The cost-effectiveness of blue light cystoscopy in bladder cancer detection: United States projections based on clinical data showing 4.5 years of follow up after a single hexaminolevulinate hydrochloride instillation

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Introduction: *Several studies, including the recently published phase III study by Stenzl and colleagues have demonstrated that hexaminolevulinate hydrochloride, when used with blue light fluorescence cystoscopy, improves detection of non-muscle invasive bladder tumors compared to white light cystoscopy and transurethral resection of bladder tumors (TURB) alone.*

Materials and methods: *The objective of this study was to conduct a detailed assessment of the cost-effectiveness of using hexaminolevulinate hydrochloride with blue light cystoscopy as an adjunct to white light versus white light cystoscopy alone at time of initial TURB in the United States. A probabilistic decision tree model, using TreeAge Pro 2011 software, was developed using base case scenario cost and utility estimates.*

Results: *Incorporation of hexaminolevulinate hydrochloride into diagnostic cystoscopy results in lower costs over 5 years ($25,921) as compared to those patients who initially receive white light cystoscopy ($30,581). Those patients who initially receive hexaminolevulinate hydrochloride blue light TURB also experience a lower overall cancer burden.*

Conclusions: *Hexaminolevulinate hydrochloride may be cost effective when used at first TURB for patients with suspected new or recurrent non-muscle invasive bladder cancer.*

Key Words: white light cystoscopy, bladder cancer, bladder cancer detection, Cysview, cystoscopy, cost-effectiveness, outcomes, utility, cystectomy, transurethral resection of the bladder

Introduction

Bladder cancer is the second most common genitourinary malignancy in the United States and the fifth most common cancer overall. Approximately 554,347 men and women in the United States have a history of cancer of the urinary bladder (411,234 men and 142,113 women). An estimated 37 per 100,000 men and 8.9 per 100,000 women are diagnosed with bladder cancer each year in the United States.[1] For all bladder cancer stages combined, the 5 year relative survival rate was 77.7% for 2002-2008. Five year survival rate varies by stage at diagnosis. When diagnosed at a localized stage, the 5 year survival was 70.2% but for regional and distant stages, 5 year survival rates were 32.9% and 5.5%, respectively.[1]

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Hexaminolevulinate hydrochloride (HAL; Cysview, PhotoCure Inc., Princeton, New Jersey, USA) is approved by the Food and Drug Administration (FDA) for photodynamic blue light cystoscopy performed with KARL STORZ Photodynamic Diagnostic (PDD) system (El Segundo, California, USA) as an adjunct to white light cystoscopy in the detection of non-muscle invasive papillary bladder cancer in patients with known or suspected bladder cancer on the basis of a prior cystoscopy.[2] HAL works by exploiting the fluorescent properties of naturally occurring molecules called photoactive porphyrins (PAPs), which are selectively taken up by malignant tissues, thus improving the visibility of malignant lesions in the bladder by fluorescing when exposed to blue light. The technique of Cysview has been previously described in detail.[3]

The results of the published phase III study by Stenzl and colleagues,[4] which was the basis for the FDA approval, are consistent with previously published studies[5-7] and showed that HAL cystoscopy at the time of transurethral resection of bladder tumors (TURB) improves detection of non-muscle invasive papillary bladder tumors compared to white light cystoscopy and TURB alone. In 16.4% of the patients with Ta or T1 tumors, at least one additional tumor was detected with HAL blue light cystoscopy ($p = 0.001$). The study also demonstrated for the first time that improved detection of bladder tumors enables a more complete resection resulting in a significant reduction of recurrence rates at 9 months. During the 9 month surveillance period, for the per protocol analysis, 20/72 patients (36%) in the blue light group and 92/202 patients (46%) in the white light group had tumor recurrence ($p = 0.029$).

Recently, Grossman and colleagues published the results of a study that extended the follow up period of the Stenzl trial to an average of 4.5 years in all available patients.[8] The objectives of the study were to assess: long term estimates of recurrence-free rates after HAL and standard cystoscopy/TURB, numbers and types of recurrences, amount and type of treatment given, and risk of death. The study population included 551 patients with suspected non-muscle invasive papillary bladder cancer (271 in the blue light group, and 280 in the white light group), enrolled in the previously completed

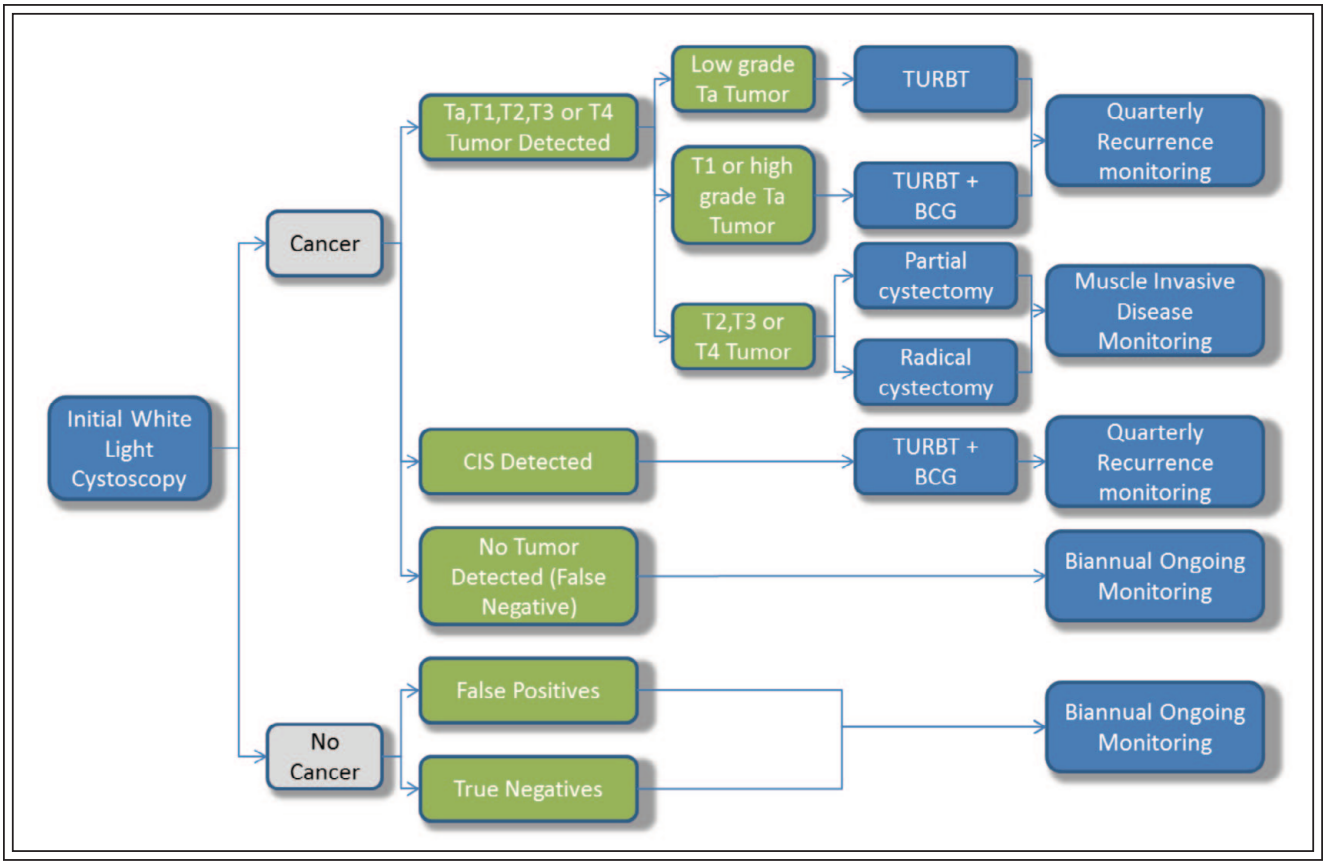

Figure 1. Initial TURB.

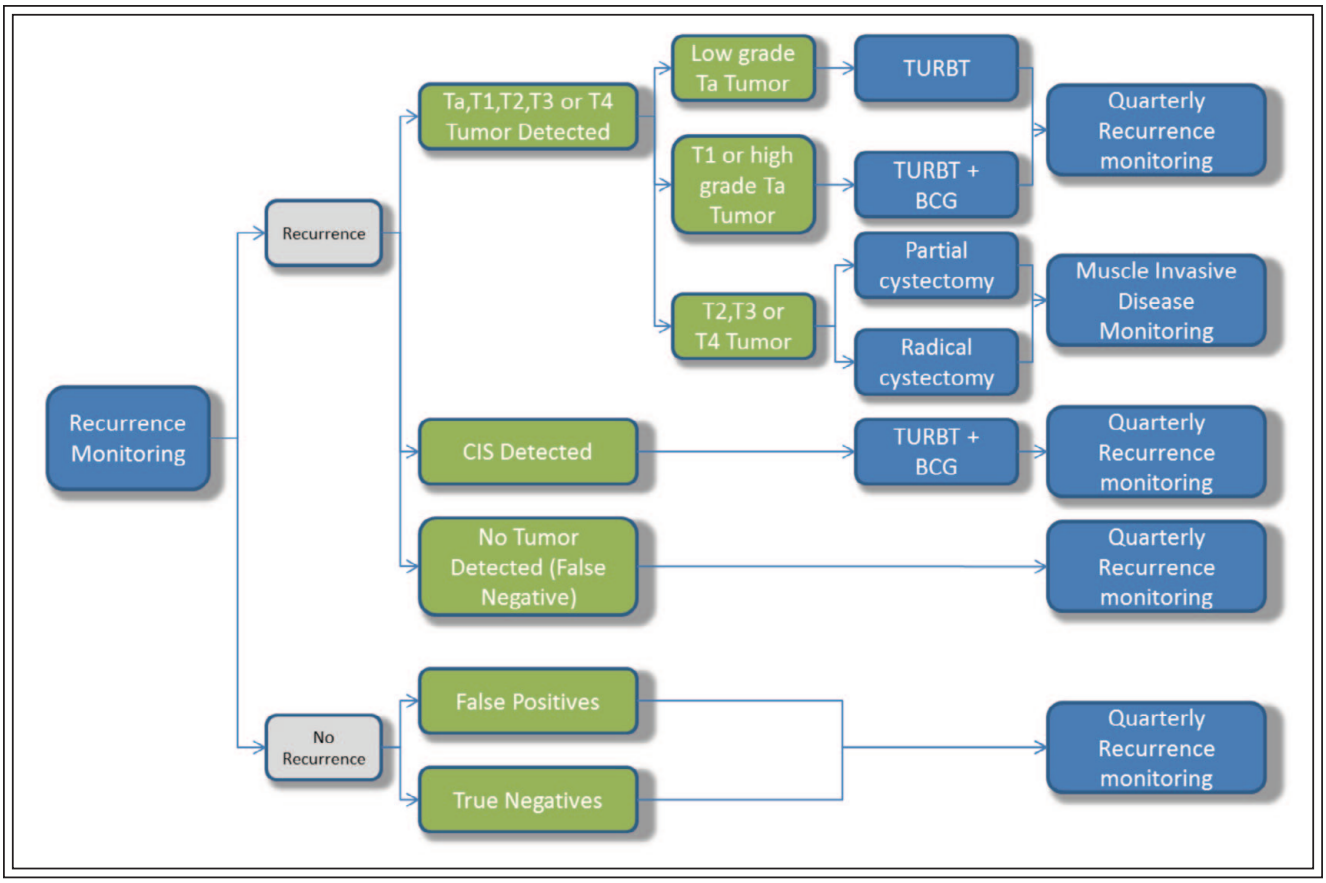

Figure 2. Recurrence monitoring.

Stenzl study who were followed for recurrence (defined as the intent-to-treat [ITT] population). The analysis set in the Grossman study was comprised of subjects from the ITT population from the Stenzl study who had recurrence confirmed by pathology from either the pivotal trial or the extension trial, or where no recurrence was indicated in both studies.

In the Grossman study, follow up information was obtained for 261 of the 280 (93%) participants in the white light group and 255 of the 271 (94%) participants in the blue light group. Median follow up in the white light and blue light group were 53.0 and 55.1 months, respectively. In the white light and blue light groups, 83 (31.8%) and 97 (38%) of the participants remained tumor free for an average of 4.5 years, respectively. The median time to recurrence was 9.6 months in the white light group and 16.4 months in the blue light group, p = 0.04. The overall development of T2-T4 tumors was 6.1% in the white light group and 3.1% in the blue light group (p = 0.066). Cystectomies based on tumor progression were performed more often in the white light group, 22/280 (7.9%) than in the blue light group, 13/271 (4.8%, p = 0.16).

Bladder cancer is the most expensive urological malignancy on a per patient basis primary based on the need for long term care.[9] The analysis presented herein follows from the clinical findings in the extension study. Based on data from the extension study and other sources related to the detection and treatment of bladder cancer, we have estimated the cost-effectiveness of initial diagnostic HAL blue light cystoscopy as an adjunct to white light cystoscopy versus white light cystoscopy alone over 5 years as the primary clinical endpoint.

Materials and methods

Decision analysis model

For purposes of this analysis, a model was developed to assess the cost-effectiveness of bladder cancer detection comparing hexaminolevulinate blue light cystoscopy as an adjunct to white light cystoscopy versus white light cystoscopy alone at time of TURB for patients with suspected new or recurrent non-muscle invasive bladder cancer.[10,11] Figures 1-3 depict the structure of the model tree for initial TURB, recurrence monitoring

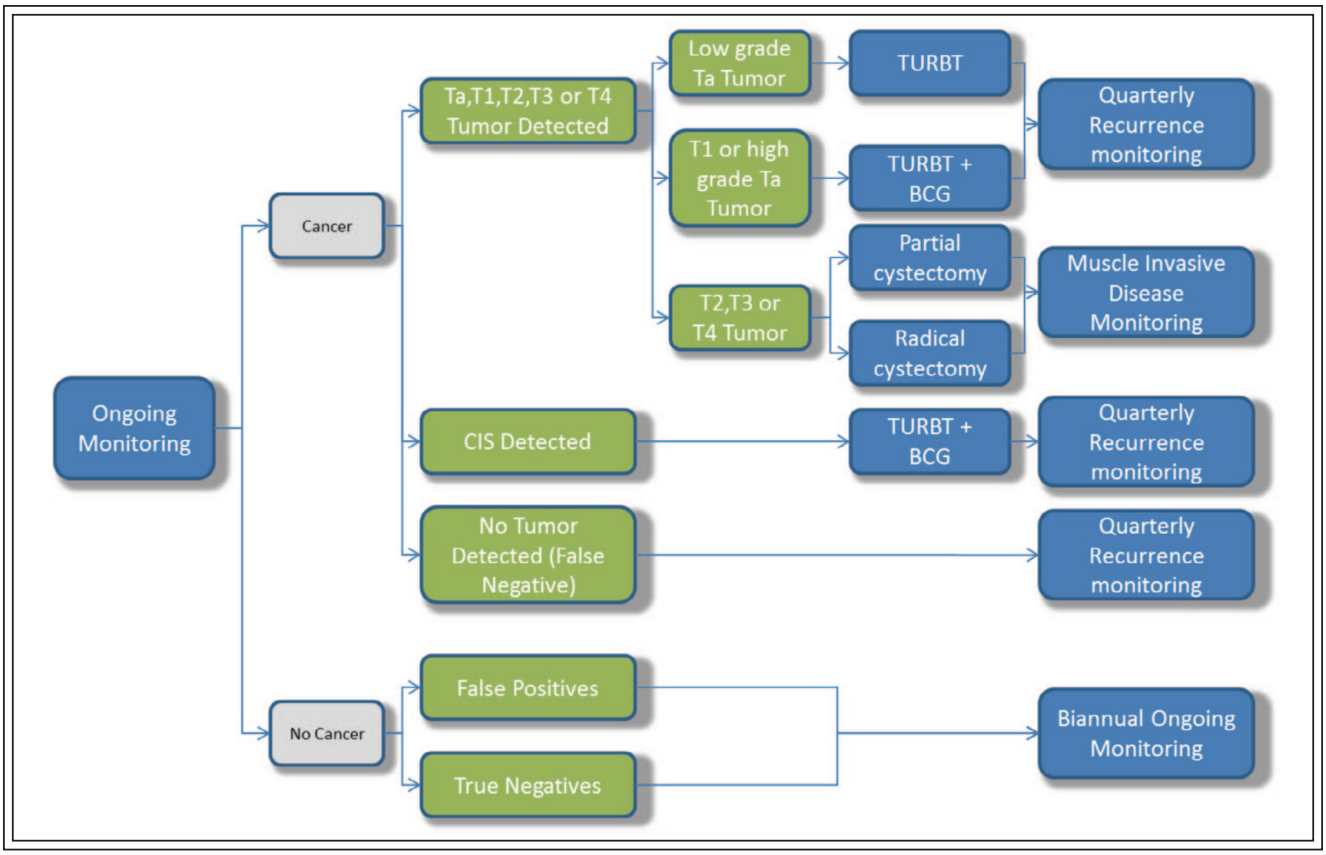

Figure 3. Ongoing monitoring.

and ongoing monitoring, respectively. Probabilistic decision-tree estimates have been derived from published sources and embedded within the model using TreeAge Pro 2011 (TreeAge Software, Inc., Williamstown, MA, USA), an established software package for health economic modeling utilized in over fifty peer-reviewed, published analyses.[12]

The model takes the perspective of the health care system, comparing reimbursement (payment) on behalf of health care payers and the associated patient outcomes (utility) depending on whether a patient was diagnosed with cancer or is cancer-free. As the costs of capital equipment are not borne by the payer directly, the cost of the KARL STORZ PDD System, which provides the blue light source used in the procedure, is not considered in this analysis. Hexaminolevulinate has a specific temporary code and was granted pass-through status in the Hospital Outputs Prospective Payment System (HOPPS).

Tables 1 and 2 identify the variables included in the model. Table 1 provides details of the cost variables that were included.[13-17] Table 2 provides clinical variables estimates used in the model.[1,4,8,18]

TABLE 1. **Cost estimates**

Costs/payment	**Medicare payment (median)**
Cystoscopy (CPT 52000)	$601.06
TURBT (CPT 52214-52240)	$1984.61
BCG therapy	$2012.82
Radical cystectomy (DRG 655)	$24,433.27
Partial cystectomy (DRG 664)	$16,577.69
Hexaminolevulinate hydrochloride	$600.00
Biopsy (CPT CPT 52224 + pathology	$248.82
Urine cytology (CPT 88112)	$102.45
Chemotherapy	$6000.00
Neoadjuvant chemotherapy	$6000.00
Imaging studies	$715.13
Ongoing surveillance of muscle invasive disease	$18,638.88

TURBT = transurethral resection of bladder tumor
BCG = Bacillus Calmette–Guérin

TABLE 2. **Probabilities and utilities**

Probabilities	**Base case**	**Low estimate**	**High estimate**
Bladder cancer prevalence	0.17	0.07	0.27
Blue light sensitivity, Ta-T4 tumors	1.0	0.9	1.0
Blue light sensitivity, CIS tumors	1.0	0.9	1.0
Blue light specificity, all tumors	0.88	0.78	0.98
White light sensitivity, Ta-T4 tumors	0.84	0.74	0.94
White light sensitivity, CIS tumors	0.68	0.58	0.78
White light specificity, all tumors	0.89	0.79	0.99
Tumor detection rate, CIS tumors	0.08	0	0.18
Tumor detection rate, Ta,T1 tumors	0.504	0.404	0.604
Tumor detection rate, T2-T4 tumors	0.16	0.06	0.26
Partial cystectomy rate, BL	0.06	0.05	0.07
Partial cystectomy rate, WL	0.09	0.08	0.10
Recurrence rate, BL	0.267	0.167	0.367
Recurrence rate, WL	0.349	0.249	0.449
Maximum tumor stage at recurrence, BL, CIS tumors	0.31	0.21	0.41
Maximum tumor stage at recurrence, BL, Ta, T1 tumors	0.639	0.539	0.739
Maximum tumor stage at recurrence, BL, T2-T4 tumors	0.0635	0	0.1635
Maximum tumor stage at recurrence, WL, CIS tumors	0.3	0.2	0.4
Maximum tumor stage at recurrence, WL, Ta, T1 tumors	0.6124	0.5124	0.7124
Maximum tumor stage at recurrence, WL, T2-T4 tumors	0.1111	0.0111	0.2111
Cancer	0		
Cancer-free	1		
% initial low grade Ta tumors	.6125		
% initial high grade Ta tumors	.0605		
% initial T1 tumors	.1382		
% initial CIS tumors	.117		
% initial T2-T4 tumors	.0716		

BL = blue light cystoscopy; WL = white light cystoscopy

Event probabilities

The model assumes three potential outcomes following initial TURB: recurrence monitoring for those patients where non-muscle invasive cancer is detected and treated, ongoing monitoring for those patients where cancer is not detected, and muscle invasive surveillance, where a patient is diagnosed and treated for muscle invasive bladder cancer and continues to undergo surveillance for recurrence of that cancer following treatment.

Data from various sources have been used to populate the model; however, the majority of the estimates used in this analysis come from the Grossman publication.[8] The model assumes that after the initial TURB with HAL, all future cystoscopies and any necessary TURB for recurrence are conducted using white light only, consistent with HAL FDA approved labeling.[2]

Financial data

Cost estimates and reimbursement amounts are based on published Medicare and private payer data sources.[13-15] According to the most recent SEER data, 72.1% of bladder cancer patients are over 65 years of age at diagnosis, with a mean age at diagnosis of 73[4]

making Medicare the primary source of funding for care for this population in the United States. Therefore, the model utilizes Medicare cost data and supplements with published data where Medicare estimates were not available.

Utility measures

As described above, the clinical outcome of interest in this study is the avoidance of bladder cancer burden over 5 years, using a similar approach to quality of life measures. The utility scores have been fixed accordingly.

Patients are assigned points on a scale of 0 to 1, where 0 is existence cancer and 1 is cancer free. Patients are assigned .75 value for each cycle they spend in either the recurrence monitoring or ongoing monitoring branch and a 0 for each cycle they spend in the muscle invasive surveillance branch. Additionally, patients are assigned a disutility value for each diagnosis and treatment for bladder cancer, where a non-muscle invasive diagnosis receives a score of -.25 and muscle invasive diagnosis receives a score of -.75. All patients receive a disutility score of 0 following treatment for bladder cancer when they return to a "cancer free" state.

Results

Using the base case estimates shown in Table 1, the variables have been modeled comparing initial TURB using either adjunctive HAL (blue light) or white light alone.

The cost-effectiveness data, including the cost (as defined above) and utility estimates, as well as the composite cost-effectiveness ratios, which are based on the cost and utility estimates, are summarized in Table 3.

As shown, costs over 5 years are lower for patients who initially receive HAL blue light TURB ($25,921) as compared to those patients who initially receive white light TURB ($30,581). As bladder cancer is the most expensive cancer from diagnosis to death, with average per patient costs ranging from $96,000 to $187,000,[19] this 15% reduction in 5 year costs would be substantial on a population basis.

The utility estimates shown in Table 2 follow a similar pattern. Patients who initially receive HAL blue light TURB receive a higher score for cancer burden avoided, indicating they spend less of those 5 years managing disease recurrence and progression, 4.4 for white light versus 4.9 for blue light, an 11% improvement compared to white light. This improvement demonstrates a lower burden of recurrent non-muscle invasive disease and a lower burden of progression to muscle invasive disease in the blue light group.

TABLE 3. **Summary of cost-effectiveness results**

Detection method			
Hexaminolevulinate hydrochloride blue light		**White light**	
Cost or payment	Utility or effectiveness	Cost or payment	Utility or effectiveness
$25,921	4.9	$30,581	4.4

Discussion

Stenzl and colleagues demonstrated that HAL blue light cystoscopy significantly improves the detection of Ta and T1 lesions and significantly reduces the rate of tumor recurrence at 9 months.[4] The additional follow up study conducted by Grossman and colleagues demonstrates that, over time, patients who have an initial TURB with HAL continue to have longer recurrence free survival intervals than patients that undergo initial white light TURB.[8] Neither the 9 month nor 4.5 year follow up studies specifically addressed cost or cost-effectiveness, though analyses have been undertaken in Europe.[20] To our knowledge, this is the first health economic examination of the impact of the use of HAL to detect and manage bladder cancer in the United States, which is a unique healthcare reimbursement system.

Based on a combination of clinical data and the results of this economic analysis, we have identified effectiveness and cost benefit of adding HAL to the standard of care for detecting and treating bladder cancer. The clinical value of HAL is that it improves detection of non-muscle invasive bladder cancer, including hard-to-detect tumors such as CIS, as compared to white-light cystoscopy. Improved tumor detection with HAL blue light cystoscopy facilitates more complete resection at time of TURB and leads to improved treatment and patient management and reduction in the rate of recurrences. The Grossman study also identified a trend toward reduction in progression requiring more aggressive later stage management. This trend was strong but did not reach statistical significance, due to not having been statistically powered for that endpoint.

Combining the findings of the clinical studies with the financial benefits identified herein, it becomes apparent that incorporation of HAL into the initial

diagnostic pathway for patients with known or suspected non-muscle invasive bladder cancer offers benefits to various stakeholders. Clinicians will be able to more accurately detect tumors earlier in the disease process, enabling more adequate treatment. Payers will benefit from detecting disease more thoroughly, allowing more complete resection and, based on the results of this economic analysis, may incur lower costs associated with ongoing surveillance and treatment of patients with bladder cancer. Patients will benefit by remaining recurrence- and possibly progression-free longer.

Cost has not typically been a consideration in Medicare coverage decisions, though the issue has arisen on numerous occasions since the mid-1980s.[21,22] With the current focus on deficit reduction, especially in entitlement programs such as Medicare, the fact that clinically significant results can be achieved in a cost effective way may be attractive to policymakers.

Limitations

There are several limitations to the economic analysis that should be considered. First, while the authors based assumptions on the treatment received by patients on current treatment guidelines along with the guidance of urologists, individual patient treatment decision-making is varied and may impact the overall cost of treating and monitoring a bladder cancer patient. It is not possible to predict whether urologists will reduce surveillance or treatment regimens with the knowledge that recurrence rates have been reduced in patients who receive HAL blue light cystoscopy, but any occurrence of this behavior would even further favor economic benefit to using HAL. Since the results of the Stenzl and Grossman studies focused on tumor stage, not grade, our assumptions on treatment do not differentiate by high, medium, or low grade disease. An additional limitation to consider is the fact that current FDA labeling for HAL indicates that it can only be used once in a patient lifetime. This usage limitation is not imposed in other markets where HAL (marketed as Hexvix outside the United States) is available. This limitation may not reflect the potential to detect and treat bladder cancer and therefore may understate the potential economic benefit of its repetitive use. Finally, this model focuses on the direct medical costs associated with the incorporation of HAL into current treatment standards. The model does not consider costs such as the side effects associated with treatment, nor does it consider the emotional ramifications of the treatment and ongoing monitoring associated with bladder cancer. Nevertheless, safety data from the aforementioned studies suggest that complications are transient and mild or moderate in intensity. Based on data obtained from 1324 patients in six clinical trials, the most common adverse reaction was bladder spasm (reported in 2.2%) followed by dysuria, hematuria and bladder pain.[2] No patients experienced anaphylaxis in the controlled clinical study; adverse reactions were similar in nature and rate between the study drug group and the control group.

While these are important costs to consider, it was the intention of this model to focus specifically on those treatment decisions that are impacted by use of HAL and outline their associated costs and both Stenzl and Grossman demonstrated no difference in the safety of HAL blue light versus white light TURB.

Conclusion

The results of the analyses presented here have implications for the incorporation of HAL into the standard of care for detection of bladder cancer in the United States. The clinical benefits outlined by the Stenzl and Grossman studies demonstrate statistically significant improvement in detection of non-muscle invasive tumors using HAL blue light cystoscopy, and the present economic analysis provides evidence that inclusion of HAL into the standard of care may be cost saving for providers and payers. While cost-effectiveness information may not be directly incorporated into the decisions of agencies such as CMS, the results of this study do provide a reasonable basis for the determination of value. As payers strive to focus healthcare dollars on medical interventions of value, this study demonstrates the value that HAL can provide to clinicians, patients and payers from both a clinical and cost perspective.

Disclosure

S. S. Garfield, M. B. Gavaghan and S. O. Armstrong work for GfK Bridgehead, a paid consultant of GE Healthcare, Princeton, New Jersey USA. GE Healthcare provided funding for this research.
J. S. Jones is a paid clinician advisor of Photocure, Princeton, New Jersey USA. □

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