M	$29.1M	$38.1M	$46.7M	$55.2M	$63.9M	$72.4M	$81.0M	$420.0M
Total Costs	**$31.5M**	**$53.2M**	**$70.7M**	**$86.2M**	**$99.5M**	**$111.5M**	**$123.5M**	**$135.7M**	**$147.5M**	**$159.5M**	**$1,018.7M**

M=Million; K=Thousand; BLC=Blue-light cystoscopy; WLC=White-light cystoscopy; TURBT=Transurethral resection of bladder tumors; QALY=Quality adjusted life year

*Note: The cost of recurrence also includes the cost of TURBT. Therefore, the component costs presented in the table do not add up to the total costs

** Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

Scenario D: 25% WLC, 75% BLC; This scenario was recommended by clinical advisors

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7.3.5 Budget and health impact

The overall 10-year budget and health impact for adoption of scenario B, C and D relative to the reference scenario (Scenario A) are summarized in Table 7.5. A more detailed overview of these comparisons, presenting the annual budget and health impacts is provided in Appendix F.

7.3.5.1 Scenario B vs. Scenario A (reference scenario)

If 100% of eligible patients received BLC starting in 2021, over the next 10 years the benefits observed in this patient population includes an estimated 4,164 recurrences avoided (22.66% decrease relative to patients managed with WLC), 118 deaths avoided (1.11% decrease relative to patients managed with WLC). Further, inclusion of BLC in patient's care also results in an incremental survival gain of 563 life-years (0.24% increase relative to patients managed with WLC) and 882 QALYs (0.45% increase relative to patients managed with WLC).

The overall impact on costs is estimated at approximately $14.8 million in costs *avoided* over 10 years, which is equivalent to approximately 1.44% *decrease* in the overall budget estimated for the health care management of NMIBC patients with WLC alone. Looking at specific service areas, over a 10-year period, provision of BLC leads to an incremental cost *reduction* of $9.0 million in management of tumor recurrences (10.32% decrease relative to when patients are managed on WLC alone), and $49.2 million in costs to manage patients who experience an early relapse, have a cystectomy or progress (10.77% decrease relative to when patients are managed on WLC alone). Over 10 years the cost of surveillance increased by $43.3 million (8.92% increase relative to patients managed with WLC) and TURBT costs alone

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increased by $62.4 thousand (0.13% increase relative to when patients are managed on WLC alone).

7.3.5.2 Scenario C vs. Scenario A (reference scenario)

If 25% of eligible patients received BLC starting in 2021, over the next 10 years the benefits observed in this patient population includes an estimated 1,041 recurrences avoided (5.67% decrease relative to patients managed with WLC), 29 deaths avoided (0.28% decrease relative to patients managed with WLC). Further, inclusion of BLC in patient's care also results in an incremental survival gain of 141 life-years (0.06% increase relative to patients managed with WLC) and 220 QALYs (0.11% increase relative to patients managed with WLC).

The overall impact on costs is estimated at approximately $3.7 million in costs *avoided* over 10 years, which is equivalent to approximately an 0.36% *decrease* in the overall budget estimated for the health care management of NMIBC patients with WLC alone. Looking at specific service areas, over a 10-year period, provision of BLC to 25% of the eligible patient population, leads to an incremental cost *reduction* of $2.2 million in management of tumor recurrences (2.58% decrease relative to when patients are managed on WLC alone), and $12.3 million in costs to manage patients who experience an early relapse, have a cystectomy or progress (2.69% decrease relative to when patients are managed on WLC alone). Over 10 years the cost of surveillance increased by $10.8 million (2.23% increase relative to patients managed with WLC) and TURBT costs alone increased by $15.6 thousand (0.03% increase relative to when patients are managed on WLC alone).

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7.3.5.3 Scenario D vs. Scenario A (reference scenario)

If 75% of eligible patients received BLC starting in 2021, over the next 10 years the benefits observed in this patient population includes an estimated 3,123 recurrences avoided (17.0% decrease relative to patients managed with WLC), 88 deaths avoided (0.83% decrease relative to patients managed with WLC). Further, inclusion of BLC in patient's care also results in an incremental survival gain of 423 life-years (0.18% increase relative to patients managed with WLC) and 661 QALYs (0.34% increase relative to patients managed with WLC).

The overall impact on costs is estimated at approximately $11.1 million in costs *avoided* over 10 years, which is equivalent to approximately an 1.08% *decrease* in the overall budget estimated for the health care management of NMIBC patients with WLC alone. Looking at specific service areas, over a 10-year period, provision of BLC to 75% of the eligible patient population, leads to an incremental cost *reduction* of $6.7 million in management of tumor recurrences (7.74% decrease relative to when patients are managed on WLC alone), and $36.9 million in costs to manage patients who experience an early relapse, have a cystectomy or progress (8.08% decrease relative to when patients are managed on WLC alone). While, over 10 years the cost of surveillance increased by $32.5 million (6.69% increase relative to patients managed with WLC) and TURBT costs alone increased by $46.8 thousand (0.10% increase relative to when patients are managed on WLC alone).

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Table 7.5 Overall budget and health impact over 10 years (undiscounted)

	Budget and health impact (2021-2030)		
	Scenario B vs. A	**Scenario C vs. A**	**Scenario D vs. A**
Outcomes			
QALY	882	220	661
Recurrence	- 4,164	-1,041	-3,123
Life years	563	141	423
Death	-118	-29	-88
Costs			
Cost of recurrence*	- $9.0M	- $2.2M	- $6.7M
Cost of surveillance	$43.3M	$10.8M	$32.5M
Cost of TURBT	$62.4K	$15.6K	$46.8K
Other costs**	- $49.2M	- $12.3M	- $36.9M
Total budget and impact	**- $14.8M**	**- $3.7M**	**- $11.1M**

M=Million; K=Thousand; BLC=Blue-light cystoscopy; WLC=White-light cystoscopy; TURBT=Transurethral resection of bladder tumors; QALY=Quality adjusted life year

*Note: The cost of recurrence also includes the cost of TURBT. Therefore, the component costs presented in the table do not add up to the total costs

** Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

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7.4 Discussion

Incorporating the best available evidence for the BC context into a decision-analytic simulation model demonstrated that adoption of BLC for patients with NMIBC can result in a reduction in recurrences experienced by patients and overall QALY gains. Relative to the management of this patient group with WLC, the incremental impact of providing BLC to *all* eligible patients for 10 years in BC can result in $14.8 million of savings to the health care system, equivalent to a 1.44% reduction in overall costs, and 882 QALY gains (0.45% increase relative to patients managed with WLC).

Overall, even with the additional cost associated with provision of BLC, the incremental cost of managing recurrences over 10 years was cost saving, at approximately $9.0 million . The observed cost savings are attributed to an overall reduction in the number of recurrences experienced by the patients (i.e. 4,164 recurrences avoided over 10 years). The benefits of the addition of BLC in terms of cost-savings to the system are further realized in reducing the proportion of patients that progress to more severe and costly disease states, such as cystectomy or metastatic disease, thus reducing the downstream costs associated with disease progression. These savings include an incremental cost saving of $49.2 million in “other costs”, reflecting the costs associated with management of patients who experience an early relapse, have a cystectomy or progress.

Consideration of other implementation scenario, where either 25% and 75% of eligible patients receive BLC, was still cost saving to the system over 10 years, yielding $3.7 million and $11.1, respectively, in overall savings. Lastly, when evaluating the *annual* budget impact in all

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adoption scenarios considered (Figure 7.1), the overall cost savings are not realized until the fourth year of implementation (Appendix F).

In consideration of these results, it should be noted that the modelling framework developed for the cost-effectiveness analysis (CEA) (see Section 6.2) was used for the budget impact analysis. Therefore, the assumptions and limitations discussed in the previous chapter should also be considered in the interpretation of the budget impact results (Section 6.2 and 6.4). Further, as it was not within the scope of the present analysis to incorporate all implementation considerations, the following points should be considered in implementation of BLC.

In this analysis it was assumed that there are no barriers for patients with NMIBC accessing care and receiving TURBTs within an appropriate time frame. However, as noted by stakeholders, NMIBC is associated with the highest number of hospital visits and appointments (i.e. required as apart of surveillance; cystoscopy, urine cytology) of all cancers. This leads to logistical difficulties for patients (and caregivers) to attend all appointments required as part of the patient's surveillance, which is required every three months. This problem can disproportionally impact patients in rural/remote settings due to distance and geographical access. Given this, decentralized provision of BLC across the province is likely most beneficial to patients receiving care.

Stakeholders indicated that a separate fee code for HAL-assisted TURBT (i.e. BLC) is not required. Intraoperatively the procedure is identical to WLC with the only difference being a pedal for the surgeon to flip between white and blue light. However, the procedure can take longer as the surgeon will view the bladder with both white and blue light. Implementation of

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BLC will also require additional nursing time for perioperative instillation of the chemical. Further, once the HAL solution is instilled in the bladder it does require a minimum of one-hour dwell time. Therefore, with the addition of BLC each patient would occupy the bed for at least an additional hour compared to WLC. Nonetheless, the additional hospital time per patient is expected to be offset by fewer TURBT procedures done overall due to reduced recurrences.

Lastly, part of the infrastructure needed for provision of BLC includes the appropriate endoscopy system to accommodate the addition of BLC, including the electronics, commonly referred to as the 'Tower', and the instrument set that is sterilized for patient use. In the reference case of the CEA, the capital cost of equipment (this includes the tower and instrument sets) was built into the analysis and amortized over 10 years. This was included in the analysis as a conservative approach, as site specific information on the availability of equipment, capacity and surgical slate was not available. Therefore, it was not possible to incorporate the initial investment required for purchasing the necessary equipment as an upfront cost in the budget impact analysis.

The results of this analysis indicate that public funding of BLC for patients with NMIBC may allow for cost savings over 10 years. Therefore, the estimates provided in the present analysis can offer a reasonable starting point for the assessment of the policy design with regards to affordability, feasibility and consideration of additional potential simulations to better inform next steps.

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Appendix A Search Strategies

A.1 Medline

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 26, 2021>
Search Strategy:
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1 Urinary Bladder Neoplasms/ (55314)
2 ((urothelial or bladder* or urinary) and (cancer* or neoplasm* or tumor* or tumour* or carcinom* or malignan* or adenocarcinom* or precancerous or malignan* or lump* or lesion* or masses* or sarcom* or metastas*)).mp. (138139)
3 Carcinoma, Transitional Cell/ (18995)
4 transitional cell carcinoma*.mp. (9673)
5 urothelial carcinoma.mp. (9089)
6 NMIBT.mp. [non-muscle invasive bladder tumours] (17)
7 NMIBC.mp. [non-muscle invasive bladder cancer] (1584)
8 Neoplasm Recurrence, Local/ (120945)
9 Neoplasm Invasiveness/ (83723)
10 Neoplasm, Residual/ (10783)
11 Neoplasm Staging/ (177505)
12 (transurethral adj4 resection*).mp. (13625)
13 TURBT.mp. (916)
14 or/8-13 (355030)
15 urinary bladder/ (50760)
16 bladder.tw,kw,kf. (163757)
17 or/15-16 (176366)
18 14 and 17 (19441)
19 or/1-7,18 (142448)

20 Cystoscopy/ (7675)
21 Cystoscop*.tw,kw,kf. (10549)
22 or/20-21 (14830)

23 Light/ (103395)
24 Photochemotherapy/ (20013)
25 Aminolevulinic Acid/ (5614)
26 Photosensitizing Agents/ (16593)
27 Image Enhancement/ (44526)
28 Hexaminolevulinate.mp. (129)
29 Hexvix.mp. (49)
30 Photocure.mp. (44)
31 luminescence/ or fluorescence/ (53132)
32 blue light.mp. (9523)
33 fluorescen*.tw,kw,kf. (488161)
34 Microscopy, Fluorescence/ (78455)
35 Coloring Agents/ (46836)
36 colo?ring agent*.tw,kw,kf. (519)
37 Fluorescent Dyes/ (75229)
38 Cysview.mp. (6)

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39 Aminolevulinic Acid.tw,kw,kf. (6576)
40 Aminolevulinate.mp. (3180)
41 photosensitizing.tw,kw,kf. (2752)
42 photodynamic.mp. (26268)
43 Hexyl aminolevulinate.mp. (30)
44 hexyl 5-aminolevulinate.mp. (9)
45 5-ALA hexylester.mp. (2)
46 Hexyl 5-amino-4-oxopentanoate.mp. (1)
47 5-ALAHE.mp. (0)
48 ALA hexyl ester.mp. (22)
49 hexylaminolevulinate.mp. (32)
50 hexa ALA.mp. (3)
51 G7H20TKI67.rn. (187)
52 5-aminolevulinic acid hexyl ester.mp. (190)
53 or/23-52 (785739)

54 22 and 53 (749)

55 (fluorescence adj5 diagnos*).mp. (2035)
56 (photodynamic adj5 diagnos*).mp. (766)
57 or/54-56 (3187)

58 19 and 57 (849)

59 animals/ not (animals/ and humans/) (4747531)
60 58 not 59 (832)
61 limit 60 to yr="2017 -Current" (173)
62 limit 61 to English language (157)

A.2 Embase

Database: Embase <1974 to 2021 January 26>
Search Strategy:
---
1 bladder cancer/ (49618)
2 non muscle invasive bladder cancer/ (4191)
3 bladder tumor/ (18901)
4 transurethral resection of bladder tumor/ (111)
5 TURBT.mp. (2302)
6 ((urothelial or bladder* or urinary) and (cancer* or neoplasm* or tumor* or tumour* or carcinom* or malignan* or adenocarcinom* or precancerous or malignan* or lump* or lesion* or masses* or sarcom* or metastas*)).mp. (226179)
7 NMIBT.mp. [non-muscle invasive bladder tumours] (62)
8 NMIBC.mp. [non-muscle invasive bladder cancer] (3183)
9 or/1-8 (226239)
10 transurethral resection/ (20999)
11 (transurethral adj4 resection*).tw,kw. (17598)
12 or/10-11 (25946)
13 bladder*.mp. (286382)

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14 12 and 13 (15463)
15 or/9,14 (229345)

16 blue light flexible cystoscopy/ (5)
17 BLC/ (28)
18 fluorescence cystoscopy/ (51)
19 or/16-18 (83)
20 15 and 19 (82)

21 Cystoscopy/ (22682)
22 Cystoscop*.tw,kw. (17876)
23 or/21-22 (28218)
24 photodynamics/ (3050)
25 aminolevulinic acid hexyl ester/ (528)
26 blue light/ (6156)
27 aminolevulinic acid/ (9499)
28 5-aminolevulinic acid hexyl ester/ (116)
29 fluorescence/ (135449)
30 fluorescent lighting/ (1748)
31 photodynamic therapy/ (27037)
32 photosensitizing agent/ (15739)
33 Hexaminolevulinate.mp. (244)
34 Hexvix.mp. (184)
35 Photocure.mp. (346)
36 blue light.tw,kw. (10234)
37 fluorescen*.tw,kw. (573811)
38 colo?ring agent*.tw,kw. (691)
39 Fluorescent Dye*.tw,kw. (18161)
40 Cysview.mp. (37)
41 Aminolevulinic Acid.tw,kw. (7707)
42 Aminolevulinate.mp. (3252)
43 photosensitizing.tw,kw. (3176)
44 photodynamic*.tw,kw. (31765)
45 Hexyl aminolevulinate.mp. (40)
46 hexyl 5-aminolevulinate.mp. (9)
47 5-ALA hexylester.mp. (2)
48 Hexyl 5-amino-4-oxopentanoate.mp. (0)
49 5-ALAHE.mp. (0)
50 ALA hexyl ester.mp. (23)
51 hexylaminolevulinate.mp. (60)
52 hexa ALA.mp. (4)
53 5-aminolevulinic acid hexyl ester.tw,kw. (15)
54 or/24-53 (646421)

55 23 and 54 (1140)

56 (fluorescence adj5 diagnos*).mp. (4500)
57 (photodynamic* adj5 diagnos*).mp. (1228)
58 or/55-57 (6262)
59 15 and 58 (1412)

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60 20 or 59 (1416)
61 limit 60 to yr="2012 -Current" (759)
62 limit 61 to English language (712)
63 editorial/ or letter/ or note/ (2543988)
64 62 not 63 (673)
65 limit 64 to conference abstracts (289)
66 64 not 65 (384)
67 limit 66 to medline (51)

68 66 not 67 (333)

69 "systematic review"/ (279988)
70 68 and 69 (24)

A.3 CENTRAL

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <December 2020>
Search Strategy:
---
1 Urinary Bladder Neoplasms/ (1484)
2 ((urothelial or bladder* or urinary) and (cancer* or neoplasm* or tumor* or tumour* or carcinom* or malignan* or adenocarcinom* or precancerous or malignan* or lump* or lesion* or masses* or sarcom* or metastas*)).mp. (10720)
3 Carcinoma, Transitional Cell/ (584)
4 transitional cell carcinoma*.mp. (931)
5 urothelial carcinoma.mp. (683)
6 NMIBT.mp. [non-muscle invasive bladder tumours] (9)
7 NMIBC.mp. [non-muscle invasive bladder cancer] (398)
8 Neoplasm Recurrence, Local/ (4210)
9 Neoplasm Invasiveness/ (778)
10 Neoplasm, Residual/ (330)
11 Neoplasm Staging/ (6590)
12 (transurethral adj4 resection*).mp. (2544)
13 TURBT.mp. (340)
14 or/8-13 (12765)
15 urinary bladder/ (744)
16 bladder.tw,kw. (14285)
17 or/15-16 (14437)
18 14 and 17 (1819)
19 or/1-7,18 (11162)

20 Cystoscopy/ (302)
21 Cystoscop*.tw,kw. (1369)
22 or/20-21 (1461)
23 Light/ (648)
24 Photochemotherapy/ (846)
25 Aminolevulinic Acid/ (449)
26 Photosensitizing Agents/ (691)
27 Image Enhancement/ (856)
28 Hexaminolevulinate.mp. (44)
29 Hexvix.mp. (21)

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30 Photocure.mp. (12)
31 luminescence/ or fluorescence/ (256)
32 blue light.mp. (658)
33 fluorescen*.tw,kw. (4983)
34 Microscopy, Fluorescence/ (97)
35 Coloring Agents/ (689)
36 colo?ring agent*.tw,kw. (38)
37 Fluorescent Dyes/ (185)
38 Cysview.mp. (3)
39 Aminolevulinic Acid.tw,kw. (510)
40 Aminolevulinate.mp. (235)
41 photosensiti#ing.tw,kw. (124)
42 photodynamic.mp. (2430)
43 Hexyl aminolevulinate.mp. (3)
44 hexyl 5-aminolevulinate.mp. (2)
45 5-ALA hexylester.mp. (0)
46 Hexyl 5-amino-4-oxopentanoate.mp. (0)
47 5-ALAHE.mp. (0)
48 ALA hexyl ester.mp. (2)
49 hexylaminolevulinate.mp. (8)
50 hexa ALA.mp. (0)
51 5-aminolevulinic acid hexyl ester.mp. (1)
52 or/23-51 (10405)

53 22 and 52 (107)
54 (fluorescence adj5 diagnos*).mp. (228)
55 (photodynamic adj5 diagnos*).mp. (80)
56 or/53-55 (353)

57 19 and 56 (113)

58 animals/ not (animals/ and humans/) (3)
59 57 not 58 (113)
60 limit 59 to yr="2017 -Current" (26)
61 limit 60 to English language (24)

A.4 MEDLINE economic search

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to February 15, 2021>
Search Strategy:
---
1 Urinary Bladder Neoplasms/ (55439)
2 ((urothelial or bladder* or urinary) and (cancer* or neoplasm* or tumor* or tumour* or carcinom* or malignan* or adenocarcinom* or precancerous or malignan* or lump* or lesion* or masses* or sarcom* or metastas*)).mp. (138460)
3 Carcinoma, Transitional Cell/ (19026)
4 transitional cell carcinoma*.mp. (9678)
5 urothelial carcinoma.mp. (9128)
6 NMIBT.mp. [non-muscle invasive bladder tumours] (18)
7 NMIBC.mp. [non-muscle invasive bladder cancer] (1597)

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8 Neoplasm Recurrence, Local/ (121330)
9 Neoplasm Invasiveness/ (83995)
10 Neoplasm, Residual/ (10820)
11 Neoplasm Staging/ (177928)
12 (transurethral adj4 resection*).mp. (13659)
13 TURBT.mp. (924)
14 or/8-13 (356059)
15 urinary bladder/ (50829)
16 bladder.tw,kw,kf. (164137)
17 or/15-16 (176755)
18 14 and 17 (19497)
19 or/1-7,18 (142772)
20 Cystoscopy/ (7687)
21 Cystoscop*.tw,kw,kf. (10573)
22 or/20-21 (14863)
23 Light/ (103578)
24 Photochemotherapy/ (20109)
25 Aminolevulinic Acid/ (5620)
26 Photosensitizing Agents/ (16677)
27 Image Enhancement/ (44559)
28 Hexaminolevulinate.mp. (129)
29 Hexvix.mp. (49)
30 Photocure.mp. (44)
31 luminescence/ or fluorescence/ (53277)
32 blue light.mp. (9583)
33 fluorescen*.tw,kw,kf. (489596)
34 Microscopy, Fluorescence/ (78564)
35 Coloring Agents/ (46904)
36 colo?ring agent*.tw,kw,kf. (523)
37 Fluorescent Dyes/ (75448)
38 Cysview.mp. (6)
39 Aminolevulinic Acid.tw,kw,kf. (6597)
40 Aminolevulinate.mp. (3182)
41 photosensitizing.tw,kw,kf. (2758)
42 photodynamic.mp. (26425)
43 Hexyl aminolevulinate.mp. (30)
44 hexyl 5-aminolevulinate.mp. (9)
45 5-ALA hexylester.mp. (2)
46 Hexyl 5-amino-4-oxopentanoate.mp. (1)
47 5-ALAHE.mp. (0)
48 ALA hexyl ester.mp. (21)
49 hexylaminolevulinate.mp. (33)
50 hexa ALA.mp. (3)
51 G7H20TKI67.rn. (187)
52 5-aminolevulinic acid hexyl ester.mp. (190)
53 or/23-52 (787741)
54 22 and 53 (748)
55 (fluorescence adj5 diagnos*).mp. (2047)
56 (photodynamic adj5 diagnos*).mp. (769)
57 or/54-56 (3203)
58 19 and 57 (853)

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59 animals/ not (animals/ and humans/) (4754820)
60 58 not 59 (836)
61 limit 60 to yr="2017 -Current" (177)
62 limit 61 to English language (161)
63 cost$.mp. (742940)
64 cost benefit analys$.mp. (85836)
65 health care costs.mp. (51088)
66 or/63-65 [HiRU Economics Hedge] (742940)
67 62 and 66 (15)
68 Economics/ (27291)
69 exp "Costs and Cost Analysis"/ (242497)
70 Economics, Nursing/ (4002)
71 Economics, Medical/ (9117)
72 Economics, Pharmaceutical/ (2969)
73 exp Economics, Hospital/ (24951)
74 Economics, Dental/ (1915)
75 exp "Fees and Charges"/ (30583)
76 exp Budgets/ (13794)
77 budget*.ti,ab,kf. (31107)
78 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (239840)
79 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (309137)
80 (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf. (172537)
81 (value adj2 (money or monetary)).ti,ab,kf. (2548)
82 exp models, economic/ (15429)
83 economic model*.ab,kf. (3507)
84 markov chains/ (14772)
85 markov.ti,ab,kf. (23977)
86 monte carlo method/ (29062)
87 monte carlo.ti,ab,kf. (51626)
88 exp Decision Theory/ (12340)
89 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (26378)
90 or/68-89 [CADTH Econ Filter] (765071)
91 62 and 90 (10)
92 Economics/ (27291)
93 "costs and cost analysis"/ (49297)
94 Cost allocation/ (2008)
95 Cost-benefit analysis/ (83358)
96 Cost control/ (21556)
97 Cost savings/ (12110)
98 Cost of illness/ (28231)
99 Cost sharing/ (2580)
100 "deductibles and coinsurance"/ (1776)
101 Medical savings accounts/ (538)
102 Health care costs/ (40751)
103 Direct service costs/ (1199)
104 Drug costs/ (16414)
105 Employer health costs/ (1093)

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106 Hospital costs/ (11356)
107 Health expenditures/ (20988)
108 Capital expenditures/ (1995)
109 Value of life/ (5730)
110 exp economics, hospital/ (24951)
111 exp economics, medical/ (14240)
112 Economics, nursing/ (4002)
113 Economics, pharmaceutical/ (2969)
114 exp "fees and charges"/ (30583)
115 exp budgets/ (13794)
116 (low adj cost).mp. (63950)
117 (high adj cost).mp. (15673)
118 (health?care adj cost$).mp. (12769)
119 (fiscal or funding or financial or finance).tw. (156872)
120 (cost adj estimate$).mp. (2402)
121 (cost adj variable).mp. (46)
122 (unit adj cost$).mp. (2659)
123 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (323165)
124 or/92-123 [SIGN Economic Filter] (772496)
125 62 and 124 (6)
126 67 or 91 or 125 (17)
127 62 not 126 (144)
128 "202102*".dt. (70123)
129 62 and 128 (5)
130 129 not 126 (4)

A.5 Embase economic search

Database: Embase <1974 to 2021 February 15>
Search Strategy:
---
1 bladder cancer/ (49982)
2 non muscle invasive bladder cancer/ (4251)
3 bladder tumor/ (18966)
4 transurethral resection of bladder tumor/ (111)
5 TURBT.mp. (2321)
6 ((urothelial or bladder* or urinary) and (cancer* or neoplasm* or tumor* or tumour* or carcinom* or malignan* or adenocarcinom* or precancerous or malignan* or lump* or lesion* or masses* or sarcom* or metastas*)).mp. (227625)
7 NMIBT.mp. [non-muscle invasive bladder tumours] (62)
8 NMIBC.mp. [non-muscle invasive bladder cancer] (3235)
9 or/1-8 (227687)
10 transurethral resection/ (21128)
11 (transurethral adj4 resection*).tw,kw. (17688)
12 or/10-11 (26096)
13 bladder*.mp. (288251)
14 12 and 13 (15546)
15 or/9,14 (230798)
16 blue light flexible cystoscopy/ (5)
17 BLC/ (28)
18 fluorescence cystoscopy/ (51)

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19 or/16-18 (83)
20 15 and 19 (82)
21 Cystoscopy/ (22886)
22 Cystoscop*.tw,kw. (18002)
23 or/21-22 (28444)
24 photodynamics/ (3058)
25 aminolevulinic acid hexyl ester/ (529)
26 blue light/ (6224)
27 aminolevulinic acid/ (9563)
28 5-aminolevulinic acid hexyl ester/ (116)
29 fluorescence/ (136110)
30 fluorescent lighting/ (1769)
31 photodynamic therapy/ (27241)
32 photosensitizing agent/ (15834)
33 Hexaminolevulinate.mp. (244)
34 Hexvix.mp. (184)
35 Photocure.mp. (347)
36 blue light.tw,kw. (10317)
37 fluorescen*.tw,kw. (576670)
38 colo?ring agent*.tw,kw. (695)
39 Fluorescent Dye*.tw,kw. (18231)
40 Cysview.mp. (38)
41 Aminolevulinic Acid.tw,kw. (7743)
42 Aminolevulinate.mp. (3263)
43 photosensitizing.tw,kw. (3190)
44 photodynamic*.tw,kw. (31977)
45 Hexyl aminolevulinate.mp. (40)
46 hexyl 5-aminolevulinate.mp. (9)
47 5-ALA hexylester.mp. (2)
48 Hexyl 5-amino-4-oxopentanoate.mp. (0)
49 5-ALAHE.mp. (0)
50 ALA hexyl ester.mp. (23)
51 hexylaminolevulinate.mp. (60)
52 hexa ALA.mp. (4)
53 5-aminolevulinic acid hexyl ester.tw,kw. (15)
54 or/24-53 (649817)
55 23 and 54 (1146)
56 (fluorescence adj5 diagnos*).mp. (4523)
57 (photodynamic* adj5 diagnos*).mp. (1230)
58 or/55-57 (6292)
59 15 and 58 (1420)
60 20 or 59 (1424)
61 limit 60 to yr="2012 -Current" (766)
62 limit 61 to english language (719)
63 editorial/ or letter/ or note/ (2582760)
64 62 not 63 (680)
65 limit 64 to conference abstracts (291)
66 64 not 65 (389)
67 limit 66 to medline (51)
68 66 not 67 (338)
69 (cost or costs).tw. [HiRU Economic Hedge E] (784764)

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70 68 and 69 (34)
71 Economics/ (241768)
72 Cost/ (59532)
73 exp Health Economics/ (878973)
74 Budget/ (30490)
75 budget$.ti,ab,kw. (41197)
76 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. (296395)
77 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or pharmaco-economic$ or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (433655)
78 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$ or analy$ or outcome or outcomes)).ab,kw. (243133)
79 (value adj2 (money or monetary)).ti,ab,kw. (3468)
80 Statistical Model/ (165405)
81 economic model$.ab,kw. (5189)
82 Probability/ (114890)
83 markov.ti,ab,kw. (31476)
84 monte carlo method/ (42262)
85 monte carlo.ti,ab,kw. (53010)
86 Decision Theory/ (1765)
87 Decision Tree/ (14264)
88 (decision$ adj2 (tree$ or analy$ or model$)).ti,ab,kw. (37325)
89 or/71-88 [CADTH Econ Filter Embase] (1705727)
90 68 and 89 (43)
91 Socioeconomics/ (144980)
92 Cost benefit analysis/ (86902)
93 Cost effectiveness analysis/ (158088)
94 Cost of illness/ (19811)
95 Cost control/ (70192)
96 Economic aspect/ (115783)
97 financial management/ (115800)
98 Health care cost/ (197395)
99 Health care financing/ (13767)
100 Health economics/ (33652)
101 Hospital cost/ (22305)
102 (fiscal or financial or finance or funding).tw. (216834)
103 Cost minimization analysis/ (3609)
104 (cost adj estimate$).mp. (3597)
105 (cost adj variable$).mp. (283)
106 (unit adj cost$).mp. (4734)
107 or/91-106 [SIGN Economic Filter E] (967644)
108 68 and 107 (26)
109 70 or 90 or 108 (49)
110 remove duplicates from 109 [Econ] (48)
111 68 not 109 (289)
112 remove duplicates from 111 (286)

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Appendix B Canadian jurisdictional scan- standardized questions

The British Columbia Ministry of Health is undertaking a health technology assessment to determine the clinical effectiveness, cost-effectiveness and budget impact of blue light cystoscopy (BLC) with hexaminolevulinate hydrochloride, compared with white light cystoscopy (WLC), in transurethral resection to treat patients with non-muscle invasive bladder cancer (NMIBC) in British Columbia (BC). This technology is a diagnostic agent that preferentially accumulates in cancerous tissue and aims to improve detection of tumours and enable optimal resection of small, difficult to see tumours.

We are interested in understanding how (and if) other provinces are offering this technology, and if so, what type of criteria were used in adopting them.

1. Is blue light cystoscopy publicly funded in your jurisdiction?
    a. If yes, to what capacity (which locations, across the whole province; i.e. is this a centralized or decentralized service)?
    b. If yes, what are the clinical eligibility criteria for receiving a blue light cystoscopy? Please provide a brief description.
    c. If no, is there a specific reasons why blue light cystoscopy is not used?
2. If blue light cystoscopy is publicly funded in your province, can you share more information with us on the following:
    a. What are the criteria/policy/protocol in place in your province in order for patients to qualify for coverage by the public health system for this technology?
    b. Other than evidence of clinical effectiveness, what factors influence the decision on whether to use blue light cystoscopy (i.e. cost, patient preference, convenience, availability in your jurisdiction, other barriers)?
    c. Is there any clinical, cost or cost-effectiveness information (or data) on the use of blue light cystoscopy in your jurisdiction available that you can share with us?
3. Is there someone else we may contact for more information?

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Appendix C Economic literature review

C.1 Included economic studies: Overview of study characteristics and analytic approach

	Klaassen et al. (2017)	HQO 2020
Funding	BioSyent Pharma Inc.	Publicly funded
Type of Economic Evaluation	Cost-consequence analysis	Cos-utility analysis
Target Population	Patients with suspected new or recurrent NMIBC	Patients undergoing their 1st TURBT for suspected new NMIBC
Intervention	HAL-guided TURBT	HAL-guided TURBT; NBI-guided TURBT
Comparator(s)	WL-guided TURBT	WL-guided TURBT
Analytic Method	Deterministic	Probabilistic; Sequential analysis
Modelling	Combines a decision tree & a Markov cohort state transition	Markov microsimulation model with eight health sates
Effectiveness	Treatment effect informed by a published meta-analysis of recurrence relative risk for BLC with HAL vs. WLC.	
Country	Canada	Canada
Perspective	Public payer	Public payer
Time Horizon	5 years	15
Discount Rate (Costs & Outcomes)	NR	1.5%
Cycle length	NR	3 months
Reported Outcomes	Bed days saved, Number of recurrences prevented	QALYs
Resource Use and Costs	Costing informed from 3 large, academic teaching hospitals from Ontario, British Columbia, and Quebec. Individual patient data were reviewed for costs associated with TURBT, surveillance, cystectomy, and palliative care. For each province costs were estimated according to: initial cost, follow-up cost, five-year amortized cost, cost-difference per case, bed day use, and recurrences.	Cost and resource use were obtained from Ontario sources and published literature. A micro costing exercise was done to inform the following cost categories: Professional fees, Hospital costs (stays and day surgeries), diagnostics test, lab fee, equipment & consumables.
Uncertainty/ Sensitivity analysis	Scenario analyses & one-way sensitivity analyses	Scenario analyses & one-way sensitivity analyses

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	Klaassen et al. (2017)	HQO 2020
Main Assumptions	• Only initial TURBT was BLC (with HAL); all subsequent TURBT with WLC • Patients with NMIBC have recurrent monitoring • Patients with MIBC have radical cystectomy + continuous post-operative surveillance • All patients receive post-operative dose of mitomycin after TURBT (accounting for downstream costs) • After tumor recurrence patients leave the model • Tumors first missed by WLC assumed to be detectable with in 2years of f/u • All patients with intermediate/high risk (including CIS) received 6 weeks of induction BCG therapy Baseline risk of progression assumed to be equal between groups (i.e. RR=1.0)	• After the first TURBT, all future TURBTs are conducted with white light • Patients do not progress directly from the NMIBC state to the metastases state, circumventing the local muscle-invasive state • For patients with NMIBC, initial risk classification and TURBT diagnostic accuracy do not differ between interventions or comparators • After a patient's first recurrence, those in the low-risk category move up one level, while the intermediate and high-risk categories remain unchanged • The relative risks of recurrence for HAL and NBI compared with white light alone are constant over the model's time horizon and across all risk categories • Most existing equipment purchased for conducting TURBT with white light can be used for NBI-guided TURBT (i.e., no additional capital equipment expenses are incurred for NBI) • A patient who moves to a higher risk level due to tumor recurrence follows the same progression rate as someone who initially diagnosed at that risk level (i.e., start at time zero)

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C.2 Included economic studies: Quality of reporting (CHEERS)

CHEERS Criteria[36]	Included Economic Studies	
	Klaassen 2017[35]	HQO 2020[22]
Title	Yes	Yes
Abstract	No	Yes
Background/Objectives	Yes	Yes
Target population and subgroups	Yes	Yes
Setting and location	Yes	Yes
Study perspective	Yes	Yes
Comparators	No	Yes
Time horizon	Yes	Yes
Discount rate	Unknown	Yes
Choice of health outcomes	N/A	N/A
Measurement of effectiveness	No	Yes
Measurement and valuation of preference-based outcomes	N/A	N/A
Estimating resources and costs	Yes	Yes
Currency, price date, and conversion	Unknown	Yes
Choice of model	No	No
Assumptions	Yes	Yes
Analytic methods	No	Yes
Study parameters	Yes	Yes
Incremental costs and outcomes	Yes	Yes
Characterizing uncertainty	Yes	Yes
Characterizing heterogeneity	N/A	N/A
Study Findings and Discussion of limitations	Yes	Yes
Source of Funding	Yes	Yes
Conflict of Interest	Yes	Yes

CHEERS: Consolidated Health Economic Evaluation Reporting Standards; (Green=yes and adequately reported, red= not reported or inadequately performed, Grey=not mentioned/unknown, Blue=not applicable)

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C.3 Excluded economic studies

Article	Reason for exclusion
Todenhöfer et al. (2021)	Outcome
Dansk et al. (2016)	Intervention
Rose et al. (2016)	Outcome
Johnson et al. (2015)	Outcome
Witjes et al. (2014)	Outcome
Gayed et al. (2013)	Intervention
Rink et al. (2013)	Outcome
Wong et al. (2013)	Intervention

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Appendix D Overview of detailed costing

D.1 Cost of TURBT

Item	Total cost	Source
TURBT	[redacted]	
surgical		
anesthesia		
Day surgery expenses		
Pathology		
BLC consumables		
Nursing time (assuming 15 min)		
Cysview solution		
Additional equipment		
Total TURBT Cost-WLC		**$2,547.36**
Total TURBT Cost-BLC		**$3,298.27**

Estimate of additional equipment cost per patient

Total capital cost per case	[redacted]
Equivalent annual capital cost	
Interest rate	
Number of patients per year per center	
Service life of device (Year)	
Capital cost of Instrument set & tower	
Average number of instrument sets per site	

*Number of instrument sets will be determined based on each site's surgical slate; the present estimate was based on the median number of instrument sets used in two sites identified by the manufacturer.

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D.2 Cost of surveillance

Item	Cost	Source
Cystoscopy procedure *Professional fee* *Anesthesia* *Day surgery expenses* Urine cytology	[redacted]	
Total cost per patient for each surveillance	**$568.15**	
Surveillance cost applied in model per cycle		
Year 1, 2 (cycle 0-7)	**$568.15**	Cystoscopy and urine cytology every 3 months
Year 3,4 (cycle 8-15)	**$284.08**	Cystoscopy and urine cytology every 6 months
Year 5-10 (cycle 16-39)	**$47.37**	Cystoscopy and urine cytology every 12 months

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D.3 Cost of treatment

Calculation of treatment cost used in the model

Stage of Therapy	Type of therapy	Total cost	Cost applied in model
Chemotherapy		[redacted]	
Intra-operative (single-dose):	Gemcitabine		
	Mitomycin		
Induction	Gemcitabine		
	Gemcitabine and Docetaxel		
	Mitomycin		
Maintenance	Gemcitabine		
	Gemcitabine and Docetaxel		
	Mitomycin		
BCG			
Induction (year 1)	BCG		
Maintenance (Year 1)	BCG		
Maintenance (Year 2,3,4)	BCG		

IR=Intermediate risk; HR=High risk; BCG= Bacillus Calmette–Guérin
*average of the total cost of each drug option was taken**BCG for IR: [50% induction BCG + 50% 1st year BCG]; ***BCG for HR: [50% induction BCG + 50% (1st year BCG+ year 2,3,4 BCG regimen)]

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Calculation of total dose and cost per treatment regimen

Drug	Dose (mg)	Schedule	cost ($)/mg	Total dose	Drug cost	Administration cost	Total Cost
Gemcitabine							
Intra-operative (single-dose):	2000	This is a single dose given in operating room or within 24 hours of transurethral bladder tumor resection.					
Induction	2000	weekly for 6 doses					
Maintenance	2000	monthly for 10 doses, starting 6 weeks after end of induction (i.e. at 3 months)					
Gemcitabine and Docetaxel							
Induction							
gemcitabine	*1000*	Weekly for 6 weeks (6 doses)					
docetaxel	*37.5*	Weekly for 6 weeks (6 doses)					
Maintenance							
gemcitabine	*1000*	*Duration: Once monthly for 10 months (10 doses), starting 6 weeks after last dose of induction.*					
docetaxel	*37.5*	*Duration: Once monthly for 10 months (10 doses), starting 6 weeks after last dose of induction.*					
Mitomycin							
Intra-operative (single-dose):	*40*						
induction	*40*	weekly for 6 doses					
Maintenance	*40*	Maintenance: monthly for 10 doses, starting 6 weeks after end of induction (i.e., at 3 months)					

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Drug	Dose (mg)	Schedule	cost ($)/mg	Total dose	Drug cost	Administration cost	Total Cost
BCG			**Cost per weekly instillation**	**Total # of instillations**			
Induction	6-week regimen (one dose weekly) Total of 6 doses		[redacted]				
Maintenance (Year 1)*	1st year BCG definition (excluding induction): 6 doses a. At 3, 6 months: Get another 3 weeks of BCG once per week i. 3 months: 3 weeks = 3 doses ii. 6 months: 3 weeks = 3 doses --> 9 doses in year 1 (excluding induction)						
Maintenance (Year 2,3,4)*	Year 2-3 BCG definition: 15 doses Year 2,3,4 BCG definition: 15 doses a. At 12, 18, 24,30,36 months after the first does: Get another 3 weeks of BCG once per week --> 15 doses starting from 12 months onwards (i.e. year 2-4)						

*BC cancer agency: If maintenance BCG is to be used to prolong remission give IVe BCG one vial weekly for 3 consecutive weeks at 3, 6, 12,18, 24, 30, 36 months.

Cost per dose

	Cost per mg	source
Docetaxel	$11.42	https://www.cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_nsclc_fn_egr.pdf
Gemcitabine	$0.06	https://www.cadth.ca/sites/default/files/pcodr/pcodr-abraxane-mpc-fn-egr.pdf
Mitomycin	$19.20	note: this the total cost inflated to 2020 CAD for Perioperative intravesical tx. Sourced from Klassen et al.2017[35];used to calculate cost per mg ($768.13/40mg which is the indicated dose)
Physician fee (administration of Therapy)	$68.11	MSC: 33583

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Appendix E Cost-effectiveness sensitivity analysis results

Variable	Δ Cost	Δ QALYs	Δ Recurrence	ICER(/QALY)	ICER(/Recurrence avoided)
Reference Case	**-$1,059**	**0.03**	**-0.10**	**Dominant**	**Dominant**
Time horizon: 10 years					
1 year	$594	0.00	-0.03	$327,431	$19,909
3 years	$142	0.01	-0.08	$19,299	$1,817
5 years	-$249	0.016	-0.09	Dominant	Dominant
Discount rate (Cost & Effect): 1.5%					
Cost & Effect: 0%	-$1,092	0.03	-0.10	Dominant	Dominant
Cost & Effect: 3%	-$1,028	0.03	-0.10	Dominant	Dominant
Cost & Effect: 5%	-$987	0.03	-0.10	Dominant	Dominant
Discharge cutoff (year): 5 years					
1 year	-$907	0.03	-0.09	Dominant	Dominant
10 years	-$1,061	0.03	-0.10	Dominant	Dominant
Early Relapse cutoff (Months): 6 months					
None	-$1,277	0.04	-0.10	Dominant	Dominant
12 months	-$574	0.03	-0.11	Dominant	Dominant
36 months	-$248	0.02	-0.12	Dominant	Dominant
Recurrence Risk					
Half of reference case	-$259	0.02	-0.06	Dominant	Dominant
Double reference case	-$2,136	0.06	-0.17	Dominant	Dominant
Treatment effect					
RR=0.75 in all model cycles	-$1,097	0.03	-0.10	Dominant	Dominant
Cost of Tower: Included					
Not included	-$1,079	0.03	-0.10	Dominant	Dominant
Life time of device: 10 years					
5 years	-$1,014	0.03	-0.10	Dominant	Dominant
HAL solution cost: $707					
Double ($1,414)	-$110	0.03	-0.10	Dominant	Dominant
Surveillance cost*					
Double	-$946	0.03	-0.10	Dominant	Dominant
Medications costs**					

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Variable	Δ Cost	Δ QALYs	Δ Recurrence	ICER(/QALY)	ICER(/Recurrence avoided)
Reference Case	**-$1,059**	**0.03**	**-0.10**	**Dominant**	**Dominant**
Double the costs	-$1,334	0.03	-0.10	Dominant	Dominant

*Reference case Surveillance cost per model cycle (i.e. 3 months): Year 1, 2 ($568.15); Year 3,4 ($284.08); Year 5-10($47.35)

**Reference case medication costs per recurrence: Chemo-intraoperative ($514.18);Chemo-Induction ($3,173.42); Chemo-Maintenance ($5,289.04); BCG-IR ($1,448.68); BCG-HR ($3,038.18)

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Appendix F Annual budget and health impact results

F.1 Annual budget impact- Scenario B vs. Scenario A

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2021-2030
Outcomes											
QALY	2	13	27	46	69	93	118	145	171	197	882
Recurrence	-42	-237	-334	-394	-441	-475	-513	-547	-576	-605	-4,164
Life years	0	2	11	25	42	60	78	97	116	132	563
Death	0	-4	-11	-14	-17	-16	-15	-16	-13	-12	-118
Costs											
Cost of recurrence*	- $58.8K	- $491.7K	- $721.4K	- $859.1K	- $959.4K	- $1,033.1K	- $1,113.4K	- $1,187.1K	- $1,248.1K	- $1,310.8K	- $8,982.7K
Cost of Surveillance	$3.1M	$3.5M	$3.8M	$4.1M	$4.3M	$4.5M	$4.7M	$4.9M	$5.1M	$5.3M	$43.3M
Cost of TURBT	- $5.0K	$0.4K	$2.3K	$4.4K	$6.8K	$7.3K	$9.3K	$11.0K	$12.0K	$13.7K	$62.4K
Other costs**	- $127.9K	- $1,016.0K	- $2,081.0K	- $3,120.6K	- $4,257.7K	- $5,360.6K	- $6,478.8K	- $7,698.2K	- $8,896.8K	- $10,156.0K	- $49,193.6K
Total Costs	**$2.9M**	**$2.0M**	**$981.2K**	**$97.5K**	**- $916.8K**	**- $1,891.5K**	**- $2,885.8K**	**- $3,970.5K**	**- $5,022.9K**	**- $6,135.2K**	**- $14,836.9K**

M=Million; K=Thousand; BLC=Blue-light cystoscopy; WLC=White-light cystoscopy; TURBT=Transurethral resection of bladder tumors

*Note: The cost of recurrence also includes the cost of TURBT. Therefore, the component costs presented in the table do not add up to the total costs

** Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

Scenario A: 100% WLC

Scenario B: 100% BLC

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F.2 Annual budget impact- Scenario C vs. Scenario A

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2021-2030
Outcomes											
QALY	1	3	7	12	17	23	30	36	43	49	220
Recurrence	-11	-59	-83	-99	-110	-119	-128	-137	-144	-151	-1,041
Life years	0	0	3	6	10	15	20	24	29	33	141
Death	0	-1	-3	-3	-4	-4	-4	-4	-3	-3	-29
Costs											
Cost of recurrence*	- $14.7K	- $122.9K	- $180.3K	- $214.8K	- $239.8K	- $258.3K	- $278.4K	- $296.8K	- $312.0K	- $327.7K	- $2,245.7K
Cost of Surveillance	$780.7K	$869.6K	$945.9K	$1.0M	$1.1M	$1.1M	$1.2M	$1.2M	$1.3M	$1.3M	$10.8M
Cost of TURBT	- $1.2K	$0.1K	$0.6K	$1.1K	$1.7K	$1.8K	$2.3K	$2.8K	$3.0K	$3.4K	$15.6K
Other costs**	- $32.0K	- $254.0K	- $520.2K	- $780.2K	- $1,064.4K	- $1,340.1K	- $1,619.7K	- $1,924.6K	- $2,224.2K	- $2,539.0K	- $12,298.4K
Total Costs	**$734.1K**	**$492.7K**	**$245.3K**	**$24.4K**	**- $229.2K**	**- $472.9K**	**- $721.5K**	**- $992.6K**	**- $1,255.7K**	**- $1,533.8K**	**- $3,709.2K**

M=Million; K=Thousand; BLC=Blue-light cystoscopy; WLC=White-light cystoscopy; TURBT=Transurethral resection of bladder tumors

*Note: The cost of recurrence also includes the cost of TURBT. Therefore, the component costs presented in the table do not add up to the total costs

** Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

Scenario A: 100% WLC

Scenario C: 75% WLC, 25% BLC

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F.3 Annual budget impact- Scenario D vs. Scenario A

Year	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2021-2030
Outcomes											
QALY	2	10	20	35	52	70	89	109	128	147	661
Recurrence	-32	-178	-250	-296	-330	-356	-385	-410	-432	-454	-3,123
Life years	0	1	8	19	31	45	59	73	87	99	423
Death	0	-3	-9	-10	-12	-12	-12	-12	-10	-9	-88
Costs											
Cost of recurrence*	- $44.1K	- $368.8K	- $541.0K	- $644.3K	- $719.5K	- $774.8K	- $835.1K	- $890.3K	- $936.1K	- $983.1K	- $6,737.0K
Cost of Surveillance	$2.3M	$2.6M	$2.8M	$3.1M	$3.2M	$3.4M	$3.5M	$3.7M	$3.8M	$4.0M	$32.5M
Cost of TURBT	- $3.7K	$0.3K	$1.8K	$3.3K	$5.1K	$5.5K	$7.0K	$8.3K	$9.0K	$10.3K	$46.8K
Other costs**	- $95.9K	- $762.0K	- $1,560.7K	- $2,340.5K	- $3,193.3K	- $4,020.4K	- $4,859.1K	- $5,773.7K	- $6,672.6K	- $7,617.0K	- $36,895.2K
Total Costs	**$2.2M**	**$1.5M**	**$735.9K**	**$73.1K**	**- $687.6K**	**- $1,418.6K**	**- $2,164.4K**	**- $2,977.9K**	**- $3,767.2K**	**- $4,601.4K**	**- $11,127.7K**

M=Million; K=Thousand; BLC=Blue-light cystoscopy; WLC=White-light cystoscopy; TURBT=Transurethral resection of bladder tumors

*Note: The cost of recurrence also includes the cost of TURBT. Therefore, the component costs presented in the table do not add up to the total costs

** Includes the costs associated with management of patients who experience an early relapse, have a cystectomy or progress

Scenario A: 100% WLC

Scenario C: 25% WLC, 75% BLC

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