



Shaping the Future of Endoscopy with you



Citizen Petition

Date: October 21, 2022

Division of Dockets Management
U.S. Food and Drug Administration,
5630 Fishers Lane, Room 1061,
Rockville, MD 20857.

To whom it may concern,

The undersigned submits this petition under 513(f)(2) of the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs to amend a regulation.

We believe that this petition contains all the required information in the format prescribed by 21CFR10.30.

However, should you have any questions or require additional information, please contact the undersigned by e-mail.

We request for your earliest attention to and favorable decision on this petition.

Thank you for your time and consideration.

Sincerely yours,

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Reclassification Petition

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Section A: Action Requested

(1) Specification of the type of device for which reclassification is Requested

This petition is being submitted in accordance with the provisions of Section 513(f)(3) of the FD&C Act) for reclassification of these devices to Class II subject to 510(k) (Special Controls).

The petitioner requests the FDA Commissioner to take all administrative actions required for reclassification or the medical devices associated with Product Code OAY; FDA regulatory classification details of which as on May 17.2019. are as mentioned in Table 1.1 below:

Table 1.1	
FDA regulatory classification details (as of Oct. 1, 2022) for medical devices associated with Product Code: OAY	
Product Classification	
FDA Home Medical Devices Databases	
New Search	Back to Search Results
Device Definition	Light Source System, Diagnostic Endoscopic A fluorescence system intended for use as an adjunct to white light cystoscopy when used in combination with a photosensitizer for the detection of bladder cancer. Patients with known or suspected bladder cancer and/or recurrence of bladder cancer, in patients undergoing diagnostic testing for bladder cancer by cystoscopy or positive urine cytology or who present with hematuria and/or a positive urine cytology test.
Physical State	System includes a PPD light source, specific PDD telescopes for cystoscopy), camera system (PDD camera control unit, and PDD camera heads) fluid light cable, and PC based software communication program
Technical Method	1. excitation and emission filters in the PDD telescopes and PDD camera heads limit light to the blue portion of the visible spectrum The combination of these 2 filters in conjunction with the photo-fluorescent drug Hexvix? enables visualization of carcinoma in situ (CIS) as a red fluorescent image against normal tissue that appears blue.
Target Area	Urinary Bladder
Review Panel	Gastroenterology/Urology
Product Code	OAY
Premarket Review	Reproductive_Gynecology_and_Urology_Devices (DHT3B) Reproductive, Gynecology and Urology Devices (DHT3B)
Submission Type	PMA
Device Class	3
Total Product Life Cycle (TPLC)	TPLC Product Code Report
GMP Exempt?	No
Summary Malfunction Reporting	Ineligible
Implanted Device?	No
Life-Sustain/Support Device?	No
Third Party Review	Not Third Party Eligible

Table 1.2 on the next page provides the list of FDA-approved medical devices (as of Oct,1 2022) associated with FDA Product Code: OAY

These devices are currently classified into Class III subject to premarket approval under Section 513(f)(1) of the FD&C Act.

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Table 1.2				
List of FDA-approved medical devices (as on Oct. 1, 2022) associated with Product Code: OAY				
Premarket Approval (PMA)				
<small>• FDA Home • Medical Devices • Databases</small> 1 to 29 of 29 Results productcode OAY Decision Date To 09/30/2022				
Device	Applicant	PMA Number	Decision Date	
Karl Storz D-Light C Pdd System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S030	03/17/2022	
Karl Storz D-Light C Pdd System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S028	02/04/2022	
Karl Storz D-Light C Pdd System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S029	10/13/2021	
D-Light C Pdd System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S027	01/08/2021	
Karl Storz Photodynamic Diagnostic (Pdd) D-Light S...	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S026	01/06/2021	
Karl Storz Photodynamic D-Light C Pdd System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S022	08/17/2020	
Karl Storz Photodynamic D-Light C Pdd System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S023	08/17/2020	
Karl Storz Photodynamic D-Light C Pdd System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S024	08/17/2020	
Karl Storz Photodynamic Diagnostic (Pdd) D-Light C...	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S025	07/29/2020	
Karl Storz Photodynamic D-Light C Pdd System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S021	06/05/2020	
Karl Storz Photodynamic Diagnostic D-Light C Syste...	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S020	03/25/2020	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S018	12/20/2019	
Karl Storz Photodynamic Diagnostic (Pdd) D-Light C...	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S019	07/25/2019	
Karl Storz Photodynamic Diagnostic (Pdd) D-Light C...	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S017	04/22/2019	
Karl Storz Photodynamic Diagnostic D-Light C (Pdd)...	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S014	02/21/2019	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S013	10/23/2018	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S012	05/22/2018	
Karl Storz D-Light C Pdd System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S011	02/15/2018	
Karl Storz Photodynamic Diagnostic D-Light C (Pdd)...	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S009	11/30/2017	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S010	11/30/2017	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S008	03/17/2017	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S007	09/09/2014	
Karl Storz Photodynamic D-Light C(Pdd) System -D-L...	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S006	08/07/2014	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S005	09/23/2013	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S004	09/10/2012	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S003	08/27/2012	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S002	05/02/2012	
Karl Storz Photodynamic D-Light C (Pdd) System	KARL STORZ ENDOSCOPY-AMERICA,	P050027 S001	08/10/2010	
Karl Storz Photodynamic Diagnostic D-Light C (Pdd)...	KARL STORZ ENDOSCOPY-AMERICA,	P050027	05/28/2010	

As evident from Table 1.2, all FDA-approved medical devices associated with FDA Medical Device Product Code OAY as of Oct. 10, 2022, are modifications to the original device KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System with the following regulatory classification and pre-market approval details as mentioned in Table 1.3 below:

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Table 1.3

Details as on Oct. 1, 2022, of regulatory classification and original PMA (P050027)

along with PMA supplements (S001-S030) of

KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System and its subsequent modifications

New Search

Back to Search Results

Note: this medical device has supplements. The device description/function or indication may have changed. Be sure to look at the supplements to get an up-to-date information on device changes. The labeling included below is the version at time of approval of the original PMA or panel track supplement and *may not represent the most recent labeling*.

Device KARL STORZ PHOTODYNAMIC DIAGNOSTIC D-LIGHT C (PDD)
SYSTEM
Generic Name Light Source System, Diagnostic Endoscopic
KARL STORZ ENDOSCOPY-AMERICA, INC.
Applicant 2151 E. Grand Ave.
El Segundo, CA 90245
PMA Number P050027
Date Received 07/31/2005
Decision Date 05/28/2010
Product Code OAY
Docket Number 10M-0294
Notice Date 06/14/2010
Advisory Committee Gastroenterology/Urology
Expedited Review Granted? No
Combination Product No

Approval Order Statement

APPROVAL FOR THE KARL STORZPHOTODYNAMIC DIAGNOSTIC D-LIGHT C (PDD) SYSTEM. THE KARL STORZ PHOTODYNAMIC DIAGNOSTIC D-LIGHTC (PDD) SYSTEM IN COMBINATION WITH THE OPTICAL IMAGING DRUG CYSVIEW(HEXAMINOLEVULINATE HYDROCHLORIDE) FOR INTRAVESICAL SOLUTION IS INDICATED FOR PHOTODYNAMIC BLUELIGHT CYSTOSCOPY, AS AN ADJUNCT TO WHITE LIGHT CYSTOSCOPY FOR THE DETECTION OF NON-MUSCLE INVASIVEPAPILLARY CANCER OF THE BLADDER IN PATIENTS SUSPECTED OR KNOWN TO HAVE THE LESION ON THE BASIS OF A PRIOR CYSTOSCOPY.

Approval Order [Approval Order](#)

Summary [Summary Of Safety And Effectiveness](#)

Labeling [Labeling](#)

Supplements: [S001](#) [S002](#) [S003](#) [S004](#) [S005](#) [S006](#) [S007](#) [S008](#) [S009](#) [S010](#) [S011](#) [S012](#) [S013](#) [S014](#) [S017](#) [S018](#) [S019](#) [S020](#) [S021](#) [S022](#) [S023](#) [S024](#) [S025](#) [S026](#) [S027](#) [S028](#) [S029](#) [S030](#)

FDA-approved intended uses of and warnings for the originally approved KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System have been described in Section B subsection (2.1) and (2.2) of this reclassification petition.

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(2) Actions Requested by the petitioner

Accordingly, the petitioner is requesting the FDA Commissioner to take following actions:

- I. To take all administrative actions ultimately resulting in reclassification of the medical devices associated with FDA Medical Device Product Code OAY: currently classified into Class III (subject to pre-market approval), into Class II subject to 510(k) pre-market notification (special controls)
2. To establish special controls and issue special controls guidance or guideline to mitigate the risks associated with these devices to provide reasonable assurance or safety and effectiveness of the devices associated with Product Code OAY post their reclassification into Class II subject to 510(k) pre-market notification (special controls)
3. To further take any other form of administrative action necessary to effectuate the above-mentioned actions

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Section B: Statement of Grounds

(1) Basis for disagreement with the present classification status of the device

As previously mentioned in this reclassification petition, all FDA approved medical devices, as of Oct. 10, 2022, associated with the FDA Medical Device Product Code OAY are modifications to the original device KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System regulatory classification and pre-market approval details of which are available at the following link:

<https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P050027>

The parent device [KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System], PMA Number P050027 was a post-amendment device of a new type that FDA had not previously classified based on the criteria at section 513(a)(1) or the FD&C Act.

Hence the petitioner strongly believes that this device has been "automatically" or "statutorily" classified into class III by operation of section 513(f)(1) of the FD&C Act regardless of the level of risk(s) it posed or the ability of general and special controls to assure its safety and effectiveness.

Moreover, since the approval of KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System on May 2010, as no other manufacturer or importer intended to market any similar device in the US, there is no similar device with same intended use which has been classified into Class II subject to 510k premarket notification (special controls) through the "De Novo classification process" in accordance with section 513(1)(2) or the FD&C Act.

Furthermore, to the best of the petitioner's knowledge, to date, no person or organization has filed a reclassification petition requesting the FDA Commissioner to reclassify the devices associated with FDA Product Code: OAY from Class III (subject to pre-market approval) into Class II subject to 510k pre-market notification (special controls).

Hence, the medical devices associated with FDA Product Code: OAY continue to remain automatically classified into Class III (subject to pre-market approval) by operation of section 513(f)(1) or the FD&C Act without due consideration being given to the actual level of risk(s) associated with these devices or the ability of general and special controls to assure their safety and effectiveness.

The FDA has classified and approved other devices with similar technology and similar intended use, more specifically, the detection of tumors utilizing selected bands of excitation and observation light to visualize an exogenous fluorophore, through the De Novo process as Class II subject to 510k pre-market notification (special controls).

Leica Microsystems filed a De Novo 510(k) under 513(f)(2) of the FD&C Act for the FL400 diagnostic neurosurgical microscope filter which is a surgical microscope accessory used in fluorescent visualization of suspected grade III or IV gliomas during neurosurgery, DEN180024 (attachment 1). The FL400 utilizes an excitation filter (380 nm – 430 nm) in the light path and an emission filter (a long pass filter allowing light wavelengths greater than 444) in the camera module to visualize the fluorophore. On March 28, 2019, FDA cleared the device under product code QFX. The Decision Summary for DEN180024 list a set of bench tests used to evaluate the clinical performance of the device.

A similar device, the Carl Zeiss Blue 400 was clear on July 22, 2022, through a pre-market submission, K211346 (attachment 2), under product code QFX using the Leica FL400 as a predicate and the same set of performance test as those listed in the DEN180024 Decision Summary.

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Since the excitation light and observation light pass bands of these devices are almost identical to the KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System, we believe a similar set of performance tests would provide a reasonable assurance of safety and effectiveness.

Other devices utilizing similar excitation and emission light filter technology to visualize an exogenous fluorophore that were cleared in a Pre-market Notification include those in Product Codes IZI (i.e., Carl Zeiss Meditec, Inc. YELLOW 560 Fluorescence Module, K162991 (Attachment 3) and Leica FL560, K170239 (Attachment 4)) and OWN (i.e., Visionsense Ltd. VS3 Iridium System, K210265 (Attachment 5), KARL STORZ ICG Imaging System, K212695) (Attachment 6).

As part of the 2014-2015 Strategic Priorities (Attachment 7) the FDA reviewed 69 percent of the product codes subject to a PMA that had been on the market to determine whether or not to shift some premarket data collection to the postmarket setting or to pursue reclassification. Product Code OAY is included in Table 1, titled "Medical devices (by product code) determined to be candidates for reclassification to Class II".

(2) Reasons why the device should not be classified into its present classification

As described in Section A of this reclassification petition, all FDA-approved medical devices associated with Product Code OAY as of Oct 10, 2022, are serial modifications to a same original device KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System.

PMA Number P050027 KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System was the first device with Product Code OAY which was approved by FDA in May 2010 as a class III device.

FDA-approved intended use and suitable types of tumors for the originally approved KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System as follows:

(2.1) P050027, approved May 10, 2010.

The system is approved for use in combination with the optical imaging drug Cysview® (hexaminolevulinate hydrochloride) for Intravesical Solution is indicated for photodynamic blue light cystoscopy, as an adjunct to white light cystoscopy for the detection of non-muscle invasive papillary cancer of the bladder in patients suspected or known to have the lesion on the basis of a prior cystoscopy.

(2.2) P050027 S011, approved Feb. 15, 2018

The supplement included the addition of a flexible cystoscope in place of the rigid cystoscope, camera head and fluid light cable; the camera control unit was replaced with a model that is compatible with the flexible cystoscope. Additionally, the intended use was expanded to include the detection of carcinoma in situ (CIS) and patients undergoing surveillance cystoscopy for bladder cancer.

All other supplements were modifications to existing components or changes to user instructions.

The use of the KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System is not intended as the sole basis for the diagnosis of non-muscle invasive bladder cancer. The KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System is used with standard white light cystoscopy followed by pathology confirmation as the primary means of diagnosis. The KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System is used as an adjunct to the primary diagnosis.

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Thus, the devices associated with FDA Product Code OAY do not present a potential, unreasonable risk of illness or injury.

Moreover, these devices do not support or sustain human life and are not of substantial importance in preventing impairment of human health.

Thus, there are no high risk(s) of false negative or false positive test results associated with any of the devices currently approved with FDA Product Code OAY.

As previously discussed, the medical devices associated with FDA Product Code: OAY continue to remain "automatically" and "statutorily" classified into Class III (subject to pre-market approval) by application of section 513(f)(1) of the FD&C Act without due consideration being given to the actual level of risk(s) associated with these devices or the ability of general and special controls to assure their safety and effectiveness.

The petitioner strongly believes that, given the moderate risk associated with these devices, the current classification i.e., Class III (subject to pre-market approval) of the medical devices associated with Product Code OAY is unreasonable as special controls along with general controls can adequately mitigate the risks associated these devices to reasonably assure their safety and effectiveness.

The petitioner also believes that the reclassification and subsequent reduction in the regulatory burden for this indication would increase the availability of the technology to physicians and patients, as Olympus and Richard Wolf already have photodynamic diagnostics systems on the market Europe and other OUS global markets. For KARL STORZ, the reclassification would allow the technology to be included in our standard urology imaging systems instead of as a standalone blue light (PDD) system. Thereby reducing the cost of the technology to hospitals and clinics.

(3) Reasons justifying how the proposed classification will provide reasonable assurance of the safety and effectiveness of the device

The petitioner strongly believes that, given the moderate risk associated with these devices, the current classification i.e., Class III (subject to pre-market approval) of the medical devices associated with Product Code OAY is unreasonable as special controls along with general controls can adequately mitigate the risks associated these devices to reasonably assure their safety and effectiveness.

Hence, Class II subject to 510k pre-market notification (special controls) will be the most appropriate FDA regulatory classification for the medical devices associated with Product Code OAY.

The petitioner believes that information discussion in this section qualifies as valid scientific evidence, as defined in 21 CFR 860.7 for the purpose of determining the safety and effectiveness of the medical devices associated with Product Code OAY in light of requested reclassification of these devices from Class III (subject to pre-market approval) to Class II subject to 510(k) pre-market notification (special controls).

The petitioner also believes that valid scientific evidence, discussed in this section along with other evidence which may be available to the FDA, when taken as a whole, is adequate to support a determination that there is reasonable assurance that the devices associated with Product Code OAY will be safe and effective for their intended uses and conditions for use even after their reclassification from Class III (subject to pre-market approval) to Class II subject to 510(k) pre-market notification (special controls).

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The petitioner strongly believes that, even after reclassification or the devices associated with Product Code OAY to Class II subject to 510(k) pre-market notification (special controls), probable benefits to health from use of these devices for their intended uses and conditions for use, when accompanied by adequate directions and warnings against unsafe use, will outweigh any probable residual risks.

Following is the summary of relevant supportive information being submitted which the petitioner believes, qualifies as "valid scientific evidence" in support of requested reclassification of the medical devices associated with Product Code OAY from Class III (subject to pre-market approval) to Class II subject to 510(k) pre-market notification (special controls):

(3.1) Well-established safety and effectiveness of devices associated with Product Code OAY:

As discussed previously in this reclassification petition, PMA Number P050027, KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System was the first device with Product Code OAY which was approved by FDA in May 2010 as a class III device intended as an aid in the detection of non-muscle invasive bladder cancer and was modified in P050027-S011 to include a flexible version of the endoscope with an expanded indication, including detection of CIS and repetitive use.

As evident from Table 3.1 below. KARL STORZ Photodynamic Diagnostic D-Light C (PDD) System offers clear benefits as a modern alternative to the conventional White Light (WL) visualization for the detection of non-muscle invasive bladder cancer.

Table 3.1		
Comparative benefits of KARL STORZ D-Light C PDD System versus WL Visualization		
Potential benefit	D-Light C PDD System	WL Visualization
1.) Improved quality of TURB, risk-stratification, detection rate (sensitivity and specificity) and rate of complete resection	It improves the detection rate in both papillary lesions and carcinoma-in situ (high-risk) due to higher sensitivity and specificity compared with WL. This leads to a reduction of residual tumor and higher rate of complete resection	Many recurrences may be due to small tumors, which are often overlooked under white light during TURBT, or because of incomplete resection resulting in positive tumor resection margins.
2.) Reduces recurrence rate and lower progression	Reduction of residual tumor for better detection rate (sensitivity and specificity)	Recurrence depending on overlooked tumors or incomplete resection
3.) Reduces understaging and progression rate	It's able to detect high-risk tumor (carcinoma in situ) in addition of low-risk which ensure early detection and treatment.	Lower detection rate (lower sensitivity and specificity) of high-risk tumor which can progress over time and invade the bladder wall
4.) Cost effectiveness	It improves patients care by reducing recurrences and decreases the need for repeated TURBT and hospital beds after them. Improving progression rates, there would be considerably improved cost-effectiveness.	Need of repeated TURB and hospital beds after TURB due to overlooked and residual tumors to be resected

References

(1) Improved quality of TURB, see Attachments 10 -12
Thorsten Bach1, et al. **Optimised photodynamic diagnosis for transurethral resection of the bladder (TURB) in German clinical practice: results of the noninterventional study OPTIC III**, Received: 16 May 2016 / Accepted: 13 August 2016 / Published online: 30 August 2016, World J Urol (2017) 35:737–744 / DOI 10.1007/s00345-016-1925-0

Paramananthan Mariappan1, et al., **Early recurrence and the need for re-resection following Photodynamic diagnosis-assisted Transurethral Resection of Bladder Tumours: Multi-centre real-world experience of the UK PDD Users Group**, Article reuse guidelines: sagepub.com/journals-permissions / DOI: 10.1177/2051415819890464 / journals.sagepub.com/home/uro

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Siamak Daneshmand,M.D.a, et al., **Blue lightcystoscopyforthediagnosisofbladdercancer: Results from the US prospective multicenter registry**, Received 18 December 2017; received in revised form 16 April 2018; accepted 23 April 2018 *Urologic Oncology:Seminars and Original Investigations* 36 (2018) 361.e1–361.e6

- (2) Reduces recurrence rate, see attachments 13 - 14

Kevin M. Gallagher¹ , et al., '**Real-life experience': recurrence rate at 3 years with Hexvix® photodynamic diagnosis-assisted TURBT compared with good quality white light TURBT in new NMIBC—a prospective controlled study**', Received: 4 May 2017 / Accepted: 31 July 2017 / Published online: 12 August 2017 © The Author(s) 2017. This article is an open access publication *World J Urol* (2017) 35:1871–1877 / DOI 10.1007/s00345-017-2077-6

Georgios Gakisa, et al., **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* 2 (2016) 293–300 DOI 10.3233/BLC-160060 IOS Press

- (3) Reduces understaging, see attachment 15

Ashish M. Kamata, et al., **The Impact of Blue Light Cystoscopy with Hexaminolevulinate (HAL) on Progression of Bladder Cancer – A New Analysis**, *Bladder Cancer* 2 (2016) 273–278 / DOI 10.3233/BLC-160048

- (4) Cost effectiveness, see attachments 16 - 17

Tilman Todenhöfer^{1,2} , et al., **Retrospective German claims data study on initial treatment of bladder carcinoma (BCa) by transurethral bladder resection (TURB): a comparative analysis of costs using standard white light-(WL-) vs. blue light- (BL-) TURB**, Received: 27 September 2020 / Accepted: 29 December 2020 / Published online: 10 February 2021 © The Author(s) 2021, *World Journal of Urology* (2021) 39:2953–2960 https://doi.org/10.1007/s00345-020-03587-0

Zachary Klaassen, , et al., **Contemporary cost-consequence analysis of blue light cystoscopy with hexaminolevulinate in non-muscle-invasive bladder cancer**, Cite as: *Can Urol Assoc J* 2017;11(6):173-81. <http://dx.doi.org/10.5489/cuaj.4568>

As the moderate risk profile of these devices has become more apparent, FDA should revisit their classification to ensure that only reasonable controls are being applied to ensure that existing and new products associated with FDA Medical Device Product Code OAY are both safe and effective for their intended uses.

Hence, Class II subject to 510k pre-market notification (special controls) is the most appropriate FDA regulatory classification for the medical devices associated with Product Code OAY which are currently classified as Class III devices subject to premarket approval.

(3.2) The American Urological Association / Society of Urological Oncology Guideline for Diagnosis and Treatment of Non-muscle Invasive Bladder Cancer: AUA/SUO Guideline 2016, Amended 2021 (Attachment 8).

The guidelines are based on a systematic review, conducted in 2019, of recently published literature. The body of evidence for a particular treatment was assigned a strength rating of A (high), B (moderate) or C (low) for support of Strong, Moderate, or Conditional Recommendations. In the absence of sufficient evidence, additional information was provided as Clinical Principles and Expert Opinions. The guidelines include the recommendation "In a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B).

(3.3) The European Association of Urology (EAU) in 2022 for Non-muscle-invasive Bladder Cancer (TaT1 and CIS) (Attachment 9).

The EAU made the recommendation "If the equipment is available, perform fluorescence-guided (PDD) biopsies" with a strength rating of "Strong". The strength rating was developed using a modified GRADE

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approach. The strength of each recommendation was determined by the balance between desirable and undesirable consequences of alternative management strategies, the quality of the evidence (including certainty of estimates), and nature and variability of patient values and preferences.

(3.4) DEN180024, Leica FL400 De Novo (Attachment 1)

On March 28, 2019, FDA issued a Reclassification Order for DEN180024, under section 513(f)(2) of the FD&C Act, concluding that the Leica FL400 should be classified into Class II. In the Reclassification Order, the FDA stated believes that class II (special) controls provide reasonable assurance of the safety and effectiveness of the device type. The Identified Risks to Health included false positive (i.e., visualization of fluorescence when in fact no target fluorophore is present) and false negative (i.e., no visualization of fluorescence when in fact the target fluorophore is present). The FDA determined that the risks were adequately mitigated through non-clinical performance testing and labeling.

Risk(s) associated with the use of devices associated with Product Code OAY is certainly not higher than that associated with the Leica FL400 Diagnostic Neurosurgical Microscope Filter classified to Class II under 21 CFR 882.4950.

Accordingly, special controls along with general controls can adequately mitigate the risks associated these devices to reasonably assure their safety and effectiveness.

Hence, Class II subject to 510k pre-market notification (special controls) is the most appropriate FDA regulatory classification for the medical devices associated with Product Code OAY which are currently classified as Class III devices subject to premarket approval.

(4) Representative data and information known to the petitioner that are unfavorable to the petitioner's position.

To the best of petitioner's knowledge and understanding, there is no data and information known to the petitioner that are unfavorable to the petitioner's position.

(5) Summary of new information

As per 21 CFR 860.123 (a) (8). if the reclassification petition is based upon new information under Section 513(c). 514(b). or 515(b) or the F D&C Act. the petition should include a summary of the new information.

To the best of the petitioner's knowledge and understanding. Section 513(c) of. the FD&C Act applies to reclassification of a previously classified pre-amendment device based on "new information".

This petition is intended for requesting reclassification into Class II (special controls) for a post-amendment device which was automatically classified into class III under section 513(f)(1) of the FD&C Act.

Accordingly. this reclassification petition is being submitted under Section 513(f)(3) and not under Section 513(e) of the FD&C Act.

Hence, to the best of petitioner's knowledge and understanding, identifying the "new information" and including a "summary of the new information" are not applicable to this reclassification petition.

Reclassification Petition

(6): Financial certification and/or disclosure statement as required by 21 CFR Part 54

To meet the requirements of 21 CFR 860.123(a)(6), supportive information which the petitioner believes to qualify as "valid scientific evidence" as per §860.7, has been summarized in Section E of this reclassification petition.

This supportive information has been derived mainly from two recent guidelines released by US AUA and European EAU respectively.

The US AUA Guidelines include a recommendation that for patients with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence.

The recommendation was developed based on a systematic review of recently published literature. A strength rating was determined based on the body of evidence for a particular treatment or, in the absence of sufficient evidence, additional information was provided as clinical principles and expert opinions.

The EAU recommendation to perform fluorescence-guided (PDD) biopsies, if the equipment is available was made based on evidence identified, collated, and appraised through a structured assessment of the literature. The search was restricted to articles published between May 29th 2020 and June 3rd 2021. The strength rating was developed using a modified GRADE approach.

Accordingly, in the petitioner's opinion, neither of these two guidelines may be considered as Covered a Clinical Study.

Moreover, this reclassification petition is not based on any clinical investigation sponsored by KARL STORZ Endoscopy.

Hence, the petitioner strongly believes that submission of neither FDA Form 3454 (Certification: Financial Interests and Arrangements or Clinical Investigators) nor FDA Form 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) is relevant for this reclassification petition.

However, if FDA, anytime during the review of this reclassification petition, requires the petitioner to submit duly filled FDA Form 3454 and/or FDA Form 3455, the sponsor will submit the same as per FDA's guidance.

Reclassification Petition

Section C Environmental Impact

We claim categorical exclusion under 25.30, 25.31, 25.32, 25.33, or 25.34 of this chapter or an environmental assessment under 25.40 of this chapter.

Reclassification Petition

Section D Economic Impact

Economic impact information will be submitted upon request of the commissioner.

Reclassification Petition

Section E Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



(Signature)

Leigh Spotten, Director of Regulatory Affairs (Name of petitioner)

Director of Regulatory Affairs

KARL STORZ Endoscopy - America, Inc. (Mailing address)

2151 E. Grand Ave.

El Segundo, CA 90245

(310) 658-4842 (Telephone number))

Attachment 1

De Novo Decision Summary DEN180024

**DE NOVO CLASSIFICATION REQUEST FOR
LEICA FL400**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Diagnostic neurosurgical microscope filter. A diagnostic neurosurgical microscope filter is a device intended for use during neurosurgery to visualize fluorescence and enhance visualization of tissue associated with a specific disease or condition.

NEW REGULATION NUMBER: 21 CFR 882.4950

CLASSIFICATION: Class II

PRODUCT CODE: QFX

BACKGROUND

DEVICE NAME: Leica FL400

SUBMISSION NUMBER: DEN180024

DATE DE NOVO RECEIVED: May 8, 2018

CONTACT: Leica Microsystems (Schweiz) AG
Max Schmidheiny-Strasse 201
CH-9435 Heerbrugg, Switzerland

INDICATIONS FOR USE

The Leica FL400 is a surgical microscope accessory filter set for viewing fluorescence of fluorophores comprising an excitation filter for blue spectral range 380 nm – 430 nm and an observation filter comprising the long-wave blue, green, yellow and red spectrum in the spectral band greater than 444 nm.

The FL400 is a surgical microscope accessory used in fluorescent visualization of suspected grade III or IV gliomas during neurosurgery.

LIMITATIONS

For prescription use only.

Compatibility of the FL400 has only been demonstrated with Leica M525 and M530 surgical operating microscopes.

A pre-operational check of the FL400 device should be performed before surgery using

the FL400 Test Phantom.

The FL400 is not intended for diagnosis including the diagnosis of glioma.

**REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS,
PRECAUTIONS AND CONTRAINDICATIONS.**

DEVICE DESCRIPTION

The Leica FL400 is a fluorescence accessory that consists of an excitation (illumination) filter module and an emission (observation) filter module that are intended to be inserted into the optical beam path of compatible Leica surgical operating microscopes models M525 and M530. The excitation filter (380 nm – 430 nm), when placed into the light path, provides a fluorescence excitation light system for use in conjunction with an approved fluorophore selective for grade III or IV malignant gliomas.

The emission filter is a long pass filter allowing light wavelengths greater than 444 nm to pass. The fluorophore emits light at a longer wavelength than the excitation light. Once passed through the emission filter module, a camera adapted to the surgical microscope detects the fluorescence signal, allowing the user to visualize the fluorophore in the open neurosurgery field.

The Leica FL400 is supplied with a test phantom to confirm proper pre-operative fluorescence set-up. The Leica FL400 Test Phantom offers multiple levels of fluorescence intensity, which provides the clinician with a visual assessment of the FL400 pre-operative set-up. The clinician is advised to confirm the fluorescence spots are visible to confirm functionality prior to utilization.

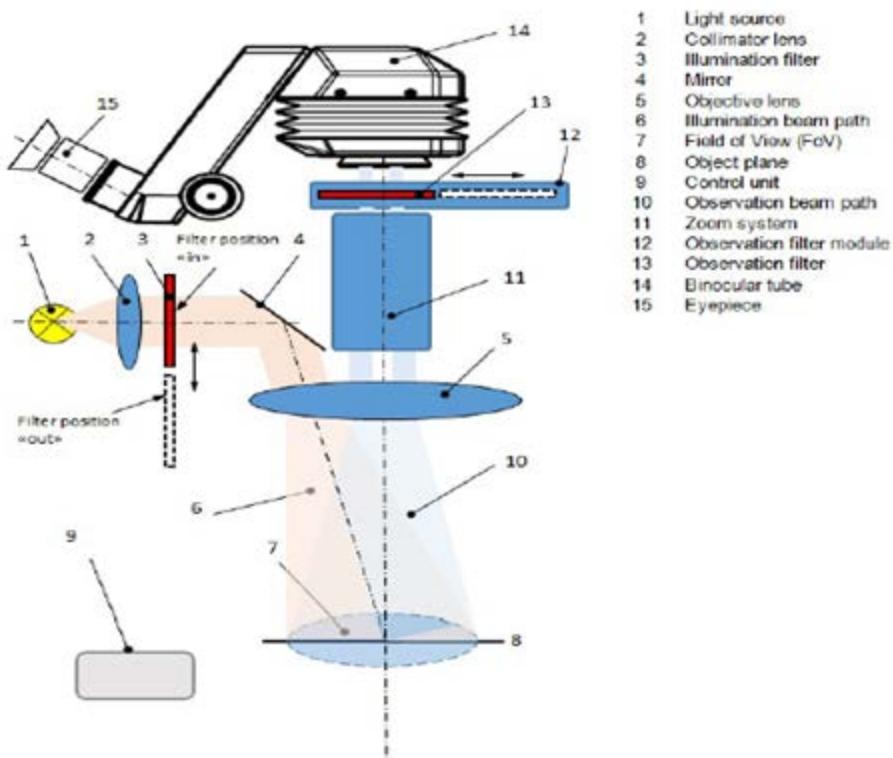


Figure 1: Leica FL400 Illumination Path

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The device does not have patient-contacting materials; therefore, a biocompatibility assessment is not needed for this device.

STERILITY

The device is provided non-sterile. Cleaning instructions are provided in the user manual that direct users to follow the cleaning procedures of the surgical operating microscope that the FL400 is installed in.

PERFORMANCE TESTING - BENCH

Testing was performed to verify device specifications for proper visualization of fluorescing agents, including the following:

- **Spectrum of the Illumination Source:** The irradiance spectrum (300 nm – 1100 nm, mW/cm²) of the illumination source was measured and verified with a spectrometer. These measurements were assessed prior to application of the excitation filter module.

- Maximum Power and Irradiance of the Illumination Source: The maximum output power and irradiance of illumination sources were measured and verified with a power meter at the end of the microscope light guide. These measurements were assessed prior to application of the excitation filter module.
- Irradiance Spectrum of the Excitation Light and Spectral Response of the Excitation Filter: The irradiance spectrum (300 nm – 1100 nm) of the illumination light, following passage through the excitation filter module, was measured at a working distance of 30 cm for the M525 surgical operating microscope and 35 cm for the M530 with a spectrometer. This was divided by the irradiance spectrum of the illumination source without excitation filter module at the same working distance to provide the spectral response of the excitation filter.
- Maximum Excitation Power and Power Density: The maximum power (mW) and power density (mW/cm^2) of the excitation light was measured with a thermopile and a UV diode, calibrated set to 300 nm, at multiple different working distances and zoom settings, including the maximum and minimum zoom. These power density measurements were then compared to the excitation power densities observed in the clinical trials assessing the efficacy of the fluorophore.
- Optical Path Loss: To determine the overall detectable light output and the total losses in relation to device working distance and zoom setting, optical path loss was calculated by dividing the output signal measured at the microscope eyepiece (without emission filter) by the illumination signal measured at the microscope focal plane for the same zoom setting. A reflection standard (white silicon remission disc) was used at a working distance of 30 cm or 35 cm depending upon the model as described above.
- Spectrum of the Emission Filter: The spectrum (300 nm – 1100 nm) of the emission filter when integrated in the surgical operating microscope was measured to include all the coating and optics that affects the spectrum of the observation path. For this test the excitation filter was removed, and a reflection standard was used at the device focal plane with different zoom settings. Transmission of the emission filter was calculated from white light remission spectra at the oculars with emission filter in place versus without the filter.
- Homogeneity of the Excitation Light at the Focal Point: The reflected signal from a white sheet of paper positioned at 30 cm working distance was imaged by the surgical operating microscope camera and the intensity profile was calculated to demonstrate the homogeneity of the excitation light.
- System Sensitivity: A diffusely reflecting and fluorescent disc made of silicone was positioned at a microscope working distance of 30 cm. The device output spectrum was measured by a spectrometer at the microscope eyepiece for different zoom settings. The fluorescence/remission ratio was calculated by dividing the integral of intensities in the fluorescence bandwidth by the integral of intensities in remission bandwidth.

- **Pre-Operative Phantom Test:** This test was conducted to demonstrate that the Leica FL400 test phantom is suitable for the pre-operative checks of the Leica FL400 device. The optical phantom has 4 dots with different fluorophore concentrations and was imaged by the surgical operating microscope camera at different working distances and different magnification or zoom settings. The same tests were repeated by observation through the microscope eyepieces.
- **Spectrum of Camera Filter:** The spectrum of camera filter was measured to demonstrate that it can block near infrared and infrared leakage of excitation light to the camera.

SUMMARY OF CLINICAL INFORMATION

No clinical studies were evaluated assessing the safety or effectiveness of the Leica FL400 for the visualization of grade III or IV gliomas during neurosurgery in support of this De Novo request.

Pediatric Extrapolation

In this De Novo request, clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

User manual labeling was provided that:

- Describes the device specifications.
- States that the device should not be used in conjunction with an optical imaging agent that is not compatible with the device specifications.
- States that the device is not intended for diagnosis.
- States that medical decisions remain the responsibility of the clinician.
- Describes preparations to take prior to surgery including adjusting the surgical operating microscope, confirming appropriate settings, and providing operational instructions.
- Describes instructions for performing a pre-operational check utilizing the FL400 Test Phantom to ensure proper functionality prior to each use.
- Describes proper use with external light sources and compatible cameras for viewing.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the diagnostic neurosurgical microscope filter and the measures necessary to mitigate these risks.

Table 1 – Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Mitigation Measures
Incorrect or misinterpreted results, including: <ul style="list-style-type: none"> • False positive: visualization of fluorescence when in fact no target fluorophore is present • False negative: no visualization of fluorescence when in fact the target fluorophore is present 	Non-clinical performance testing; and Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the diagnostic neurosurgical microscope filter is subject to the following special controls:

- (1) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use, and verify and validate filter specifications and functional characteristics, including the following:
 - (i) Spectrum and intensity of the illumination source;
 - (ii) Spectrum of the excitation and emission filter modules when integrated in the surgical operating microscope;
 - (iii) Excitation power and power density;
 - (iv) Optical path loss from illumination source to objective lens or microscope camera;
 - (v) Homogeneity of the excitation light at the focal plane;
 - (vi) Fluorescence detection sensitivity;
 - (vii) Verification of calibration or pre-operative procedures; and
 - (viii) If camera-based, spectral sensitivity of the camera.

- (2) Labeling must include:
 - (i) Identification of the filter characteristics in conjunction with a compatible surgical operating microscope, to include the following:
 - (A) Illumination spectrum and power density; and
 - (B) Excitation and emission filter spectra.
 - (ii) Instructions for calibration or pre-operative checks to ensure device functionality prior to each use;
 - (iii) Instructions for use with compatible surgical operating microscopes, external light sources, and cameras;
 - (iv) A warning that the device should only be used with fluorophores approved for use within the specified spectral ranges; and
 - (v) A warning that the device is not a standalone diagnostic.

BENEFIT-RISK DETERMINATION

The Leica FL400 has significant clinical value as an adjunct to surgery for the fluorescent visualization of grade III or IV gliomas in patients that have been pre-operatively dosed with an FDA-approved tumor-selective substance (fluorophore). The performance capability of the device is dependent upon the ability of the fluorophore to accurately identify the pathological

tumor tissue, and upon compatibility of the technological characteristics of the device with the excitation and emission spectra of the fluorophore.

Prior clinical studies were conducted to demonstrate the efficacy of optical imaging agent aminolevulinic acid hydrochloride (ALA HCl). These studies utilized standard surgical operating microscopes with illumination sources with power density 40-80 mW/cm² adapted to visualize fluorescence excitation in the wavelength range from 400 nm to 410 nm and for observation from 620 nm to 710 nm. These clinical studies were reviewed by FDA's Center for Drug Evaluation and Research (CDER) under NDA 208630.¹

The efficacy of ALA HCl as an adjunct for the visualization of grade III or IV gliomas during neurosurgery was demonstrated across three studies with consistent observed results: the PPV ranged from 96% to 98% and the NPV ranged from 19% to 24%. This demonstrates a high probability that fluorescence visualization corresponds to the presence of grade III or IV gliomas; however, this also demonstrates a high probability that grade III or IV gliomas are present where no fluorescence is visualized.

The risks of the device are based on the non-clinical testing described above, taken into consideration with the observed results in the drug trials briefly summarized previously. The risk of the Leica FL400 is failure to provide appropriate excitation and emission filter spectra when used with a compatible surgical operating microscope to effectively visualize an FDA-approved tumor-selective substance (fluorophore) for tissue characterization in the open neurosurgery field. This risk is mitigated by non-clinical testing demonstrating that the interactions between the illumination source, excitation filter module, and emission filter module are appropriately designed to visualize an approved fluorophore. This risk is further mitigated by labeling in the device's Instructions for Use that 1) allows for users to determine what fluorophores could be visualized by using the device, 2) ensures users properly calibrate or check to ensure functionality of the device prior to each use, and 3) explains the device is not intended for diagnosis. The ultimate responsibility in determining the acceptable degree of tumor resection resides with the neurosurgeon.

The probable benefits of the device are also based on the non-clinical testing described above, taken into consideration with the observed results in the drug trials briefly summarized previously. Although Leica M525 and M530 surgical operating microscopes adapted with the Leica FL400 filter set were not used in the clinical studies that were performed evaluating the efficacy of ALA HCl evaluated under NDA 208630, the non-clinical testing provided in this submission adequately demonstrates that the previously evaluated clinical data are representative of the expected benefits and risks when utilizing the subject device for visualization.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

¹ https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208630Orig1s000TOC.cfm

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indications for use statement:

The Leica FL400 is a surgical microscope accessory filter set for viewing fluorescence of fluorophores comprising an excitation filter for blue spectral range 380 nm – 430 nm and an observation filter comprising the long-wave blue, green, yellow and red spectrum in the spectral band greater than 444 nm.

The FL400 is a surgical microscope accessory used in fluorescent visualization of suspected grade III or IV gliomas during neurosurgery.

The probable benefits outweigh the probable risks for the Leica FL400. The device provides benefits and the risks can be mitigated using general controls and the identified special controls.

CONCLUSION

The De Novo request for the Leica FL400 is granted and the device is classified as follows:

Product Code: QFX

Device Type: Diagnostic neurosurgical microscope filter

Regulation Number: 21 CFR 882.4950

Class: II

Attachment 2

Carl Zeiss Blue 400 510(k) K211346 Summary



July 22, 2022

Carl Zeiss Meditec AG
% Maria Golovina
Head of Regulatory Affairs - USA
5300 Central Parkway
Dublin, California 94568

Re: K211346

Trade/Device Name: BLUE 400

Regulation Number: 21 CFR 882.4950

Regulation Name: Diagnostic Neurosurgical Microscope Filter

Regulatory Class: Class II

Product Code: QFX

Dated: June 16, 2022

Received: June 21, 2022

Dear Maria Golovina:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems>.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance>) and CDRH Learn (<https://www.fda.gov/training-and-continuing-education/cdrh-learn>). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice>) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Adam D. Pierce, Ph.D.
Assistant Director
DHT5A: Division of Neurosurgical,
Neurointerventional
and Neurodiagnostic Devices
OHT5: Office of Neurological
and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

Indications for Use510(k) Number (*if known*)

K211346

Device Name

BLUE 400

Indications for Use (Describe)

BLUE 400 is an accessory of the surgical microscope and allows the fluorescence observation of fluorophores with an excitation peak between 400 nm and 410 nm and the fluorescence emission observation comprising the spectrum in a spectral band of 620 - 710 nm.

The ZEISS BLUE 400 is a surgical microscope accessory used in fluorescent visualization of suspected grade III and IV gliomas during neurosurgery.

Type of Use (Select one or both, as applicable) Prescription Use (Part 21 CFR 801 Subpart D) Over-The-Counter Use (21 CFR 801 Subpart C)**CONTINUE ON A SEPARATE PAGE IF NEEDED.**

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

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In accordance with 21 CFR 807.92 the 510(k) Summary for the BLUE 400 is provided below.

1. SUBMITTER

Applicant: Carl Zeiss Meditec AG
Goeschwizer Strasse 51-52
D-07745 Jena
Germany

Primary Correspondent Maria Golovina
Head of Regulatory Affairs - USA
Carl Zeiss Meditec, Inc.
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E-mail: maria.golovina@zeiss.com (preferred)

Secondary Correspondent Chaitali Gawde
Senior Regulatory Affairs Specialist
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5300 Central Parkway | Dublin, CA 94568
(925) 557-4202 Phone
E-mail: chaitali.gawde@zeiss.com

Date Prepared: July 22, 2022

2. DEVICE

Device Trade Name: BLUE 400
Classification: 21 CFR 882.4950 Diagnostic Neurosurgical Microscope Filter
Regulatory Class: II
Product Code: QFX

3. PREDICATE DEVICE

Predicate Device: Leica FL400 (DEN180024)
Classification: 21 CFR 882.4950 Diagnostic Neurosurgical Microscope Filter
Regulatory Class: II
Product Code: QFX

4. DEVICE DESCRIPTION

The BLUE 400 is an accessory to the Zeiss surgical microscopes (OPMI PENTERO 800, OPMI PENTERO 900, and KINEVO 900), intended to allow intraoperative viewing of malignant glioma tissue under fluorescence. The BLUE 400 accessory is entirely composed of optical filters: the “Excitation” filter and the “Emission” filters. The Excitation filter is designed to filter all light wavelengths except 400 – 470 nanometers and is optimized to pass light between 400 – 410 nanometers. The Emission filters are designed to filter all light wavelengths except 430 – 800 nanometers and is optimized to pass light between 620 – 710 nanometers.

When installed in the surgical microscopes (class I), the BLUE 400 introduces optical filters to the illumination and viewing optical paths. The BLUE 400 includes installation of a software license that facilitates use of the accessory. After the SW license is installed, the user has the option to switch from the normal white light mode of the surgical microscope to the BLUE 400 mode.

510(k) Summary**K211346 Page 4 of 7**

The BLUE 400 accessory, when installed in the surgical microscopes, is intended to be used in conjunction with an approved optical imaging agent that is excited mainly in the wavelength range of 400 – 410 nanometers and fluoresces in the wavelength range of 620 – 710 nanometers.

5. INDICATIONS FOR USE

BLUE 400 is an accessory of the surgical microscope and allows the fluorescence observation of fluorophores with an excitation peak between 400 nm and 410 nm and the fluorescence emission observation comprising the spectrum in a spectral band of 620 - 710 nm.

The ZEISS BLUE 400 is a surgical microscope accessory used in fluorescent visualization of suspected grade III and IV gliomas during neurosurgery.

6. SUBSTANTIAL EQUIVALENCE**Table 1.** Subject to Predicate Device Comparison Table – Indications for Use

Attribute	Subject Device BLUE 400 K211346	Predicate Device Leica FL400 DEN180024	Equivalency Analysis
Indications for use	BLUE 400 is an accessory of the surgical microscope and allows the fluorescence observation of fluorophores with an excitation peak between 400 nm and 410 nm and the fluorescence emission observation comprising the spectrum in a spectral band of 620 - 710 nm. The ZEISS BLUE 400 is a surgical microscope accessory used in fluorescent visualization of suspected grade III and IV gliomas during neurosurgery.	The Leica FL400 is a surgical microscope accessory filter set for viewing fluorescence of fluorophores comprising an excitation filter for blue spectral range 380 nm – 430 nm and an observation filter comprising the long-wave blue, green, yellow and red spectrum in the spectral band greater than 444 nm. The FL400 is a surgical microscope accessory used in fluorescent visualization of suspected grade III or IV gliomas during neurosurgery.	Similar
Intended Use	Patients undergoing neurological procedures.	Patients undergoing neurological procedures.	Identical
Type of Component	Accessory to the microscope (Filter)	Accessory to the microscope (Filter)	Identical

Table 2. Subject to Predicate Device Comparison Table – Technical Characteristics

Attribute	Subject Device K211346	Predicate Device DEN180024	Equivalency Analysis
Device name	BLUE 400	Leica FL400	Different
Manufacturer	Carl Zeiss Meditec AG Goeschwitzer Strasse 51-52 D-07745 Jena, Germany	Leica Microsystems (Schweiz) AG	Different
Classification Product Code	QFX	QFX	Identical
Regulation #	21 CFR 882.4950 (Diagnostic neurosurgical microscope filter)	21 CFR 882.4950 (Diagnostic neurosurgical microscope filter)	Identical
Fluorescence Excitation Spectral Window	400 nm - 430 nm	380 – 430 nm	Equivalent for fluorescence agent
Spectrum of the Emission Filter	430 - 800 nm	300 – 1100 nm	Equivalent for detecting the fluorescence agent
Combination Device	No	No	Identical
Visualization Result	Fluorescent image of distribution of the accumulated protoporphyrin IX (PpIX) in malignant tissue during operation.	Fluorescent image of distribution of the accumulated protoporphyrin IX (PpIX) in malignant tissue during operation.	Identical
Visualization of Real-Time Images	Yes	Yes	Identical
Visualization on Interface/Display	Yes	Yes	Identical
Light Specifications – Type	White Light – Fluorescence	White Light – Fluorescence	Identical

7. SUMMARY OF STUDIES

Sterilization and Shelf Life

The device is provided non-sterile. Cleaning instructions are provided in the user manual that direct users to follow the cleaning procedures of the surgical operating microscope that the BLUE 400 is installed in. Shelf-Life is not applicable.

Biocompatibility

The device does not have patient-contacting materials; therefore, a biocompatibility assessment is not needed for this device.

Performance Testing - Bench

In order for BLUE 400 filter to work, it has to be installed onto a surgical microscope and a software license to the microscope has to be installed. Software verification testing was performed in accordance with FDA Guidance “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices” to demonstrate that software is performing as intended.

Non-clinical system testing provided an evaluation of the performance of the system relevant to each of the system specifications. The functional and system level testing showed that the system met the defined specifications.

The testing was completed for the predicate and subject device and the performance of the subject device was compared to the predicate.

Finally, special controls testing has also been performed and met the defined specifications. The following special controls testing has been conducted with and without cover glass.

Test	Test Method Summary	Results
Spectrum of the Illumination Source	The irradiance spectrum (250 nm – 1020 nm, mW/cm ²) of the illumination source was measured and verified with a spectrometer. These measurements were assessed prior to application of the excitation filter module.	Passed
Maximum Power and Irradiance of the Illumination Source	The maximum output power and irradiance of illumination sources were measured and verified with a power meter at the end of the microscope light guide. These measurements were assessed prior to application of the excitation filter module.	Passed
Irradiance Spectrum of the Excitation Light and Spectral Response of the Excitation Filter	The irradiance spectrum (250 nm – 1020 nm) of the illumination light, following passage through the excitation filter module, was measured at a working distance of 30 cm with a spectrometer. The edges at 50% decrease of the blue excitation peak were calculated respectively.	Passed
Maximum Excitation Power and Power Density	The maximum power (mW) and power density (mW/cm ²) of the excitation light was measured with a thermopile, at multiple different working distances (22.5 - 30 cm) and zoom settings, including the maximum and minimum zoom. The power density measurements of the subject device were compared to the predicate device.	Passed
Optical Path Loss	To determine the overall detectable light output and the total losses in relation to device working distance and zoom setting, optical path loss was calculated by dividing the output signal measured at the microscope eyepiece (without emission filter) by the illumination signal measured with a spectrometer at the microscope focal plane for the same zoom setting. A reflection standard (white silicon remission disc) was used at a working distance of 35 cm.	Passed
Spectrum of the Emission Filter	The spectrum (350 nm – 1050 nm) of the emission filter when integrated in the surgical operating	Passed

Test	Test Method Summary	Results
	microscope was measured with a spectroradiometer to include all the coating and optics that affects the spectrum of the observation path. For this test the excitation filter was removed, and a reflection standard was used at the device focal plane with different zoom settings. To compare the light that passes the observation optics and emission filter, the 50% edge of the spectrum was calculated.	
Homogeneity of the Excitation Light at the Focal Point	The reflected signal from a white sheet of paper positioned at 30 cm working distance was imaged by the surgical operating microscope camera and the intensity profile was calculated to demonstrate the homogeneity of the excitation light.	Passed
System Sensitivity	<p>As a diffusely reflecting and fluorescent disc the ZEISS BLUE 400 fluorescent target was used and positioned at a microscope working distance of 22.5 cm. The zoom setting was chosen to lead to the same image size of the target for all three devices.</p> <p>The fluorescence signal in the eyepiece of the subject device was compared to the predicate device.</p>	Passed
Pre-Operative Phantom Test	This test was conducted to demonstrate that the ZEISS BLUE 400 test phantom is suitable for the pre-operative checks of the KINEVO 900 and OPMI PENTERO 900. The phantom has one fluorescent area and was imaged by the surgical microscope camera. The same test was repeated by observation through the microscope eyepiece.	Passed
Spectrum of Camera Filter	The spectrum at the camera interface was measured with a spectroradiometer to demonstrate that camera filter can block near infrared and infrared leakage of excitation light to the camera.	Passed

BLUE 400 has not been evaluated to support the use of the device in a pediatric patient population.

8. CONCLUSION

The indications for use of the subject device, BLUE 400, are equivalent to the indications for use of the predicate device, Leica FL400. The technological characteristics and risk profile of the subject device are similar to the predicate device. Based on the similarities of the indications for use, technological characteristics, and the results of the non-clinical performance testing, the BLUE 400 filter is substantially equivalent to the legally marked predicate device, Leica FL400.

Attachment 3

Zeiss Meditec, Inc. YELLOW 560 Fluorescence Module, 510(k) K162991 Summary



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

July 24, 2017

Carl Zeiss Meditec Ag
% Mandy Ambrecht
Staff Regulatory Affairs Specialist
Carl Zeiss Meditec, Inc.
5160 Hacienda Drive
Dublin, California 94568

Re: K162991

Trade/Device Name: Yellow 560 Fluorescence Module
Regulation Number: 21 CFR 876.1500
Regulation Name: Endoscope And Accessories
Regulatory Class: Class II
Product Code: IZI
Dated: June 22, 2017
Received: June 23, 2017

Dear Mandy Ambrecht:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-

related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address

<http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm> for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address

<http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>.

Sincerely,

For Binita S. Ashar, M.D., M.B.A., F.A.C.S.
Director
Division of Surgical Devices
Office of Device Evaluation
Center for Devices and Radiological Health

SECTION 5.

510(K) SUMMARY

5 510(K) SUMMARY

510(k) SUMMARY (as per 21 CFR §807.92)

YELLOW 560 Fluorescence Module

GENERAL INFORMATION

Manufacturer: Carl Zeiss Meditec AG
Goeschwitzer Strasse 51-52
D-07745 Jena, Germany
+49 3641220-667 (phone)
+49 3641220-282 (fax)
Establishment Registration Number: 9615030

Contact Person: Mandy Ambrecht
Staff Regulatory Affairs Specialist
Carl Zeiss Meditec, Inc.
5160 Hacienda Drive
Dublin, CA 94568
(925) 557-4561 Phone
(925) 557-4259 Fax
E-mail: mandy.ambrecht@zeiss.com

Date prepared: July 21, 2017

Device System, X-Ray, Angiographic

Classification: 21 CFR 892.1600

Product Code and Class: IZI - class II

Common Name: Angiographic x-ray system

Trade/Proprietary Name: YELLOW 560 Fluorescence Module

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PREDICATE DEVICES

Company: Carl Zeiss Surgical GmbH
Device: INFRARED 800 with FLOW 800 option
(K100468)

Company: Leica Microsystems
Device: Leica FL800
(K061871)

Company: Heidelberg Engineering GmbH
Device: Heidelberg Retina Angiograph FA/ICGA (HRA/C)
(K971671)

Reference Device

Company: Novadaq Technologies, Inc.
Device: SPY Intra Operative Imaging System: SP2000
(K072222)

INDICATIONS FOR USE (21 CFR §807.92(a)(5))

The ZEISS YELLOW 560 is a surgical microscope accessory used in viewing and visual assessment of intraoperative blood flow in the cerebral vascular area including, but not limited to, assessing cerebral aneurysm and vessel branch occlusion, as well as patency of very small perforating vessels.

It also aids in the real-time visualization of blood flow and visual assessment of vessel types before and after Arteriovenous Malformation (AVM) surgery.

DEVICE DESCRIPTION(21 CFR §807.92(a)(4))

The YELLOW 560 Fluorescence Module is an accessory to the ZEISS surgical microscope OPMI PENTERO 800 and OPMI PENTERO 900 for visualizing blood flow intraoperatively. The YELLOW 560 Fluorescence Module integrated into the OPMI PENTERO 800 / OPMI PENTERO 900 surgical microscope allows the surgical microscope to produce filtered light to illuminate the fluorescence properties of the sodium fluorescein dye and to detect the emitted fluorescent signal to examine the human vascular system during surgery. This is achieved by placing a filter in the illumination path and a second filter in the optical (viewing) path.

The filters of the YELLOW 560 Fluorescence Module are optimized to deliver excitation

SECTION 5.

510(K) SUMMARY

wavelengths ranging from 460 to 500 nm and to emphasize fluorescence signals in wavelengths ranging from 540 to 690 nm that typically correspond to the excitation and emission spectrum of sodium fluorescein. The option to place the filters for YELLOW 560 is controlled via either the handgrip of the surgical microscope or the foot control.

Sodium fluorescein may be used as a fluorescence contrast agent to examine arteriovenous malformations (AVM), aneurysms, and vessel anastomoses. The dye helps to visualize intraoperative blood flow and vessel patency. Sodium fluorescein can be used as contrast agent with YELLOW 560 without changes to the formulation, mode of action, approved dose or route of administration.

RISK MANAGEMENT AND GENERAL SAFETY AND EFFECTIVENESS

The device labeling contains instructions for use and any necessary cautions and warnings to provide for safe and effective use of the device. The YELLOW 560 Fluorescence Module description is integrated in the user manual of the OPMI PENTERO 800 / OPMI PENTERO 900 as it is an accessory to these devices.

Risk management is ensured via a risk analysis, which is used to identify potential hazards and mitigations. These potential hazards are controlled by design means (hardware and software means), protection measures and user instructions. To confirm that the measures are effective and that the product meets its intended uses, verification of requirements and standards, and validation of the clinical workflow was performed. Carl Zeiss Meditec adheres to recognized and established industry practice and relevant international standards where indicated.

TECHNOLOGICAL CHARACTERISTICS AND SUBSTANTIAL EQUIVALENCE (21 CFR §807.92(a) (6)):

The YELLOW560 Fluorescence Module is substantially equivalent to the primary predicate device, INFRARED 800 with FLOW 800 option (K100468). Each system utilizes the same surgical stereo microscope system. Each device utilizes a fluorescent agent to visualize blood flow and the fluorescence of the dye is displayed by using emission and excitation filters.

The indications for use for the YELLOW 560 Fluorescence Module is a subset of the previously cleared indications for INFRARED 800 with FLOW 800 option. The technological characteristics and operating principles of the YELLOW 560 Fluorescence Module are the same as that of the predicate device.

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The YELLOW 560 Fluorescence Module and INFRARED 800 with FLOW 800 option are both accessories to the OPMI PENTERO 800 and OPMI PENTERO 900 surgical microscopes. The microscope itself including the light source is identical. Both accessories (YELLOW 560 Fluorescence Module and INFRARED 800 with FLOW 800) have the same basic functions for viewing, recording, and replaying fluorescent images.

YELLOW 560 is an accessory to a surgical microscope, as is Leica's FL800 (K061871). Both offer functions regarding viewing, recording and replaying of fluorescent videos, both use illumination conditions for excitation and detection realized by filter and sensor specifications, and both use a fluorescent agent, Sodium Fluorescein with YELLOW 560 and Indocyanine Green (ICG) with Leica's FL800.

The YELLOW 560 utilizes a surgical stereo microscope while the Heidelberg Retina Angiograph (HRA) (K971671) uses a confocal laser scanning angiography system. While the systems are different, they each have the functions for viewing and recording fluorescent images. Both devices use Sodium Fluorescein as a contrast agent to visualize vascular structures – HRA for ophthalmic indications and YELLOW 560 for neurovascular indications. Both devices use filters that enable fluorescent images to be visualized after Sodium Fluorescein has been used as a fluorescent agent.

YELLOW 560 and Novadaq's SPY SP2000 (K072222) both provide the surgeon with the capability to view, record and replay fluorescent images of blood vessels. Both use a light source to illuminate the surface. Both use a fluorescent agent: Sodium Fluorescein with YELLOW 560 and Indocyanine Green (ICG) with Novadaq SPY. A fluorescent image results from the absorption of light causing excitation of the dye followed by emission of infrared energy. Both systems use a camera to capture the image. These images may then be used to evaluate the integrity of the vasculature.

Evaluation performed on the YELLOW 560 Fluorescence Module supports the indications for use statement and demonstrates that the device is substantially equivalent to the predicate devices and does not raise new questions regarding safety and effectiveness.

SUBSTANTIAL EQUIVALENCE TO PREDICATE (21 CFR §807.92(B)(1)):

The OPMI PENTERO 800 / OPMI PENTERO 900 with YELLOW 560 Fluorescence Module has been tested to meet the product requirements (PRS) and software requirements (SRS) and is considered to be substantially equivalent to the predicates as indicated above.

Verification Testing to Standards

YELLOW 560 Fluorescence Module was designed and verified to the applicable standards. Testing was conducted on the YELLOW 560 Fluorescence Module and it was found to perform as intended. Each function and/or feature was tested by means of an appropriate test case or test specification.

Testing with the YELLOW 560 Fluorescence Module integrated in the OPMI PENTERO 900

SECTION 5.

510(K) SUMMARY

surgical microscope has been conducted to demonstrate conformance to the following standards:

- ANSI / AAMI 60601-1:2005/(R)2012 and A1:2012, C1:2009/(R)2012 and A2:2010/(R)2012 (3rd Edition) Electrical equipment -- Part 1: General requirements for basic safety and essential performance
- IEC 60601-1-2: 2014 Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests (EMC)
- IEC 62471:2006 Photobiological safety of lamps and lamp systems
- IEC 60825-1:2007 Safety of laser products - Part 1: Equipment classification, and requirements [Including: Technical Corrigendum 1 (2008), Interpretation Sheet 1 (2007), Interpretation Sheet 2 (2007)]

Bench Testing

Internal verification testing was conducted to verify the optical performance of the YELLOW 560 Fluorescence Module, its fluorescent target and the system performance of the YELLOW 560 Fluorescence Module as integrated into the OPMI PENTERO 800 and PENTERO 900. The results indicate that the YELLOW 560 Fluorescence Module met all the requirements.

Verification and Validation

In addition to systems testing, software verification activities completed were divided into three phases:

- Tests accompanying development (including code inspections)
- Integration test phase – stabilization phase
- System verification

Validation and usability testing was conducted with the YELLOW 560 Fluorescence Module in conjunction with the OPMI PENTERO surgical microscope to ensure that the medical device meets the product and user requirements and to support a determination of substantial equivalence to the predicate devices.

Verification and validation activities were successfully completed and prove that the YELLOW 560 Fluorescence Module meets its requirements and performs as intended.

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510(K) SUMMARY

Clinical Evaluation

Clinical data on YELLOW 560 has been collected by various researchers and is reported in the clinical literature. A review of the clinical literature that discusses the relevant studies has been included in this Premarket Notification. The review includes citations from peer-reviewed medical literature demonstrating the effective intraoperative use of the YELLOW 560 Fluorescence Module in sodium fluorescein angiography in the cerebrovascular area, especially in arteriovenous malformation (AVM) and aneurysm surgery.

One clinical publication provides a comparison of the YELLOW 560 Fluorescence Module used in combination with sodium fluorescein and the predicate device INFRARED 800 with FLOW 800 option used in combination with Indocyanine Green (ICG) in aneurysm surgery in the same patients.

In particular, the literature provides evidence of the effective real-time visualization of blood flow and visual assessment of vessel types in AVM surgery by the use of YELLOW 560. Moreover, it was demonstrated that YELLOW 560 was effectively used in the visual assessment of intraoperative blood flow in assessing cerebral aneurysms, vessel branch occlusion, as well as patency of very small perforating vessels in neurosurgery.

Comparing ICG videoangiography using INFRARED 800 with FLOW 800 option and fluorescein angiography using YELLOW 560, each technique exhibited specific attributes. YELLOW 560 provided an improved visualization of vasculature at high magnification in deep surgical fields and can be used within the full range of magnification whereas the INFRARED 800 with FLOW 800 option was considered especially beneficial for detection of blood flow within branching and small perforating vessels.

Specifically, the clinical literature supports the indications for use in demonstrating that the YELLOW 560 Fluorescence Module can be used and is beneficial:

- in viewing and visual assessment of intraoperative blood flow in the cerebral vascular area including, but not limited to, assessing cerebral aneurysm and vessel branch occlusion, as well as patency of very small perforating vessels.
- to aid in the real-time visualization of blood flow and visual assessment of vessel types before and after arteriovenous malformation (AVM) surgery.

In summary, fluorescence angiography in the cerebrovascular area using the YELLOW 560 Fluorescence Module and INFRARED 800 with FLOW 800 option is considered comparable in terms of safety and effectiveness. Both methods are considered to be complementary to each other.

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510(K) SUMMARY (21 CFR §807.92(C)):

Based on the successful verification and validation testing and clinical literature review, it is Carl Zeiss Meditec AG's opinion that the YELLOW 560 Fluorescence Module, as an accessory to the OPMI PENTERO 800 / OPMI PENTERO 900 surgical microscope, does not introduce any new potential safety risks and is substantially equivalent to, and performs as well as, the predicate devices.

Additionally, all testing deemed necessary was conducted on the YELLOW 560 Fluorescence Module integrated into the OPMI PENTERO 800 / OPMI PENTERO 900 surgical microscope to ensure that the device is as safe and effective when used in accordance with its Instructions for Use as the predicate devices.

Attachment 4
Leica FL560, 510(k) K170239 Summary



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

July 5, 2017

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

Leica Microsystems (Schweiz) AG
Ms. Grainne Griffin
Senior RA Specialist
Max Schmidheiny-Strasse 201
Heerbrugg, Sankt Gallen, Switzerland 9435 CH

Re: K170239

Trade/Device Name: Leica FL560
Regulation Number: 21 CFR 892.1600
Regulation Name: Angiographic X-Ray System
Regulatory Class: Class II
Product Code: IZI
Dated: June 5, 2017
Received: June 5, 2017

Dear Ms. Griffin:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. However, you are responsible to determine that the medical devices you use as components in the kit have either been determined as substantially equivalent under the premarket notification process (Section 510(k) of the act), or were legally on the market prior to May 28, 1976, the enactment date of the Medical Device Amendments. Please note: If you purchase your device components in bulk (i.e., unfinished) and further process (e.g., sterilize) you must submit a new 510(k) before including these components in your kit/tray. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be

found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

In addition, we have determined that your device kit contains Sodium Fluorescein which is subject to regulation as a drug.

Our substantially equivalent determination does not apply to the drug component of your device. We recommend you first contact the Center for Drug Evaluation and Research before marketing your device with the drug component. For information on applicable Agency requirements for marketing this drug, we suggest you contact:

Director, Division of Drug Labeling Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
(301) 594-0101

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address

<http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to

<http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm> for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address

<http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm>.

Sincerely,

Michael J. Hoffmann -S

for Carlos L. Peña, PhD, MS
Director
Division of Neurological
and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (*if known*)

K170239

Device Name

Leica FL560

Indications for Use (*Describe*)

The Leica FL560 is a surgical microscope accessory used in viewing intra-operative blood flow in the cerebral vascular area.

Type of Use (*Select one or both, as applicable*)

Prescription Use (Part 21 CFR 801 Subpart D)

Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

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"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

Overview

This 510(k) summary has been prepared in accordance with the requirements of 21CFR §807.92.

Trade Name	Leica FL560
Common Name	Fluorescent Angiographic System
Classification	Class II; Angiographic x-ray system (21 CFR 892.1600)
Product Code	IZI
Manufacturer	Leica Microsystems (Schweiz) AG., (Registration # 3003974370) Max Schmidheiny-Strasse 201 Heerbrugg, Sankt Gallen 9435, Switzerland.
Contact Name	Grainne Griffin
Tel	+353 86 7710135
email	grainne.griffin@leica-microsystems.com
Predicate Device	Primary Leica FL800 ULT – clearance K141136 Auxiliary Leica FL800 – clearance K061871 & K080612
Preparation Date	20 th December 2016

Device Description

Similar to the predicate device (Leica FL800 ULT approved under K141136), the Leica FL560 is an accessory to the Leica Microsystems (LMS) Class I 510(k) exempt surgical operating microscope (SOM).

The Leica FL560 utilizes the illumination light source, supplied as standard with the SOM to produce excitation light which is filtered using an illumination filter (also referred to as the excitation filter) within the 460 - 500nm wavelength.

An observation filter is introduced into the observer light path within the optics carrier of the SOM to enable visualization of the resulting fluorescence emission comprising of the green, yellow and red spectrum in a spectral band above ~510nm.

Device Intended Use

The Leica FL560 is a surgical microscope accessory used in viewing fluorescence of fluorophores with an excitation peak between ~460 nm and ~500 nm (blue) and the fluorescence emission observation comprising the green, yellow and red spectrum in a spectral band above ~510 nm.

Device Indication for Use

The Leica FL560 is a surgical microscope accessory used in viewing intra-operative blood flow in the cerebral vascular area.

Testing

Pre-clinical studies, human factors studies, electrical safety testing, and bench testing have been conducted to demonstrate the substantial equivalence of the Leica FL560 to the Leica FL800 ULT.

Summary Table

See 'Substantial Equivalence Summary Table: Comparison to Predicate Device' on following pages for a summary of all predicate and subject device comparative features and supporting substantial equivalence testing.

Conclusion

Based on the technological characteristics, principle of operation, intended use, environment of use, and indications for use, the Leica FL560 has been determined to be substantially equivalent to the predicate device, the Leica FL800 ULT (K141136) in terms of safety, effectiveness and performance.

Substantial Equivalence Summary Table: Comparison to Predicate Device

	Primary Predicate	Subject Device	
Device → What↓	Leica FL800 ULT (K141136)	Leica FL560 (Proposed new accessory)	Demonstration of Substantial Equivalence (SE)
SUMMARY OF GENERAL FEATURES			
Indications for use	The Leica FL800 is a surgical Microscope accessory used in viewing intra-operative blood flow in the cerebral vascular area and by-pass grafts during coronary artery bypass (CABG) surgery, as well as blood flow during plastic and reconstructive surgery.	The Leica FL560 is a surgical Microscope accessory used in viewing intra-operative blood flow in the cerebral vascular area.	Identical to subset of predicate indications for use
For use with	Standard Leica Surgical Operating Microscope M520 / M525 / M720 & M530 product range	Standard Leica M530 OH6/OHX Surgical Operating Microscope (Class I Exempt) Note: FL560 will not be available for the M520 / M525 / M720 SOM as these are older models scheduled for phase out	Identical to subset of predicate equipment platforms
Device Components	<ul style="list-style-type: none"> • Observation filter • Illumination filter • Filter housing ICG Filter • Beam Splitter • Built in Dual Video Adaptor consisting of Internal NIR Camera 	<ul style="list-style-type: none"> • Observation filter • Illumination filter • Filter housing 	Equivalent to subset of predicate components (filters equivalent but for different wavelength specifications)
Software	No Software	No Software	Identical
Required but not supplied	<ul style="list-style-type: none"> • Leica Surgical Microscope • Recording device 	<ul style="list-style-type: none"> • Leica Surgical Microscope 	Identical to subset of predicate
Drug	ICG	Fluorescein Sodium (fluorescein)*	Difference does not impact substantial equivalence, both drugs are fluorophores for visualizing blood flow and have longstanding FDA approvals

	Primary Predicate	Subject Device	
Device → What↓	Leica FL800 ULT (K141136)	Leica FL560 (Proposed new accessory)	Demonstration of Substantial Equivalence (SE)
SUMMARY OF GENERAL FEATURES, CONTINUED			
Illumination Filter [nm]	400 – 780nm	460 - 500nm	Equivalent, both are band pass filters with overlapping ranges
Observation Filter [nm]	800 – 880nm	Above ~ 510nm	Equivalent, the FL560 high pass filter range contains the FL800 band pass filter range
Light Source	Xenon 300 – 400watt	Xenon 400watt	Identical to subset of predicate
Test Card	Pre-operative check test card	Pre-operative check test card	Equivalent
Procedure Kit	None supplied	FL560 procedure kit containing: <ul style="list-style-type: none"> • AK-FLUOR (fluorescein) • FL560 test card • Procedure kit IFU 	Difference does not impact substantial equivalence
*Reference Device CIS EyeScan Portable Modular Imaging System, K092374, also enables visualization of fluorescein (a technical feature of both the subject and reference device) for a different Indication for Use (ophthalmology imaging) but a generally equivalent intended use (fluorescence vascular angiography)			
SUMMARY OF SUPPORTING TESTING			
Electrical Safety	Conformance to the following standards tested and confirmed: <ul style="list-style-type: none"> • IEC 60601-1:2005: Medical electrical equipment - Part 1: General requirements for basic safety and essential performance • IEC 60601-1-2:2007 (Modified): Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests • IEC 60601-1-6:2010-06: Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral Standard: Usability 	Conformance to the following standards tested and confirmed: <ul style="list-style-type: none"> • IEC 60601-1:2005: Medical electrical equipment - Part 1: General requirements for basic safety and essential performance • IEC 60601-1-2:2007 (Modified): Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral standard: Electromagnetic compatibility - Requirements and tests • IEC 60601-1-6:2010-06: Medical electrical equipment - Part 1-6: General requirements for basic safety and essential performance - Collateral Standard: Usability 	Identical, both met all acceptance criteria

	Primary Predicate	Subject Device	
Device → What↓	Leica FL800 ULT (K141136)	Leica FL560 (Proposed new accessory)	Demonstration of Substantial Equivalence (SE)
SUMMARY OF SUPPORTING TESTING, CONTINUED			
Bench	<p><u>Summary of Test Objective and Design:</u> In house design verification testing was performed on FL560 to ensure that mechanical and functional requirements including design specifications were met.</p> <p>This was a protocol-driven verification with pre-established pass/fail criteria, ties to design specification and other quality and design control documents, and significant experiential basis drawn from the 10-year marketing history of predicate device FL800.</p> <p>As is typical for design verification, this was a one-arm study using only the subject device FL560 on microscope platform M530 OH6 and assessed vs. historical experience with predicate FL800 (historical control).</p>	<p>Equivalent</p> <p><u>Results:</u> All tests completed met their pre-established acceptance criteria. Specifically, verification of (technical) Intended Use to produce light transference for an excitation peak between 460 nm and 500 nm and an observation peak above 510 nm was achieved.</p>	
	<p><u>Predicate Device:</u></p> <p>Historical controls via marketing and CAPA experience with predicate device FL800 were utilized instead of direct comparative testing.</p>	<p><u>Subject Device:</u></p> <ul style="list-style-type: none"> • <u>Filter specification:</u> Filters were optically (spectrally), mechanically and geometrically assessed. Optical performance regarding spectral transmission and sufficiency of pass-through illumination was verified. • <u>Mechanical:</u> The Leica FL560 assembly geometric, mechanical, and functional integration into the Leica Microsystems M530 OH6 Surgical Operating Microscope was verified. • <u>Labeling:</u> Product labels and User Manual were reviewed for completeness, understandability, and accuracy. 	<p>Review of FL560 test results vs. historical experience with predicate FL800 and vs. current QC standards for FL800 established that FL560 has functionally equivalent ability to produce excitation and observation peaks for use in viewing fluorescence of fluorophores intraoperatively on a Leica surgical microscope platform.</p>

	Primary Predicate	Subject Device	
Device → What↓	Leica FL800 ULT (K141136)	Leica FL560 (Proposed new accessory)	Demonstration of Substantial Equivalence (SE)
SUMMARY OF SUPPORTING TESTING, CONTINUED			
Bio-compatibility	Not patient contacting, only external surface is anodized aluminum, so ISO 10993 testing is not applicable	Not patient contacting, only external surface is anodized aluminum, so ISO 10993 testing is not applicable	Identical
Preclinical	<p><u>Summary of Test Objective and Design:</u> A contracted, protocol-driven comparative preclinical study was prospectively performed to confirm that the subject device FL560 enabled viewing of intra-operative blood flow in the cerebrovascular area in a manner that was functionally equivalent to predicate device FL800ULT.</p> <p>Testing was completed at the University of Mainz, Germany Institute of Neurosurgical Pathology by neurosurgeons and veterinarians using test cases, pass/fail criteria, and independent scoring assessments that were predefined within the protocol.</p> <p>Six comparative image sets of the same cerebrovascular anatomy in either non-occluded (patent, native) or occluded (clipped) status and representative of neurosurgical procedures were visualized by both the FL560 and FL800ULT systems.</p>	<p><u>Results Summary:</u></p> <p>Equivalent</p> <p>The testing confirmed that the Leica FL560 meets the Indications for Use and provides functionally equivalent flow visualization to FL800ULT.</p> <p>All individual evaluations of comparative images confirmed that the Leica FL560 enabled visualization of intra-operative blood flow and vessel architecture in the cerebrovascular area in a functionally equivalent manner to the predicate device Leica FL800 ULT (n=18 comparative reviews, 100% confirmation).</p> <p>The FL560 additionally enabled concurrent visualization of background anatomical structures.</p>	
	<u>Predicate Device:</u> Data was collected using indocyanine green (ICG) fluorescent dye introduced into the vascular system of a porcine model. Data regarding the ability to visualize blood flow and vascular structures was collected and compared directly to data collected with the subject device Leica FL560 on the same porcine model and using Fluorescein Sodium (FS) fluorescent dye.	<u>Subject Device:</u> Data was collected using Fluorescein Sodium (FS) fluorescent dye introduced into the vascular system of a porcine model. Data regarding the ability to visualize blood flow and vascular structures was collected and compared directly to data collected with the predicate device Leica FL800ULT on the same porcine model and using ICG fluorescent dye.	

	Primary Predicate	Subject Device	
Device → What↓	Leica FL800 ULT (K141136)	Leica FL560 (Proposed new accessory)	Demonstration of Substantial Equivalence (SE)
SUMMARY OF SUPPORTING TESTING, CONTINUED			
Human Factors	<p><u>Summary of Test Objectives and Design:</u> Human factors and usability testing was completed at the University of Utah Department of Neurosurgery using pre-defined test cases and objective pass/fail criteria pre-defined within the protocol. Two distinct user groups (neurosurgeons, nurses/techs) were assessed for their ability to perform specific clinical use demands. 15 users per group were assessed via observational analysis. The 10-year marketing history of predicate device FL800 and the FL560 risk analysis provided the basis for establishing key test elements and acceptance criteria.</p> <p>The study was conducted in a simulated operating room and involved typical work flow scenarios including certain troubleshooting scenarios related to safety-critical tasks. Testing was conducted using a Leica Surgical Microscope fitted with the Leica FL560 module and using a cerebral vascular aneurysm phantom model flushed in with fluorescein and water in an alternating manner. Studies were conducted to reflect standard use cases, parameter adjustments, and interfaces encountered during routine use of the Leica FL560 module by surgeons and operating room personnel.</p> <p>The study was designed in accordance with the published FDA guidance "draft Guidance for Industry and Food and Drug Administration Staff – Applying Human Factors and Usability Engineering to Optimize Medical Device Design, 2011."</p>	<p><u>Results Summary:</u></p> <p>Equivalent</p> <p>Human factors testing confirmed that the FL560 usability was equivalent to Leica prior experience with FL800.</p> <p>Similar controls and interfaces enabled 100% of users in both groups to perform key functions.</p> <p>FL560 consistently visualized test card fluorescence and fluorescein fluorescence in a phantom vascular model.</p>	
	<u>Predicate Device:</u> Historical controls via marketing and CAPA experience with predicate device FL800 were utilized instead of direct comparative testing.	<u>Subject Device:</u> Neurosurgeons performed tasks with the optics carrier (with control handle) containing the Leica FL560 observation filter and representative of their product interaction within the sterile field during surgery. Circulating nurses performed tasks utilizing the interface screen outside of the sterile field before and during surgery. Both groups performed test card verifications of FL560 function in accordance with User Manual instructions for preoperative checks.	

Attachment 5

Visionsense Ltd. VS3 Iridium System, 510(k) K210265 Summary



November 22, 2021

Visionsense Ltd.
Nancy Sauer
Regulatory Director
20 Hamagshimim St.
Petach Tikva, Hamerkaz, Central District 4934829
Israel

Re: K210265

Trade/Device Name: VS3 Iridium System
Regulation Number: 21 CFR 876.1500
Regulation Name: Endoscope And Accessories
Regulatory Class: Class II
Product Code: OWN
Dated: August 4, 2021
Received: August 5, 2021

Dear Nancy Sauer:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems>.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance>) and CDRH Learn (<https://www.fda.gov/training-and-continuing-education/cdrh-learn>). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (<https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice>) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

for Neil R. P. Ogden
Assistant Director
DHT4A: Division of General Surgery Devices
OHT4: Office of Surgical
and Infection Control Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (*if known*)

K210265

Device Name
VS3 Iridium System

Indications for Use (*Describe*)

Upon intravenous administration and use of an ICG consistent with its approved labeling, the Iridium Module of the VS3-IR System is used to perform intraoperative fluorescence angiography.

Upon interstitial administration and use of ICG consistent with its approved labeling, the Endoscope configuration of the VS3-IR System is used to perform intraoperative fluorescence imaging and visualization of the lymphatic system, including lymphatic vessels and lymph nodes.

Upon administration and use of pafolacianine consistent with its approved labeling, the VS3-IR 785 nm System is used to perform intraoperative fluorescence imaging of tissues that have taken up the drug.

Type of Use (*Select one or both, as applicable*)

Prescription Use (Part 21 CFR 801 Subpart D)

Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

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Department of Health and Human Services
Food and Drug Administration
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PRAStaff@fda.hhs.gov

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K210265

510(k) Summary

VS3 Iridium System

The contents of the 510(k) Summary have been provided in conformance with 21 CFR 807.92.

1. Submitter

510(k) Submitter: Visionsense Ltd. (Medtronic)
 20 Hamagshimim Street
 Petach Tikva, Hamerkaz
 4934829 Israel

Contact Person: Nancy Sauer, Regulatory Director Lung Health and Visualization

Phone: 720-361-5290
 Email: nancy.k.sauer@medtronic.com

Date Prepared: August 20, 2021

2. Subject Device

Trade Name : VS3 Iridium System
 Common Name: Confocal Optical Imaging
 Classification Name: Endoscope and Accessories
 21 CFR Part 876.1500
 Product code: OWN
 Regulatory Class: II
 Manufacturer: Visionsense Ltd. (Medtronic)

3. Predicate Devices

Predicate Device Trade Name	VS3 Iridium System (Primary Predicate)	VS3 Iridium System (Secondary Predicate)
510(k) Number	K183453	K191851
510(k) Holder	Visionsense Ltd. (Medtronic)	Visionsense Ltd. (Medtronic)
Classification Name	Confocal Optical Imaging	Confocal Optical Imaging
Product Code and Regulation	OWN- 21 CFR Part 876.1500	OWN- 21 CFR Part 876.1500
Classification	II	II

The predicate devices have not been subject to a design-related recall.

4. Device Description

The VS3 Iridium System is an advanced stereoscopic visualization system made up of a combination of hardware and software to provide high definition visible and near infrared (IR) fluorescent imaging. The visualization system can incorporate an endoscope for minimally invasive surgical procedures and a microscope positioned above the patient during open surgical procedures.

The VS3 Iridium System including the endoscope and the microscope is designed to work with an approved infrared dye (Indocyanine green (ICG) or pafolacianine sodium injection or pafolacianine). ICG may be excited at excitation at either 785 or 805 nm, and pafolacianine is excited only by the 785 nm wavelength. The principle of operation is the same for both infrared dyes. That is, the VS3 Iridium System provides excitation light to the surgical field to excite the dye molecules and captures emission from the dye using an IR camera, enabling qualitative and quantitative measurement of the IR intensity. Near IR fluorescence imaging with ICG permits the system to visualize blood flow and related tissue circulation, of lymphatic flow.

The VS3 Iridium System allows the capture of normal (white) light image in parallel with the fluorescence IR image and displays both to the surgeon to provide a view of the anatomy. In addition, the VS3 Iridium System permits recording surgical procedures, storing them on removable storage devices, and replaying the procedures.

This Traditional 510(k) premarket notification is to expand the indication for use statement to include the additional cleared infrared dye, pafolacianine sodium injection, for use with infrared imaging.

5. Intended Use

The VS3 Iridium System is intended for viewing anatomical structures during invasive surgery and for viewing fluorescent images for the visual assessment of blood flow and lymphatic flow. The unit is indicated for viewing internal surgical sites during general surgical procedures. It provides an adjunctive method for the evaluation of tissue perfusion and related tissue transfer circulation in tissue and free flaps used in general, plastic, micro-and reconstructive surgical procedures. It also enables the identification of functional lymphatic vessel, and/or lymph nodes. The VS3 Iridium System is also intended to visualize tissues that have taken up the pafolacianine during procedures that are consistent with the approved labeling of that dye.

6. Indications for Use

Upon intravenous administration and use of an ICG consistent with its approved labeling, the Iridium Module of the VS3-IR System is used to perform intraoperative fluorescence angiography.

Upon interstitial administration and use of ICG consistent with its approved labeling, the Endoscope configuration of the VS3-IR System is used to perform intraoperative fluorescence imaging and visualization of the lymphatic system, including lymphatic vessels and lymph nodes.

Upon administration and use of pafolacianine in accordance with its approved labeling, the VS3-IR 785 nm System is used to perform intraoperative fluorescence imaging of tissues that have taken up the drug.

7. Summary of Characteristics Compared to Predicate Device

The VS3 Iridium System has the same performance as the predicate device which is the equivalent VS3 Iridium System. This 510(k) expands the indication for use to include an additional fluorescent dye, pafolacianine for use with the system.

8. Performance Data

There are no performance standards or special controls developed for confocal optical imaging systems. The expansion of the indication of the subject device does not change the biocompatibility, electrical safety, electromagnetic compatibility, or sterilization from the previous clearance in K191851. Software validation data was provided for minor included software updates.

9. Clinical Data

Performance of the VS3 Iridium System with pafoalacianine was demonstrated through a phase 3, randomized, single dose, open-label study (clinicaltrials.gov study NCT03180307). The study was designed to investigate the safety and efficacy of OTL38 injection (OTL38) for intra-operative imaging of folate receptor positive ovarian cancer in females 18 years old or older. The proportion of patients with at least one confirmed FR+ ovarian cancer evaluable lesion detected by the combination of OTL38 and NIR fluorescent light but not under normal light or palpation was 33% (95% CI [0.243, 0.427]). Safety results related to the VS3 Iridium System imaging subgroup (n=127) showed that there were 0 treatment-emergent adverse device effects (TEAE). The ability of OTL38 coupled with the Visionsense VS3 Iridium system to detect evaluable lesions in 33% of patients coupled with the lack of TEAE demonstrate that the VS3 Iridium System is safe to use in conjunction with the OTL38 drug.

10. Conclusion

The VS3 Iridium System has the same general intended use, materials, design, energy source, principle of operation and performance as the primary predicate device, VS3 Iridium System cleared under 510(k) K183453 and the secondary predicate device, VS3 Iridium System cleared under 510(k) K191851. Therefore, the VS3 Iridium System is found to be substantially equivalent to the legally marketed predicate device, VS3 Iridium System (K183453 and K191851) as the differences do not raise new questions of safety and efficacy.

Attachment 6

KARL STORZ ICG Imaging System, 510(k) K212695 Summary



KARL STORZ Endoscopy America
Mario Trujillo
Regulatory Affairs Specialist
2151 E. Grand Avenue
El Segundo, California 90245

November 15, 2021

Re: K212695

Trade/Device Name: KARL STORZ ICG Imaging System
Regulation Number: 21 CFR 876.1500
Regulation Name: Endoscope And Accessories
Regulatory Class: Class II
Product Code: OWN, GWG
Dated: October 28, 2021
Received: October 29, 2021

Dear Mario Trujillo:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm> identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part

801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 4, Subpart B) for combination products (see <https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products>); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to <https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems>.

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Sincerely,

Neil R.P. Ogden
Assistant Director
DHT4A: Division of General Surgery Devices
OHT4: Office of Surgical
and Infection Control Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

Indications for Use

510(k) Number (*if known*)

K212695

Device Name

KARL STORZ ICG Imaging System

Indications for Use (*Describe*)

The KARL STORZ ICG Imaging System is intended to provide real-time visible (VIS) and near-infrared (NIR) fluorescence imaging.

Upon intravenous administration and use of ICG consistent with its approved label, the KARL STORZ Endoscopic ICG System enables surgeons to perform minimally invasive surgery using standard endoscopic visible light as well as visual assessment of vessels, blood flow and related tissue perfusion, and at least one of the major extra-hepatic bile ducts (cystic duct, common bile duct and common hepatic duct), using near infrared imaging. Fluorescence imaging of biliary ducts with the KARL STORZ Endoscopic ICG System is intended for use with standard of care white light and, when indicated, intraoperative cholangiography. The device is not intended for standalone use for biliary duct visualization.

Additionally, the KARL STORZ Endoscopic ICG System enables surgeon to perform minimally invasive cranial neurosurgery in adults and pediatrics and endonasal skull base surgery in adults and pediatrics > 6 years of age using standard endoscopic visible light as well as visual assessment of vessels, blood flow and related tissue perfusion using near infrared imaging.

The KARL STORZ VITOM II ICG System is intended for capturing and viewing fluorescent images for the visual assessment of blood flow, as an adjunctive method for the evaluation of tissue perfusion, and related tissue-transfer circulation in tissue and free flaps used in plastic, micro- and reconstructive surgical procedures. The VITOM II ICG System is intended to provide a magnified view of the surgical field in standard white light.

Upon interstitial administration and use of ICG consistent with its approved label, the KARL STORZ Endoscopic ICG System is used to perform intraoperative fluorescence imaging and visualization of the lymphatic system, including lymphatic vessels and lymph nodes.

Type of Use (*Select one or both, as applicable*)

Prescription Use (Part 21 CFR 801 Subpart D)

Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

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K212695

510(k) Summary

This 510(k) Summary is being submitted in accordance with the requirements of the Safe Medical Devices Act (SMDA) of 1990 and 21 CFR 807.92 and the FDA guidance document titled "The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]" issued on July 28, 2014. All data included in this document is accurate and complete to the best of KARL STORZ SE & Co. KG knowledge.

Submitter:	KARL STORZ SE & Co. KG Dr.-Karl-Storz-Straße 34 78532 Tuttlingen, Germany
Contact:	Mario Trujillo Regulatory Affairs Specialist Tel.: (424) 218-8481 Email: Mario.Trujillo@karlstorz.com
Date of Preparation:	October 21, 2021
Type of 510(k) Submission:	Traditional
Device Identification:	Trade Name: KARL STORZ ICG Imaging System Classification Name: Confocal Optical Imaging 21 CFR 876.1500 (Endoscope and Accessories) 21 CFR 882.1480 (Neurological Endoscopes)
Regulatory Class:	2
Product Code:	OWN, GWG
Guidance Document:	Not Applicable
Predicate Device:	Primary predicate device KARL STORZ ICG Imaging System (K202925). Secondary predicate device: KARL STORZ ICG Imaging System (K180146). Reference device: TIPCAM1 Rubina Video Endoscope System (K201526)
Device Description:	The modified KARL STORZ ICG Imaging System is identical to the KARL STORZ ICG Imaging System recently cleared under K202925. The modified KARL STORZ ICG Imaging System now includes the following components: i) TIPCAM®1 Rubina Videoscope (0°, 30°): a 3D image capable videoendoscope with 2D auto-leveling (auto-rotation) and 2D auto-switch display modes.
Intended Use:	The KARL STORZ ICG Imaging System is intended to provide real-time visible and near-infrared fluorescence imaging.

Indications For Use:	<p>The KARL STORZ ICG Imaging System is intended to provide real-time visible (VIS) and near-infrared (NIR) fluorescence imaging.</p> <p>Upon intravenous administration and use of ICG consistent with its approved label, the KARL STORZ Endoscopic ICG System enables surgeons to perform minimally invasive surgery using standard endoscopic visible light as well as visual assessment of vessels, blood flow and related tissue perfusion, and at least one of the major extra-hepatic bile ducts (cystic duct, common bile duct and common hepatic duct), using near infrared imaging. Fluorescence imaging of biliary ducts with the KARL STORZ Endoscopic ICG System is intended for use with standard of care white light and, when indicated, intraoperative cholangiography. The device is not intended for standalone use for biliary duct visualization. Additionally, the KARL STORZ Endoscopic ICG System enables surgeon to perform minimally invasive cranial neurosurgery in adults and pediatrics and endonasal skull base surgery in adults and pediatrics > 6 years of age using standard endoscopic visible light as well as visual assessment of vessels, blood flow and related tissue perfusion using near infrared imaging.</p> <p>The KARL STORZ VITOM II ICG System is intended for capturing and viewing fluorescent images for the visual assessment of blood flow, as an adjunctive method for the evaluation of tissue perfusion, and related tissue-transfer circulation in tissue and free flaps used in plastic, micro- and reconstructive surgical procedures. The VITOM II ICG System is intended to provide a magnified view of the surgical field in standard white light.</p> <p>Upon interstitial administration and use of ICG consistent with its approved label, the KARL STORZ Endoscopic ICG System is used to perform intraoperative fluorescence imaging and visualization of the lymphatic system, including lymphatic vessels and lymph nodes.</p>
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Technological Characteristics:	<p>The clinical application for the subject KARL STORZ ICG Imaging System is identical to the cleared KARL STORZ ICG Imaging System, K202925.</p> <p>The 4mm, 5mm & 10mm Endoscopes and VITOM ICG telescopes connected to the optical coupler of the Image1 S 4U Rubina camera head, and the TIPCAM®1 Rubina Videoendoscope which connects to the Image1 S Camera Control Unit for image processing, as well as to the Power LED Rubina light source light source via compatible light cable as the source of illumination to allow visualization of internal anatomy. Visualization and navigation is performed initially using VIS imaging. NIR imaging is selected when visual assessment and/or confirmation of vessels, blood flow or tissue perfusion is desired.</p> <p>For the NIR image, the user has three presentations of the ICG imagery to choose from:</p> <ul style="list-style-type: none"> a. Overlay: The white light image is overlaid with the NIR image. The NIR image could either by blue or green b. Intensity Map: The white light image is overlaid with color transformed NIR image. c. Monochromatic: The NIR image is indicated by the color white against a dark background. <p>The KARL STORZ ICG Imaging System can output a 4K image to the monitor 12G/3G-SDI, DVI-D and DisplayPort digital outputs and also offers 7 increments of zoom ranging from 1x to 2.5x.</p> <p>The reference device, TIPCAM1 Rubina Video Endoscope System, is identical in design and materials of construction to the subject device. The only difference is that the ICG functionality was not included as part of K201526.</p>
Non-Clinical Performance Data:	<p>There are no performance standards or special controls developed under Section 514 of the FD&C Act for endoscopes.</p> <p>However, the KARL STORZ ICG Imaging System, as well as the primary, secondary and reference devices follow the FDA recognized consensus standards and is tested according to the following standards and FDA Guidance:</p> <ul style="list-style-type: none"> • Electrical Safety and EMC <ul style="list-style-type: none"> ◦ IEC 60601-1 ◦ IEC 60601-1-2 ◦ IEC 60601-2-18 • ISO Endoscopic Standards <ul style="list-style-type: none"> ◦ ISO 8600-1 ◦ ISO 8600-3 ◦ ISO 8600-4 ◦ ISO 8600-5

	<ul style="list-style-type: none"> o ISO 8600-6 • Software Verification and Validation Testing <ul style="list-style-type: none"> o Guidance for the Content of Premarket Submissions for Software Contained in Medical Device o Level of concern: Moderate <p>Cleaning and sterilization validations were conducted for the Image1 S 4U Rubina camera head.</p> <p>Additional bench testing was performed to ensure the device met its design specifications. The bench testing performed verified and validated that the KARL STORZ ICG Imaging System has met all its design specification and is substantially equivalent to its predicate device.</p> <p>Conformance to these standards was not the basis upon which substantial equivalence was determined.</p>
Clinical Performance Data:	Clinical testing was not required to demonstrate the substantial equivalence to the predicate devices. Non-clinical bench testing was sufficient to establish the substantial equivalence of the modifications.
Conclusion:	The conclusions drawn from the nonclinical tests demonstrate that the subject device, the KARL STORZ ICG Imaging System performs as well as or better than the predicate devices that are currently marketed for the same intended use.

Attachment 7

FDA 2014-2015 Strategic Priorities Strike the Right Balance Between Premarket
and Postmarket Data Collection

2014 - 2015 Strategic Priorities

Strike the Right Balance Between Premarket and Postmarket Data Collection

Goal: Assure the appropriate balance between premarket and postmarket data collection to facilitate and expedite the development and review of medical devices, in particular high-risk devices of public health importance.

Target

By December 31, 2014, review 50 percent of product codes subject to a PMA that have been on the market to determine whether or not to shift some premarket data collection to the postmarket setting or to pursue reclassification, and communicate those decisions to the public.

Results

In 2014, CDRH reviewed 69 percent of product codes subject to a PMA that have been on the market.

Table 1. Medical devices (by product code) determined to be candidates for reclassification to Class II.

Product Code (PROCODE)	PROCODE Description
LFD	Saliva, artificial
LLX	Catheter, sampling, chorionic villus
LMF	Agent, absorbable hemostatic, collagen based
LNC	Applicator, hyperthermia, superficial, rf/microwave
LOA	Device, testicular hypothermia
LOB	Dilator, cervical, synthetic osmotic
LOC	System, rf/microwave hyperthermia, cancer treatment
LOF	Bone growth stimulator
LPQ	Stimulator, ultrasound and muscle, for use other than applying therapeutic deep
LTF	Stimulator, salivary system
LZR	Ultrasound, cyclodestructive
MBU	Condom, female, single-use
MRK	System, imaging, fluorescence
MVF	System, laser, photodynamic therapy
MVG	System, laser, fiber optic, photodynamic therapy
MYL	Assay, enzyme linked immunosorbent, parvovirus b19 igg
MYM	Assay, enzyme linked immunosorbent, parvovirus b19 igm
MYN	Analyzer, medical image
NXG	Fluorescence in situ hybridization, topoisomerase ii alpha, gene amplification and deletion
NZC	Stent, urethral, prostatic, semi-permanent
OAY	Light source system, diagnostic endoscopic

Table 2. Medical devices (by product code) determined to be candidates for reduction of premarket data collection through reliance on postmarket controls or shift of data collection from premarket to postmarket.

Product Code (PROCODE)	PROCODE Description	Proposed Change or Shift
FHW	Device, impotence , mechanical/hydraulic	Significantly reduce premarket and postmarket follow-up times. FDA is considering approximately a 50% reduction in both cases. FDA is also considering eliminating certain endpoints, including the connective tissue disease (CTD) endpoint. This is based on current clinical experience which shows that the majority of adverse events and revision surgeries occurred within a more acute timeframe following device implantation than initially expected. FDA will rely on postmarket controls to verify that the safety and effectiveness of use of the device is maintained long term.
FTR	Prosthesis, breast, noninflatable, internal, silicone gel-filled	FDA is considering changing clinical data requirements from a single-arm study with a large number of patients to a controlled study with pre-specified endpoints and potentially fewer patients.
FWM	Prosthesis, breast, inflatable, internal, saline	FDA is considering changing clinical data requirements from a single-arm study with a large number of patients to a controlled study with pre-specified endpoints and potentially fewer patients.
JCW	Prosthesis, penis, inflatable	Significantly reduce premarket and postmarket follow-up times. FDA is considering approximately a 50% reduction in both cases. FDA is also considering eliminating certain endpoints, including the connective tissue disease (CTD) endpoint. This is based on current clinical experience which shows that the majority of adverse events and revision surgeries occurred within a more acute timeframe following device implantation than initially expected. FDA will rely on postmarket controls to verify that the safety and effectiveness of use of the device is maintained long term.
LOK	Kit, test, alpha-fetoprotein for neural tube defects	FDA is considering requiring performance standards or non-clinical tests that have been developed as potential surrogates for some of the clinical testing. Since there is enough experience with these devices, FDA is considering that objective criteria can eliminate the need for controlled studies.
MJP	Toric IOL	Issues for higher cylinder power (i.e., higher myopes) related to visual distortions have been previously documented in other PMAs. For the approval to add a higher cylinder power lens to an already approved toric IOL platform, FDA is considering allowing a shift from premarket to postmarket for some clinical data requirements.
MKQ	Processor, cervical cytology slide, automated	FDA is considering collecting additional data on severe abnormal cases post-market, in order to reduce a potentially very large premarket study, but to ensure effectiveness of the device in rare, but severe abnormal cells in cervical cytology

Product Code (PROCODE)	PROCODE Description	Proposed Change or Shift
MNM	Reader, cervical cytology slide, automated	<p>cases.</p> <p>FDA is considering collecting additional data on severe abnormal cases post-market, in order to reduce a potentially very large premarket study, but to ensure effectiveness of the device in rare, but severe abnormal cells in cervical cytology cases.</p>
MTF	Total, prostate specific antigen (noncomplexed & complexed) for detection of prostate cancer	<p>FDA is considering requiring performance standards or non-clinical tests that have been developed as potential surrogates for some of the clinical testing.</p>
MTG	Test, prostate specific antigen, free, (noncomplexed) to distinguish prostate cancer from benign conditions	<p>FDA is considering requiring performance standards or non-clinical tests that have been developed as potential surrogates for some of the clinical testing.</p>
MVC	System, test, her-2/neu, ihc	<p>FDA is considering clinical trial data to demonstrate that the test can select a patient population to demonstrate the clinical benefits of the drug may not be necessary for premarket approval for the same intended use. Instead, FDA will rely on postmarket controls to verify the demonstration of patient population selection and benefits for the same intended use.</p>
MVD	System, test, her-2/neu, nucleic acid or serum	<p>FDA is considering clinical trial data to demonstrate that the test can select a patient population to demonstrate the clinical benefits of the drug may not be necessary for premarket approval for new intended use. Instead, FDA will rely on postmarket controls to verify the demonstration of patient population selection and benefits for the same intended use.</p>
NAF	Antigen (complexed), prostate specific, (cpsa)	<p>FDA is considering requiring performance standards or non-clinical tests that have been developed as potential surrogates for some of the clinical testing.</p>
NAW	Microspheres radionuclide	<p>FDA is considering shifting clinical testing for potential indications for use to a post market requirement or to be completed via meta-analysis. FDA is also considering that extensive dosimetry (radiation physics) data or composition of matter type discussions may not be required for premarket approval for some potential expanded indications for use, if the microspheres remain the same.</p>
NKF	Immunohistochemistry antibody assay, c-kit	<p>FDA is considering that clinical trial data to demonstrate that the test can select a patient population to demonstrate the clinical benefits of the drug may not be required for premarket approval for the same intended use. Instead, FDA will rely on postmarket controls to verify the demonstration of patient population selection and benefits for the same intended use.</p>
NQF	Immunohistochemistry assay,	<p>FDA is considering that clinical trial data to demonstrate that</p>

Product Code (PROCODE)	PROCODE Description	Proposed Change or Shift
	antibody, epidermal growth factor receptor	the test can select a patient population to demonstrate the clinical benefits of the drug may not be required for premarket approval for the same intended use. Instead, FDA will rely on postmarket controls to verify the demonstration of patient population selection and benefits for the same intended use.
NYQ	Chromogenic in situ hybridization, nucleic acid amplification, her2/neu gene, breast cancer	FDA is considering that clinical trial data to demonstrate that the test can select a patient population to demonstrate the clinical benefits of the drug may not be required for premarket approval for the same intended use. Instead, FDA will rely on postmarket controls to verify the demonstration of patient population selection and benefits for the same intended use.
OAD	Catheter, percutaneous, cardiac ablation, for treatment of atrial flutter	FDA is considering developing Objective Performance Criteria (OPC) to streamline clinical trials for this device type.
OWD	Somatic gene mutation detection system	FDA is considering collecting clinical trial data post-market to support claims of new or rare variants.
OWE	Fluorescence in situ hybridization, anaplastic lymphoma kinase, gene rearrangement	FDA is considering that clinical trial data to demonstrate that the test can select a patient population to demonstrate the clinical benefits of the drug may not be required for premarket approval for the same intended use. Instead, FDA will rely on postmarket controls to verify the demonstration of patient population selection and benefits for the same intended use.
OYM	Prostate cancer genes nucleic acid amplification test system	FDA is considering that the study sample size required for premarket approval may be reduced by prescreening to enrich for abnormal cases that are of greater interest.

Table 3. Medical devices (by product code) with reduction or shift in data collection and/or reclassification in 2014, during FDA's retrospective review of PMAs.

Product Code (PROCODE)	PROCODE Description	Description of FDA Action
IMK	Wheelchair, stair climbing	Reclassification to Class II, special controls, completed April 14, 2014.
MIH	System, endovascular graft, aortic aneurysm treatment	Reductions in premarket data collections have been implemented in the past year. FDA previously required 1 year of premarket data collection for the submission of a PMA supplement for next generation abdominal and thoracic aortic devices. This requirement has been reduced to 6 months premarket data collection with a minimum of 1 year postmarket data collection for certain types of device modifications. Previously, FDA also allowed a shift from surgical controls to use of clinically relevant performance goals to evaluate effectiveness of abdominal and thoracic aortic devices.
MWA	System, nucleic acid amplification, mycobacterium tuberculosis complex	Reclassification to Class II, special controls, completed May 30, 2014

Table 4. Additional medical devices (by product code) determined to remain class III with no changes in data collection.

Product Code (PROCODE)	PROCODE Description
DTB	Permanent pacemaker Electrode (870.3680)
DXY	Implantable, pacemaker, pulse-generator
DYE	Replacement heart valve
GZC	Stimulator, neuromuscular, implanted
KGG	Tissue adhesive for use in embolization of brain arteriovenous malformations
KWG	Prosthesis, finger, constrained, metal/polymer
LGB	Gonococcal antibody tests
LHE	Controller, closed-loop blood glucose
LKK	Pump, infusion, implanted, programmable
LKV	Fetal fibronectin
LMG	Agent, absorbable hemostatic, non-collagen based
LMW	Solution, removal, carries
LMX	Meter, Jaundice
LMY	Monitor, skin resistance/skin temperature, for insulin reactions
LNB	Applicator, hyperthermia, deep heating, ultrasound
LNR	System, photopheresis, extracorporeal
LNY	Catheter, percutaneous, long term, intraspinal
LOM	Test, hepatitis b (b core, be antigen, be antibody, b core igm)
LOY	Cardioconverter, implantable
LPD	System, pacing, antitachycardia
LSX	Controller, closed-loop, blood-pressure
LTI	Implant, Intragastric for morbid obesity
LWL	Fluid, intraocular
LWO	Pulse-generator, single chamber, sensor-driver, implanatable
LWP	Implantable, pulse-generator, pacemaker (non-CRT)
LWQ	Heart valve, mechanical
LWR	Heart valve non allograft tissue
LWS	Implantable cardioverter defibrillator (non-CRT)
LWT	Occluder, balloon, vena-cava
LWW	Pulse-generator, single chamber, single
LWY	Pulse-generator, dual chamber, antitachycardia
LXA	Tissue graft of 6,mm or greater
LYJ	Stimulator, autonomic nerve, implanted for epilepsy
LZS	Excimer laser system
MAQ	Kit, DNA detection, human papillomavirus
MCM	Cochlear implant
MDS	Invasive glucose sensor
MER	Stent, urethral, prostatic, permanent or semi-permanent
MES	Stent, urethral, bulbous, permanent or semi-permanent
MFE	Agent, injectable, embolic
MFK	Lens, multifocal intraocular
MHE	Auditory brainstem implant
MHR	Test, antitumor cell susceptibility

MIP	Implanted fecal incontinence device
MJB	Antigen, cancer 549
MJO	Prosthesis, intervertebral disc
MJS	Contrast media, ultrasound
MKD	Stimulator, functional walking neuromuscular, non-invasive
MKT	Hepatitis viral b DNA detection
MNO	System, laser, transmyocardial revascularization
MPV	Implant, hearing, active, middle ear, partially implanted
MPW	Filler, recombinant human bone morphogenetic protein, collagen scaffold, osteoinduction
MRA	Prosthesis, hip, semi-constrained, metal/ceramic/ceramic/metal, cemented or uncemented
MRM	Defibrillator, implantable, dual-chamber
MTA	Lens, intraocular, phakic
MUZ	Stimulator, Autonomic nerve, implanted (depression)
MWH	Pulmonic valved conduit
MWL	Rigid Gas Permeable contact lenses
MXM	Cap, cooling (infants)
MXQ	Stent, urethral, external sphincter, permanent
MZO	Assay, enzyme linked immunosorbent, hepatitis c virus
MZP	Assay, hybridization and/or nucleic acid amplification for detection of hepatitis c RNA, hepatitis c virus
NAA	Lens, intraocular, accommodative
NAH	System, test, tumor marker, for detection of bladder cancer
NCD	Test, immunity, cell mediated, mycobacterium tuberculosis;
NCL	Imager, breast, electrical impedance
NEK	Filler, recombinant human bone morphogenetic protein, collagen scaffold with metal prosthesis, osteoinduction
NIK	Defibrillator, automatic implantable cardioverter, with cardiac resynchronization
NIM	Stent, carotid
NIN	Stent, renal
NIP	Stent, superficial femoral artery
NJL	Total mobile bearing knees
NKE	Pulse-generator, pacemaker, implantable, with cardiac resynchronization (CRT-P)
NQA	Biologic material, dental
NQO	Prosthesis, spinous process spacer/plate
NQR	Sealant, dural
NRM	Pulse generator, dual chamber, ventricular rescue shock, implantable
NUU	Temporary reduction of myopia or refractive error
NVN	Drug eluting permanent right ventricular (RV) or right atrial (RA) pacemaker electrodes
NVY	Permanent defibrillator electrodes
NVZ	Pulse-generator, permanent, implantable
NWX	Catheter, percutaneous transluminal coronary angioplasty (ptca), cutting/scoring
NXT	Prosthesis, hip, semi-constrained, metal/metal, resurfacing
OAF	Implant, hearing, active, middle ear, totally implanted
OBF	ASSAY, GENOTYPING, HEPATITIS C VIRUS;{Export only}
OCB	RT-PCR multigene expression test, sentinel lymph node, cancer metastasis detection
OJN	Mycobacterium tuberculosis, cell mediated immune response, enzyme-linked

	immunospot test
OJX	Drug eluting permanent left ventricular (LV) pacemaker electrode
OTE	Digital breast tomosynthesis
OYA	P2psa
OYB	Kit, RNA detection, human papillomavirus
OYC	Invasive glucose sensor w insulin pump
OZA	Test, urea adult and pediatric (breath)
PAA	Automated breast ultrasound
PAB	Cytomegalovirus (cmv) DNA quantitative assay
PEJ	Salivary estriol test

Attachment 8

Diagnosis and Treatment of Non-muscle Invasive Bladder Cancer: AUA/SUO
Guideline 2016, Amended 2021

Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline



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Purpose: Although associated with an overall favorable survival rate, the heterogeneity of non-muscle invasive bladder cancer (NMIBC) affects patients' rates of recurrence and progression. Risk stratification should influence evaluation, treatment and surveillance. This guideline attempts to provide a clinical framework for the management of NMIBC.

Materials and Methods: A systematic review utilized research from the Agency for Healthcare Research and Quality (AHRQ) and additional supplementation by the authors and consultant methodologists. Evidence-based statements were based on body of evidence strength Grade A, B, or C and were designated as Strong, Moderate, and Conditional Recommendations with additional statements presented in the form of Clinical Principles or Expert Opinions.¹

Results: A risk-stratified approach categorizes patients into broad groups of low-, intermediate-, and high-risk. Importantly, the evaluation and treatment algorithm takes into account tumor characteristics and uniquely considers a patient's response to therapy. The 38 statements vary in level of evidence, but none include Grade A evidence, and many were Grade C.

Conclusion: The intensity and scope of care for NMIBC should focus on patient, disease, and treatment response characteristics. This guideline attempts to improve a clinician's ability to evaluate and treat each patient, but higher quality evidence in future trials will be essential to improve level of care for these patients.

Key Words: urinary bladder neoplasms, cystectomy, drug therapy, immunotherapy

Abbreviations and Acronyms

AUA = American Urological Association

BCG = bacillus Calmette-Guérin

CIS = carcinoma *in situ*

EORTC = European Organization for Research and Treatment of Cancer

FDA = Food and Drug Administration

LVI = lymphovascular invasion

NMIBC = non-muscle invasive bladder cancer

SUO = Society of Urologic Oncology

TURBT = transurethral resection of bladder tumor

WLC = white light cystoscopy

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The complete guideline is available at <http://www.auanet.org/common/pdf/education/clinical-guidance/Non-Muscle-Invasive-Bladder-Cancer.pdf>.

This document is being printed as submitted independent of editorial or peer review by the editors of *The Journal of Urology*®.

For another article on a related topic see page 1270.

BACKGROUND

Epidemiology

NMIBC represents approximately 80% of the 74,000 estimated new bladder cancer cases diagnosed in the United States in 2015 and primarily affects Caucasian Americans and those older than 65 years.^{2–5} National registry data from the U.S.

Surveillance Epidemiology and End Results program demonstrates that the incidence of all stages of NMIBC has been relatively stable from 1988-2006.⁵ Multiple factors are associated with bladder carcinogenesis; however, tobacco smoking is the most significant and common risk factor.⁶

Staging and Grading

Staging for bladder cancer is separated into clinical and pathologic stage, as outlined by the American Joint Committee on Cancer.⁷ Pathological staging is based on the extent of disease following surgical resection of the bladder and adjacent pelvic lymph nodes.

Tumor grade is an important prognostic factor for determining risk of recurrence and progression. The World Health Organization/International Society of Urological Pathology 2004 classification, which designates tumors as “low-” or “high-grade,” is currently the most widely utilized system in the U.S.^{8,9}

Prognosis

The cancer-specific survival in high-grade NMIBC is approximately 70-85% at 10 years.^{10,11} Long-term follow-up of low-grade Ta lesions demonstrates a progression rate of approximately 6%, whereas high-grade T1 lesions have an increased chance of progression of approximately 17%.^{10,12} Therefore, the ability to predict recurrence and progression risk based on patient-specific disease characteristics holds prognostic significance.

METHODOLOGY

The AUA categorizes body of evidence strength as Grade A, B, or C based on both individual study

quality and consideration of study design, consistency of findings across studies, adequacy of sample sizes, and generalizability of samples, settings, and treatments for the purposes of the Guideline.

Evidence-based statements are provided as *Strong*, *Moderate*, and *Conditional Recommendations* with additional statements provided in the form of *Clinical Principles* or *Expert Opinion* (table 1).

GUIDELINE STATEMENTS

Diagnosis. 1. At the time of resection of suspected bladder cancer, a clinician should perform a thorough cystoscopic examination of a patient's entire urethra and bladder that evaluates and documents tumor size, location, configuration, number, and mucosal abnormalities. (Clinical Principle)

2. At initial diagnosis of a patient with bladder cancer, a clinician should perform complete visual resection of the bladder tumor(s), when technically feasible. (Clinical Principle)

3. A clinician should perform upper urinary tract imaging as a component of the initial evaluation of a patient with bladder cancer. (Clinical Principle)

Table 1. AUA nomenclature linking statement type to level of certainty, magnitude of benefit or risk/burden, and body of evidence strength

	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence		

4. In a patient with a history of NMIBC with normal cystoscopy and positive cytology, a clinician should consider prostatic urethral biopsies and upper tract imaging, as well as enhanced cystoscopic techniques (blue light cystoscopy, when available), ureteroscopy, or random bladder biopsies. (Expert Opinion)

The most common presenting symptom is painless hematuria (gross or microscopic). Irritative voiding symptoms may also be associated with carcinoma *in situ* in patients with no sign of urinary tract infection. A bimanual exam may be performed under anesthesia at the time of transurethral resection of bladder tumor and should be performed if the tumor appears invasive. Although not indicated for routine screening and evaluation of hematuria, urinary cytology may be used in the diagnosis and surveillance of bladder cancer. Contrast-based axial imaging, such as computerized tomography or magnetic resonance imaging is the recommended imaging modality during the work-up for bladder cancer. Retrograde pyelogram and intravenous urography may be used when computerized tomography or magnetic resonance imaging is unavailable.

Bladder cancer is confirmed by direct visualization of the tumor and other mucosal abnormalities with endoscopic excision using cystoscopy and TURBT.

Risk Stratification. 5. At the time of each occurrence/recurrence, a clinician should assign a clinical stage and classify a patient accordingly as “low-,” “intermediate-,” or “high-risk.” (Moderate Recommendation; Evidence Strength: Grade C)

Significant effort has been put forth to develop tools for risk stratification and prognostication. A widely published system is the European Organization for Research and Treatment of Cancer risk calculator, based on the combined data from seven trials involving patients with NMIBC.¹³ The EORTC calculator provides a probability of recurrence and progression at one and five years. Important factors for recurrence identified by the EORTC study include prior recurrence rate, number of tumors, and tumor size. With respect to progression, important factors include T-stage,

presence of CIS, and grade. A second risk stratification tool is that developed by the Club Urologico Español de Tratamiento Oncológico.¹⁴ Both tools are limited by lack of applicability to current patient populations because few patients from the development cohort received BCG maintenance, underwent re-staging transurethral resection, or received single-dose post-operative mitomycin C. A recent update of the EORTC nomogram for risk stratification attempted to address the lack of BCG maintenance, but the updated study cohort lacked patients with CIS and again was limited by absence of routine re-resection.¹⁵

Despite the lack of evidence confirming a positive influence on clinical outcome, the Panel agrees that there is value to creating fundamental categories that broadly estimate the likelihood of recurrence and progression. The Panel set out to create such a system, with categories summarized as low, intermediate, and high risk for recurrence and/or progression (table 2). This risk grouping system is intended for use in clinical practice as a general framework for guiding patient counseling and aiding in treatment and surveillance decisions (see figure). It should be noted that these risk categories are not based on a meta-analysis or original studies and represent the Panel’s consensus regarding the likelihood of recurrence and progression.

Unique to the AUA/SUO System is the incorporation of prior bacillus Calmette-Guérin intravesical therapy on prognosis. Limited data demonstrate that patients who have persistent or recurrent disease at six months following BCG therapy are at increased risk of disease progression.^{16,17} The Panel understands that within each of these risk strata, an individual patient may have more or less concerning features that influence care.

The Panel acknowledges the need for validation of these risk groups in large, contemporary patient cohorts in order to assess the model’s performance for predicting disease recurrence and progression.

Variant Histologies. 6. An experienced genitourinary pathologist should review the pathology of a patient with any doubt in regards to variant or suspected variant histology (e.g., micropapillary, nested, plasmacytoid,

Table 2. AUA risk stratification for non-muscle invasive bladder cancer

Low Risk	Intermediate Risk	High Risk
Low grade solitary Ta ≤ 3 cm Papillary urothelial neoplasm of low malignant potential	Recurrence within 1 year, low grade Ta Solitary low grade Ta >3 cm Low grade Ta, multifocal High grade Ta, ≤3 cm Low grade T1	High grade T1 Any recurrent, high grade Ta High grade Ta, >3 cm (or multifocal) Any CIS Any BCG failure in high grade case Any variant histology Any LVI Any high grade prostatic urethral involvement

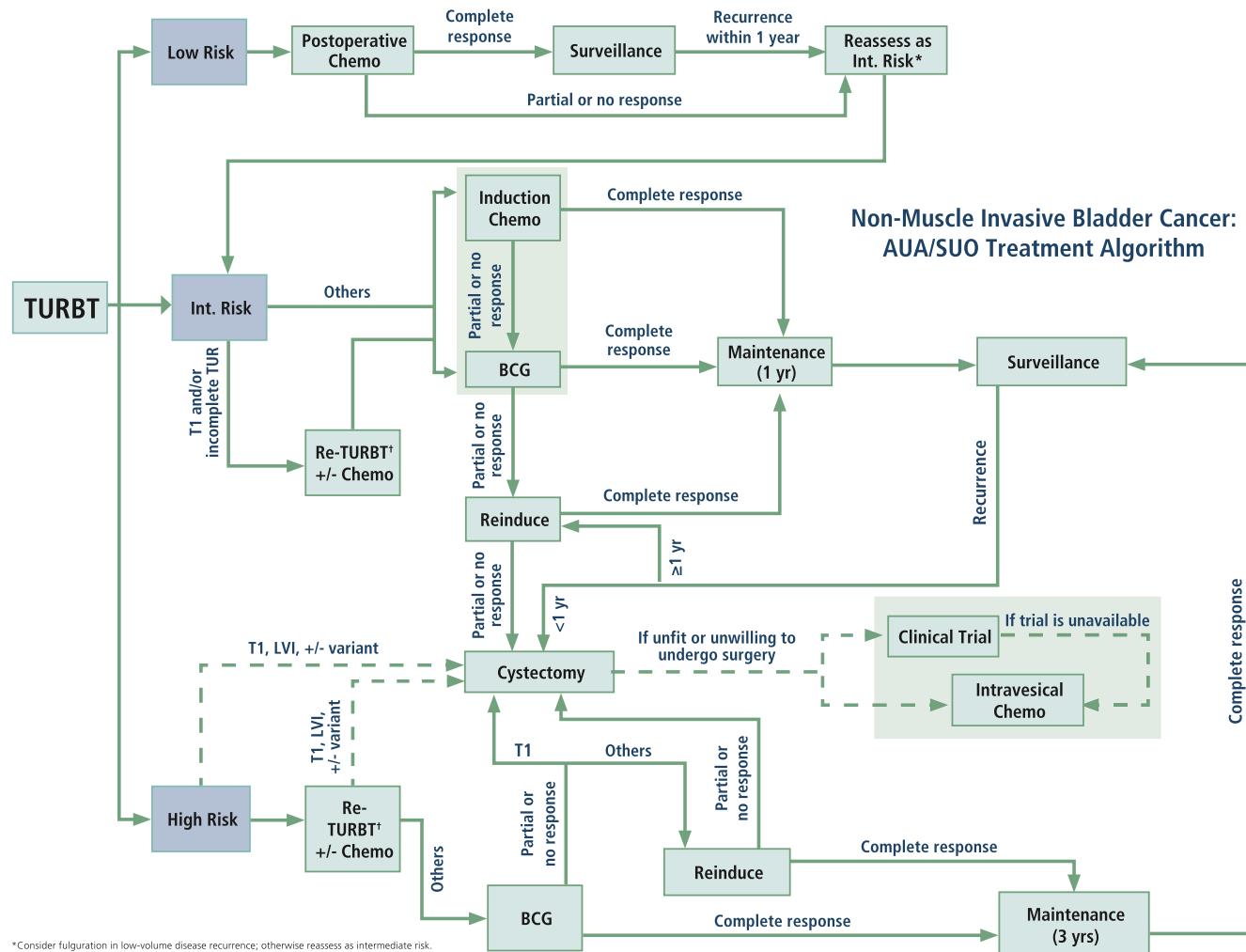


Figure. AUA/SUO treatment algorithm for non-muscle invasive bladder cancer

neuroendocrine, sarcomatoid), extensive squamous or glandular differentiation, or the presence/absence of LVI. (Moderate Recommendation; Evidence Strength: Grade C)

7. **If a bladder sparing approach is being considered in a patient with variant histology, then a clinician should perform a restaging TURBT within four to six weeks of the initial TURBT. (Expert Opinion)**

8. **Due to the high rate of upstaging associated with variant histology, a clinician should consider offering initial radical cystectomy. (Expert Opinion)**

Historically, variant histologies have been underappreciated and under-reported, but data are accumulating in regards to their aggressiveness. Studies suggest that variant differentiation may affect survival; however, there is a paucity of data due to the rarity of most variants. The pathology report should specify the presence and percentage

of variant histology as well as the presence or absence of lymphovascular invasion.

The presence of variant histology within the TURBT specimen is uniformly associated with high-grade disease and almost always invasive. In one study, 86% of patients with variant histology presented with muscle-invasive disease at TURBT compared with 53% of those with high-grade pure urothelial carcinoma. At cystectomy, 64% of the patients with variant histology were found to have T3-T4 disease compared to 34% of those with pure high-grade urothelial carcinoma.¹⁸ As such, patients with mixed histologic features are generally not good candidates for bladder sparing protocols and are best served with an aggressive treatment modality.¹⁹

Urine Markers after Diagnosis of Bladder Cancer.

9. **In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of**

cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

10. In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)

11. In a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)

Researchers have long attempted to identify and utilize urinary markers for bladder cancer detection. Five markers are currently approved by the FDA and/or commercially available in the U.S. (table 3).^{20–22} At present, urinary biomarkers are insufficiently accurate to replace cystoscopy for diagnosis/surveillance, though some appear to have predictive utility for assessing response to intravesical BCG and may help interpret indeterminate cytology.

TURBT/Repeat Resection: Timing, Technique, Goal, Indication. 12. In a patient with non-muscle invasive disease who underwent an incomplete initial resection (not all visible tumor treated), a clinician should perform repeat transurethral resection or endoscopic treatment of all remaining tumor, if technically feasible. (Strong Recommendation; Evidence Strength: Grade B)

13. In a patient with high-risk, high-grade Ta tumors, a clinician should consider

performing repeat transurethral resection of the primary tumor site within six weeks of the initial TURBT. (Moderate Recommendation; Evidence Strength: Grade C)

14. In a patient with T1 disease, a clinician should perform repeat transurethral resection of the primary tumor site to include muscularis propria within six weeks of the initial TURBT. (Strong Recommendation; Evidence Strength: Grade B)

Incomplete resection is likely a significant contributing factor to what have been described and diagnosed as early recurrences, as tumors have been noted at the first follow-up cystoscopic evaluation in up to 45% of patients.²³ Larger and multifocal tumors are at a particularly increased risk for incomplete initial resection. Moreover, repeat resection for patients with T1 tumors achieves diagnostic, prognostic, and therapeutic benefit.

Intravesical Therapy, BCG/Maintenance, Chemotherapy/BCG Combinations. 15. In a patient with suspected or known low- or intermediate-risk bladder cancer, a clinician should consider administration of a single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT. In a patient with a suspected perforation or extensive resection, a clinician should not use postoperative chemotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

16. In a low-risk patient, a clinician should not administer induction intravesical

Table 3. Performance characteristics of commonly used and FDA approved urinary markers

Marker	Sensitivity	Specificity	Pos. Likelihood Ratio (95% CI)	Neg. Likelihood Ratio (95% CI)
NMP22® quantitative				
Overall	69%	77%	3.05 (2.28-4.10)	0.40 (0.32-0.50)
Diagnosis	67%	84%		
Surveillance	61%	71%		
NMP22® qualitative				
Overall	58%	88%	4.89 (3.23-7.40)	0.48 (0.33-0.71)
Diagnosis	47%	93%		
Surveillance	70%	83%		
BTA® quantitative				
Overall	65%	74%	2.52 (1.86-3.41)	0.47 (0.37-0.61)
Diagnosis	76%	53%		
Surveillance	58%	79%		
BTA® qualitative				
Overall	64%	77%	2.80 (2.31-3.39)	0.47 (0.30-0.55)
Diagnosis	76%	78%		
Surveillance	60%	76%		
UroVysion® FISH				
Overall	63%	87%	5.02 (2.93-8.60)	0.42 (0.30-0.59)
Diagnosis	73%	95%		
Surveillance	55%	80%		
ImmunoCyt™				
Overall	78%	78%	3.49 (2.82-4.32)	0.29 (0.20-0.41)
Diagnosis	85%	83%		
Surveillance	75%	76%		
Cxbladder™	82%	85%	5.53 (4.28-7.15)	0.21 (0.13-0.36)

therapy. (Moderate Recommendation; Evidence Strength: Grade C)

17. In an intermediate-risk patient, a clinician should consider administration of a six week course of induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)

18. In a high-risk patient with newly diagnosed CIS, high-grade T1, or high-risk Ta urothelial carcinoma, a clinician should administer a six-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)

19. In an intermediate-risk patient who completely responds to an induction course of intravesical chemotherapy, a clinician may utilize maintenance therapy. (Conditional Recommendation; Evidence Strength: Grade C)

20. In an intermediate-risk patient who completely responds to induction BCG, a clinician should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)

21. In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)

BCG is a heterogeneous organism with at least eight different strains being used for intravesical therapy worldwide.²⁴ A meta-analysis performed in 2013 found that adjuvant BCG followed by maintenance therapy is the appropriate standard of care when compared with combination therapy.²⁵ Meta-analysis performed for this guideline found that single dose intravesical chemotherapy is more effective than no intravesical therapy for prevention of recurrence. This benefit is reduced in low-risk patients who have a lower risk of recurrence/progression.²² Additionally, while BCG and certain other intravesical therapies were associated with a lower risk of recurrence, BCG was the only therapy associated with a decreased risk of progression.

BCG Relapse and Salvage Regimens. 22. In an intermediate- or high-risk patient with persistent or recurrent disease or positive cytology following intravesical therapy, a clinician should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)

23. In an intermediate- or high-risk patient with persistent or recurrent Ta or CIS disease after a single course of induction intravesical

BCG, a clinician should offer a second course of BCG. (Moderate Recommendation; Evidence Strength: Grade C)

24. In a patient fit for surgery with high-grade T1 disease after a single course of induction intravesical BCG, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

25. A clinician should not prescribe additional BCG to a patient who is intolerant of BCG or has documented recurrence on TURBT of high-grade, non-muscle-invasive disease and/or CIS within six months of two induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)

26. In a patient with persistent or recurrent intermediate- or high-risk NMIBC who is unwilling or unfit for cystectomy following two courses of BCG, a clinician may recommend clinical trial enrollment. A clinician may offer this patient intravesical chemotherapy when clinical trials are unavailable. (Expert Opinion)

Approximately 50% of patients who have persistent or recurrent NMIBC following a single induction course of BCG respond to a second induction course of BCG.²⁶⁻²⁹ Evidence on treatment of patients who relapse following BCG treatment is very limited. However, data have demonstrated adverse cancer-specific survival among patients with NMIBC recurrence after BCG who undergo delayed versus early cystectomy.³⁰

The timing of tumor recurrence following BCG may be incorporated into the decision process for treatment as this has been identified as an additional prognostic feature.¹⁶

Role of Cystectomy in NMIBC. 27. In a patient with Ta low- or intermediate-risk disease, a clinician should not perform radical cystectomy until bladder-sparing modalities (staged TURBT, intravesical therapies) have failed. (Clinical Principle)

28. In a high-risk patient who is fit for surgery with persistent high-grade T1 disease on repeat resection, or T1 tumors with associated CIS, LVI, or variant histologies, a clinician should consider offering initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

29. In a high-risk patient with persistent or recurrent disease within one year following treatment with two induction cycles of BCG or BCG maintenance, a clinician should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

Low-grade, noninvasive tumors very rarely metastasize, and even large-volume, multifocal cancers can usually be managed with techniques such as staged resection. Many patients with low-grade recurrences can be successfully managed with intravesical chemotherapy or BCG.^{31–34} However, substantial literature recommend radical cystectomy for patients who are fit for surgery with high-risk urothelial cancer that persists or recurs despite adequate intravesical BCG therapy. Patients with early, high-risk recurrences after BCG therapy are at significant risk of progression, and salvage intravesical therapies have poor success rates.

Enhanced Cystoscopy. 30. In a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence. (Moderate Recommendation; Evidence Strength: Grade B)

31. In a patient with NMIBC, a clinician may consider use of narrow band imaging (NBI) to increase detection and decrease recurrence. (Conditional Recommendation; Evidence Strength: Grade C)

Standard bladder cancer surveillance utilizes white light cystoscopy (WLC); however, bladder tumors can display various gross morphological features, and CIS in particular can appear as normal urothelium under WLC. Use of fluorescent cystoscopy improves the detection of urothelial carcinoma, especially CIS, and can decrease progression/recurrence rates.³⁵ Importantly, however, researchers have reported higher false-positive results for HAL-blue light cystoscopy (BLC) compared to WLC, particularly in patients who have undergone recent TURBT, who have concurrent urinary tract infection or inflammation, or who have recently received intravesical BCG or chemotherapy.

Risk Adjusted Surveillance and Follow-up Strategies. 32. After completion of the initial evaluation and treatment of a patient with NMIBC, a clinician should perform the first surveillance cystoscopy within three to four months. (Expert Opinion)

33. For a low-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent surveillance cystoscopy six to nine months later, and then annually thereafter; surveillance after five years in the absence of recurrence should be based on shared-decision making between the patient and clinician. (Moderate Recommendation; Evidence Strength: Grade C)

34. In an asymptomatic patient with a history of low-risk NMIBC, a clinician should not

perform routine surveillance upper tract imaging. (Expert Opinion)

35. In a patient with a history of low-grade Ta disease and a noted sub-centimeter papillary tumor(s), a clinician may consider in-office fulguration as an alternative to resection under anesthesia. (Expert Opinion)

36. For an intermediate-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every 3-6 months for 2 years, then 6-12 months for years 3 and 4, and then annually thereafter. (Expert Opinion)

37. For a high-risk patient whose first surveillance cystoscopy is negative for tumor, a clinician should perform subsequent cystoscopy with cytology every three to four months for two years, then six months for years three and four, and then annually thereafter. (Expert Opinion)

38. For an intermediate- or high-risk patient, a clinician should consider performing surveillance upper tract imaging at one to two year intervals. (Expert Opinion)

The natural history of NMIBC is often characterized by recurrence, even for solitary, small, low-grade papillary tumors. At the time of first evaluation and treatment, none of the existent risk stratification tools or urinary biomarkers are sufficiently sensitive and specific to predict which patient will have an early tumor recurrence. Therefore, the most reliable way to know whether patients are at risk for early recurrence is by cystoscopic visualization.

FUTURE DIRECTIONS

The future of NMIBC will likely be driven forward by basic science, novel technologies, new therapeutics and clinical trials. The bladder cancer genome atlas project provided analysis of 131 muscle-invasive urothelial carcinomas in an effort to describe molecular alterations and, ideally, provide insight into the use of molecularly targeted agents.³⁶ The NMIBC community is fortunate to have a multitude of clinical trials currently in this disease space, the vast majority of which are studying novel agents to improve outcomes of BCG or treat BCG failures, but there are also several trials investigating new technology, surgical techniques, radiation, and surveillance schedules.

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DISCLAIMER

This document was written by the Non-Muscle Invasive Bladder Cancer Guideline Panel of the American Urological Association Education and Research, Inc., which was created in 2015. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the panel included specialists in urology/oncology with specific expertise on this disorder. The mission of the panel was to develop recommendations that are analysis-based or consensus-based, depending on panel processes and available data, for optimal clinical practices in the treatment of non-muscle invasive bladder cancer.

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While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process.

AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

CONFLICT OF INTEREST DISCLOSURES

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Attachment 9

EAU Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

EAU GUIDELINES ON NON-MUSCLE-INVASIVE (TaT1, CIS) BLADDER CANCER

(Limited text update March 2022)

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Epidemiology

Bladder cancer (BC) is the 7th most commonly diagnosed cancer in the male population worldwide, while it drops to the 10th position when both genders are considered. The worldwide age-standardised incidence rate (per 100,000 person/years) is 9.5 in men and 2.4 in women.

Staging and classification systems

The 2017 TNM (Tumour, Node, Metastasis Classification) is used for staging (Table 1). For grading, both the 1973 and 2004/2016 WHO grading classifications are used (Table 2).

Table 1: TNM Classification 2017

T - Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma <i>in situ</i> : 'flat tumour'
T1	Tumour invades subepithelial connective tissue
T2	Tumour invades muscle
T2a	Tumour invades superficial muscle (inner half)
T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3	Metastasis in common iliac lymph node(s)

M - Distant Metastasis

M0	No distant metastasis
M1a	Non-regional lymph nodes
M1b	Other distant metastases

Carcinoma *in situ*

Carcinoma *in situ* (CIS) is a flat, high-grade, non-invasive urothelial carcinoma, and classified into the following clinical types:

- Primary: isolated CIS with no previous or concurrent papillary tumours and no previous CIS;
- Secondary: CIS detected during follow-up of patients with a previous tumour that was not CIS;
- Concurrent: CIS in the presence of any other urothelial tumour in the bladder.

Subtypes of urothelial carcinoma and lymphovascular invasion

Some subtypes of urothelial carcinoma (micropapillary, plasmacytoid, sarcomatoid) have a worse prognosis than pure high-grade (HG) urothelial carcinoma. The presence of lymphovascular invasion (LVI) in transurethral resection of the bladder (TURB) specimens is associated with worse prognosis.

Recommendations for bladder cancer classification	Strength rating
Use the 2017 TNM system for classification of the depth of tumour invasion (staging).	Strong
Use both the 1973 and 2004/2016 WHO classification systems.	Weak
Do not use the term 'superficial bladder cancer'.	Strong

Diagnosis

A comprehensive patient history is mandatory. Haematuria is the most common finding. Physical examination does not reveal NMIBC.

Recommendations for the primary assessment of non-muscle invasive bladder cancer	Strength rating
Take a patient history, focusing on urinary tract symptoms and haematuria.	Strong
Use renal and bladder ultrasound and/or computed tomography intravenous urography (CT-IVU) during the initial work-up in patients with haematuria.	Strong
Once a bladder tumour has been detected, perform a CT urography in selected cases (e.g., tumours located in the trigone, multiple- or high-risk tumours).	Strong
Perform cystoscopy in patients with symptoms suggestive of bladder cancer or during surveillance. It cannot be replaced by cytology or by any other non-invasive test.	Strong
In men, use a flexible cystoscope, if available and apply irrigation 'bag squeeze' to decrease procedural pain when passing the proximal urethra.	Strong
Describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities during cystoscopy. Use a bladder diagram.	Strong
Use voided urine cytology as an adjunct to cystoscopy to detect high-grade tumour.	Strong

Perform cytology on at least 25 mL fresh urine or urine with adequate fixation. Morning urine is not suitable because of the frequent presence of cytolysis.	Strong
Use the Paris system for cytology reporting.	Strong

Papillary (TaT1) tumours

The diagnosis of papillary BC ultimately depends on cystoscopic examination of the bladder and histological evaluation of the tissue resected during TURB. Transurethral resection of the bladder is a crucial procedure in the diagnosis and treatment of TaT1 tumours and should be performed systematically in individual steps (see recommendations below). A complete resection, performed by either fractionated or *en-bloc* technique, is essential to achieve a good prognosis.

The technique selected depends on the size of the lesion, its location and experience of the surgeon. In selected cases, due to the risk of tumour persistence and understaging after initial TURB, a second resection (2nd TURB) is recommended.

Carcinoma *in situ*

Carcinoma *in situ* is diagnosed by a combination of cystoscopy, urine cytology, and histological evaluation of bladder biopsies taken from suspicious areas or as mapping biopsies from normal looking mucosa (for details, please consult the extended guidelines). Carcinoma *in situ* cannot be eradicated by TURB and further treatment is mandatory.

Recommendations for transurethral resection of the bladder (TURB), biopsies and pathology report	Strength rating
In patients suspected of having bladder cancer, perform a TURB followed by pathology investigation of the obtained specimen(s) as a diagnostic procedure and initial treatment step.	Strong
Outpatient fulguration or laser vaporisation of small papillary recurrences can be used in patients with a history of TaG1/LG tumours.	Weak
<p>Perform TURB systematically in individual steps:</p> <ul style="list-style-type: none"> • bimanual palpation under anaesthesia; • insertion of the resectoscope, under visual control with inspection of the whole urethra; • inspection of the whole urothelial lining of the bladder; • biopsy from the prostatic urethra (if indicated); • cold-cup bladder biopsies (if indicated); • resection of the tumour; • recording of findings in the surgery report/record; • precise description of the specimen(s) for pathology evaluation. 	Strong
Performance of individual steps	
Perform <i>en-bloc</i> resection or resection in fractions (exophytic part of the tumour, the underlying bladder wall and the edges of the resection area).	Strong

Avoid cauterisation as much as possible during TURB to avoid tissue deterioration.	Strong
Take biopsies from abnormal-looking urothelium. Biopsies from normal-looking mucosa (mapping biopsies from the trigone, bladder dome, right, left, anterior and posterior bladder wall) are recommended if cytology or urinary molecular marker test is positive. If equipment is available, perform fluorescence-guided (PDD) biopsies.	Strong
Take a biopsy of the prostatic urethra in cases of bladder neck tumour, if bladder carcinoma <i>in situ</i> is present or suspected, if there is positive cytology or urinary molecular marker test without evidence of tumour in the bladder, or if abnormalities of the prostatic urethra are visible. If biopsy is not performed during the initial procedure, it should be completed at the time of the second resection.	Strong
Take a prostatic urethral biopsy from the pre-collicular area (between the 5 and 7 o'clock position) using a resection loop. In case any abnormal-looking areas in the prostatic urethra are present at this time, these need to be biopsied as well.	Weak
Use methods to improve tumour visualisation (fluorescence cystoscopy, narrow-band imaging) during TURB, if available.	Weak
Refer the specimens from different biopsies and resection fractions to the pathologist in separately labelled containers.	Weak

The TURB record must describe tumour location, appearance, size and multifocality, all steps of the procedure, as well as extent and completeness of resection.	Strong
In patients with positive cytology, but negative cystoscopy, exclude an upper tract urothelial carcinoma, CIS in the bladder (by mapping biopsies or PDD-guided biopsies) and tumour in the prostatic urethra (by prostatic urethra biopsy).	Strong
Perform a 2 nd TURB in the following situations: <ul style="list-style-type: none"> • after incomplete initial TURB, or in case of doubt about completeness of a TURB; • if there is no muscle in the specimen after initial resection, with the exception of Ta LG/G1 tumours and primary CIS; • in T1 tumours. 	Strong
If indicated, perform a 2 nd TURB within 2–6 weeks after the initial resection. This 2 nd TURB should include resection of the primary tumour site.	Weak
Register the pathology results of a 2 nd TURB as it reflects the quality of the initial resection.	Weak
Inform the pathologist of prior treatments (intravesical therapy, radiotherapy, etc.).	Strong
The pathological report should specify tumour location, tumour grade and stage, lymphovascular invasion, subtypes of urothelial carcinoma (variant histologies), presence of CIS, and detrusor muscle.	Strong

Predicting disease recurrence and progression and defining risk groups

After TURB, patients should be stratified, according to prognostic factors, into risk groups which will facilitate treatment recommendations (see Table 3). For individual prediction of the risk of tumour progression at different intervals after TURB, use of the 2021 EAU NMIBC Risk Calculator (www.nmibc.net) is strongly recommended.

For bacillus Calmette-Guérin (BCG)-treated patients, separate scoring models and risk groups have been created by the CUETO and the EORTC, respectively. For prediction of tumour recurrence in individual patients, the 2006 EORTC scoring model and calculator may be used.

Recommendations for stratification of non-muscle invasive bladder cancer	Strength rating
Stratify patients into 4 risk groups according to Table 3. A patient's risk group can be determined by using the 2021 EAU risk group calculator available at www.nmibc.net . Android and iOS smartphone apps are also available.	Strong
For information about the risk of disease progression in a patient with primary TaT1 tumours, use the EAU NMIBC 2021 risk group calculator.	Strong
Use the 2006 EORTC scoring model to predict the risk of tumour recurrence in individual patients not treated with bacillus Calmette-Guérin (BCG).	Strong

Use the 2016 EORTC scoring model or the CUETO risk scoring model to predict the risk of tumour recurrence in individual patients treated with BCG intravesical immunotherapy (the 2016 EORTC model is calculated for 1-3 year of maintenance, the CUETO model for 5 to 6 months of BCG).	Strong
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Table 3: Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems

- Only one of the two grading systems (WHO 1973 or WHO 2004/2016) is required to use this table.
- If both grading systems are available in an individual patient, the Panel recommends using the risk group calculation based on the WHO 1973, as it has better prognostic value.
- The category of low-grade (LG) tumours (WHO 2004/2016) also includes patients with tumours classified as PUNLMP.
- Additional clinical risk factors are*:
 - age > 70;
 - multiple papillary tumours;
 - tumour diameter ≥ 3 cm.

Risk Group	Description
Low Risk	<ul style="list-style-type: none"> A primary, single, Ta/T1 LG/G1 tumour < 3 cm in diameter without CIS in a patient ≤ 70 years
	<ul style="list-style-type: none"> A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors*
Intermediate Risk	Patients without CIS who are not included in either the low-, high- or very high-risk groups

High Risk	<ul style="list-style-type: none"> • All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group • All CIS patients, EXCEPT those included in the very high-risk group.
	<p>Stage, grade with additional clinical risk factors:</p> <ul style="list-style-type: none"> • Ta LG/G2 or T1 G1, no CIS with all 3 risk factors • Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors • T1 G2 no CIS with at least 1 risk factor
Very High Risk	<p>Stage, grade with additional clinical risk factors:</p> <ul style="list-style-type: none"> • Ta HG/G3 and CIS with all 3 risk factors • T1 G2 and CIS with at least 2 risk factors • T1 HG/G3 and CIS with at least 1 risk factor • T1 HG/G3 no CIS with all 3 risk factors

The scoring model is based on individual patient data, but does not consider patients with primary CIS (high-risk) or with recurrent tumours, as well as some pathologic parameters like subtypes of urothelial carcinoma (*micropapillary, plasmacytoid, sarcomatoid, small-cell, neuroendocrine*) and LVI. Nevertheless:

- Based on data from the literature, all patients with CIS in the prostatic urethra, with subtypes of urothelial carcinoma (variant histologies) or with LVI should be included in the very high-risk group.
- Patients with recurrent tumours should be included in the intermediate-, high- or very high-risk groups according to their other prognostic factors.

Disease management

Adjuvant treatment

Since there is considerable risk for recurrence and/or progression of tumours after TURB, adjuvant intravesical therapy is recommended for all stages (TaT1, and CIS).

- **Immediate single post-operative instillation of chemotherapy** immediate single post-operative instillation of chemotherapy after TURB can reduce the recurrence rate in patients with low-risk and selected intermediate-risk tumours. The difference in efficacy between individual drugs (mitomycin C, epirubicin, or doxorubicin) has not been confirmed.
- **Further chemotherapy** instillations can improve recurrence-free survival in intermediate-risk tumours, but do not prevent progression. These instillations are associated with minor side effects.
- **Intravesical immunotherapy with BCG** (induction and maintenance) is superior to intravesical chemotherapy in reducing recurrences and in preventing or delaying progression to MIBC.

The individual choice of further intravesical adjuvant therapy depends on the patient's risk (Table 3). In patients at very high risk of progression, immediate radical cystectomy (RC) should be considered.

Bacillus Calmette-Guérin failure

Several categories of BCG failures, broadly defined as any HG recurrence following BCG therapy, have been proposed.

Whenever a MIBC is detected during follow-up.

BCG-refractory tumour

1. If T1 HG/G3 tumour is present at 3 months (LE: 3).
2. If Ta HG/G3 tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance (LE: 4).
3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance (LE: 1b). If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases (LE: 1b).
4. If HG tumour appears during BCG maintenance therapy*.

BCG-relapsing tumour

Recurrence of HG/G3 (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response (LE: 3).

BCG-unresponsive tumour

BCG-unresponsive tumours include all BCG refractory tumours and those who develop TaT1/ HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure** (LE: 4).

BCG intolerance

Severe side effects that prevent further BCG instillation before completing treatment.

* Patients with low-grade recurrence during or after BCG treatment are not considered to be a BCG failure.

** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.

General recommendations for adjuvant therapy in TaT1 tumours and for therapy of CIS	Strength rating
Counsel smokers with confirmed NMIBC to stop smoking.	Strong
The type of further therapy after transurethral resection of the bladder should be based on the risk groups shown in Table 3. For determination of a patient's risk group use the 2021 EAU risk group calculator available at www.nmibc.net .	Strong
In patients with tumours presumed to be at low risk and in those with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB, one immediate chemotherapy instillation is recommended.	Strong
In patients with intermediate-risk tumours (with or without immediate instillation), one-year full-dose bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality.	Strong

<p>In patients with high-risk tumours, full-dose intravesical BCG for one to three years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated. The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side effects and problems connected with BCG shortages. Immediate radical cystectomy (RC) may also be discussed with the patient.</p>	Strong
<p>In patients with very high-risk tumours, discuss RC. Offer intravesical full-dose BCG instillations for one to three years to those who refuse or are unfit for RC.</p>	Strong
<p>Offer transurethral resection of the prostate, followed by intravesical instillation of BCG to patients with CIS in the epithelial lining of the prostatic urethra.</p>	Weak
<p>The definition of 'BCG unresponsive' should be respected as it most precisely defines the patients who are unlikely to respond to further BCG instillations.</p>	Strong
<p>Offer a RC to patients with BCG-unresponsive tumours.</p>	Strong
<p>Offer patients with 'BCG-unresponsive' tumours, who are not candidates for RC due to comorbidities, preservation strategies (intravesical chemotherapy, chemotherapy and microwave-induced hyperthermia, electromotive administration of chemotherapy, intravesical- or systemic immunotherapy; preferably within clinical trials).</p>	Weak

Recommendations – technical aspects for treatment	
<i>Intravesical chemotherapy</i>	
If given, administer a single immediate instillation of chemotherapy within 24 hours after TURB.	Weak
Omit a single immediate instillation of chemotherapy in any case of overt or suspected bladder perforation or bleeding requiring bladder irrigation.	Strong
Give clear instructions to the nursing staff to control the free flow of the bladder catheter at the end of the immediate instillation.	Strong
The optimal schedule and duration of further intravesical chemotherapy instillation is not defined; however, it should not exceed one year.	Weak
If intravesical chemotherapy is given, use the drug at its optimal pH and maintain the concentration of the drug by reducing fluid intake before and during instillation.	Strong
The length of individual instillation should be one to two hours.	Weak
<i>BCG intravesical immunotherapy</i>	
Absolute contraindications of BCG intravesical instillation are: <ul style="list-style-type: none"> • during the first two weeks after TURB; • in patients with visible haematuria; • after traumatic catheterisation; • in patients with symptomatic urinary tract infection. 	Strong

Guidelines for the treatment of TaT1 tumours and carcinoma <i>in situ</i> according to risk stratification	Strength rating
<i>EAU risk group: Low</i>	
Offer one immediate instillation of intravesical chemotherapy after TURB.	Strong
<i>EAU Risk Group: Intermediate</i>	
In all patients either one-year full-dose bacillus Calmette-Guérin (BCG) treatment (induction plus 3-weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year is recommended. The final choice should reflect the individual patient's risk of recurrence and progression as well as the efficacy and side effects of each treatment modality. Offer one immediate chemotherapy instillation to patients with small papillary recurrences (presumably Ta LG/G1) detected more than one year after previous TURB.	Strong
<i>EAU risk group: High</i>	
Offer intravesical full-dose BCG instillations for one to three years or radical cystectomy (RC).	Strong
<i>EAU risk group: Very High</i>	
Offer RC or intravesical full-dose BCG instillations for one to three years to those who refuse or are unfit for RC.	Strong

Table 4: Treatment options for the various categories of BCG failure

Category	Treatment options
BCG-unresponsive	1. Radical cystectomy (RC). 2. Enrollment in clinical trials assessing new treatment strategies. 3. Bladder-preserving strategies in patients unsuitable or refusing RC.
Late BCG-relapsing: TaT1/HG recurrence > 6 months or CIS > 12 months of last BCG exposure	1. Radical cystectomy or repeat BCG course according to a patient's individual situation. 2. Bladder-preserving strategies.
LG recurrence after BCG for primary intermediate-risk tumour	1. Repeat BCG or intravesical chemotherapy. 2. Radical cystectomy.

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ;

LG = low-grade.

Follow-up

As a result of the risk of recurrence and progression, patients with NMIBC need to be followed-up. However, the frequency and duration of cystoscopy and imaging should reflect the individual patient's degree of risk.

Recommendations for follow-up in patients after transurethral resection of the bladder	Strength rating
Base follow-up of TaT1 tumours and carcinoma <i>in situ</i> (CIS) on regular cystoscopy.	Strong
Patients with low-risk Ta tumours should undergo cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later, and then yearly for 5 years.	Weak
Patients with high-risk and those with very high-risk tumours treated conservatively should undergo cystoscopy and urinary cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for a period of 2 years, and every 6 months thereafter until 5 years, and then yearly.	Weak
Patients with intermediate-risk Ta tumours should have an in-between (individualised) follow-up scheme using cystoscopy.	Weak
Regular (yearly) upper tract imaging (computed tomography-intravenous urography [CT-IVU] or IVU) is recommended for high-risk and very high-risk tumours.	Weak
Perform endoscopy under anaesthesia and bladder biopsies when office cystoscopy shows suspicious findings or if urinary cytology is positive.	Strong

During follow-up in patients with positive cytology and no visible tumour in the bladder, mapping-biopsies or PDD-guided biopsies (if equipment is available) and investigation of extravesical locations (CT urography, prostatic urethra biopsy) are recommended.	Strong
In patients initially diagnosed with TaLG/G1–2 bladder cancer, use ultrasound of the bladder, and/or a urinary marker during surveillance in case cystoscopy is not possible or refused by the patient.	Weak

This short booklet text is based on the more comprehensive EAU Guidelines (ISBN 978-94-92671-16-5) available to all members of the European Association of Urology at their website, <http://www.uroweb.org/guidelines/>.

Attachment 10

Optimized photodynamic diagnosis for transurethral resection of the bladder
(TURB) in German clinical practice



ORIGINAL ARTICLE

Optimised photodynamic diagnosis for transurethral resection of the bladder (TURB) in German clinical practice: results of the noninterventional study OPTIC III

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Abstract

Purpose White light cystoscopy (WLC) is the standard procedure for visualising non-muscle invasive bladder cancer (NMIBC). However, WLC can fail to detect all cancerous lesions, and outcomes with transurethral resection of the bladder differ between institutions, controlled trials, and possibly between trials and routine application. This noninterventional study assessed the benefit of hexaminolevulinate blue light cystoscopy (HALC; Hexvix®, Ipsen Pharma GmbH, Germany) plus WLC versus WLC alone in routine use.

Methods From May 2013 to April 2014, 403 patients with suspected NMIBC were screened from 30 German centres to perform an unprecedented detailed assessment of the additional detection of cancer lesions with HALC versus WLC alone.

Results Among the histological results for 929 biopsy samples, 94.3 % were obtained from suspected cancerous lesions under either WLC or HALC: 59.5 % were

carcinoma tissue and 40.5 % were non-cancerous tissue. Of all cancer lesions, 62.2 % were staged as Ta, 20.1 % as T1, 9.3 % as T2, 7.3 % as carcinoma in situ (CIS), and 1.2 % were unknown. Additional cancer lesions (+6.8 %) and CIS lesions (+25 %, $p < 0.0001$) were detected by HALC plus WLC versus WLC alone. In 10.0 % of patients, ≥ 1 additional positive lesion was detected with HALC, and 2.2 % of NMIBC patients would have been missed with WLC alone. No adverse events were observed.

Conclusions The results of this study demonstrate that HALC significantly improves the detection of NMIBC versus WLC alone in routine clinical practice in Germany. While this benefit is statistically significant across all types of NMIBC, it seems most relevant in CIS.

Keywords Blue light cystoscopy · Hexaminolevulinate · Non-muscle invasive bladder cancer · Observational studies · White light cystoscopy

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Introduction

Suspected non-muscle invasive bladder cancer (NMIBC) is diagnosed using white light cystoscopy (WLC), followed by biopsy [1]; however, WLC can fail to detect 4–41 % of papillary Ta and T1 tumours, carcinoma in situ (CIS), dysplasia, multifocal growth, and microscopic lesions [2, 3]. Visualisation of bladder lesions including residual tumour tissue, small tumours, and CIS during transurethral resection of the bladder (TURB) can be improved with hexaminolevulinate blue light cystoscopy (HALC; Hexvix®, Ipsen Pharma GmbH, Ettlingen, Germany) [3–6]. Results from randomised controlled trials (RCTs) show that WLC plus HALC can detect an additional 7–30 % of cancer lesions versus WLC alone [6–11].

The quality of TURB and outcomes achieved in clinical studies can vary considerably [6]. Therefore, observational studies reflecting routine clinical practice are useful to assess the benefit of HALC outside of RCTs, since the effect of photodynamic diagnosis may differ between these settings. Prior observational studies conducted in Italy [7], Spain [8] and France [12] showed that in daily clinical practice, HALC can enhance the diagnostic accuracy of WLC, resulting in a lower tumour recurrence rate. Detection rates again varied, potentially reflecting different clinical settings between series.

Because of the observed differences in different countries, and as changes in EU regulations promote post-authorisation studies in different countries in Europe [13], we conducted a study to assess additional detection of cancerous lesions with HALC plus WLC versus WLC alone in patients with NMIBC undergoing TURB in routine clinical practice in various urology departments in Germany in unprecedented detail.

Patients and methods

Study design

During this multicentre, prospective, noninterventional study, patients with suspected NMIBC undergoing TURB in daily clinical practice were screened from 30 inpatient surgical urological German centres between May 2013 and April 2014. Centres utilising HALC were prospectively selected for inclusion. All enrolled patients received HALC and WLC.

The study followed recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research, and the International Society for Pharmacoepidemiology, Good Pharmacoepidemiological Practice Guidelines. Applicable local independent ethics committee and institutional review board approvals were obtained before study initiation.

The primary objective was to assess additional detection of NMIBC with HALC compared with WLC alone based on lesions in patients undergoing TURB, by analysing the detection rate with HALC and WLC versus WLC alone.

Patients

All patients with suspected NMIBC and indication for TURB were included. Exclusion criteria included: repeat TURB (control TURB) 4–6 weeks after initial TURB, and Bacillus Calmette–Guérin (BCG) or mitomycin/intravesical chemotherapy instillation therapy \leq 12 weeks before TURB. Inclusion and exclusion criteria followed recommendations in the HALC Summary of Product Characteristics (SmPC) [14]: contraindications include porphyria and hypersensitivity to the active substances/any of the excipients [14].

Procedure

HALC and WLC were performed during the same surgical procedure after administration of hexaminolevulinate, according to the SmPC and local clinical practice procedure.

Hexaminolevulinate solution (50 ml of 8 mmol/l) should be instilled into the bladder via a catheter and retained for \geq 1 h. After emptying the bladder, examination using blue light should be started $<$ 3 h after instillation. The entire bladder was examined and mapped using white light, then blue light, and biopsies of mapped lesions were taken [14, 15].

Lesion detection

In each patient, lesions detected with WLC were numbered and their location recorded in a detailed bladder map; this was repeated using HALC. It was noted if lesions were detected with HALC and/or WLC, and whether lesions were confluent or not. Directly following cystoscopy, findings were recorded in a detailed online system, thereby minimising delay between the procedure and documentation.

Histology

Histology was performed by the local pathology team of the participating centre, and results were added to the online patient records at a later stage. Lesions were resected using TURB, and biopsies were taken for histological evaluation by local pathologists. The biopsy method—cold biopsy or resection—was recorded. Lesions were histologically classified as carcinoma, dysplasia, hyperplasia, healthy tissue, inflammation, or unknown.

Carcinoma lesions were staged according to the tumour, nodes, metastasis classification of malignant tumours, and graded using the WHO classification (1973 and 2004). Individuals with confirmed tumour stage Ta, T1, or CIS were assigned to the European Organisation for Research and Treatment of Cancer (EORTC) risk scores (i.e. estimated probability of recurrence and progression in patients with NMIBC).

Adverse event monitoring

All related adverse events (AEs; serious and non-serious) were reported as spontaneous cases.

Monitoring

For each patient, an electronic case report form (eCRF) was used; into this eCRF, the investigator entered the collected data, the validity of which they were responsible for. Upon entry, data were automatically checked for completeness and plausibility. Random monitoring to confirm the study was being conducted in compliance with the protocol, and to verify data were being accurately reported on the eCRF, was conducted in approximately 10 % of the participating centres.

Statistical analysis

Efficacy analysis was at a patient level and lesion level in the per protocol (PP) population, which included all treated patients in the intent-to-treat (ITT) population with no major protocol deviation, and valid cystoscopy and pathology/histology results. The safety analysis was performed on the ITT population (i.e. all enrolled patients).

As the study was exploratory, lesions within patients were considered quasi-independent (no clustered analysis).

The ratio of true-positive and false-positive fractions (rTPF and rFPF) was calculated from measures of sensitivity (=TPF) and specificity (=1-FPF) for HALC and WLC, respectively. The TPF was the proportion of lesions or patients positively tested during cystoscopy out of all lesions or patients, respectively, with histologically confirmed carcinoma. The FPF was the proportion of lesions or patients positively tested during cystoscopy out of all lesions or patients, respectively, with histologically confirmed non-carcinoma tissue.

Detection rate was defined as the proportion of lesions or patients with lesions detected during the procedure out of all lesions or patients, respectively. By definition, detection rate was 100 % for HALC plus WLC.

The primary efficacy endpoints were rTPF and rFPF (with 95 % confidence intervals [CI]) for HALC plus WLC versus WLC alone. The McNemar test was used to test

the null hypothesis of equal sensitivities ($r\text{TPF} = 1$). rTPF was estimated (with 95 % CI) to assess the primary objective by evaluating the impact of HALC plus WLC versus WLC alone on the detection of NMIBC. Secondary efficacy endpoints were to assess detection rates with HALC plus WLC versus WLC alone for risk groups according to EORTC scores. Detection and false-positive rates were also compared on a patient level between HALC plus WLC and WLC alone. Pearson–Clopper 95 % CIs were calculated for these secondary efficacy endpoints.

The planned sample size was 364 patients using the assumptions: discordant test results between HALC plus WLC versus WLC alone of 12, 80 % power, 5 % alpha level, a fraction of the smallest subgroup investigated (15 %), and patients with missing histology (13 %).

Post hoc analysis included assessment of additional CIS lesion detection with HALC plus WLC versus WLC alone and of the number needed to treat for one patient to benefit from additional examination with HALC.

Results

Participant flow is summarised in Fig. 1. Overall, 395 patients received hexaminolevulinate and 379 had valid histology from the diagnostic procedure; 97 % of enrolled patients completed the procedure.

Baseline patient and disease characteristics for the ITT population are summarised in Table 1.

Histology

Of the 941 biopsy samples collected, 929 were histologically evaluated. Of these, 876 (94.3 %; 95 % CI 92.6–95.7) were from lesions suspicious under WLC and/or HALC, while 53 (5.7 %; 95 % CI 4.3–7.4) were random samples taken from unsuspicious tissue and excluded from analyses. Results from histological analysis are summarised in Table 2.

Primary and secondary outcome measures

Of the 403 enrolled patients, 24 (6.0 %) were not submitted to cystoscopy or were without valid cystoscopy results (Fig. 1).

Overall, 499 cancerous lesions and 340 non-cancerous lesions in the PP population were identified with HALC and WLC. HALC identified 6.8 % (34/499) more positive lesions than WLC (Fig. 2). The rTPF and rFPF indicated that HALC plus WLC detected statistically significantly more true-positive and false-positive lesions. From the 839 suspected lesions, 223 (26.6 %) were false positive under WLC and an additional 117 (13.9 %) were false positive under HALC.

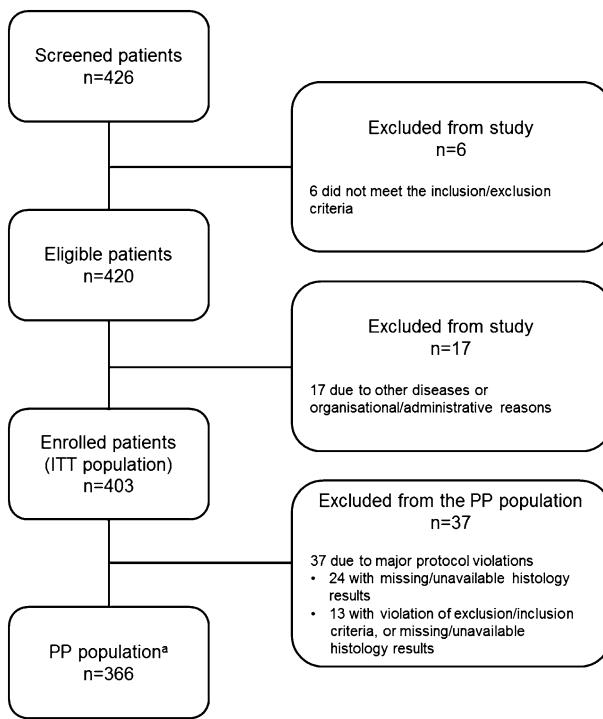


Fig. 1 Participant flow chart. *ITT* intent to treat, *PP*, per protocol.

^aPatients with available and completed histological data; 8 patients included in the PP population received WLC, but did not receive HALC, due to either technical problems or organisational issues

Within the PP population, 270 (73.8 %) and 96 (26.2 %) NMIBC patients had histologically confirmed cancerous lesions and non-cancerous lesions, respectively. Of these patients, 234 (86.7 %; 95 % CI 82.0–90.5) had all confirmed tumour lesions detected with HALC and WLC, and 27 (10.0 %; 95 % CI 6.7–14.2) had ≥ 1 additional positive lesion detected with HALC. In the PP population, 2.2 % (95 % CI 0.8–4.8) of NMIBC patients would have been missed with WLC alone. In these patients, lesions with the following tumour stages were documented: two CIS, two pTaG1, four pTaG2, and two pT1G3.

On a patient level, and taking into account a study-design-related 100 % detection rate for HALC and WLC, detection rate was 95.4 % (95 % CI 92.7–97.3) for WLC alone. The resulting ratio of detection rates of 1.049 (95 % CI 1.028–1.079; $p = 0.0027$) indicated that a statistically significant increase in the number of patients with cancerous lesions was observed with WLC plus HALC versus WLC alone. The rFPF was 1.157 (95 % CI 1.080–1.283; $p < 0.0001$), indicating that with WLC plus HALC versus WLC alone a statistically significantly increased number of patients with false-positive lesions was observed.

With WLC and HALC, 12 (8.2 %) additional cancerous lesions were detected in patients at high risk of

Table 1 Baseline patient and disease characteristics (ITT population)

Characteristics	ITT population ($N = 403$)
Age (years)	
Mean (SD)	69.9 (10.7)
Sex, n (%)	
Female	114 (28.3)
Male	289 (71.7)
Current diagnosis is based on n (%)	
Positive urine cytology	34 (8.4)
Cystoscopy results	356 (88.3)
Other	65 (16.1)
Suspicion of NMIBC, n (%)	
Primary tumour	275 (68.2)
Recurrence	126 (31.3)
Missing	2 (0.5)
Suspicion of CIS, n (%)	
Yes	51 (12.7)
No	350 (86.8)
Missing	2 (0.5)
Suspicion of high-grade tumour, n (%)	
Yes	83 (20.6)
No	318 (78.9)
Missing	2 (0.5)
Previous BCG instillation, n (%)	20 (5.0)
Mean time between first diagnosis and end of the last BCG instillation (months)	27.1
EORTC recurrence risk ^{a,b}	
High risk	5 (2.3)
Intermediate risk	181 (83.4)
Low risk	31 (14.3)
Missing	65
EORTC progression risk ^{a,b}	
High risk	65 (30.0)
Intermediate risk	102 (47.0)
Low risk	50 (23.0)
Missing	65

BCG Bacillus Calmette–Guérin, *CIS* carcinoma in situ, *EORTC* European organisation for research and Treatment of cancer, *NMIBC* non-muscle invasive bladder cancer, *SD* standard deviation

^a Percentages are calculated based on the number of histologically evaluated patients with cancerous lesions ($n = 282$) minus missing patients ($n = 65$), i.e. $N = 217$

^b EORTC is only applicable to patients with cancerous lesions, with respective stage Ta, T1, and CIS

progression (according to EORTC scores) versus with WLC ($p < 0.0001$). No statistical difference was detected between HALC and WLC in those at low ($n = 1$ [2.1 %]; $p = 1.0000$) and intermediate ($n = 8$ [4.3 %]; $p = 0.0711$) risk of progression.

Table 2 Summary of histology results (PP population)

Parameter statistic/value	N (%)
Biopsy samples collected (ITT population), N	941
Histologically evaluated samples (ITT population), N	929
Samples obtained from suspicious lesions, n	839
Histological findings ^a	
Carcinoma	499 (59.5)
Dysplasia	26 (3.1)
Hyperplasia	29 (3.5)
Healthy tissue	83 (9.9)
Inflammation	202 (24.1)
Unknown ^b	0 (0.0)
Missing	0 (0.0)
Tumour staging ^c	
Ta	310 (62.1)
T1	99 (19.8)
T2	48 (9.6)
T3	0 (0.0)
T4	0 (0.0)
CIS	36 (7.2)
Unknown	6 (1.2)
Grading WHO 1973 ^c	
G1	130 (26.1)
G2	205 (41.1)
G3	108 (21.6)
Unknown	23 (4.6)
Not selected	33 (6.6)
Grading WHO 2004 ^c	
PUNLMP	5 (1.0)
Low grade	251 (50.3)
High grade	146 (29.3)
Unknown	62 (12.4)
Not selected	35 (7.0)

CIS carcinoma in situ, PUNLMP papillary urothelial neoplasm of low malignant potential, WHO world health organisation

^a Percentages are calculated based on the number of samples obtained from suspicious lesions ($n = 839$)

^b Histology result is either “not selected” or “unknown”

^c Only applicable to carcinoma lesions. Percentages are calculated based on the number of lesions found to be carcinoma ($n = 499$)

In a post hoc analysis, WLC plus HALC identified 9 (25.0 %) additional CIS lesions in the PP population versus WLC alone (Fig. 2), with the rTPF indicating that HALC detected statistically significantly more CIS lesions ($p < 0.0001$).

Based on the 282 patients in the ITT population with histologically confirmed lesions, post hoc analysis showed that 16 patients must be examined using HALC versus WLC alone to detect one additional patient with

a cancerous lesion (irrespective of risk of recurrence or progression).

No AEs related to treatment with HALC were reported.

Discussion

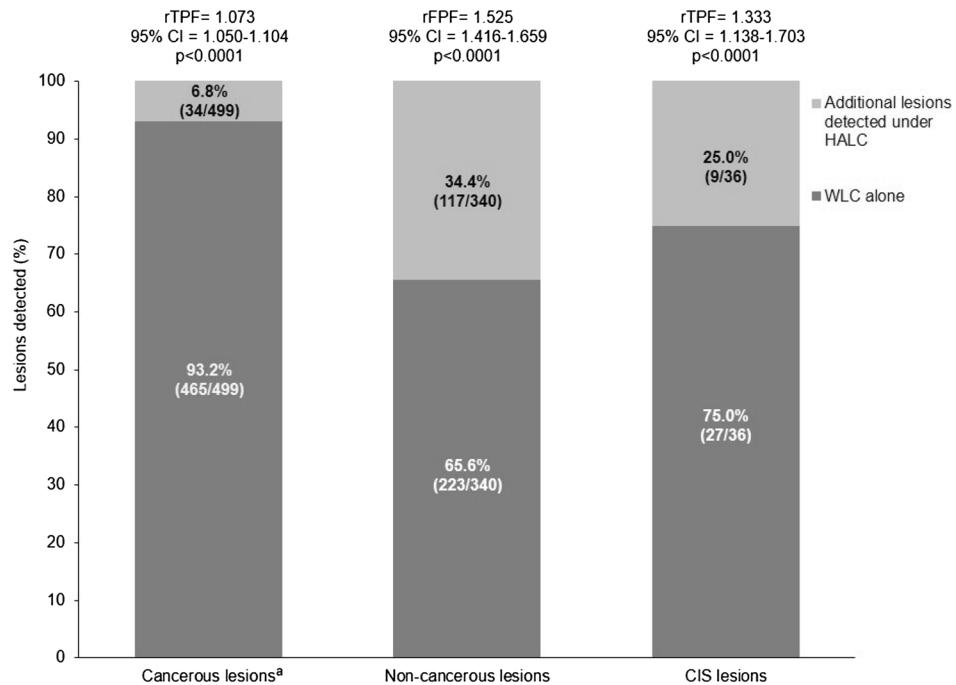
This study showed that in patients with NMIBC undergoing TURB in routine clinical practice, WLC plus HALC detected an additional 34 (6.8 %) cancerous lesions in the PP population versus WLC alone ($p < 0.0001$). While this proportion is markedly lower than in a previous observational study (23.2 %) [7], findings from both are consistent with results from RCTs (range 7–30 %) [6–11]. Large ranges in reported results could be due to different documentation procedures and clinical settings across countries. Nevertheless, HALC provides a diagnostic benefit over WLC alone for patients with suspected NMIBC, supporting its use in daily clinical practice. Indeed, the EAU guidelines now recommend use of this imaging modality when available for high-risk patients (when cytology is positive or when high-risk exophytic tumour is expected) [17]. The validity of this approach is confirmed by the current study, in which 8.2 % of additional cancerous lesions were detected in patients at high risk of progression. Initially targeting HALC to high-risk patients seems an appropriate means of introducing the use of this technique within a treatment centre. Thus, while HALC may lead to long-term benefits across all risk groups compared with WLC, high-risk patients seem to benefit most [16].

Importantly, significantly more CIS lesions were detected with WLC plus HALC versus WLC alone. While the effect of HALC was weaker than in a previous observational study, the rate of CIS was also lower (7.2 % here vs. 19.4 % in an observational series) [7]. RCTs also reported a greater (31.9–70.6 %) detection of additional CIS lesions with HALC [3].

In the PP population, 10 % of patients had ≥ 1 additional positive lesion detected with HALC, and WLC would have missed 2.2 % of NMIBC patients. Therefore, with WLC plus HALC versus WLC alone, more appropriate risk classification and optimised treatment management may be possible.

Comparisons with findings from RCTs should be viewed with caution. In RCTs, carefully selected patient populations managed at specialist centres with potentially more experienced surgeons may produce results that are not easily transferrable to routine practice at larger or more diverse centres. Indeed, TURB is a teaching procedure often performed by less experienced surgeons. Likewise, local pathology laboratories may yield different results, and generally a central pathology laboratory is used in RCTs. Hence, results from studies of routine HALC use are

Fig. 2 Histologically confirmed lesions detected with HALC and WLC (PP Population). *CIS* carcinoma in situ, *HALC* hexaminolevulinate blue light cystoscopy, *rFPF* ratio of false-positive fractions, *rTPF* ratio of true-positive fractions, *WLC* white light cystoscopy. By definition, the detection rate was 100 % for HALC plus WLC.
a2.8 % of cancerous lesions were detected by WLC only



important to better understand the potential benefits of this approach. As outlined above, there is good evidence that HALC may offer benefits in terms of detection and outcome in a range of patients; this benefit may be most significant in those with high-risk tumours (as the data from this study support), and optimising detection of positive lesions will rely on optimising the technique more than via patient selection. Furthermore, differences in local histology/pathology assessments may contribute to varied results between observational studies and clinical trials; conformity in staging and grading is 50–60 % [1]. Importantly, this study included sites experienced and inexperienced with HALC, reflecting routine practice in Germany.

Enhanced detection during TURB with the use of HALC may improve diagnosis of NMIBC in clinical practice, improve outcomes, and reduce recurrence rates [4]. The finding that HALC detected a significantly higher rate of true-positive lesions in patients with high risk of progression (according to EORTC scores) than WLC may indicate that HALC use could improve detection of these patients in routine clinical practice, potentially reducing morbidity and mortality [8, 11, 17, 18]. While false-positive rates were relatively high with WLC alone and when HALC was added, these were within the ranges reported in a previous observational study that highlighted the wide variation in the rate of false positives at different centres (2.6–28.6 % with WLC alone and 6.1–39.3 % with the addition of HALC) [8]. The present study highlights the importance of thoroughly assessing patients in true need of a TURB in advance to avoid biopsy in merely inflamed tissue, as a rather large fraction of patients showed inflammation only (24.1 %).

Although this study did not assess recurrence rate or survival, it is clear that improved visualisation techniques allow for more appropriate disease staging and risk classification and thus guide more appropriate subsequent treatment decisions, as well as allow for better resection of the tumour. It is reasonable, therefore, to expect that use of HALC would result in longer recurrence-free survival compared to WLC alone. The benefits of improved detection with HALC have already been demonstrated in several studies, with significantly reduced recurrence rates at 1 year. This could potentially reduce the requirement for patients to undergo frequent TURBs, which not only have a significant negative impact on patient quality of life, but also incur a considerable cost [3]. A recent study from Sweden modelling the cost consequences of HALC found that the technique had a minimal cost impact if introduced across all risk groups, and reduced TURBs, cystectomies, bed days, and operating room time. Notably, the use of HALC translated into cost savings from year 2–5 in this model [16].

Despite the large number of patients with primary tumours (68.6 %) versus previous studies (43.3 %) [3], this study represents a typical population of patients with suspected diagnosis of NMIBC within in-patient surgical urological institutions in Germany. Similar to other observational studies, there were no reports of spontaneous AEs related to hexaminolevulinate [7, 8].

No subgroup analyses by tumour type were conducted in the present study; however, a meta-analysis that did conduct such analyses found the benefit of HALC was in patients with Ta, T1, CIS, primary and recurrent cancer, and was

independent of the level of risk [3]. Additional detection rates with HALC (compared with WLC alone) ranged from 9.7 to 40.2 % for Ta tumours, with 239 of 1621 (14.7 %) of additional Ta tumours only being detected with HALC. For T1 tumours, detection of additional tumours with HALC ranged from 3.6 to 54.5 % of the total T1 tumours detected. In total, 40 of 372 (10.8 %) of additional T1 tumours were detected only by HALC. As in the present study, the benefit of HALC was most pronounced in CIS; detection of additional CIS lesions ranged from 31.9 to 70.6 % of the total CIS lesions detected; and 215 of 527 (40.8 %) of additional CIS lesions were detected with HALC alone [3].

Despite meticulous online documentation with detailed bladder maps and minimised time delay between procedures and documentation, there remained a number of study limitations. Limitations were consistent with other observational studies and include: incomplete information versus RCTs, and lack of blinding between WLC and HALC, which could bias true-positive and false-positive observations. However, achieving blinding in routine clinical settings is impossible and also hard to accomplish in a diagnostic study. Of note, no tertiary or academic centres—both of which institutions treat a significant number of patients—were included in the present study, and not all regions of Germany were equally reflected; either or both of these factors may have introduced bias.

Study strengths included observation of a complete and typical spectrum of patients with a realistic high number of primary tumours and staging distribution, and prevention of patient selection bias through recruitment of consecutive patients with the required diagnosis.

In conclusion, this study demonstrates that HALC significantly improves the detection of NMIBC versus WLC alone in daily clinical practice in Germany.

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Authors' contribution M Burger carried out project/protocol development, data interpretation, manuscript editing. T Bach, PJ Bastian, A Blana, A Kaminsky, S Keller, T Knoll, C Lang, S Promnitz, B Ubrig contributed to patient recruitment, data generation, manuscript review. T Keller carried out protocol development, data analysis, manuscript review. B Qwick contributed to project/protocol development, project management, data interpretation, manuscript editing.

Compliance with ethical standards

Conflict of interest The OPTIC III study was funded by Ipsen Pharma, Germany. TB has been an invited speaker and participated in a workshop for Ipsen; TKnoll has participated in workshops for Ipsen; SP has received financial support for symposia from Janssen-Cilag, Bayer, and GlaxoSmithKline; TKeller was responsible for the statistical analysis on behalf of Ipsen Pharma; BQ is an employee of Ipsen; MB has consulted and lectured for Ipsen Pharma, Janssen, Astellas, and Bayer. PJB, AB, AK, SK, CL, BU have no conflicts to disclose. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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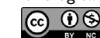
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Attachment 11

Early recurrence and the need for re-resection following Photodynamic diagnosis–
assisted Transurethral Resection of Bladder Tumours

Early recurrence and the need for re-resection following Photodynamic diagnosis-assisted Transurethral Resection of Bladder Tumours: Multi-centre real-world experience of the UK PDD Users Group

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Abstract

Objective: This study aimed to investigate the association between Photodynamic Diagnosis (PDD) with hexaminolevulinate (HAL) and the rate of complete resection and disease persistence at first follow-up cystoscopy for non-muscle-invasive bladder cancer (NMIBC) in UK real-world practice.

Methods: Audit data were pooled from six UK centres where HAL PDD was used in patients with a new NMIBC diagnosis undergoing transurethral resection of bladder tumours (TURBT) since 2008. Patients received adjunctive intravesical therapy and surveillance in line with European and UK guidelines, including early re-resection in high-grade NMIBC.

Results: PDD-assisted TURBT was done in 837 patients with new NMIBC. The detrusor muscle was present in 69.4% of cases. At early re-TURBT in 207 high-risk patients, 13.0% had residual disease. Multifocal disease was the most significant factor in increasing the rate of residual disease (odds ratio excluding cases of CIS=4.1; 95% confidence interval 1.5–11.3). The recurrence rate at first follow-up cystoscopy (RRFFC) was 10.6% (8.9% in patients with complete initial TURBT). In the historical cohort undergoing good-quality white-light TURBT, RRFFC was 31%; 40.5% of high-risk patients had residual disease at early re-TURBT.

Conclusion: HAL PDD may increase the rates of complete resection, reducing the risk of early recurrence and the need for routine re-resection in high-grade NMIBC.

Level of evidence: 2b.

Keywords

Fluorescence cystoscopy, hexaminolevulinate, recurrence, transitional cell carcinoma, urinary bladder neoplasms, urothelial carcinoma

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Introduction

Transurethral resection of bladder tumours (TURBT) is the mainstay of treatment for non-muscle-invasive bladder cancer (NMIBC). However, although the intention of such treatment is curative, recurrence rates are high, necessitating regular and often prolonged follow-up.¹ As a result, bladder cancer places a heavy and long-term burden on health-care resources and on patients.²

The European Association of Urology recommends repeat TURBT after two to six weeks for patients at high risk of recurrence.¹ For example, the prevalence of tumour persistence in patients with Ta and T1 tumours has been reported at approximately 39–47%.^{3,4} However, a blanket policy of early re-resection is burdensome for service providers and patients alike. We believe that the rate of residual disease after initial resection could be reduced by emphasising better-quality initial TURBT, thus obviating the need for default early re-resection in every high-risk case.

Clinical trials and real-world experience show that use of photodynamic diagnosis (PDD; also known as fluorescence cystoscopy) increases detection of tumours, especially carcinoma *in situ* (CIS), compared to white-light cystoscopy (WLC) alone and improves clearance of tumour margins.^{5–7} Long-term follow-up of the largest randomised clinical trial of hexaminolevulinate (HAL) indicates that this improved detection translates into a clinically significant reduction in recurrence-free survival ($p=0.04$),⁸ with a trend towards reduced progression rates compared to WLC.⁹

To date, there is limited evidence on the role of HAL PDD in reducing residual disease at early re-TURBT, with one single-centre study ($N=446$) indicating a significant reduction in recurrence rate at the six-week re-TURBT from 31.2% with WLC to 11.1% with PDD ($p=0.0001$).¹⁰ The objective of the present analysis was to describe residual disease rates and recurrence in a large population of patients, using pooled audit data from an ongoing collaboration between urological teams at seven centres across the UK.

Methods

Data were collected as an audit of outcomes/quality prospectively (Edinburgh) or retrospectively (Barnet, Middlesbrough, Exeter, Bridgend and Basingstoke) on all new NMIBC patients receiving HAL PDD-guided cystoscopy or TURBT from 2008 until May 2011 in the participating centres, with analysis focusing on risk of residual disease at early re-TURBT in patients with high-grade NMIBC, recurrence rate at the first follow-up cystoscopy (RRFFC) and comparison of the above end points between TURBT guided by PDD (PDD-TURBT) and TURBT performed under white-light (WL-TURBT) in a historical cohort from Edinburgh.

Medical procedures

Mitomycin C was given to all patients within 24 hours of initial resection in most centres unless contraindicated or if it was felt inappropriate by the clinician. Further intra-vesical instillation of mitomycin C or bacille Calmette–Guérin (BCG) in line with European and UK guidelines was dependent on local policy following discussion at the multidisciplinary meeting. None of the patients received BCG prior to the early re-TURBT, and a six-week course of mitomycin C was used in only one centre for 16 patients with intermediate-risk NMIBC.

In patients with high-grade NMIBC, re-TURBT was performed within six weeks of initial TURBT, and cystoscopy + biopsy was performed at three months where re-TURBT was felt inappropriate by the local team. High-grade NMIBC was defined according to the World Health Organization 1973 and 2004 classifications as high-grade (anaplastic) CIS or papillary urothelial carcinoma (PUC). All patients with low- to intermediate-risk NMIBC had the first check cystoscopy at three months. Completeness of resection post TURBT was assessed visually by the consultant carrying out the TURBT or by the supervising consultant if the TURBT procedure was carried out by a trainee.

Data collection

To ensure uniform data reporting and minimise bias across centres, a standardised pro forma based on bladder mapping and tumour features (Figure 1) was used to collect specific information, including tumour size, number, appearance, completeness of resection, use of mitomycin C, clinical stage, presence or absence of detrusor muscle in the resection specimen and surgeon experience. Residual or recurrent disease was defined as histologically proven cancer on resection or biopsy. RRFFC was used as a measure of the quality of TURBT and therefore included results from early re-TURBT for high-grade NMIBC, as well as data from the three-month follow-up visit in patients with low- or intermediate-risk disease.

As this was a single-arm analysis of routinely collected data, no sample size calculation was performed. Multivariate logistic regression analysis was carried out where appropriate. Statistical analysis was carried out using SPSS for Windows v16 (SPSS, Inc., Chicago, IL). To provide a real-world context in which to assess the impact of PDD, early recurrence rates in patients undergoing PDD-TURBT were also compared informally to those in a control group of patients from one of the centres (Western General Hospital, Edinburgh, UK) who had received good-quality WL-TURBT (GQ-WLTURBT) involving (a) cystoscopic mapping using a bladder diagram, (b) documented complete resection of the tumour, (c) resection performed or supervised by an experienced surgeon (consultant or trainee at year 5 or beyond), (d) presence of detrusor muscle in the specimen and (e) mitomycin C instillation within 24 hours

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Bladder cancer operation notes/ proforma Ver. 3

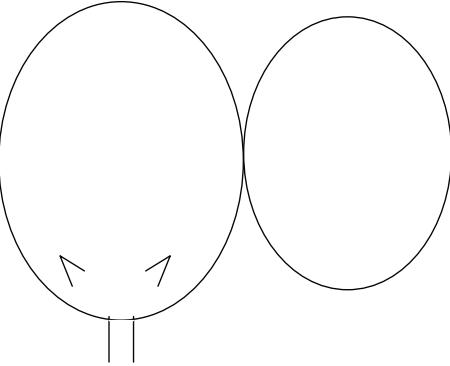
Name:	Date:
DOB:	Consultant:
Hospital Number:	Anaesthesia:
Operation:	
Surgeon:	
Supervisor: (scrubbed/ un-scrubbed) Supervisor completed op: Yes/ No	
Indication: First cystoscopy/ new tumour / recurrence / check	
Findings (delete or circle accordingly):	
Tumour number: 1 2 3 >3 Appearance: papillary/ solid/ mixed/ Red patch Size of largest tumour (mm): <5 5-10 10-30 >30	
Site(s): R UO L UO Trigone Bl. neck posterior wall anterior wall R lateral wall L lateral wall Urethra Dome Diverticulum	
	
Complete resection: yes / no / not sure / Biopsy and diathermy only	
Extra-peritoneal perforation: yes / no / thin wall/ cystoscopy only	
EUA: cTa cT1 cT2 cT3 cT4 (2) Bladder mobile: yes / no / not sure	
Postoperative Instructions: <ol style="list-style-type: none"> (1) Irrigation: yes / no (2) Intravesical 40mg Mitomycin C within 6 hours: yes / no (3) TWOC after 24H: yes / no If <u>no</u> keep catheter for _____ days (4) MDT discussion: yes / no If <u>yes</u>, please complete yellow form (5) Needs imaging: yes / no If <u>yes</u>, please specify: (6) Other: 	
Follow up (Please tick): <ol style="list-style-type: none"> (1) <input type="checkbox"/> GA cystoscopy urgent/ in 6 weeks/ in 3 months (2) <input type="checkbox"/> GA cystoscopy + Biopsy/ diathermy (urgent) (3) <input type="checkbox"/> TURBT (urgent)/ TURBT + PDD (4) <input type="checkbox"/> Flexible cystoscopy in 3 months (5) <input type="checkbox"/> Pending histology and MDT decision 	
Signature + initials:	

Figure 1. Bladder cancer operation notes/pro forma v3.

after the resection. Detailed findings for this control group have been published previously.^{6,11}

Results

In total, PDD-assisted surgery was carried out in 1127 patients, of whom 1008 had new bladder cancer of any

stage (including stages T2–T4). The present analysis focuses on the 837 patients with new NMIBC, comprising 295 from Edinburgh, 192 from Basingstoke, 163 from Barnet, 85 from Middlesbrough, 64 from Exeter and 38 from Bridgend. The mean age of patients with newly diagnosed NMIBC was 70.5 years. Baseline demographics are described in Table 1.

Table 1. Patient demographics, tumour characteristics and surgeon category at first transurethral resection of the bladder for all patients with newly diagnosed NMIBC.

Characteristics		Patients, n (%)
Patients with new NMIBC		837
NMIBC without tumour features recorded		192 (22.9)
Tumour size	<5 mm	145 (22.5)
	5–10 mm	139 (26.8)
	10–30 mm	173 (21.6)
	>30 mm	188 (29.2)
Tumour multiplicity	Single	358 (63.9)
	2	90 (13.9)
	3	43 (6.7)
	>3	154 (23.9)
Tumour appearance	Papillary	518 (80.3)
	Solid	28 (4.3)
	Mixed papillary and solid	86 (13.3)
	Flat lesion (red patch or carpet like)	13 (2.0)
Primary grade (World Health Organization 1973 and 2004)	G1 (including PUNLMP)	233 (27.8)
	G2 (low-grade ^a PUC)	315 (37.6)
	G3 (includes high-grade ^b G2)	242 (28.9)
	G3+CIS	22 (2.6)
	Primary CIS	25 (2.9)
Primary stage	Ta	593 (70.7)
	T1	191 (22.8)
	Ta/T1 + Tis	21 (2.5)
	Tis	25 (2.9)
	Tx	7 (0.8)
Complete resection	Yes	759 (90.7)
	No	49 (5.9)
	Biopsy and diathermy	5 (0.6)
	Unsure	22 (2.6)
Detrusor muscle in specimen	Present	581 (69.4)
	Absent	233 (27.8)
	Not sure	23 (2.8)
Surgeon category	Senior (consultant or trainee ≥5 years)	694 (82.9)
	Junior (trainee <5 years)	117 (13.9)
	Unknown	26 (3.1)

^aLow-grade PUC defined as a neoplasm of urothelium lining papillary fronds which shows an orderly appearance but easily recognisable variations in architecture and cytologic features.

^bHigh-grade G2 (PUC) defined as a neoplasm of urothelium lining papillary fronds which shows a predominant pattern of disorder with moderate-to-marked architectural and cytologic atypia.

NMIBC: non-muscle-invasive bladder cancer; CIS: carcinoma *in situ*; PUC: papillary urothelial carcinoma; PUNLMP: papillary urothelial neoplasm of low malignant potential.

Table 2. Univariate and multivariate regression analysis to determine association between primary tumour features and risk of residual disease following initial complete PDD-TURBT for high-grade NMIBC.

Variable	Residual disease status, n (%)		OR (95% CI), p	
	Present	Absent	Univariate	Multivariate
Tumour size	Large (>3 cm)	11/69 (15.9)	58/69 (84.1)	1.2 (0.15–2.9), 0.7
	Small (≤ 3 cm)	13/98 (13.3)	85/98 (86.7)	–
Tumour number	1–2	8/104 (7.1)	96/104 (92.9)	4.1 (1.5–11.3), 0.001
	≥ 3	16/63 (25.4)	47/63 (74.6)	3.1 (1.3–9.5), <0.01
Tumour appearance	Papillary	15/128 (11.7)	113/128 (88.3)	2.3 (0.8–6.2), 0.07
	Solid or mixed	9/39 (23.1)	30/39 (76.9)	–
Pathological stage	pTa	7/75 (9.3)	68/75 (90.7)	2.2 (0.8–6.7), 0.1
	pT1	17/92 (18.5)	75/92 (81.5)	–

The analysis includes data from 167 patients, of whom 154 had re-TURBT and 13 had cystoscopy in three months; excludes patients with primary CIS. PDD: photodynamic diagnosis; TURBT: transurethral resection of bladder tumours; OR: odds ratio; CI: confidence interval.

Table 3. Recurrence rates at first follow-up cystoscopy (RRFFC) and at one year (RR-1y).

	RRFFC, ^a n/N (%)	RR-1y, n/N (%)
Overall	85/801 (10.6)	41/225 (18.2)
After complete PDD-TURBT	65/730 (8.9)	38/209 (18.2)
By recurrence risk		
Low	7/185 (3.8)	3/63 (4.8)
Intermediate	23/182 (12.6)	17/83 (20.5)
High	25/171 (14.6)	17/75 (22.7)

^aIncludes re-TURBT at two to six weeks for patients with high-grade disease and first follow-up visit at three months for patients with low- or intermediate-risk disease at the Edinburgh, Middlesbrough and Exeter centres.

Overall, 759 (90.7%) patients with new NMIBC were deemed by the surgeon to have had a complete initial PDD-TURBT; the remainder had incomplete resection, were managed with biopsy and fulguration or the completeness of resection was uncertain. The detrusor muscle was present in 581 (69.4%) NMIBC cases.

At early re-TURBT, residual disease was found in 27 (13.0%) of 207 cases of high-grade NMIBC, with upstaging to T2 cancer in three (1.5%) cases. Table 2 describes the association between primary tumour features and residual disease in patients with high-grade NMIBC, excluding those with CIS ($n=167$). Patients with multiple tumours, solid- or mixed-appearing tumours and T1 tumours appeared more likely to have residual disease following complete PDD-TURBT for high-grade NMIBC compared to the historical control group.⁶ Residual cancer was found in 22 (17.6%) of 125 patients with the detrusor muscle present in the specimen and in eight (19.1%) of 42 patients when the detrusor muscle was absent.

The overall RRFFC (including early re-TURBT for high-grade NMIBC) following complete PDD-TURBT was 8.9%. Table 3 describes RRFFC and recurrence rates at one year stratified by baseline recurrence risk groups.

Respective end points in the historical control group of patients undergoing GQ-WLTURBT are shown in Table 4.⁶

Discussion

This audit by the UK PDD Users Group has collected records from more than 1000 patients to date, providing the largest evidence base for HAL and for PDD in the UK, as well as being one of the largest patient pools globally. This collaboration represents the first multi-centre study in the UK to collect real-world data on recurrence/residual disease rates with HAL PDD.

In our study, RRFFC with PDD was 11%, the detrusor muscle was absent in only 31% of specimens and the residual disease rate was only 13% of high-grade NMIBC cases.

Table 4. Outcomes after PDD-TURBT compared to findings in a control group of patients undergoing good-quality WL-TURBT at the Western General Hospital.⁶

	PDD-TURBT, n (%)	WL-TURBT, ⁶ n (%)	Univariate OR (95% CI), p
Patients with newly diagnosed NMIBC	837	302	
Complete initial TURBT	759 (90.7)	225 (74.5)	3.3 (2.4–4.7), 0.001
Detrusor muscle in specimen	581 (69.4)	187 (61.9)	1.4 (1.1–1.8), 0.02
Residual disease at early re-TURBT in patients with high-risk NMIBC	27/207 (13.0)	17/42 (40.5)	4.5 (2.2–9.5), <0.001
Upstaging after re-TURBT	3/207 (1.5)	2/44 (4.5)	N/A (too small values)
Overall RRFFC	85/801 (10.6)	48/155 (31.0)	3.8 (2.5–5.7), <0.001
RRFFC in low-risk NMIBC	1/57 (0.02)	15/68 (22.1)	N/A (too small values)
RRFFC in intermediate-risk NMIBC	7/69 (10.2)	16/47 (34.0)	4.6 (1.7–12.3), 0.002

This is in line with the 11% residual disease rate observed with the use of advanced optical imaging tools in the study by Geavlete *et al.*¹⁰ and appears favourable in comparison to historical studies of early re-TURBT, where residual disease rates of up to 76%^{12,13} and rates of complete resection (including muscle) of 20–84%^{14–16} were observed.

This analysis is a single-arm audit, without a contemporary control group. However, the results can be considered in light of experiences at one of the centres (Western General Hospital), which offers a historical control group of patients managed by experienced urologists who were also involved in the present audit. Despite the GQ-WLTURBT, the RRFFC was 31%, with 40.5% residual disease at early re-TURBT in high-risk patients, and the detrusor muscle was absent in almost 40% of specimens.⁶

The reduction in residual disease and recurrence rates could be attributed to: the high level of experience of the surgeons performing TURBT; good-quality training, with overall improved attention to detail and close supervision; dedicated lists for TURBT at participating centres; including the detrusor muscle in the specimen^{11,17}; state-of-the-art cystoscopes and video equipment; and use of advanced optical imaging tools such as PDD. In addition, the number of incorrectly staged patients was minimal (1.5% in our study compared to up to one third in historical TURBT series^{13,15,16}). This means that appropriate treatment is initiated without delay.

With such potential to improve detection and resection with PDD in the majority of patients, we hypothesise that the number of cases requiring early re-TURBT could be substantially reduced, allowing resources to be prioritised in the subgroups most likely to benefit. One such subgroup is those with multifocal disease, which was found to be the most significant factor in increasing the residual disease rate. Another subgroup that could benefit is those where the muscle is absent from the specimen. Indeed, in a large multi-centre cohort, Gontero *et al.* found that re-TURBT

had no impact on recurrence, progression, cancer-specific survival or overall survival in cases where the muscle was present in the initial resection specimen.¹⁸ This has been shown to be an indicator of high-quality resection.¹⁹ The use of PDD could potentially reduce the burden of repeat surgery and its possible complications, including the risk of tumour seeding and spread, in other patient subgroups such as those with large lesions or only one or two stage T1 lesions.²⁰ This approach would currently be at odds with international guidelines^{1,21} but, if validated by further research, could represent a new direction of travel to reduce the burden of NMIBC management on patients and health-care services.

We believe that we have provided an important foundation on which to build a long-term evidence base for the use of HAL PDD in the management of NMIBC. Our aim in the future is to try to standardise prospectively collected information on each PDD case across centres, so that, in time, we can undertake high-quality analyses of consistent data from as large a pool of patients as possible. We encourage all centres using HAL PDD to join this initiative, regardless of how much experience they currently have, as one of our aims is to show the increasing benefit of PDD over time, not just in terms of improving results versus WLC, but also because we believe that PDD can improve our surgical technique overall.

Limitations

The audit results that we present here come from both prospectively and retrospectively collected data from different centres, with varying levels of experience using HAL PDD and with, in some cases, restrictions on the patients in whom HAL PDD is used. In addition, each centre initially set up its own methods of recording details for each patient. The heterogeneity of the data and limited information available for some of the factors that potentially influence

outcome need to be borne in mind when considering our results. For example, data on the use of mitomycin C are only available from the Edinburgh centre, where 74% of patients received a single mitomycin C instillation within 24 hours of initial cystoscopy. Such challenges with data collection from multiple UK centres in relation to bladder cancer were also experienced in the BAUS radical cystectomy audit, where only 37% of in the Hospital Episode Statistics data were entered into the database with significant data heterogeneity.²²

Conclusion

In conclusion, our audit data suggest the use of HAL PDD may improve bladder visualisation, thereby increasing the probability of complete resection and reducing the risk of recurrence. This was evident in this multi-centre audit across all risk groups, including those with high-grade or multifocal tumours or CIS. Further high-quality, prospective data collection across UK centres is needed to confirm this.

Conflicting interests

The authors declare that there is no conflict of interest.

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Ethical approval

This is an audit of practice and outcomes.

Informed consent

This is an audit of practice and outcomes.

Guarantor

All authors.

Contributorship

P. M. conceived the study and designed the pro forma for data collection, in collaboration with all authors. All authors were involved in data collection. P.M. carried out data analysis. P.M. wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Attachment 12

Blue light cystoscopy for the diagnosis of bladder cancer



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Original article

Blue light cystoscopy for the diagnosis of bladder cancer: Results from the US prospective multicenter registry

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Abstract

Introduction: Blue light cystoscopy (BLC) using hexaminolevulinate (HAL/Cysview/Hexvix) has been previously shown to improve detection of non-muscle-invasive bladder cancer (NMIBC). Herein, we evaluated the detection of malignant lesions in a heterogeneous group of patients in the real world setting and documented the change in risk category due to upstaging or upgrading.

Methods: Prospective enrollment during April 2014 to December 2016 of consecutive adult patients with suspected or known non-muscle-invasive bladder cancer based on prior cystoscopy or imaging, undergoing transurethral resection of bladder tumor at 9 different referral medical centers. HAL was instilled in the bladder for 1 to 3 hours before evacuation and inspection. Sensitivity and specificity of BLC, white light cystoscopy (WLC), and the combination of both BLC and WLC for detection of any malignancy was reported on final pathology. Number of patients with a change in American Urological Association (AUA) risk category based on BLC findings leading to a possible change in management and adverse events were recorded.

Results: Overall, 1,632 separate samples from bladder resection or biopsy were identified from 641 BLC procedures on 533 patients: 85 (16%) underwent repeat BLC (range: 2–5). Sensitivity of WLC, BLC, and the combination for diagnosis of any malignant lesion was 76%, 91%, and 98.5%, respectively. Addition of BLC to standard WLC increased detection rate by 12% for any papillary lesion and 43% for carcinoma in-situ. Within the WLC negative group, an additional 206 lesions in 133 (25%) patients were detected exclusively with BLC. In multifocal disease, BLC resulted in AUA risk-group migration occurred in 33 (6%) patients and a change in recommended management in 74 (14%). False-positive rate was 25% for WLC and 30% for BLC. One mild dermatologic hypersensitivity reaction (0.2%).

Conclusions: BLC increases detection rates of carcinoma in-situ and papillary lesions over WLC alone and can change management in 14% of cases. Repeat use of HAL for BLC is safe. © 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Keywords: Bladder cancer; Blue light cystoscopy; Diagnosis; Photodynamic

1. Introduction

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Bladder cancer is the fourth most common cancer and the eighth most common cause of cancer-related mortality

in men from the United States [1]. In 2016, roughly 79,030 new cases were diagnosed including 4.6% of all new cancer cases, and 16,870 deaths in the USA were recorded, equating to 2.8% of all cancer deaths [1]. Although most patients are diagnosed with non-muscle-invasive bladder cancer (NMIBC), recurrence rates remain high even at the lowest grade and stage [2]. These patients are also at risk of progression to MIBC [2]. Hence, improvement in initial staging and optimal management is important to reduce risk of recurrence and progression.

The current standard of care for diagnosis is white light cystoscopy (WLC) and urine cytology. Transurethral resection of bladder tumor (TURBT) is key to establishing the pathologic diagnosis and clinical stage. Complete visualization of the entire bladder and resection of all visible tumors is recommended whenever feasible [3]. The main limitation of WLC is difficulty in identifying all areas of malignancy given the multifocal nature of the disease and the presence of often inconspicuous but significant lesions such as carcinoma in-situ (CIS) [4]. EAU guidelines recommend biopsy of any abnormal looking urothelium, or even random biopsy of normal mucosa in case of positive cytology [5]. Current data suggest that early recurrence in patients with NMIBC may be the result of previously undetected lesions at prior TURBT [6–8].

Blue light cystoscopy (BLC) using hexaminolevulinate (HAL/Cysview/Hexvix) is the most validated technique used today to improve tumor detection. Five prospective multicenter trials with over 1,800 patients have shown that HAL-assisted BLC improves detection of NMIBC [6,9–11]. Current published data includes phase III trials from Europe, US, and Canada, systematic reviews, meta-analyses, and cost-analysis studies [12,13]. HAL was approved in EU and US for the detection of non-muscle-invasive papillary cancer in patients with suspected bladder lesions.

Although randomized clinical studies are the backbone of regulatory approval and clinical guidelines, they have limitations in terms of patient population. Here, we report on our experience from the multicenter prospective BLC with Cysview Registry. The core objective of this study was to evaluate the detection of malignant lesions in real world patients and to document the change in risk category due to upstaging or upgrading.

2. Materials and methods

2.1. Study populations

Following IRB approval and informed consent, consecutive patients from 9 different referral centers undergoing TURBT using both blue light (BL) and white light (WL) during cystoscopy and biopsy/resection, were enrolled in a registry starting in 2014. Inclusion criteria included adult (>18 y old) patients with suspected or known NMIBC based on a prior cystoscopy or imaging, patients undergoing

repeat resection for restaging or recurrence, and those who had positive urine cytology but no apparent lesion. Exclusion criteria were gross hematuria, porphyria, and known hypersensitivity to hexaminolevulinate or aminolevulinate derivatives, patients who refused catheter insertion, had pure upper tract or prostatic urethral lesions or were lost to follow up. Patients were generally scheduled for BLC at least 6 weeks after any prior bacillus Calmette-Guerin (BCG) immunotherapy or intravesical chemotherapy, as well as previous TURBT.

2.2. Study protocol

The procedure requires instillation of HAL, a photosensitizer, into the bladder, resulting in preferential accumulation of protoporphyrins in rapidly proliferating cells such as malignant bladder tumors. They are subsequently converted to photoactive porphyrins, which emit a red fluorescence under blue light (360–450 nm). HAL is made up of 100 mg hexaminolevulinate hydrochloride mixed with 50 ml of diluent. HAL was instilled via an indwelling catheter 1 to 3 hours before planned TURBT. BLC and WLC were performed using the KARL STORZ D-Light C Photodynamic Diagnostic (PDD) system which enables both WLC and BLC (wavelength 360–450 nm) fluorescence cystoscopy. The procedure began with a cystoscopic examination of the entire bladder under WL and then a repeated examination under blue light. Abnormalities of the bladder mucosa during BLC are characterized by the detection of red, homogenous fluorescence. The margins of the abnormal lesions are typically well-demarcated, in contrast to normal urothelium, which appears blue. Then based on the treatment protocol, the lesions which had been found during WLC or BLC, were resected or biopsied for the pathological evaluations. In some cases, random biopsies from visually normal bladder mucosa had been performed.

2.3. Data collection and analysis

Clinicopathologic data were collected including intraoperative findings with WL and BL, lesion characteristics (flat vs. papillary), location, and size. We considered any severe dysplasia, carcinoma in situ, or T1–4 bladder cancer as a positive result of pathology for malignancy. The anonymized data were entered through the secure registry website into the database. The incremental increased detection rate of BLC over conventional WLC was calculated. False-positive (FP) detection rates were calculated as the number of biopsies where no cancer was found, divided by the total number of biopsies/resections where biopsies were taken in either WL or BL categories. Analysis was performed using IBM SPSS statistics ver. 21. by a single investigator (S.T.B.).

2.4. Outcome measures

The independent variable was the final pathology report of the samples from biopsies/resections. The primary outcome measures included the sensitivity and specificity of BLC, WLC, and the combination of both BLC and WLC for detection of any malignancy reported on final pathology, among all patients and sub-analysis among those who had recently received intravesical therapy. We also recorded the number of patients who had a change in the American Urological Association (AUA) risk category [3] based on findings on BLC leading to a possible change in management. Adverse events (AEs) following HAL instillation were recorded with particular attention to repeat use.

3. Results

3.1. Cohort characteristics

Between April 2014 and Dec 2016, 533 patients entered the prospective registry ([Supplementary Fig. 1](#)). Overall, 1,632 separate pathology samples from biopsies or resections have been identified from 641 BLC procedures. Eighty-five patients (16%) underwent repeat BLC with HAL (2–5 total instillations). Mean age was 72 years, and 84% of patients were males. One hundred and forty-eight (28%) patients had primary tumors and 385 (72%) had recurrent tumors; prior intravesical treatments were used in 243 (46%) patients; BCG in 199 (37%); and mitomycin C in 92 (18%). Among 1,632 biopsies, pathologic tumor stages were T0 or not applicable in 925 (56%), Ta in 471 (29%), T1 in 176 (11%), and T2–4 in 60 (4%). CIS was detected in 341 of biopsies (21%), alone or concomitantly with papillary lesions. Pathologic grade of the 1,632 lesions were described as benign or not mentioned in 933 (57%), PUNLMP in 4 (<1%), low grade in 224 (14%), and high grade in 471 (29%). Demographic details are shown in [Table 1](#).

3.2. Detection rates

Using final pathology as the reference standard, the sensitivity of WL, BL, and the combination for any malignant lesion was 76%, 91%, and 98.5%, respectively. The addition of BL to standard WLC increased the detection rate by 12% for any papillary lesion and 43% for CIS ([Table 2](#)).

Within the group of WL negative lesions, an additional 206 lesions in 133 (25%) patients were detected exclusively with BL. In patients who had no tumors detected by WLC, malignant lesions were exclusively discovered by BLC in 41 (8%). In multifocal disease, BLC resulted in AUA risk-group upward migration in 33 (6%) patients ([Table 3](#)). Thus, the total rate of upgrading or upstaging was 14% using BLC. Change in management in this series was defined as receipt of intravesical therapy when it was not planned, increase in duration of therapy, or proceeding with radical cystectomy.

Table 1
Clinical and pathological characteristics of patients in blue light cystoscopy registry

N = 533	N (%)
Median age, y (range)	72 (23–101)
Male	446 (84)
Primary occurrence	148 (28)
Intravesical treatment	243 (46)
BCG	199 (37)
Others	92 (17)
Cytology	
Positive	192 (12)
Suspicious	154 (9)
Pathological stage (n = 1,632)	
T0	925 (56)
Ta	471 (29)
T1	176 (11)
T2–4	60 (4)
CIS (alone or concomitant with papillary)	341 (20)
Pathological grade (n = 1,632)	
Benign	933 (57)
PUNLMP	4 (0.2)
Low grade	224 (14)
High grade	471 (29)
Cystectomy	49 (9%)

3.3. FP and false-negative rates

Overall FP rate was 25% for WL and 30% for BL. Surgeons who performed more than 10 procedures in the study period had a median WL-FP of 19.6% (interquartile range: 15.2–30.4) and median BL-FP of 27.7% (interquartile range: 20.3–33.7), with significant correlation between WL and BL FP-rates per individual surgeon (Pearson correlation coefficient = 0.78, *P* = 0.002) ([Supplementary Fig. 2](#)). Overall false-negative rates in BLC for papillary and flat lesions were 3.8% and 1.8%, respectively. A total of 79 biopsies have been done from areas which were WL and BL negative. Among those samples the rate of malignancy was 0.4%.

3.4. Detection rates in different settings

One hundred and ninety-nine (37%) patients received BCG at least 6 weeks prior to BLC, with a positive

Table 2
Detection rate, positive and negative predictive value of different bladder lesions using white and blue-light cystoscopy

Detection rate (sensitivity)	Any malignancy			Any papillary (%)	Low papillary (%)	High papillary (%)	CIS (%)
	Sensitivity (%)	PPV (%)	NPV (%)				
White light only	76	64	56	87	86	86	55
Blue light only	91	63	70	91	91	92	91
Either white or blue light	98	59	82	99	99	99	98

NPV = negative predictive value; PPV = positive predictive value.

Table 3

AUA risk category migration due to lesions detected by blue light cystoscopy for non-muscle-invasive bladder cancer among registry patients

Final pathology	Number	AUA risk migration
LG Ta multifocal	14	Low to intermediate
HG Ta	1	Low to intermediate
HG T1	7	Intermediate to high
CIS	11	Low to high (1) Intermediate to high (10)

HG = high grade; LG = low grade.

predictive value of BLC-detected malignancy being 55% (Fig.). Ninety-five biopsies were taken from margins of a previous resection site (with more than 6 wks' interval), and the positive predictive value of BLC was 52% for malignancy (FP = 31%) (Fig.).

Among patients with positive or suspicious cytology within 8 weeks of BLC who had no lesions seen with WLC (111 total), BLC detected an additional 58 malignant lesions in 36 patients (sensitivity 97%). On the other hand, in patients who had negative cytology and no lesions with WLC (150 total), BLC was able to detect 35 new malignant lesions (sensitivity 83%).

3.5. Complications and AEs

AE data was obtained on follow up of 629 BLC procedures. Eighteen patients (2.9%) had minor complications after HAL instillation, including bladder pain (8), and urinary tract pain (12). None were definitively attributable to HAL. There was 1 mild dermatologic hypersensitivity reaction (0.2%).

3.6. Cystectomy

Forty-nine patients (9.3%) eventually underwent radical cystectomy and urinary diversion. The indications for cystectomy were detection of T2–4 (14), recurrent

multifocal HGT1 ± CIS (22), and BCG unresponsive CIS (13). Four of the cystectomies (8%) were performed exclusively because of findings detected by BLC (1 due to T2–4, 2 due to HGT1, and 1 due to CIS).

4. Discussion

Results of this prospective, multicenter registry from the United States confirm that BLC with HAL improves detection rates of any malignancy by 23%, papillary lesions by at least 12%, and CIS by 43%, over conventional WLC. Within the WL negative group, use of BLC resulted in detection of additional lesions in 25% of patients. In multifocal disease, BLC resulted in a change in recommended management in 14% of patients. Furthermore, 8% of cystectomies were performed due to upstaging or increase in AUA risk category with lesions detected exclusively by BLC. Use of HAL is very safe with no adverse reactions, including with multiple repeat use.

Several prior randomized controlled studies have shown that BLC with HAL facilitates the detection of bladder tumors [4–8]. Stenzl et al. in their large international RCT showed that among the Ta/T1 group, in 16% of patients at least one of the tumors was detected only with BLC-HAL. Grossman et al. [5] found in their RCT that additional lesions could be detected by BLC in each stage of bladder cancer over WLC. They concluded that at least 1 more tumor was detected by BLC in 29% of patients. Jocham et al. found 19% overall improved detection rates with BLC, which was more prominent in CIS (27%) and dysplasia (49%). This is in line with the overall additional detection rate of 25% in our study. Fradet et al. [4] used BLC for the detection of CIS, and reported that 41.5% more CIS lesions were found by BLC. Finally, Hermann et al. reported that WLC left residual tumors undetected in 49% of patients that were identified by BLC. These rates are also consistent with the 43% additional detection rate of CIS in this study [6].

In our prospective cohort, within the WL negative group, BL was able to detect additional lesions in 25% of patients. This included the 8% population in whom new malignant lesions were exclusively discovered by BLC. Kausch et al. showed in their systematic review of 13 trials, half of which were done with BLC with HAL, that 20% more patients were detected with BLC with HAL in all patients with non-muscle-invasive tumors and 39% more patients among the CIS population.

Any change in tumor grade from low to high was considered upgrading and any increase in tumor stage (from PUNLMP to any T, from Ta to CIS/T1, CIS to T1, \geq T2 stage) was regarded as upstaging. In order to better stratify and prognosticate outcomes, several groups have developed risk groups for NMIBC including the European Organization for Research and Treatment of Cancer (EORTC) and the AUA. In the most recently published AUA guidelines, NMIBC disease is categorized as low, intermediate, or

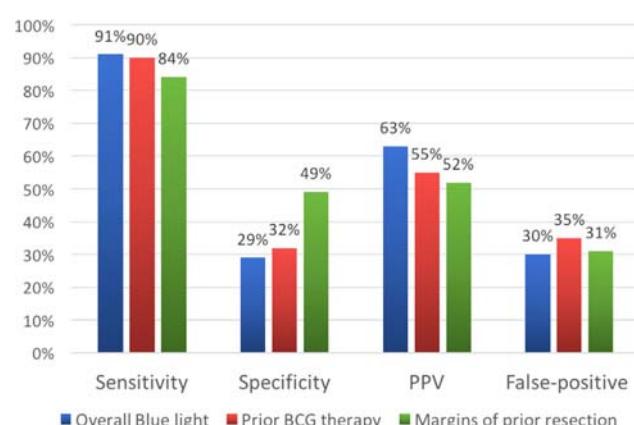


Fig. Detection rate of BLC after BCG therapy and at the margins of a prior resection.

high-risk in order to aid clinicians in appropriate management [3]. Our study showed that in multifocal disease, BLC resulted in a change in AUA risk category in 6% of patients. This, together with 8% newly diagnosed lesions by BLC, resulted in a 14% change in recommended management of patients. Similarly, Jocham et al. found in their prospective multicenter trial that 17% of patients received more appropriate therapy due to BLC. In our study, 8% of cystectomies were performed due to lesions detected exclusively by BLC.

The FP rate of WLC (30%) was similar to that of BLC (25%) although there was significant variability among surgeons. Kausch et al. [14], in their earlier systematic review showed that the FP rate among trials with BLC-HAL was 11% to 37% for BLC and 9% to 31% for WLC, consistent with our observation. The possible increase in biopsy of false positive lesions with BLC is balanced by increased detection of cancerous lesions and the unmeasured lack of biopsy of equivocal lesions on WLC.

There has been some controversy about which side-effects are attributable to BLC-HAL. Clearly the majority of adverse effects following BLC can be attributed to the TURBT. True adverse drug reactions to HAL are extremely rare. We observed a 2.8% overall complication rate, with a single case of a mild hypersensitivity reaction.

At least 5 systematic reviews and meta-analyses have been performed between 2012 and 2016 reporting long term outcomes of BLC with regard to recurrence and progression of disease [9–15]. Compared to WLC, BLC with HAL was associated with lower 12-month recurrence rates [4]. A lower recurrence rate and improved recurrence-free survival has also been reported for BLC at 1 and 2 years [13]. More recently, Gakis et al. [10] showed in their meta-analysis that in BLC-HAL patients, the rate of progression was significantly lower than those who underwent WLC alone. Also, Kamat et al. [11] revealed a trend toward a lower rate of progression and significantly prolonged time to progression in BLC-HAL patients, particularly in those progressing from Ta to CIS.

Limitations of this study include lack of randomization and possible observation bias. In addition, we did not report any recurrence data. The variation in FP rates in WLC and BLC may be interpreted as lack of consistency among study sites given the lack of concrete objective criteria for assignment of a blue light positive lesion. The aim of this study was to report on the detection of malignant lesions in a heterogeneous and diverse group of patients in a real world setting and to document the change in risk category due to upstaging or upgrading. Effort aimed at documenting disease recurrence, progression, recurrence-free, and overall survival are under way with further follow up in the registry.

5. Conclusion

BLC significantly increases detection rates of CIS and papillary lesions compared to WLC alone and can result in

upstaging or upgrading in about 14% of patients. Repeat use of HAL for BLC is safe.

Conflict of interests

Dr. Siamak Daneshmand and Kamal Pohar serve as consultants for Photocure.

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Blue light cystoscopy with Cysview Registry Group

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.urolonc.2018.04.013>.

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Attachment 13

Real-life experience': recurrence rate at 3 years with Hexvix® photodynamic diagnosis-assisted TURBT



ORIGINAL ARTICLE

‘Real-life experience’: recurrence rate at 3 years with Hexvix® photodynamic diagnosis-assisted TURBT compared with good quality white light TURBT in new NMIBC—a prospective controlled study

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Abstract

Purpose To compare the recurrence rate at 3 years (RR-3y) for non-muscle invasive bladder cancer (NMIBC) between good quality (GQ) PDD-TURBT and GQWL-TURBT where PDD is used in routine practice for all new tumours.

Methods All new, consecutive, NMIBC that received “good quality” criteria first TURBT across a university hospital service were prospectively recruited to this study over a 4-year period. Data were prospectively collected on all WL-TURBTs performed in 2007/8 and compared with PDD-TURBT from 2009/10. Only resection meeting strict “good quality criteria” were included from each cohort to control for resection quality, then cases were further matched

1:1 based on demographic and pathological criteria. The primary outcome was overall and risk group-specific recurrence rate at 3 years.

Results Of 808 patients recruited, 345 had GQ-TURBT for NMIBC and were included. RR-3y was significantly less for GQ-PDD overall [RR-3y: GQ-PDD: 57/146 (39.0%), GQ-WL: 72/135 (53.3%) OR = 0.56 (0.35–0.90) $p = 0.02$] and on a 1:1 matched pair basis [RR GQ-PDD: 29/118 (24.6) vs. 59/118 (50.0) OR 0.33 (0.19–0.57) $p < 0.001$]. Benefit was most marked in high-risk patients: RR-3y in high-risk patients treated with GQ-PDD was 25/48 (52.1%) vs. 28/35 (80%) for GQ-WL [OR 0.27 (0.10–0.74) $p = 0.01$].

Conclusion When adopted for all new bladder tumour resections in routine practice, PDD appears to be associated with significantly reduced recurrence rates at 3 years in our “real life” experience, particularly in high-risk patients.

Electronic supplementary material The online version of this article (doi:[10.1007/s00345-017-2077-6](https://doi.org/10.1007/s00345-017-2077-6)) contains supplementary material, which is available to authorized users.

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Keywords Bladder cancer · Non-muscle invasive bladder cancer (NMIBC) · Transurethral resection of bladder tumour (TURBT) · Photodynamic diagnosis (PDD)

Introduction

The long-term impact of photodynamic diagnosis (PDD)-assisted trans-urethral resection of bladder tumour (TURBT) on non-muscle invasive bladder cancer (NMIBC) recurrence rates is not known. There are no prospective controlled studies that examine NMIBC recurrence rates after routine use of hexaminolevulinate (HAL)-PDD-TURBT. There are four randomised controlled clinical trials (RCTs) examining recurrence rates with HAL-PDD-TURBT vs. white light (WL) [1–7] but all have some limitations. Only one [6] has shown benefit of PDD beyond 1 year (24 months). There are three “real-life” observational studies of HAL-PDD all of

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which are within-patient analyses of *detection* rates and do not examine recurrence rates [8–10]. Prospective controlled studies of a new technique in routine use are required to augment RCTs since RCTs may not represent what happens in the real-life setting [11–13].

The only RCT with follow-up beyond 2 years did not show benefit of PDD [3]. This and all but one [7] other trial included new *and* recurrent tumours. No trial had resection quality standardization and only 2/4 gave any mitomycin C [3]. We know that the quality of resection is a critical determinant of NMIBC recurrence [14, 15] and mitomycin C is proven to significantly reduce recurrence rates [16]. Thus, in addition to the need for a prospective study of PDD in routine use, the other limitations of the RCTs should be addressed. We, therefore, planned this study to provide the first long-term prospective data comparing recurrence rates after routine PDD use vs. WL and to address the limitations in the RCTs. We wanted to demonstrate: (1) Long-term recurrence rates associated with *routine* use of PDD (we have previously demonstrated the benefit of PDD for 3-month recurrence rates in the real-life setting [17]). (2) Long-term recurrence rates with PDD and WL, where *only new* tumours are included and (3) a comparison between PDD and WL where the *quality* of the initial resection can be controlled for and mitomycin C is given to all patients.

Therefore, the aim of this study was to compare total and risk group-specific recurrence rates in “good quality” (GQ) PDD-TURBT and “good quality” WL-TURBT when PDD is used in routine practice for *all new* NMIBC across a service.

Patients and methods

In 2006, based on national guidelines [18], it was planned that Hexvix® PDD would be introduced for all *new* bladder tumour resections in the coming years. In anticipation of this, we planned a prospective study to collect data on all (consecutive patients) new tumour WL resections performed in 2007/2008 (the baseline control data) and continue once PDD was introduced for all new tumour resections in 2009/2010. The attainment of quality indicators, along with all other study data was prospectively documented on the dedicated study proforma (Figure S1). The quality criteria that were aimed for and documented were: (1) resection done on lists by or with close supervision of the consultant; (2) a standardized proforma with cystoscopic bladder mapping used; (3) TURBT performed with the aim to completely resect all visible tumour and attainment of this documented; and (4) detrusor muscle was to be obtained and histologically confirmed. Patients were only included in the analysis if they had a first TURBT for new NMIBC and all the above quality criteria were met.

All patients received Mitomycin C within 24 h of TURBT, unless contraindicated. Risk stratification was based on 2002 EAU definitions to facilitate comparison with our series of studies [14, 15, 17]. All patients were discussed by cancer multi-disciplinary team that followed local criteria for chemo/immunotherapy usage, criteria for which did not change over the study. It was local policy that only patients with CIS or multi-focal G3 would receive immediate BCG therapy (provided an early re-TURBT did not demonstrate MIBC). For all others, BCG was deferred until detection of residual disease at re-TURBT or until high-grade recurrence. All high-risk patients had early re-TURBT unless the risks outweighed the benefits. All other patients followed standard cystoscopic surveillance. WL resections were performed on the lists of six experienced consultants and PDD resections on lists of two consultants. Throughout the study period, all TURBT pathology specimens were assessed by the same two specialist, senior uro-pathologists using standardized reporting criteria.

The primary end point was the recurrence rate at 3 years (RR-3y). Recurrence was defined as histologically proven tumour occurring any time after first (deemed to be complete) TURBT including at re-TURBT.

Rate of progression to MIBC and any grade and/or stage progression compared with initial resection was also examined.

To further control for confounder, patients were matched one to one on demographic and pathological criteria. Finally, logistical and Cox regression were performed to determine if observed differences were independent of the surgeon performing the resection.

Patients were excluded from end point analysis (censored) if they had not had a documented recurrence and were lost to follow-up, died or became palliative or unfit.

Mean recurrence-free duration was assessed by Kaplan–Meir analysis and log-rank test. Snapshot recurrence and progression rates were compared by Chi-squared test and matched pair analysis by McNemar’s test. Medians (25th, 75th) were compared by Mann–Whitney *U* test. Statistical analysis was performed using SPSS v21.

Results

Of 808 patients screened for inclusion, 554/808 (68.5%) had NMIBC, 345/554 (62.3%) of whom had confirmed “good quality” resections and were included (Table 1). After censoring of patients who had not had a documented recurrence and who did not achieve 3 years of follow-up, 135/153 (88.2%) WL and 146/192 (76.0%) PDD patients were assessed for recurrence at 3 years (Figure S2).

Table 1 Study population break down

	All patients	WL-TURBT	PDD-TURBT	<i>p</i> value
Screened	438	370		
Median age (25, 75)	71.9 (64.4–80.1)	72.1 (62.2–79.8)	0.30	
NMIBC at first TURBT	296 (66.8)	258 (69.7)	0.51	
Good quality TURBT for NMIBC (included)	153/296 (51.7)	192/258 (74.4)	<0.001	
Risk groups				
Low (G1/G2 Ta, single and <3 cm)	65 (43.0)	57 (29.7)	0.01	
Intermediate (G1/G2, Ta/T1, ≥3 cm or multiple and <3 cm)	45 (29.8)	71 (37.0)	0.14	
High (high risk: G3, Ta/T1 including cis)	41 (27.2)	64 (33.3)	0.19	
CIS at first resection	6/153 (3.9)	10/192 (5.2)	0.57	
T1	27/153 (17.6)	45/192 (23.4)	0.19	
Unifocal	113/153 (73.9)	98/192 (51.0)	<0.001	
>3 tumours	12/157 (7.8)	59/192 (30.7)	<0.001	
Re-TURBT in high-risk patients	34/41 (82.9)	55/64 (85.9)	0.95	
Primary BCG in high-risk patients ^a	11/41 (26.8)	13/64 (20.3)	0.45	
Follow-up				
Median follow-up (25, 75)	53.0 (19.9–65.5)	36.6 (22.3–43.2)	<0.001	
Completed 3-year follow-up	105/153 (68.6)	127/192 (66.1)	0.65	

^a Local guidelines for BCG therapy were followed and did not change through the study, these stipulated that BCG would only be given immediately after first TURBT if there was CIS or multifocal G3, otherwise BCG could be deferred until detection of recurrent or residual high-grade disease

Recurrence rates

The recurrence rate at 1 year (RR-1y) and RR-3y were significantly less with PDD than WL overall (Table 2A). There was significantly longer mean recurrence-free survival with PDD than WL [PDD: 52.9 (48.4–57.4) vs. WL: 42.4 (36.7–48.1) months *p* = 0.001] (Fig. 1a). There was no significant difference in median time to first recurrence [PDD: 8.7 (3, 21) vs. WL: 5.9 (3, 14.0) months *p* = 0.17].

Binary logistical regression and Cox regression were performed to determine if the benefit of PDD was independent of the surgeon performing the resection. Surgeon A and B performed 89% of all resections and were compared with the four other surgeons grouped. PDD was associated with significantly reduced recurrence rates at 3 years and significantly better recurrence-free survival independent of surgeon [multivariate Cox HR for PDD vs. WL adjusted for surgeon = 0.57 (0.39–0.83) *p* = 0.003] (Table 3). Considering only the two higher volume surgeons, recurrence rate at 3 years was still significantly less with PDD vs. WL [57/146 (39.0) vs. 52/97 (53.0) OR 0.55 (0.33–0.93) *p* = 0.02]. Since there was more multi-focal, intermediate and high-risk disease identified in the PDD group, this adjusted regression in favour of PDD and thus multi-focality and risk group were not included as variables in the regression analysis.

Matched pair analysis

Subjects from WL and PDD groups were matched 1:1 based on age (± 10 years), grade (exact), stage (exact), risk group (exact) and follow-up time (<6 months, 6 months to 1 year, >1–3 years and ≥ 3 years). 236/345 (68.4%) patients were successfully matched into 118 pairs. Matched recurrence rate was significantly less for PDD than WL overall (Table 2B).

Risk groups

The PDD group was significantly less likely to have unifocal disease declared, significantly more likely to have >3 tumours identified and significantly less likely to have low-risk disease (Table 1).

RR-1y was significantly less in low- and high-risk groups with trend to significance in intermediate risk (Table 2A). This difference in snapshot recurrence was only maintained at 3 years in the high-risk group (Table 2A). Recurrence-free survival was significantly better in low- and high-risk subgroups (Fig. 1b–d) with trend to significance in intermediate risk. In the matched pair analysis, PDD was associated with significantly reduced RR in intermediate and high-risk patients (Table 2B).

Table 2 Recurrence rates with GQWL-TURBT vs. GQPDD-TURBT

A. All patients

	1 year			3 years		
	RR-1y (%)	OR (95% CI)	p value	RR-3y (%)	OR (95% CI)	p value
GQ-WL	56/144 (38.9)	0.43 (0.26–0.71)	<0.001	72/135 (53.3)	0.56 (0.35–0.90)	0.02
GQ-PDD	37/172 (21.5)			57/146 (39.0)		
Low risk						
GQ-WL	15/58 (25.9)	0.11 (0.02–0.54)	0.006	20/56 (35.7)	0.48 (0.19–1.19)	0.11
GQ-PDD	2/51 (3.9)			9/43 (20.9)		
Intermediate risk						
GQ-WL	18/44 (40.9)	0.48 (0.21–1.09)	0.08	23/42 (54.8)	0.61 (0.27–1.38)	0.24
GQ-PDD	16/64 (25.0)			23/54 (42.6)		
High risk						
GQ-WL	24/39 (61.5)	0.34 (0.15–0.79)	0.01	28/35 (80.0)	0.27 (0.10–0.74)	0.01
GQ-PDD	20/57 (35.1)			25/48 (52.1)		

B. Individual subject-matched pair analysis recurrence rate at last follow-up

RR-3y	WL (%)	PDD (%)	OR (95% CI)	p value*
All	59/118 (50.0)	29/118 (24.6)	0.33 (0.19–0.57)	<0.001
Low	14/47 (29.8)	7/47 (14.9)	0.41 (0.15–1.14)	0.14
Intermediate	23/39 (59.0)	10/39 (25.6)	0.24 (0.09–0.63)	0.006
High	22/32 (68.8)	12/32 (37.5)	0.27 (0.10–0.77)	0.02

A. 1- and 3-year recurrence rates in all study patients (excluding those who were censored before the end point). B. Individual subject matched-pair analysis of 3-year recurrence rates overall and stratified by risk group. * McNemar's paired test. Subjects matched on age (± 10 years), tumour grade (exact), tumour stage (exact), EAU 2002 risk group (which provides relevant matching for multifocality and tumour size) (exact), length of follow-up (<6 months, 6 months to 1 year, 1–3 years and ≥ 3 years). 72% of patients in the matched pair analysis had ≥ 3 years follow-up, 89.8% had >1 year follow-up all had at least one check cystoscopy

Progression

There was less new high-grade disease or MIBC discovered later in initially low/intermediate-risk disease with PDD compared with WL [PDD: 8/146 (5.5%) vs. WL: 18/135 (13.3%) OR 0.38 (0.16–0.90) $p = 0.03$]. The progression rate to MIBC was 9/135 (6.7%) for WL and 9/146 (6.2%) for PDD. MIBC was found at a median of 19.4 (9.2–27.0) months follow-up.

Discussion

This study is unique and adds significant data to the current literature. It is the only prospective controlled study, to our knowledge, that examines NMIBC recurrence rates with routine PDD use.

This study benefits from high-quality prospective data collection and the ability to compare resections that are matched for “quality criteria” providing control of confounders potentially inherent in the non-randomised design.

The question of long-term impact of PDD on recurrence rates, particularly in high-risk patients has remained

unanswered for some time [19]. PDD is considered as a tool which improves operative quality. Operative quality theoretically impacts short-term recurrence. In this study (despite otherwise identical operative quality), in high-risk GQ-PDD, 48% went 3 years with no recurrence compared with 20% of high-risk GQ-WL.

These findings are at odds with the only other large long-term study of patients receiving HAL-PDD where no difference was shown between WL and PDD. The crucial difference between that study and this is that 60% of patients in that study were *recurrent* bladder cancers (average bladder cancer history of 4.4–5 years) [2, 3]. It is possible that the impact of PDD on long-term recurrence rates is only possible if applied at first presentation. Then a truly complete resection identifying all tumours followed by Mitomycin C installation—may result in durable recurrence-free rates. This hypothesis is supported by the significantly greater number of tumours identified in the PDD group here. Although only documented, fully mapped and fully resected disease was included in this study, it is likely that there were more unseen tumours in the WL group resulting in higher recurrence rate. In contrast to other studies [7, 20], our data does not suggest that additional PDD-identified tumours

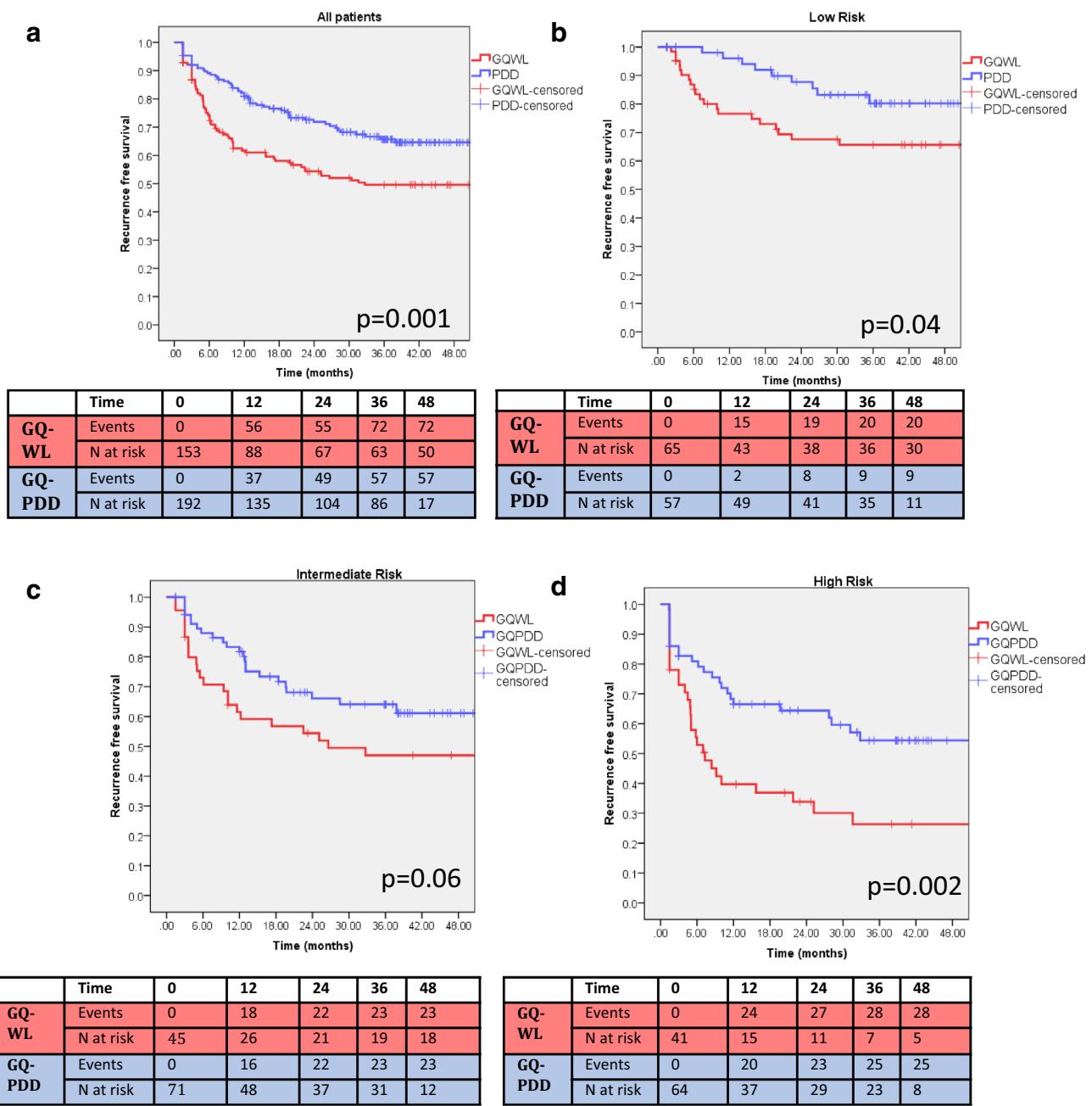


Fig. 1 **a** Kaplan–Meir graphs of recurrence-free survival in all patients for GQWL vs. GQPDD ($p = 0.001$, log-rank test). **b–d** Kaplan–Meir graphs of recurrence-free survival stratified by risk group

were CIS (no significant difference in CIS rates in WL vs. PDD). The reason for this is not clear but may be due to the select “good quality” resection population included in this study and relatively low CIS rates.

We accept that we do not offer within-patient analysis of findings with and without PDD. However, we feel that the difference in multifocality between WL and PDD is unlikely to be due to a true difference in multifocality

but rather due to increased tumour detection by PDD. Increased tumour detection and correct staging may result in more appropriate subsequent management at the time of the index TURBT [21]. The difference in multifocality between the groups is thus not a confounder but a benefit of PDD and identification of this difference is a benefit of the study design (which may not be possible in the trial setting).

Table 3 Binary logistical and Cox regression of GQWL vs. GQPDD and operating surgeon

Variable	Binary logistical regression for snapshot 3-year recurrence rate		Cox regression for disease-free survival	
	p value	Multi-variate odds ratio (95% CI)	p value	Multi-variate hazard ratio (95% CI)
WL (ref)		1.00		1.00
PDD	0.001	0.44 (0.27–0.71)	0.003	0.57 (0.39–0.83)
Surgeon A (ref)		1.00		1.00
Surgeon B	0.94	0.98 (0.52–1.85)	0.86	1.05 (0.64–1.71)
Surgeons (other)	0.83	1.08 (0.52–2.24)	0.84	1.05 (0.63–1.75)

Risk group was not included as a variable in regression since there was more intermediate and high-risk disease identified in the PDD group thus would adjust regression in favour of PDD

Due to local BCG policy (“[Patients and methods](#)” section), our BCG usage appears low [22] but our overall BCG rates (after residual disease or recurrence) are higher (not reported). Only the immediate pre-recurrence BCG reported is relevant to the outcome of this study (recurrence rate). Furthermore, both cohorts were managed with identical policy for BCG instillations.

We accept that this is not a randomized trial. We cannot conclusively determine PDD per-se resulted in the improvements observed. It is possible that PDD acted as a learning tool—this itself may be a benefit. We also accept that the sequential temporal nature of these two cohorts is a limitation to our study. We went to great lengths to control for this: sequential patients from each cohort were all included, patients from each cohort that received the highest possible standard of resection could be identified and compared, and further matched one to one based on demographic, risk group, and pathological criteria.

Finally, to be able to recommend routine adoption of PDD for all new tumours, cost–benefit analysis will be required.

Conclusion

The adoption of PDD for all new bladder tumour resections in routine practice appears to be associated with significantly reduced recurrence rates at 3 years in our “real-life” experience, particularly in high-risk disease.

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Author contributions KMG, PM project development, data collection, data analysis, manuscript writing. KG, HL, SS data collection. CHA data collection, project development. RD project development, data collection.

Compliance with ethical standards

Conflict of interest KMG has received conference travel and accommodation contributions from GE Healthcare and IPSEN on one occasion each. PM has been a consultant for GE Healthcare and IPSEN in relation to HEXVIX. All other authors have nothing to disclose.

Ethical approval statement This study was registered as an audit. All data collection and storage were approved by the Caldicott data guardian.

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Attachment 14

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

Research Report

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

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Abstract.

Introduction: Although there is evidence that hexaminolevulinate (HAL)-based transurethral bladder tumor resection (TURBT) improves the detection of Ta-T1 non-muscle-invasive bladder cancer (NMIBC) as well as carcinoma *in situ* there is uncertainty about its beneficial effects on progression.

Material and Methods: A systematic literature search was conducted according to the PRISMA statement to identify studies reporting on HAL- vs. white-light (WL-) based TUR-BT in non-muscle invasive bladder cancer between 2000 and 2016. A two-stage selection process was utilized to determine eligible studies. Of a total of 294 studies, 5 (4 randomized and one retrospective) were considered for final analysis. The primary objective was the rate of progression.

Results: The median follow-up for patients treated with HAL- and WL-TURBT was 27.6 (1–55.1) and 28.9 (1–53) months, respectively. Of a total of 1301 patients, 644 underwent HAL- and 657 WL-based TURBT. Progression was reported in 44 of 644 patients (6.8%) with HAL- and 70 of 657 patients (10.7%) with WL-TURBT, respectively (median odds ratio: 1.64, 1.10–2.45 for HAL vs. WL; $p=0.01$). Data on progression-free survival was reported in a single study with a trend towards improved survival for patients treated with HAL-TURBT ($p=0.05$).

Conclusions: In this meta-analysis the rate of progression was significantly lower in patients treated with HAL- vs. WL-based TURBT. These results support the initiation of randomized trials on HAL with progression as primary endpoint.

Keywords: Aminolevulinate, bladder cancer, fluorescence, hexaminolevulinate, photodynamic diagnosis, progression, and transurethral resection

INTRODUCTION

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Hexaminolevulinic acid (HAL) is a hexyl ester of 5-aminolevulinic acid (ALA) and has been approved for photodynamic diagnosis (PDD) of bladder tumors [1]. Following intravesical administration, HAL acts

as precursor molecule which is taken up by urothelial cells and incorporated into heme biosynthesis resulting in intracellular accumulation of photoactive porphyrines especially within neoplastic urothelial cells [2]. When these enriched cells are exposed to blue light they emit red light of characteristic wavelength that can be visualized with the use of specific filters during transurethral bladder tumor resection (TUR-BT).

Based on the results of randomized trials HAL-based TUR-BT has been implemented into clinical practice as the standard for fluorescence-based TUR-BT [1]. In an updated meta-analysis of raw data, an increase in the detection rate of Ta-T1 lesions by 20% and carcinoma *in situ* (CIS) by 40% was reported [3].

Given the improved detectability of CIS with HAL [3], there is a rationale for hypothesizing that HAL-based TURBT may also impact on progression in non-muscle invasive bladder cancer (NMIBC). Prior meta-analyses aimed to address possible effects of HAL-TURBT on progression but did not report on a beneficial impact. Taking a closer look on these meta-analyses it has to be assumed that their results could have been biased by the duration of follow-up and definition of progression of the included studies [4–6].

Given these possible limitations we aimed to systematically re-review the current body of evidence with regard to updated data reporting on the effects of HAL-based TUR-BT on progression in patients with NMIBC.

MATERIAL AND METHODS

Search strategy

A systematic literature search was conducted according to the PRISMA statement [7] to identify studies reporting on progression after HAL- and WL-based TUR-BT for NMIBC between 2000 and 2016. The Pubmed database was searched along with a free-text hand search using one or several combinations of the following items: aminolevulinic acid, bladder cancer, fluorescence, hexaminolevulinate, photodynamic diagnosis, progression, and transurethral resection. The selection process was conducted at two stages; the first stage was performed via initial screening of the title and abstract to identify eligible publications. The second stage was done via full-text reading including a manual search of publications in journals not listed in PubMed to further avoid missing any eligible study. For this systematic review, we

excluded (I) non-English articles, (II) non-original articles (i.e. review articles with or without systematic review or meta-analysis), (III) editorials or case reports (IV) studies on ALA-based TURBT and (V) repeated publications on the same cohort to avoid publication bias. After completion of the systematic search, a risk of bias assessment was conducted according to the Cochrane handbook for systematic reviews of randomized studies [8] and Newcastle-Ottawa scale for retrospective studies [9].

Data extraction

Data was initially extracted independently by both authors. Then double check was performed. The following variables were extracted: number of patients, early intravesical instillation, adjuvant treatment, duration of follow-up, follow-up strategy, modality of TURBT (HAL- vs. WL-) and rate of progression.

Outcome measures

The rate of progression was the primary objective of this study. Analysis of progression-free survival (PFS) was not conducted as only one study reported on data of PFS [10]. Progression was defined according to the definitions of the respective publications as outlined in Table 1. One study defined progression as stage T2 disease and another according to the criteria of the International Bladder Cancer Group (IBCG) [11]. Some studies did not explicitly define progression in their publication.

Statistical analysis

Review Manager (RevMan) software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen) was utilized for this meta-analysis. Fixed and random effect models were used according to the I^2 value of heterogeneity; for $I^2 \leq 50\%$, a fixed effect model was applied, whereas for $I^2 > 50\%$ a random model was used. A p -value < 0.05 was considered as level of significant difference.

RESULTS

A CONSORT diagram for the selection process of included studies is provided in Fig. 1. The initial online search resulted in the identification of 294 publications out of which 263 were excluded after initial assessment. Of the 31 publications subjected to full text assessment, 26 were excluded after the second

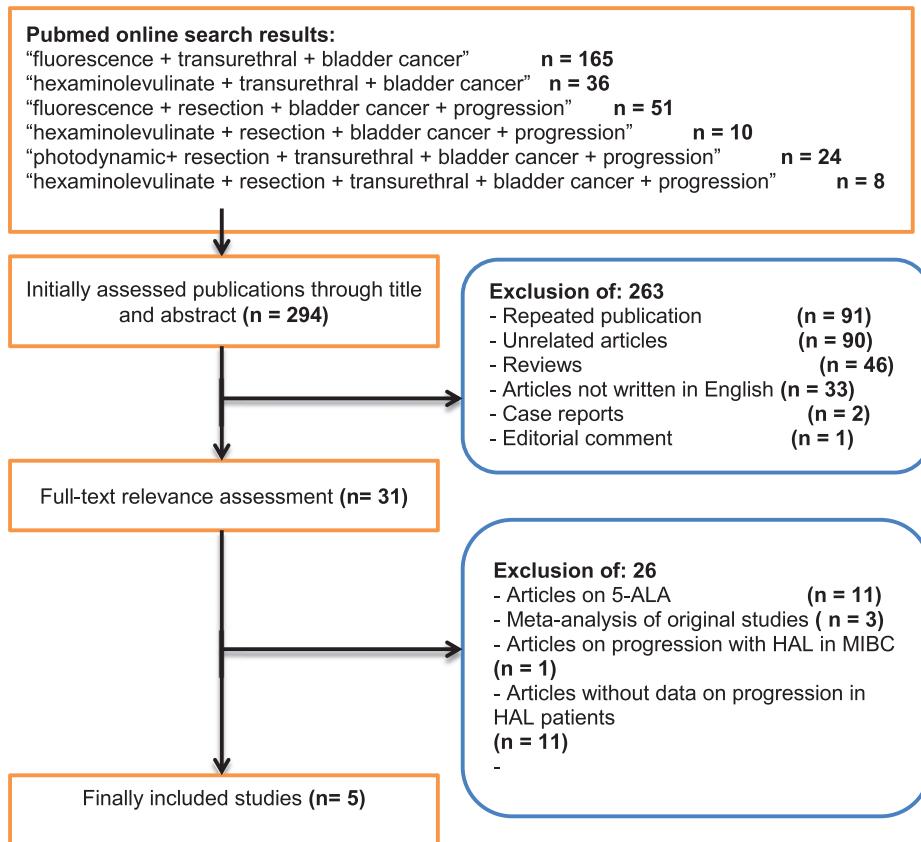


Fig. 1. A CONSORT diagram which outlines the selection process of the included studies.

stage. Finally, 5 studies including 1301 patients were considered for final analysis [10, 12–15]. Of these, 4 were randomized trials [10, 13–15] and one a retrospective study [12]. Table 1 summarizes the basic data of the included studies. A risk of bias assessment for the included studies is given in Tables 2 and 3. Overall, the risk of bias was low to moderate for the majority of randomized studies and low for the one retrospective study.

The median follow-up (total range) of patients treated with HAL- and WL-TURBT was 27.6 (1–55.1) and 28.9 (1–53) months, respectively. Of the 1301 patients, 644 underwent HAL-TURBT (49.5%) and 657 WL-based TURBT (50.5%). Progression was found in 44 of the 644 patients (6.8%) with HAL-TURBT and 70 of the 657 patients (10.7%) with WL-TURBT, respectively (median odds ratio: 1.64, 1.10–2.45 for HAL vs. WL; $p = 0.01$). Figure 2 provides the corresponding forest and funnel plots. Data on PFS was reported in a single study with a trend towards improved PFS for patients treated with HAL vs. WL-based TURBT ($p = 0.05$).

DISCUSSION

In NMIBC, randomized studies have shown that HAL-TUR-BT facilitates the detection of tumor-suspicious areas in the bladder that might be overseen during conventional resection under WL [15]. In these trials, intravesical recurrence-free survival was used as primary endpoint and was proven to be significantly longer for patients treated with HAL-guided TURBT. Despite a significantly improved detection rate of CIS these studies could not confirm an impact of HAL-TUR-BT on progression [16]. One reason for this finding is that these studies were not adequately powered to either confirm or disprove an impact of HAL-TURBT on progression.

The results of this meta-analysis suggest for the first time that the performance of HAL-based TURBT confers a prognostic benefit to patients with NMIBC in terms of progression. Four of the five included studies were conducted as clinical trials [10, 13–15]. In these studies a total of 1024 patients were randomized to either HAL or WL-TURBT. This relates to

Table 1
Studies comparing progression rates in patients treated with HAL- vs. WL- TURBT (Leg: CYT: cystoscopy; CYT: urinary cytology, EAU GL: adjuvant therapy as indicated in the guidelines of the European Association of Urology; F/U: follow-up; HAL: hexaminolevulinate; IBCG: International Bladder Cancer Group; MMC: mitomycin-C; mo.: months; N: number of patients; n.s.r.: not separately reported; perf.: performed; q3m: every 3 months; q6m: every 6 months; RETRO: retrospective; RANDO: randomized; SCFP: standard clinical practice; WL: white-light; yr: year)

Author	Study design	N	Median F/U WL [mo.]	Median F/U [mo.] HAL	Follow-up strategy	Early instillation	Adjuvant therapy	Definition of progression	Progression WL (in %)	Progression HAL (in %)
Burger et al. [11]	RETRO	277	23	21 (1–36)	CYS+CYT q3 m for 2 yrs, q6 m thereafter	n.s.r.	EAU GL	stage T2	4/142 (2.8)	5/135 (3.7)
Dragoescu et al. [12]	RANDO	44	n.s.r.	n.s.r.	CYS q3 m in isty	Perf.	EAU GL	n.s.r.	2/22 (9.1)	1/22 (4.6)
Geavlete et al. [13]	RANDO	362	n.s.r.	n.s.r.	CYS+CYT q3 m for 2 yrs.	Perf.	EAU GL	n.s.r.	13/181 (7)	7/181 (4)
Kamat et al. [11]	RANDO	516	53	55.1	CYS after 3, 6 and 9 mo.	n.s.r.	BCG in T1/CIS+SCP	IBCG	46/261 (17.6)	31/255 (12.2)
Karaolides et al. [14]	RANDO	102	14	17.5	CYS at 3 mo., EAU GL	Perf.	EAU GL	n.s.r.	5/51 (9.8)	0/51 (0)
Total		1301	28.9	27.6					70/657 (10.7)	44/644 (6.8)

Table 2

Risk of bias assessment according to the Cochrane methods of bias assessment for randomized studies included in this meta-analysis (Leg.: GREEN: low risk of bias; YELLOW: unclear risk of bias; RED: high risk of bias)

Study	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of outcomes (Detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Draogescu et al.	?	?	?	+	+	+
Geavlete et al.	+	?	+	+	+	+
Kamat et al.	+	+	?	+	?	+
Karaolides et al.	-	-	?	?	+	+

79% of the total number of included patients in this meta-analysis. To avoid any publication bias we only considered the most updated data on the same cohort [10, 17].

Generally, the definition of progression in NMIBC is crucial as it indicates worsening of the disease. However, until now, there is no unequivocal definition of progression [11]. In the study by Burger et al. progression was defined as stage T2 disease [12]. In three of the five included studies no definition of progression was provided in the respective full-text publications [13–15]. Of note, these three studies did not report on a beneficial impact of HAL-TURBT on progression. The largest and most recent publication re-analyzed the dataset of a phase III randomized trial on HAL vs. WL-TURBT with regard to progression [10] using a new definition provided by the International Bladder Cancer Group (IBCG) [11]. In detail, any increase in tumor grade from low to high or stage (from Ta to CIS/T1, CIS to T1, \geq T2 stage, or N+ or M+) is herein defined as progression. This definition takes several biological considerations on bladder cancer into account. Tumor cells that penetrate the basement membrane are capable of invading lymphatic and blood vessels and causing clinical progression [1]. Likewise, an increase in the tumor grade or presence of CIS clearly indicates a higher propensity of tumor cells to invade the submucosa [1]. On this occasion, it should be also noted that this definition does not comprehensively reflect urothelial carcinoma biology as, i.e. it does not consider worsening of the disease in patients with stage T1 NMIBC who exhibit lymphovascular invasion in the

resection specimen during follow-up [18]. Notwithstanding, by using this new definition, progression was reported in 31 (12.2%) HAL-patients and 46 (17.6%) WL-patients ($p=0.085$) [10]. By contrast, in the initial publication in which stage \geq T2 disease was used for definition of progression, less patients (8 (3.1%) patients in the HAL- and 16 (6.3%) in the WL-group) were considered to have experienced progression [17]. Nonetheless, it has to be borne in mind that this new analysis did not provide an update on the follow-up of patients [10]. Thus, the observed differences in progression might have become even more pronounced with longer follow-up. While in all five studies the reported rates of progression were numerically lower for patients treated with HAL-guided TURBT, the median periods of follow-up differed extremely across studies ranging between 14 to 55 months [10, 12–15]. Of note, the largest study which randomized 516 patients to HAL and WL-TURBT reported on progression rates after a long-term follow-up of 53–55 months [10].

Taken the results of this meta-analysis, one may hypothesize that a delay of progression may also result in a prognostic benefit of those who would need to undergo radical surgery as curative treatment. Radical cystectomy (RC) represents the mainstay of treatment of muscle-invasive bladder cancer [5] or NMIBC at high risk of progression [19, 20]. Pathological tumor and nodal stage as well as the surgical margin status (STSMs) represent well-established histopathological risk factors for recurrence-free (RFS), cancer-specific (CSS) and overall survival (OS) [19]. Whether photodynamic diagnosis-based

Table 3
Risk of bias assessment according to the Newcastle-Ottawa scale for the non-randomized study [9] included in this meta-analysis (Leg.: scores ≥ 7 -9, 4-6, <4 are considered as low, intermediate, and high risk, respectively); * = 1 point

Study	Selection			Comparability of cohorts			Assessment	Outcome length	Adequate follow-up	Adequacy of follow-up	Overall
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome present at start	*	*					
Burger et al. REF	*	*	*	*	*	*	*	*	*	*	7/9

TUR-BT exerts any impact on the long-term oncological outcomes of patients with bladder cancer who will need to undergo RC during their course of disease remains elusive.

In this regard, a single-center series of 224 consecutive patients who were treated with RC with standard bilateral pelvic lymph node dissection for bladder cancer between 2002 and 2010 retrospectively investigated outcomes with regard to the modality of TURBT prior to RC (HAL vs. ALA vs. WL) [21]. After a median follow-up of 29 months, the median 3-year-RFS, CSS and OS survival rates were significantly longer for patients who underwent HAL-TURBT compared to WL or ALA-TURBT prior to RC. In multivariable analysis, histopathological tumor and nodal stage, soft-tissue margin status and the modality of TUR-BT (HAL vs. non-HAL) were independent predictors for RFS, CSS and OS. In conclusion, these results suggest that HAL-based TURBT may provide also a beneficial impact on survival even for those patients who will need to undergo RC during the course of their disease.

This meta-analysis has limitations which need to be taken into account in the interpretation of the results. First, we were not able to conduct a meta-analysis on PFS as only one study reported on hazard ratios [10]. The heterogeneous definition of progression and differences in duration of follow-up across studies may have impacted on our results. A selection bias might also exist for patients who were treated with WL-based TUR-BT only as they might have undergone a more intense follow-up by the treating urologist. However, based on the assessment of the risk of bias applied in this study the risk is rather low which supports our interpretation of the results. Differences in the utilization of adjuvant instillation regimens may have also influenced outcomes. Yet, in the largest study included in this meta-analysis, similar rates of intravesical instillation therapy were reported between both groups (45% for HAL, 46% for WL) [17]. Our meta-analysis differs from previous ones as follows: one study [16] which was included in the most recent meta-analysis by Lee et al. [4] reported on early data on progression with 5 and 7 patients progressing to T2 stage disease in the WL- and HAL-group, respectively. Yet, a trend towards an increased rate of “worrisome” cancers (Tis/T1) was noted in that study ($p=0.17$). By contrast, an updated report from the same cohort published in 2012 reported on a longer follow-up period with 16 and 8 patients in the WL- and HAL group exhibiting muscle-invasive disease, respectively ($p=0.066$).

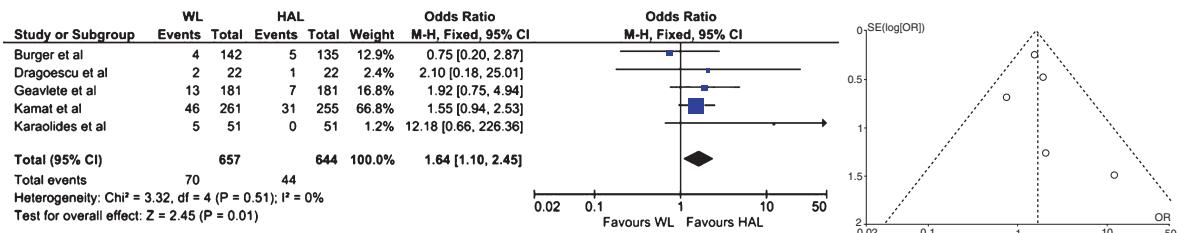


Fig. 2. Meta-analysis of the included studies with regard to progression as illustrated by forest and funnel plots (Leg.: ALA: 5-aminolevulinic acid; HAL: hexaminolevulinate; WL: white-light, CI: confidence interval).

A recent update of the same study cohort reanalyzed outcomes based on a new definition of progression according to the IBCG criteria. A trend towards reduced risk of progression was noted ($p=0.085$). The meta-analysis by Yuan et al. [6] included the same studies for analysis of progression as the study by Lee et al. [4]. In the meta-analysis by Shen et al. data on progression from HAL and ALA-studies were analyzed in one group [5]. Of the three publications which were considered for that meta-analysis two were exclusively based on ALA [22, 23].

In summary, this is the first meta-analysis which shows a significant beneficial impact of HAL-TURBT on progression in NMIBC. By contrast to recent recommendations for trial designs in NMIBC [24] the results of this study support the performance of randomized trials with progression as primary endpoint to improve our understanding of the therapeutic potential of HAL-guided TURBT in NMIBC.

CONCLUSIONS

This meta-analysis supports the assumption that the detection and resection of NMIBC with HAL-guided TURBT reduces the risk of progression. Therefore, patients should receive hexaminolevulinate- rather than white-light-guided TURBT at their first resection as this might allow more patients at risk of progression to be treated timely and adequately.

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DISCLOSURES

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Attachment 15

The Impact of Blue Light Cystoscopy with Hexaminolevulinate (HAL) on
Progression of Bladder Cancer

Research Report

The Impact of Blue Light Cystoscopy with Hexaminolevulinate (HAL) on Progression of Bladder Cancer – A New Analysis

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Abstract.

Background: The International Bladder Cancer Group (IBCG) recently proposed a new definition of disease progression in non-muscle invasive bladder cancer (NMIBC), including change in T-stage, change to T2 or higher or change from low to high grade.

Objective: To establish whether blue light cystoscopy with hexaminolevulinate (HAL) impacts the rate of progression and time to progression using the revised definition.

Methods: An earlier long-term follow-up of a controlled Phase III study reported outcomes following blue light cystoscopy with HAL (255 patients) or white light (WL) cystoscopy (261 patients) in NMIBC patients. The data was re-analysed according to the new definition.

Results: In the original analysis, after 4.5 years (median), eight HAL and 16 WL patients were deemed to have progressed (transition from NMIBC to muscle invasive bladder cancer, (T2-4)).

According to the new definition, additional patients in both groups were found to have progressed: 31 (12.2%) HAL vs 46 (17.6%) WL ($p = 0.085$) with four (1.6%) HAL and 11 (4.2%) WL patients progressing from Ta to CIS. Time to progression was longer in the HAL group ($p = 0.05$).

Conclusions: Applying the new IBCG definition there was a trend towards a lower rate of progression in HAL patients, particularly in those progressing from Ta to CIS. Time to progression was significantly prolonged. This suggests that patients should receive blue light cystoscopy with HAL rather than WL at resection. Adoption of the new definition could allow more patients at risk of progression to be treated appropriately earlier.

Keywords: Hexaminolevulinate, bladder cancer, progression, NMIBC, blue light cystoscopy

INTRODUCTION

Progression is one of the most important clinical outcomes in non-muscle invasive bladder cancer (NMIBC) as it indicates a worsening of disease.

Despite this, the definition of “progression” is neither precise nor consistent and until now, there has been no standard definition which can be determined by reproducible and reliable procedures.

As a result, previous studies have employed different definitions for disease progression, or have failed to specify any method of defining advancing disease. An increase in stage is the most commonly used definition, but this fails to include other important

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indicators of advancing disease such as progression to invasion of the *lamina propria* or increases in grade. Prevention of progression is a major goal in the treatment of NMIBC but a standardized definition is required for comparisons to be meaningful.

A recent publication by the International Bladder Cancer Group (IBCG) highlighted this issue and the need for a new standard definition of disease progression in NMIBC to more accurately determine patient prognosis and to provide a better comparison of treatment options [1].

The new definition proposed by the IBCG includes any one of: an increase in T stage from Ta to CIS or T1, CIS to T1 (indicating invasion of the *lamina propria*), development of T2 or greater, lymph node disease (N+), distant metastasis (M1) or an increase in grade from low to high.

In the current analysis, the new definition of progression was applied to data from a previous long-term follow-up study of blue light cystoscopy with HAL in patients with NMIBC bladder tumors [2]. In the original analysis the definition of progression was from non-muscle invasive to muscle invasive bladder cancer. The original analysis showed that the impact of improved tumor detection and resection using blue light cystoscopy with HAL resulted in a trend in progression rates in favor of the patients undergoing blue light cystoscopy with HAL. The current re-analysis applied the new IBCG definition to see whether the progression rate would be reduced and time to progression would be prolonged using blue light cystoscopy with HAL.

MATERIALS AND METHODS

An earlier controlled, randomized, Phase III multi-center study investigated the impact of improved detection of NMIBC using blue light cystoscopy with HAL on early recurrence rates [3].

In the Phase III study, all patients underwent WL cystoscopy followed by TURB if indicated. Patients in the HAL group underwent additional inspection with HAL and inspection under blue light before and after TURB, where indicated. Follow up cystoscopies were carried out with white light at 3, 6 and 9 months or until recurrence. After completion of the study patients were treated according to standard clinical practice.

An extension to the Phase III study was carried out extending the follow up to approximately 4.5 years [2]. The extension study collected data retrospectively and time from inclusion to follow-up was not pre-specified. The study extension obtained additional follow up information for 255 HAL (94%) and 261 WL (93%) patients with a median follow up of 55.1 and 53.0 months respectively.

The data from the extension study have now been re-analysed at time points of 1, 3 and 4.5 years using the new definition for progression proposed by the IBCG [1].

Fischer's exact test was used to test differences in rate of progression and Kaplan Meier estimates to test differences in time to progression.

RESULTS

Using the new IBCG definition, 31 (12.2%) HAL and 46 (17.6%) WL patients had progressed by 4.5 years ($p=0.085$), see Table 1. This trend was particularly pronounced in patients progressing from Ta to CIS: four (1.6%) in the HAL group compared to 11 (4.2%) in the WL group.

The numbers progressing in year one were 15 (5.9%) in the HAL group and 23 (8.8%) in the WL group; while by year three the numbers were 26 (10.2%) and 38 (14.6%) respectively.

Time to progression was significantly longer in the HAL group ($p=0.05$), see Fig. 1.

Table 1
Progression rate at 4.5 years (ITT recurrence population)

	1 year		3 years		4.5 years	
	HAL (n = 255)	WL (n = 261)	HAL (n = 255)	WL (n = 261)	HAL (n = 255)	WL (n = 261)
Number (%) of patients with progression	15 (5.9) [‡]	23 (8.8)	26 (10.2) [†]	38 (14.6)	31 (12.2)*	46 (17.6)
Ta to CIS	2 (0.8)	5 (1.6)	2 (0.8)	10 (3.8)	4 (1.6)	11 (4.2)
Ta to T1	4 (1.6)	7 (2.7)	9 (3.5)	8 (3.0)	10 (3.9)	9 (3.4)
Ta to \geq T2	2 (0.8)	3 (1.2)	4 (1.6)	5 (1.9)	4 (1.6)	8 (3.1)
CIS to T1	2 (0.8)	1 (0.4)	3 (1.2)	2 (0.8)	3 (1.2)	2 (0.8)
T1 to \geq T2	3 (1.2)	3 (1.1)	3 (1.2)	5 (1.9)	3 (1.2)	5 (1.9)
Grade 1 to Grade 3	0	2 (0.8)	3 (1.2)	5 (1.9)	4 (1.6)	7 (2.7)
Death due to bladder cancer	2 (0.8)	2 (0.8)	2 (0.8)	3 (1.1)	3 (1.2)	4 (1.5)

[‡] p -value = 0.239 (Fisher's exact test). [†] p -value = 0.143 (Fisher's exact test). * p -value = 0.085 (Fisher's exact test).

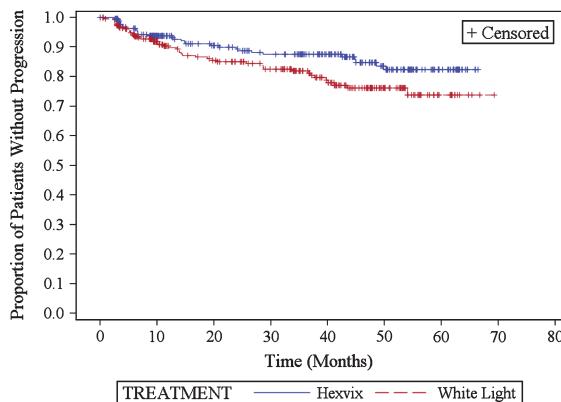


Fig. 1. Kaplan Meier plot for time to progression (ITT recurrence population).

With reference to the original analysis of the follow-up study data, there was a trend ($p=0.066$) that fewer HAL patients progressed to muscle-invasive disease at first recurrence (8 vs 16, see Table 2), a total of 24 patients. The definition of progression was transition from non-muscle invasive to muscle invasive bladder cancer, (T2-4).

Using the revised definition proposed by the IBCG, it can be seen that a number of patients in both treatment groups who were previously classified as recurring without progression had in fact progressed to a higher grade, or to CIS, a total of 77 patients (Table 2, $p=0.085$).

DISCUSSION

Improved detection of NMIBC tumors with HAL compared to WL cystoscopy has already been shown to lead to a lower rate of recurrence and a longer recurrence-free interval [2]. Using a new definition for disease progression in NMIBC, which aims to identify patients with high risk of developing muscle invasion at an earlier stage, we found a shorter time to progression and a trend towards a higher rate

of progression in WL cystoscopy patients compared to HAL, confirming the importance of the ability of HAL to improve detection and removal of tumors.

In addition to the removal of areas of suspicious tissue, improved identification, particularly of CIS, may lead to adjustment of the treatment strategy with a subsequent impact on progression [4]. In the original study, participants with high grade bladder cancer, T1 or CIS were to receive an induction course of BCG followed by three weekly maintenance instillations at 3 and 6 months. Following completion of the study, patients were to be managed according to standard clinical practice.

Improved progression rates might be caused by differences in use of intravesical therapy in the period following initial treatment, as greater use of intravesical therapy could have an impact on progression. In the original study BCG was administered to 50 (19%) participants in the HAL group and 55 (20%) in the WL group [3]. When the study extension data is included, 123 (45%) of the HAL group and 130 (46%) of the WL group received some form of intravesical therapy [2]. As the rates of intravesical therapy were similar in the two groups, this can be ruled out as the explanation for improved progression rates in the HAL group.

The definition of progression in bladder cancer is extremely important as it indicates advancing disease. One of the most commonly used definitions of progression in NMIBC is an increase in tumor stage to muscle invasive disease (stage T2 or greater) which recognizes the fact that prognosis and treatment of patients whose tumors have invaded muscle are very different to those in patients who have NMIBC.

However, there are other indicators of advancing disease, such as invasion of the basement membrane, that signal the capability of the tumor to metastasise. These changes are rarely or inconsistently used to indicate progression.

High grade Ta lesions carry a high risk of invasion into the *lamina propria* and beyond, with some studies suggesting that up to 40% of patients with Ta

Table 2
Comparison of progression rates at 4.5 years (ITT recurrence population)

	4.5 years, re-analysis New definition of progression	4.5 years original study data Progression defined as T2 – T4		
	HAL (n = 255)	WL (n = 261)	HAL (n = 255)	WL (n = 261)
Number (%) of patients with recurrence	158 (62)	178 (68)	158 (62)	178 (68)
Number (%) recurrence without progression	127 (50)	132 (50.4)	150 (59)	162 (62)
Number (%) recurrence with progression	31 (12.2)	46 (17.6)	8 (3)*	16 (6)

* p -value = 0.066 (Fisher's exact test).

tumors can experience invasion of the *lamina propria*, and up to 25% can experience muscle invasive disease [5–8]. As progression to T1 disease clearly indicates advancement of NMIBC the IBCG recommended that tumor changes from Ta to T1 be included in the definition of progression. In the original study upon which this analysis was based, there were 47 patients (16%) in whom at least one Ta or T1 tumor was seen with blue light cystoscopy but was missed during inspection under white light [3]. In 43% of these patients the tumors that were detected with HAL only were high grade or T1 [3].

There is good evidence that grade is a better prognostic indicator of progression and mortality than recurrence [8–10] with a noticeable effect on overall survival [11]. Based on this evidence the IBCG recommended that grade progression be included in a standard definition of progression. Likewise, the development of CIS in a patient with low grade disease can be interpreted as a clear indication of grade progression [12].

The presence of CIS is of particular concern as detection rates using visual inspection are quite low. In this respect, it has been reported that detection of CIS can be improved with the addition of blue light cystoscopy to standard WL cystoscopy [3, 13–20]. In the original study, 13/41 (32%) patients with CIS had CIS detected only with blue light and not WL ($p < 0.0001$) [3]. The significant increase in time to progression with blue light cystoscopy is clearly important and is probably due to better detection and resection at an early stage.

In the re-analysis reported here, using the new definitions, a greater number of patients at risk of progression to muscle invasive disease were identified: a total of 77 compared to 24 in the original analysis. It is clearly of great clinical importance to detect these changes at an early stage: finding changes early enables treatment decisions to be made that can minimize the risk of tumors progressing to full-scale muscle-invasion.

It is also of note that in this study more patients progressed to CIS in the WL than in the HAL group. Although the original study was not powered to show this difference, there is an indication of a trend even in this relatively small study.

In a recently published study, a retrospective analysis was carried out on 224 patients undergoing radical cystectomy (RC) for bladder cancer. It was found that patients who had previously received HAL TURB had significantly better 3-year recurrence-free survival (77.8% vs 52.4%, $p = 0.002$), cancer-specific

survival (83.9% vs 59.7%, $p = 0.023$) and overall survival (74.0% vs 56.5%, $p = 0.037$) following RC than patients who had previously undergone white light TURB [21]. Patients who had received blue light TURB (with either HAL or 5-ALA) also received a higher number of TURBs and re-resections before RC.

There have been reports of the use of HAL cystoscopy which have found no benefit in terms of progression through the use of this technique. A study by Geavlete et al. (2012) found no significant difference in progression-free survival but did not report the parameters used to define progression [22]. Also, follow up in this study was quite short at one and two years.

As was noted above, studies have variously defined progression as invasion of the detrusor muscle, progression to a higher T stage, or presence of CIS making comparisons difficult. We suggest that re-analysis of the data using the definition of progression proposed by the IBCG, may produce different conclusions.

Recurrence of high grade T1 disease or CIS following complete resection and effective intravesical chemotherapy is associated with an increased risk of progression that can be reduced by radical cystectomy. Therefore, it is common practice to perform cystectomy before progression to muscle invasion occurs. A more precise method for defining progression may help to avoid unnecessary cystectomies.

These findings highlight the importance of using a definition for progression that is sensitive to early changes that indicate advancing disease and a higher risk for progression. They also highlight the importance of proper detection and resection of tumors as early as possible in the disease course, the role that inspection with blue light can have in improving the detection and removal of early tumors and CIS, and the impact of this on rate of progression and time to progression.

CONCLUSIONS

Improved detection of NMIBC tumors with HAL has already been shown to affect rate of progression. A new definition by the IBCG includes indicators of advancing disease with the aim of identifying progression at an earlier stage. Applying the new definition to data from an earlier study, more patients at risk were identified in both groups, with a trend towards a lower rate of progression in HAL patients,

particularly in those patients progressing from Ta to CIS. Also, time to progression was significantly prolonged. This suggests that patients should receive HAL rather than WL at first resection. Adoption of this broader definition could allow more patients with indicators of advancing disease, and at risk of progression to be treated appropriately at an earlier stage.

SOURCE OF FUNDING

Photocure Inc, Princeton, NJ provided funding for the statistical analysis.

APPROVALS

Approval of the study by an internal review board was not required.

CLINICAL TRIAL NUMBER

No registration was required for the re-analysis. The clinical trial number of the original study was NCT00233402 (www.clinicaltrials.gov).

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

For Kamat & Cookson: research/trial support from Photocure, NA.

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Attachment 16

Retrospective German claims data study on initial treatment of bladder carcinoma (BCa) by transurethral bladder resection (TURB)



Retrospective German claims data study on initial treatment of bladder carcinoma (BCa) by transurethral bladder resection (TURB): a comparative analysis of costs using standard white light- (WL-) vs. blue light- (BL-) TURB

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Abstract

Purpose Photodynamic diagnosis using hexaminolevulinate (HAL)—guided BL-TURB may reduce the recurrence risk in non-muscle invasive BCa compared to standard WL-TURB due to more sensitive tumor detection. The impact of the initial use of WL- vs. BL-TURB on follow-up costs was evaluated in this real-world data analysis.

Methods Anonymous claims data of German statutory health insurances (GKV) from 2011 to 2016 were analyzed in a primary and adjusted study population. Selection criteria included five quarters before enrolment, one index quarter (InQ) of initial TURB and BCa diagnosis, either within two years for the primary analysis or within four years for the adjusted analysis, and a follow-up period (FU) of either eleven or three quarters, respectively.

Results In the primary analysis ($n=2331$), cystectomy was identified as an important cost driver masking potential differences between cohorts. Therefore, patients undergoing cystectomy (InQ+FU) were excluded from the adjusted study population of $n=4541$ patients (WL: 79%; BL: 21%). Mean total costs of BL-TURB were initially comparable to WL-TURB (WL: EUR 4534 vs. BL: EUR 4543) and tended to be lower compared to WL-TURB in the first two quarters of FU. After one year (3rd FU quarter), costs equalized. Considering total FU, mean costs of BL-TURB were significantly lower compared to WL-TURB (WL: EUR 7073 vs BL: EUR 6431; $p=0.045$).

Conclusion This retrospective analysis of healthcare claims data highlights the comparability of costs between BL-TURB and WL-TURB.

Keywords Urothelial cancer · Transurethral bladder resection · Hexaminolevulinate · Photodynamic diagnosis · Retrospective health service research · German claims data

Introduction

Bladder cancer (BCa) is among the ten most common cancers worldwide, with every third new case occurring in Europe [1], and also one of the most cost-consuming cancer diseases [2]. Its incidence is higher for men than for women and increases with age [3, 4]. The most common histological

form, accounting for approximately 70% of primary diagnosed bladder tumors, is non-muscle-invasive BCa [1, 3].

Patients with suspected BCa are visually examined by white light (WL) cystoscopy as a standard diagnostic procedure [3, 5, 6]. To confirm the diagnosis and establish the tumor state, a transurethral resection of the bladder (TURB) is routinely performed, which for non-muscle-invasive tumors also constitutes the initial treatment option, generally followed by immediate intravesical instillation of chemotherapy [3, 6]. Only 10–20% of non-muscle-invasive tumors progress to muscle-invasive tumors, but 50–70% of non-muscle-invasive tumors will recur, highlighting the need for optimal initial detection and treatment to ensure optimal prognosis [1]. Hexaminolevulinate (HAL) was approved in

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the EU and the US for assessment of non-muscle-invasive BCa by photodynamic diagnosis. After instillation of HAL into the bladder, photoactive porphyrin accumulates in neoplastic cells and facilitates their detection by emitting red fluorescence during cystoscopy with blue light (BL) [7]. The detection rate of tumors is improved by BL-cystoscopy compared to WL-cystoscopy by 10–20% for non-invasive papillary carcinoma and by up to 40% for carcinoma *in situ* [8–11]. Furthermore, the recurrence rate is reduced [10, 12–14] and recurrence-free survival is prolonged [13, 15] when using BL- compared to WL-cystoscopy. The impact on progression remains unclear [16–19] and depends on the criteria used to define progression [18].

Due to the high recurrence risk of BCa, patients require continuous monitoring. The quality of the initial TURB, however, impacts prognosis and thereby also treatment costs. Models evaluating cost-effectiveness of BL- compared to WL-TURB predict increased quality-adjusted life years and lower long-term costs for BL-TURB despite BL-TURB being more expensive than WL-TURB [20–23]. So far there is only limited information available concerning initial use of WL- or BL-TURB. Using German claims data, the objective of this study was to analyze the real-world impact on costs in case of either WL- or BL-TURB applied as initial treatment in patients with BCa.

Materials and methods

Data source

For this retrospective analysis, routine healthcare claims data from more than 60 German statutory health insurances (GKV, *Gesetzliche Krankenversicherung*) were used [24]. The sample comprised more than 4.5 Million individuals, GKV-insured at least one day between 2011-01-01 and 2016-12-31 and was representative concerning age, gender and morbidity in Germany. As anonymized and pseudonymized healthcare claims data were evaluated, the study was exempt from ethical approval.

Study population

The step-by-step selection process to generate the study population is shown in Fig. 1. The total study population was adjusted for further analysis of costs as indicated.

Study time periods

The primary analysis included patients whose index quarter (InQ) comprising initial TURB and concurrent diagnosis of BCa fell in the selection period of two years between Q2/2012 and Q1/2014. A pre-index period without any

TURB or cystoscopy before first index TURB included five quarters, from Q1/2011 until Q1/2012. The follow-up period (FU) lasted eleven quarters, ending latest Q4/2016. Each patient's individual study period was determined by the index date.

For the analysis of the adjusted study population collecting patients without cystectomy, the FU was shortened to three quarters ending latest Q4/2016. The main focus was on the first FU quarters to detect possible direct cost effects after the initial TURB. The pre-index period remained unchanged, resulting in an extended selection period of four years between Q2/2012 and Q1/2016, thus increasing the corresponding study population.

Treatments

The study population was divided into two cohorts depending on whether they underwent initial WL- or initial BL-TURB. The cohorts were further divided depending on cystectomy for subgroup analysis and for the adjusted study population without cystectomy in InQ and FU.

Statistics

Descriptive analyses were applied for evaluation, using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Differences were considered statistically significant if p values were < 0.05 .

Results

Characteristics of the study population

The total study population comprised 2331 patients, 1855 (79.6%) in the WL-cohort and 476 (20.4%) in the BL-cohort; significantly more patients received initial WL- than BL-TURB in the total study population as well as in both male and female subgroups. Likewise, in all persons continuously insured between 2011 and 2016 ($n=3,038,323$) the incidence rate of initial WL-TURB according to cohort selection (0.06%) was significantly higher than of BL-TURB (0.02%; $p < 0.001$).

The demographic data of the study population are summarized in Table 1. Mean age and gender ratio were comparable between both cohorts, with more than three quarters of patients being men. More than 98% of patients had non-metastatic disease at the time of diagnosis in the InQ (Table 1).

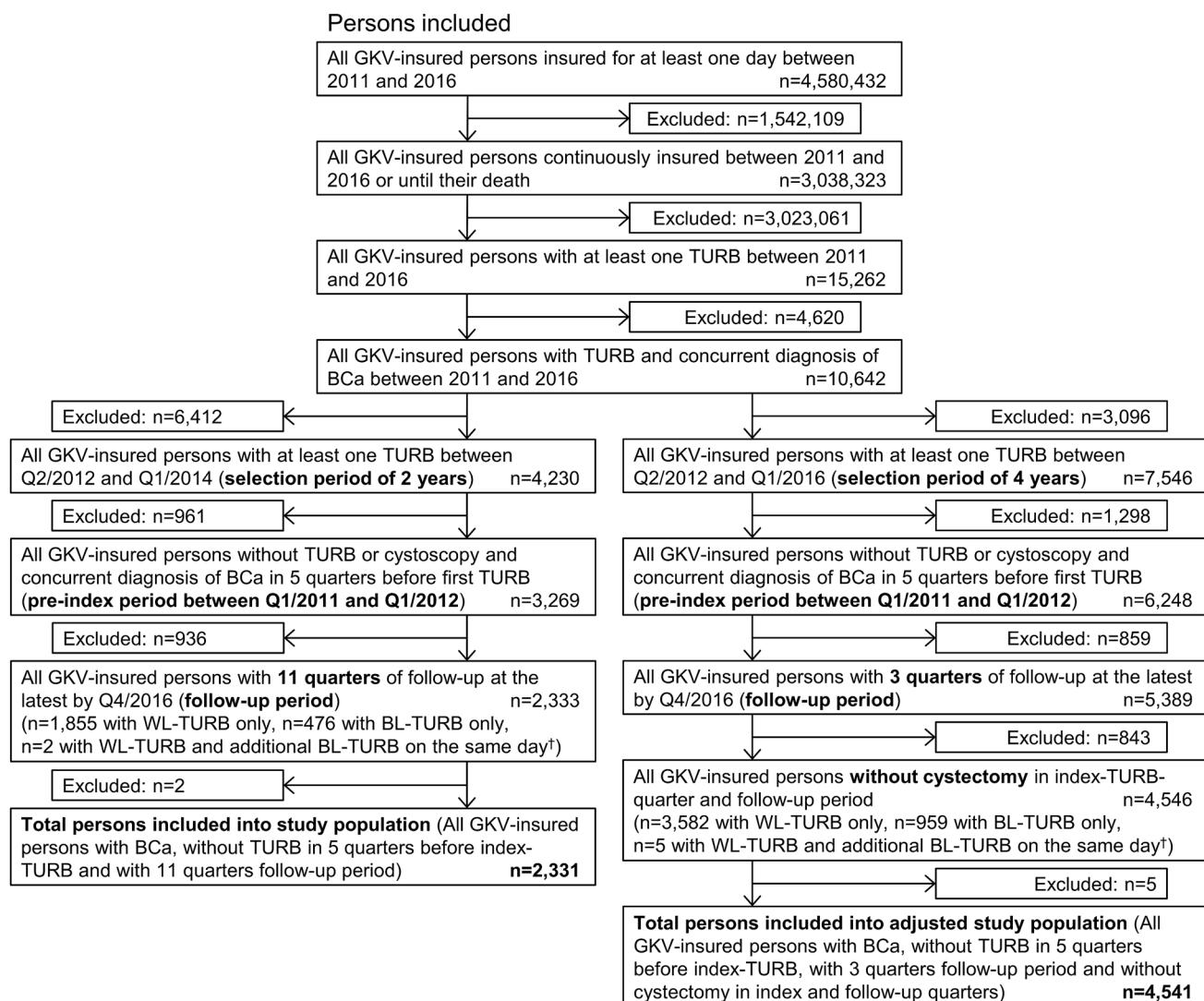


Fig. 1 Selection of study population (left) and adjusted study population (right). Inclusion criteria were applied stepwise. Diagnosis of bladder cancer (BCa) was based on International Classification of Diseases, 10th Revision, German Modification (ICD-10-GM): C67, malignant neoplasm of bladder or D09.0, carcinoma in situ of the bladder; inpatient or outpatient confirmed. TURB, cystoscopy and

cystectomy were based on German Operations and Procedures Key (OPS Code): 5-573.40 (WL-TURB), 5-573.41/5-573.4x (BL-TURB), inpatient (OPS code 5-573.2 for transurethral excision was not included); 1-661/1-663/1-693.2 (cystoscopy), inpatient or outpatient; 5-575 (partial cystectomy), 5-576 (simple/radical cystectomy), inpatient. [†]n < 5 excluded ensuring statistical anonymity.

Cost analysis of the study population

Costs¹ were calculated from the perspective of a statutory health insurance (Table 2A). In the InQ, the mean total costs of EUR 5687 in the BL-cohort were significantly higher than the mean total costs of EUR 4609 in the WL-cohort ($p < 0.001$), resulting from both higher inpatient and medicinal product costs in the BL-cohort. However, in the FU, mean total costs were not significantly different between

both cohorts (WL: EUR 20,442; BL: 20,253; $p = 0.794$). Altogether, total costs over time were EUR 25,940 in the BL-cohort and hence not significantly higher than in the WL-cohort (EUR 25,051; $p = 0.525$).

Subgroup analysis of costs: cystectomy

To investigate the impact of cystectomy in the total study population, a subgroup with cystectomy ($n = 351$) was compared to a subgroup without cystectomy in InQ and FU ($n = 1980$). Cystectomy rates were not significantly different between both cohorts (WL: 15.3%, BL: 14.1%; $p = 0.502$). Regarding total costs over time, subgroup analysis showed

¹ Total costs considered the following cost domains: outpatient, inpatient, medicinal products, appliances, remedies, and sick pay.

Table 1 Demographic data and disease states of bladder cancer of the total study population and per cohort in the index quarter

Characteristics	Study population			p^{\dagger}
	Total (N=2331)	WL-TURB cohort (N=1855)	BL-TURB cohort (N=476)	
Sex				
Male (%)	79.45	79.78	78.15	0.431
Female (%)	20.55	20.22	21.85	
Age (years)				
Mean \pm SD	69.16 \pm 10.88	69.48 \pm 10.86	67.90 \pm 10.86	0.663
Median	71	71	69	
Age group (%)				
0–39	0.90	0.97	0.63	
40–49	4.63	4.20	6.30	
50–59	13.47	13.32	14.08	
60–69	25.48	24.53	29.20	
70–79	38.61	39.46	35.29	
80–89	16.39	17.04	13.87	
90+	0.51	0.49	0.63	
Stage of bladder cancer according to Coding[‡] (%)				
N0 and M0	98.93	98.98	98.74	0.655
N1 and M0	0.86	0.81	1.05	0.610
N0 and M1	0.21	0.22	0.21	0.981
N1 and M1	0.00	0.00	0.00	—

[†]WL- vs. BL-cohort. [‡]The findings are based on the International Classification of Diseases, 10th Revision, German Modification (ICD-10-GM) and do not result from clinical histopathological TNM staging. No lymph node metastases (=N0); no distant metastases (=M0); lymph node metastases (=N1); distant metastases (=M1)

that expenses were more than twice as high for patients with cystectomy as for patients without cystectomy (Table 2B). In the cystectomy subgroup, mean total costs were significantly higher in the InQ, resulting from higher inpatient and medicinal product costs. During FU, costs remained on a high, but not significantly different level in both BL- and WL-cohorts. In the subgroup without cystectomy, the mean total costs were considerably lower and similar between the WL- and the BL-cohort in both InQ and FU.

Cost analysis of the adjusted study population

As cystectomy was identified as an important cost driver contributing greatly to the total costs in both cohorts, an additional cost analysis was performed for an adjusted study population only including patients without cystectomy in InQ and FU. To evaluate any possible direct effects of the first TURB, only the first three quarters of follow-up were included in the analysis. This shortening of the FU resulted in an increased selection period from two to four years yielding a higher number of patients included.

The adjusted study population comprised 4541 patients, with 3582 (78.9%) in the WL- and 959 (21.1%) in the BL-cohort. In accordance with the first results of the subgroup

analyses without cystectomy (Table 2B), mean total costs in the InQ were comparable in both cohorts (BL: EU 4543 vs WL: EUR 4534). Over the entire three FU quarters, the mean total costs of EUR 6431 in the BL-cohort were significantly lower ($p=0.045$) than the mean total costs of EUR 7073 in the WL-cohort (Fig. 2).

Regarding median values, total costs in the InQ were slightly higher in the BL-cohort (EUR 3704 vs EUR 3320). However, over the FU period, also the median total costs of EUR 4426 in the BL-cohort were below the total of the WL-cohort (EUR 4655), thereby “compensating” the higher median initial costs in the BL-cohort.

Considering the individual quarters, the mean total costs in each FU quarter were clearly lower as in the InQ in both cohorts. In each FU quarter, the quarterly costs tended to be lower in the BL- than in the WL-cohort; those differences were most prominent in the second FU quarter but decreased in the third FU quarter. After one year a comparable cost level was reached (Fig. 2).

Table 2 Cost tables for study population

2A: Total costs and main cost domains per cohort in index quarter and follow-up period

Cohort	Total (index quarter+11 quarters follow-up)			Index quarter			Follow-up period (11 quarters)		
	WL	BL	p	WL	BL	p	WL	BL	p
Study population									
N	1,855	476							
Total costs [†] (€)									
Mean±SD	25,051±21,607	25,940±42,550	0.525	4609±3974	5687±14,505	<0.001	20,442±20,480	20,253±31,017	0.794
Median	18,904	17,803		3174	3552		14,261	13,510	
Cost domains (€)									
Outpatient treatment									
Mean±SD	3977±2754	3875±2110	0.772	402±355	379±270	0.174	3574±2648	3497±1979	0.549
Median	3397	3419		298	309		3032	3065	
Inpatient treatment									
Mean±SD	15,261±16,054	14,261±14,117	0.215	3857±3821	4309±4388	<0.001	11,405±15,203	9,953±13,092	0.056
Median	10,262	9419		2322	2811		6726	5329	
Medicinal products									
Mean±SD	3823±7997	5847±35,455	0.025	286±619	949±12,946	<0.001	3537±7573	4897±23,822	0.037
Median	2295	2304		110	109		2022	2074	

2B: Total costs per cohort in index quarter and follow-up period for subgroups with and without cystectomy

Cohort	Total (index quarter+11 quarters follow-up)			Index quarter			Follow-up period (11 quarters)		
	WL	BL	p	WL	BL	p	WL	BL	p
SUBGROUP WITH CYSTECTOMY^{††}									
N	284	67							
Total costs (€)									
Mean±SD	45,947±26,076	58,278±94,333	0.056	7753±6662	14,412±37,038	0.005	38,194±26,729	43,866±60,580	0.719
Median	38,232	42,513		4659	5262		31,744	33,491	
SUBGROUP WITHOUT CYSTECTOMY^{††}									
N	1,571	409							
Total costs (€)									
Mean±SD	21,273±18,317	20,642±21,645	0.551	4040±2922	4258±2912	0.179	17,233±17,298	16,384±20,489	0.396
Median	16,221	15,922		3074	3398		12,433	12,016	

[†]Beside the main cost domains outpatient, inpatient, and medicinal products, the cost domains appliances, remedies, and sick pay were also included in total costs but are not shown individually

^{††}Cystectomy was based on German Operations and Procedures Key (OPS Code): 5-575 (partial cystectomy), inpatient; 5-576 (simple/radical cystectomy), inpatient

Subsequent cystoscopies/TURB of the adjusted study population

After the initial TURB, most patients of the BL-cohort and the WL-cohort were subsequently examined by at least one cystoscopy in InQ and FU. Regarding TURB, in total a higher proportion of patients was subsequently examined by WL-TURB than by BL-TURB in both cohorts. The rate of subsequent WL-TURB was significantly higher in the WL-cohort than in the BL-cohort. A significantly higher

proportion of the BL-cohort than of the WL-cohort subsequently received further BL-TURB (*data not shown*).

Discussion

This comparative retrospective analysis of real-world data on prevailing TURB treatments of BCa showed that in Germany only 20% of GKV-insured persons with BCa receive initial BL-TURB, despite its therapeutic benefits compared

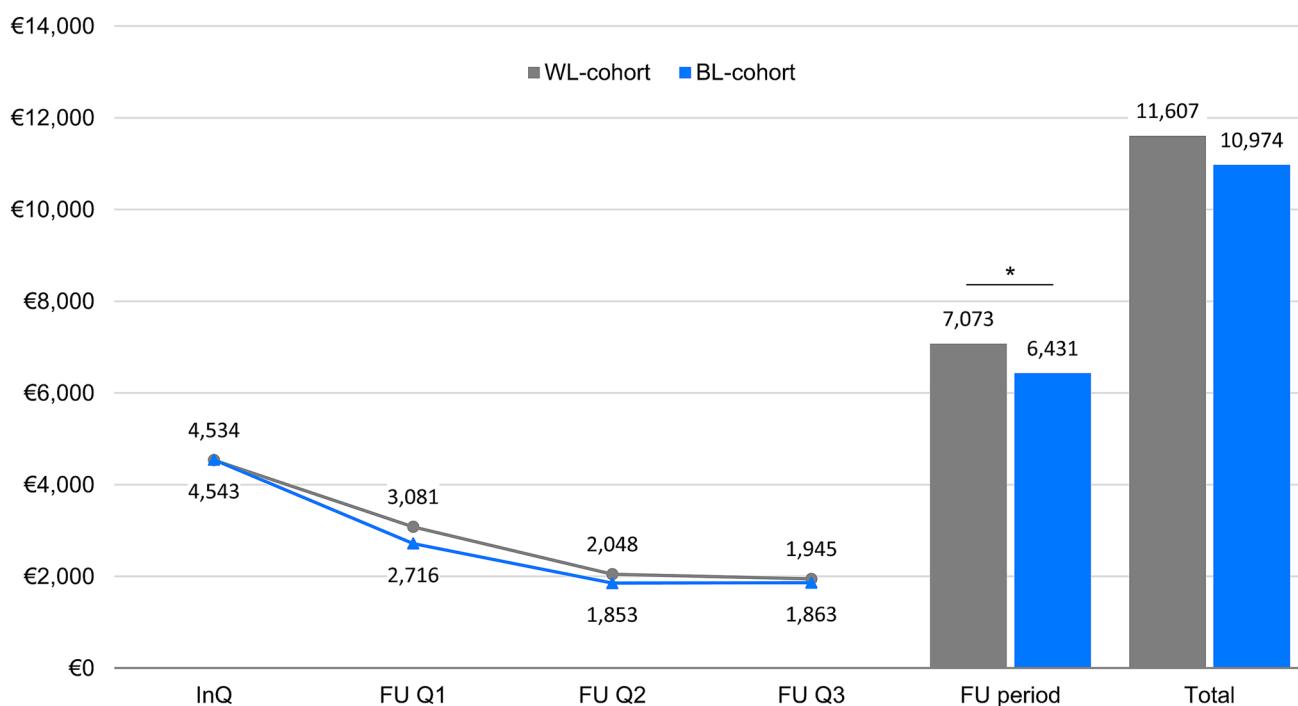


Fig. 2 Total costs and development of costs per cohort in the index quarter and follow-up period (adjusted study population). Data are given as mean. WL- vs. BL-cohort * $p < 0.05$. FU, follow-up period (3 quarters); InQ, index quarter; Total (index quarter + 3 quarters follow-up)

to WL-TURB and its recommendation in guidelines [3, 25]. Availability of equipment and acquisition costs as well as additional costs of HAL may restrict the use of BL-TURB in clinical practice. Furthermore, a bias due to incorrect coding of surgical procedures with a possible impact on the unbalanced distribution ratio cannot be excluded.

In this study, initial BL-TURB resulted only in the primary study population in higher initial costs compared to WL-TURB. Subgroup analysis identified cystectomy as a main contributor to costs, masking potential directly TURB-mediated differences. When cystectomy was excluded for further analyses in an adjusted study population, the initial mean total costs of BL-TURB were comparable to WL-TURB, and in the FU, costs of BL-TURB even tended to be lower compared to WL-TURB until they equalized after one year. The view on the median costs supports the trend of the superiority of BL-TURB compared to WL-TURB regarding total costs in the first year: Albeit the initial median costs of the BL-cohort tended to be higher, they were compensated by the lower mean FU costs. The findings of this study are in line with previous results of models for the cost-utility analysis of BL-TURB. Here, higher or similar initial costs of BL-TURB compared to WL-TURB are predicted which are compensated by cost benefits in the long term due to improved patient outcomes [20–23]. In a Markov model calculated for Germany, additional initial BL-TURB reduced costs by EUR 537 per patient compared to only WL-TURB.

At the same time, quality-adjusted life years were increased [22]. Witjes et al. [20] suggest that previous restrictions of BL-TURB due to budget need to be adjusted to recent long-term follow-up data and cost analyses.

The study specifically focused on real-world BCa-treatment costs of initial WL- versus BL-TURB in Germany based on claims data, whose original function is reimbursement of healthcare costs. Therefore, the study results were dependent on the quality of coding and classification and apply for German statutory health insurances only. Outcomes irrelevant for reimbursement may be precluded, resulting in under-representation or inadequately documentation of clinical factors like metastases.

The analyzed claims data do not allow the confirmation of the medical hypothesis that BL-TURB is associated with a higher risk reduction of recurrence than WL-TURB. The design of this study involved a pre-index period without TURB or cystectomy and concurrent diagnosis of BCa to ensure that only patients with their initial TURB in the selection period were included. However, this approach does not exclude subsequent TURB completely. Furthermore, low and varying numbers of patients in the subgroup analysis may impact the respective results. Unfortunately, the retrospective study feature does not allow to evaluate the assignment reason to the two procedures WL or BL which is one aspect of the main limitation of this healthcare study: the lack of clinical parameters.

Conclusion

This comparative retrospective analysis of healthcare claims data provides information on real-world costs of standard WL- or HAL-guided BL-TURB for treatment of BCa in Germany. The application of a BL-TURB does not imply higher initial and consecutive costs than the WL-TURB. In combination with a higher tumor detection rate and consequently lower recurrence risk, described in a variety of clinical trials and publications, BL-TURB constitutes a valuable addition to standard WL-TURB. Nonetheless, initial BL-TURB was still only performed in every fifth GKV-insured patient with BCa. However, limitations of the analysis of healthcare claims data need to be considered, when interpreting the study results.

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Author contributions TT, BQ and AS: project development, manuscript editing. MM: manuscript editing. MK, NK: data collection, management and analysis. CC: project development, manuscript writing and editing.

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Compliance with ethical standards

Conflict of interest Tilman Todenhöfer: speaker/advisor for Amgen, Astellas, AstraZeneca, Bayer, BMS, Ipsen, Janssen, MSD, Roche. Moritz Maas: none. Miriam Ketz: none. Nils Kossack: none. Christiane Colling: former employee of Ipsen Pharma. Bryan Qwick: employee of Ipsen Pharma. Arnulf Stenzl: speaker/advisor for Alere, Amgen, Astellas, Bristol Myers Squibb, CureVac, Ferring, Ipsen, Janssen, Roche, Sanofi Aventis, Stebabiotech, Synergo.

Informed consent This work is based on routine healthcare claims data. As anonymized and pseudonymized healthcare claims data were evaluated, the study was exempt from ethical approval, no informed consent was required.

Research involving human participants and/or animals This work did not include animal studies. Data concerning human patients were collected retrospectively.

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Attachment 17

Contemporary cost-consequence analysis of blue light cystoscopy with hexaminolevulinate in non-muscle-invasive bladder cancer



Contemporary cost-consequence analysis of blue light cystoscopy with hexaminolevulinate in non-muscle-invasive bladder cancer

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Abstract

Introduction: Previous studies have suggested cost-savings using blue light cystoscopy (BLC) with hexaminolevulinate (HAL) compared to white light cystoscopy (WLC) during transurethral resection of bladder tumour (TURBT) for non-muscle-invasive bladder cancer (NMIBC), secondary to improvements in recurrence and progression rates; however, these studies have used 'best case scenario' recurrence rate probabilities, thus decreasing generalizability of the findings. The objective of this study was to perform a contemporary cost-effectiveness assessment of BLC compared to WLC at the time of TURBT.

Methods: A decision and cost-effectiveness model with a five-year time horizon following initial TURBT was used. The model was created from the healthcare payer perspective. Comprehensive literature review was performed to obtain contemporary recurrence and progression rates. These values were meta-analyzed for inclusion into the model. Cost variables included in the model were from three large Canadian bladder cancer centres. Model outputs were number of recurrences prevented, bed days saved, and overall costs. One-way sensitivity and scenario analyses were performed to assess model robustness.

Results: The five-year amortized cost of using BLC with HAL on all incident NMIBC compared to WLC assistance was \$4 832,908 for Ontario (n=4696; \$1372/patient); \$1 168 968 for British Columbia (n=1204; \$1295/patient); and \$2 484,872 (n=2680; \$1236/patient) for Quebec. Use of BLC with HAL would result in 87 338 fewer recurrences annually. On sensitivity/scenario analyses for Ontario data, if BLC with HAL equipment were provided to the province at no cost, five-year costs would be \$4 158 814 and \$1181 cost per patient. If BLC with HAL were only used for cystoscopically appearing aggressive tumours, the five-year amortized cost would be \$3 874 098, with a cost per patient of \$1222. If there was a 20% or 50% improvement in progression rates with BLC plus HAL, the five-year amortized cost would be \$2 660 529 and -\$598 039 (cost-saving), respectively.

Conclusions: TURBT using BLC with HAL for patients with NMIBC is associated with a five-year cost of approximately \$1–5 million for jurisdictions of 4–13 million people. Although this translates to

a cost of \$1200–1400 per patient for their initial TURBT, BLC with HAL improves patients care, reduces recurrences, and decreases the need for hospital beds after TURBT. If this diagnostic procedure eventually improves progression rates, there would be considerably improved cost-effectiveness.

Introduction

Bladder cancer (BCa) is the fourth and twelfth most common malignancy by incidence in Canadian men and women, respectively.¹ In Canada, the lifetime probability of developing BCa is one in 27 men and one in 84 women.¹ Most patients diagnosed with BCa have non-muscle-invasive BCa (NMIBC), which carries a high risk of recurrence (up to 78% within five years of initial resection) and a risk of progression of up to 45% at five years from diagnosis.² Secondary to these risks, rigorous followup with periodic cystoscopy is necessary, often for the remainder of the patient's life. As such, BCa is the most expensive malignancy to treat, with lifetime cost per patient estimates ranging from \$65 000 187 000 USD.^{3,4} Furthermore, bladder surveillance for tumour recurrence and treatment of eventual recurrences account for 60% of the total costs of managing BCa patients.⁴ Given these economic burdens in today's fiscally challenged healthcare systems, additional cost-effective measures for surveillance and treatment are necessary.

In addition to tumour number and size, stage, grade, and presence of carcinoma in situ (CIS),² an additional risk factor for recurrence is incomplete resection at initial transurethral resection of bladder tumour (TURBT).⁵ This can occur in the setting of multiple lesions where one is missed and/or when there is difficulty identifying the exact extent and location of tumours, particularly CIS, using standard white light cystoscopy (WLC).⁵ To improve tumour visualization in these situations, hexaminolevulinate (HAL) hydrochloride (Photocure®, Oslo, Norway) has been used with blue light cystoscopy (BLC) for aiding detection of NMIBC. HAL has

been commercially available in Europe since 2006 (marketed as Hexvix®), in the U.S. since 2010, and recently became available in Canada (2015). Several randomized, controlled trials (RCTs) have reported improvements in NMIBC recurrence rates; however, widespread adoption of the technique varies because of equipment availability and cost constraints.⁶

Previous cost-effectiveness studies have generally demonstrated potential cost savings using BLC with HAL compared to WLC-assisted TURBT for NMIBC, primarily due to an improvement in recurrence rates;⁷⁻¹² however, these studies often use 'best case scenario' recurrence rate probabilities, thus decreasing generalizability of the findings. The objective of this study was to provide the first decision analysis using updated, meta-analyzed probabilities for risk of recurrence (BLC with HAL TURBT vs. WLC TURBT). We performed a cost-effectiveness analysis of BLC with HAL at initial TURBT compared to WLC assisted TURBT at the population level.

Methods

Evidence synthesis

A systematic review was performed using the PRISMA guidelines to identify appropriate studies for inclusion (Fig. 1). Ovid Medline (R), Ovid Epub Ahead of Print, and Embase were queried, generating 2806 articles. After removing duplicates and unsuitable manuscripts, 33 studies were selected for inclusion in the decision-tree analysis. Among these 33 studies were 10 RCTs of BLC with HAL vs. WLC that were used to meta-analyze sensitivities and specificities.¹³⁻²² Burger et al recently used raw data of RCTs to meta-analyze recurrence relative risk (RR) for BLC with HAL vs. WLC-assisted TURBT, and this RR (0.761) was used in the baseline decision-tree analysis.²³

Decision model

A decision model created and first used by the National Health Service (NHS, U.K.) was adapted to assess the cost-effectiveness of BLC with HAL-assisted vs. conventional WLC-assisted TURBT for patients with suspected new or recurrent NMIBC (Fig. 2).²⁴ Specifically, we modified the model for BLC TURBT only (i.e., therapeutic) as opposed to BLC used for routine cystoscopy (i.e., diagnostic). Furthermore, we updated sensitivities, specificities, and recurrence rates with up-to-date published values (see below). The model was populated with provincial, population-based incident BCa cases per year (for 2013–2015 based on province) as follows: Ontario, n=4696; British Columbia, n=1204; Quebec, n=2680.²⁵⁻²⁷ We assumed a NMIBC rate of 75% based on the known distribution of incident BCa cases. The model was based on the Canadian universal (single-payer) healthcare system with a period of five years following initial BLC

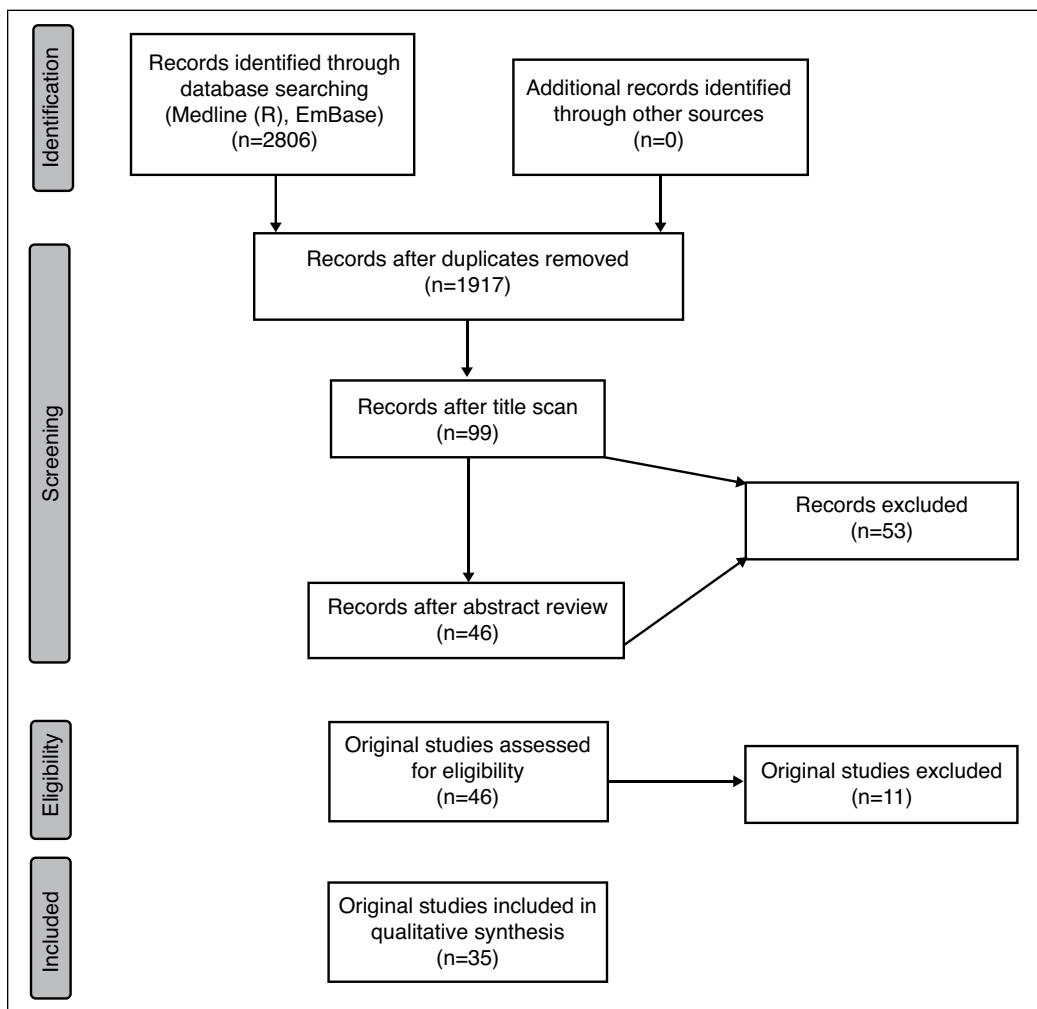


Fig. 1. PRISMA diagram for systematic review of the literature to identify appropriate studies to include for meta-analysis.

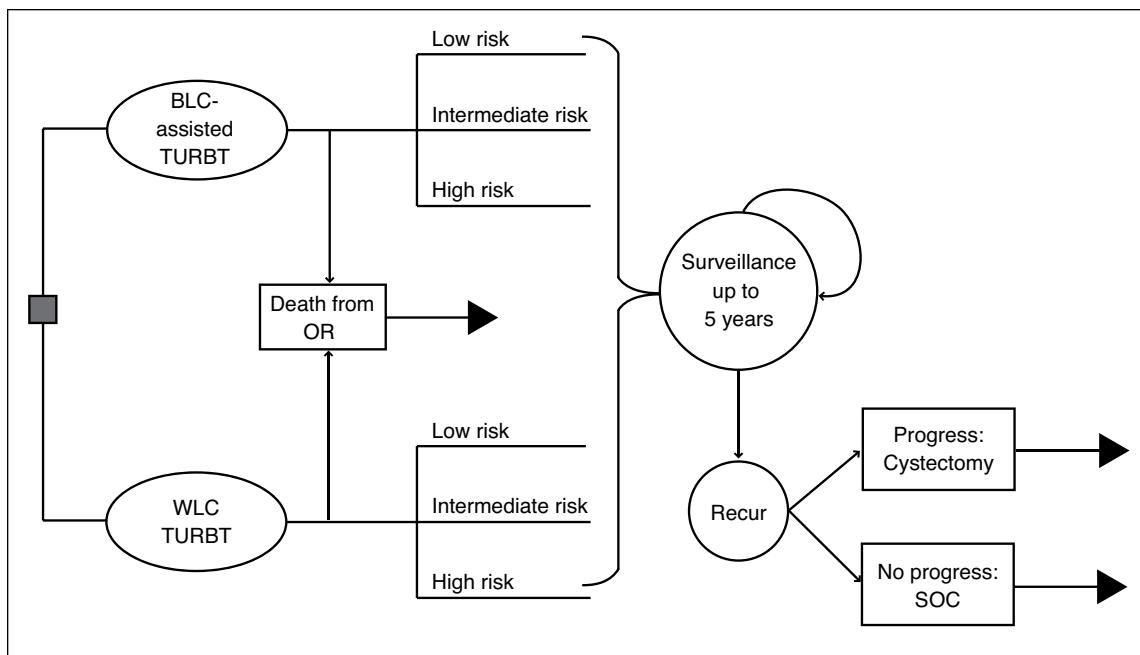


Fig. 2. Structure of the decision model tree. BLC: blue light cystoscopy; OR: operating room; SOC: standard of care; TURBT: transurethral resection of bladder tumour; WLC: white light cystoscopy.

with HAL. Fig. 2 depicts the structure of the model tree for initial TURBT, recurrence monitoring, and ongoing surveillance. After initial TURBT, patients were classified as low-, intermediate-, or high-risk based on existing guidelines.²⁸ Recurrence and progression probabilities at three months, 12 months, and then annually were incorporated to determine long-term risks of recurrence.

Model assumptions

The model assumes the following potential outcomes following initial TURBT: 1) recurrence monitoring for patients with NMIBC; 2) radical cystectomy for muscle-invasive disease and continued postoperative surveillance; and 3) palliative care for patients with metastatic disease. Patients with progressive disease incur the costs for radical cystectomy and possible downstream metastasis. Further general assumptions include: 1) all patients received a postoperative dose of mitomycin after TURBT; 2) after tumour recurrence, regardless of disease progression (accounting for downstream costs of progression), patients are removed from the model; 3) tumours that were initially missed by WLC were assumed to eventually become detectable within two years of followup; 4) after initial BLC with HAL TURBT, all future TURBTs are conducted with WLC assistance; 5) all patients with intermediate- and high-risk (including CIS) disease received six weeks of induction bacillus Calmette-Guerin (BCG) therapy; and 6) baseline relative risk for progression was 1.0 (equal between groups).

Cost estimates and probabilities

Micro-costing data were obtained from three large, academic teaching hospitals from Ontario, British Columbia, and Quebec, representing 75% of the entire Canadian population. Specifically, individual patient data at the University of Toronto (University Health Network), University of British Columbia (Vancouver General Hospital), and McGill University (McGill University Health Centre) were reviewed for costs associated with TURBT, surveillance, cystectomy, and palliative care. Every effort was made to obtain micro-cost data for each variable in every province; however, when a cost variable was not obtainable, the average cost for that variable between the other two provinces was included as a surrogate cost metric. Input probabilities were calculated from meta-analysis of the existing literature for sensitivities, specificities, and recurrence probabilities.¹³⁻²² As mentioned, the previous meta-analyzed RR for recurrence was used (0.761; 95% confidence interval [CI] 0.627–0.924).²³ Provincial base outcomes were assessed, including: initial cost, followup cost, five-year amortized cost, cost-difference per case, bed day use, and recurrences.

Scenario and sensitivity analyses

To assess model robustness, one-way sensitivity and scenario analyses were performed with Ontario data, as the most complete cost data were from this jurisdiction. The specific scenario analyses assessed cost-effectiveness: 1) when the cost of additional BLC equipment was \$0 (if the additional

equipment were provided by the company); 2) without a postoperative dose of mitomycin; 3) when 20–50% improvement in progression RR was assumed; and 4) when BLC with HAL was only used at TURBT for in clinic cystoscopically appearing CIS and intermediate-/high-risk cases (not low-risk). These analyses allowed comparison of outcomes to the baseline model. Sensitivity analysis of selected exposure variables and outcome (five-year amortized cost) was performed for recurrence RR, progression RR, consumable costs (i.e., HAL), and additional equipment costs.

Results

Table 1 summarizes details of cost variables included in the model from across the three provinces, in addition to probabilities for recurrence stratified by bladder tumour risk.

Table 2 shows the base case estimates for each province, comparing initial TURBT using BLC with HAL vs. WLC. The initial cost of establishing a BLC with HAL provincial program ranged from \$2 064 033–9 620 422 at the population level for a single year of incident NMIBC tumours. After five years, the amortized cost of using BLC with HAL on every patient compared to WLC assisted TURBT dropped

Table 1. Provincial cost estimates and probabilities

Variable	Ontario	British Columbia	Quebec
Cost estimates			
Cystoscopy (\pm 25%)	\$394 (\$295, \$492)	\$362 (\$271, \$452) ^a	\$330 (\$247, \$412)
WLC-assisted TURBT (\pm 25%)	\$3946 (\$2959, \$4933)	\$3002 (\$2252, \$3753) ^a	\$2059 (\$1544, \$2573)
BLC-assisted TURBT (\pm 25%)	\$4890 (\$3667, \$6113)	\$3930 (\$2947, \$4913)	\$2990 (\$2242, \$3737)
CT scan (\pm 25%)	\$263 (\$197, \$329)	\$650 (\$487, \$812)	\$400 (\$300, \$500)
Cystectomy (\pm 25%)	\$24 486 (\$18 364, \$30 608)	\$21 190 (\$15 892, \$26,487) ^a	\$17 894 (\$13 420, \$22 367)
Palliative care (\pm 25%)	\$55 215 (\$41 411, \$69 018)	\$55 215 (\$41 411, \$69 018)	\$55 215 (\$41 411, \$69 018)
Perioperative mitomycin intravesical therapy (\pm 25%)	\$754 (\$565, \$943)	\$739 (\$554, \$924) ^a	\$725 (\$543, \$906)
BCG intravesical therapy** (\pm 25%)	\$204 (\$153, \$256)	\$134 (\$100, \$168) ^a	\$64 (\$48, \$80)
BLC-extra nursing time (\pm 25%)	\$25 (\$18, \$31)	\$9 (\$7, \$11)	\$10 (\$7, \$12)
BLC-extra staffing cost (\pm 25%)	\$15 (\$11, \$18)	\$9 (\$7, \$11)	\$12 (\$9, \$15) ^b
BLC-consumables (\pm 25%)	\$708 (\$531, \$885)	\$712 (\$534, \$891)	\$712 (\$534, \$891)
BLC-additional equipment (\pm 25%)	\$195 (\$146, \$244)	\$195 (\$146, \$244)	\$195 (\$146, \$244)
WLC sensitivity (95% CI)	0.65 (0.55–0.74)	0.65 (0.55–0.74)	0.65 (0.55–0.74)
BLC sensitivity (95% CI)	0.93 (0.90–0.96)	0.93 (0.90–0.96)	0.93 (0.90–0.96)
*RR, BLC vs. WLC (95% CI)	0.761 (0.627–0.924)	0.761 (0.627–0.924)	0.761 (0.627–0.924)
Probabilities***			
3-month recurrence, low-risk		0.02	
3-month recurrence, int-risk		0.04	
3-month recurrence, high-risk		0.094	
12-month recurrence, low-risk		0.15	
12-month recurrence, int-risk		0.26	
12-month recurrence, high-risk		0.39	
2-year recurrence, low-risk		0.10	
2-year recurrence, int-risk		0.13	
2-year recurrence, high-risk		0.11	
3-year recurrence, low-risk		0.05	
3-year recurrence, int-risk		0.06	
3-year recurrence, high-risk		0.06	
4-year recurrence, low-risk		0.08	
4-year recurrence, int-risk		0.05	
4-year recurrence, high-risk		0.02	
5-year recurrence, low-risk		0.07	
5-year recurrence, int-risk		0.03	
5-year recurrence, high-risk		0.03	

^aAverage of Ontario and Quebec values; ^baverage of Ontario and British Columbia values; *relative risk for recurrence;²³ **cost per weekly instillation; ***from references 13-22.

BCG: bacillus Calmette-Guerin; BLC: blue light cystoscopy; CI: confidence interval; CT: computed tomography; PDD: photodynamic diagnosis; RR: relative risk; TURBT: transurethral resection of bladder tumour; WLC: white light cystoscopy.

Table 2. Baseline provincial decision analysis

	Ontario (n=3522)			British Columbia (n=903)			Quebec (n=2010)		
	BLC	WLC	Net	BLC	WLC	Net	BLC	WLC	Net
Initial costs	\$26 165 385	\$16 544 963	\$9 620 422	\$5 374 301	\$3 310 268	2 064 033	\$9 029 938	\$5 294 536	\$3 735 401
Followup costs									
No recurrence	\$6 480 842	\$5 804 944	\$675 898	\$1 526 481	\$1 367 282	\$159 199	\$3 097 022	\$2 774 029	\$322 994
Recurrences	\$8 049 965	\$13 513 376	-\$5 463 411	\$1 606 304	\$2 660 568	-\$1 054 264	\$2 558 788	\$4 132 311	-\$1 573 523
5-year costs (total)	\$40 696 192	\$35 863 283	\$4 832 908	\$8 507 086	\$7 338 118	\$1 168 968	\$14 685 748	12 200 876	\$2 484 872
Cost-difference/case			\$1372			\$1295			\$1236
Events									
Bed days (n)	7167	8212	-1045	1837	2105	-268	4,090	4687	-597
Bed days/patient	2.03	2.33	-0.30	2.03	2.33	-0.30	2.03	2.33	-0.30
Recurrences (n)	1351	1689	-338	346	433	-87	771	964	-193
Recurrences/patient	0.38	0.48	-0.10	0.38	0.48	-0.10	0.38	0.48	-0.10

BLC: blue light cystoscopy; WLC: white light cystoscopy.

to \$1 168 968–4 832 908 annually across the provinces, as additional recurrences in the WLC cohort added to overall costs. Cost per patient ranged from \$1236–1372, resulting in 87–338 fewer recurrences and 268–1045 saved bed days. In terms of cost-effectiveness (initial difference in cost between BLC with HAL and WLC, divided by recurrences prevented), this corresponds to \$28 463/recurrence saved in Ontario, and \$23 724 and \$19 354/recurrence saved in British Columbia and Quebec, respectively.

Using the Ontario cost and probability data, several scenario analyses were performed to assess for cost differences compared to the baseline model (Table 3). If BLC with HAL equipment were provided to the province at no charge, the five-year amortized cost would be \$4 158 814 and \$1191 per patient. If postoperative mitomycin were excluded, the five-year amortized cost would be \$4 200 398 and \$1193 per patient. If BLC with HAL were only used in patients deemed on preoperative cystoscopy to be at risk of CIS, the five-year amortized cost would be \$484 327, with a higher price per case of \$1528 secondary to more upfront use of BCG. Similarly, if BLC with HAL were only used for cystoscopically appearing, aggressive tumours (intermediate- and high-risk), the five-year amortized cost would be \$3 874 098, with a cost per patient of \$1222. If there was a 20% or 50% improvement in progression rates with BLC plus HAL, the five-year amortized cost would be \$2 660 529 (\$755 per patient) and -\$598,039 (-\$170 per patient; cost saving), respectively.

Sensitivity analyses provide further insight into changes in the model that may impact cost-effectiveness (Figs. 3A–D). Although no study to date has definitively demonstrated an improvement in NMIBC progression rates, scenario (Table 3) and sensitivity analyses (Fig. 3B) show that even a modest improvement in progression RR in favour of BLC with HAL would provide substantial economic benefit over a five-year time period. Additionally, BLC consumables (Fig. 3C), which contribute to the main cost of HAL, are a big driver of the overall cost.

Discussion

There have been several RCTs comparing BLC with HAL to WLC-assisted TURBT for patients with NMIBC.^{13–22} Systematic reviews and meta-analyses have concluded that BLC with HAL improves recurrence rates, particularly in patients with high-risk bladder tumours.^{6,23–24,28–32} The current study is the first analysis conducted in the setting of a universal, public-access healthcare system using updated meta-analyzed sensitivities, specificities, and relative risk for recurrence based on prior RCTs. We were also able to incorporate a meta-analyzed progression RR based on recent data as an exploratory, scenario analysis.³³ We demonstrate that despite an initial cost for implementing a comprehensive BLC with HAL program, it decreases bladder tumour recurrences and saves bed days. At five years after implementation, the jurisdictional differential cost for BLC with HAL is approximately \$1–5 million (based on populations of 4–13 million people). This initial cost leads to improved tumour identification, which supports better disease management through decreased recurrence rates. The reduced recurrence rates would lead to more time between procedures, potentially contributing to a patient's state of well-being.

Previous cost-effectiveness studies have been conducted in Germany,^{7,8} Sweden,¹⁰ France,¹² the U.K.,⁹ and the U.S.¹¹ An early study from Germany⁸ assessing use of BLC with HAL for newly diagnosed cases of BCa reported a cost of €584 per patient, although this study did not assess cost of followup and ongoing management. A more detailed study from Germany in 2009 reported cost savings for BLC with HAL of €140 per patient considering HAL instillation, equipment amortized over 10 years, staffing, pathology, and repeat resection after 3–6 months for the WLC-assisted group;⁷ however, this study assumed a 20% chance of second TURBT after 3–6 months, cost of €458 for WLC TURBT, and an overly optimistic €0 (no recurrence cost) for BLC with HAL. A Swedish study looked at newly diagnosed BCa, reporting a cost savings of €73 per

Table 3. Ontario data scenario analyses

	BLC	WLC	Net	Difference*
Without BLC-additional equipment				
Initial costs	\$25 524 410	\$16 544 963	\$8 976 447	
Followup costs				
No recurrence	\$6 480 842	\$5 804 944	\$675 898	
Recurrences	\$8 016 845	\$13 513 376	-\$5 496 531	
5-year costs (total)	\$40 022 097	\$35 863 283	\$4 158 814	-\$674 095
Cost-difference/case			\$1181	-\$191
Recurrences	1351	1689	-338	0
Without postoperative mitomycin				
Initial costs	\$23 706 733	\$14 826 550	\$8 880 182	
Followup costs				
No recurrence	\$6 480 842	\$5 804 944	\$675 898	
Recurrences	\$7 519 289	\$12 874 972	-\$5 355 683	
5-year costs (total)	\$37 706 864	\$33 506 466	\$4 200 398	-\$632 511
Cost-difference/case			\$1193	-\$179
Recurrences	1351	1689	-338	0
20% improvement in progression				
Initial costs	\$26 165 385	\$16 544 963	\$9 620 422	
Followup costs				
No recurrence	\$6 571 009	\$5 804 944	\$766 065	
Recurrences	\$8 049 965	\$13 513 376	-\$5 463 411	
Progression	\$9 901 680	\$12 164 226	-\$2 262 546	
5-year costs (total)	\$50 688 039	\$48 027 509	\$2 660 529	-\$2 172 380
Cost-difference/case			\$755	-\$617
Recurrences	1351	1689	-338	0
50% improvement in progression				
Initial costs	\$26 165 385	\$16 544 963	\$9 620 422	
Followup costs				
No recurrence	\$6 706 259	\$5 804 944	\$901 316	
Recurrences	\$8 049 965	\$13 513 376	-\$5 463 411	
Progression	\$6 507 861	\$12 164 226	-\$5 656 365	
5-year costs (total)	\$47 429 470	\$48 027 509	-\$598 039	-\$5 430 948
Cost-difference/case			-\$170	-\$1542
Recurrences	1351	1689	-338	0
Only CIS** (n=317) [#]				
Initial costs	\$2 968 779	\$1 918 103	\$1 050 676	
Followup costs				
No recurrence	\$536 891	\$478 850	\$58 041	
Recurrences	\$852 863	\$1 476 374	-\$623 511	
5-year costs (total)	\$4 358 233	\$3 873 327	\$484 327	
Cost-difference/case			\$1528	\$156
Recurrences	136	169	-33	
Only intermediate-/high-grade (n=3170) [#]				
Initial costs	\$22 096 531	\$13 875 308	\$8 221 222	
Followup costs				
No recurrence	\$5 773 887	\$5 168 103	\$605 784	
Recurrences	\$6 997 063	\$11 949 972	-\$4 952 909	
5-year costs (total)	\$34 867 481	\$30 993 383	\$3 874 098	
Cost-difference/case			\$1222	-\$150
Recurrences	1246	1560	-314	

*Compared to baseline; **assumption – CIS is 20% of high-risk disease; [#]adjusted for no perioperative mitomycin instillation. BLC: blue light cystoscopy; CIS: carcinoma in situ; WLC: white light cystoscopy.

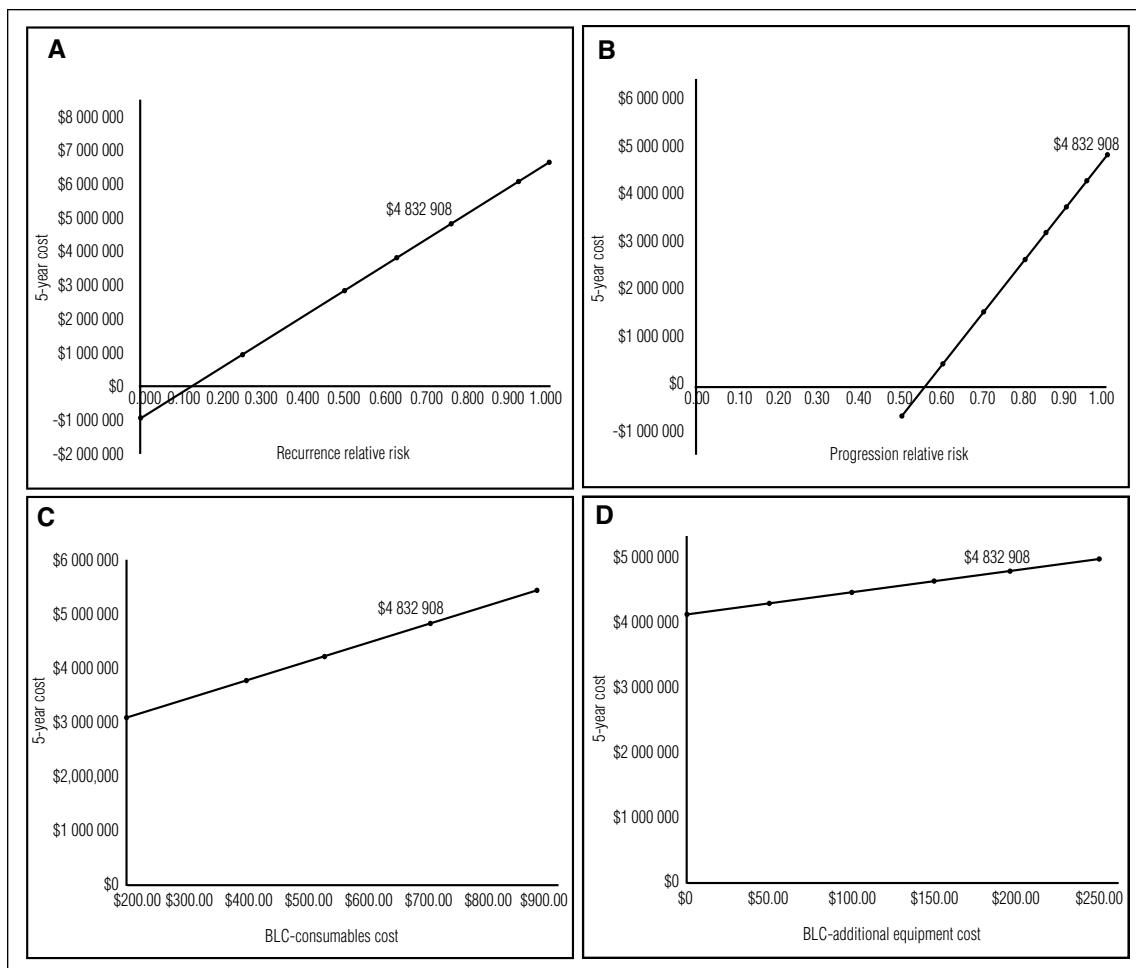


Fig. 3. Sensitivity analyses for Ontario data including (A) recurrence relative risk; (B) progression relative risk; (C) blue light cystoscopy (BLC) consumable cost; and (D) BLC additional equipment cost.

patient over the first year, accounting for cost of cystoscopy, TURBT, post-TURBT treatment (i.e., BCG for NMIBC, cystectomy for muscle-invasive disease, etc.), and annual monitoring.¹⁰ Although this study delineated patients based on European Association of Urology (EAU) risk guidelines, the authors presumed a very optimistic 40% reduction in recurrence rates using BLC with HAL compared to WLC. In a U.S. study of new NMIBC cases, Garfield et al looked at all costs in the management of these patients (cystoscopy, TURBT, radical or partial cystectomy, Hexvix®, biopsy and pathology, BCG therapy, chemotherapy, imaging studies, ongoing surveillance of muscle-invasive disease) demonstrating a cost saving using BLC with HAL of \$4660 per patient over five year compared to patients initially receiving WLC;¹¹ however, the generalizability of these results is concerning since the probabilities used were primarily from best case scenario prior analyses. Taken together, these studies are heterogeneous with regards to use of HAL, cost variation between countries, variables implemented in the decision analysis, length and rigor of followup, and complexity of the decision analysis models.

As demonstrated in this study, there is an initial cost to establish a BLC with HAL program. Additional drivers of five-year expenditure include the cost of the HAL medication, as well as the equipment required to perform BLC-assisted TURBT; however, despite these additional costs, optimization of patient care is reliant on a complete TUR resection. The Canadian Urological Association (CUA) guidelines are well-established that for the management of NMIBC “TURBT is the first and gold standard treatment option. The quality of the initial TURBT is of utmost importance. Complete resection of the tumour, including focal areas of suspected CIS and abnormal areas in the prostatic urethra and bladder neck, should be performed.”³⁴ Similarly, the American Urologic Association / Society of Urologic Oncology (AUA/SUO) guidelines recommend, “in a patient with NMIBC, a clinician should offer blue light cystoscopy at the time of TURBT, if available, to increase detection and decrease recurrence (moderate recommendation; evidence strength: Grade B).”³⁵ BLC with HAL supports the most complete resection possible by enabling the visualization and complete resection of bladder tumours.

Undoubtedly, BLC with HAL decreases NMIBC recurrence rates⁶ and thus improves patient care, as recognized by several urology associations worldwide. Furthermore, particularly in settings where patients are admitted to the ward for overnight postoperative observation, BLC with HAL decreases the number of bed days associated with TURBTs. In Ontario, this may save an estimated \$842 per bed/day,³⁶ and importantly allocate beds to other types of patients with acuity requiring admission. In a healthcare system reliant on reducing/limiting cost, urologists likely need to be judicious with which NMIBC patients may receive maximal benefit from a BLC with HAL TURBT (e.g., CIS). Although the cost-per-patient in those with CIS is increased compared to the base case scenario (secondary to usage of BCG induction), improved visualization of grossly resected but perhaps microscopically unresected disease at the time of BLC with HAL TURBT will have the greatest impact for improving patient care and outcomes. Furthermore, this may obviate the need for post-operative mitomycin instillation in these cases, which has been advocated in the recent literature^{28,37} and would also contribute to cost savings.

To date, prior studies have not demonstrated a discernible improvement in BCa progression rates using BLC with HAL compared to WLC-assisted TURBT. A recent study analyzing long-term followup of a controlled, phase 3 study¹⁵ demonstrated a trend toward improved progression rates in patients treated with BLC with HAL, although the findings were not statistically significant due to lack of power.³⁸ This study had 255 patients in the BLC with HAL arm and 261 patients in the WLC cystoscopy arm. In the original analysis, after a median followup of 4.5 years, eight HAL patients and 16 WLC patients had progressed to muscle-invasive disease (T2–T4) ($p=0.066$).¹⁵ Using a new definition for progression proposed by the International Bladder Cancer Group (IBCG)³⁹ (change in T-stage, change to T2 or higher, or change from low- to high-grade disease), additional patients were deemed as having progressed: 21 (12.2%) HAL patients compared to 46 (17.6%) WLC patients ($p=0.085$).³⁸ This included four HAL patients and 11 WLC patients progressing from Ta to CIS. A recent systematic review and meta-analysis of 14 RCTs assessing outcomes of HAL and 5-aminolevulinic acid (5-ALA) with BLC demonstrated no overall improvement in progression (RR 0.74; 95% CI 0.52–1.03);³³ however, when performing a subanalysis of four HAL trials, there was a significant improvement in progression (RR 0.51; 95% CI 0.28–0.96), albeit based on only 14 events in the treatment arm and 28 events in the control arm. These findings must be interpreted with caution, as actual event rates are low and the meta-analyzed RR for progression is from subgroup analyses, which may be prone to bias. Overall, these results are encouraging and hopefully BLC with HAL will lead to significant improvements in progression rates for NMIBC.

patients with longer followup. As we have demonstrated in the scenario analyses (20% and 50% improvement in progression RR), an improvement in progression rates for BLC with HAL would have important economic implications for implementing this procedure for NMIBC patients.

The strength of the current decision/cost-effectiveness analysis for BLC with HAL is that this is the first model to use meta-analyzed probabilities for recurrence rates from previous RCTs. Earlier cost-effectiveness analyses used data from single RCTs or ‘best case scenario’ probabilities, thus the results from the current analysis are likely more generalizable. Second, the current manuscript provides scenario and sensitivity analyses that guide where future cost savings may be attained. Third, our study uses patient level, micro-costing data. Limitations to this study are as follows. First, the costs were derived from a universal healthcare model, which may not be generalizable to other private insurance-based or two-tiered (private insurance and public sector) healthcare systems. Second, the model design does not allow for cost-analyses to be performed beyond five years after initial TURBT; thus, potential cost-effectiveness beyond five years is not ascertainable and we cannot delineate the time point when BLC with HAL generates cost savings. Third, the model does not account for the fact that, in WLC, an early recurrence secondary to incomplete resection may lead to repeat induction BCG in the WLC group, thus underestimating cost savings possible in the base case. Finally, the decision model did not allow for consideration of utilities (measures of global health-related quality of life) or quality-adjusted life years (QALY), thus preventing reporting of quality-adjusted outcome data or incremental cost-effectiveness ratios.

Conclusion

BLC with HAL decreases disease recurrence in patients with NMIBC, with a five-year cost of approximately \$1–5 million for jurisdictions of 4–13 million people. Of interest to healthcare administrators, this also reduces the bed-day requirement of patients undergoing TURBT, allowing redistribution of hospital resources, including the treatment of more patients. If BLC with HAL truly improves progression rates, this would considerably improve cost-effectiveness and may even yield cost savings.

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