Farmeconomia. Health economics and therapeutic pathways 2014; 15(3): 81-94
http://dx.doi.org/10.7175/fe.v15i3.944

ORIGINAL RESEARCH

Cost-effectiveness analysis of hexaminolevulinate (Hexvix®) guided cystoscopy in Non-Muscle Invasive Bladder Cancer patients (NMIBC) in Italy

Craig Bennison [1], Stephanie Stephens [1], Giario Natale Conti [2]
[1] Pharmerit Ltd, York, England
[2] Sant'Anna Hospital, Como, Italy

ABSTRACT

OBJECTIVE: To estimate the incremental cost-effectiveness of hexaminolevulinate (Hexvix®) + Blue Light (H+BL) cystoscopy (compared to white light cystoscopy only) when used at initial transurethral resection of the bladder tumour (TURBT) for patients diagnosed with non-muscle invasive bladder cancer (NMIBC) in Italy.
METHODS: A cost-effectiveness model has been developed to estimate the incremental cost-effectiveness of introducing H+BL at initial TURBT for patients diagnosed with NMIBC in Italy. The model consists of two parts: 1) a short term decision tree which estimates the outcome of the initial diagnostic procedure, and 2) a Markov cohort model which is used to estimate long term outcomes through extrapolation based on data and assumptions about patient management, the natural history of the disease and the empirical efficacy of H+BL in improving diagnosis detection and reducing recurrence. Cost-effectiveness results are expressed as incremental costs per QALY gained. Univariate and probabilistic sensitivity analyses are conducted to test the robustness of the model to changes in inputs and assumptions.
RESULTS: Base case results suggest that Hexvix® is a dominant strategy when used in the resection of NMIBC. Hexvix® is expected to be associated with 0.070 incremental QALYs, with cost savings of € 435 per patient. Sensitivity analyses suggest that the cost of Hexvix® and the relative risk of recurrence in intermediate and low risk groups are key drivers in the model. Probabilistic analyses indicate that Hexvix® is expected to be cost-effective in >99% of iterations, assuming a willingness to pay threshold of € 25,000 per QALY.
CONCLUSION: In conclusion, Hexvix® is expected to be a cost-effective strategy when used in the resection of NMIBC in Italy.

Keywords

Cost-effectiveness; Hexvix®; Cystoscopy; NMIBC

INTRODUCTION

Bladder cancer is a disease in which the cells lining the urinary bladder lose the ability to regulate their growth. As a consequence the cells start dividing uncontrollably. This abnormal growth results in a mass of cells that form a tumour. Symptoms of bladder cancer typically include gross haematuria and urinary tract symptoms [1]. Due to the highly recurrent nature of the disease, bladder cancer patients undergo intensive and costly routine monitoring and treatment, which combined with long survival makes bladder cancer one of the most expensive cancers to treat [1]. Bladder cancer can be broadly categorized into two main groups depending on the extent of penetration into the bladder wall: non-muscle invasive bladder cancer (NMIBC) or muscle invasive bladder cancer (MIBC). NMIBC is categorized by frequent recurrence of tumours and the potential to progress to muscle invasive disease [2]. The likelihood of recurrence and progression is determined by the risk profile of the patients, which is dependent on the severity of their disease [3]: low (solitary, primary low-grade Ta tumour), intermediate (multiple or recurrent low-grade tumours), and high risk (any T1 and/or G3 and/or carcinoma *in situ*).
Bladder cancer accounts for approximately 4.4% and 2.2% of all cancer cases worldwide in men and woman, respectively [4].

Corresponding author
Craig Bennison
cbennison@pharmerit.com

Disclosure
This analysis was funded by Ipsen.

In Italy during 2006-2009 urinary bladder cancer ranked 5th among the most frequently diagnosed cancers after colorectal, breast, prostate, and lung (10% of all cancers among males and 2.8% of all cancers among females) [5,6]. Regarding mortality, bladder cancer represents 3.6% of all cancer deaths (4.9% among male and 1.8% among females) [5].

Cigarette smoking and occupational exposure to urothelial carcinogens (aromatic amines such as benzidine and beta-naphthylamine) are the two most well-established risk factors for bladder cancer. Compared with non-smokers, cigarette smoking is associated with a 2 to 4 fold risk increase and an estimated population attributable risk for tobacco smoking of approximately 50% in both men and women [7].

The primary approach to the treatment of NMIBC in Italy is transurethral resection of the bladder tumour (TURBT) as indicated in the Italian Association of Medical Oncology (AIOM) guidelines [8]. During a diagnosis or patient follow up the physician passes a thin, rigid, tube-like telescope called cytoscape into the bladder through the patient's urethra and white light is used to help locate any abnormal growths or tumours. If any unusual growths or tumours are located on the bladder wall, the physician will resect by inserting a special wire loop through the cytoscope and passing an electric current down the wire loop. The electric current is used to cut or burn off the growth or tumour and border of healthy tissue around it. Immediately following the TURBT, patients may receive intravescical therapy with either chemotherapy (mitomycin C) or Bacillus Calmette-Guerin (BCG) [3]. This therapy is aimed at destroying any post-TURBT floating tumour cells which could end up replanting in the bladder wall. Follow-up after cystectomy includes clinical assessment and CT scanning.

Hexvix® (hexaminolevulinate) is an optical imaging agent designed to enhance detection and resection of bladder cancer by inducing selective accumulation of photoactive porphyrins in neoplastic cells, which fluoresce red under blue light accumulation. It has been shown in clinical trials that when compared to white light cystoscopy (WLC), Hexvix® enhances detection of lesions [9-11], furthermore by improving the completeness of the lesion resection and the subsequent tumour staging, Hexvix® results in a reduced number of recurrences and a more accurate risk classification [3].

Indeed, more carcinoma *in situ* (CIS) lesions were found by Hexvix® guided cystoscopy than by white light cystoscopy in 41.5% of patients [12], furthermore 32% of the patients with CIS and 16% of the patients with TaT1 tumours were detected with Hexvix® + blue light cystoscopy (H+BLC) only [13].

Improved resection and tumour staging allows the urologist/surgeon to make a more appropriate treatment decision (follow up cystoscopies and choice of adjuvant therapy), leading to improved recurrence free survival as shown in Jocham and colleagues' study [14] where 22% of patients received more appropriate treatment at the time of the study because of a more exact assessment of risk categories following H+BLC cystoscopy. Moreover, in patients with Ta/T1 lesions, H+BLC demonstrated a 16% relative reduction of short term tumour recurrence, compared to WLC alone ($p = 0.026$) [13]. With H+BLC urologists optimize management and increase control of their patients' bladder cancer by improving time to recurrence in the long-term, as shown in the Grossman and colleagues study [15] where median time to recurrence was 9.4 months in the WLC group and 16.4 months in the H+BLC group [15]. In an additional analysis of the 4.5 year follow up data, 83 patients (31.8%) in the WLC group and 97 patients (38%) in the H+BLC group remained tumour free after initial resection, respectively ($p = 0.14$). Finally, T2-T4 bladder cancer occurred twice as much in the WLC group (16 cases, 6.1%) compared to the H+BLC group (8 cases, 3.1%; $p = 0.066$) [15].

The objective of the present analysis is to estimate the incremental cost-effectiveness of Hexvix® + blue light cystoscopy (H+BLC) compared to white light cystoscopy (WLC) when used at initial TURBT in patients diagnosed with NMIBC in Italy.

METHODS

A cost-effectiveness model has been developed to estimate the incremental cost-effectiveness of H+BLC (compared to WLC only) when used at initial TURBT in patients diagnosed with NMIBC in Italy. The analysis was conducted with the perspective of the Italian National Health Service and over a lifelong time horizon to capture the entire incremental effect on costs and health outcomes over a patient's life. Incremental effects associated with H+BLC are estimated by following and comparing two realities: one representing WLC which is the standard of care and one in which Hexvix® is featured in the initial NMIBC treatment pathway.

The model is split into two parts: a short term decision tree which estimates the outcome of the initial diagnostic procedure, and a Mar-

kov cohort model which is used to estimate long term outcomes through extrapolation based on data and assumptions about patient management (based on the Italian clinical setting), the natural history of the disease and the empirical efficacy of H+BLC in improving diagnosis detection and reducing recurrence (Figure 1).

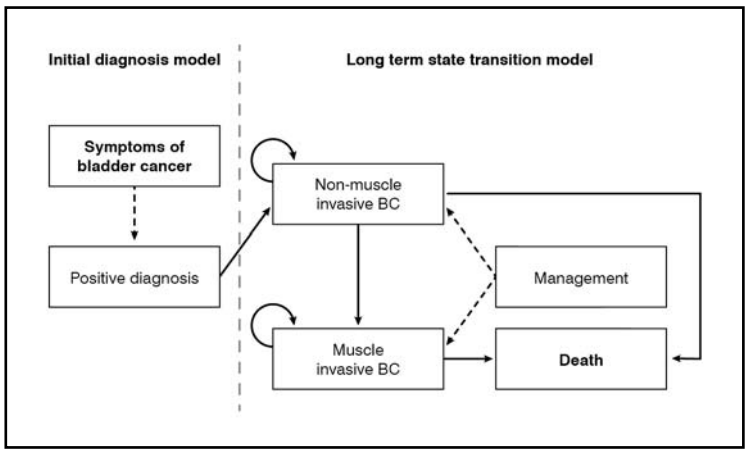

Figure 1. *Aggregate model structure*
BC = bladder cancer

Model structure

Decision tree for initial diagnosis

A cohort of 1000 patients who are presenting with symptoms of bladder cancer (microscopic or gross haematuria or lower urinary tract symptoms) enter the model at baseline. A certain percentage of these patients will have NMIBC. Muscle invasive bladder cancer (MIBC) patients are not considered at the start of the model. However, patients may progress to MIBC in the extrapolation period, in line with the natural progression of the disease.

The initial diagnosis is presented as a decision tree (Figure 2); patients enter the decision tree with symptoms of bladder cancer and then receive an initial test/patient work-up, which takes place in an outpatient setting. The exact nature of this initial test is not specified explicitly in the model as it does not create any incremental difference. It may consist of a mixture of flexible cystoscopy, cytology and/or biomarkers and may vary by country. This initial test is defined by a sensitivity and specificity, which when combined with a prevalence rate of NMIBC, determines the likelihood of a true positive, false positive, true negative or false negative test result.

It is assumed that all patients who test positive in the initial test will be taken forward to the operating room (OR) for a TURBT, either by H+BLC (intervention arm) or WLC only (standard of care arm).

Although it is acknowledged that this diagnosis process from start to finish may take weeks, or even months, the decision tree has no concept of time and instead represents a static 'snapshot' of the expected outcome distribution of a cohort of patients moving through such a diagnostic pathway. Each outcome of the decision tree is linked to a health state in the Markov model to establish starting health state distributions for the extrapolation period.

False positive patients incur the cost of the initial test and the cost of a TURBT (with a proportion getting mitomycin). It is then assumed that their status as false positives will be established at the post-TURBT biopsy, and they will also be discharged. False positive and true negative patients are moved to a cancer free state for the start of the extrapolation.

True positive patients incur the cost of an initial test and a TURBT (with a proportion getting mitomycin). Based on what was discovered during the initial TURBT, true positive patients are stratified into one of three risk groups – defined by the stage and grade of the tumours present in their bladder. The following definitions of risk group are used, according to the European Organisation for

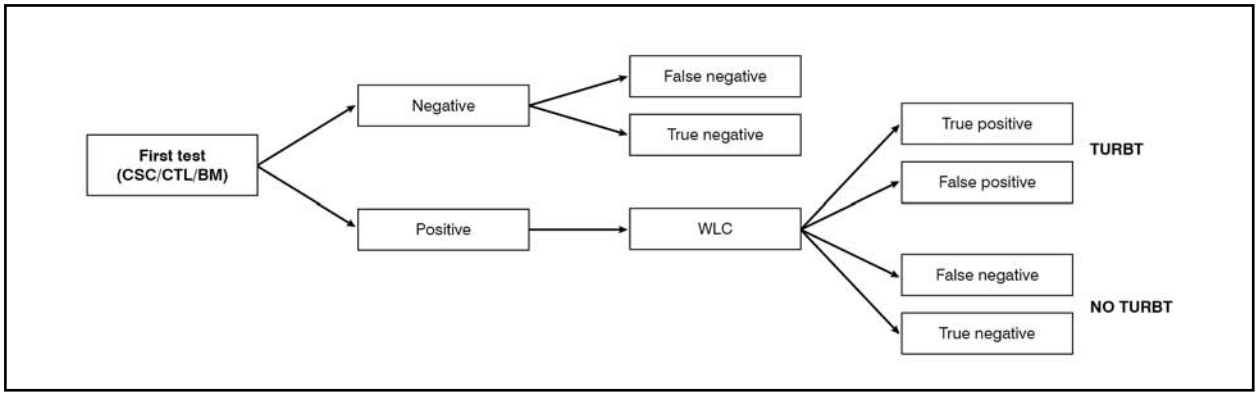

Figure 2. *Structure of the decision tree for the initial diagnosis*

Research and Treatment of Cancer (EORTC) risk tables [9]:

- low-risk: solitary, primary low-grade TaG1/G2 tumour;
- intermediate risk: multiple or recurrent low-grade TaG1/G2 tumours;
- high risk: any T1 and/or TaG3 and/or carcinoma in situ.

In line with the European Urology Association (EUA) guidelines [3] and usual patient management in Italy [16], high risk patients will receive an early TURBT at 6 weeks, followed by BCG treatment, which consists of an induction course of weekly injections over a 6 week period, followed by instillations of weekly injections over 3 weeks at 3 months, 6 months, 12 months, 18 months, 24 months and 30 months.

The extrapolation period of the model uses a patient's risk group to determine their chance of both recurrence and progression, as well as their frequency of follow-up and post-TURBT management.

Patients who receive a false negative diagnosis become 'missed' patients, as they have been discharged despite having cancer. These patients are followed and assumed to re-enter the model at a later stage (for example when their symptoms worsen or no other cause for their symptoms is found). While untreated, it is assumed that these patients have a higher relative risk of progression to reflect the fact that they have cancer which has not been appropriately remedied.

Markov model

The second stage of the model is a Markov cohort model, which captures the prognosis of patients following their initial diagnostic procedure. In the base case, the model follows all patients who received a TURBT (true positive and false positive patients). The structure of the model reflects the current guidelines for NMIBC patient follow-up [3], and is based on real-life evidence of bladder cancer evolution in terms of recurrence and progression as observed from observational studies; with inputs adapted to reflect Italian clinical practice with regards to patient management, from initial resection to follow up and monitoring for recurrence and progression (for details see the paragraph Model Parameters). The model time horizon is adjustable, but set to lifetime for the base case to capture the entire incremental effect on costs and QALYs over a patient's life. The starting age of the cohort is 67, in line with a systematic literature review conducted to inform a previously published HTA [1]. The cycle length of the model is set to 3 months, which has been chosen to adequately capture the frequency of follow-up in bladder cancer patients in all risk groups.

In total, the extrapolation phase of the model consists of 21 health states which are reflective of the status any given patient may have at any given time in the model and are defined by a patient's risk group, and the outcome of the initial diagnosis, or the outcome of a patient's most recent follow-up: no tumour (true negative), false positive, recurrence (true positive), false negative (false negative at follow-up) and missed patient (a false negative at primary diagnosis). Note that there is no recurrence state for low risk patients, this is because low risk patients who have a recurrence are subsequently considered to be intermediate risk patients [3].

The health states are further differentiated according to whether or not a patient is pre-recurrence or post-recurrence. There is no evidence to suggest that any residual benefit from an initial H+BLC resection should persist beyond a subsequent resection by WLC due to a recurrence. Therefore, patients are only able to experience the benefit of Hexvix® up until their first recurrence. Post-recurrent patients will face the same recurrence risk as WLC patients, to reflect that their most recent resection was conducted under WLC. There are also two states representing patients who have progressed to MIBC, locally muscle invasive (LMI) and metastases, as well as a state for patients who are cancer free (true negative and false positive patients at initial diagnosis). An absorbing state for patients who are dead (from cancer, treatment, procedure or otherwise) is also considered.

The frequency of patient follow-up is dependent on risk group. The following frequencies are based on the EUA guidelines [3], and have been validated by an Italian clinical expert [16]:

- low risk patients are followed up at 3 months, 9 months and then annually thereafter;
- intermediate patients are followed up at 3 months, 9 months and then bi-annually;
- high risk patients are followed up at 3 months, then every 3 months thereafter.

The health states in the Markov model are linked to the outcomes of the decision tree to establish starting distributions (Figure 3).

For NMIBC patients, follow-up visits involve a similar diagnostic procedure as the initial diagnostic pathway. Instead of an unspecified initial test, patients will be first examined with a flexible cystoscopy, followed by a TURBT if required. The base case model will only include H+BLC at the primary diagnosis, therefore all follow-up TURBTs will be assisted by WLC. True negative or false

negative patients will incur the cost of flexible cystoscopy only, and will be discharged until their next follow-up visit.

Management of true positive or false positive patients depends on the patient's risk group [16]:

- low risk patients will incur the cost of a TURBT, and will receive one instillation of mitomycin, and move to intermediate risk in the event of recurrence;
- intermediate risk patients incur the cost of a TURBT, and will receive one instillation of mitomycin. These patients also have a chance of being re-evaluated as being high risk;
- high risk patients will incur the cost of a TURBT, and will receive one instillation of mitomycin. Patients will receive BCG therapy with re-TURBT.

Patients who have progressed to MIBC are assumed to receive a TURBT, a computerized tomography (CT) scan and either cystectomy if LMI or cystectomy and palliative care if metastatic [16]. These patient management pathways are in alignment with the EAU guidelines [3] and have been validated by an Italian expert [16].

Throughout the extrapolation phase of the model, patients may move between health states according to how their disease recurs or progresses, and the outcomes of their follow-up visits. In any particular cycle, NMIBC patients may stay in their no tumour state, recur, progress to MIBC or die. Local MIBC patients may stay in their state, progress to metastases, or die. Metastatic patients may either stay in their state or die (Figure 4). These transitions are given further granularity according to the outcome of patient follow-up. If the patient has a follow-up visit during a cycle, it may result in recurrence (true positive), no tumour recurrence (true negative), false positive, false negative, progression or death. The risk group split reflects each patient's probability to recur, progress and die, as well as move to a higher risk group.

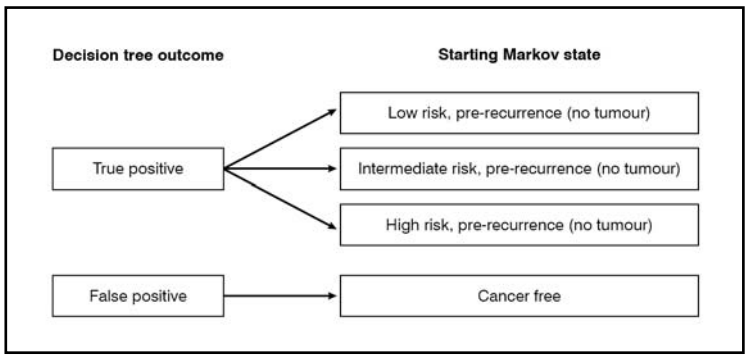

Figure 3. *Link between decision tree primary diagnosis and the Markov health states*

Model parameters

Prevalence of bladder cancer

The prevalence of bladder cancer in the symptomatic population is not available from the literature. Based on estimates provided by expert opinion, it is assumed that 20% of patients who present with bladder cancer symptoms are indeed true positive patients [16].

Technology performance

The performance of flexible cystoscopy and of WLC has been taken from a UK-based

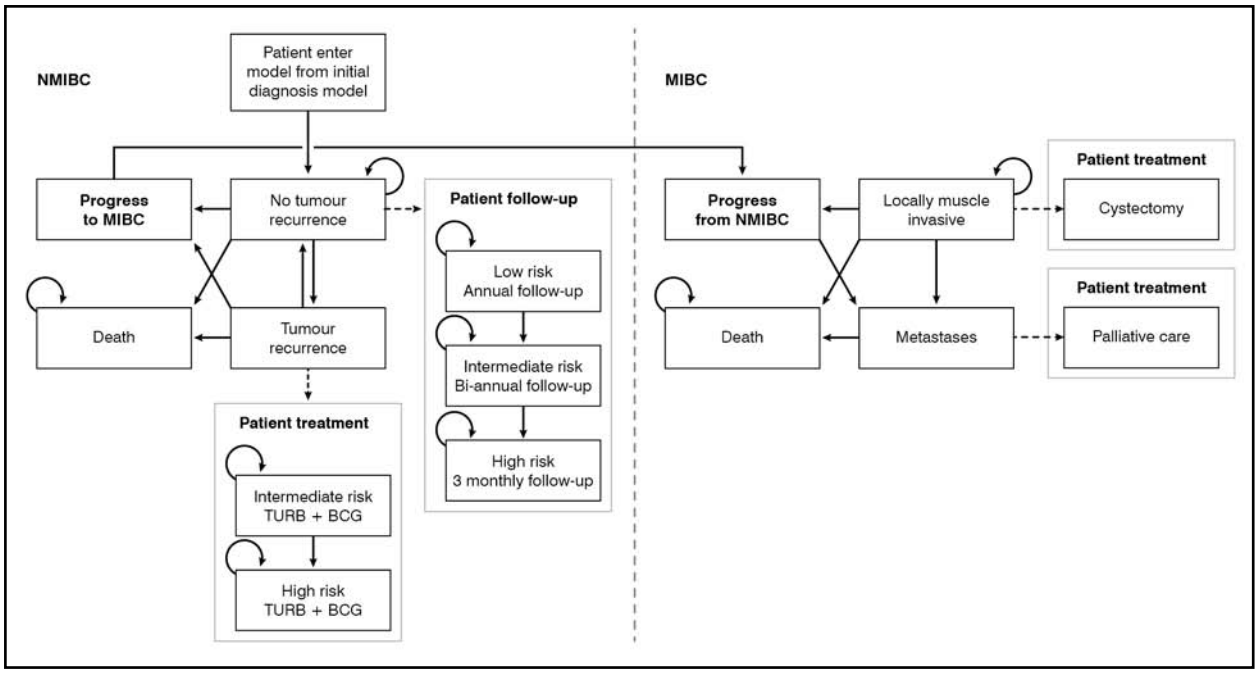

Figure 4. *Health states transitions*

model [1]. The estimates for WLC have been adjusted to estimate the sensitivity and specificity of H+BLC based on the results from the meta-analysis of Burger and colleagues [17]. This adjustment is based on the additional detection that H+BLC exhibited over white light in patients with a solitary CIS. In the meta-analysis, H+BLC detected 15.38% more solitary CIS (i.e. true positive patients vs. false negative patients) than WLC. Therefore, the sensitivity of H+BLC (relative to WL) has been inflated by 15.38%, resulting in a sensitivity of 0.82. This value is reached by estimating the relative detection with H+BLC versus WLC (60/52) and multiplying this with the sensitivity of WLC (71.0).

Risk distribution

Different risk stratifications for WLC and H+BLC are assumed due to the improved detection rates observed when using Hexvix®. For WLC it is assumed that 20% of patients are low risk, 50% are intermediate risk and 30% are high risk [16]. For Hexvix® it is assumed that fewer patients will be in low risk, more patients in intermediate risk and similar proportions in high risk, based on the findings from the meta-analysis of Burger and colleagues (18.93%, 51.07% and 30.00%, respectively) [17].

General population mortality rates

General population mortality rates have been taken from Italian life tables [18]. Because bladder cancer specific mortality rates are applied on top of the general population mortality rates, there may be some degree of double counting as population bladder cancer mortality will be captured to a small extent in the general population rates. The general population mortality estimates have been weighted to reflect the fact that approximately 70% of bladder cancer patients are male.

Recurrence progression and cancer specific mortality rates

The recurrence, progression and mortality rates for NMIBC have been taken from a study by Millan-Rodriguez and colleagues [10]. This was a retrospective cohort study of 1,529 patients with primary NMIBC recorded in Spain in the years 1968-96. The model follow-up was only 5 years and so the recurrence, progression and mortality rates for subsequent years in the current model were estimated from the mean data for the last 3 years of the 5 year data. Recurrence, progression and mortality rates for local MIBC have been taken from a retrospective cohort study from Canada [11], in which 1,054 patients with MIBC were treated with radical cystectomy between 1971 and 1997. The patient characteristics in the study (80% male, mean age of 66) compare well to the cohort considered in the current model. Data was available for 10 years of follow-up. To allow population of the remaining model time horizon, it was assumed that the recurrence, progression and mortality rates are the same as the last 5 years of this 10 year data.

Mortality rates associated with metastatic disease have been estimated based on a study by von der Maase and colleagues [19]. The study investigated the long-term survival of metastatic bladder cancer patients in Denmark. The follow-up in the study was 5 years, beyond this time frame the mortality rate of metastatic cancer is assumed the same as between year 3 and 5 of the 5 year data.

Relative risk of recurrence for H+BLC

Evidence suggests that H+BLC results in a 'better quality' resection than WLC, resulting in more cancer being removed, fewer residual cancer cells remaining and a subsequently lower resulting probability of future recurrence [15]. This lower recurrence has been modelled using a relative risk of recurrence for each of the three risk groups: 0.661, 0.741, and 0.767 for low, intermediate, and high risk respectively [17].

Treatment

Based on clinical opinion, the following assumptions around concomitant treatment have been made [16]:

- 100% of patients receive mitomycin with their TURBT;
- 0% of recurrent intermediate risk patients will receive BCG therapy;
- 100% of high risk patients will receive BCG therapy.

Utilities and disutilities

Due to lack of evidence specific to NMIBC, it is assumed that the base utility value of patients in the model is in line with the UK EQ-5D index score for a 67 year old patient [20]. This utility value (0.78) is applied to all NMIBC patients and to local MIBC patients. The utility value for metastases (0.436) and disutilities for various treatments (cystectomy: 0.17-; TURBT: 0.1; BCG: 0.02) are derived from a cost-utility analysis, with 6 month cycles, conducted by Kulkarni and collegues [21].

Costs

The costs used in the analysis, alongside their sources, are shown in Table I (cost year 2012).

The cost of a CT scan, cystectomy, WL-assisted TURBT, and the cost of mitomycin and BCG have been provided by Italian experts [16]. The Healthcare Resource Groups

	Cost (€)	Source
TURBT (WL)	2,350.00	Average of TURBT (WL) cost from two regions: Regione Lombardia and Regione Friuli venezia Giulia [16]
TURBT (BL)	2,882.40	Assumed to be cost of WL-assisted TURBT plus the additional costs for Hexvix® (see Table II)
Flexible cystoscopy	540.98	UK National Health Service (NHS) reference costs 2011-2012 [22]. Reference cost LB14E, day case converted to € using exchange rate 15/01/13 (1GBP = 1.20846 Euro)
CT scan	744.00	[16]
Cystectomy	10,600.00	Average of cystectomy cost from two regions: Regione Lombardia and Regione Friuli venezia Giulia [16]
Palliative care	17,764.36	UK NHS reference costs 2011-2012 [22]. Assumed cost £392 per day for 37.5 days [16]. Reference cost SD01A, special palliative care: inpatient converted to € using exchange rate 15/01/13 (1GBP = 1.20846 Euro)
Mitomycin C	66.00	Internal evaluation at Sant'Anna Hospital [16]
BCG	70.00	Internal evaluation at Sant'Anna Hospital [16]

Table I. *Costs and their sources used in the model (cost year 2012)*

(HRGs) used to estimate the costs of palliative care and flexible cystoscopy have been verified with UK and Italian experts and have been converted to Euros (1GBP = 1.20846 Euros). The cost of Hexvix® is added to the cost of WL-assisted TURBT to get the Hexvix® assisted TURBT cost. The additional costs associated with using Hexvix® are shown in Table II.

Additional model assumptions

This model is based on real-life evidence, a meta-analysis of clinical evidence, Italian expert opinion, and assumptions if information was not available.

An assumption of this model concerns the probability of cancer detection in missed patients that was taken from the aforementioned published HTA [1] and has been validated with clinical experts (detection of missed patients: 25%, 50%, 75%, 100% for first 3 months, first year, end of second year, and end of third year, respectively), while the probability of moving from intermediate risk to high risk upon recurrence (0.133) was taken from the Kulkarni study [21]. Finally, if at any point a patient receives a false negative diagnosis, it is assumed that there is a higher chance for them to progress relative to a patient with a true positive result, who has been appropriately treated. The relative risk of progression is set to 2.56. This value was derived from the additional progression in patients who only received TURBT, compared to patients who received TURBT + BCG in the Millan-Rodriguez study [10]. This value was also used in the UK HTA report [1] and in a cost impact model developed by the UK's National Health System (NHS) [24].

Base case setting

The base case scenario evaluates (over a lifetime horizon) the cost-effectiveness of Hexvix® guided cystoscopy when:

- H+BLC is used at the resection stage in patients diagnosed with NMIBC;
- the starting age of the cohort is 67 years;
- the test at follow up is a flexible CSC;
- WLC is used for follow up TURBT's, for both arms.

Sensitivity analyses

The cost-effectiveness model has many parameters that work interactively to provide the model outcomes. It is often unclear without further analyses which parameters have the most significant impact on the model outcomes, although the cost and efficacy of the intervention under consideration are usually key drivers in any economic model. Hence, sensitivity analyses are used to investigate how sensitive a model is to changes in input parameter values. Uncertainty margins are applied to each input parameter of interest based on corresponding margins provided in the literature or based on assumptions if information is unavailable.

Univariate sensitivity analyses have been generated applying the assumption that the standard deviation is equal to 10% of the mean for all inputs. Lower and upper values for parameters varied in the univariate sensitivity analyses are reported in Appendix A.

	Cost (€)	Source
Consumables	10.00	[16]
Additional equipment	522.40	PhotoDynamic Diagnosis (PDD) light source, light cable, dedicated camera, and dedicated optic [16,23]. The equipment costs for each procedure are based upon costs of Hexvix® at € 430 (2012) and these costs of equipment from the KARL STORZ Gmbh&Co. data [23]. It is assumed that the lifespan of the equipment is 5 years with 100 procedures each year

Table II. *Additional costs for Hexvix®*

A probabilistic sensitivity analyses was also conducted. Here, each parameter is varied simultaneously and the resulting ICER is recorded. This constitutes one 'simulation'. A thousand simulations are performed, which gives a distribution of ICERs, and consequently, an idea of the overall uncertainty surrounding the ICER estimate presented in the base case analysis. For the probability of events occurring (such as the probability of moving from intermediate to high risk), sensitivity and specificity, and utility values a beta distribution was applied. This is because the beta distribution is restricted to the 0-1 space, in the same way as a probability is. A gamma distribution was fitted to costs and any resource use, as the gamma distribution cannot fall below zero (but is otherwise unrestricted). A normal distribution was used to model the relative risk of progression if not

	H+BLC	WLC	Incremental
Life expectancy (years)	11.003	10.970	0.033
QALYs	8.06	7.99	0.070
Total costs (€)	28,086	28,521	-435
Recurrence (n.)	195	229	-34
TURBTs (n.)	365	399	-34
Progression to MIBC (n.)	24	25	-1
ICER (€)		Dominant	

Table III. *Base case cost-effectiveness results in when H+BLC is used at initial TURBT (life expectancy, QALYs, and total costs are per patient)*

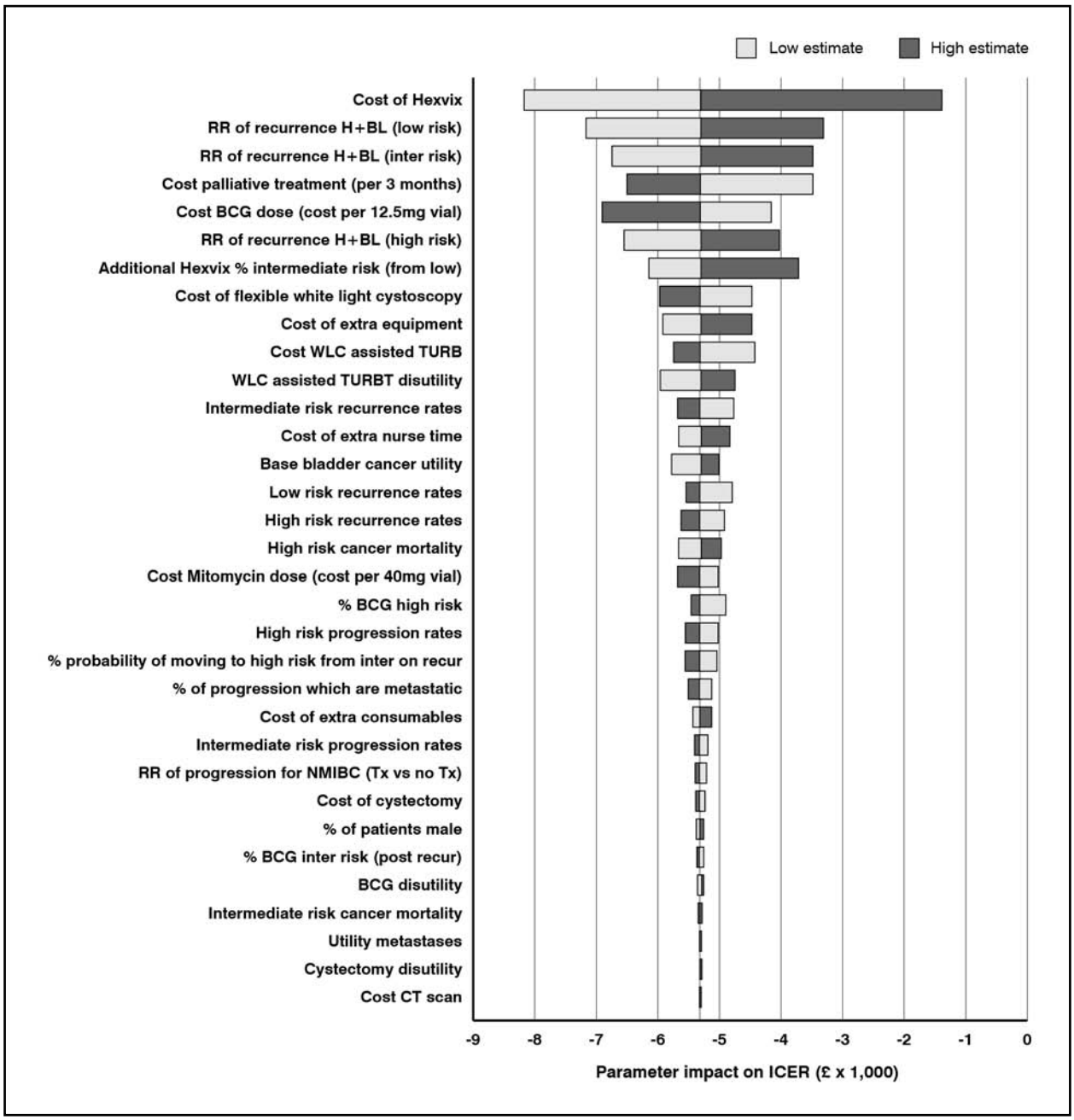

Figure 5. *Univariate sensitivity analysis: impact of parameters change on ICER*

treated. The mean of the distribution was set as the point estimate in the model. Due to not having appropriate observations to estimate the standard deviation for each parameter, the standard deviation was assumed to be equal to 10% of the mean. Distributions applied in the probabilistic sensitivity analyses are reported in Appendix A.

Scenario analysis

In the base case analysis, patients who were initially misdiagnosed to be false negative are not taken into account, and are discharged at the initial diagnosis procedure. In terms of false negative patients, it is likely that they will return later onwards and will be treated with Hexvix®. This analysis assumes that these patients will at some point return for further diagnostics, due to persistent or worsening symptoms. A second analysis assumes a shorter model time horizon of 5 years.

RESULTS

Base case analysis

The base case analysis shows that when H+BLC is used at initial TURBT, it is considered a dominant strategy when compared to WLC only. H+BLC is associated with cost savings related to additional patients diagnosed, treated and followed-up (-€ 435), but also with better health outcomes (0.070 QALYs gained and 0.033 life years gained), as well as a reduction in the number of recurrences, number of TURBTs and progression rates (Table III).

Sensitivity analysis

Univariate sensitivity analysis

Given the current inputs and assumptions in terms of the uncertainty surrounding these inputs, the cost of Hexvix® is expected to have the largest impact on the ICER. This is shown by the widest bar at the top of Figure 5. This is expected because the cost of the intervention under investigation is often a key driver of results from economic models. Other key model drivers appear to include the relative risk of recurrence in low risk patients, the relative risk of recurrence in intermediate risk patients and the cost of palliative treatment.

Probabilistic sensitivity analysis

The cost-effectiveness acceptability curve demonstrates the probability that Hexvix® is cost-effective at various willingness-to-pay thresholds, taking into account the uncertainty surrounding input parameters in a simultaneous manner. Figure 6 illustrates that at a cost-effectiveness threshold of 25,000 €/QALY, H+BLC is expected to be cost-effective in >99% of probabilistic iterations [25].

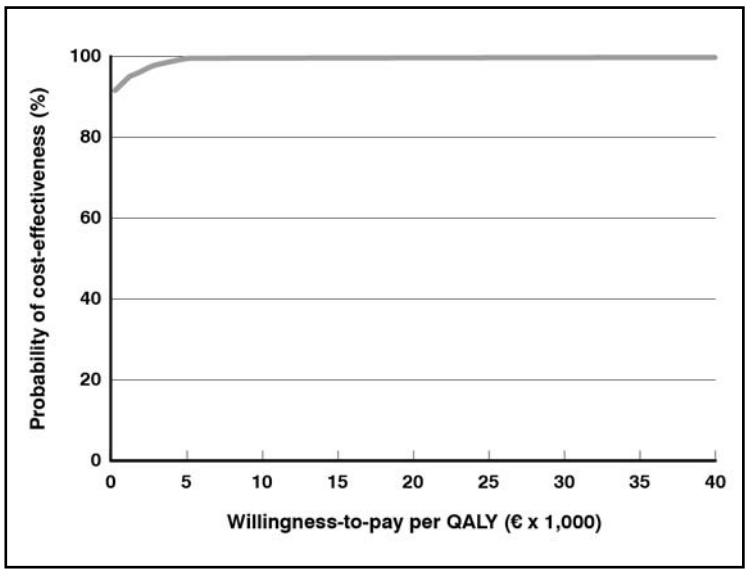

Figure 6. *Cost-effectiveness acceptability curve*

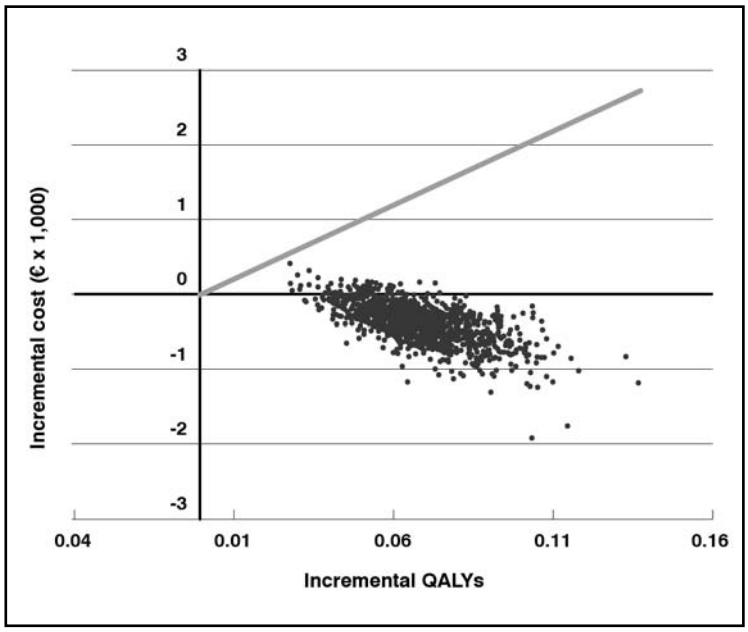

Figure 7. *Cost-effectiveness plane. Note: no simulations produced negative incremental QALYs.*

The cost-effectiveness plane plots each iteration of the probabilistic sensitivity analysis in order to illustrate the variation in incremental costs and effects when parameters are varied simultaneously within their specified uncertainty boundaries.

Given the current inputs and the assumption that each input has an uncertainty margin calculated based on a standard deviation equal to 10% of the mean, and assuming the distributions presented in Appendix, Figure 7 demonstrates that H+BLC is expected to be cost-saving in almost all cases (iterations are plotted on the bottom half of the figure).

	H+BLC	WLC	Incremental
Life expectancy (years)	12.034	12.027	0.007
QALYs	9.27	9.26	0.014
Total costs (€)	6,114	6,172	-58
Recurrence (n.)	256	302	-46
TURBTs (n.)	495	542	-47
Progression to MIBC (n.)	36	37	-1
ICER (€)		Dominant	

Table IV. *Cost-effectiveness results when Hexvix® is used in positive and false negative patients (calculated on 1000 patients with suspected bladder cancer; life expectancy, QALYs, and total costs are per patient) – lifelong timeframe*

	H+BLC	WLC	Incremental
Life expectancy (years)	4.333	4.331	0.001
QALYs	3.01	2.97	0.033
Total costs (€)	14,071	14,075	-4
Recurrence (n.)	92	115	-23
TURBTs (n.)	248	272	-24
Progression to MIBC (n.)	24	25	-1
ICER (€)		Dominant	

Table IV. *Cost-effectiveness results assuming a 5 year model time horizon (calculated on 1000 patients with suspected bladder cancer; life expectancy, QALYs, and total costs are per patient)*

According to the current model inputs and estimates of uncertainty surrounding these, H+BLC will always result in additional QALYs versus WLC.

Scenario analysis

H+BLC used in positive and false negative patients

When used in positive and false negative patients H+BLC is a dominant strategy as compared to WLC only and it is associated with better patients' health outcomes (0.014 QALYs gained and 0.007 life years gained), a reduction in healthcare expenditures (€ 58 decrease in total costs) and a lower risk of recurrence, TURBTs and progression (Table IV).

In this scenario the additional cost of Hexvix® is the biggest driver of the ICER and the PSA suggests that H+BLC has a probability of being cost-effective at a willingness to pay threshold of 25,000 €/QALY of >99%.

5 years model horizon

This analysis has demonstrated that H+BLC may still be considered a dominant strategy compared to WLC when analysed over a 5 year time horizon (Table V). Hexvix® is expected to be cost-effective in >99% of PSA interactions in this scenario.

DISCUSSION

Bladder cancer is the fourth most common malignancy among men in the Western world (after prostate, lung, and colon cancers) [26] and accounts for approximately 5-10% of all cancers in Europe and the United States [27]. The incidence of bladder cancer increases with age [27] and is up to 3-fold more common in men than in women [28].

The majority of bladder cancer (approximately 75-85%) are NMIBC which is characterized by its tendency to recur after resection and to progress to muscle invasive disease. Bladder cancer has the highest lifetime treatment costs per patient of all cancers from diagnosis to death due in particular to the subsequent high recurrence rates and need for ongoing invasive monitoring requirements [29].

Treatment of NMIBC is based on transurethral resection of the bladder (TURBTs) with post-treatment bladder instillations of chemotherapy or immunotherapy (adjuvant treatment). Due to the tendency of NMIBC tumors to recur, TURBTs are often repeated. Therefore, TURBTs usually represent the largest costs in terms of treatment expenditure for bladder cancer patients. The quality and result of the initial TURBT strongly determines the patient's prognosis and overall bladder cancer treatment costs. Better initial resection and staging could avoid additional TURBTs resulting in clinical, quality of life, and economic benefits.

The EAU guidelines recommend that if equipment is available, fluorescence-guided biopsy should be performed when bladder CIS is suspected (e.g. positive cytology, recurrent tumor with previous history of a high-grade lesion) [3].

Hexvix® is an optical imaging agent designed to enhance detection of bladder cancer. Furthermore, H+BLC helps improve resection and leads to more accurate staging and fewer residual tumours in patients with NMIBC [12,13].

A European expert panel recommended that H+BLC be used in patients with positive urine cytology but negative WLC for the assessment of tumour recurrences in patients not previously assessed with Hexvix® [30]. The recommendations also postulated that the use of H+BLC is likely to be advantageous in the initial follow-up of patients with CIS or multifocal tumours.

European economic studies have demonstrated that costs of fluorescence cystoscopy can be reduced through savings from fewer transurethral resections of the bladder (TURBTs) in follow-up. Sievert et al. [29] indicated that

initial H+BLC costs can potentially be offset by fewer TURBT follow-ups. In a Swedish study, Malmstrom et al. [2] reported that the avoidance of TURBTs and cystectomies by using H+BLC instead of WLC would result in a saving of € 137,461 to the health service. Finally, a cost impact model developed by the UK's NHS Technology Adoption Centre (NTAC) [24] estimated that H+BLC with TURBT could save over 2100 bed days across the NHS over 5 years.

The cost-effectiveness model presented here is based on Markov modeling techniques. The model was developed to assess the cost-effectiveness of Hexvix® when used in the resection of NMIBC over a lifelong time horizon in the Italian National Health Service.

Base case results suggest that Hexvix® is a dominant strategy when used in the resection of NMIBC. H+BLC is expected to be associated with 0.070 incremental QALYs, with cost savings of € 435 per patient. Hexvix® is also associated with a decrease in invasive procedures due to earlier diagnosis.

Sensitivity analyses suggest that the cost of H+BLC and the relative risk of recurrence in intermediate and low risk groups are key drivers in the model. Probabilistic analyses indicate that H+BLC is expected to be cost-effective in >99% of iterations, assuming a willingness to pay threshold of 25,000 €/QALY.

H+BLC is found to be dominant versus WLC when used in positive and false negative patients. In this scenario, H+BLC is associated with better patient outcomes and a reduction in healthcare expenditure offsetting the investment for Hexvix® technology (€ 58 decrease in total costs; 0.014 QALYs gained). Furthermore, improvement in resection completeness and tumor staging, and the subsequent lower risk of recurrence allow for more effective management of patients and decrease the number of recurrences and repeated procedures. This leads to better health outcomes for patients and offers some long-run savings to the Italian NHS.

Finally, H+BLC is considered dominant when modeled over a 5 year time horizon, demonstrating that the benefits of H+BLC in term of recurrence, TURBTs and progressions avoided are already evident over a short time-frame.

A key strength of the model presented here is its flexibility to model various scenarios, including various assumed risk distributions and NMIBC population assumptions. The model has a lifetime horizon, thus capturing all potential benefits of Hexvix® use. In particular, the benefits of H+BLC in terms of the evidence showing its enhanced detection of lesions, and benefits in terms of complete resection are explicitly modelled.

A limitation of the model concerns the inputs used for this Italian analysis. For some inputs, UK-based cost estimates have been converted to Euros to estimate the Italian input. Whilst this is not ideal, the UK costs were checked by an Italian clinical expert who confirmed that they were representative of expected costs in Italy. Furthermore, one-way sensitivity analyses have demonstrated that these cost estimates are not key drivers of the model results.

The results of the model presented here are in line with previously developed models of NMIBC which have demonstrated promising results for PDD [1,2].

CONCLUSIONS

This cost-effectiveness analysis demonstrates improved patients' health outcomes, with less procedures and hospital visits, and savings in health care expenditures offsetting investment in Hexvix® technology in the long-term. Even over a shorter timeframe, H+BLC is associated with lower overall costs compared to WLC.

From a public health perspective, this analysis shows that the use of H+BLC in the management of NMIBC may lead to an enhanced use of clinical services with less hospitalization for MIBC and better support for patients.

In conclusion, Hexvix® is expected to be a cost-effective strategy when used in the resection of NMIBC in Italy.

REFERENCES

1. Mowatt G, Zhu S, Kilonzo M, et al. Systematic review of the clinical effectiveness and cost-effectiveness of photodynamic diagnosis and urine biomarkers and cytology for the detection and follow-up of bladder cancer. *Health Technol Assess* 2010; 14: 1-331; http://dx.doi.org/10.3310/hta14040
2. Malmström PU, Hedelin H, Thomas YK, et al. Fluorescence-guided transurethral resection of bladder cancer using hexaminolevulinate: analysis of health economic impact in Sweden. *Scand J Urol Nephrol* 2009; 43: 192-8; http://dx.doi.org/10.1080/00365590902808541

3. Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. Eur Urol 2013; 64: 639-53; http://dx.doi.org/10.1016/j.eururo.2013.06.003

4. WHO. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence worldwide in 2012. Available at http://globocan.iarc.fr/Pages/fact_sheets_population.aspx

5. AIOM-AIRTUM. I numeri del cancro in Italia 2013. Available at http://www.registri-tumori.it/cms/it/node/2888

6. AIRTUM-ITACAN: Tumori in Italia, Versione 2.0. Associazione Italiana dei Registri Tumori. Available at http://www.registri-tumori.it

7. Freedman ND, Silverman DT, Hollenbeck AR, et al. Association between smoking and risk of bladder cancer among men and women. JAMA 2011; 306: 737-45; http://dx.doi.org/10.1001/jama.2011.1142

8. AIOM. Linee guida Carcinoma della vescica. Edizione 2013

9. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with Stage Ta T1 bladder cancer using EORTC Risk tables. Eur Urol 2006; 49: 466-5; discussion 475-7

10. Millán-Rodríguez F, Chéchile-Toniolo G, Salvador-Bayarri J, et al. Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. J Urol 2000; 164: 680-4; http://dx.doi.org/10.1016/S0022-5347(05)67280-1

11. Stein JP, Lieskovsky G, Cote R, et al. Radical cystectomy in the treatment of invasive bladder: long-term results in 1,054 patients. J Clin Oncol 2001; 19: 666-75

12. Fradet Y, Grossman HB, Gomella L, et al.; PC B302/01 Study Group. 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: 68-73; http://dx.doi.org/10.1016/j.juro.2007.03.028

13. Stenzl A, Burger M, Fradet Y, et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. J Urol 2010; 184: 1907-13; http://dx.doi.org/10.1016/j.juro.2010.06.148

14. Jocham D, Witjes F, Wagner S, et al. Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. J Urol 2005; 174: 862-6; http://dx.doi.org/10.1097/01.ju.0000169257.19841.2a

15. Grossman HB, Stenzl A, Fradet Y, et al. Long-term decrease in bladder cancer recurrence with hexaminolevulinate enabled fluorescence cystoscopy. J Urol 2012; 188: 58-62; http://dx.doi.org/10.1016/j.juro.2012.03.007

16. Expert Opinion of Prof. Giario Conti, director of Urology Division at Sant'Anna Hospital, Como

17. Burger M, Grossman HB, Droller M, 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: 846-54; http://dx.doi.org/10.1016/j.eururo.2013.03.059

18. Demo Istat.it. Available at http://demo.istat.it/index.html

19. von der Maase H, Sengelov L, Roberts JT, et al. Long term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, cinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005; 23: 4602-8; http://dx.doi.org/10.1200/JCO.2005.07.757

20. EQ-5D™. Available at http://www.euroqol.org/

21. Kulkarni GS, Finelli A, Fleshner NE, et al. Optimal management of high-risk T1G3 bladder cancer: a decision analysis. PLoS Med 2007; 4: e284; http://dx.doi.org/10.1371/journal.pmed.0040284

22. NHS reference costs guidance for 2011-2012. Available at https://www.gov.uk/government/publications/reference-costs-guidance-for-2011-12

23. KARL STORZ Gmbh&Co. Data

24. NHS Technology Adoption Centre (NTAC). The Cost Impact of Implementing Photodynamic Diagnosis of Non-Muscle Invasive Bladder Cancer in England. Final Report, 2011

25. Associazione Italiana di Economia Sanitaria (AIES). Proposta di linee guida per la valutazione economica degli interventi sanitari. PharmacoEconomics. Italian Research Articles 2009; 11: 83-93

26. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 2005; 66: 4-34; http://dx.doi.org/10.1016/j.urology.2005.07.062

27. Parkin DM, Whelan SL, Ferlay J, et al. Cancer Incidence in Five Continents. Lyon: IARC Publications, 2002

28. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55: 74-108; http://dx.doi.org/10.3322/canjclin.55.2.74

29. Sievert KD, Amend B, Nagele U, et al. Economic aspects of bladder cancer: what are the benefits and costs? World J Urol 2009; 27: 295-300; http://dx.doi.org/10.1007/s00345-009-0395-z

30. Witjes JA, Redorta JP, Jacqmin D, et al. Hexaminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: review of the evidence and recommendations. Eur Urol 2010; 57: 607-14; http://dx.doi.org/10.1016/j.eururo.2010.01.025

APPENDIX

Variable	Base Case	Lower Limit	Upper Limit
QALY discount rate	3.50%		
Cost discount rate	3.50%		
% of patients male	70.00%	55.47%	82.72%
Bladder cancer prevalence	20.00%	16.23%	24.06%
Sensitivity Flexible cystoscopy	0.95	0.65	1.00
Sensitivity White light cystoscopy	0.95		
Specificity Flexible cystoscopy	0.72	0.57	0.85
Specificity White light cystoscopy	0.72		
RR of progression for NMIBC (Tx vs. no Tx)	2.56	2.06	3.06
RR of recurrence H+BL (low risk)	0.66	0.53	0.78
RR of recurrence H+BL (intermediate risk)	0.74	0.58	0.87
RR of recurrence H+BL (high risk)	0.77	0.60	0.90
Probability of progression with metastases	0.25	0.20	0.30
Cost CSC per use	€ 541	€ 259	€ 924
Cost WLC assisted TURBT	€ 2,350	€ 1,127	€ 4,015
Cost of cystectomy	€ 10,600	€ 5,083	€ 18,110
Cost Palliative treatment (per 3 months)	€ 17,764	€ 8,519	€ 30,350
Cost CT scan	€ 744	€ 357	€ 1,271
Cost mitomycin dose (cost per 40mg vial)	€ 66	€ 32	€ 113
Cost BCG dose (cost per 12.5 mg vial)	€ 70	€ 34	€ 120
Additional cost of Hexvix® + BL	€ 532	€ 255	€ 910
Base bladder cancer utility (annual)	0.780	0.610	0.911
Utility metastases (annual)	0.436	0.352	0.522
Cystectomy disutility	0.340	0.275	0.408
CSC disutility	0.000	0.000	0.000
WLC disutility	0.000	0.000	0.000
W&BLC disutility	0.000	0.000	0.000
WLC assisted TURBT disutility	0.200	0.162	0.241
BCG disutility	0.040	0.033	0.048
Move to high risk from inter on recur	0.130	0.108	0.160
% mitomycin post-initial TURBT	1.000	1.000	1.000
% BCG inter risk (post recur)	0.000	0.000	0.000
% BCG high risk	1.000	1.000	1.000
% of metastatic patients receiving cystectomy	1.000	1.000	1.000

Lower and upper values for parameters varied in the univariate sensitivity analyses

Variable	Base Case	Distribution	St. dev	alpha	beta
% of patients male	70.00	Beta	0.07	29.3	12.6
Bladder cancer prevalence	20.00%	Beta	0.02	79.8	319.2
Sensitivity Flexible cystoscopy	0.95	Beta	0.095	4.05	0.2
Sensitivity White light cystoscopy	0.95	Beta			
Specificity Flexible cystoscopy	0.72	Beta	0.07	27.3	10.6
Specificity White light cystoscopy	0.72				
RR of progression for NMIBC (Tx vs no Tx)	2.56	Normal	0.256		
RR of recurrence H+BL (low risk)	0.66	Beta	0.07	33.2	17.0
RR of recurrence H+BL (intermediate risk)	0.74	Beta	0.07	25.2	8.8
RR of recurrence H+BL (high risk)	0.77	Beta	0.08	22.5	6.8
Distribution WL (low risk)	0.20	Dirichlet	0.04	19.8	variable
Distribution WL (intermediate risk)	0.50	Dirichlet	0.05	49.5	variable
Distribution WL (high risk)	0.30	Dirichlet	0.05	29.7	variable
Difference in Distribution WL+BL (intermediate risk)	0.011	Beta	0.00107	98.9193	9145.875
Probability of progression with metastases	0.25	Beta	0.03	74.8	224.3
Cost CSC per use	€ 541	Gamma	54.1	10	54.1
Cost WLC assisted TURBT	€ 2,350	Gamma	235	10	235
Cost of cystectomy	€ 10,600	Gamma	1,060	10	1,060
Cost Palliative treatment (per 3 months)	€ 17,764	Gamma	1,777	10	1,777
Cost CT scan	€ 744	Gamma	74.4	10	74.4
Cost Mitomycin dose (cost per 40mg vial)	€ 66	Gamma	6.6	10	6.6
Cost BCG dose (cost per 12.5mg vial)	€ 70	Gamma	7	10	7
Additional cost of Hexvix® + BL	€ 532	Gamma	53.24	10	53.24
Base bladder cancer utility (annual)	0.780	Beta	0.08	21.2	6.0
Utility metastases (annual)	0.436	Beta	0.04	56.0	72.4
Cystectomy disutility	0.34	Beta	0.03	65.7	127.5
WLC assisted TURBT disutility	0.20	Beta	0.02	79.8	319.2
W&BLC assisted TURBT disutility	0.20	Beta	0.02	79.8	319.2
BCG disutility	0.04	Beta	0.00	96.0	2,303.0
Move to high risk from inter on recur	0.13	Beta	0.01	86.6	564.3
% mitomycin post-initial TURBT	1.00	Beta	0.10	-1.0	0.0
% BCG high risk	1.00	Beta	0.10	-1.0	0.0
% of metastatic patients receiving cystectomy	1.00	Beta	0.10	-1.0	0.0

Distributions applied in the probabilistic sensitivity analyses