Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Enhanced Visualization Methods for First Transurethral Resection of Bladder Tumour in Suspected Non-muscle-invasive Bladder Cancer: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Bladder cancer is often diagnosed before tumours have invaded the muscle of the bladder wall or spread to other organs. This early-stage disease is called non-muscle-invasive bladder cancer and can be treated effectively with surgical resection (removal) of the tumours. To avoid recurrence after resection, it is important that at the early stage of the disease all tumors be completely removed.

Standard treatment for early-stage bladder cancer is a procedure called transurethral resection of bladder tumour, or TURBT. The surgeon uses a cystoscope—a tube equipped with a light source and a lens—to find and remove tumours. Conventionally, TURBT is done using white light. However, small or flat tumours can be missed under white light. To improve outcomes after first TURBT, new technologies for detecting tumours have been developed. Two of these technologies are available in Canada. One is known as HAL (short for hexaminolevulinate hydrochloride), a solution put into the bladder to make tumours glow under blue–violet light. The other is narrow band imaging, or NBI, a technology that filters white light into wavelengths that make tumours more visible.

This health technology assessment looked at the safety, effectiveness, and cost-effectiveness of HAL and NBI as an adjunct (addition) to white light during first TURBT for people with suspected non-muscle-invasive bladder cancer. It also looked at the budget impact of publicly funding HAL and NBI to help guide first TURBTs for these people. We did not engage directly with people with bladder cancer for this report because we expected that their preferences and values would closely line up with the potential for better health outcomes from the use of these technologies.

What Did This Health Technology Assessment Find?

TURBT guided by HAL as an adjunct to white light, compared with TURBT using white light alone, likely reduces the rate of bladder cancer recurrence and likely results in more people still being alive with no recurrence of cancer at 5 years after their first treatment. TURBT guided by NBI as an adjunct to white light likely results in little to no difference in recurrence compared with using white light alone, and we did not find evidence on whether NBI improves survival without tumours recurring. Both technologies are generally safe to use.

Using HAL as an adjunct to white light during TURBT is likely cost-effective when compared with using either NBI as an adjunct to white light or using white light alone. We estimate that publicly funding HAL as an adjunct to white light in first TURBT for people in Ontario with suspected non-muscle-invasive bladder cancer would cost an additional $0.6 million to $2.5 million per year over the next 5 years.

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Abstract

Background

Bladder cancer begins in the innermost lining of the bladder wall and, on histological examination, is classified as one of two types: non-muscle-invasive bladder cancer (NMIBC) or muscle-invasive bladder cancer. Transurethral resection of bladder tumour (TURBT) is the standard treatment for people with NMIBC, but the high rate of cancer recurrence after first TURBT is a challenge that physicians and patients face. Tumours seen during follow-up may have been missed or incompletely resected during first TURBT. TURBT is conventionally performed using white light to see the tumours. However, small papillary or flat tumours may be missed with the use of white light alone. With the emergence of new technologies to improve visualization during TURBT, better diagnostic and patient outcomes may be expected. We conducted a health technology assessment of two enhanced visualization methods, both as an adjunct to white light to guide first TURBT for people with suspected NMIBC—hexaminolevulinate hydrochloride (HAL), a solution that is instilled into the bladder to make tumours fluoresce under blue–violet light, and narrow band imaging (NBI), a technology that filters light into wavelengths that can be absorbed by hemoglobin in the tumours, making them appear darker. Our assessment included an evaluation of effectiveness, safety, cost-effectiveness, and the budget impact of publicly funding these new technologies to improve patient outcomes following first TURBT. The use of NBI in diagnostic cystoscopy was out of scope for this health technology assessment.

Methods

We performed a systematic literature search of the clinical evidence from inception to April 15, 2020. We searched for randomized controlled trials (RCTs) that compared the outcomes of first TURBT with the use of HAL or NBI, both as an adjunct to white light, with the outcomes of first TURBT using white light alone, or studies that made such comparison between HAL and NBI. We conducted pairwise meta-analyses using a fixed effects model where head-to-head comparisons were available. In the absence of any published RCT for comparison between HAL and NBI, we indirectly compared the two technologies through indirect treatment comparison (ITC) analysis. We assessed the risk of bias of each included study using the Cochrane risk-of-bias tool. We assessed the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted a cost–utility analysis with a 15-year time horizon from a public payer perspective. We also analyzed the budget impact of publicly funding HAL and NBI as an adjunct to white light in people undergoing their first TURBT for suspected non-muscle-invasive bladder cancer in Ontario.

Results

In the clinical evidence review, we identified 8 RCTs that used HAL or NBI as an adjunct to white light during first TURBT. Pairwise meta-analysis of HAL studies showed that HAL-guided TURBT as an adjunct to white light significantly reduces recurrence rate at 12 months compared with TURBT using white light alone (risk ratio 0.70, 95% confidence interval [CI] 0.51–0.95) (GRADE: Moderate). Five-year recurrence-free survival was significantly higher when HAL was used as an adjunct to white light than when white light was used alone (GRADE: Moderate). There was little to no difference in the tumour progression rate (GRADE: Moderate).

Meta-analysis of NBI studies did not show a significant difference between NBI-guided TURBT as an adjunct to white light and TURBT using white light alone in reducing the rate of recurrence at 12 months (risk ratio 0.94, 95% CI 0.75–1.19) (GRADE: Moderate). No evidence on the effect on recurrence-free

survival or tumour progression rate was identified for NBI-guided TURBT. The indirect estimate from the network analysis showed a trend toward a lower rate of recurrence after HAL-guided TURBT than after NBI-guided TURBT but the difference was not statistically significant (risk ratio 0.76, 95% CI 0.51–1.11) (GRADE: Low). Studies showed that use of HAL or NBI during TURBT was generally safe.

The incremental cost-effectiveness ratio of HAL-guided TURBT compared with NBI-guided TURBT, both as an adjunct to white light, is $12,618 per quality-adjusted life-year (QALY) gained. Compared with TURBT using white light alone and using adjunct NBI, the probability of HAL-guided TURBT being cost-effective is 69.1% at a willingness-to-pay value of $50,000 per QALY gained and 74.6% at a willingness-to-pay of $100,000 per QALY gained. The annual budget impact of publicly funding HAL-guided TURBT in Ontario over the next 5 years ranges from an additional $0.6 million in year 1 to $2.5 million in year 5.

Conclusions

First TURBT guided by HAL as an adjunct to white light likely reduces the rate of recurrence at 12 months and increases 5-year recurrence-free survival when compared with first TURBT using white light alone. There is likely little to no difference in the tumour progression rate. First TURBT guided by NBI as an adjunct to white light likely results in little to no difference in the rate of recurrence at 12 months when compared with first TURBT using white light alone. Based on an indirect comparison, there may be little to no difference in cancer recurrence rate between HAL-guided and NBI-guided first TURBT. Use of HAL or NBI during first TURBT is generally safe. For people undergoing their first TURBT for suspected non-muscle-invasive bladder cancer, using HAL as an adjunct to white light is likely to be cost-effective compared with using white light alone or with using NBI as an adjunct to white light. We estimate that publicly funding HAL as an adjunct to white light to guide first TURBT for people in Ontario with suspected NMIBC would result in additional costs of between $0.6 million and $2.5 million per year over the next 5 years.

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Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of two enhanced visualization methods—hexaminolevulinate hydrochloride (HAL) and narrow band imaging (NBI)—used as adjuncts to white light during the first transurethral resection of bladder tumour (TURBT) in people with non-muscle-invasive bladder cancer (NMIBC). It also evaluates the budget impact of publicly funding these technologies.

Background

Health Condition

Bladder cancer has two distinct types: muscle-invasive bladder cancer (MIBC) and non-muscle-invasive bladder cancer (NMIBC).[1] NMIBC is the most common type and is characterized by one or more small tumours that have not yet invaded the muscle of the bladder wall, whereas in MIBC the tumour is at a more advanced stage and has invaded the muscle. MIBC is more serious than NMIBC, has a high risk for local spread and distant metastasis (cancer spreading to another part of the body), and requires more invasive treatment.

Most bladder cancers initially develop as tumours in the urothelium, the innermost layer of the bladder wall.[1] The bladder wall has three other layers: the lamina propria, which is a thin layer of connective tissue, blood vessels, and nerves; the muscularis propria, a thick layer of muscle; and a layer of fatty connective tissue that separates the bladder from nearby organs. Bladder cancer may be restricted to the urothelium for some time, but when the tumour becomes more advanced, it extends beyond this layer and invades the muscle, affecting the outer layers of the bladder wall and eventually invading structures outside the bladder.

About 75% of patients with bladder cancer present with NMIBC that is confined to the urothelium and the lamina propria.[1,2] For these patients, visible tumours can be removed from the bladder wall during a surgical procedure called transurethral resection of bladder tumour (TURBT), described below.

Bladder cancer can also be described histologically based on microscopic examination of tumour tissue to determine the type of cells involved. More than 90% of bladder cancers are urothelial carcinoma, also known as transitional cell carcinoma.[3] Non-urothelial cancers of the bladder often present at an advanced stage and have a poor prognosis.[4]

Clinical Need and Target Population

Bladder cancer is the sixth most common cancer in Canada[3] and is one of the most common cancers of the urinary tract.[5] It is most common among older adults and occurs more frequently in men than in women.[1] It is the fourth most common cancer in Canadian men and the twelfth most common in Canadian women.[6]

Risk factors for bladder cancer are increasing age; tobacco smoking; occupational exposure to dyes, tar, rubber, solvents, aromatic amines, or polycyclic aromatic hydrocarbons; and chronic bladder irritation and infections.[2] Smoking is the most common risk factor and accounts for approximately half of all bladder cancers.[2] The importance of primary prevention through smoking cessation programs has been emphasized in the literature.[7]

The projected estimate of new cases of bladder cancer in Canada for the year 2020 was 12,200 (9,400 men and 2,800 women), including 4,450 in Ontario (3,400 men and 1,050 women).[8] These estimates are reflected in the projected age-standardized incidence rates per 100,000 people for bladder cancer in Canada for 2020: 42 for men and 10.7 for women. In Ontario, these figures are 44.2 for men and 26.2 for women.[8]

The projected estimate of deaths from bladder cancer in Canada for the year 2020 was 2,570 (1,850 men and 720 women), and the projected age-standardized mortality rate per 100,000 people was 9.6 for men and 2.8 for women. In Ontario, it was estimated that 980 people could die from bladder cancer in the year 2020 (690 men and 290 women), reflecting a projected age-standardized mortality rate of 9.3 deaths per 100,000 people for men and 5.7 for women.[8]

Recurrence, Progression, and Survival

Non-muscle-invasive bladder cancer has a high rate of recurrence (return of cancer) after TURBT. To check for possible recurrence, people must have surveillance care including diagnostic cystoscopy and urine cytology (a test to look for abnormal cells) every 3 to 6 months following first TURBT. Follow-up surveillance is often necessary for the rest of the person's lifetime.

Progression typically means the tumour has advanced to a higher grade (the cells have changed to a different form) or to a higher stage (the tumour has grown deeper into the bladder wall or into adjacent organs/tissues). The short- and long-term risks of cancer recurrence and progression after TURBT were estimated in a large study that analyzed individual data for 2,596 patients with early-stage bladder cancer. The probability of recurrence after TURBT ranged from 15% to 61% at 1 year, and from 31% to 78% at 5 years. The probability of tumour progression after TURBT ranged from less than 1% to 17% at 1 year, and from less than 1% to 45% at 5 years.[9] In a large population-based study of patients with high-grade NMIBC, at 10 years after treatment, the risk of recurrence without progression was 74.3%, the risk of progression was 33.3%, and the mortality rate was 12.3%.[10] (See below for more information on stage and grade in bladder cancer.)

Survival following bladder cancer depends on the type of tissue where the cancer originates and the presence or absence of metastasis. For example, the average 5-year survival rate for people with bladder cancer in the United States is 77%, but the 5-year survival rate for people with bladder cancer who experience metastasis is about 5%.[11]

The high rate of recurrence and risk of progression in NMIBC means that patients with this disease need effective initial treatment and thorough follow-up surveillance.

Diagnosis and Management of Bladder Cancer

People with bladder cancer may present with painful or difficult urination, urinary frequency, urinary urgency, and/or visible blood in the urine. The initial assessment of a patient who presents with symptoms of suspected bladder cancer includes a comprehensive history and physical examination, imaging studies, urine cytology, and a diagnostic cystoscopy. Imaging studies include the entire urinary system as well as other parts of the body to determine the absence or presence of metastasis, since the presence of distant metastasis greatly impacts the treatment plan. For urine cytology, a sample of urine is examined under a microscope to see if there are any cancerous or pre-cancerous cells in the urine. Urine cytology can help find some cancers, but it has low sensitivity, particularly for low-grade cancers.

Diagnostic cystoscopy is a crucial step in the diagnosis of bladder cancer and is initially performed in an outpatient clinic using a flexible cystoscope. This procedure allows the urologist to view the inner lining of the bladder and take biopsies. A flexible cystoscope consists of a thin tube with a light source to illuminate the field of view, an endoscopic lens, and a camera that transmits images to a monitor for viewing. With flexible cystoscopy, it may also be possible for small, low-grade, recurring tumours to be fulgurated (burned). This procedure typically requires only mild sedation.

Transurethral Resection of Bladder Tumour

TURBT is the standard treatment for early-stage NMIBC. The goal of the procedure is to remove all cancerous lesions along with a portion of the underlying muscle layer to determine the depth of involvement and whether the tumour has invaded the muscle. Guidelines agree that complete removal of all visible lesions during a patient's first TURBT is paramount and an important determinant of prognosis.[12] TURBT involves the use of a rigid cystoscope, also called a resectoscope. This type of cystoscope allows for a more comprehensive examination of the bladder wall than would be possible with a flexible cystoscope and allows for complete lesion removal. A rigid cystoscope has a wider diameter than a flexible cystoscope and must be used in an operating room with the patient under general or regional anesthesia. During TURBT, an irrigation solution is used to distend the bladder, clear the surgical site, and wash away resected tissue and blood. Resected tumours are sent for pathological examination to confirm the presence, type, and grade of cancer, as well as to provide information required for tumour staging.

Following TURBT, according to tumour characteristics and guideline recommendations, intravesical chemotherapy and Bacillus Calmette-Guérin (BCG) immunotherapy are used in the immediate postoperative setting to prevent recurrence and progression.[13,14] Maintenance therapy with these agents is recommended for patients at specific risk levels.[13,14] A TURBT procedure does not require cutting into the abdomen, and the patient can usually go home the same day.

In some cases, a second TURBT procedure may be needed. If the initial tumour resection was incomplete, there was no muscle in the specimen, the tumour is invading the lamina propria, or the tumour is high grade, a second TURBT is recommended within 2 to 6 weeks.[12,13]

The intraoperative complications of TURBT are a risk of bleeding, which can be controlled by cauterizing the bleeding sites, and a small (about 5%) risk of bladder perforation. Perforation, if it occurs, is typically outside the peritoneal space (cavity containing most of the intestines and abdominal organs). This can be managed by prolonged drainage using a urethral catheter. However, perforation that involves the peritoneal space requires surgical intervention.[5] Postoperative complications include minor bleeding, irritative symptoms, and pain during urination in the immediate postoperative period, which often does not last long. Clot retention can sometimes occur, especially after an extensive resection. Transurethral resection (TUR) syndrome is a rare complication that may occur when a hypotonic fluid is used for bladder irrigation during the TURBT procedure. In TUR syndrome, the hypotonic fluid, which does not contain electrolytes, is absorbed into the circulation, causing hypervolemia and an electrolyte imbalance. Symptoms include nausea and vomiting, vision alteration, and confusion. In severe cases, TUR syndrome may lead to cardiopulmonary compromise.

Bladder Cancer Stage, Grade, and Risk Classification

Staging and grading bladder cancer are the most crucial factors in determining a patient's risk and subsequent treatment plan. Staging describes how far the cancer has spread, while grading describes how the cancer cells look under a microscope compared to normal, healthy cells.

TUMOUR STAGING

The tumour-node-metastasis (TNM) system is used for staging bladder cancer. The system was developed by the American Joint Committee on Cancer and the Union for International Cancer Control and is widely employed in clinical practice and research on patients with cancer. In the TNM system, T describes the depth of the tumour and whether it has grown into the muscle of the bladder wall; N describes whether the cancer has spread to nearby lymph nodes; and M describes whether the cancer has metastasized to distant sites such as the lungs, liver, or distant lymph nodes. Together, these three key pieces of information determine the spread of the cancer.[16]

In NMIBC, the tumour is restricted to the inner layers of the bladder; therefore, both N and M are given a value of 0, and only the T subcategory needs to be determined. T0 is used when there is no evidence of a primary tumour, while Tx indicates the primary tumour cannot be assessed. In stage Ta, the tumours are confined to the urothelium (mucosal) and have not grown beyond this layer. In stage T1, the cancer has grown into the lamina propria (submucosal) but has not invaded muscle of the bladder wall. During TURBT, a deep resection that includes the detrusor muscle of the bladder wall is necessary to determine whether the muscles of the bladder are involved, as the initial treatment plan depends on this distinction.

Flat tumours on the surface of the urothelium are called carcinoma in situ (CIS, also called Tis). This type of tumour often appears as reddened and velvety mucosa that is slightly elevated and may be missed during TURBT. Although CIS is confined to the urothelium, it is considered a high-grade tumour and a precursor lesion for the development of invasive high-grade cancer.

In NMIBC, approximately 70% of patients present with Ta tumours, 20% have T1 tumours, and 10% have CIS.[18]

T2, T3, and T4 tumours are considered muscle invasive and require aggressive surgical intervention and adjuvant treatment, such as chemotherapy and immunotherapy.[17]

TUMOUR GRADING

The grade describes the aggressiveness of cancer cells based on their microscopic appearance. Grading is important for understanding the prognosis of a person's cancer. To establish the tumour grade, the pathologist examines resected tissues under a microscope and determines how different the cells are from normal cells as well as other features of the tumour such as the shape of the cells and how they are arranged.

In 1973, the World Health Organization (WHO) published the first international systematic approach to grading urothelial carcinomas, which classified tumours into three categories: low, intermediate, and high grade. In 2004, the WHO and the International Society of Urological Pathology (ISUP) published a new histological classification of urothelial carcinomas, classifying tumours as either low or high grade. In 2016, an updated version of the 2004 WHO grading classification was published without major changes.[19] The WHO and ISUP grading system classifies urothelial bladder cancers as papillary urothelial

neoplasm of low malignant potential (PUNLMP), noninvasive low-grade papillary urothelial carcinoma (NILGC), and noninvasive high-grade papillary urothelial carcinoma (NIHGC) (see Glossary). The PUNLMP grade does not carry the name "cancer," and this is important for younger patients with this condition who would otherwise have to carry a diagnosis of cancer with all its psychological consequences. However, some data show that PUNLMP is not a completely benign tumour and may progress or recur, and long-term follow-up is recommended for this grade as well.[19]

Low-grade cancers tend to grow slowly and have low likelihood of progression. They have a more favourable shape and structure, lending themselves to biopsy and fulgurations that can often be accomplished in the outpatient setting. High-grade tumours have cancer cells that are poorly differentiated or are undifferentiated and tend to grow more quickly. They are more likely to grow into the muscle layer of the bladder and metastasize. They are also more likely to recur after treatment.[20] As noted, carcinoma in situ is considered to be a high-grade tumour and is often seen around a Ta high-grade tumour.[19] Although T1 could be low or high grade, it is increasingly recognized that most T1 tumours are probably high grade as they invade the lamina propria layer of the bladder wall; therefore, invasion to the lymphatic system and metastasis can be seen even in some patients at T1 stage.[19]

RISK CLASSIFICATION

Risk classification is important for treatment planning and achieving optimal outcomes for each patient. Several organizations have developed risk classification systems, but the system and risk tables from the European Organization for Research and Treatment of Cancer (EORTC)[9] are the most widely used and validated for NMIBC.[21,22] This classification system is based on the six most significant clinical and pathological factors (T, CIS, grade, tumour size, number of tumours, and prior recurrence). Using this scoring system, the European Association of Urology has categorized patients with NMIBC into three risk categories—low, intermediate, and high—to facilitate treatment recommendations.[13] Their guidelines for NMIBC, updated in 2019, state that identifying patients as low, intermediate, or high risk is pivotal to the recommendation of adjuvant treatment.[13]

There is general agreement among urological organizations toward more conservative treatment and regular monitoring via surveillance cystoscopy for people with low-risk tumours.

Conventional Technique for Visualizing Bladder Tumours

For several decades, TURBT guided by white light has been the standard method to visualize and remove bladder tumours. This conventional method is reliable for the detection of large papillary tumours that protrude from the lining of the bladder wall. However, small papillary tumours and lesions that are flat, such as carcinoma in situ, can be overlooked and these missed tumours may be high grade or become unexpectedly invasive. In addition, relying on white light to assist TURBT has some limitations in differentiating between inflammation and malignancy and in accurately determining tumour margins.[23] These issues have led to the development of new technologies to improve tumour detection.[24]

Health Technologies Under Review

Enhanced visualization methods for performing TURBT are tools that help to make tumours more visible, allowing for a more complete resection.[23] These methods include the use of various photosynthesizing agents, narrow band imaging (NBI), optical coherence tomography (OCT), and confocal laser endomicroscopy (CLE). The OCT and CLE technologies, as well as the photosynthesizing agent 5-alpha aminolevolinic acid (5-ALA), are not available in Canada for use during TURBT and are not used in clinical practice in Ontario. Therefore, these technologies are out of scope of this review.

Hexaminolevulinate Hydrochloride

The use of a photosynthesizing agent that makes cancer cells fluoresce (glow) under blue–violet light has emerged as an adjunct to the conventional white light commonly used during TURBT. A number of studies have shown that this method, known as blue light cystoscopy or photodynamic diagnosis, allows detection of more tumours, especially CIS.[5,25] The improved detection rate would be expected to benefit patients through a more complete resection of the tumours, which helps reduce the risk of recurrence and improve disease-free survival.[26]

Originally, 5-ALA was the agent used; it is administered orally prior to TURBT and requires several hours to reach the tumour cells. Hexaminolevulinate hydrochloride (HAL), a derivative of 5-ALA, is another photosynthesizing agent subsequently developed that can be instilled directly into the bladder through a urinary catheter. Following instillation, the HAL solution penetrates the membrane of cancer cells and interacts with the heme biosynthetic pathway, which leads to intracellular accumulation of photoactive porphyrins (PAP) (see Glossary). The PAPs selectively accumulate in rapidly proliferating cells like tumour cells. After one hour, those cells glow pink under the blue–violet light (wavelengths of 380–440 nm), enabling detection of tumours. The cystoscope used for HAL-guided TURBT allows the surgeon to switch between white light and blue–violet light during the procedure.

Narrow Band Imaging

The white light conventionally used for TURBT consists of three waves: blue, green, and red. NBI technology uses a special filter that cancels the red wave so that only the narrow bandwidths of blue (440–460 nm) and green (540–560 nm) are emitted. The blue–green light is absorbed by hemoglobin in the blood inside the vessels of the tumours, making them appear a darker colour. NBI technology does not require instillation of an agent into the bladder. A switch on the cystoscope allows the surgeon to switch between white light and NBI during the TURBT procedure. NBI cystoscopy is currently performed only with the Olympus flexible cystoscope that has an NBI function.

Regulatory Information

HAL has been commercially available in Europe since 2006, in the United States since 2010, and in Canada since 2015. HAL is approved by Health Canada as a diagnostic agent to be instilled into the bladder to assist visualization of tumours during TURBT (drug identification number: 02436639). The solution is provided in vials of 50 ml (100 mg per vial). The trade name for HAL is Cysview in North America and Hexvix in European countries. HAL is manufactured by Photocure ASA, Oslo, Norway, and is supplied in Canada by BioSyent Pharma, a Canadian subsidiary of BioSyent Inc.

HAL-guided TURBT requires the use of the Karl Storz D-Light C system (Karl Storz Co, Tuttlingen, Germany) which consists of a light source, a camera, and a telescope. The D-light C unit is a 300-watt short arc xenon light source with two modes of operation: white light mode and blue light mode.[27] HAL-guided TURBT should only be performed by trained specialists.

The flexible cystoscope with NBI function, developed by Olympus Medical Systems, was approved by Health Canada in 2011 (model CYF-VH, device licence 87706, Class II). Under the same licence, the cystoscope is also available in a model with suction (CYF-VHA) and a model with reverse angulation (CYF-VHR). Olympus Canada is the distributor of the flexible cystoscope with NBI function in this country. All rigid Olympus cystoscopes can be integrated with NBI using an appropriate Olympus camera head. The Olympus camera head with NBI function can be attached to any rigid resectoscope for bladder inspection with NBI (Olympus Canada, email communication, February 27, 2020).

Ontario, Canadian, and International Context

As outlined above, HAL is currently licensed and available in Canada for use during TURBT. As of March 2020, 137 units of Karl Storz D-light C System for performing HAL-guided TURBT had been sold in Canada (BioSyent Pharma, in-person communication, March 5, 2020). In Ontario, the use of HAL is restricted to operating rooms in inpatient settings.

Also as noted above, NBI is licensed in Canada but the rigid cystoscope with integrated NBI function is not available. In Ontario, NBI is not generally in use for performing TURBT. NBI with flexible cystoscopy is used in outpatient settings for initial diagnosis and follow-up surveillance (urology specialist, email communication, April 30, 2020), but these uses are out of scope for this health technology assessment.

Canadian Urological Association guidelines for management of NMIBC, published in 2015, state that HAL or NBI to guide TURBT may improve tumour detection and reduce early recurrence, although the clinical impact of either technology on long-term recurrence or progression of the disease is unknown.[14]

The use of HAL during TURBT is also recommended by the American Urological Association[28] and the European Association of Urology.[13] The National Institute of Health and Care Excellence (NICE) guidance document[29] recommends offering TURBT using white light and one of either photodynamic diagnosis, NBI, cytology, or a urinary biomarker test to people with suspected bladder cancer.

The care pathway map for bladder cancer diagnosis, treatment, and follow-up provided by Ontario Health (Cancer Care Ontario) notes the potential for using these two technologies in the management of bladder cancer.[30]

Terminology

For simplicity in this report, we use the terms “HAL-guided” and “NBI-guided” to mean the use of these enhanced visualization methods as adjuncts to white light during TURBT. These technologies do not replace the use of white light during the procedure, they complement it.

Expert Consultation

We engaged with experts in the specialty area of urology to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42020194151), available at https://www.crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the effectiveness and safety of hexaminolevulinate hydrochloride (HAL) or narrow band imaging (NBI) as an adjunct to white light during first transurethral resection of bladder tumour (TURBT), compared with TURBT using white light alone, in people with suspected non-muscle-invasive bladder cancer (NMIBC)?

Methods

Clinical Literature Search

We performed a clinical literature search on April 15, 2020, to retrieve studies published from database inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords.

We created database auto-alerts in MEDLINE and Embase, and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites as well as clinical trial and systematic review registries. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from database inception until April 15, 2020
- Randomized controlled trials (RCTs)
- Observational studies for specific outcomes where no RCT has been published
- Health technology assessment and systematic reviews with low risk of bias, as determined by the Risk of Bias in Systematic Reviews (ROBIS) tool[31]

Exclusion Criteria

- Animal and in vitro studies
- Studies in which the proportion of patients with recurrent tumour was more than 30% of the study sample
- Editorial, commentaries, case reports, conferences abstracts, letters

PARTICIPANTS

Inclusion Criteria

- Patients 18 years of age or older undergoing their first TURBT for suspected NMIBC

Exclusion Criteria

- Patients less than 18 years of age
- Patients undergoing follow-up surveillance and re-TURBT

INTERVENTIONS

Inclusion Criteria

- TURBT guided by HAL
- TURBT guided by NBI

Exclusion Criteria

- TURBT guided by 5-alpha aminolevolinic acid (5-ALA)
- TURBT guided by optical coherence tomography (OCT)
- TURBT guided by confocal laser endomicroscopy (CLE)

COMPARATORS

Inclusion Criteria

- TURBT using white light alone
- TURBT guided by HAL (for comparison with NBI)
- TURBT guided by NBI (for comparison with HAL)

OUTCOME MEASURES

- Cancer recurrence rate at 3, 6, 9, 12 months and up to 10 years
- Recurrence-free survival
- Overall survival
- Tumour progression rate
- Diagnostic outcomes
- Adverse events

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[32] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. A single reviewer also examined reference lists for any additional relevant studies not identified through the search.

Data Extraction

A single reviewer extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of outcomes, whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

Statistical Analysis

We conducted a pairwise meta-analysis of the data for recurrence rate at 12 months to combine the results of different studies for each intervention. We performed the Cochran *Q* test (*Q* statistic) to determine whether a fixed or a random effects model should be used. The degree of statistical heterogeneity was quantified using the I^2 measure. In the absence of considerable heterogeneity among the studies, we used a fixed effects model for meta-analyses.

We used two summary measures (risk ratio and risk difference) for meta-analyses to ensure that the choice of summary statistic did not affect the conclusion of meta-analyses. The Cochrane Handbook (Chapter 10.4.3) suggests that it is often sensible to use one statistic for meta-analysis and to re-express the results using a second, more easily interpretable statistic.[33]

In the absence of a head-to-head comparison between TURBT with HAL and TURBT with NBI, we carried out an adjusted indirect treatment comparison (ITC) analysis[34] using white light as a common comparator to obtain an indirect assessment of their comparative effectiveness. We used the frequentist approach for conducting ITC and applied a fixed effects model. We conducted the ITC analysis by running the netmeta package (version 1.2-1) in R, version 4.0.2.[35] We used Stata, version 11.2,[36] to produce the graphs and perform meta-regression analysis.

We provided a network plot as a visual representation of the available evidence, along with a contribution plot to demonstrate how each direct comparison contributed to the network estimates. Since it is possible that each direct comparison contributes differently to the network estimate, the contribution plot helps to identify which comparison was most influential.[37]

Where data permitted, we presented the effect sizes from direct and indirect comparisons on two scales (risk ratio and risk difference) along with their 95% confidence intervals (CI). The direct estimate of effect for each pair of interventions was obtained by pooling the results of head-to-head comparisons, and the indirect estimate of effect for each pair of interventions was obtained from the network using data from head-to-head comparisons that shared a common comparator (i.e., white light).

Since the validity of an indirect comparison relies on underlying assumptions of homogeneity and similarity between studies, we tested whether the evidence could satisfy the assumptions of homogeneity by using the *Q* statistic and I^2 measure. Through decomposition of the *Q* statistic into different study designs, we obtained a more detailed analysis of heterogeneity (if any) in the network.

We used the PICOT (population, intervention, comparator, outcome, setting, timing) approach[38] to ensure that studies in the pairwise and ITC meta-analyses were sufficiently similar.

Further, to examine the distribution of potential effect modifiers in the two groups, we assessed whether potential effect modifiers (i.e., patients' age and the inclusion of studies in which some patients had recurrent cancer) may have influenced cancer recurrence outcomes. We used meta-regression analysis to examine the relationship between these study-level covariates and recurrence rate at 12 months.

Conducting meta-analysis for diagnostic accuracy was not possible due to lack of data to form a 2 × 2 contingency table for diagnostic outcome and to calculate sensitivity, specificity, and diagnostic accuracy. In our analysis, we considered the results of histopathological examination of the removed specimens as the clinical reference standard. If the tissues removed from the bladder wall showed cancerous cells on examination under a microscope, we considered this to be a true-positive detection; otherwise it was considered a false-positive detection. We undertook a descriptive summary of true-positive and false-positive detection rates and presented these rates in a table.

We performed subgroup analysis for risk categories (low, intermediate, and high) and for tumour grade. Data did not permit subgroup analysis for non-muscle-invasive subtypes.

Critical Appraisal of Evidence

We assessed risk of bias using the Cochrane risk-of-bias tool for randomized controlled trials for clinical outcomes[39] (Appendix 2). Since data were not available for calculating sensitivity and specificity of HAL and NBI, we were unable to apply the Quality Assessment on Diagnostic Accuracy Studies (QUADAS-2) tool for diagnostic accuracy studies.[40]

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook.*[41] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence presented.

Results

Clinical Literature Search

The database search of the clinical literature yielded 1,687 citations published from database inception until April 15, 2020. We identified eight additional studies from grey literature. In total, we identified eight studies (randomized controlled trials) that met our inclusion criteria. If multiple studies reported on the same patients, we selected the latest study, unless a different outcome related to our research questions was reported. None of the previous systematic reviews met our eligibility criteria and research questions. See Appendix 3 for a list of primary studies and systematic reviews excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

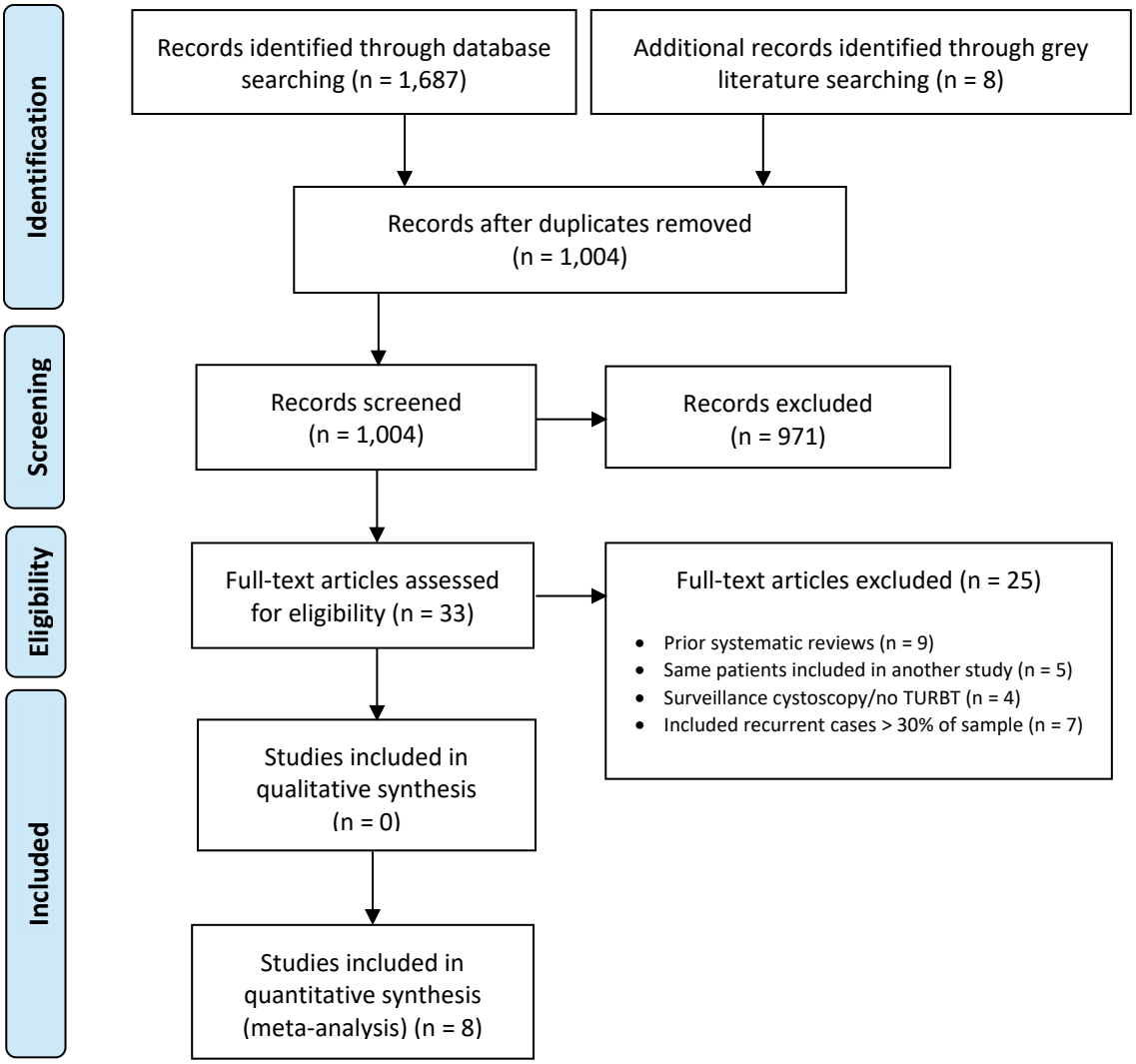

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al, 2009.[42]

Characteristics of Included Studies

Five RCTs reported on clinical outcomes[43-47] including two that also reported diagnostic outcomes.[43,45] Three RCTs reported only on diagnostic outcomes.[48-50] Five RCTs[43-47] reported on cancer recurrence rates in patients who underwent first TURBT. Three of these studies[43,44,47] compared recurrence rates after HAL-guided TURBT versus TURBT using white light alone, and two studies[45,46] compared recurrence rates after NBI-guided TURBT versus TURBT using white light alone.

We did not identify any study that directly compared cancer recurrence rates after HAL-guided versus NBI-guided TURBT. Two RCTS on HAL reported recurrence-free survival and cancer progression rate after first TURBT.[43,44] One study on HAL and two studies on NBI reported on adverse events.[46,47,49]

Table 1 shows study and patient characteristics.

Table 1: Characteristics of Included Randomized Controlled Trials

Author, Year	Country, No. of Sites	Study Period	Randomized, N (Intervention/ Control)	Analyzed, N (Intervention/ Control)	Age, Y, Mean (SD)	M/F, N	Adjuvant Therapies	Follow-Up Duration, Mo	Reported Outcomes
HAL Studies									
Dragoescu et al, 2017[43]	Romania, 1	2009–2011	113 (57/56)	113	HAL: 59.4 (9.9) WL: 60.3 (10.2)	HAL: 45/12 WL: 43/13	Single postoperative chemotherapy instillation and subsequent adjuvant treatment depending on tumour risk *Intermediate risk* Adjuvant chemotherapy *High-risk* Immunotherapy or chemotherapy	60 (range, 60–83) Mean 72.1 ± 6	Detection rate Recurrence Recurrence-free survival Tumour progression
Neuzillet et al, 2014[50]	France, 2	Nov 2009 –Sep 2012	151 (72/79)	151 (72/79)	HAL: 74 (10.3) WL: 74 (10.4)	133/18	NR	6 wk	Detection rate
O'Brien et al, 2013[47]	UK, 1	Mar 2005 –Apr 2010	249 (129/120)	3- and 12-mo follow-up: 168 (86/82)	HAL: 68 (range, 31–95) WL: 68 (range, 29–90)	HAL: 95/34 WL: 88/32	Single shot intravesical mitomycin C Intravesical BCG	12	Recurrence Adverse events
Karaolides et al, 2012[44]	Greece and UK, NR	Nov 2008 –Jul 2010	102 (49/53)	86 (41/45)	HAL: 66.29 (range, 37–82) WL: 63.82 (range, 39–88)	HAL: 33/8 WL: 40/5	*Moderate risk* 6 intravesical instillations of epirubicin 6 wk after TURBT *High risk* Intravesical BCG	18 *Median* HAL: 17.5 (6–25) WL: 14 (4.5–25)	Recurrence Recurrence-free survival Tumour progression
Geavlete et al, 2010[48]	Romania, 1	Dec 2007–Nov 2009	446 (223/223)	335 (176/159)	64 (range, 32–86)	327/119	A single postoperative mitomycin C instillation	6 wk	Detection rate

Author, Year	Country, No. of Sites	Study Period	Randomized, N (Intervention/ Control)	Analyzed, N (Intervention/ Control)	Age, Y, Mean (SD)	M/F, N	Adjuvant Therapies	Follow-Up Duration, Mo	Reported Outcomes
NBI Studies									
Mukherjee et al, 2019[49]	India, 1	Sep 2013–Jul 2015	178	110 NBI first: 56 WL first: 54	> 50: n = 79 ≤ 50: n = 31	NBI first: 51/5 WL first: 46/8	NR	NA	Detection rate
Kim et al, 2018[45]	Korea, 1	Dec 2013–Jun 2017	198 (101/97)	*For diagnostic* 152 (85/67) *For recurrence:* 72 (39/35)	NBI: 64.54 (12.01) WL: 66.96 (11.51)	NBI: 62/23 WL: 54/13	NR	12	Detection rate Recurrence
Naito et al, 2016[46]	16 countries, 26 sites	Aug 2010–Oct 2014	ITT 965 (484/481)	*For recurrence* 3-mo follow-up: 327/316 12-mo follow-up: 354/345	*ITT* NBI: 66.7 (12.3) WL: 65.8 (12.5) *Per protocol* NBI: 67.3 (12.0) WL: 66.5 (11.9)	*ITT* NBI: 390/94 WL: 383/98 *Per protocol* NBI: 300/79 WL: 293/72	Immediate adjuvant instillation	12	Recurrence Adverse events

Abbreviations: BCG, bacillus Calmette–Guérin; F, female; HAL, hexaminolevulinate hydrochloride; ITT, intention to treat; M, male; mo, month(s); NBI, narrow band imaging; NA, not applicable; NR, not reported; SD, standard deviation; TURBT, transurethral resection of bladder tumour; wk, week(s); UK, United Kingdom; WL, white light; Y, year(s).

Risk of Bias in the Included Studies

We used the Cochrane risk-of-bias tool for randomized controlled trials to assess risk of bias for clinical outcomes.[39] Among studies that reported clinical outcomes, two reported random sequence generation and allocation concealment,[46,49] one study reported only random sequence generation,[45] two studies[47,48] reported only allocation concealment, and two studies did not report on these criteria.[43,44] Due to the nature of the investigation, it was not possible to blind the physicians to the intervention in any study. For RCTs that reported on diagnostic outcomes, it was not possible to construct 2 × 2 tables to calculate sensitivity and specificity. Therefore, as noted above, we were unable to use the QUADAS-2 tool to assess risk of bias for these studies.

Appendix 2 shows our assessment of the risk of bias in included studies (Table A1) and the GRADE for each outcome (Table A2).

Cancer Recurrence Rate

Recurrence rate at 12 months was reported by three studies of HAL-guided TURBT versus TURBT using white light alone[43,44,47] and two studies of NBI-guided TURBT versus TURBT using white light alone.[45,46] Only one study reported recurrence rate up to 5 years.[43] We tested for heterogeneity among studies for this outcome and used the *Q* statistic test to determine whether a fixed or a random effects model is suitable. The *Q* statistic was not significant (HAL studies: *P* = .240; NBI studies: *P* = .191), and we chose a fixed effects model for meta-analysis.

PAIRWISE META-ANALYSIS

HAL-Guided TURBT Versus TURBT Using White Light Alone

Three studies compared the effectiveness of TURBT using HAL as an adjunct to white light versus white light alone in reducing the rate of cancer recurrence at 12 months after first TURBT.[43,44,47] One of these studies reported recurrence rates up to 5 years.[43] Meta-analysis of data on recurrence rates at 12 months showed a significant difference between the two groups, and heterogeneity between studies was low (29.9%) and not significant. The risk ratio was 0.70 (95% CI 0.51 to 0.95) and the risk difference was −0.11 (95% CI −0.21 to −0.02). The number needed to treat was calculated as 9. We rated the certainty of the evidence as moderate, downgrading due to risk of bias (Table A2).

Figure 2 is the forest plot based on the risk ratio scale for cancer recurrence rate at 12 months comparing HAL-guided TURBT versus TURBT using white light alone. Figure A1 (Appendix 4) is the forest plot based on the risk difference scale.

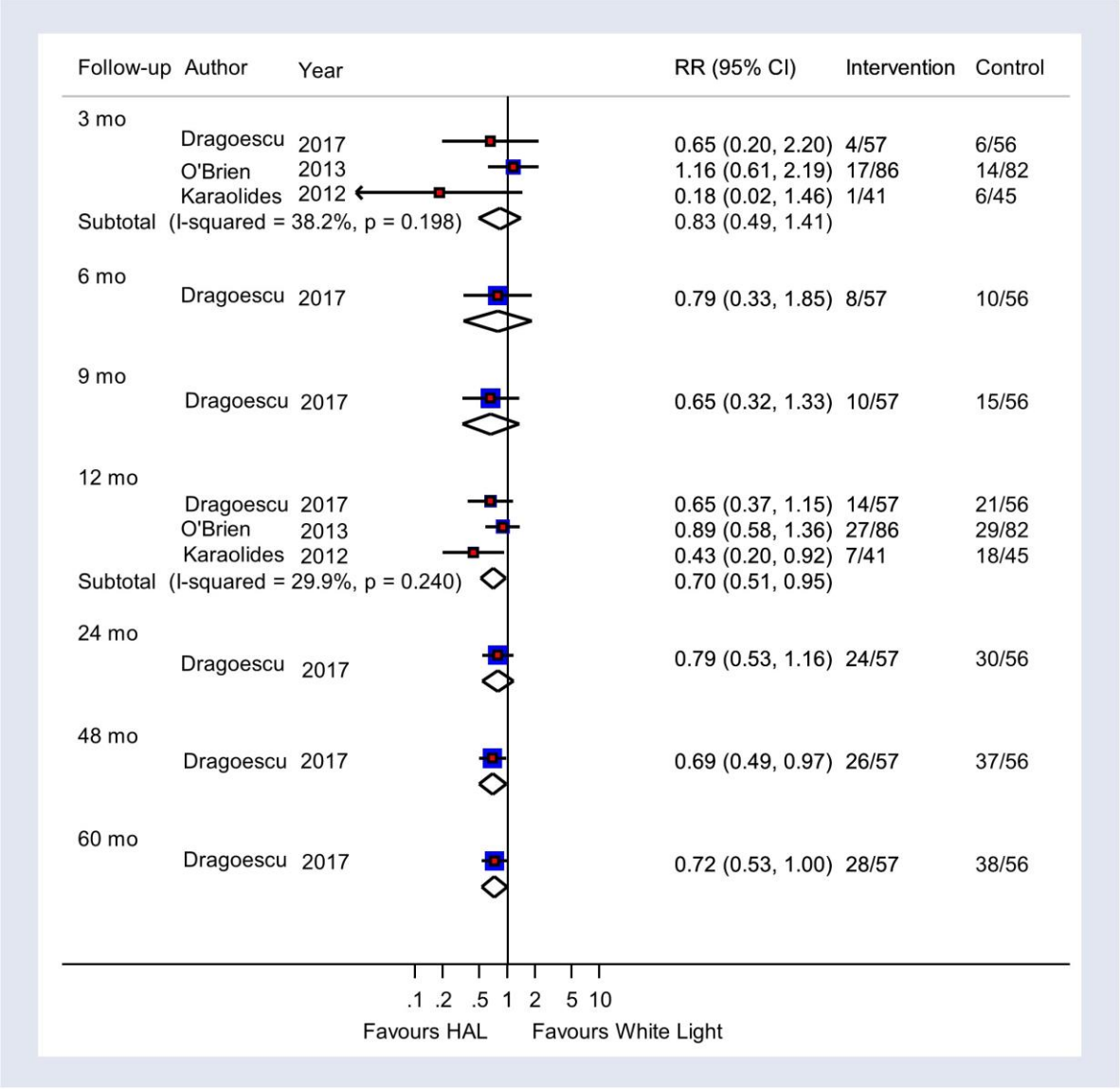

Figure 2: Risk Ratios for Bladder Cancer Recurrence Rate After TURBT Guided by HAL Versus White Light Alone

Abbreviations: CI, confidence interval; HAL, hexaminolevulinate hydrochloride; mo, months; RR, risk ratio.
Sources: Dragoescu et al, 2017[43]; Karaolides et al, 2012[44]; O'Brien et al, 2013.[47]

NBI-Guided TURBT Versus TURBT Using White Light Alone

Two studies compared the effectiveness of TURBT using NBI as an adjunct to white light versus white light alone in reducing the rate of cancer recurrence at 12 months.[45,46] Meta-analysis of data on recurrence rates at 12 months showed no significant difference between the two groups. The risk ratio was 0.94 (95% CI 0.75 to 1.19) and the risk difference was −0.02 (95% CI −0.08 to 0.04) (. We rated the certainty of the evidence as moderate, downgrading due to risk of bias (Table A2). Heterogeneity between studies was low (41.5%) and not significant.

Figure 3 is the forest plot based on the risk ratio scale for cancer recurrence rates at 12 months comparing NBI-guided TURBT and TURBT using white light alone. Figure A2 (Appendix 4) is the forest plot based on the risk difference measure.

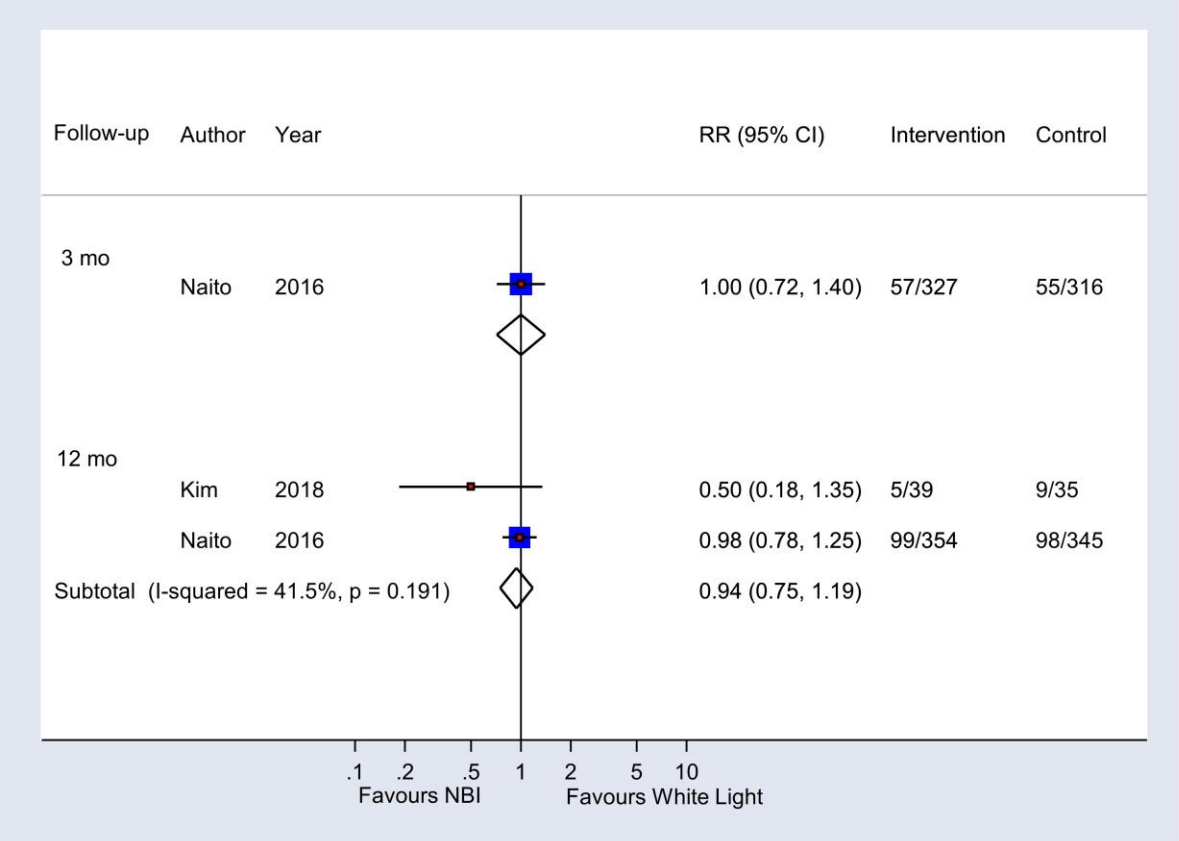

Figure 3: Risk Ratio for Bladder Cancer Recurrence Rates After TURBT Guided by NBI Versus White Light Alone

Abbreviations: CI, confidence interval; NBI, narrow band imaging; mo, months; RR, risk ratio.
Sources: Kim et al, 2018[45]; Naito et al, 2016.[46]

INDIRECT TREATMENT COMPARISON META-ANALYSIS

We conducted an indirect treatment comparison (ITC) meta-analysis through the network of interventions to obtain an indirect estimate of the comparative effectiveness of HAL-guided versus NBI-guided TURBT in reducing the rate of cancer recurrence. TURBT using white light alone was the common comparator in our ITC analysis.

First, we generated a plot of the network of interventions as a visual representation of the available evidence (Figure 4). The nodes (large dots in the figure) represent the individual interventions, and the size of the nodes shows that white light was the most frequently used comparator across the studies. The edges (lines that connect the nodes) represent the direct (head-to-head) comparisons, and we adjusted the thickness of the lines to be proportional to the number of patients in each comparison.

One NBI study had a large sample size, giving more weight to the thickness of the line for studies of NBI versus white light alone.[46] The dashed line represents the lack of direct evidence comparing NBI and HAL and, therefore, the need to obtain an indirect estimate through the network.

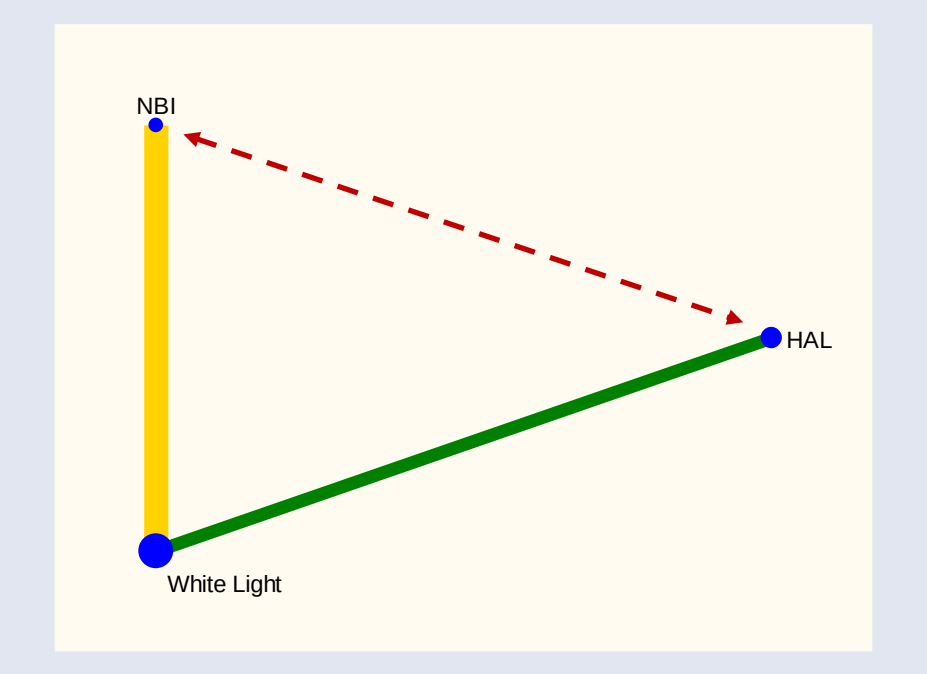

Figure 4: Network Plot Demonstrating Hypothetical Triangle Comparing Three Technologies for Visualization of Bladder Tumours

Abbreviations: HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging.

Second, we generated a contribution plot to identify the most influential head-to-head comparison for network estimates (Figure 5). The contribution plot is a matrix with columns and rows corresponding to the direct estimates and network estimates, respectively. The columns in our plot represent the two direct comparisons and the percentage of their contribution to the network estimate, which is presented in a weighted square in the corresponding column. The plot shows that 100% of information for network estimates for HAL-guided TURBT versus white light alone and NBI-guided TURBT versus white light alone comes from head-to-head comparisons. The network estimate for HAL versus NBI is informed indirectly and equally (50%/50%) by HAL and NBI studies (Figure 5).

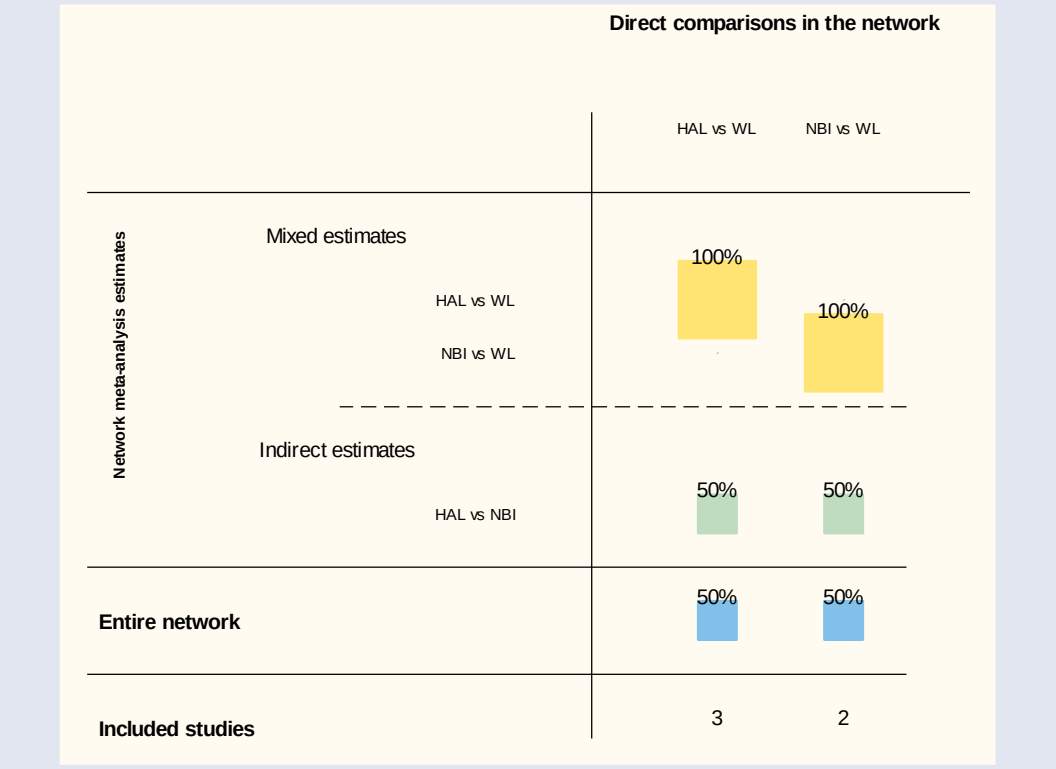

Figure 5: Contribution Plot Presenting Influence of Direct Estimates on Network Estimates

Abbreviations: HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging.

Our ITC analysis of cancer recurrence rates at 12 months showed that the direction and magnitude of the effect estimates for direct and indirect comparisons for HAL-guided TURBT versus white light alone and for NBI-guided TURBT versus white light alone, and their associated confidence intervals, were very close and the two estimates did not conflict.

Indirect treatment comparison of HAL-guided and NBI-guided TURBT showed a lower risk of recurrence in favour of HAL, but this difference did not reach statistical significance (risk ratio 0.76, 95% CI 0.51–1.11).

Table 2 shows point estimates and associated confidence intervals for direct evidence from head-to-head comparisons and indirect evidence provided by ITC analysis, as well as ratings of the quality of these estimates.

Table 2: Direct and Indirect Treatment Comparison, Cancer Recurrence Rate at 12 Months After First TURBT

Comparison	Patients, N (RCTs, N)	Risk Ratio (95% CI)		Risk Difference (95% CI)		Certainty of Evidence	
		Direct Estimate	Indirect Estimate	Direct Estimate	Indirect Estimate	Direct Estimate	Indirect Estimate
HAL vs. WL	367 (3)	0.70 (0.51 to 0.95)	0.72 (0.52 to 0.98)	−0.11 (−0.21 to −0.02)	−0.12 (−0.21 to −0.02)	⊕⊕⊕[a] Moderate	⊕⊕⊕ Moderate
NBI vs. WL	773 (2)	0.94 (0.75 to 1.19)	0.95 (0.75 to 1.19)	−0.02 (−0.08 to 0.04)	−0.02 (−0.08 to 0.04)	⊕⊕⊕[a] Moderate	⊕⊕⊕ Moderate
HAL vs. NBI	1,140 (0)	NA	0.76 (0.51 to 1.11)	NA	−0.09 (−0.21 to 0.02)	NA	⊕⊕ Low

Abbreviations: CI, confidence interval; HAL; hexaminolevulinate hydrochloride; NA, not available; NBI, narrow band imaging; TURBT, transurethral resection of bladder tumour; WL, white light.
[a]Described in Appendix 2 (TableA2).

We tested whether the evidence could satisfy the assumptions of homogeneity by using *Q* statistic and I^2 measure. The *Q* statistic from ITC analysis showed no significant heterogeneity among these studies and I^2 measure was low. Decomposition of *Q* statistic for two different designs (i.e., HAL-guided versus white light alone and NBI-guided versus white light alone) was also nonsignificant. The results are shown in Appendix 5, Tables A5 and A6.

We used the PICOT approach[38] and ensured that studies in the ITC meta-analysis were sufficiently similar. Studies used similar methodology and the population, interventions, and comparator were all similar or very close. All studies were conducted in inpatient settings and the outcome for ITC analysis was measured at the same time point.

In the comparison of HAL-guided TURBT versus TURBT using white light alone and of NBI-guided TURBT versus TURBT using white light alone, the direct and indirect estimates were also very close and consistent. Therefore, we rated the quality of the estimates from ITC analysis for these comparisons as moderate, similar to the quality for the direct evidence. However, the assumption of transitivity and consistency between direct and indirect estimates of effect for comparison between HAL-guided TURBT and NBI-guided TURBT could not be met due to the absence of direct evidence.[51] Therefore, we assumed less certainty for this comparison and rated the quality of the indirect evidence for this comparison as low (Table 2).

Validity of the ITC also rests on the assumption that there is no intervening important covariate that could confound the outcome. To ensure that potential confounders (effect modifiers) did not influence the outcome, we performed meta-regression analysis considering patients' mean age and the percentages of patients with primary (nonrecurrent) NMIBC as covariates. We used recurrence rate at 12 months as a dependent variable and age and percentages of patients with primary cancer as predictor variables. The meta-regression analysis for HAL studies showed that these variables were not

significant predictors of treatment effect. For NBI studies the number of observations were not sufficient for meta-regression analysis.

SUBGROUP ANALYSES

Cancer Recurrence Rate Stratified by Risk Categories

One study of HAL-guided TURBT reported the proportion of low-, intermediate-, and high-risk patients diagnosed with NMIBC as 22%, 50%, and 28%, respectively, but did not provide any subgroup analysis by risk category.[44]

One NBI study did report a subgroup analysis of recurrence rates based on risk categories.[46] In this study, high risk was defined as CIS, T1 grade 3, or multiple tumours. Low risk was defined as a solitary Ta grade 1, tumour less than 30 mm, and no CIS. All other Ta and T1 cases were classified as intermediate risk. This study showed that only low-risk patients who underwent NBI-guided TURBT had significantly less recurrence at 3 and 12 months in comparison with those who underwent TURBT using white light alone. The difference was not significant for intermediate- or high-risk patients (Table 3).

Table 3: Cancer Recurrence Rate After TURBT Guided by NBI Versus White Light Alone, Stratified by Risk

Author, Year	Low Risk, % (N)	Intermediate Risk, % (N)	High Risk, % (N)
Naito et al, 2016[46]	*3-mo follow-up* NBI: 0 (0/52) WL: 15.1 (8/53) *P* = .006	*3-mo follow-up* NBI: 11.1 (12/108) WL: 5.7 (6/106) *P* > .05	*3-mo follow-up* NBI: 27 (45/167) WL: 26.1 (41/157) *P* > .05
	12-mo follow-up NBI: 5.6 (3/54) WL: 27.3 (15/55) *P* = .002	*12-mo follow-up* NBI: 17/6 (21/119) WL: 16.8 (20/119) *P* > .05	*12-mo follow-up* NBI: 41.4 (75/181) WL: 36.8 (63/171) *P* > .05

Abbreviations: HAL, hexaminolevulinate hydrochloride; mo, months; NBI, narrow band imaging; TURBT, transurethral resection of bladder tumour; WL, white light.

Cancer Recurrence Rate Stratified by Tumour Grade

One study of HAL stratified data on cancer recurrence rates based on the grade of the tumour.[47] This study did not find any significant difference between patients who underwent HAL-guided TURBT and those who underwent TURBT with white light alone for low- or high-grade tumours (Table 4).

Table 4: Cancer Recurrence Rate After TURBT Guided by HAL Versus White Light Alone, Stratified by Tumour Grade

Author, Year	Low Grade, % (N)	High Grade, % (N)
O'Brien et al, 2013[47]	*3-mo follow-up* HAL: 19 (9/48) WL: 9 (4/46) *P* = .23 *> 3–12 mo* HAL: 16 (6/37) WL: 22 (9/41) *P* = .57	*3-mo follow-up* HAL: 21 (8/38) WL: 28 (10/36) *P* = .59 *> 3–12 mo* HAL: 15 (4/26) WL: 23 (6/26) *P* = .72

Abbreviations: HAL, hexaminolevulinate hydrochloride; mo, months; TURBT, transurethral resection of bladder tumour; WL, white light.

Recurrence-Free Survival

Two studies on HAL reported recurrence-free survival.[43,44] In both studies, recurrence-free survival was significantly better in patients who underwent HAL-guided TURBT than in those who underwent TURBT with white light alone. We rated the certainty of the evidence as moderate, downgrading due to risk of bias (Table A2). None of the studies on NBI reported on recurrence-free survival.

Dragoescu et al[43] reported a significant difference in recurrence-free survival between the two groups of patients at 5 years (hazard ratio 0.566, 95% CI 0.343–0.936; *P* = .0267). Karaolides et al[44] did not report the overall difference in this outcome between the two groups but reported the difference between the two groups for each tumour characteristic at 12 and 18 months. Analysis by log rank test showed that, for all tumour characteristics except solitary tumours, recurrence-free survival was significantly better in patients who received HAL-guided TURBT than those who had the procedure using white light alone (Figure 6).

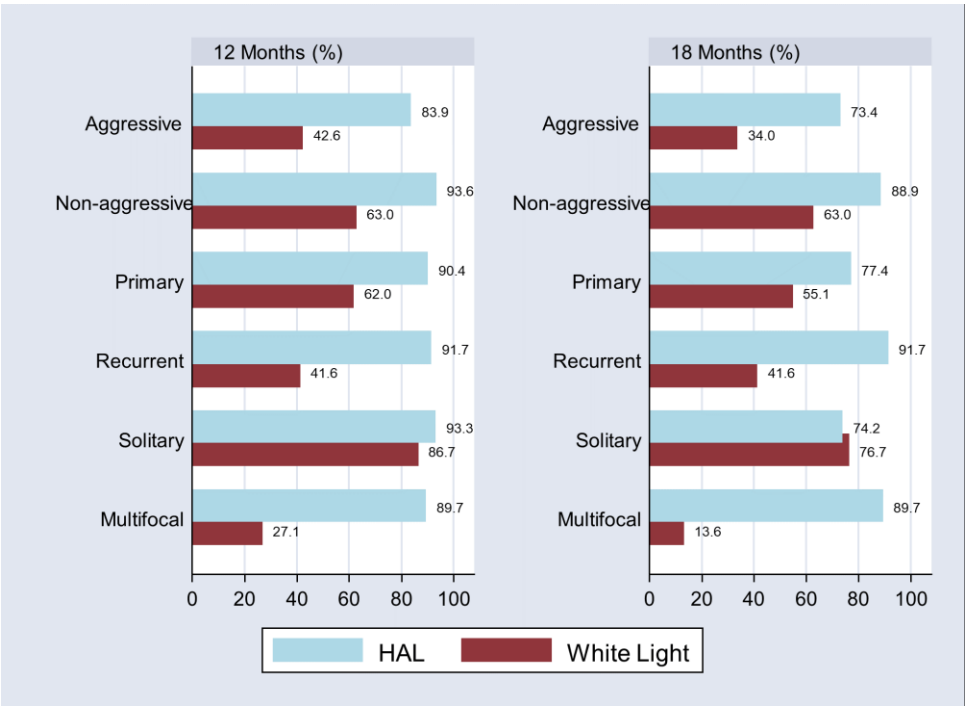

Figure 6: Recurrence-Free Survival Rate by Tumour Characteristic, HAL-Guided TURBT Versus TURBT Using White Light Alone

Abbreviations: HAL, hexaminolevulinate hydrochloride; TURBT, transurethral resection of bladder tumour.

Overall Survival

Overall survival was reported by one HAL study. Dragoescu et al[43] reported that there were no cancer-related deaths within 5 years of follow-up in their study but two deaths due to cardiovascular reasons. We rated the certainty of the evidence as moderate, downgrading due to risk of bias (Table A2).

Tumour Progression Rate

Two HAL studies reported on the rate of tumour progression (Table 5).[43,44] None of the NBI studies reported on tumour progression rate.

Dragoescu et al[43] reported tumour progression rates at 5 years in 11 of 113 patients (9.7%; 5 in the HAL group [8.7%], 6 in the white light group [10.6%]). Seven patients had tumour grade progression and four had depth progression. The investigators reported that the data were insufficient for a thorough analysis of tumour progression rates. Two patients (3.5%) in the HAL group and three patients (5.2%) in the white light group underwent radical cystectomy, and the difference was not significant (We rated the certainty of the evidence as moderate, downgrading due to risk of bias (Table A2).

Karaolides et al[44] reported that at 12-month follow-up there was no tumour progression in patients who underwent HAL-guided TURBT. Tumours progressed in five patients who underwent TURBT with white light alone, including two people who required radical cystectomy because their cancer had progressed and became muscle invasive (GRADE: Moderate).

Table 5: Tumour Progression Rate After TURBT Guided by HAL Versus White Light Alone

Author, Year	12-Month Follow-Up, % (N)	5-Year Follow-Up, % (N)
Dragoescu et al, 2017[43]	NR	HAL: 8.7 (5/57) WL: 10.7 (6/56) *P*: NR
Karaolides et al, 2012[44]	HAL: 0 (0/41) WL: 4.4 (2/45) *P*: NR	NR

Abbreviations: HAL, hexaminolevulinate hydrochloride; NR, not reported; TURBT, transurethral resection of bladder tumour; WL, white light.

Diagnostic Outcomes

Although data from the included studies did not allow us to compute the diagnostic accuracy of the new technologies, we were able to determine the true-positive and false-positive detection rates of these technologies relative to white light alone. In evaluating technologies used to guide TURBT, it is important to know the proportion of tissue specimens found to be false-positive because each specimen taken from the bladder wall must include some of the muscle underneath to determine whether the tumor has grown into the muscle. Scar tissue then gradually replaces the muscle. Taking too many samples can result in the formation of scar tissue at several spots in the bladder wall, which can impair the bladder's ability to hold urine and lead to problems such as frequent urination or difficulty with urine control.[15] Avoiding removal of noncancerous specimens by more accurate detection during surgery is, therefore, desirable.

Five RCTs reported on the number of lesions detected by each method and how many of those were cancer, based on histopathological examination as the clinical reference standard. Three of these studies compared HAL-guided TURBT and TURBT using white light alone[43,48,50]; one study compared NBI-guided TURBT and TURBT using white light alone[45]; and another study[49] compared NBI and white light alone through a sequential order design in which each method was the first or the second light source.

HAL VERSUS WHITE LIGHT

Dragoescu et al[43] evaluated cancer detection rates during first TURBT in patients with primary NMIBC. The investigators randomized 113 patients into two parallel arms. In the white light arm (n = 56), lesions were detected and removed using white light only. In the HAL arm (n = 57), lesions were first detected using white light and then HAL was instilled into the bladder to repeat the detection process. All identified lesions were then removed and sent for histopathological examination.

In the white light arm, a total of 92 lesions were identified. In the HAL arm, white light identified 99 lesions and HAL identified 125 lesions, of which 5 were found to be false-positive. Seven lesions detected by white light were missed by HAL (false-negative). In the HAL arm, the probability of detecting cancer was 94.5% (120/127 lesions) when the TURBT procedure was guided by HAL alone and 82.5% (99/120) when the procedure was guided by white light alone.

In the study by Neuzillet et al,[50] 151 patients undergoing their first TURBT for suspected NMIBC were randomized into two arms: TURBT with white light alone (n = 79) and TURBT with HAL plus white light

(n = 72). In this study, the number of lesions visualized were not significantly different between the two groups. In white light arm, 82 lesions were detected, of which 5 were false-positive. In the HAL arm, 70 lesions were detected, of which 3 were false-positive. The probability of detecting cancer was 95.7% (67/70) in the HAL arm and 93.9% (77/82) in the white light arm (difference not significant). The authors also reported the results of repeat TURBT guided by HAL performed after 4 to 6 weeks to identify residual or recurrent tumours. During the second procedure, the number of detected tumours did not significantly differ whether patients' first TURBT had been guided by HAL or had used white light alone.

The study by Geavlete et al[48] had a larger sample size and reported a significant difference in cancer detection rates between the study arms. A total of 446 patients suspected of having NMIBC and undergoing first TURBT were randomized to have the procedure using white light alone (n = 233) or HAL plus white light (n = 233). In this trial 75% (335) of the patients were diagnosed with NMIBC. Muscle-invasive cancer was found in 15% of the patients (n = 65) and no cancer was detected in 10% (n = 46). The proportion of high-risk patients in this study was 30%. In the HAL arm, the bladder was first visualized under white light and then HAL was instilled into the bladder to detect more lesions. The urologist performing the procedure was informed about whether HAL would be available only after finishing the inspection under white light to ensure their maximum attention to that initial investigation. In both arms, patients received a second TURBT after 6 weeks to assess and compare the two arms with respect to cancer recurrence or presence of residual tumours.

This study reported detection rates based on per-patient assessment. In the white light arm, lesions were detected in 159 patients. In the HAL arm, lesions were detected in 176 patients by either HAL and/or white light. White light detected lesions in 85.2% of those patients (150/176) and HAL detected lesions in 95.5% (168/176), and the difference between the two visualization methods was significant (*P* = .0001).

During the repeat TURBT, significantly more patients had residual or recurring tumours in the white light arm than in the HAL arm among high-risk patients (white light 31.2%, HAL plus white light 11.1%; *P* = .0001) and among patients with high-grade tumour (white light 37%, HAL plus white light 17.2%; *P* = .018).

NBI VERSUS WHITE LIGHT

Mukherjee et al[49] investigated the performance of NBI during TURBT as the first or second light source (i.e., after and before white light). The investigators randomized 110 patients into two arms. In one arm (n = 54), the bladder was first inspected under white light and tumours were resected. Then the bladder was washed and cleared of all tumour chips and blood clots. Re-inspection of the bladder immediately followed, this time using NBI, and additional suspicious lesions were identified and resected under NBI. In the other arm (n = 56), the process was reversed: NBI was used first and lesions were resected under NBI, followed by a further inspection and resection under white light. All lesions removed were sent for histopathological examination and the pathologist was blinded to the specimens' assigned groups.

NBI as the second light source identified lesions in 20 patients but in 11 patients the identified lesions were not cancerous (false-positive detection rate: 55%). White light as the second light source identified lesions in 5 patients but none were cancerous (false-positive detection rate: 100%).

In the study by Kim et al,[45] 152 patients suspected of having NMIBC and undergoing first TURBT were randomized into two arms: white light alone (n = 67) and NBI plus white light (n = 85). In the NBI arm,

white light was first used to identify and remove lesions and then NBI was used to detect and remove additional lesions.

This study reported detection rates per patient and per lesion. In the white light arm, a total of 55 patients had cancer; therefore, the probability of detecting cancer in this arm was 82.1% (55/67). In the NBI arm, white light detected cancer in 72 patients and the probability of detecting cancer with white light was 84.7% (72/85). NBI as the second light source, after lesions detected by white light were removed, identified additional lesions in 37 patients but these lesions were cancerous in only 13 of the patients (detection rate 35.1%, 13/37). The false-positive detection rate for NBI was 64.9% (24/37).

In the white light group, the per-lesion rate of detecting cancer was 80.9% (114/141): a total of 141 lesions were identified, of which 114 were cancerous. In the NBI group, the probability of detecting cancer with white light was 85.5% (159/186) and the false-positive detection rate for white light was 14.5%. Using NBI as the second light source, after lesions detected by white light were removed, produced a detection rate of 42.2% (64 additional lesions but only 27 were cancerous) and a false-positive detection rate of 57.8% (37/64).

Table 6 summarizes the diagnostic outcomes reported by RCTs.

Table 6: Diagnostic Outcomes: True-Positive and False-Positive Detection Rates

	Experimental Group, % (N)		Control Group, % (N)	
Author, Year	True-Positive	False-Positive	True-Positive	False-Positive
HAL Studies				
Dragoescu et al, 2017[43,a]	HAL: 94.5 (120/127) WL: 82.5 (99/120)	HAL: 4 (5/125) WL: NR	92 lesions	NR
Neuzillet et al, 2014[50,a]	HAL: 95.7 (67/70)	HAL: 4.3 (3/70)	WL: 93.9 (77/82)	WL: 6.1 (5/82)
Geavlete et al, 2010[48,b]	HAL: 95.5 (168/176) WL: 85.2 (150/176) *P* = .0001	NR	WL: 71.3 (159/223)	NR
NBI Studies				
Mukherjee et al, 2019[49,b]	NBI as second light: 45 (9/20)	NBI as second light: 55 (11/20)	WL as second light: 0 (0/5)	WL as second light: 100 (5/5)
Kim et al, 2018[45,a]	WL as first light: 85.5 (159/186) NBI as second light: 42.2 (27/64)	WL as first light: 14.5 (27/186) NBI as second light: 57.8 (37/64)	WL: 80.9 (114/141)	WL: 19.1 (27/141)
Kim et al, 2018[45,b]	WL as first light: 84.7 (72/85) NBI as second light: 35.1 (13/37)	WL: NR NBI as second light: 64.9 (24/37)	WL: 82.1 (55/67)	NR

Abbreviations: HAL; hexaminolevulinate hydrochloride; NBI, narrow band imaging; NR, not reported; WL, white light.
[a]Based on the number of lesions.
[b]Based on the number of patients.
Note: *P*-values are shown if reported by the authors.

After abstracting data from RCTs and observing that the data reported by RCTs were not sufficient to construct 2 × 2 tables to determine diagnostic accuracy, we examined all published observational studies to see whether additional diagnostic outcomes were reported. No observational study on HAL met our inclusion criteria. Two observational studies on NBI met our inclusion criteria but we did not find any additional information beyond that reported by RCTs.[52,53]

The GRADE for diagnostic outcomes was determined as very low (Table A2).

Adverse Events

One HAL study and two NBI studies reported on adverse events.[46,47,49] O'Brien et al[47] reported that there were no adverse events related to HAL in their study.

Naito et al[46] reported on the frequency of intraoperative and perioperative complications in the NBI and white light study arms. The authors reported no significant differences between the two arms with respect to intraoperative bleeding (NBI 2.1%, white light 1.7%; *P* = .644) and bladder perforation (NBI 2.3%, white light 1.5%; *P* = .348). Table 7 shows perioperative complications reported by Naito et al.[46]

Mukherjee et al,[49] who experimentally used NBI as the first light source (followed by white light) in one of the two arms of their study, reported 7 breaches of protocol in the NBI-first arm. Six were due to poor visibility, prompting surgeons to switch to white light, and one was due to bladder perforation. The other arm had no breach of protocol due to poor visibility (*P* = .032). The investigators reported that the poor visibility in the NBI-first arm was caused by bleeding during resection, which released hemoglobin. The wavelength of NBI was absorbed by the hemoglobin on the surface of the bladder wall, limiting visibility.

We rated the certainty of the evidence as moderate, downgrading due to risk of bias (Table A2).

Table 7: Perioperative Complications in TURBT Guided by NBI Versus White Light Alone

Complication	NBI, N (%)	White Light, N (%)	*P* Value
Bleeding	36 (8.4)	27 (6.5)	.311
Fever	9 (2.1)	7 (1.7)	.666
UTI	8 (1.9)	10 (2.5)	.569
Bladder cramps	19 (4.5)	10 (2.5)	.111
DVT	0 (0)	0 (0)	NA
CVA/TIA	2 (0.5)	0 (0)	.5
Lung embolism	0 (0)	0 (0)	NA
Sepsis	2 (0.5)	0 (0)	.5
Acute abdomen	1 (0.2)	1 (0.2)	1.000
Other	9 (2.1)	13 (3.2)	.342

Abbreviations: CVA, cerebrovascular accident; DVT, deep vein thrombosis; NBI, narrow band imaging; TIA, transient ischemic attack; TURBT, transurethral resection of bladder tumour; UTI, urinary tract infection; WL, white light.
Source: Naito et al, 2016,[46] based on intention-to-treat analysis.

Both NBI studies that reported on adverse events used the Clavien-Dindo classification for grading surgical interventions[54] to compare the frequency of perioperative complications in the study arms, and both reported no significant differences in scores between patients who underwent NBI-guided TURBT and patients who underwent TURBT using white light alone (Table 8).

Table 8: Clavien-Dindo Grading of Surgical Complications in NBI Studies

Grade[a]	Mukherjee et al, 2019[49] N (%)		Naito et al, 2016[46] N (%)	
	NBI	WL	NBI	WL
I	0	7 (12.5)	23 (6.1)	16 (4.4)
II	0	0	20 (5.3)	16 (4.4)
IIIA	1 (1.8)	2 (3.6)	7 (1.9)	2 (0.5)
IIIB	0	0	3 (0.8)	4 (1.1)
IVA	0	2 (3.6)	0	0
IVB	0	0	0	0
V	0	0	1 (0.3)	0

Abbreviations: NBI, narrow band imaging; WL, white light.

[a]For detail, see Appendix 6, Table A7.

Ongoing Studies

We are not aware of any ongoing randomized controlled trials that might potentially affect this review.

Discussion

To the best of our knowledge, the present systematic review is the first review to address the effectiveness of new technologies in reducing the risk of cancer recurrence in people with suspected NMIBC when used during their first TURBT. Previous systematic reviews were not designed to focus on this specific patient population; therefore, we excluded them from our report.

NMIBC has high risk of recurrence, making it a labour-intensive and costly disease to manage and highlighting the need for effective interventions to reduce this risk. Improving the identification and management of bladder cancer would benefit a large number of people in Ontario, since the projected estimate of new cases in this province is about 4,500 per year.[8] About 75% of these are NMIBC,[2] which can be effectively treated with TURBT, which is the initial and critical step in the treatment for these patients. However, the effectiveness of TURBT is highly dependent on the visibility and complete removal of the tumours. Studies have shown the impact of residual tumours on patients' clinical outcomes,[55,56] and TURBT guided by white light alone may fail to identify small papillary tumours and carcinoma in situ.[57]

Our analysis of published evidence demonstrated that first TURBT using HAL in conjunction with white light significantly reduces the rate of cancer recurrence at 12 months compared with the conventional method of performing TURBT under white light alone. One study showed that this reduction in recurrence rate continues for at least 5 years. In addition, two studies showed that recurrence-free survival also significantly improved when HAL was used during first TURBT.[43,44] There was no significant impact on tumour progression rate using HAL during the first TURBT. Meta-analysis of NBI studies did not show a significant difference in rates of cancer recurrence at 12 months between people whose first TURBT used NBI in conjunction with white light and those whose first TURBT used white light alone.

Our ITC analysis showed no significant difference between HAL-guided and NBI-guided TURBT in reducing the rate of recurrence at 12 months. The direction of the effect was in favour of HAL but it did

not reach statistical significance. However, due to the absence of direct evidence to compare HAL and NBI, we could not test the assumption of consistency for this estimate.

The true diagnostic accuracy of TURBT using HAL and NBI as adjuncts to white light remains unclear. The literature indicates that white light is an imperfect reference standard, making it difficult to determine the actual number of tumours missed when TURBT is performed using white light alone. However, the false-positive detection rate is a useful diagnostic outcome for this technology that can be considered in clinical decision-making. Studies showed that the false-positive detection rate of NBI was high when NBI was used as the second light source: 58% of the additional lesions found were not cancerous. In contrast, when HAL was used after white light, it had a false-positive detection rate of 4%. This is an important consideration during TURBT as each surgical specimen must include some tissue from the muscle layer, and taking too many specimens results in scar tissue that may affect bladder function. With respect to safety, it appears that HAL and NBI both have acceptable safety profiles when used as an adjunct to white light during TURBT.

Strengths and Limitations

Our systematic review, meta-analysis, and ITC analysis had several strengths: (i) stringent methodology used for literature searching, (ii) inclusion of all randomized controlled trials published from database inception to the search date, (iii) inclusion of a specific target population, and (iv) generation of an indirect estimate to compare competing technologies where a direct estimate was not available. A limitation of our systematic review was the lack of direct evidence for comparison between HAL and NBI for their effectiveness in reducing the risk of recurrence.

Conclusions

Clinical Outcomes

In patients with suspected NMIBC undergoing their first TURBT:

- HAL-guided TURBT likely reduces the rate of recurrence at 12 months (GRADE: Moderate) and likely increases 5-year recurrence-free survival (GRADE: Moderate) when compared with TURBT using white light alone. There is likely little to no difference in the tumour progression rate (GRADE: Moderate)
- NBI-guided TURBT likely results in little to no difference in the rate of recurrence at 12 months when compared with TURBT using white light alone (GRADE: Moderate). No evidence on the effect on recurrence-free survival or tumour progression rate was identified for NBI-guided TURBT
- Based on an indirect comparison, there may be little to no difference in recurrence rates between HAL-guided and NBI-guided TURBT (GRADE: Low)
- Use of HAL or NBI during TURBT is generally safe. However, using NBI as the first light source can be limited by poor visibility. Since the wavelength of NBI is absorbed by hemoglobin, bleeding from the resection sites (which releases hemoglobin) can affect visibility (GRADE: Moderate)

Diagnostic Outcomes

- Most lesions identified by HAL were true-positive and only about 4% were false-positive (GRADE: Very low)
- About half of the lesions identified by NBI were false-positive (GRADE: Very low)

Economic Evidence

Research Question

What is the cost-effectiveness of hexaminolevulinate hydrochloride (HAL) or narrow band imaging (NBI) as an adjunct to white light during first transurethral resection of bladder tumour (TURBT), compared with TURBT using white light alone, in people with suspected non-muscle-invasive bladder cancer (NMIBC)?

Methods

Economic Literature Search

We performed an economic literature search on April 15, 2020, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them for the duration of the assessment period. We also performed a targeted grey literature search of health technology assessment agency websites, clinical trial and systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See the Clinical Literature Search section, above, for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- Studies published from database inception until April 15, 2020
- Cost–benefit analyses, cost–utility analyses, cost-effectiveness analyses, or cost-consequence analyses

Exclusion Criteria

- Cost analysis
- Narrative reviews, editorials, case reports, commentaries, and abstracts

POPULATION

- Patients 18 years of age or older undergoing their first TURBT for suspected non-muscle-invasive bladder cancer

INTERVENTIONS

- TURBT guided by HAL
- TURBT guided by NBI

COMPARATOR

- TURBT using white light alone

Outcome Measures

- Costs
- Health outcomes (e.g., quality-adjusted life-years)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[32] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

We contacted study authors to provide clarification as needed.

Study Applicability

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[58] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. We then assessed the applicability of each study to the research question (directly, partially, or not applicable).

Results

Economic Literature Search

The database search of the economic literature yielded 192 citations published from database inception until April 15, 2020. We identified eight additional studies from other sources, for a total of 134 after removing duplicates. We excluded a total of 97 articles based on information in the title and abstract. We then obtained the full texts of 37 potentially relevant articles for further assessment. See Appendix 7 for a list of selected studies excluded after full-text review. Figure 7 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

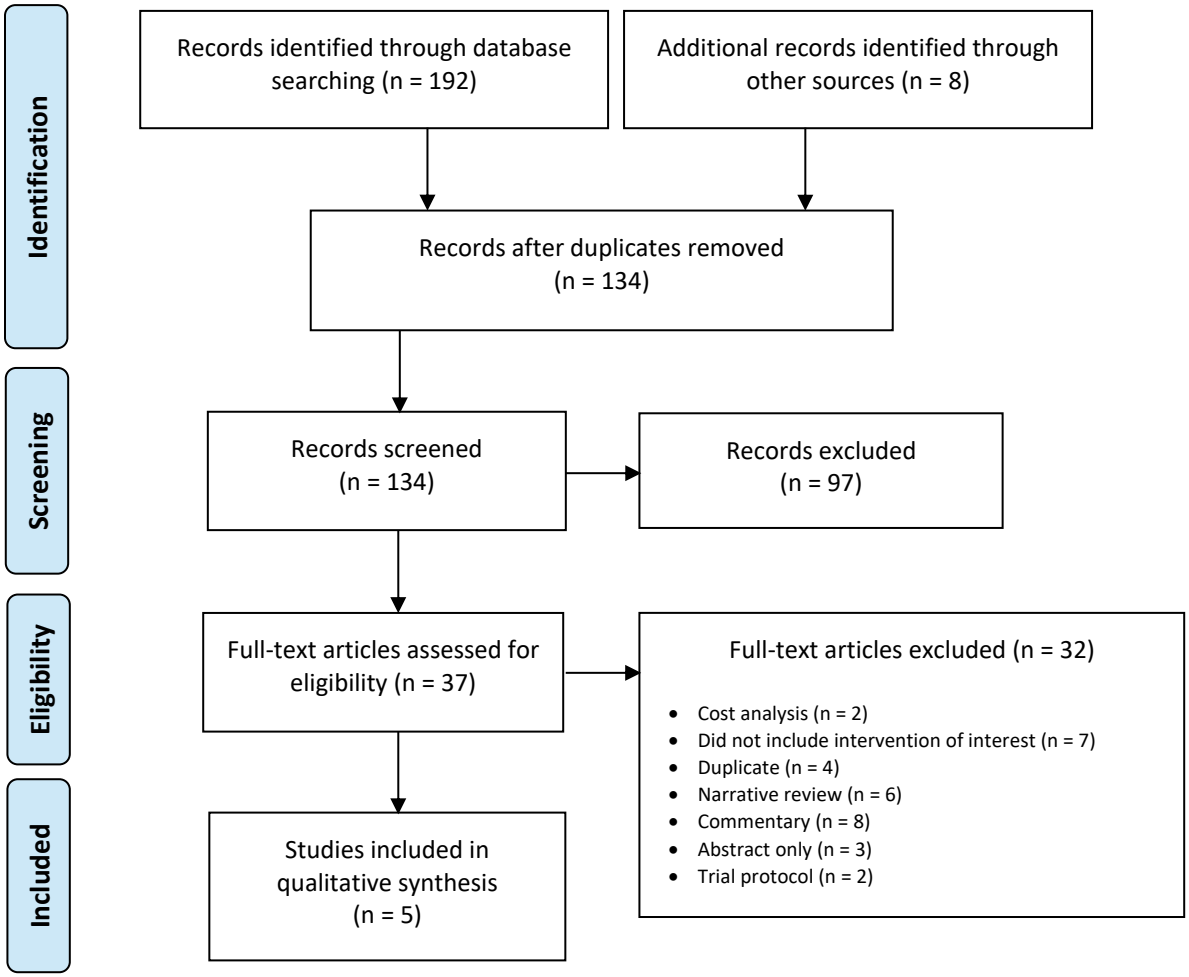

Figure 7: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al, 2009.[42]

Overview of Included Economic Studies

Table 9 provides a summary of the five included studies.

Malmstrom et al[59] conducted a cost-consequence and budget impact analysis comparing HAL-guided TURBT and TURBT using white light alone in a population of people with muscle-invasive bladder cancer (MIBC) and NMIBC. The authors constructed a series of decision tree models for each histological risk classification, over a 1-year time horizon from the Swedish health service perspective. Because of the 1-year time horizon, there was no discounting. Clinical inputs were primarily based on assumptions, although the authors explained their inputs were based on a review of the literature and adjusted to the Swedish clinical urology experience. Specifically, a reduction in tumour recurrence for HAL-guided TURBT was based on literature observed with use of 5-ALA as the optical agent. All sources for costs were not explicitly stated, and differential costs between treatments were primarily the cost of HAL instillation and the cost of equipment for fluorescence cystoscopy. Both surgeon time to perform procedures and nurse time in preparing HAL before instillation were not costed. The results of the base case analysis indicated that, over a year, there was a 44%, 7%, and 1% reduction in cystectomies, repeat TURBTs, and monitoring cystoscopies, respectively, when HAL was used in first TURBT. The reduction in the number of invasive procedures led to a total cost saving of 1,321,716 Swedish krona (SEK) for HAL-guided TURBT. They conducted a one-way sensitivity analysis and found HAL remained cost-saving if the reduction in the tumour recurrence rate for HAL was above 34%.

Garfield et al[60] carried out a cost–utility analysis comparing HAL-guided TURBT and TURBT using white light alone in a population of people with suspected new or recurrent NMIBC. Three decision tree models were used to represent (i) the first TURBT, (ii) recurrence monitoring for patients whose NMIBC is detected and treated, and (iii) ongoing monitoring for patients where cancer is not detected. A 5-year time horizon was used and a discount rate was not specified. The model used the US health care system perspective, specifically reimbursement from health care payers and associated patient outcomes. Due to costs being evaluated from the payer perspective, the authors omitted the costs of the capital equipment associated with HAL-guided TURBT, stating capital equipment costs are not borne by the payer directly. All cost inputs were derived from published Medicare and private payer data sources. Clinical inputs were mainly derived from a trial published by Grossman et al,[61] with an average patient follow-up of 4.5 years (this study was not included in our clinical evidence review as recurrent cases comprised over 30% of the target population). Utility inputs were arbitrarily derived by the authors, with 0 representing bladder cancer and 1 representing being cancer free, and other utility and disutility values were assigned for each model cycle.[60] The model results found HAL-guided TURBT resulted in both lower costs ($25,921 vs. $30,581 USD) and higher utilities/effectiveness (4.9 vs. 4.4) compared to TURBT using white light alone. No sensitivity analyses were reported to test model assumptions or parameter uncertainty.

Roupret et al[62] published a cost–utility analysis comparing HAL-guided TURBT and TURBT using white light alone in a population of patients diagnosed with symptoms consistent with NMIBC. The model began with a decision tree to simulate the initial diagnostic cystoscopy followed by TURBT; next the Markov model simulated the long-term follow-up. Patients entering the Markov model were classified by their risk of recurrence, which impacted patient monitoring, recurrences, and progression. The model was run over a lifetime horizon from the French health care system perspective and used a 2.5% discount rate. Base utilities for NMIBC were derived from an unlisted source that used the EQ-5D (a health-related quality-of-life instrument), while all other utilities (e.g., metastases and cystectomies) were derived from Kulkarni et al,[63] who primarily calculated bladder cancer utilities from the utilities of

other populations that the authors deemed to have similar health states/issues. Costs consisted of direct medical costs from various sources, inclusive of all funders (state, health insurance, and patients). The results found HAL had lower costs (€22,967 vs. €23,813) and higher QALYs (11.29 vs. 11.19). The cost-effectiveness scatter plot from the probabilistic analysis indicated that the vast majority of HAL iterations were dominant (lower cost and more QALYs), but exact values were not specified. One-way sensitivity analyses were conducted and the results remained robust, where HAL-guided TURBT was cost-saving.

Klaassen et al[6] performed a cost-effectiveness analysis comparing HAL-guided TURBT and TURBT using white light alone in a population of patients with suspected new or recurrent NMIBC. The model began with a decision tree to simulate the first TURBT and patients' monitoring and treatment following risk classification, while a Markov model evaluated long-term recurrence and progression of cancer post TURBT. The model was simulated over 5 years using three distinct Canadian health care payer perspectives (Ontario, British Columbia, and Quebec). The authors did not specify a discount rate. For clinical inputs, the relative risk of recurrence for HAL versus white light was calculated from the work of Burger et al[26] (this study was not included in our clinical evidence review as recurrent cases comprised over 30% of the target population). Other clinical inputs, including sensitivity and specificity, were derived from a meta-analysis the authors conducted.[6] For the Ontario perspective, micro-costing data were derived from individual patient data at the University of Toronto (University Health Network). The base case analysis found the average cost was higher for HAL-guided TURBT ($11,554 vs. $10,182 CAD), but HAL-guided TURBT led to a lower average number of recurrences (0.38 vs. 0.48) and bed days associated with TURBT (2.03 vs. 2.33); this resulted in a cost per recurrence prevented of $28,463. The authors did conduct sensitivity analyses, primarily evaluating variables that impact the total 5-year cost; they found one of the most influential variables was the extent to which HAL-guided TURBT improved NMIBC progression rates (given no definitive evidence on this outcome, the base case assumed no improvement).

Gakis et al[64] conducted a cost–utility analysis comparing HAL-guided TURBT and TURBT using white light alone in patients diagnosed with NMIBC. A decision tree simulated both TURBT treatment arms, as well as diagnostic outcome (whether the TURBT led to a true-positive or false-positive) and the patient's resultant risk level. Following the decision tree, individuals entered the Markov model, which simulated long-term outcomes such as progression from NMIBC to MIBC. The model took the perspective of the German health care system and was run over a lifetime horizon, with a 3.5% discount rate. Clinical inputs for recurrence and progression after TURBT with white light alone were based on Mowatt et al,[65] the relative risk of recurrence after HAL-guided TURBT was based on Burger et al,[26] and other inputs were informed by the authors' survey of clinical experts. Utilities were derived from the work of Kulkarni et al,[63] where health state utilities were assigned for bladder cancer and metastases, and disutilities were assigned for procedures (e.g., TURBT, cystectomy). Cost inputs were not provided, but were explained in the methods as being informed by a clinical expert. The probabilistic analysis found HAL-guided TURBT was dominant and, at a willingness-to-pay of €20,000 per QALY, 100% of simulations were cost-effective. Sensitivity analyses were conducted altering various parameters and the results remained robust; specifically, HAL-guided TURBT remained cost-effective from a time horizon as short as 2 years and longer.

Table 9: Results of Economic Literature Review—Summary

Author, Year, Country	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Malmstrom et al, 2009[59] Sweden	Cost-consequence analysis Series of decision tree models Swedish health service perspective 1-year time horizon No discount rate	Patients with MIBC and NMIBC Population characteristics not provided	HAL-guided TURBT WL-guided TURBT	Total cystectomies[a]: HAL: 29 WL: 52 Total TURBTs[a]: HAL: 2,266 WL: 2,446 Total monitoring cystoscopies[a]: HAL: 3,890 WL: 3,919	2008 Swedish kronas (SEK) Total cost[a]: HAL: 69,869,488 WL: 71,191,201	NA
Garfield et al, 2013[60] US	Cost–utility analysis Series of decision tree models Health care payer perspective 5-year time horizon No discount rate (not specified)	Patients with suspected new or recurrent NMIBC Population characteristics not provided	HAL-guided TURBT WL-guided TURBT	Total utility[b]: HAL: 4.9 WL: 4.4	2011 US dollars ($USD) Total cost: HAL: 25,921 WL: 30,581	HAL was dominant[c]
Roupret et al, 2015[62] France	Cost–utility analysis Decision tree and Markov model French health care system perspective Lifetime time horizon 2.5% discount rate	Patients diagnosed with symptoms consistent with NMIBC; 82.2% male	HAL-guided TURBT WL-guided TURBT	Total QALYs: HAL: 11.29 WL: 11.19 Total LYG: HAL: 15.31 WL: 15.25	2013 Euros (€) Total cost: HAL: 22,967 WL: 23,813	HAL was dominant[c]

Author, Year, Country	Analytic Technique, Study Design, Perspective, Time Horizon	Population	Intervention and Comparator	Results		
				Health Outcomes	Costs	Cost-Effectiveness
Klaassen et al, 2017[6] Canada	Cost-effectiveness analysis Decision tree and Markov model Ontario health care system perspective 5-year time horizon No discount rate (not specified)	Patients with suspected new or recurrent NMIBC Population characteristics not provided	HAL-guided TURBT WL-guided TURBT	Total recurrences: HAL: 0.38 WL: 0.48 Total bed days: HAL: 2.03 WL: 2.33	2016 Canadian dollars ($CAD) Total cost: HAL: 11,554 WL: 10,182	Cost per recurrence prevented: $28,463
Gakis et al, 2019[64] Germany	Cost-utility analysis Decision tree and Markov model German health care system perspective Lifetime time horizon 3.5% discount rate	Patients diagnosed with NMIBC Mean age 67 years	HAL-guided TURBT WL-guided TURBT	Total QALYs: HAL: 8.14 WL: 8.07 Total LYG: HAL: 11.08 WL: 11.04	2018 Euros (€) 5-year total cost: HAL: 16,144 WL: 16,680	HAL was dominant[c]

Abbreviations: HAL, hexaminolevulinate; LYG, life-years gained; MIBC, muscle-invasive bladder cancer; NA, not applicable; NMIBC, non-muscle-invasive bladder cancer, QALY, quality-adjusted life-years; TURBT, transurethral resection of bladder tumour; UK, United Kingdom; US, United States; WL, white light.

[a]Outcomes were not calculated at a per-person level and therefore reflect the aggregate totals from the entire population.

[b]The authors defined a scale of "utility or effectiveness" from 0 (bladder cancer) to 1 (cancer free) for patients, and 0.75 for recurrence monitoring, etc.

[c]Dominant: HAL-guided TURBT was less costly and more effective than TURBT using white light alone.

Applicability of the Included Studies

Appendix 8, Table A8, provides the results of the applicability checklist for economic evaluations applied to the included studies. All five studies were deemed partially applicable to the research question.

Despite Klaassen et al[6] conducting their analysis from the Ontario health care payer perspective, we did not deem the study to be directly applicable. Major factors contributing to this assessment included the lack of NBI-guided TURBT as a comparator, the fact that no common health economic outcomes (i.e., life-years gained or quality-adjusted life-years) for health technology assessments were used, and the absence of reported discounting.

Discussion

The economic evidence review identified five studies with differing methodological approaches to evaluating the cost-effectiveness of HAL-guided TURBT compared with TURBT using white light alone for suspected NMIBC. All cost–utility analyses found HAL was dominant (lower cost and more effective) over white light, and the cost-consequence analysis also favoured HAL. The single cost-effectiveness analysis from an Ontario health system perspective found HAL was more expensive than white light ($11,554 vs. $10,182) but had better health outcomes, resulting in an ICER of $28,463 per recurrence prevented.[6] We found no studies evaluating the cost-effectiveness of NBI-guided TURBT for suspected NMIBC. The majority of the identified economic evaluations shared a similar model structure, categorizing patients based on their post-TURBT risk levels and evaluating disease progression and recurrence over time. Furthermore, the majority of studies also declared competing industry interests.

Despite the commonality of HAL being cost-effective across the studies, they had some notable differences. The average cost per patient was noticeably higher in the studies from France and the United States.[60,62] Interestingly, the US study reported the highest average cost despite omitting the capital cost of the Karl Storz D-Light C system, necessary equipment to conduct HAL-guided TURBT.[60] Another difference was the sources used to inform the clinical benefits of HAL-guided TURBT. For example, Malmstrom et al[59] included studies on both HAL and 5-ALA to inform HAL-specific parameters.

Most cost–utility analyses identified in the economic evidence review derived their utility scores using a common source that resulted in reduced accuracy. These utility values were based on the work of Kulkarni et al,[63] who used the standard gamble method to derive the utility of an uncomplicated post-cystectomy health state, based on feedback from 25 urologists rather than people with bladder cancer. Unfortunately, using physician responses as a proxy for patients deviates from recommended methodologies and is likely subject to measurement bias. Additionally, Kulkarni et al[63] derived other health state utility values for people with bladder cancer based on what the authors felt were comparable health states from other fields of medicine. Although the authors acknowledged the literature in this field on health-related quality of life was limited at the time, since the original publication, these limited utility scores have continued to be used 10 years later and appear in the most recent cost–utility analysis we found.[64]

Conclusions

The economic literature review identified five studies comparing cystoscopy guided by HAL and by white light alone for people undergoing their first TURBT for suspected NMIBC. No studies were identified evaluating NBI-guided TURBT. Overall, the identified literature found HAL-guided TURBT was likely to be cost-effective: in three studies HAL was dominant (less costly and more effective) over white light, and in one study from Ontario HAL was more effective but more costly.

Primary Economic Evaluation

The published economic evaluations identified in the economic literature review only addressed one intervention of interest. Owing to this and other limitations of the identified studies, such as differing perspectives and outcomes, we conducted a primary economic evaluation.

Research Question

What is the cost-effectiveness of hexaminolevulinate hydrochloride (HAL) or narrow band imaging (NBI) as an adjunct to white light during first transurethral resection of bladder tumour (TURBT), compared with TURBT using white light alone, in people with suspected non-muscle-invasive bladder cancer (NMIBC), from the perspective of the Ontario Ministry of Health?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[66]

Type of Analysis

We conducted a cost–utility analysis to determine the costs and health outcomes (i.e., quality-adjusted life-years [QALYs]) associated with each intervention. We chose this type of analysis because utility inputs are available and a generic outcome measure such as QALYs allows decision-makers to make comparisons across different conditions and interventions. The outcomes reported are total costs and total QALYs for each intervention, and incremental cost per QALY gained. For this analysis, incremental costs and QALYs are key outcomes considered by decision-makers, while total costs and QALYs of treatment options are informative measures for decision-makers.

Our reference case and sensitivity analyses adhered to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines[67] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions.

Target Population

Our target population was people undergoing their first TURBT for suspected non-muscle-invasive bladder cancer. The use of cystoscopy for bladder cancer diagnosis or surveillance or for subsequent TURBTs were considered out of scope, and so were not evaluated.

Based on Ontario data, the model's population was on average 73 years old and consisted of 75% males and 25% females.[68]

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

According to the Ontario Health (Cancer Care Ontario) clinical care pathway map for bladder cancer, people with symptoms suggestive of bladder cancer should receive various tests (e.g., urinalysis, urine cytology), as well as a diagnostic flexible cystoscopy to examine the lining of the bladder.[30] If suspicious lesions indicative of bladder cancer are seen during the cystoscopy, the person should undergo an

inpatient TURBT procedure (using a rigid cystoscope) to remove detected lesions for pathological examination. This examination determines whether the lesions are cancerous, whether they have invaded the muscles of the bladder, and how aggressive the cancer is (tumour grade). As described in the Background, above, TURBT is traditionally conducted using white light; enhanced visualization methods for TURBT include HAL and NBI. HAL is a form of fluorescence cystoscopy that illuminates cancer cells, while NBI filters the white light into blue and green wavelengths that improve visibility of blood vessels of the tumour. During the TURBT procedure, surgeons can easily switch from NBI or HAL to white light without surgical instrument changes. Both these technologies are adjunctive to TURBT using conventional white light.

Table 10 summarizes the interventions evaluated in the economic model. For this economic analysis we conducted evaluations for HAL-guided and NBI-guided TURBT compared with TURBT using white light alone.

Table 10: Interventions and Comparators Evaluated in the Primary Economic Model

Interventions	Comparator	Population	Outcome
HAL-guided TURBT NBI-guided TURBT	WL-guided TURBT	People undergoing their first TURBT for suspected NMIBC	Costs QALYs ICER

Abbreviations: HAL, hexaminolevulinate hydrochloride; ICER, incremental cost-effectiveness ratio; NBI, narrow band imaging; NMIBC, non-muscle-invasive bladder cancer; QALYs, quality-adjusted life years; TURBT, transurethral resection of bladder tumour; WL, white light.

Time Horizon and Discounting

We used a 15-year time horizon in our reference case analysis, which approximates the longest-term data available for NMIBC recurrence and progression.[9] Given the population's average age was 73 years, this time horizon captured the majority of the simulated patients' life expectancy. We also conducted scenario analyses with time horizons of 1 and 5 years to represent the longest studies of comparative recurrence rates after TURBT guided by white light versus NBI and HAL, respectively.[43,45]

In accordance with the CADTH guidelines,[67] we applied an annual discount rate of 1.5% to both costs and QALYs incurred after the first year.

Model Structure

We developed a Markov microsimulation model to estimate the long-term clinical and economic outcomes following HAL-guided and NBI-guided TURBT and TURBT using white light alone. The cycle length was 3 months, which represents the conventional interval between follow-up appointments for NMIBC. The model was built using TreeAge Pro 2020.[69]

The model included five states:

- **First TURBT:** individuals undergoing their first TURBT procedure, who then transition to one of two health states representative of their initial bladder cancer diagnosis (i.e., NMIBC, local muscle-invasive)
- **NMIBC**: individuals who are diagnosed with NMIBC and assigned a risk level, which impacts their treatment pathway, follow-up time, progression, and cancer-specific mortality rate. This state also accounts for recurrence, which alters a patient's risk level
- **Local muscle-invasive**: individuals whose bladder cancer has progressed to invading local muscle. This state accounts for progression and has a distinct cancer-specific mortality rate
- **Metastases**: individuals whose bladder cancer has spread beyond the bladder. This state has a distinct cancer-specific mortality rate
- **Death**: an absorbing state accounting for both the cancer-specific and general mortality in the cohort over time

In the model, people start with suspected bladder cancer in the TURBT state, where following the procedure and its pathology report, they are diagnosed with NMIBC or local muscle-invasive disease and transition to those health states. People do not initially transition to the metastases health state as this advanced stage is often determined before the first TURBT; therefore, it would be unlikely for them to undergo an initial NBI-guided or HAL-guided TURBT (Girish Kulkarni, MD, and Chris Morash, MD, email communications, January 2021). As all patients undergo TURBT before the stage of their bladder cancer is fully identified, we assumed that the clinical benefit of reduced recurrence of non-muscle-invasive tumours for NBI- and HAL-guided TURBT would not apply to those initially transitioning to the local muscle-invasive health state. Therefore, these individuals incur the additional procedural costs of HAL and NBI without our study's main clinical benefit (i.e., reduced NMIBC recurrence rate, compared with those receiving TURBT guided by white light alone).

Following TURBT, most people transition to NMIBC where they are assigned a European Organization for Research and Treatment of Cancer (EORTC) risk score: low, intermediate, or high. The risk score indicates a person's prognosis or risk of the cancer progressing and, in both clinical practice and our economic model, dictates their treatment pathway. The treatment pathway for NMIBC in our model approximates the care outlined in the bladder cancer pathway map published by Ontario Health (Cancer Care Ontario).[30] For example, low-risk patients have a follow-up at 3 and 12 months post TURBT, followed by annual follow-up for 5 years; high-risk patients have a follow-up every 3 months for 2 years, then every 6 months for 2 years, followed by indefinite annual follow-ups. Individuals' initial risk score can also advance one risk category (i.e., low risk to intermediate risk) on their first tumour recurrence. In the reference case, we assumed risk category changes would only impact the low-risk group; people with initially intermediate risk could not increase to high risk in the event of their first recurrence. Treatment pathways post recurrence vary depending on whether the recurrence is considered early (≤ 12 months) or late (> 12 months). To simplify the post-recurrence pathway, we assumed that, at recurrence, those at low or intermediate risk were staged as having a low-grade Ta (noninvasive papillary carcinoma), while those at high risk were assumed to remain high risk. In addition to being at risk of recurrence while in the NMIBC health state, patients are also at risk of progression to local muscle-invasive bladder cancer and at risk of death due to NMIBC-specific mortality.

People in the local muscle-invasive health state follow a simplified pathway that approximates the bladder cancer pathway map by Ontario Health (Cancer Care Ontario).[30] Specifically, they either undergo a radical cystectomy (surgery to remove the bladder) or decide to pursue bladder-preserving treatment. For model simplification, we costed bladder-preserving treatment (chemoradiation, chemotherapy alone, or radiation alone) as a course of external beam radiation therapy, consisting of therapy sessions 5 days per week for 6 weeks. Ongoing follow-up costs for monitoring were also included and consisted of chest imaging and CT urograms (imaging of the bladder and urinary tract). While in the local muscle-invasive health state, patients are at risk of progressing to the metastases or death health states due to mortality rates specific to local muscle-invasive bladder cancer.

Those progressing to the metastases health state are at elevated risk of dying based on mortality rates specific to metastatic bladder cancer. For model simplification, the cost of this health state consisted of palliative care costs, and its full cost was incurred upon death (i.e., cancer-specific mortality).

In addition to the previously mentioned transitions, throughout the model individuals have a risk of death based on Canadian age- and sex-specific life tables.[70] This general mortality rate is in addition to the cancer-specific mortality noted above.

Figure 8 presents a simplified diagram of the model structure that we used to simulate the care that people with bladder cancer receive over time, following their first TURBT guided by either white light alone, HAL, or NBI. Appendix 9 (Figures A3 to A6) shows the model's detailed clinical pathway, which approximates the required steps within the bladder cancer pathway map published by Ontario Health (Cancer Care Ontario).[30]

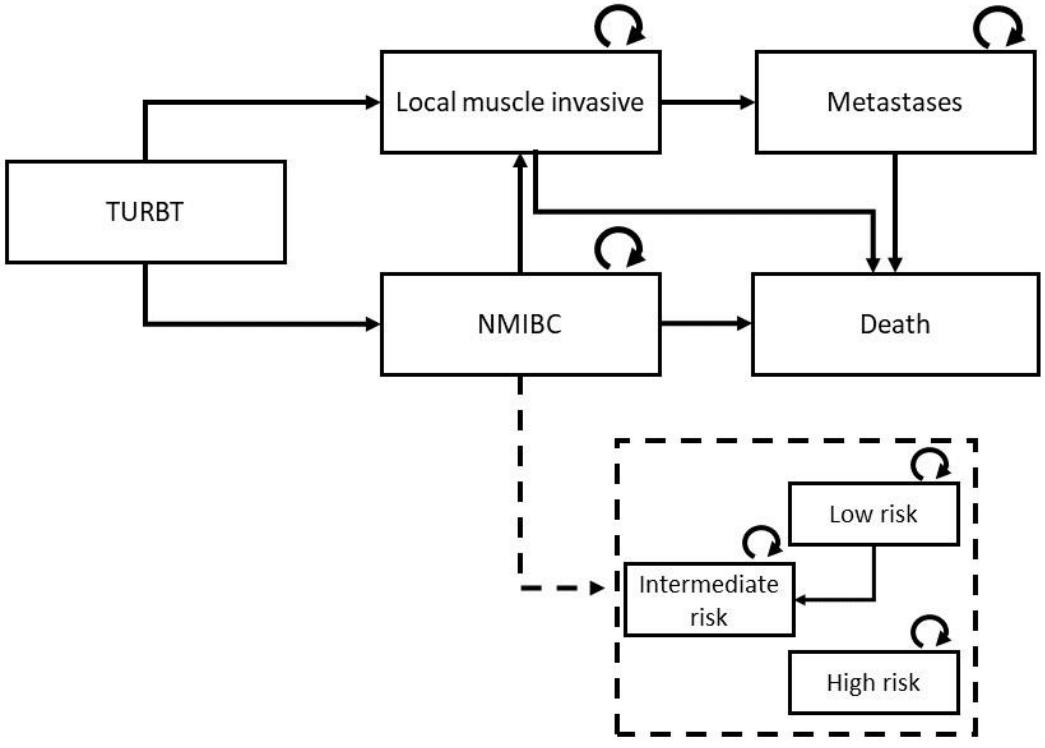

Figure 8: Model Structure

Abbreviations: NMIBC, non-muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumour.

Main Assumptions

The model's main assumptions were as follows:

- Patients do not progress directly from the NMIBC state to the metastases state, circumventing the local muscle-invasive state
- After the first TURBT, all future TURBTs are conducted with white light
- 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 tumour recurrence follows the same progression rate as someone who initially diagnosed at that risk level (i.e., start at time zero)

Clinical Outcomes and Utility Parameters

HEALTH STATE AND EVENT OCCURRENCES

Table 11 summarizes the proportion of people in the model diagnosed with bladder cancer at each stage and risk level.

As previously stated, those with an initial diagnosis of metastatic bladder cancer are often diagnosed before a first TURBT. Therefore, we assumed it would be unlikely for them to undergo an initial NBI-guided or HAL-guided TURBT. We recalculated the proportions to account for this change, resulting in 80% of people being diagnosed with NMIBC following their first TURBT (low risk: 17.7%, intermediate risk: 40.0%, high risk: 22.3%). The remaining 20%, diagnosed with local muscle-invasive bladder cancer following TURBT, represents a group of people who would incur the additional cost of these enhanced visualization methods but not benefit from the evaluated clinical benefit of reduced cancer recurrence.

Table 11: Initial Bladder Cancer Diagnosis

Model Parameter	Proportion, %	Reference
Non-muscle-invasive	75.0	Mowatt et al, 2010[65]
Low risk	*22.1*	Karaolides et al, 2012[44]
Intermediate risk	*50.0*	Karaolides et al, 2012[44]
High risk	*27.9*	Karaolides et al, 2012[44]
Muscle-invasive	25.0	Mowatt et al, 2010[65]
Local	*75.0*	Mowatt et al, 2010[65]
Metastases	*25.0*	Mowatt et al, 2010[65]

Figures 9, 10, and 11 show the cumulative probabilities of recurrence, progression, and cancer-specific mortality in the NMIBC health state. The figures were digitized from their original source publications using the online platform WebPlotDigitizer.[71] The probabilities vary by risk score, where high-risk patients are more likely than those in other risk categories to have any events. Data on recurrence were defined as time to first recurrence; therefore the model only incorporates the first recurrence. In cases where event data do not reach the time horizon, the last value was carried forward when calculating the probability of event occurrence. As previously stated, in the event of a recurrence, an individual may increase one risk level (from low to intermediate), which in turn increases their risk of cancer-specific mortality and disease progression. If an individual in the NMIBC state progresses, they transition to the local muscle-invasive health state. These cumulative probabilities, shown in Figures 9, 10, and 11, were converted into transitional probabilities by first pulling the cumulative values at each 3-month time point (i.e., model cycle length). Then we calculated the probability of the event occurring for each time point as the percentage of patients with an event at the specific time point divided by the patients at risk at that same specific time point.

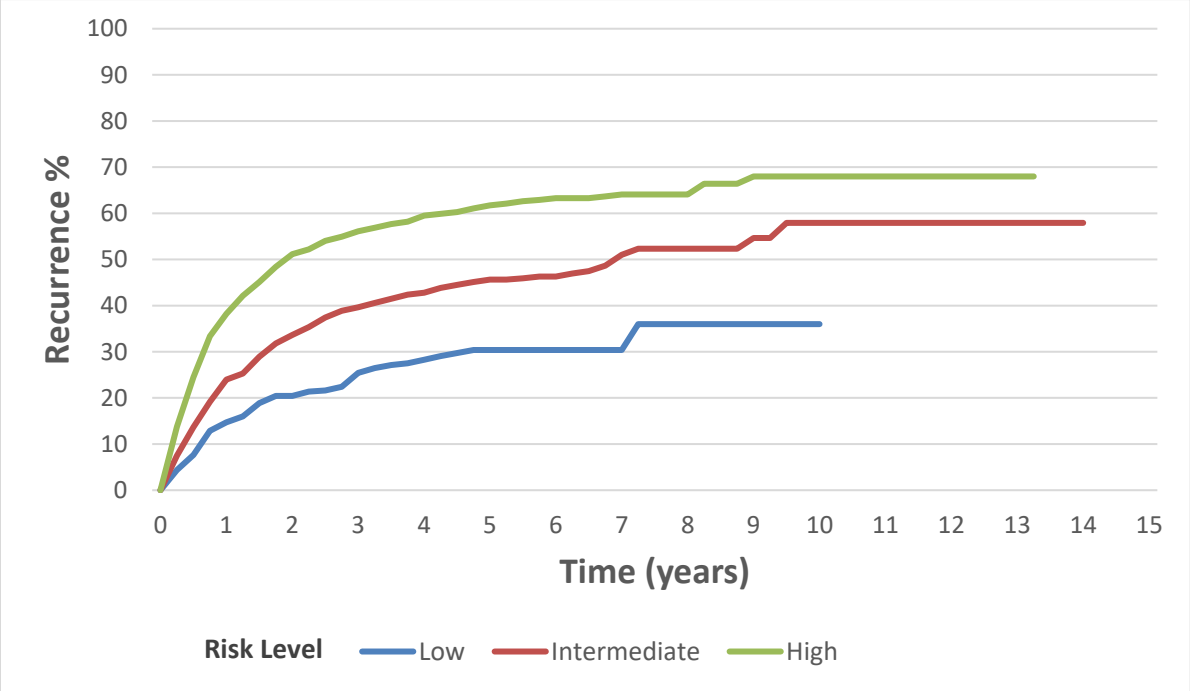

Figure 9: Cumulative Time to First Recurrence in People With Non-muscle-invasive Bladder Cancer, by Risk Level

Source: Sylvester et al, 2006.[9]

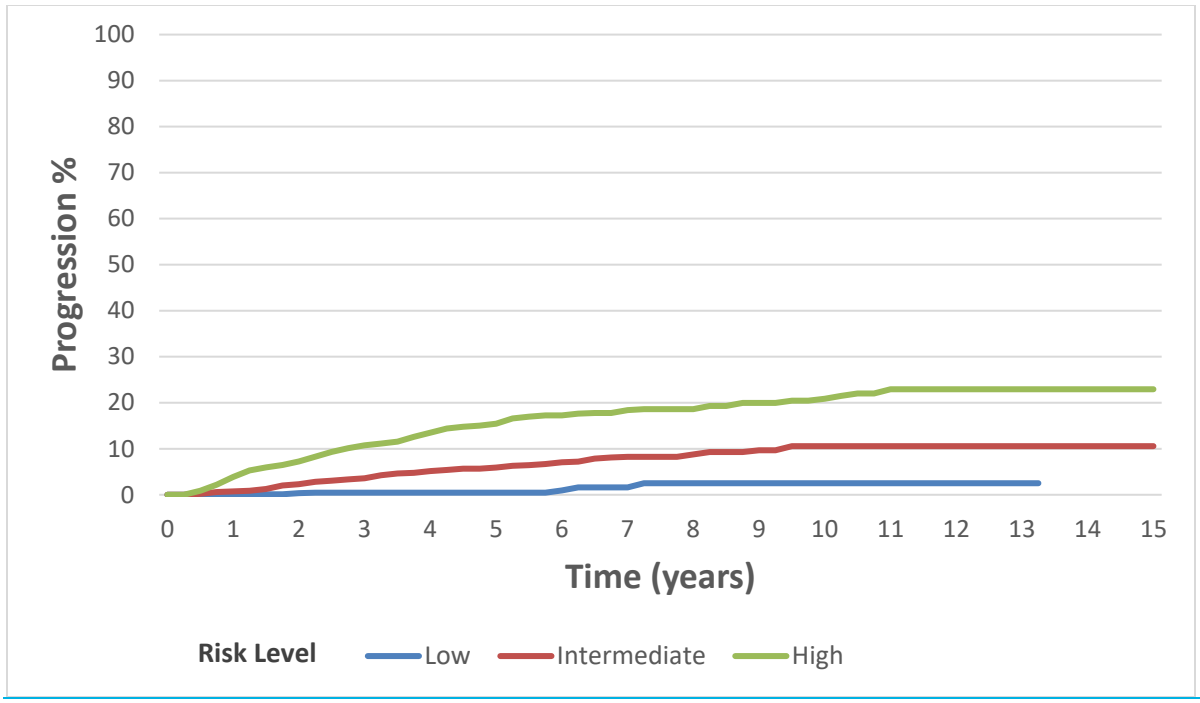

Figure 10: Cumulative Time to Local Muscle-Invasive Progression in People With Non-muscle-invasive Bladder Cancer, by Risk Level

Source: Sylvester et al, 2006.[9]

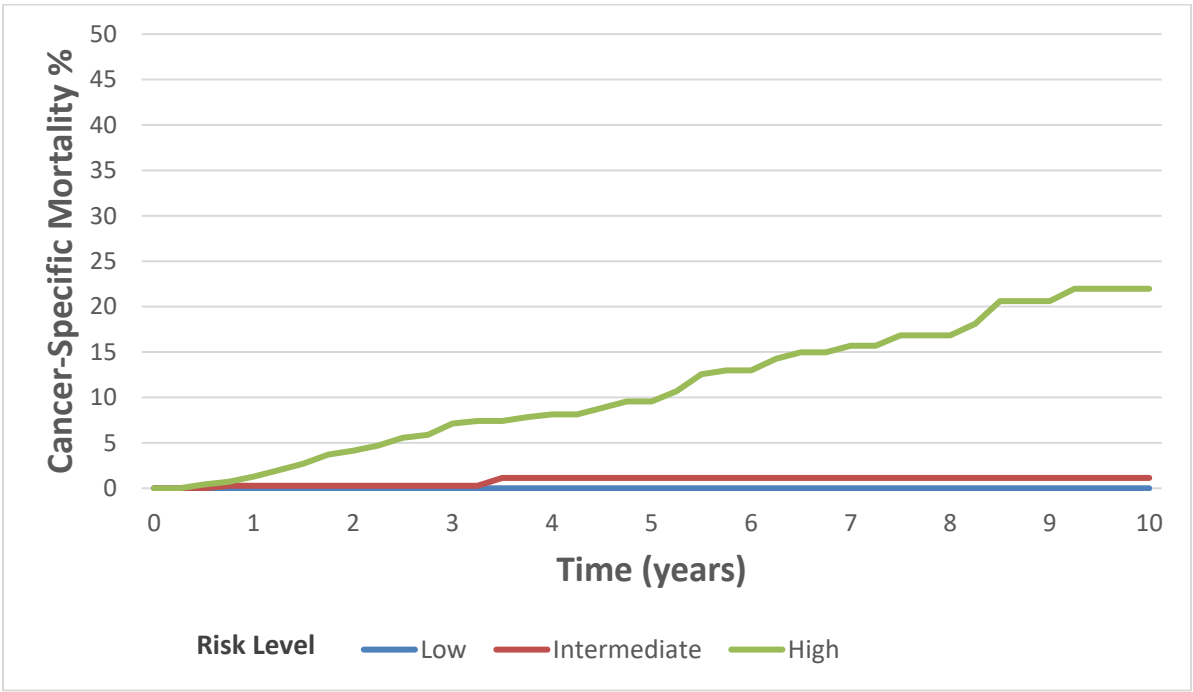

Figure 11: Cumulative Cancer Mortality in People With Non-muscle-invasive Bladder Cancer, by Risk Level

Source: Millan-Rodriguez et al, 2000.[72]

Table 12 lists the results of our indirect treatment comparison evaluating the relative risk of recurrence across all interventions (i.e., TURBT guided by HAL, NBI, and white light alone). See the Clinical Evidence section of this report for details on the methodology. We found that HAL-guided TURBT had significantly lower recurrence rates at 12 months compared with white light alone, while NBI-guided TURBT was not significantly different than white light. The results of this indirect treatment comparison drive the primary difference between interventions in our model. Specifically, recurrences immediately result in costlier treatment pathways, but also have a cascading effect by changing the patient's risk level (from low to intermediate risk), which in turn increases the risk of progression and cancer-specific mortality. Based on consistent long-term results on relative risk seen in the literature,[43,44,47] we used this 12-month recurrence rate over the model's time horizon.

Table 12: Meta-analyzed Evidence for 12-Month Recurrence Rates

	Direct Evidence		Indirect Evidence
Comparison	Number of Studies	Relative Risk (95% CI)	Relative Risk (95% CI)
HAL vs. white light	3[a]	0.70 (0.51–0.95)	0.72 (0.52–0.98)
NBI vs. white light	2[b]	0.94 (0.75–1.19)	0.95 (0.75–1.19)
HAL vs. NBI	0	NA	0.76 (0.51–1.11)

Abbreviations: CI, confidence interval; HAL, hexaminolevulinate hydrochloride; NA, not applicable; NBI, narrow band imaging.
[a]*Sources: Dragoescu et al, 2017[43]; O'Brien et al, 2013[47]; Karaolides et al, 2012.[44]*
[b]*Sources: Naito et al, 2016[46]; Kim et al, 2018.[45]*

Figures 12 and 13 show the cumulative probabilities for progression and mortality in the local muscle-invasive and metastases health states. As seen, once individuals progress from NMIBC to one of these two health states, their risk levels have no impact on event probabilities. Similar to the cumulative probabilities for non-muscle-invasive disease, in cases where event data do not reach the time horizon, the model carried forward the last value.

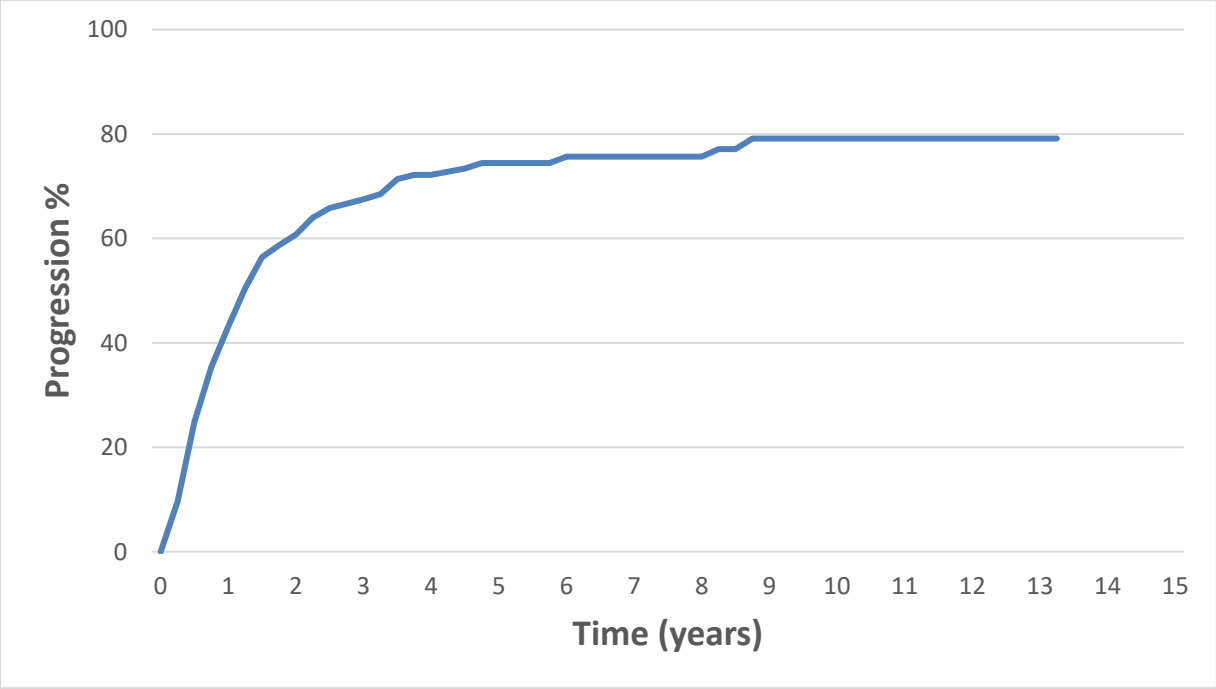

Figure 12: Cumulative Time to Metastases Progression in People With Local Muscle-Invasive Bladder Cancer

Source: Kwon et al, 2014.[73]

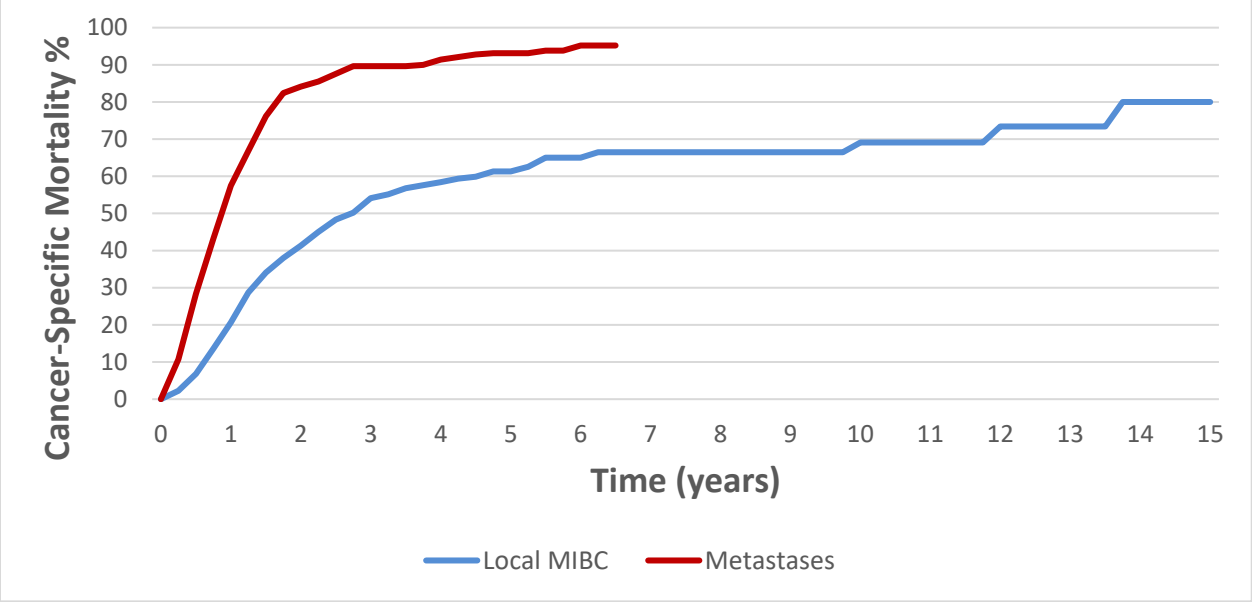

Figure 13: MIBC and Metastatic Cancer Cumulative Cancer Mortality in People With Local Muscle-Invasive and Metastatic Bladder Cancer

Abbreviation: MIBC, muscle-invasive bladder cancer.
Sources: Kwon et al, 2014[73] *(MIBC); von der Maase et al, 2005*[74] *(metasteses).*

MORTALITY

In addition to cancer-specific mortality, we also used age- and sex-specific mortality rates from the Ontario general population to model general mortality.[70]

HEALTH STATE UTILITIES

A health state utility represents a person's preference for a certain health state or outcome, such as having bladder cancer. Utilities are often measured on a scale ranging from 0 (death) to 1 (full health) and can be derived using various methods, including common questionnaires such as the Short-Form Six-Dimension (SF-6D) and the EQ-5D.

We performed a targeted literature search in MEDLINE for health state utility values on April 15, 2020, to retrieve studies published from database inception until the search date. We based the search on the population of the clinical search strategy with a methodologic filter applied to limit retrieval to health state utility values.[75] See Appendix 1 for our literature search strategies, including all search terms.

Utility data are summarized in Table 13, and all values were derived from published EQ-5D scores. The two utility values for NMIBC are differentiated by whether one had a recurrence. Similarly, the local muscle-invasive health state has two utility values. The lower value represents people who recently underwent a radical cystectomy, while those who are 2 or more years post cystectomy and have not progressed to metastases have a higher utility value. Given a lack of data, we assumed those undergoing bladder-preserving treatment had similar utility values to those undergoing cystectomy, and the utility value in the metastases health state would approximate those with local muscle-invasive bladder cancer who recently underwent a radical cystectomy.

Table 13: Utilities Used in the Economic Model

Health State	Utility	SE	Reference
NMIBC			
Pre-recurrence	0.846	0.006	Cox et al, 2020[76]
Post-recurrence	0.763	0.026	Cox et al, 2020[76]
Local Muscle-Invasive			
Early MIBC[a]	0.746	0.037	Cox et al, 2020[76]
Late MIBC[b]	0.840	0.018	Mak et al, 2016[77]
Metastases	0.746	0. 037	Assumption

Abbreviations: SE, standard error; NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer.
[a]Early MIBC was defined as < 2 years in the local muscle-invasive health state.
[b]Late MIBC was defined as ≥ 2 years in the local muscle-invasive health state.

Cost Parameters

We included all relevant costs that individuals incurred following TURBT. These costs included:

- Professional fees
- Hospitalization and day surgery costs

- Diagnostic tests
- Laboratory fees
- Equipment and consumable costs

All costs were reported in 2020 Canadian dollars. Cost inputs were obtained from standard Ontario sources and the published literature. The fees for professional visits, procedures, and consultations were obtained from the Ontario Schedule of Benefits for Physician Services.[78] Both inpatient and day surgery hospitalization costs were obtained from the Ontario Case Costing Initiative (OCCI).[79] Diagnostic and laboratory fees were obtained from the Ontario Schedule of Benefits for Laboratory Services.[80]

Table 14 presents definitive costs used in each health state, while other costs, as outlined in Table 15, can be incurred in each state depending on an individual's treatment pathway. We assumed that the costs of NBI-guided TURBT and TURBT using white light alone are equal, as the equipment needed for NBI is widely available in equipment being used for conventional TURBT. HAL-guided TURBT has the additional consumable cost of the HAL solution, priced at $708 per procedure, as well as the added nursing time to instill HAL via catheter. Equipment costs for HAL include the incremental cost ($10,000) of all required equipment to enable the use of HAL during TURBT, compared with standard white light equipment (~$75,000). We distributed these capital costs among each HAL-guided TURBT procedure, and calculated a value using the average yearly number of patients treated, the number of anticipated facilities, and assuming a 5-year lifespan of equipment (see Table 14, footnote b). Radical cystectomy and external beam therapy are one-time costs for the local muscle-invasive health state. We assumed 50% of individuals would choose external beam radiation therapy over cystectomy in order to preserve their bladder. For the metastases health state, individuals are assigned a cost up front, representing the average cost of palliative care once someone is diagnosed with metastatic bladder cancer.

Table 14: Health State Costs Used in the Economic Model

Variable	Unit Cost, $	Quantity	Total Cost, $	Reference
TURBT: NBI or WL alone			**2,306.76**	
Professional fees[a]				
Surgical	491.90		491.90	SoB Z634; E751
Anesthesia	15.29	6 BU; 3 TU	137.61	SoB Z634
Day surgery expenses	1,621.00		1,621.00	CCI 1.PM.87.BA
Pathology	18.75	3 blocks of tissue	56.25	SoBL L720
TURBT: HAL			**3,106.78**	
Professional fees[a]				
Surgical	491.90		491.90	SoB Z634; E751
Anesthesia	15.29	6 BU; 4 TU	152.90	SoB Z634
Day surgery expenses	1,621.00		1,621.00	CCI 1.PM.87.BA
Pathology	18.75	3 blocks of tissue	56.25	SoBL L720
Consumables	708.00		708.00	Klaassen et al, 2017[6]
Additional equipment[b]	10,000.00		52.73	Manufacturer
Additional nursing time[c]	48.00	3 nurses @ 10 min	24.00	Klaassen et al, 2017[6]

Variable	Unit Cost, $	Quantity	Total Cost, $	Reference
Local muscle-invasive: radical cystectomy			**31,921.80**	
Anesthesia consult	107.25		107.25	SoB A015
Professional fees[a]				
Surgical	1,250.30		1,250.30	SoB S453
Anesthesia	15.29	15 BU; 74 TU	1,360.81	SoB S453
Assistant	12.25	9 BU; 70 TU	967.75	SoB S453
Surgical	630.00		630.00	SoB S438
Anesthesia	15.29	7 BU; 4 TU	168.19	SoB S438
Assistant	12.25	7 BU; 4 TU	134.75	SoB S438
Inpatient expenses	27,410.00		27,410.00	CCI 1.PM.91.^^
Local muscle-invasive: external beam radiation therapy			**10,514.60**	
Radiation treatment planning	374.60		374.60	SoB X311
Ambulatory care expenses	338.00	6 wk (5 d/wk)	10,140.00	1.PM.27.JA
Metastasis[d]			**55,215.00**	
Palliative care	55,215		55,215.00	Klaassen et al, 2017[6]

Abbreviations: BU base units; CCI, Canadian Classification of Interventions; d, day(s); min, minute(s); HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging; SoB, Schedule of Benefits for Physician Services; SoBL, Schedule of Benefits for Laboratories Services; TU, time units; TURBT, transurethral resection of bladder tumour; wk, week(s); WL, white light.

[a]Basic and time units were multiplied by either the anesthesiologist unit fee ($15.29) or the assistant fee ($12.25) to calculate total cost.

[b]Total capital cost per case $= \frac{Equivalent\ Annual\ Capital\ Cost}{Number\ of\ Patients\ per\ Year\ per\ Centre}$, where Equivalent Annual Capital Cost $= \frac{Capital\ Cost}{\frac{1-\left(\frac{1}{1+r}\right)^{t}}{r}}$,

and where t is the service life (duration) in years and r is the annual interest rate.

[c]Based on Government of Canada wage data for registered nurses and registered psychiatric nurses in Ontario, where the median salary is approximately $36 per hour.[81] When the cost of employee benefits (i.e., employment insurance, pension plan, and extended health coverage) are estimated to be approximately 33% of salaries,[82] the total hourly cost of nursing rises to $48 per hour.

[d]Based on the high mortality rate of this health state, palliative care costs were incurred up front, upon entering the health state, and represented the average cost of palliative care once someone is diagnosed with metastatic bladder cancer.

SoB Z634: Endoscopy cystoscopy – excision of multiple tumours

CCI 1.PM.87.BA – excision partial, bladder – using endoscopic per orifice approach

SoBL L711: Cytology and histology – fluids

SoB A015: Anesthesia consult

SoB S453: Bladder cystectomy – complete – with ureteroileal conduit

SoB S438: Retroperitoneal lymph node dissection for bladder cancer

CCI 1.PM.91.^^: Excision radical, bladder

SoB X311: Radiation treatment planning – intermediate treatment planning

1.PM.27.JA: Radiation, bladder – using external beam

Table 15 lists other procedures and diagnostic tests that may occur within a patient's treatment pathway. Table A9 (Appendix 10) provides the parameter estimates (i.e., means and standard errors) of the costs of these treatments. As noted, we used the bladder cancer pathway map from Ontario Health (Cancer Care Ontario) to map the diagnostic, treatment, and follow-up care for people with NMIBC.[30] For patients who receive intravesical therapy (e.g., Bacillus Calmette-Guerin[BCG]) for intermediate- or high-risk NMIBC, we assumed they would have weekly therapy for 6 weeks, followed by intravesical maintenance therapy for 3 weeks, every 3 months, for a year. For neoadjuvant chemotherapy before radical cystectomy, we assumed patients would receive treatment every 3 weeks for 3 cycles.

Table 15: Treatment Pathway Costs Used in the Economic Model

Variable	Unit Cost, $	Quantity	Total Cost, $	Reference
Cystoscopy				
Professional fees[a]				
Surgical	71.00		71.00	SoB Z606
Anesthesia	15.29	5 BU; 2 TU	107.03	SoB Z606
Day surgery expenses	313.00		313.00	CCI 2.PM.70.BA
Intravesical Therapy[b]				
Professional fees[a]				
Surgical	90.20		90.20	SoB Z607 & E751
Anesthesia	15.29	5 BU; 2 TU	107.03	SoB Z607 & E751
Day surgery expenses	372.00		372.00	CCI 1.PM.35.^^
Systemic Chemotherapy[c]				
Ambulatory care expenses	2,236.00		2,236.00	CCI 1.ZZ.35.HA-M5
Ultrasound of Pelvis[d]				
Professional fee	26.55		26.55	SoB J162
Technical fee	48.75		48.75	SoB J162
Ultrasound of Abdomen[d]				
Professional fee	26.45		26.45	SoB J135
Technical fee	48.75		48.75	SoB J135
Chest X-Ray[d]				
Professional fee	12.40		12.40	SoB X092
Technical fee	28.15		28.15	SoB X092
CT Urogram	108.30		108.30	SoB X126
Urine Cytology	10.34		10.34	SoBL L711
Medical Oncologist Consult				
Initial	157.00		157.00	SoB A445
Radiation Oncologist Consult				
Initial	152.40		152.40	SoB A345
Urologist Consult				
Repeat	56.40		56.40	SoB A356

Notes for Table 15:
Abbreviations: BU, base units; CCI, Canadian Classification of Interventions; CT, computerized tomography; SoB, Schedule of Benefits for Physician Services; SoBL, Schedule of Benefits for Laboratories Services; TU, time units.
[a]Basic and time units were multiplied by either the anesthesiologist unit fee ($15.01) or the assistant fee ($12.04) to calculate total cost.
[b]Cost per weekly instillation.
[c]Cost per cycle.
[d]Diagnostic procedures excluded indirect costs (i.e., overhead expenses relating to the running of hospitals such as administration, finance, human resources, plant operations) and only included direct costs of nursing, diagnostic imaging, pharmacy, and labs (i.e., costs directly related to the provision of care to the patient).
SoB Z606: Endoscopy cystoscopy – diagnostic with or without urethroscopy
CCI 2.PM.70.BA: Inspection, bladder – using endoscopic per orifice approach
SoB Z607: Endoscopy cystoscopy – repeat within 30 days
SoB E751: Insertion of chemotherapeutic agent(s)
CCI 1.PM.35.^^: Pharmacotherapy (local), bladder – using cytotoxic antibiotic or using immunostimulant agent
CCI 1.ZZ.35.HA-M5: Pharmacotherapy, total body – using other antineoplastic – percutaneous approach
SoB J162: Diagnostic ultrasound – pelvis – complete
SoB J135: Diagnostic ultrasound – abdomen and retroperitoneum- complete
SoB X092: Diagnostic radiology – chest – three or more views
SoB X126: Computed tomography (CT) – abdomen – with and without IV contrast
SoBL L711: Cytology and histology – fluids
SoB A445: Medical oncology – consultation
SoB A345: Radiation oncology – consultation
SoB A356: Urology – repeat consultation

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Analysis

Following the CADTH guidelines,[67] we reported the sequential incremental cost-effectiveness ratios (ICERs). We ordered treatments by average total costs, from lowest to the highest. For sequential ICERs, after excluding treatments that were either dominated or subject to extended dominance, we calculated the ICER for a less costly comparator compared with the next more costly comparator. In addition to estimating the ICER for each comparison, we also used net monetary benefit (NMB) to evaluate the cost-effectiveness of the three included treatments.

We calculated the reference case of this analysis by using a Monte Carlo simulation with 5,000 outer loops to capture parameter uncertainty, and 1,000 inner loops to capture patient variability (i.e., cohort age). When we set distributions for variables within the model, the distributions used included gamma distributions for cost, beta distributions for utilities, and log normal distributions for relative risks. We calculated mean costs with credible intervals and mean QALYs with credible intervals for each intervention assessed. We also calculated the mean incremental costs with credible intervals, incremental QALYs with credible intervals, and ICERs for HAL-guided TURBT, NBI-guided TURBT, and TURBT guided by white light alone.

The results of the probabilistic analysis are presented in a cost-effectiveness acceptability curve. For each simulation, the treatment with the maximum NMB at the given willingness-to-pay (WTP) value was considered the most cost-effective among the three treatments we compared.[83] The probability of being

cost-effective for each treatment was equal to the proportion of the number of simulations for which this treatment had the highest NMB. Although not used as definitive WTP thresholds, including graphical indications of the location of the results relative to guideposts of $50,000 per QALY and $100,000 per QALY facilitates interpretation of the findings and comparison with historical decisions. We also present uncertainty quantitatively as the probability that an intervention is cost-effective at previously mentioned WTP guideposts. This uncertainty is also presented qualitatively, in one of five categories defined by the Ontario Decision Framework[83]: highly likely to be cost-effective (80%–100% probability of being cost-effective), moderately likely to be cost-effective (60%–79% probability), uncertain if cost-effective (40%–59% probability), moderately likely to not be cost-effective (20%–39% probability), or highly likely not to be cost-effective (0%–19% probability).

SCENARIO ANALYSES

We conducted several scenario analyses testing not only different input parameters, but also some of the model assumptions. For each scenario, we recalculated the mean incremental costs and QALYs for each treatment, along with the ICER. All scenarios were performed probabilistically.

Table 16 summarizes our scenario analyses, described here:

- In addition to scenarios with varied time horizons, one scenario altered the initial risk levels of people diagnosed with NMIBC, using risk levels reported in Mowatt et al, 2010[65]
- Similarly, another group of scenarios looked to alter how people's risk categories are reclassified following a recurrence, so that (i) there is no change in risk level; (ii) everyone moves up one risk level (i.e., intermediate can move to high, as well as low risk moving to intermediate risk); or (iii) all risk categories move to high risk following recurrence
- Another scenario analysis looked to exclude NBI-guided TURBT based on notes in the Ontario Health (Cancer Care Ontario) bladder cancer pathway map, which identifies HAL-guided TURBT as a possible adjunct during TURBT and NBI as an adjunct to diagnostic cystoscopy[30]
- We also conducted a combination scenario that excludes NBI and assumes no change in risk category following a recurrence. Another scenario tests how long the relative risk of recurrence should be applied in the model; this scenario assumes the potential protective effects of HAL-guided and NBI-guided TURBT, versus TURBT using white light alone, would only apply for the duration demonstrated in their longest respective studies
- Several scenarios explored costs:
    - One scenario looked at excluding the capital costs of cystoscopy equipment with capabilities for HAL-guided TURBT, thus assuming they are or will be equally priced with existing equipment used to conduct conventional TURBT using white light alone
    - Another scenario looked at the impact of negotiating a lower price for the solution used in HAL-guided TURBT (25% and 50% price reductions)
    - One scenario looked at only incurring the additional cost of a HAL-guided TURBT in patients with NMIBC (i.e., not those with advanced bladder cancer where HAL-guided TURBT has little to no impact on recurrence). As an individual's cancer stage is diagnosed only after a TURBT (except in the case of metastatic bladder cancer), the reference case assumes all patients suspected of bladder cancer are given HAL-guided TURBT. In this scenario, due to either a cost recovery agreement with the manufacturer,

or alternative means to identify bladder cancer stage before TURBT, the cost of a HAL-guided TURBT will only be incurred in those who can reap its benefit (i.e., reduced NMIBC recurrence)

- Cystoscopy costs were the focus of another scenario, which excluded the anesthesia fee listed in the Schedule of Benefits for Physician Services.[78] As surveillance cystoscopy is typically conducted without anesthesia, its anesthesia billing would then be replaced with a partial assessment fee of $26.70 (Schedule of Benefits code A354)
- Finally, we altered the treatment pathway for people in the local muscle-invasive health state to include a proportion of patients who would choose palliative care over radical cystectomy or bladder-preserving treatment. We assumed palliative care costs would be equal to those listed in the metastases health state

Table 16: Summary of Scenario Analyses

Parameter	Parameter/Assumption in Reference Case	Parameter/Assumption in Scenario Analysis
Time horizon	15 y	1 y, 5 y
Interventions	HAL, NBI	HAL
NMIBC initial risk level	22% low, 50% intermediate, 28% high	10% low, 45% intermediate, 45% high
Recurrence risk change	Low moves to intermediate and intermediate remains unchanged	No change in risk level; all move up one risk level; all move to high risk
NBI and recurrence risk change	Include NBI and low moves to intermediate	Exclude NBI; no change in risk levels
Duration of impact of HAL and NBI on recurrence risk	Model time horizon (15 y)	1 y, 5 y
HAL capital costs	Include incremental capital costs	Exclude capital costs, include total capital costs
HAL solution costs	Include full price ($708)	25% and 50% price reduction
TURBT guided by either HAL or NBI	Costs accrue to all new cases of bladder cancer	Costs accrue to only NMIBC cases
Cystoscopy costs	Include anesthesia fee	Exclude anesthesia fee and only include partial assessment fee
Local muscle-invasive treatment pathways	50% radical cystectomy, 50% bladder preserving	50% radical cystectomy, 10% bladder preserving, 40% palliative care

Abbreviations: HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging; NMIBC, non-muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumour; y, year(s).

Results

Reference Case Analysis

Table 17 presents the results of the sequential reference case analysis. TURBT guided by white light alone was dominated (more costly and less effective) by NBI-guided TURBT. When the non-dominated options were compared, HAL-guided TURBT had higher costs ($549) and QALY gains (0.044) compared to NBI-guided TURBT, resulting in an ICER of $12,618 per QALY gained. However, when HAL-guided and NBI-guided TURBT were both compared to TURBT using white light alone, the current standard of care, NBI-guided TURBT was dominant (less costly and more effective) and HAL-guided TURBT had an ICER of $9,615 per QALY gained.

Table 17: Reference Case Analysis Results

Strategy[a]	Average Total Costs (95% CrI), $	Incremental Cost, $[b,c]	Average Total Effects (95% CrI), QALYs	Incremental Effect (95% CrI), QALYs[c]	ICER,[c] $/QALY	White Light ICER,[c,d] $/QALY
NBI	19,713 (18,893; 20,526)	—	6.027 (5.719; 6.328)	—	—	Dominant[e]
White light	19,762 (18,962; 20,578)	—	6.019 (5.717; 6.319)	—	Dominated[f]	—
HAL	20,262 (19,412; 21,141)	549 (108; 920)	6.071 (5.719; 6.328)	0.044 (−0.030; 0.151)	12,618	9,615

Abbreviations: CrI, credible interval; HAL, hexaminolevulinate hydrochloride; ICER, incremental cost-effectiveness ratio; NBI, narrow band imaging; QALY, quality-adjusted life-year.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[c]Results may appear inexact due to rounding.

[d]This ICER assumed white light was the standard of care, so both NBI and HAL were compared against it.

[e]*Dominant* indicates NBI is less costly and more effective than white light.

[f]*Dominated* indicates white light is more costly and less effective than NBI.

Figure 14 presents the cost-effectiveness acceptability curve, which shows the probability of all treatments being cost-effective across a range of willingness-to-pay values. At commonly reported willingness-to-pay values of $50,000 per QALY and $100,000 per QALY, HAL-guided TURBT had the highest probability of being cost-effective: 69.16% and 74.62%, respectively. Based on these results, HAL-guided TURBT is moderately likely to be cost-effective.[83]

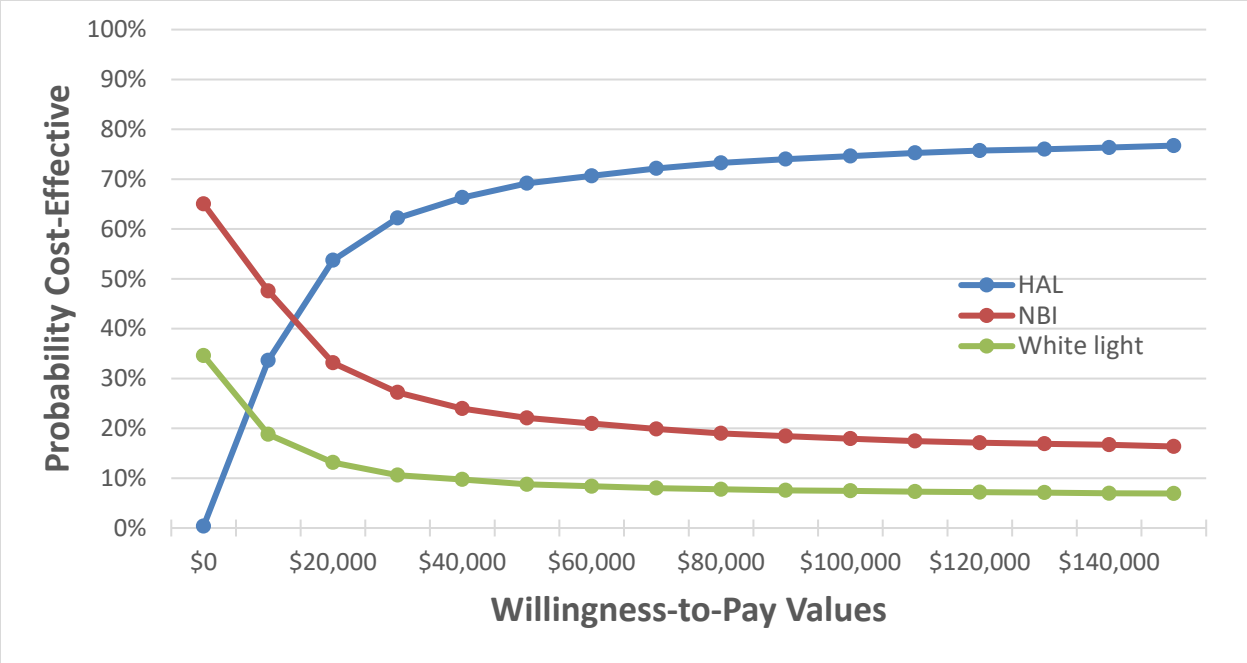

Figure 14: Cost-Effectiveness Acceptability Curve

Abbreviations: HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging; QALY, quality-adjusted life-year.

Scenario Analyses

Table 18 presents the results of all scenario analyses described above (see Table 16).

The results for HAL-guided TURBT were sensitive to the model's time horizon; however, TURBT using white light alone remained dominated (more costly and less effective) by NBI-guided TURBT. At a 1-year time horizon NBI-guided TURBT was moderately likely to be cost-effective (64.9%) compared with HAL-guided TURBT (0%) at a willingness-to-pay of $50,000 per QALY gained, and HAL-guided TURBT had an ICER of $423,099 per QALY gained. At 5 years, the probability of HAL-guided TURBT being cost-effective increased to 51.4% at a willingness-to-pay of $50,000 per QALY gained, indicating we are uncertain if it is cost-effective over the 5-year time horizon, but the ICER dropped to $37,869 per QALY gained.

The results of other scenario analyses did not substantially differ from the reference case results, which found HAL-guided TURBT to be the most cost-effective intervention. For one scenario, where the proportion of people with initially low-risk NMIBC was smaller (10%, versus 22% in the reference case), the ICER increased slightly from $12,618 to $20,349 per QALY. The scenario that excluded NBI-guided TURBT as a comparator resulted in HAL-guided TURBT having a lower ICER ($9,631) and a higher probability of being cost-effective (82.1%). Several scenarios evaluated how recurrences might change people's risk classification. Assuming there would be no change to someone's risk level following a recurrence had little impact on the reference case results; however, having all risk categories either move up one level or move to high risk after a recurrence led to ICERs below $4,000 per QALY gained, resulting in HAL-guided TURBT being highly likely to be cost-effective. Another scenario where HAL-guided TURBT is used only for patients with NMIBC (rather than for all new cases of bladder cancer) had little impact compared to the reference case results. A scenario that excluded capital costs had a marginal impact on the reference case, but when full capital costs were incorporated the ICER increased

slightly to $21,847 per QALY gained. When an alternative (less expensive) approach to costing surveillance cystoscopies was used, the results remained largely unchanged with an ICER of $13,139 per QALY gained. Finally, when palliative care was incorporated as a treatment pathway in the local muscle-invasive health state, thus decreasing the use of bladder-preserving therapy compared to the reference case, the ICER lowered slightly to $12,665 per QALY gained.

Table 18: Scenario Analysis Results

Strategy[a]	Average Total Costs, $	Average Total Effects, QALYs	ICER, $/QALY[b]	CE Probability, %[b,c]
Time Horizon				
1 year				
NBI	11,405	0.77	—	64.9
White light	11,406	0.77	Dominated[d]	35.0
HAL	12,203	0.78	423,099	0.0
5 years				
NBI	16,973	3.02	—	37.0
White light	17,009	3.01	Dominated[d]	11.6
HAL	17,592	3.03	37,869	51.4
Exclude NBI				
White light	19,762	6.02	—	17.8
HAL	20,262	6.07	9,631	82.1
Alternate NMIBC Initial Risk Levels				
NBI	23,274	4.71	—	25.9
White light	23,309	4.71	Dominated[d]	13.5
HAL	23,889	4.75	20,349	60.5
Recurrence Risk Change				
No change in risk level				
NBI	19,488	6.04	—	23.3
White light	19,529	6.03	Dominated[d]	10.3
HAL	20,080	6.08	14,435	66.4
All move up one risk level				
NBI	21,537	5.86	—	14.8
White light	21,651	5.84	Dominated[d]	2.4
HAL	21,766	5.93	3,017	82.8
All move to high risk				
NBI	22,042	5.81	—	13.9
HAL	22,169	5.89	1,477	84.2
White light	22,176	5.79	Dominated[d]	1.9

Strategy[a]	Average Total Costs, $	Average Total Effects, QALYs	ICER, $/QALY[b]	CE Probability, %[b,c]
Exclude NBI; No Change in Risk Level				
White light	19,529	6.03	—	15.6
HAL	20,080	6.08	11,285	84.4
Duration of Impact of HAL and NBI on Recurrence Risk				
1 year				
NBI	19,754	6.02	—	32.1
White light	19,762	6.02	Dominated[d]	19.6
HAL	20,514	6.05	33,816	48.3
5 years				
NBI	19,724	6.03	—	23.8
White light	19,762	6.02	Dominated[d]	10.7
HAL	20,335	6.07	15,719	65.5
HAL Capital Costs				
Exclude capital costs				
NBI	19,713	6.03	—	21.4
White light	19,762	6.02	Dominated[d]	8.6
HAL	20,210	6.07	11,407	70.0
Include full capital costs[e]				
NBI	19,713	6.03	—	26.9
White light	19,762	6.02	Dominated[d]	11.1
HAL	20,664	6.07	21,847	62.0
HAL Solution Price Reduction				
25% reduction				
NBI	19,713	6.03	—	19.9
White light	19,762	6.02	Dominated[d]	7.9
HAL	20,085	6.07	8,555	72.1
50% reduction				
NBI	19,713	6.03	—	17.8
White light	19,762	6.02	Dominated[d]	6.9
HAL	19,908	6.07	4,493	75.3
Initial HAL Costs Apply Only to NMIBC Cases				
NBI	19,713	6.03	—	20.1
White light	19,762	6.02	Dominated[d]	8.0
HAL	20,102	6.07	8,947	71.9

Strategy[a]	Average Total Costs, $	Average Total Effects, QALYs	ICER, $/QALY[b]	CE Probability, %[b,c]
Cystoscopy Costs				
NBI	18,728	6.03	—	22.2
White light	18,773	6.02	Dominated[d]	8.9
HAL	19,300	6.07	13,139	68.8
Local Muscle-Invasive Treatment Pathway				
NBI	18,213	6.03	—	22.1
White light	18,262	6.02	Dominated[d]	8.8
HAL	18,765	6.07	12,665	69.1

Abbreviations: CE, cost-effectiveness; HAL, hexaminolevulinate hydrochloride; ICER, incremental cost-effectiveness ratio; NBI, narrow band imaging; QALY, quality-adjusted life years.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Results may appear inexact due to rounding.

[c]Based on a probabilistic sensitivity analysis using a cost-effectiveness acceptability curve at a willingness-to-pay of $50,000/QALY gained.

[d]*Dominated* indicates white light is more costly and less effective than the previous less costly intervention.

[e]This scenario used the full cost of HAL equipment instead of the incremental cost used in the reference case (incremental cost of HAL equipment compared with white light equipment).

Discussion

The results of the reference case indicated that HAL-guided TURBT is likely to be cost-effective, with an ICER of $12,618 per QALY gained, compared with NBI-guided TURBT. Across various scenario analyses that tested model assumptions and alternative parameters, this trend was consistently observed, although the results were sensitive to shorter model time horizons. One reason these shorter time horizons were not selected for the reference case was because, as shown in Figure 9, the time to first recurrence does not begin to plateau until approximately 9 years after initial diagnosis. Therefore, a short time horizon likely fails to capture a significant proportion of the differential recurrence rates attributable to each intervention. Furthermore, as cancer recurrence leads to more costly treatment pathways, due to the need for more frequent follow-up, a short time horizon does not allow these differential costs to be fully accrued and accounted for, to overcome the higher cost of the first HAL-guided TURBT. In addition, the results of our clinical evidence review found HAL-guided TURBT likely increases 5-year recurrence-free survival compared with TURBT using white light alone, reinforcing the need for a longer time horizon in our reference case.

Our reference case sequential analysis found that the current standard of care, TURBT using white light alone, was more costly and less effective than NBI-guided TURBT. Furthermore, in a scenario analysis where white light was compared solely to HAL (NBI was excluded), HAL was highly likely to be cost-effective with an ICER of $9,631 per QALY gained. Across various scenario analyses, white light was consistently dominated (i.e., more costly and less effective) by NBI, and when the costs and QALYs for white light were compared with HAL over those same scenarios, favourable ICERs for HAL were the result. Our findings showed that compared with TURBT using white light alone, using either HAL or NBI as an adjunct to white light would be cost-effective for people with suspected NMIBC undergoing their first TURBT.

Although NBI as an adjunct to white light dominated white light alone across all reported analyses, there is some uncertainty in the literature regarding the use of NBI for TURBT. In Table 12 of this report, there was no significant difference in the reported 12-month recurrence rate when comparing NBI-guided TURBT and TURBT using white light alone. Therefore, we are uncertain whether the small incremental QALY gains of adding NBI during TURBT instead of using white light alone would reflect the real-world setting. Costs for NBI-guided TURBT were assumed equal to TURBT using white light alone, given the technology's wide dissemination in Ontario. Despite the technology's uptake, consultation with experts indicated that the use of NBI to guide TURBT is perceived to be low, comprising approximately 2% of all first TURBTs for suspected NMIBC (Girish Kulkarni, MD, and Chris Morash, MD, email communications, January 2021). This sentiment seems to be reflected in the Ontario Health (Cancer Care Ontario) bladder cancer pathway map, which considers NBI as an adjunct only to cystoscopy. As previously stated, we assumed that the costs for NBI-guided TURBT were equal to TURBT using white light alone. But results from our clinical evidence review, which reported a high false-positive rate for NBI-guided TURBT relative to TURBT guided by white light alone or by HAL as an adjunct, suggest there may be additional costs for using NBI not captured in our model. Therefore, based on all these findings, the model may be inaccurate in finding NBI-guided TURBT dominant (less costly and more effective) over TURBT using white light alone to visualize the bladder during TURBT procedures.

Scenario Analyses

We explored the impact of the additional capital costs needed for a HAL-guided TURBT versus standard white light. Despite equipment costing approximately $10,000 more for HAL-guided TURBT, this had little impact on the resulting ICERs, as evidenced by a scenario that excluded capital equipment costs. Another scenario included the full equipment costs for HAL-guided TURBT instead of the incremental costs, to represent a situation where the equipment would need to be purchased in addition to existing white light equipment. Although the probability of HAL-guided TURBT being cost-effective dropped from 69% to 62% (at a willingness-to-pay of $50,000 per QALY gained) and the ICER increased to $21,847 per QALY gained, most of the equipment used for HAL-guided TURBT is advertised as being multifunctional, allowing it to be used for other cystoscopy procedures that would typically use white light; therefore, we anticipate this scenario would be unlikely to occur in clinical practice. Based on both these results, equipment costs likely have minimal impact on the overall cost-effectiveness of HAL-guided TURBT.

Instead, the HAL solution itself is the larger drive, as it comprises most of the cost difference between HAL-guided TURBT and TURBT using white light alone. Scenario analyses on solution costs had marginal impact on the probability of cost-effectiveness, but price reductions did influence the ICER. To further explore the HAL solution cost, we conducted a threshold analysis between HAL-guided TURBT and TURBT using white light alone to find the price at which the HAL solution would result in an equivalent average total cost. This input was then adjusted within our reference case analysis and reported in Appendix 10, Table A10; we found that if the price of the HAL solution is reduced from $708 to $274, the average total cost per patient for HAL-guided TURBT and for TURBT using white light alone would be approximately equal.

Although HAL-guided TURBT is intended for treatment of NMIBC, the precise staging of the disease requires a TURBT to be completed. Thus, our model assumed that people ultimately diagnosed with local muscle-invasive bladder cancer would receive HAL-guided TURBT for their initial treatment. A scenario analysis explored the impact of excluding the incremental cost of a HAL-guided TURBT in patients with local muscle-invasive bladder cancer (as they do not benefit from reduced recurrence of NMIBC) and found the ICER decreased to $8,947 per QALY gained with a 71.9% probability of HAL-

guided TURBT being cost-effective at a willingness-to-pay of $50,000 per QALY gained. This resulted in a small marginal difference when compared to the reference case.

Cost-Effectiveness Literature

Overall, the results of our economic evaluation were consistent with earlier publications identified in our economic evidence review. Of the five studies we reviewed, four found HAL-guided TURBT was either less costly[59] or dominant (less costly and more effective) over TURBT using white light alone,[60,62,64] and the other study found HAL-guided TURBT was more costly but more effective in reducing recurrences.[6] Our results were likewise positive for HAL-guided TURBT, which we found likely to be cost-effective. Similar to Klaassen et al,[6] we also calculated the average total recurrences and cost per recurrence prevented (Appendix 10, Table A11) and found HAL-guided TURBT had higher costs but fewer recurrences compared to TURBT guided by white light alone.

Our analysis has distinct differences from other published cost-effective analyses and builds on their limitations. Previous cost–utility analyses based their utility values on a source that mainly derived bladder cancer health state utility values from what the authors felt were comparable health states from other fields of medicine (due to limited published evidence at the time).[63] Our model has updated these utility values with recent data from published EQ-5D scores to better approximate the preferences of the target population.[76,77] Our analysis also has several other advantages over previous studies, such as ensuring clinical inputs are specific to HAL and not a mixture of procedures using HAL or 5-ALA.

Strengths and Limitations

Our analysis had several strengths. It was the first cost–utility analysis on HAL-guided and NBI-guided TURBT from a Canadian perspective, and the first known model that used EQ-5D utility values specific to the target population. Another strength was the costing methodology used: we conducted micro-costing using Ontario-specific costs to capture local treatment pathways, thus resulting in costs that approximate the local setting.

Regarding local treatment pathways, our model evaluated both initial and downstream costs and benefits along the entire bladder cancer treatment pathway, from initial diagnosis to death. To our knowledge, our model was also the first to capture the costs of HAL-guided TURBT in people with NMIBC and people with local muscle-invasive disease, as both populations are expected to be treated with HAL-guided TURBT given that cancer staging is confirmed post TURBT. We also conducted extensive scenario analyses that analysed various model parameter and structural assumptions. Finally, our model is the first known economic analysis to evaluate NBI-guided and HAL-guided TURBT and TURBT using white light alone in people with bladder cancer.

Our analysis also had several limitations. As seen in Appendix 9, bladder cancer treatment pathways are both complex and situational and, for modelling purposes, require various assumptions and simplifications when costing. Furthermore, given the complexity of oncology as a therapeutic field, more advanced alternative modelling approaches for cancer progression are plausible. Despite these limitations, however, our model was designed to best incorporate all relevant costs and outcomes specific to the research question for decision-makers. Another limitation was the paucity of long-term comparative data on recurrence rates after NBI-guided (up to 1 year) and HAL-guided (up to 5 years) TURBT. To account for this limitation, scenario analyses explored differing assumptions about the duration of benefit from HAL-guided or NBI-guided TURBT, in terms of their impact on cancer recurrence. Despite finding relevant utility data, we did not have utility data specific to some health

states in the model. Therefore, our analysis was limited by required assumptions about people's preferences regarding metastatic bladder cancer (we assumed it likely has a lower utility value than local muscle-invasive bladder cancer) and about the utility value of undergoing bladder-preserving treatment. Finally, our analysis looked at the impact of using HAL and NBI during people's first TURBT; therefore, these results cannot infer the cost-effectiveness of using these technologies in subsequent TURBTs or for specific subpopulations such as high-risk patients with multiple recurrences.

Conclusions

Our economic analysis found that, in patients with suspected NMIBC undergoing their first TURBT, HAL-guided TURBT has on average higher costs and greater QALYs gained compared with NBI-guided TURBT or TURBT using white light alone. The results were sensitive to model time horizons. The ICER from sequential analysis of HAL versus NBI was $12,618 per QALY gained. At willingness-to-pay values of $50,000 and $100,000 per QALY gained, HAL-guided TURBT is likely to be cost-effective (69.1% and 74.6% probability of being cost-effective, respectively), compared with TURBT guided by NBI and by white light alone. Across commonly reported willingness-to-pay values, this result indicates HAL-guided TURBT is likely cost-effective in people with suspected NMIBC undergoing their first TURBT.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding hexaminolevulinate hydrochloride (HAL) and narrow band imaging (NBI) as an adjunct to white light during first transurethral resection of bladder tumour (TURBT) for people with suspected non-muscle-invasive bladder cancer (NMIBC)?

Methods

Analytic Framework

We estimated the budget impact of publicly funding HAL-guided TURBT and NBI-guided TURBT using the cost difference between two scenarios: (1) current clinical practice with minimal public funding for HAL (the current scenario) and (2) anticipated clinical practice with public funding for HAL-guided TURBT (the new scenario). Figure 15 presents the budget impact model schematic. As explained below, we assumed that NBI-guided TURBT carries no additional cost, so Figure 15 only refers to HAL-guided TURBT.

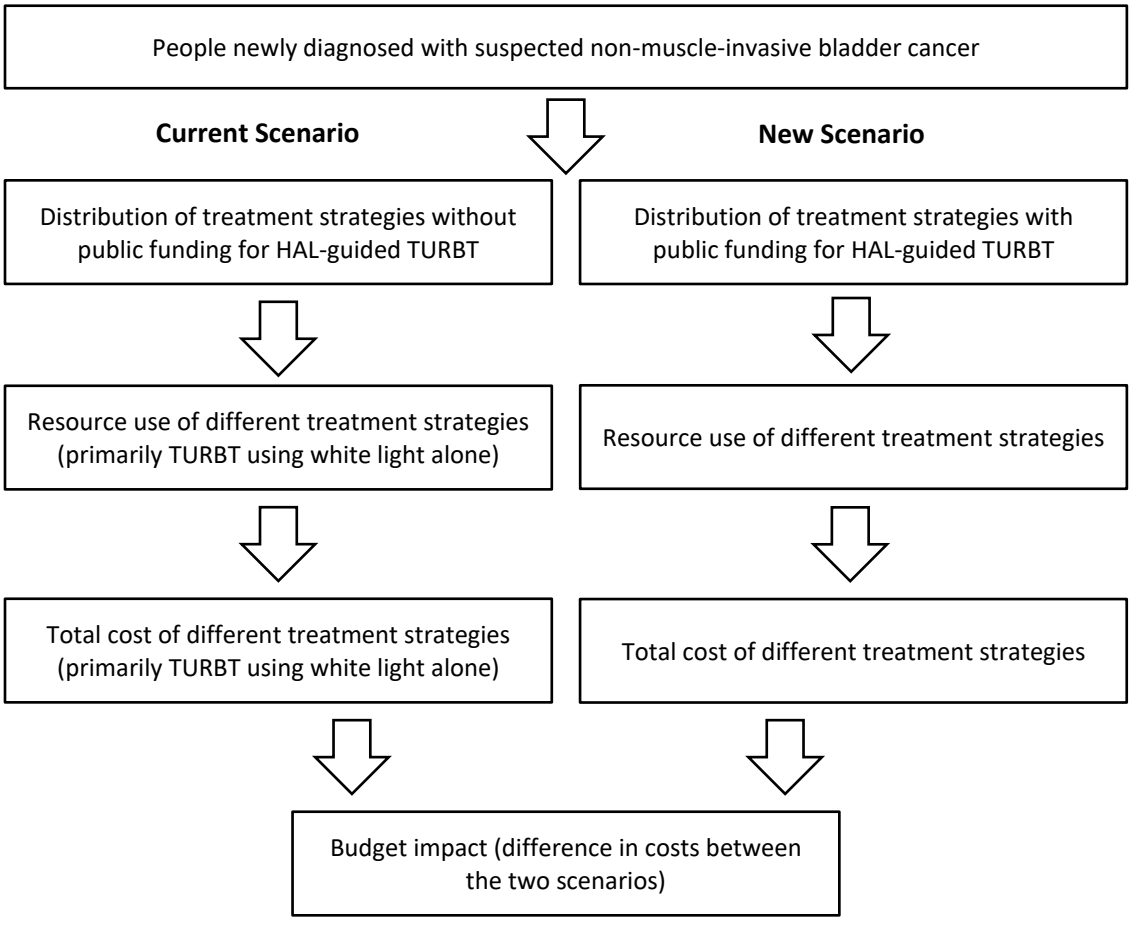

Figure 15: Schematic Model of Budget Impact

Abbreviations: HAL, hexaminolevulinate hydrochloride; TURBT, transurethral resection of bladder tumour.

Key Assumptions

- The assumptions from the companion cost-effectiveness analysis described in the primary economic evaluation apply
- NBI-guided TURBT has no additional cost because the necessary equipment is assumed to be readily available throughout the health system, as part of the equipment currently used for TURBT using white light alone
- People with metastatic bladder cancer are not given a TURBT
- Future uptake is primarily driven and limited by the remaining life span of existing equipment used to perform TURBT

Target Population

The target population was people undergoing their first TURBT for suspected non-muscle-invasive bladder cancer (incident cases). Table 19 shows the counts, derived from IntelliHealth Ontario data. Based on historical TURBT data, a linear regression was used to estimate the volume of future TURBTs over the next 5 years. In the first year, 4,575 people are estimated to undergo TURBT for suspected NMIBC, with numbers slightly rising to 4,966 individuals by the fifth year.

Table 19: Volume of Intervention

	Year 1	Year 2	Year 3	Year 4	Year 5
First TURBT[a]	4,575	4,648	4,737	4,878	4,966

Abbreviations: TURBT, transurethral resection of bladder tumour.

[a]First TURBT was defined as a first recorded transurethral resection of bladder tumour for a person diagnosed with a malignant neoplasm of the bladder. Determining an individual's first TURBT was based on the last 10 years of their medical services records.

Source: Data provided by IntelliHealth Ontario.

Current Intervention Mix

As the conventional method of visualizing bladder tumours, white light dominates the current intervention mix and is used in over 90% of all first TURBTs. HAL-guided TURBT is currently being conducted in a small number of centres in Ontario, with the solution cost funded through hospital global budgets and the diagnostic equipment purchased through fundraising. Six hospitals in Ontario are known to have the equipment necessary to conduct HAL-guided TURBT but, due to budgetary constraints, only 110 and 137 units of HAL were purchased in Ontario in 2018 and 2019, respectively. That usage indicates that 2.6% (in 2018) and 3.1% (2019) of all patients undergoing their first TURBT received a HAL-guided procedure. In Table 20, we projected the same slow rise in the use of HAL-guided TURBT over the next 5 years, assuming no dedicated public funding. To estimate the current proportion for NBI-guided TURBT, we consulted with experts, who advised that about 2% of first TURBTs use NBI and that this usage would be static (Girish Kulkarni, MD, and Chris Morash, MD, email communications, January 2021).

Table 20: Current Intervention Mix

	Year 1	Year 2	Year 3	Year 4	Year 5
White light	94.6%	94.5%	94.3%	94.0%	93.9%
HAL	3.4%	3.5%	3.7%	4.0%	4.1%
NBI	2.0%	2.0%	2.0%	2.0%	2.0%

Abbreviations: HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging.

Uptake of the New Intervention Mix

Based on the IntelliHealth Ontario data, we determined that 85% of all TURBT procedures are completed at 42 hospitals, with 38 conducting over 100 TURBTs per year. Given the larger volumes in these 38 hospitals, we assumed they would be initially targeted for the purchase of HAL-guided TURBT equipment. Based on the historical volume of TURBT procedures in these 38 hospitals, we determined that the uptake of HAL-guided TURBT could rise to a maximum of 80% of all TURBTs province-wide. Table 21 outlines the uptake of the new intervention mix where, over the next 5 years, HAL as an adjunct to white light increasingly replaces the conventional use of white light alone to guide TURBTs. This relatively rapid rise in uptake is based on the 5-year service life of equipment both for white light–guided and HAL-guided TURBT. Therefore, all targeted high-volume hospitals would have the capability to reach this uptake rate by year 5. We explored more conservative uptake rates in scenario analyses.

Table 21: New Intervention Mix

	Year 1	Year 2	Year 3	Year 4	Year 5
White light	79.2%	63.8%	48.4%	33.0%	18.0%
HAL	18.8%	34.2%	49.6%	65.0%	80.0%
NBI	2.0%	2.0%	2.0%	2.0%	2.0%

Abbreviations: HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging.

Resources and Costs

We obtained the mean cost per patient from the probabilistic analysis in our primary economic evaluation, and we separated the costs into two groups: those specific to the first TURBT and all other downstream costs. The budget impact of the new intervention mix for first TURBT would comprise all the additional costs of a HAL-guided TURBT (i.e., HAL solution, HAL equipment, and additional anesthesia and nursing time). In our companion cost-effectiveness analysis, the entire treatment pathway for people with bladder cancer was costed, and therefore we were able to capture both the device-associated and the disease-associated resources and costs in our budget impact analysis. Appendix 11, Table A12, contains the annual undiscounted per-patient costs for each intervention used in our budget impact model. All costs were reported in 2020 Canadian dollars. Costs for HAL-guided TURBT were noticeable higher than for the other interventions in the first year, given the additional expenses for this technology compared with TURBT using NBI or white light alone. However, after the first year, the annual cost per patient for HAL-guided TURBT was lower than for TURBT using NBI or white light alone, indicative of downstream savings from reduced cancer recurrences and altered clinical pathways for patient monitoring. In two scenario analyses we reduced the cost of the HAL solution,

assuming the possibility of greater use could enable price reductions. In these scenarios, the reference price of $708 per procedure was reduced by 25% and 50%.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

This analysis evaluated the budget impact of a new intervention mix for people undergoing their first TURBT for suspected NMIBC. As we assumed NBI-guided TURBT would have a constant uptake over the 5 years and the same cost as TURBT using white light alone, our analysis evaluated the cost of an increasing uptake of HAL-guided TURBT and a declining use of TURBT using white light alone. To account for per-patient expenditures during the first 5 years after a first TURBT procedure, our budget impact analysis was conducted with a companion cost-effectiveness analysis. All results accounted for both cancer-specific and general mortality in the target population.

To quantify the variability in the budget impact resulting from different assumptions, we calculated several alternative scenarios. As previously mentioned, two scenarios explored reductions to the cost of the HAL solution, while other scenarios varied the uptake rate and the initial capital equipment costs. Scenario analyses with smaller uptake rates accounted for the possibility that the service life of equipment could be longer than 5 years (the service life assumed in our reference case). A longer service life could result in slower uptake because centres might only purchase new equipment to perform HAL-guided TURBT once existing equipment nears the end of its service life. Therefore, with an annual uptake rate of 10% or 5% (slower growth than in the reference case), the market share of HAL in year 5 would be 53% or 28%, respectively.

Results

Reference Case

Table 22 presents the results of the reference case analysis. The estimated budget impact of the new intervention mix, with an increased uptake of HAL-guided TURBT, ranged from an additional $0.56 million in the first year to an additional $2.54 million in the fifth year. This produces a 5-year total budget impact of $7.83 million.

Given the higher uptake and cost of a HAL-guided procedure, TURBT-related costs were higher in the new scenario than in the current scenario. Non-TURBT costs are downstream costs not attributable to the first TURBT procedure, such as the cost of ongoing services to check for and treat any cancer recurrence. There were cost savings in non-TURBT costs, but the savings ($1.02 million over 5 years) did not offset the higher TURBT-related costs.

Table 22: Budget Impact Analysis Results

Scenario	Budget Impact, $ Million[a]					
	Year 1[b,c]	Year 2[b,c]	Year 3[b,c]	Year 4[b,c]	Year 5[b,c]	Total[b,c]
Current scenario	52.38	64.70	72.46	79.41	84.46	353.42
TURBT-related	10.68	10.85	11.07	11.41	11.62	55.62
Non-TURBT	41.71	53.84	61.40	68.01	72.84	297.80
New scenario	52.95	65.78	74.03	81.49	87.00	361.24
TURBT-related	11.24	11.99	12.81	13.79	14.63	64.46
Non-TURBT	41.71	53.79	61.23	67.70	72.36	296.78
Budget impact[b,c]	0.56	1.08	1.57	2.07	2.54	7.83
TURBT-related	0.56	1.14	1.74	2.38	3.01	8.84
Non-TURBT	−0.00[d]	−0.06	−0.17	−0.31	−0.48	−1.02

Abbreviations: TURBT, transurethral resection of bladder tumour.

[a]In 2020 Canadian dollars.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

[d]Savings of $1,721.

Sensitivity Analysis

Table 23 presents the results of our sensitivity analysis. If the uptake rate of HAL were lowered to 5% and 10%, to reflect a more gradual replacement of existing white light equipment, the 5-year budget impact would be an additional $2.5 million or $5.0 million, respectively. Scenarios with a 25% and 50% reduction in the solution cost of HAL led to a 5-year budget impact of an additional $5.7 million and $3.6 million, respectively. Finally, if the capital equipment for HAL-guided TURBT did not gradually replace white light equipment but was instead bought in year 1 for all targeted centres, the 5-year budget impact would be an additional $7.8 million.

Table 23: Budget Impact Analysis Scenario Results

Scenario	Budget Impact, $ Million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Reference Case						
Current scenario	52.38	64.70	72.46	79.41	84.46	353.42
New scenario	52.95	65.78	74.03	81.49	87.00	361.24
Budget impact	0.56	1.08	1.57	2.07	2.54	7.83
Annual 5% Increased Uptake						
New scenario	52.57	65.04	72.97	80.07	85.27	355.92
Budget impact	0.18	0.35	0.50	0.66	0.81	2.50
Annual 10% Increased Uptake						
New scenario	52.75	65.40	73.48	80.75	86.11	358.49
Budget impact	0.36	0.70	1.02	1.34	1.65	5.07
25% HAL Price Reduction						
New scenario	52.80	65.50	73.62	80.93	86.29	359.13
Budget impact	0.41	0.80	1.15	1.51	1.83	5.71
50% HAL Price Reduction						
New scenario	52.64	65.22	73.20	80.37	85.59	357.02
Budget impact	0.26	0.52	0.74	0.95	1.13	3.60
New Capital Equipment						
New scenario	56.22	65.78	74.03	81.49	87.00	361.24
Budget impact	3.84	1.08	1.57	2.07	2.54	7.83

[a]In 2020 Canadian dollars. Some results may appear inexact due to rounding.

Discussion

In the reference case analysis, the total 5-year budget impact of the new intervention mix was $7.8 million. The downstream cost savings from increased use of HAL-guided TURBT did not offset the incremental cost of the first procedure. As the cost of the HAL solution represents most of the cost difference among the interventions, we explored in scenario analyses how negotiated price reductions might limit the total budget impact. Compared with the current intervention mix, where HAL is used in only about 3% of all first TURBT procedures, the new intervention mix represents a significant increase in the use of the solution (i.e., up to 80%). Such an increase may provide support for future price negotiations. Regarding pricing, threshold analysis in our primary economic evaluation estimated that, over a 15-year time horizon, the average cost per patient for a HAL-guided TURBT and TURBT using white light alone would be equal if the cost of the HAL solution were reduced to $274.

In estimating the uptake of HAL-guided TURBT over 5 years, we assumed the 38 hospitals that currently conduct more than 100 TURBT procedures per year would be the centres targeted to receive the new equipment (these 38 hospitals were found to conduct 80% of all TURBT procedures in Ontario). While

this approach aims to maximize the number of patients treated with HAL-guided TURBT, it has the potential for equity concerns. Specifically, smaller hospitals that typically serve rural communities may not reach our threshold of 100 TURBT procedures per year, which may systematically limit access for certain population groups.

Both the current and new intervention mix (Tables 20 and 21) showed usage of conventional TURBT guided by white light alone and HAL-guided TURBT fluctuating over time but NBI-guided TURBT remaining unchanged. Given the results of the clinical evidence review and the primary economic evaluation, we anticipated no increased uptake of NBI-guided TURBT.

Strengths and Limitations

Our analysis had several strengths. One strength was the use of a companion cost-effectiveness analysis to separately measure downstream savings resulting from the first TURBT procedure, providing a more accurate prediction of overall costs. Scenario analyses also explored uncertainty regarding uptake rates and the cost of the HAL solution, the key driver of differential costs among the interventions. Our analysis was also strengthened by the use of local administrative data that provided historical trends on the number of first TURBT procedures and the number of facilities conducting TURBTs in Ontario.

Our analysis had several limitations. One limitation is related to the complexities of modeling bladder cancer, where patient characteristics, preferences, and treatment responses dynamically alter health care utilization. Therefore, in measuring downstream costs, we were required to use several assumptions about a patient's clinical pathway and the costs they would incur. Another limitation involves the purchase of capital equipment for performing HAL-guided TURBTs. We assumed one set of cystoscopy equipment would be sufficient for a hospital to conduct HAL-guided TURBTs; however, as this equipment can be used for other urologic surgeries (i.e., ureteroscopy or laparoscopy), hospitals may need to purchase additional equipment or specific components (i.e., if existing components from a different manufacturer could not be used with the new, HAL-capable equipment). Finally, the instillation of the HAL solution requires a nurse to administer it an hour before surgery; although we costed this time, staffing considerations and overall capacity constraints for holding these patients in the unit were not explored.

Conclusions

Our budget impact analysis indicates that publicly funding HAL-guided TURBT at higher volumes for people with suspected non-muscle-invasive bladder cancer may result in extra spending of $0.6 million to $2.5 million annually for the next 5 years, with a 5-year total additional cost of $7.8 million. There would likely be no additional capital cost associated with publicly funding NBI-guided TURBT, but we do not expect the market share of this technology to increase.

Patient Preferences and Values

Background

Exploring patients' preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to diagnose, manage, or treat the health condition. It includes the effect of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[84-86] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Methods

For the current health technology assessment, a member of the Patient Engagement team at Ontario Health determined the scope and direction of patient and public engagement using a formal needs assessment. The purpose of this needs assessment was threefold:

- To determine if obtaining lived-experience information about enhanced visualization methods for first transurethral resection of a bladder tumour (TURBT) for people with suspected non-muscle-invasive bladder cancer would be of value in understanding the impact of this technology
- If lived-experience information was of value, to determine goals and objectives for patient engagement to obtain this information
- To scope out the optimal engagement activity

To complete the needs assessment, we completed background research on the topic in question, which included reviewing the clinical review plan and consulting clinical experts. As we refined the needs assessment, we consulted with lived-experience advisors on the Ontario Health Technology Advisory Committee.

Through this needs assessment, we determined that lived-experience information related to patient preferences and values would not be needed to evaluate this technology, for several reasons:

- ***Patient important outcomes****:* A key component of health technology assessment is evaluating the impact of the technology on important patient outcomes. Direct patient engagement can often provide information about which outcomes are most important and relevant to patients and evaluate from the patient perspective the impact of the health technology on those outcomes. During the first TURBT procedure, the clinical evidence, reported in this health technology assessment, evaluated outcomes including comparative recurrence rates, recurrence-free survival, tumour progression, safety, and adverse events. Findings of our needs assessment, indicated these outcomes are relevant and important to patients . Because of this, direct patient engagement to further elucidate relevant outcomes was thought to not be needed.
- ***Patient preferences and values in decision-making:*** For a health technology assessment, patient engagement can often illuminate the context for patient preferences related to a technology and

how patients make decisions surrounding its use. We felt that it was unlikely that a patient's preferences and choices about enhanced visualization methods during their first TURBT procedure would affect whether or not it was used. Clinical experts suggested that patients currently have no direct input or influence on decision-making when it comes to the use or non-use of this type of technology during the procedure. We did acknowledge that patients would likely prefer the technology that would contribute to improved outcomes for the health condition. These outcomes were evaluated in the clinical evidence.

- ***Direct effect on patients****:* A number of health technologies involve devices or procedures that directly interact with and affect a person's physical state and life such as devices that are worn, or require management by patients to be effective. Direct patient engagement to determine preferences and values for these types of treatments, many of which require patients to manage the function of the technology, or wear the technology, can illuminate, among other things, the day to day issues of using the technology, the impact on the person's quality of life, and provide insights into their preferences and values for the day-to-day management of their health condition. The technology involved in the use of HAL, NBI, or white light to guide a TURBT procedure are not technologies managed by patients nor ones that will necessitate integration into a patient's daily life. Instead, these are tools used by a physician to enhance visualization of tumours during first TURBT, a time-limited medical procedure. Because of this, the types of patient insights and preferences that are informative for some health technologies—such as how the technology feels to use or wear, the issues in using the technology, or how it directly impacts a person's quality of life—are not directly relevant for this health technology assessment. In addition, patients' experiences of undergoing TURBT can be expected to be similar regardless of the type of visualization methods the physician uses. With the exception of the additional 1-hour preparation required for instillation of HAL, there is no added invasiveness with a HAL-guided TURBT.

After careful consideration of these factors through the needs assessment and through consultations, the Patient Engagement team concluded that direct patient engagement would not provide further insight into patient preferences and values for this technology. We do acknowledge that HAL-guided TURBT requires the instillation of HAL solution into the patient's bladder. Because we did not directly engage with patients, we do not know their perspectives on this aspect of the technology and it remains a limitation of our health technology assessment.

Conclusions of the Health Technology Assessment

This health technology assessment evaluated the effectiveness, safety, and cost-effectiveness of hexaminolevulinate hydrochloride (HAL) and narrow band imaging (NBI) as adjuncts to white light during the first transurethral resection of bladder tumour (TURBT) in patients with non-muscle-invasive bladder cancer (NMIBC). It also evaluates the budget impact of publicly funding these technologies.

HAL-guided TURBT is likely more effective than TURBT guided by white light alone in reducing the rate of bladder cancer recurrence and likely improves 5-year recurrence-free survival (GRADE: Moderate). The effectiveness of NBI-guided TURBT and TURBT using white light alone in reducing the rate of cancer recurrence is likely not different (GRADE: Moderate), and there is no evidence on the effectiveness of NBI-guided TURBT on recurrence-free survival. There may be little to no difference in bladder cancer recurrence rates between HAL-guided and NBI-guided TURBT (GRADE: Low). Both HAL-guided and NBI-guided TURBT are generally safe.

Our cost-effectiveness analysis found that HAL-guided TURBT is likely cost-effective in patients with suspected NMIBC undergoing their first TURBT, compared with first TURBT guided by white light alone or with adjunct NBI. TURBT guided by white light alone was dominated by NBI-guided TURBT. The resultant incremental cost-effectiveness ratio (ICER) from sequential analysis of HAL-guided versus NBI-guided TURBT was $12,618 per quality-adjusted life-year (QALY) gained, indicating cost-effectiveness across commonly reported willingness-to-pay values. Our results are consistent with previous studies comparing HAL-guided and TURBT using white light alone. (We found no relevant economic studies on NBI-guided TURBT). In our evaluation, HAL-guided TURBT had on average higher costs and greater QALYs gained compared with NBI-guided TURBT or TURBT using white light alone. The results were sensitive to time horizons.

We estimate that publicly funding HAL-guided TURBT in Ontario for people undergoing a first TURBT for suspected NMIBC would cost an additional $0.6 million to $2.5 million annually over the next 5 years, or a total additional cost of $7.8 million over 5 years. For NBI-guided TURBT, there would likely be no additional capital cost but we do not expect increased market share of this technology as an adjunct to white light during TURBT.

Based on a needs assessment, we did not conduct direct patient engagement for this health technology assessment. While the clinical evidence evaluated the impact of HAL-guided and NBI-guided TURBT on outcomes thought to be most important and relevant to patients, there may be preferences and values of either technology that have not been fully captured by forgoing direct patient engagement.

Abbreviations

5-ALA	5-alpha aminolevolinic acid
BCG	Bacillus Calmette-Guérin immunotherapy
CI	Confidence interval
CIS	Carcinoma in situ
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HAL	hexaminolevulinate hydrochloride
ICER	Incremental cost-effectiveness ratio
ITC	Indirect treatment comparison
ITT	Intention to treat
MIBC	Muscle-invasive bladder cancer
NBI	Narrow band imaging
NMIBC	Non-muscle-invasive bladder cancer
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
RR	Risk ratio
TNM	Tumour-Node-Metastasis system for cancer staging
TURBT	Transurethral resection of bladder tumour
WHO	World Health Organization
WTP	Willingness-to-pay value

Glossary

Adjusted indirect treatment comparison	An indirect comparison of different treatments adjusted according to the results of studies that directly compared each treatment with a common comparator.
Adverse event	An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.
Base case	In economic evaluations, the base case is the "best guess" scenario, including any assumptions, considered most likely to be accurate. In health technology assessments conducted by Ontario Health, the reference case is used as the base case.
Budget impact analysis	A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).
Consistency (in the context of network meta-analysis)	In a network meta-analysis, the test for consistency is a statistical assessment to see whether the evidence from the direct and indirect comparisons agree.
Cost–consequence analysis	A cost–consequence analysis is a type of economic evaluation that estimates the costs and consequences (i.e., the health outcomes) of two or more health care interventions. In this type of analysis, the costs are presented separately from the consequences.
Cost-effective	A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost-effectiveness acceptability curve	In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness analysis	Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.
Cost–utility analysis	A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.
Cystoscopy	Examination of the bladder and urethra using a cystoscope, a tube-like instrument equipped with a light and a camera lens, which transmits images to a computer for review. Cystoscopy can be used as a tool for initial diagnosis and treatment, during TURBT, as well as for surveillance for people who have been treated for bladder cancer, as part of regular monitoring to see if the cancer has returned.
Direct estimate	Estimate of effect when it is provided by a head-to-head comparison.
Discounting	Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.
Dominant	A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).
EQ-5D	The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.
False-positive detection rate	The number of non-cancerous lesions detected by one technique divided by the total number of lesions detected by that technique.

Hazard ratio	*Hazard* refers to the probability that an individual, under observation in a clinical trial at time *t*, has an event at that time. Hazard ratio is the ratio of the hazard function among exposed to the hazard function among non-exposed. A hazard ratio of 1 means there is a lack of association, a hazard ratio greater than 1 suggests an increased risk, and a hazard ratio below 1 suggests a smaller risk.
Health state	A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.
Heme biosynthetic pathway	The process by which enzymes in the body produce heme, an important component of hemoglobin and other proteins necessary for healthy cells. Heme consists of ring-shaped molecules called porphyrins surrounding a central iron ion.
Heterogeneity	Differences in effect estimates for the same outcome across studies. There are different types of heterogeneity. Clinical heterogeneity means the studies differ in their inclusion of participants, interventions, or outcomes. Methodological heterogeneity refers to differences in study design and risk of bias. Variability in the intervention effect estimate in different studies is known as statistical heterogeneity and is a consequence of clinical or methodological diversity or both among the studies.
Incremental cost	The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.
Incremental cost-effectiveness ratio (ICER)	The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.
Incremental net benefit	Incremental net benefit is a summary measure of cost-effectiveness. It incorporates the differences in cost and effect between two health care interventions and the willingness-to-pay value. Net *health* benefit is calculated as the difference in effect minus the difference in cost divided by the willingness-to-pay value. Net *monetary* benefit is calculated as the willingness-to-pay value multiplied by the difference in effect minus the difference in cost. An intervention can be considered cost-effective if either the net health or net monetary benefit is greater than zero.
Indirect estimate	Estimate of effect that is provided through a network meta-analysis or indirect treatment comparison using the direct estimates from head-to-head comparisons that shared a common comparator.

Lamina propria	A layer in the bladder wall that extends from below the urothelium to the upper boundary of the bladder muscle. This layer contains loose connective tissue, blood and lymph vessels, and nerves.
Lesion	An area of abnormal tissue that may be benign (not cancer) or malignant (cancer).
Market share	When evaluating more than two technologies, the market share is the proportion of the population that uses each technology.
Markov model	A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.
Meta-analysis	Statistical synthesis of the results of different trials that have examined the same research question and pooling of the effect estimate to determine the overall trend.
Microsimulation model	In economic evaluations, a microsimulation model (e.g., an individual-level or patient-level model) is used to simulate the health outcomes for a heterogeneous group of patients (e.g., patients of different ages or with different sets of risk factors) after receiving a particular health care intervention. The health outcomes and health events of each patient are modelled, and the outcomes of several patients are combined to estimate the average costs and benefits accrued by a group of patients. In contrast, a cohort model follows a homogeneous cohort of patients (e.g., patients of the same age or with the same set of risk factors) through the model and estimates the proportion of the cohort who will experience specific health events.
Ministry of Health perspective	The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).
Monte Carlo simulation	Monte Carlo simulation is an economic modelling method that derives parameter values from distributions rather than fixed values. The model is run several times, and in each iteration, parameter values are drawn from specified distributions. This method is used in microsimulation models and probabilistic analysis.

Network meta-analysis	A technique for comparing three or more interventions simultaneously in a single analysis. It is an extension of standard pairwise meta-analysis and can be used to compare any number of interventions or treatments.
Number needed to treat	The number of patients that one would need to treat so that one person can achieve the good outcome or one person can be prevented from having the bad outcome.
Papillary urothelial carcinoma	A common type of bladder cancer that starts in the urothelium, the innermost layer of the bladder wall.
Probabilistic analysis	A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.
Quality-adjusted life-year (QALY)	The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.
Reference case	The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.
Risk difference	Risk difference is the difference in the risk of an outcome occurring between one intervention and an alternative intervention.
Risk ratio	Risk ratio or “relative risk” is the ratio of the risk of an outcome occurring between one intervention and an alternative intervention.
Scenario analysis	A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.
Sensitivity	Ability of a test to correctly identify those with the disease (true-positive rate).

Sensitivity analysis	Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.
Short-Form–Six Dimensions (SF-6D)	The SF-6D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The classification system consists of six attributes (physical functioning, role limitations, social functioning, pain, mental health, and vitality), each associated with four to six levels, thus producing a total of 18,000 possible unique health states. A scoring table is used to convert SF-6D scores to health state values.
Societal perspective	The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).
Specificity	Ability of a test to correctly identify those without the disease (true-negative rate).
Time horizon	In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.
Transitivity	Transitivity is one of the underlying assumptions of a network meta-analysis. It means that the head-to-head comparisons are similar enough that we do not need to be concerned about the presence of effect modifiers that may introduce bias in indirect estimates. If inconsistency in the network is observed, the assumption of transitivity may not be held and the presence of effect modifiers influencing the treatment of effect should be examined.
Uptake rate	In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.
Urethra	A fibromuscular tube in the body that drains urine from the bladder out of the body.

Utility	A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.
White light	Light containing all wavelengths in the visible spectrum.
Willingness-to-pay value	A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: April 15, 2020

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2020>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 08, 2020>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2020 Week 15>, Ovid MEDLINE(R) ALL <1946 to April 14, 2020>

Search strategy:

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1 Urinary Bladder Neoplasms/ (63654)
2 (((bladder* or vesical*) adj3 (cancer* or carcinoma* or carcinogenes#s or metastas#s or neoplas* or tumo?r*)) or NMIBC or BCa).ti,ab,kf. (132628)
3 Carcinoma, Transitional Cell/ (33164)
4 (tcc or transitional cell*).ti,ab,kf. (32123)
5 or/1-4 (171936)
6 Aminolevulinic Acid/ (14526)
7 (5ALA or 5 ALA or aminol?evulin* or amino l?evulin* or gliolan* or gleolan* or levulan*).ti,ab,kf. (20183)
8 (hexaminolevulin* or hexylaminolevulinate* or hexyl aminolevulin* or HAL).ti,ab,kf. (5004)
9 Narrow Band Imaging/ (5499)
10 (((narrowband* or narrow band*) adj2 imaging*) or NBI).ti,ab,kf. (7662)
11 (((photodynamic or photo-dynamic*) adj2 diagnos#s) or (novel adj2 optic* imaging)).ti,ab,kf. (1590)
12 Cystoscopy/ (28727)
13 cystosco*.ti,ab,kf. (27715)
14 Urologic Surgical Procedures/ (19872)
15 Urinary Bladder Neoplasms/su (14738)
16 Urinary Bladder Neoplasms/dg (2182)
17 or/12-16 (74650)
18 Fluorescence/ (169647)
19 Fluorescent Dyes/ (121144)
20 Microscopy, Fluorescence/ (133460)
21 (fluorescen* or fluorescing or autofluorescen*).ti,ab,kf. (1010774)
22 (((blue or green) adj2 (light or spectrum or wavelength*)) or photo dynamic* or photodynamic*).ti,ab,kf. (83641)
23 or/18-22 (1195789)
24 17 and 23 (1912)
25 or/6-11,24 (39786)
26 5 and 25 (2558)
27 exp Animals/ not Humans/ (16537409)

28 26 not 27 (1804)
29 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5482235)
30 28 not 29 (1748)
31 limit 30 to english language [Limit not valid in CDSR; records were retained] (1475)
32 31 use medall,coch,cctr,clhta,cleed (841)
33 non muscle invasive bladder cancer/ (3610)
34 bladder tumor/ (72575)
35 bladder carcinogenesis/ (1925)
36 bladder carcinoma/ (14710)
37 bladder metastasis/ (1634)
38 (((bladder* or vesical*) adj3 (cancer* or carcinoma* or carcinogenes#s or metastas#s or neoplas* or tumo?r*)) or NMIBC or BCa).tw,kw. (133736)
39 transitional cell carcinoma/ (45743)
40 (tcc or transitional cell*).tw,kw. (33165)
41 or/33-40 (184893)
42 aminolevulinic acid hexyl ester/ (513)
43 aminolevulinic acid/ (14526)
44 (5ALA or 5 ALA or aminol?evulin* or amino l?evulin* or gliolan* or gleolan* or levulan*).tw,kw,dv,du. (23752)
45 (hexaminolevulin* or hexylaminolevulinate* or hexyl aminolevulin* or HAL).tw,kw,dv,du. (5115)
46 narrow band imaging/ (5499)
47 (((narrowband* or narrow band*) adj2 imaging*) or NBI).tw,kw,dv. (8073)
48 (((photodynamic or photo-dynamic*) adj2 diagnos#s) or (novel adj2 optic* imaging)).tw,kw,dv. (1641)
49 cystoscopy/ (28727)
50 cystosco*.tw,kw,dv. (28051)
51 urinary tract surgery/ (1110)
52 urologic surgery/ (13106)
53 or/49-52 (55422)
54 blue light/ (5557)
55 fluorescence/ (169647)
56 fluorescence imaging/ (32407)
57 fluorescence microscopy/ (147955)
58 photodynamics/ (2868)
59 (fluorescen* or fluorescing or autofluorescen*).tw,kw,dv,du. (1029788)
60 (((blue or green) adj2 (light or spectrum or wavelength*)) or photo dynamic* or photodynamic*).tw,kw,dv. (84908)
61 or/54-60 (1200091)
62 53 and 61 (1846)
63 or/42-48,62 (40672)
64 41 and 63 (2628)
65 (exp animal/ or nonhuman/) not exp human/ (10644862)
66 64 not 65 (2517)
67 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11135275)
68 66 not 67 (1940)
69 limit 68 to english language [Limit not valid in CDSR; records were retained] (1625)

70 69 use emez (846)
71 32 or 70 (1687)
72 71 use medall (736)
73 71 use emez (846)
74 71 use coch (0)
75 71 use cctr (97)
76 71 use cleed (5)
77 71 use clhta (3)
78 remove duplicates from 71 (1018)

Economic Evidence Search

Search date: April 15, 2020

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2020>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 08, 2020>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2020 Week 15>, Ovid MEDLINE(R) ALL <1946 to April 14, 2020>

Search strategy:

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3 Carcinoma, Transitional Cell/ (33164)
4 (tcc or transitional cell*).ti,ab,kf. (32123)
5 or/1-4 (171936)
6 Aminolevulinic Acid/ (14526)
7 (5ALA or 5 ALA or aminol?evulin* or amino l?evulin* or gliolan* or gleolan* or levulan*).ti,ab,kf. (20183)
8 (hexaminolevulin* or hexylaminolevulinate* or hexyl aminolevulin* or HAL).ti,ab,kf. (5004)
9 Narrow Band Imaging/ (5499)
10 (((narrowband* or narrow band*) adj2 imaging*) or NBI).ti,ab,kf. (7662)
11 (((photodynamic or photo-dynamic*) adj2 diagnos#s) or (novel adj2 optic* imaging)).ti,ab,kf. (1590)
12 Cystoscopy/ (28727)
13 cystosco*.ti,ab,kf. (27715)
14 Urologic Surgical Procedures/ (19872)
15 Urinary Bladder Neoplasms/su (14738)
16 Urinary Bladder Neoplasms/dg (2182)
17 or/12-16 (74650)
18 Fluorescence/ (169647)
19 Fluorescent Dyes/ (121144)
20 Microscopy, Fluorescence/ (133460)
21 (fluorescen* or fluorescing or autofluorescen*).ti,ab,kf. (1010774)

22 (((blue or green) adj2 (light or spectrum or wavelength*)) or photo dynamic* or photodynamic*).ti,ab,kf. (83641)
23 or/18-22 (1195789)
24 17 and 23 (1912)
25 or/6-11,24 (39786)
26 5 and 25 (2558)
27 exp Animals/ not Humans/ (16537409)
28 26 not 27 (1804)
29 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5482235)
30 28 not 29 (1748)
31 30 use coch,clhta,cleed (10)
32 economics/ (256629)
33 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (859742)
34 economics.fs. (432460)
35 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (942133)
36 exp "costs and cost analysis"/ (597205)
37 (cost or costs or costing or costly).ti. (276119)
38 cost effective*.ti,ab,kf. (347391)
39 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (227797)
40 models, economic/ (13472)
41 markov chains/ or monte carlo method/ (85830)
42 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (45430)
43 (markov or markow or monte carlo).ti,ab,kf. (137724)
44 quality-adjusted life years/ (42430)
45 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (80081)
46 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (130867)
47 or/32-46 (2670826)
48 30 and 47 (139)
49 48 use medall,cctr (80)
50 31 or 49 (90)
51 non muscle invasive bladder cancer/ (3610)
52 bladder tumor/ (72575)
53 bladder carcinogenesis/ (1925)
54 bladder carcinoma/ (14710)
55 bladder metastasis/ (1634)
56 (((bladder* or vesical*) adj3 (cancer* or carcinoma* or carcinogenes#s or metastas#s or neoplas* or tumo?r*)) or NMIBC or BCa).tw,kw. (133736)
57 transitional cell carcinoma/ (45743)
58 (tcc or transitional cell*).tw,kw. (33165)
59 or/51-58 (184893)
60 aminolevulinic acid hexyl ester/ (513)
61 aminolevulinic acid/ (14526)
62 (5ALA or 5 ALA or aminol?evulin* or amino l?evulin* or gliolan* or gleolan* or levulan*).tw,kw,dv,du. (23752)

63 (hexaminolevulin* or hexylaminolevulinate* or hexyl aminolevulin* or HAL).tw,kw,dv,du. (5115)
64 narrow band imaging/ (5499)
65 (((narrowband* or narrow band*) adj2 imaging*) or NBI).tw,kw,dv. (8073)
66 (((photodynamic or photo-dynamic*) adj2 diagnos#s) or (novel adj2 optic* imaging)).tw,kw,dv. (1641)
67 cystoscopy/ (28727)
68 cystosco*.tw,kw,dv. (28051)
69 urinary tract surgery/ (1110)
70 urologic surgery/ (13106)
71 or/67-70 (55422)
72 blue light/ (5557)
73 fluorescence/ (169647)
74 fluorescence imaging/ (32407)
75 fluorescence microscopy/ (147955)
76 photodynamics/ (2868)
77 (fluorescen* or fluorescing or autofluorescen*).tw,kw,dv,du. (1029788)
78 (((blue or green) adj2 (light or spectrum or wavelength*)) or photo dynamic* or photodynamic*).tw,kw,dv. (84908)
79 or/72-78 (1200091)
80 71 and 79 (1846)
81 or/60-66,80 (40672)
82 59 and 81 (2628)
83 (exp animal/ or nonhuman/) not exp human/ (10644862)
84 82 not 83 (2517)
85 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11135275)
86 84 not 85 (1940)
87 Economics/ (256629)
88 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (131864)
89 Economic Aspect/ or exp Economic Evaluation/ (468343)
90 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (968381)
91 exp "Cost"/ (597205)
92 (cost or costs or costing or costly).ti. (276119)
93 cost effective*.tw,kw. (359945)
94 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (239417)
95 Monte Carlo Method/ (68184)
96 (decision adj1 (tree* or analy* or model*)).tw,kw. (49277)
97 (markov or markow or monte carlo).tw,kw. (142820)
98 Quality-Adjusted Life Years/ (42430)
99 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (83973)
100 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (151845)
101 or/87-100 (2293867)
102 86 and 101 (190)
103 102 use emez (102)
104 50 or 103 (192)
105 104 use medall (68)

106 104 use emez (102)
107 104 use cleed (5)
108 104 use clhta (5)
109 104 use coch (0)
110 104 use cctr (12)
111 remove duplicates from 104 (129)

Search for Intervention-Related Health State Utilities

Search date: April 15, 2020

Search filter used: Health state utility values filter, from Glanville et al, 2016[75]

Database segment: Ovid MEDLINE(R) ALL <1946 to April 14, 2020>

Search strategy:

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1 Urinary Bladder Neoplasms/ (53955)
2 (((bladder* or vesical*) adj3 (cancer* or carcinoma* or carcinogenes#s or metastas#s or neoplas* or tumo?r*)) or NMIBC or BCa).ti,ab,kf. (56579)
3 Carcinoma, Transitional Cell/ (18608)
4 (tcc or transitional cell*).ti,ab,kf. (14207)
5 or/1-4 (79904)
6 Quality-Adjusted Life Years/ (11952)
7 (quality adjusted or adjusted life year*).ti,ab,kf. (16595)
8 (qaly* or qald* or qale* or qtime*).ti,ab,kf. (10588)
9 (illness state$1 or health state$1).ti,ab,kf. (6380)
10 (hui or hui1 or hui2 or hui3).ti,ab,kf. (1494)
11 (multiattribute* or multi attribute*).ti,ab,kf. (886)
12 (utility adj3 (score$1 or valu* or health* or cost* or measure* or disease* or mean or gain or gains or index*)).ti,ab,kf. (14335)
13 utilities.ti,ab,kf. (7033)
14 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eurqol5d or euro?qul or eur?qul5d or euro* quality of life or European qol).ti,ab,kf. (11203)
15 (euro* adj3 (5 d or 5d or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).ti,ab,kf. (3965)
16 (sf36* or sf 36* or sf thirtysix or sf thirty six).ti,ab,kf. (21854)
17 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (1877)
18 ((qol or hrqol or quality of life).ti. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improve* or declin* or reduc* or high* or low* or effect or effects of worse or score or scores or change$1 or impact$1 or impacted or deteriorate$)).ab. (31437)
19 Cost-Benefit Analysis/ and (cost effectiveness ratio* and (perspective* or life expectanc*)).ti,ab,kf. (3394)
20 *quality of life/ and (quality of life or qol).ti. (52980)
21 quality of life/ and ((quality of life or qol) adj3 (improve* or chang*)).ti,ab,kf. (24337)
22 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (11531)
23 quality of life/ and health-related quality of life.ti,ab,kf. (31285)

24 quality of life/ and ec.fs. (9939)
25 quality of life/ and (health adj3 status).ti,ab,kf. (8862)
26 (quality of life or qol).ti,ab,kf. and cost-benefit analysis/ (12390)
27 models, economic/ (9945)
28 or/6-27 (158519)
29 5 and 28 (491)
30 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (3766449)
31 29 not 30 (465)
32 limit 31 to English language (406)

Grey Literature Search

Performed: April 17, 2020
Websites searched: Alberta Health Evidence Reviews, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Health Technology Assessment Database, Epistemonikos, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Council of Australian Governments Health Technologies, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, Health Technology Wales, Oregon Health Authority Health Evidence Review Commission, Veterans Affairs Health Services Research and Development, Italian National Agency for Regional Health Services (AGENAS), Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Ministry of Health Malaysia Health Technology Assessment Section, Swedish Agency for Health Technology Assessment and Assessment of Social Services, PROSPERO, EUnetHTA, ClinicalTrials.gov, Tufts Cost-Effectiveness Analysis Registry, Canadian Task Force on Preventive Health Care, U.S. Preventive Services Task Force

Keywords used: cystoscopy, blue light, narrow band, photodynamic, hexylaminolevulinate, hexaminolevulinate, aminolevulinate, aminolevulinic, 5ALA, 5-ALA, optical, bladder cancer, NMIBC

Clinical results (included in PRISMA): 8
Economic results (included in PRISMA): 8
Ongoing clinical trials (ClinicalTrials.gov): 20
Ongoing health technology assessments (PROSPERO/EUnetHTA/MSAC): 5

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool)

Author, Year	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Incomplete Outcome Data	Selective Reporting	Other Bias
Mukherjee et al, 2019[49]	Low	Low	High[c]	Low	Low	Low
Kim et al, 2018[45]	Low	Unclear[b]	High[c]	Low	Low	Low
Dragoescu et al, 2017[43]	Unclear[b]	Unclear[b]	High[c]	Low	Low	Low
Naito et al, 2016[46]	Low	Low	High[c]	Low	Low	Low
Neuzillet et al 2014[50]	Low	Low	High[c]	Low	Low	Low
O'Brien et al, 2013[47]	Unclear[b]	Low	High[c]	Low	Low	Low
Karaolides et al, 2012[44]	Unclear[b]	Unclear[b]	High[c]	Low	Low	Low
Geavlete et al 2010[48]	Unclear[b]	Low	High[c]	Low	Low	Low

[a]Possible risk of bias levels: low, high, and unclear.

[b]No description is provided.

[c]Surgeons could not be blinded to the intervention assignment.

Table A2: GRADE Evidence Profile for the Comparison of TURBT Guided by HAL or NBI Versus White Light Alone

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
HAL Versus White Light							
Cancer Recurrence Rate							
3 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
Recurrence-Free Survival							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
Overall Survival							
1 (RCT)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
Tumour Progression Rate							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
Diagnostic Outcomes							
3 (RCTs)	Not assessed (−2)[a, b]	No serious limitations	Serious limitations (−1)[c]	No serious limitations	Undetected	NA	⊕ Very low
Adverse Events							
1 (RCT)	Serious limitations (−1)[a]	Cannot be assessed	No serious limitations	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
NBI Versus White Light							
Cancer Recurrence Rate							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate
Diagnostic Outcomes							
2 (RCTs)	Not assessed (−2)[a,b]	No serious limitations	Serious limitations (−1)[c]	No serious limitations	Undetected	NA	⊕ Very low
Adverse Events							
2 (RCTs)	Serious limitations (−1)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	NA	⊕⊕⊕ Moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HAL, hexaminolevulinate hydrochloride; NA, not applicable; NBI, narrow band imaging; RCT, randomized controlled trial.

[a]Surgeons could not be blinded to the intervention assignment.

[b]In addition to lack of blinding, the intervention and control were compared within one arm in some studies; therefore, it could not be considered as randomized.

[c]Diagnostic outcomes are indirect evidence for patient outcomes.

Appendix 3: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Table A3: Excluded Primary Studies

Citation	Primary Reason for Exclusion
HAL Studies	
Drejer D, Moltke AL, Nielsen AM, Lam GW, Jensen JB. DaBlaCa-11: Photodynamic diagnosis in flexible cystoscopy – a randomized study with focus on recurrence. Urology. 2020;137:91-6.	Surveillance cystoscopy
Kamat AM, Cookson M, Witjes JA, Stenzl A, Grossman HB. The impact of blue light cystoscopy with hexaminolevulinate (HAL) on progression of bladder cancer - a new analysis. Bladder Cancer. 2016;2(2):273-8.	Included recurrence cases > 30%
Gkritsios P, Hatzimouratidis K, Kazantzidis S, Dimitriadis G, Ioannidis E, Katsikas V. Hexaminolevulinate-guided transurethral resection of non-muscle-invasive bladder cancer does not reduce the recurrence rates after a 2-year follow-up: a prospective randomized trial. Int Urol Nephrol. 2014;46(5):927-33.	Included recurrence cases > 30%
Geavlete B, Jecu M, Multescu R, Geavlete P. Narrow-band imaging cystoscopy in non-muscle-invasive bladder cancer: a prospective comparison to the standard approach. Ther Adv Urol. 2012;4(5): 211-7.	Included recurrence cases > 30%
Grossman HB, Stenzl A, Fradet Y, Mynderse LA, Kriegmair M, Witjes JA, et al. Long-term decrease in bladder cancer recurrence with hexaminolevulinate enabled fluorescence cystoscopy. J Urol. 2012;188(1):58-62.	Included recurrence cases > 30%
Dragoescu O, Tomescu P, Panus A, Enache M, Maria C, Stoica L, et al. Photodynamic diagnosis of non-muscle invasive bladder cancer using hexaminolevulinic acid. Rom J Morphol Embryol. 2011;52(1):123-7.	Same patients in Dragoescu et al, 2017[43]
Hermann GG, Mogensen K, Carlsson S, Marcussen N, Duun S. Fluorescence-guided transurethral resection of bladder tumours reduces bladder tumour recurrence due to less residual tumour tissue in Ta/T1 patients: a randomized two-centre study. BJU Int. 2011;108(8 Pt 2):E297-303.	Included patients with new and recurrent tumours
Stenzl A, Burger M, Fradet Y, Mynderse LA, Soloway MS, Witjes JA, et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. J Urol. 2010;184(5):1907-13.	Included recurrence cases > 30%
Grossman HB, Gomella L, Fradet Y, Morales A, Presti J, Ritenour C, et al. A phase III, multicenter comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of superficial papillary lesions in patients with bladder cancer. J Urol. 2007;178(1):62-7.	Included recurrence cases > 30%

Citation	Primary Reason for Exclusion
Fradet Y, Grossman HB, Gomella L, Lerner S, Cookson M, Albala D, et al. A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. J Urol. 2007;178(1):68-73; discussion	Included recurrence cases > 30%
NBI Studies	
Tschirdewahn S, Harke NN, Hirner L, Stagge E, Hadaschik B, Eisenhardt A. Narrow-band imaging assisted cystoscopy in the follow-up of patients with transitional cell carcinoma of the bladder: a randomized study in comparison with white light cystoscopy. World J Urol. 2019;30:30.	Not TURBT, used for surveillance
Ye Z, Hu J, Song X, Li F, Zhao X, Chen S, et al. A comparison of NBI and WLI cystoscopy in detecting non-muscle-invasive bladder cancer: a prospective, randomized and multi-center study. Sci. 2015;5:10905.	Not TURBT, used flexible cystoscopy
Shen YJ, Zhu YP, Ye DW, Yao XD, Zhang SL, Dai B, et al. Narrow-band imaging flexible cystoscopy in the detection of primary non-muscle invasive bladder cancer: a "second look" matters? Int Urol Nephrol. 2012;44(2):451-7.	Not TURBT, used flexible cystoscopy
Naselli A, Introini C, Timossi L, Spina B, Fontana V, Pezzi R, et al. A randomized prospective trial to assess the impact of transurethral resection in narrow band imaging modality on non-muscle-invasive bladder cancer recurrence. Eur Urol. 2012;61(5):908-13.	Included recurrence cases > 30%
Naselli A, Introini C, Bertolotto F, Spina B, Puppo P. Feasibility of transurethral resection of bladder lesion performed entirely by means of narrow-band imaging. J Endourol. 2010;24(7):1131-4.	Included recurrence cases > 30%
de la Rosette J, Gravas S. A multi-center, randomized international study to compare the impact of narrow band imaging versus white light cystoscopy in the recurrence of bladder cancer. J Endourol. 2010;24(5):660-1.	Same patients in Naito et al, 2016[46]

Abbreviations: HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging; TURBT, transurethral resection of bladder tumour.

Table A4: Excluded Prior Systematic Reviews

Citation	Reasons for Exclusion
Chen C, Huang H, Zhao Y, Liu H, Luo Y, Sylvester RJ, et al. Diagnostic accuracy of photodynamic diagnosis with 5-aminolevulinic acid, hexaminolevulinate and narrow band imaging for non-muscle invasive bladder cancer. J Cancer. 2020;11(5):1082-93.	Included non-RCTs, non-English articles Included surveillance cystoscopy Included non-first TURBT or recurrence cases > 30%
Konecki T, Kutwin P, Łowicki R, Juszczak AB, Jabłonowski Z. Hexaminolevulinate in the management of nonmuscle invasive bladder cancer: a meta-analysis. Photobiomodul Photomed Laser Surg. 2019 Sep;37(9):551-558.	Included non-RCTs Included non-first TURBT or recurrence cases > 30% Included some studies now updated
Chou R, Selph S, Buckley DI, Fu R, Griffin JC, Grusing S, et al. Comparative effectiveness of fluorescent versus white light cystoscopy for initial diagnosis or surveillance of bladder cancer on clinical outcomes: systematic review and meta-analysis. J Urol. 2017;197(3 Pt 1):548-58.	Included non-first TURBT or recurrence cases > 30% Included some studies now updated
Gakis G, Fahmy O. Systematic review and meta-analysis on the Impact of hexaminolevulinate- versus white-light guided transurethral bladder tumor resection on progression in non-muscle invasive bladder cancer. Bladder Cancer. 2016;2(3):293-300.	Included non-RCTs Included non-first TURBT or recurrence cases > 30% Included some studies now updated
Di Stasi SM, De Carlo F, Pagliarulo V, Masedu F, Verri C, Celestino F, et al. Hexaminolevulinate hydrochloride in the detection of nonmuscle invasive cancer of the bladder. Ther Adv Urol. 2015;7(6):339-50.	Included non-RCTs, non-English articles Included surveillance cystoscopy Included non-first TURBT or recurrence cases > 30% Included some studies now updated
Lee JY, Cho KS, Kang DH, Jung HD, Kwon JK, Oh CK, et al. A network meta-analysis of therapeutic outcomes after new image technology-assisted transurethral resection for non-muscle invasive bladder cancer: 5-aminolaevulinic acid fluorescence vs hexylaminolevulinate fluorescence vs narrow band imaging. BMC cancer. 2015;15:566.	Included conference abstracts Included non-first TURBT or recurrence cases > 30% Included some studies now updated
Burger M, Grossman HB, Droller M, Schmidbauer J, Hermann G, Drăgoescu O, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: a meta-analysis of detection and recurrence based on raw data. Eur Urol. 2013;64(5):846-54.	Included non-RCTs, non-English articles Included non-first TURBT or recurrence cases > 30% Included some studies now updated
Rink M, Babjuk M, Catto JW, Jichlinski P, Shariat SF, Stenzl A, et al. Hexyl aminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: a critical review of the current literature. Eur Urol. 2013;64(4):624-38.	Included non-RCTs Included surveillance cystoscopy Included non-first TURBT or recurrence cases > 30%
Yuan H, Qiu J, Liu L, Zheng S, Yang L, Liu Z, et al. Therapeutic outcome of fluorescence cystoscopy guided transurethral resection in patients with non-muscle invasive bladder cancer: a meta-analysis of randomized controlled trials. PloS One. 2013;8(9):e74142.	Included some studies now updated

Abbreviations: RCT, randomized controlled trial; TURBT, transurethral resection of bladder tumour.

Appendix 4: Forest Plots Based on Risk Difference Measure

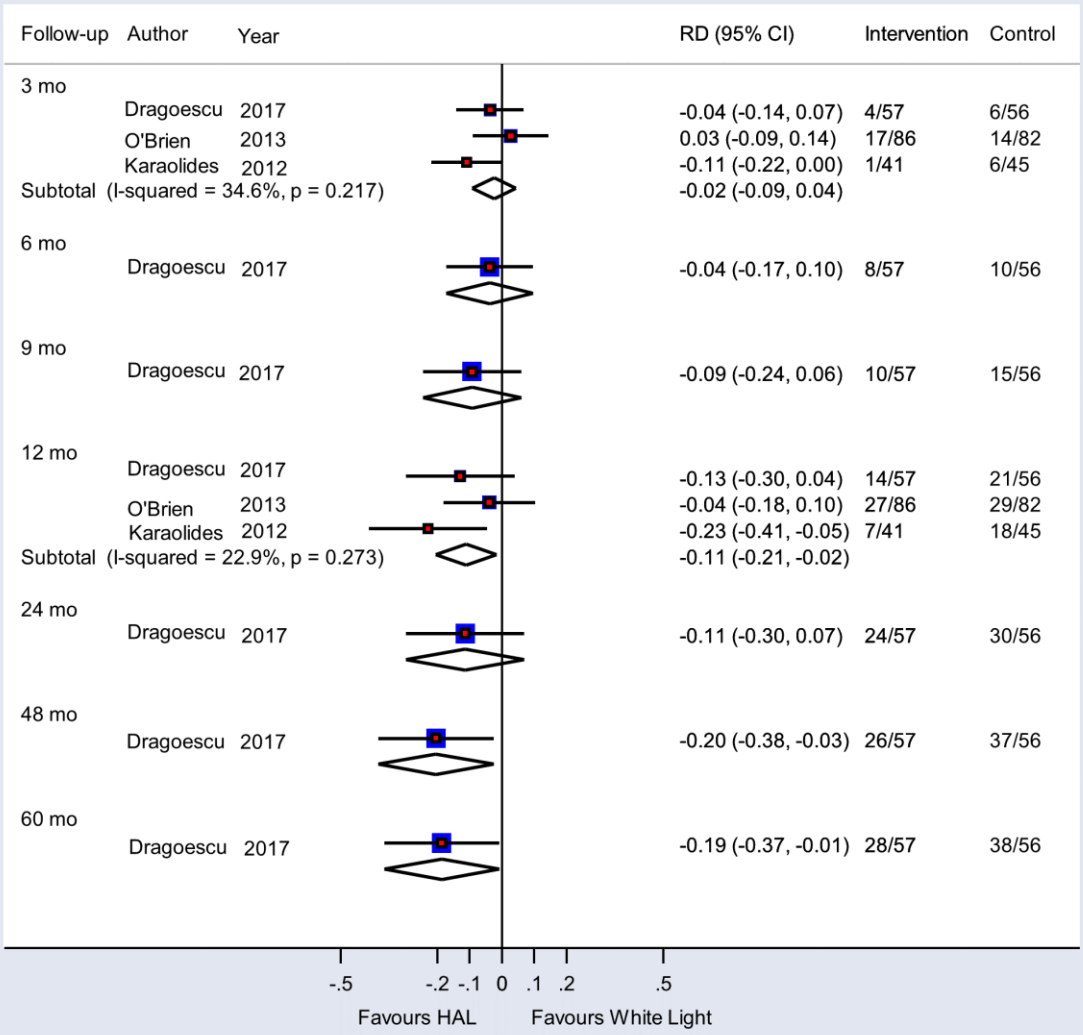

Figure A1: Risk Differences for Recurrence Rate After TURBT Guided by HAL Versus White Light Alone

Abbreviations: CI, confidence interval; HAL, hexaminolevulinate hydrochloride; mo, months; RD, risk difference.
Sources: Dragoescu et al, 2017[43]; Karaolides et al, 2012[44]; O'Brien et al, 2013.[47]

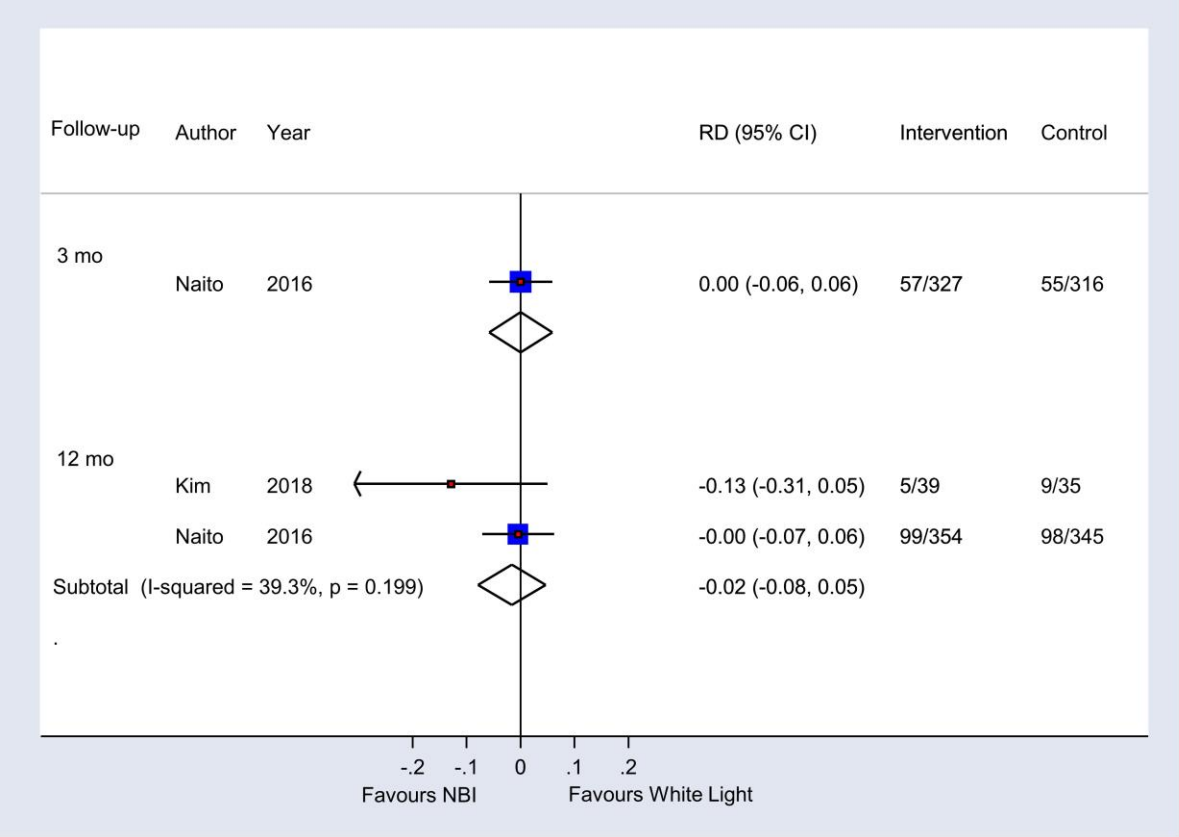

Figure A2: Risk Differences for Recurrence Rate After TURBT Guided by NBI Versus White Light Alone

Abbreviations: CI, confidence interval; NBI, narrow band imaging; mo, months; RD, risk difference.
Sources: Kim et al, 2018[45]; Naito et al, 2016.[46]

Appendix 5: Validity of Adjusted Indirect Treatment Comparison

Table A5: Heterogeneity Among Studies for Indirect Comparison

Parameter of Heterogeneity	Risk Ratio	Risk Difference
Q	4.53, df (3); P = .21	4.22, df (3); P = .24
I^2	33.8%	28.9%
τ^2	0.0494	0.0025

Abbreviation: df, degree of freedom.

Table A6: Design-Specific Decomposition of Within-Designs *Q* Statistic

Design	Risk Ratio	Risk Difference
HAL vs. WL	Q = 2.83, df (2); P = .2433	Q = 2.58, df (2); P = .2747
NBI vs. WL	Q = 1.71, df (1); P = .1916	Q = 1.64, df (1); P = .2009

Abbreviation: df, degree of freedom; HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging; WL, white light.

Appendix 6: Classification of Surgical Complications

Table A7: Clavien-Dindo Grading System for Classification of Surgical Complications

Grade	Description
I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
II	Requiring pharmacological treatment with drugs other than such allowed for grade 1 complications Blood transfusions and total parenteral nutrition are also included
III	Requiring surgical, endoscopic, or radiological intervention
IIIa	Intervention not under general anesthesia
IIIb	Intervention under general anesthesia
IV	Life-threatening complication (including CNS complications) requiring IC/ICU management
IVa	Single organ dysfunction (Including dialysis)
IVb	Multiorgan dysfunction
V	Death of a patient

Abbreviations : CNS, central nervous system; IC, intensive care; ICU, intensive care unit.
Source: Dindo et al, 2004.[54]
Note: A suffix "d" was also added to the classification where a patient suffers from a complication at the time of discharge.

Appendix 7: Selected Excluded Studies—Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary Reason for Exclusion
Dansk , V., Malmstrom, P., Blackberg, M., Malmenas, M. Hexaminolevulinate hydrochloride blue-light flexible cystoscopy in the detection and follow-up of nonmuscle-invasive bladder cancer: cost consequences during outpatient surveillance in Sweden. Future Oncology. 2016;12(8): 1025-1038.	Wrong intervention (flexible cystoscopy)
Mowatt G, Zhu S, Kilonzo M, Boachie C, Fraser C, Griffiths T R L. Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers (FISH, ImmunoCyt, NMP22) and cytology for the detection and follow-up of bladder cancer. Health Technol Assess 2010;14(4)	Wrong intervention (not specific to transurethral resection of bladder tumours)
Burger, M., Petschl, S. & Volkmer, B. Calculating the price of a new diagnostic or therapeutic option. Example of transurethral resection of bladder tumors using photodynamic diagnostics with hexaminolevulinic acid. Urologe. 2008;47: 1239–1244	Cost analysis
Burger M, Zaak D, Stief CG, et al. Photodynamic diagnostics and noninvasive bladder cancer: is it cost-effective in long-term application? A Germany-based cost analysis. Eur Urol. 2007;52(1):142-147.	Wrong intervention (5-aminolevulinic acid)
Rose JB, Armstrong S, Hermann GG, Kjellberg J, Malmström PU. Budget impact of incorporating one instillation of hexaminolevulinate hydrochloride blue-light cystoscopy in transurethral bladder tumour resection for patients with non-muscle-invasive bladder cancer in Sweden. BJU Int. 2016;117(6B):E102-E113.	Cost analysis

Appendix 8: Results of Applicability Checklist for Studies Included in the Economic Literature Review

Table A8: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of HAL and NBI for First Transurethral Resection of Bladder Tumour in Suspected Non-muscle-invasive Bladder Cancer

Author, Year, Country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Malmstrom et al, 2009[59] Sweden	Yes	Partially	No	Yes, Swedish health service	Yes	No, 1-year time horizon	No	No, not a societal perspective	Partially applicable
Garfield et al, 2013[60] US	Yes	Partially	No	Yes, health care payer	Yes	No, not specified	Yes	No, not a societal perspective	Partially applicable
Roupret et al, 2015[62] France	Yes	Partially	No	Yes, French health care system	Yes	Yes, 2.5%	Yes	No, not a societal perspective	Partially applicable
Klaassen et al, 2017[6] Canada	Yes	Partially	Yes	Yes, Ontario health care system	Yes	No, not specified	No	No, not a societal perspective	Partially applicable
Gakis et al, 2019[64] Germany	Yes	Partially	No	Yes, German health care system	Yes	Yes, 3.5%	Yes	No, not a societal perspective	Partially applicable

Abbreviations: HAL; hexaminolevulinate hydrochloride; NBI, narrow band imaging.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Appendix 9: Clinical Pathways Used in the Primary Economic Evaluation

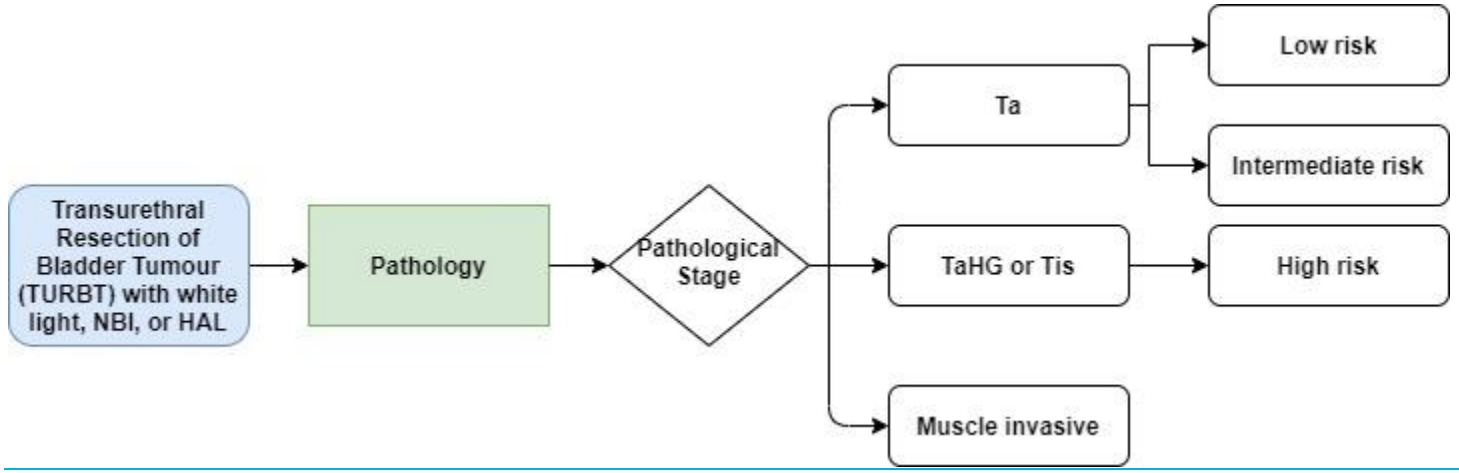

Figure A3: First Transurethral Resection of Bladder Tumour and Staging, Clinical Pathway

Abbreviations: HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging; Ta, noninvasive papillary carcinoma; TaHG, high-grade papillary urothelial carcinoma; Tis, carcinoma in situ.

Source: Cancer Care Ontario, 2018.[30]

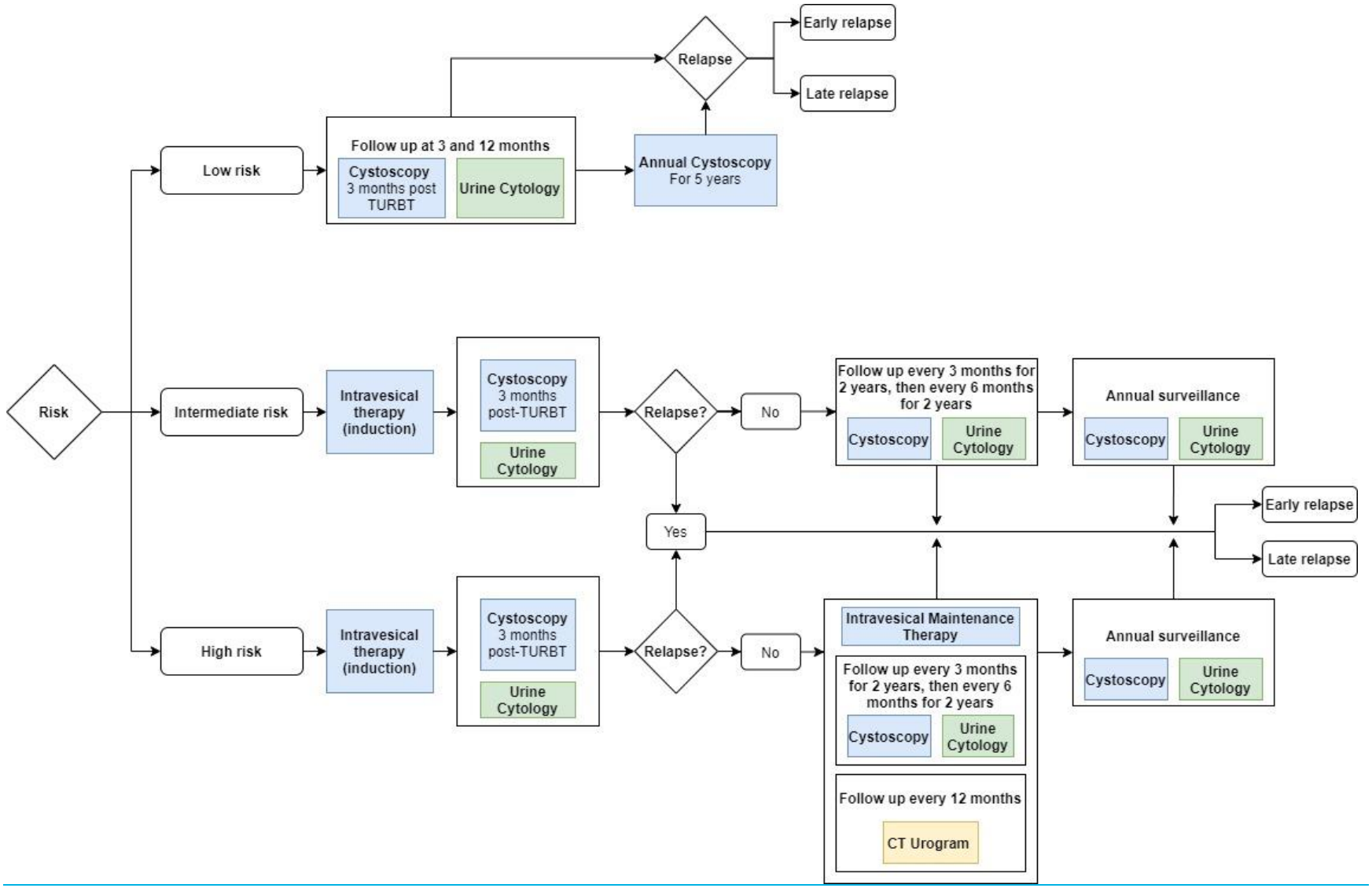

Figure A4: Non-muscle-invasive Bladder Cancer, Clinical Pathway

Abbreviations: CT, computed tomography; TURBT, transurethral resection of bladder tumour.
Source: Cancer Care Ontario, 2018.[30]

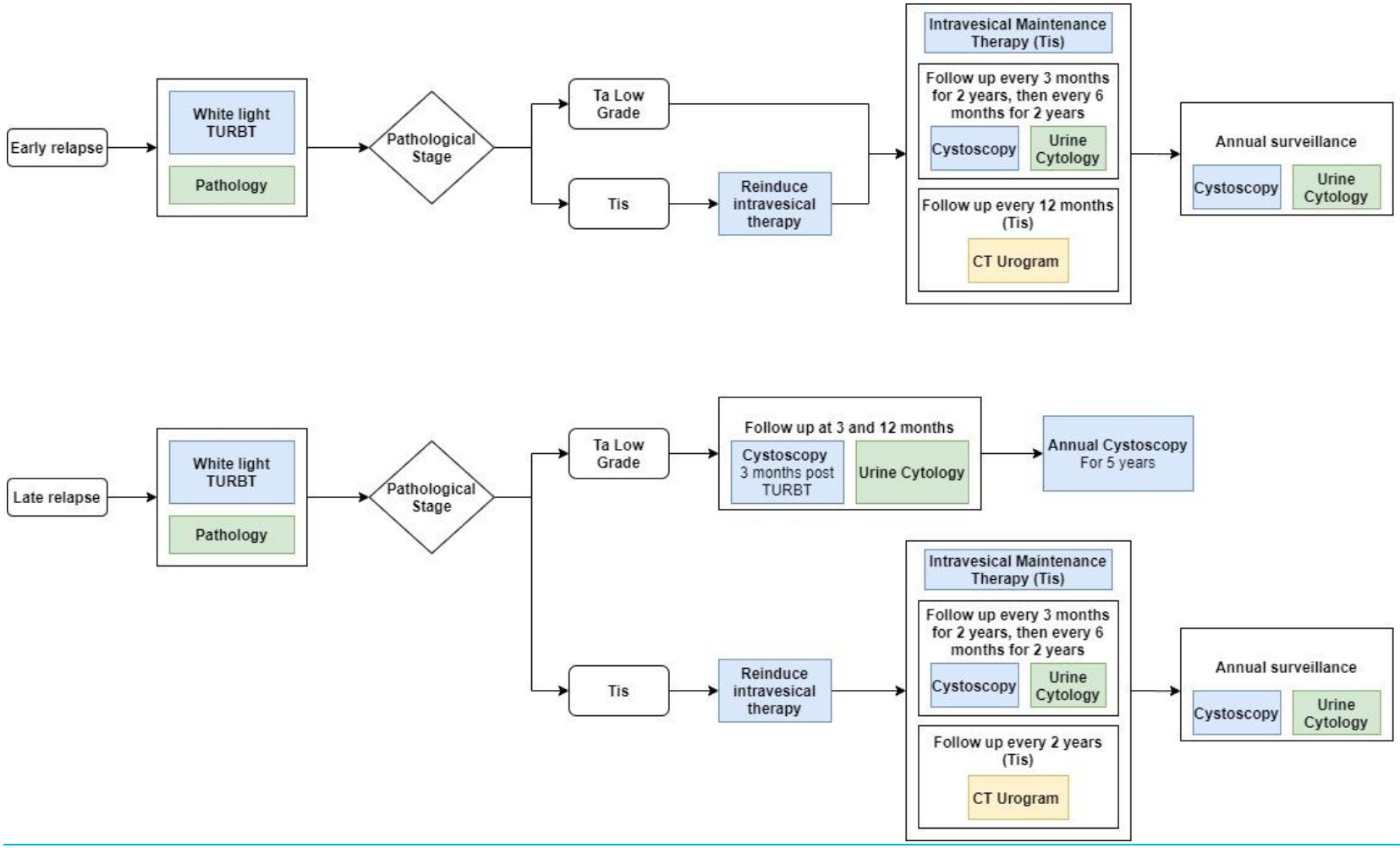

Figure A5: Non-muscle-invasive Bladder Cancer Recurrence, Clinical Pathway

Abbreviations: CT, computed tomography; Ta, noninvasive papillary carcinoma; Tis, carcinoma in situ; TURBT, transurethral resection of bladder tumour.
Source: Cancer Care Ontario, 2018.[30]

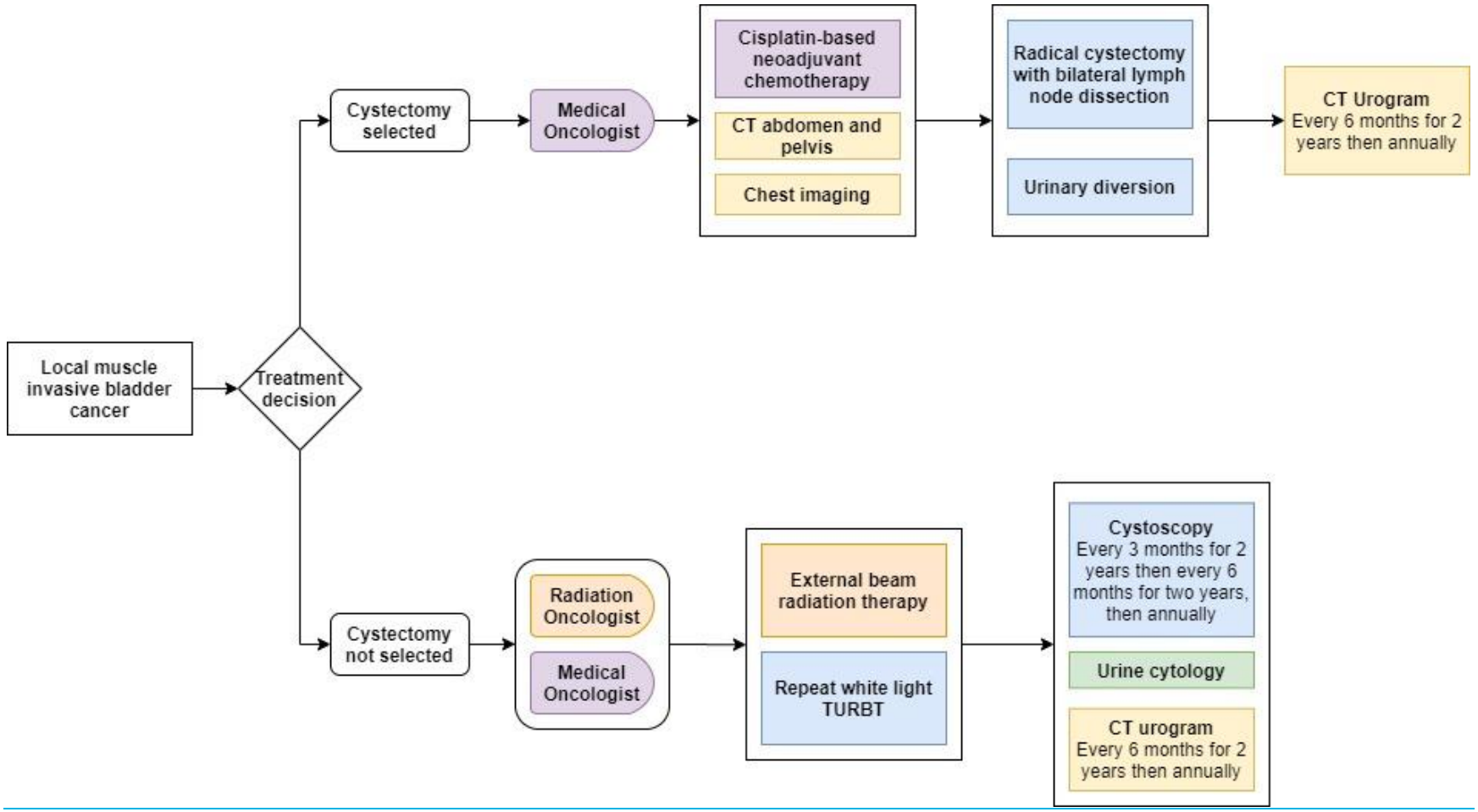

Figure A6: Muscle-Invasive Bladder Cancer, Clinical Pathway

Abbreviations: CT, computed tomography; TURBT, transurethral resection of bladder tumour.
Source: Cancer Care Ontario, 2018.[30]

Appendix 10: Primary Economic Evaluation, Additional Methods And Results

Table A9: Probabilistic Inputs for Costs

Variable	Unit Cost	Standard Error	Reference
TURBT, day surgery	1,621.00	9.52	CCI 1.PM.87.BA
Cystoscopy, day surgery	313.00	1.32	CCI 2.PM.70.BA
Intravesical therapy, day surgery	372.00	5.30	CCI 1.PM.35.^^
Radical cystectomy, inpatient admission	27,410.00	1,131.56	CCI 1.PM.91.^^
External beam radiation, ambulatory	338.00	9.78	CCI 1.PM.27.JA
Systemic chemotherapy, ambulatory	2,236.00	18.27	CCI 1.ZZ.35.HA-M5
CT urograms, ambulatory	108.30	0.91	CCI 3.PZ.20.WC

Abbreviations: CCI, Canadian Classification of Interventions; CT, computed tomography; TURBT, transurethral resection of bladder tumour.

Table A10: Probabilistic Results of Threshold Analysis on Cost of HAL Solution[a]

Strategy[b]	Average Total Costs (95% CrI), $	Incremental Cost (95% CrI), $[b,c]	Average Total QALYs (95% CrI)	Incremental QALYs[b] (95% CrI)	ICER, $/QALY[c]
White light	19,762 (18,962; 20,578)	—	6.019 (5.717; 6.319)	—	—
HAL	19,828 (19,412; 21,141)	65 (−303; 384)	6.071 (5.766; 6.361)	0.052 (−0.018; 0.146)	1,269

Abbreviations: HAL, hexaminolevulinate hydrochloride; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

[a]Assumes the HAL solution cost is $274. At this price, the per-patient costs of HAL-guided TURBT and TURBT using white light alone are approximately equal.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

Table A11: Reference Case Analysis on Average Total Recurrences

Strategy[a]	Average Total Costs (95% CrI), $	Incremental Cost, $[b,c]	Average Total Recurrences (95% CrI)	Incremental Recurrences[c]	Cost per Recurrence Prevented[c,d]
NBI	19,713 (18,893; 20,526)	—	0.370 (0.308; 0.438)	—	—
White light	19,762 (18,962; 20,578)	—	0.382 (0.352; 0.413)	—	Dominated
HAL	20,262 (19,412; 21,141)	549	0.305 (0.232; 0.388)	−0.065	8,446

Abbreviations: CrI, credible interval; NBI, narrow band imaging; HAL, hexaminolevulinate hydrochloride.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Negative costs indicate savings.

[c]Results may appear inexact due to rounding.

[d]White light was dominated, by having higher average total cost and higher average total recurrences compared to NBI. We then compared HAL versus NBI. The negative incremental recurrence (−0.065) indicated the smaller recurrence incurred in the HAL group (i.e., better health outcome). We calculated cost per recurrence prevented using the incremental cost divided by the absolute value of incremental recurrence.

Appendix 11: Budget Impact Analysis, Additional Cost Inputs

Table A12: Annual Cumulative Costs by Intervention

Scenario	Cost per Patient, $				
	Year 1	Year 2	Year 3	Year 4	Year 5
Reference Case					
White light	11,424	13,933	15,370	16,463	17,224
HAL	12,222	14,653	16,013	17,074	17,798
NBI	11,424	13,919	15,343	16,431	17,186
25% Reduction in HAL Solution Price					
HAL	12,045	14,476	15,836	16,897	17,621
50% Reduction in HAL Solution Price					
HAL	11,868	14,299	15,659	16,720	17,444

Abbreviations: HAL, hexaminolevulinate hydrochloride; NBI, narrow band imaging.

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