INITIAL EXPERIENCE WITH HEXVIX INDUCED FLUORESCENCE BLUE LIGHT CYSTOSCOPY IN BLADDER CANCER DIAGNOSIS

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Abstract

Introduction. Nowadays, Hexvix (hexyl aminolevulinate - HAL) fluorescence cystoscopy represents an increasingly acknowledged diagnostic method for patients with bladder cancer. The aim of our study was to establish the place of this procedure in superficial bladder tumors diagnosis, and to compare it with standard white light cystoscopy (WLC).

Material and methods. In December 2007, Hexvix fluorescence cystoscopy was performed in our clinical department in 15 cases. The resulting maps of the suspicious lesions were afterwards compared between the two methods. TUR was performed for all
apparent tumors detected in such manner, followed by the pathologic analysis of the specimens.

**Results.** Patients have been divided into four groups. Group I was represented by nine cases (60%), presenting a total number of 13 tumors, which have all been diagnosed by both WLC and blue light cystoscopy (BLC), and entirely confirmed by pathology. Group II consisted in four patients (26.6%), in which WLC diagnosed five tumors, while BLC discovered five additional lesions, four of which have been confirmed by the pathological exam. Group III described one case (6.6%) tumor-free according to WLC, but presenting two pathologically confirmed carcinoma in situ (CIS) lesions, according to BLC. Group IV consisted in one patient (6.6%), with two apparently flat lesions on WLC, with no fluorescence in BLC and no pathological confirmation. From the total number of 27 tumors with positive histology, WLC correctly diagnosed 18 (66.7%), with a rate of 10% (2/20) false-positive results, while BLC diagnosed 26 of them (96.3%), however presenting a rate of 3.7% (1/27) false-positive results.

**Conclusions.** Hexvix fluorescence cystoscopy is a valuable diagnostic method, with considerably better results in detecting superficial bladder tumors by comparison to WLC. This fact may lead to a significantly improved endoscopic treatment for such cases, especially in Ta tumors and CIS. The impact upon patients’ survival is yet to be determined.

**Key words:** blue light cystoscopy, CIS, fluorescence, Hexvix, hexaminolevulinate, superficial bladder tumors.
Introduction

Bladder cancer represents a common malignancy, with a severely high recurrence rate.

According to the 2007 European Association of Urology (EAU) Guidelines, WLC is regarded as the gold-standard diagnostic method for superficial bladder tumors (CIS, Ta, T1) [1].

Unfortunately, small papillary or flat urothelial lesions (CIS) can be easily overlooked in this manner, thus leading to a significant increase of the recurrence rate [2].

So, the need for a more sensitive diagnostic tool, backed-up by extensive studies occurred during the recent years. Photodynamic Diagnosis (PDD) seems to be the answer to this problem.

Since March 2005, the hexyl-aminolevulinic acid (ALA) ester (HAL - Hexvix®) has been approved for the diagnosis of bladder cancer in 27 EU/EEA countries. [3]

According to Stepp and Waidelich, this European approval constitutes an important milestone in the long-lasting history of „photodynamics” for urology in general, and fluorescence cystoscopy in particular [4].

The EAU Guidelines state that fluorescence cystoscopy, performed in blue-light and using a porphyrin-based photosensitizer, may help discovering suspicious areas for carcinoma in situ (CIS) or small papillary tumors, which can hardly be detected in white-light [1]. Consequently, TURB under fluorescence guidance seems to reduce the risk of tumor recurrence. [3]
In our country, Hexvix fluorescence cystoscopy was performed as a national premiere in the Department of Urology of “Saint John” Emergency Clinical Hospital in December 2007, thus creating the premises for remarkably improved diagnosis and treatment in superficial bladder tumors.

**Material and Methods**

In December 2007, 15 consecutive cases, 12 men and three women, with a mean age of 68 years (range 36 to 78) with hematuria and positive urinary cytology have been investigated in our Clinical Department.

All patients underwent a standard investigative protocol, including general clinical examination, blood tests, urine culture, abdominal ultrasonography and IVP. No imagistic evidence of upper urinary tract disease has been found.

After complete voiding, a 14 Ch bladder catheter was indwelled, followed by bladder instillation with Hexvix (100 mg dissolved in 50 ml phosphate buffer solution, 8 mmol), at least one hour prior to cystoscopy. The catheter was removed after instillation (except in patients with urinary incontinence, when it was simply clamped), and patients were instructed not to void.

The equipment necessary for BLC consisted in a high-power endoscopic light source with integrated excitation filter (wavelength 380-450 nm), which passes primarily blue light (D-light-C Storz system), a special light cord, a Storz rigid cystoscope with an integrated filter in the eyepiece, a foot pedal which allows convenient switching between
white and blue light, a high sensitivity version of the endoscopic camera, displaying a special “fluorescence mode” and a standard color monitor.

All procedures have been performed under spinal anesthesia.

The first step of the endoscopic procedure consisted in repeated washing of the bladder, in order to evacuate the Hexvix solution.

Consequently, the excessive fluorescence of the bladder content is prevented, thus significantly improving the contrast required for small lesions’ detection.

Afterwards, we performed careful WLC, and the lesions or suspicious areas discovered were mapped onto a bladder chart.

The following step was represented by BLC, also resulting in a classification and mapping of the diagnosed tumors, which appeared distinctively fluorescent in blue light (fig. 1).

![Figure 1: Distinctive Hexvix induced fluorescence of bladder urothelial tumors in blue light](image)

A comparison of some uncertain lesions on the two bladder charts was obtained by repeated switching from white to blue light, and backwards.
After completely drawing the two tumor maps, all the suspected lesions established by the two types of cystoscopy underwent transurethral bladder resection (TURB).

The histopathological exam of all biopsy samples provided us with a “pathological” bladder chart for each patient.

A comparison between the three bladder maps was performed, in order to establish the accuracy of each type of cystoscopy.

**Results**

According to the diagnostic established by the two types of cystoscopy, as well as to the histology results, the 15 patients included in our study have been divided into four different groups.

Group I included the cases in which the bladder maps described by WLC and BLC were identical, and confirmed by the pathological examination.

This group included nine cases (60%) in which 13 tumoral lesions were identified by both diagnostic tools. One pT1 tumor and one CIS were identified in one patient, two pT1 and one pTa tumor in one patient, two pTa tumors in one patient (fig. 2), one pTa tumor in two patients, one pT1 tumor in three patients and one pT2 tumor in one case. So, there were no false-positive lesions among these cases, according to both methods.
Group II included the cases diagnosed with bladder cancer by WLC and in which BLC showed at least one supplementary bladder tumor.

This group consisted of four patients (26.6%). In the first case, WLC described one pT1 tumor. BLC discovered an additional pTa tumor, confirmed by the hystopathological exam. In the second cases, WLC found a single pT1 tumor. BLC discovered three more pTa tumors. In the third case, WLC diagnosed one pT2 tumor. BLC described an additional papillary tumor (confirmed as pTa) and a suspicious flat lesion (unconfirmed by pathology). In the last case of this group, WLC discovered one pT1 tumor and one pTa tumor, while BLC established the presence of an additional pTa tumor and a CIS lesion (fig 3, 4). In this case, the pTa tumor described by WLC, presented no fluorescence in BLC.
Figure 3: pTa urothelial tumor not visible in white light but with specific fluorescence in blue light

Figure 4: CIS not visible in white light but with specific fluorescence in blue light

Group III consisted of one case (6.6%), in which WLC found no tumoral lesion and BLC described two CIS lesions confirmed by pathology (fig. 5).
Group IV included one case (6.6%), in which WLC showed two apparently flat lesions, with no fluorescence in BLC and no pathological confirmation (fig. 6).

After summarizing all of the above data, we may conclude that a total number of 27 tumors (12 pTa, 4 CIS, 9 pT1, 2 pT2) have been confirmed as malignant by pathology, being present in 14 of the 15 cases (93.3%).
Twenty suspicious tumoral lesions were present on the WLC bladder maps, 18 of them (90%) being pathologically confirmed (1 CIS, 6 pTa, 9 pT1, 2 pT2). Two suspect flat lesions (10%) represented a false-positive result.

So, the sensitivity of WLC was 66.7% (18 of the actual 27 tumors have been correctly diagnosed), while the specificity was 90% (18 of the 20 suspicious lesions have been pathologically confirmed).

Twenty-seven suspicious tumoral lesions were identified during BLC, of which 26 were verified according to the pathology exam (4 CIS, 11 pTa, 9 pT1, 2 pT2). The false positive results were represented by one CIS suspicious lesion. One pTa tumor described by WLC was not diagnosed by BLC.

Therefore, this diagnostic method described a sensitivity of 96.3% (26 out of the 27 pathologically confirmed tumors have also been emphasized in blue light), as well as a specificity of 96.3% (26 of the 27 diagnosed lesions proved to be tumors).

No complications related to Hexvix – BLC were encountered.

**Discussions**

BLC is a diagnostic method which emerged from the constant need to improve the efficacy of standard WLC.

The first attempts with tetracycline fluorescence took place in 1957. In 1975, the haematoporphyrin derivate (HpD) was initially proposed for bladder cancer detection by Kelly. Photofrin, a drug derived from HpD, was first applied for bladder cancer imaging
by Baumgartner in 1987. The intravesical instillation of 5-ALA, a precursor of photoactive porphyrin, was first implemented by Kenedy in 1992 [5].

ALA was the first topical agent used for PDD. Nowadays, it has been replaced by a more potent lipophilic derivate, HAL – Hexvix, an improved ester of the aminolevulinic acid, which provides the benefits of increased selectivity and brighter fluorescence [6].

Hexvix fluorescence is related to the increased preferential accumulation of the photoactive porphyrin in the neoplastic tissue, resulting in red fluorescence emitting tumor formations which have been previously undetected [7].

A considerable advantage of this new product is represented by the fact that it significantly shortens the amount of time needed for drug exposure prior to cystoscopy [8].

Marti and Jichlinski evaluated the intensity and localization of protoporphyrin IX (Pp IX) in superficial transitional cell carcinoma of the bladder, following topical administration of its precursor, either ALA or HAL. The authors underlined the fact that HAL is an excellent precursor for Pp IX synthesis in bladder cancer, providing the highest Pp IX fluorescence intensity (with the 2 + 2 hours topical administration condition, HAL fluorescence displayed double intensity by comparison to ALA), as well as remarkable fluorescence contrast between normal and malignant urothelial cells [9].

There are a number of factors that must be taken under consideration while discussing the accuracy of BLC. Much depends on the actual technique implied by the procedure. The direct illumination in front of the lesion is a very important goal, since tangential blue light due to the incorrect positioning of the endoscope may create a false
fluorescence of the normal urothelium (fig. 7). Also, the bladder must be fully distended, in order to eliminate the presence of the mucosal folds, which may also lead to false positive results.

Figure 7: False positive fluorescence of the normal urothelium in tangential view

The prostatic urethra, bladder neck and the ureteral orifices usually appear fluorescent (fig. 8).

Figure 8: Normal fluorescence of the prostatic urethra
A good modality of checking false fluorescence is by pressing the respective area with the Collins loop. If the fluorescence disappears, it is most likely that there is no tumor in place.

Also, the margins of a fluorescent bladder tumor have to appear quite sharp and well separated from the surrounding regions.

The resection should only begin after performing the two types of cystoscopy, in order to prevent biopsy related bleeding, which may alter the subsequent visualization and diagnosis, due to blue light absorption by blood and blood clots [10].

We must also take into consideration the exclusion criteria for patients who are to undergo this procedure: allergy to HAL or related compounds, pregnancy, lactation, BCG (Bacillus Calmette-Guerin) or chemotherapy intravesical instillations sooner than 3 months. These instillations may produce bladder inflammation, which determines increased fluorescence of the bladder mucosa and consequently, false-positive results [10].

In a multicenter study which included 298 patients, Fradet and Grossman aimed to draw a parallel between Hexvix - BLC and WLC regarding the detection of CIS. In 58 cases with 113 CIS lesions, BLC detected 104 (92%), while WLC only established the presence of 77 (68%). Therefore, the authors concluded that Hexvix - BLC is able to diagnose CIS lesions that may be missed by WLC [7].

In a European multicenter study, performed on 211 patients, Schmidbauer and Wijtes compared HAL fluorescence cystoscopy and standard WLC regarding the detection of CIS in cases suspected of having high risk bladder cancer. They arrived to the conclusion that HAL cystoscopy significantly improves the detection of bladder CIS,
which has important consequences for the clinical management, and may also improve the patients’ prognosis [6].

In another multicenter study performed by Grossman which took into account 311 patients, HAL fluorescence cystoscopy was compared with WLC concerning the detection of Ta and T1 papillary lesions. The conclusion was that Hexvix - cystoscopy detected at least 1 more Ta and T1 papillary tumor than WLC, as far as approximately a third of such cases have been concerned [10].

In a prospective study, Witjes and Moonen described a comparison between HAL based flexible and rigid fluorescence cystoscopy on one hand, and rigid WLC on the other hand, in bladder cancer diagnosis. They emphasized the fact that flexible fluorescence cystoscopy is feasible and seems to be comparable to rigid WLC, and slightly inferior to rigid fluorescence cystoscopy [11].

Loidl and Schmidbauer accomplished a prospective controlled study, in which they analyzed a within-patient parallel between flexible HAL cystoscopy and standard flexible cystoscopy, HAL rigid and standard white light rigid cystoscopy. The bottom line was that HAL fluorescence flexible cystoscopy compared to HAL rigid cystoscopy showed almost equivalent results in detecting papillary and flat lesions in bladder cancer patients, and both procedures were superior to standard white light flexible cystoscopy [2].

During another prospective, multicenter study, Jocham and Wijtes aimed to determine weather improved tumor detection using HAL fluorescence cystoscopy could lead to a significant improvement concerning treatment in patients with bladder cancer. After analyzing 146 cases, they draw the conclusion that 17% of patients received a more
appropriate treatment following BLC, and that 22% of patients without tumors were excluded. So, an improved treatment applied in a significant number of patients is quite evident [12].

It has been shown that recurrence at any site in the bladder at the first follow-up cystoscopy after TUR is one of the most important prognostic factors for time to progression. Therefore, PDD might be most useful for patients with primary tumors [5].

However, because of the fact that 5-ALA and HAL do not penetrate much deeper than 1 mm, fluorescence cannot indicate the invasion depth. So, a second TURB should be performed in T1 tumors, in order to rule out muscle invasion [5].

Frampton and Plosker mention two European, multicenter, phase III trials, which analyzed HAL cystoscopy as an adjunct procedure to standard cystoscopy in patients with known or suspected bladder cancer. According to one trial, HAL cystoscopy detected 96% of the patients with CIS, which represented 28% more patients with CIS than standard cystoscopy. Regarding the other trial, 17% of patients were selected to receive a more complete treatment following HAL cystoscopy, by comparison to standard cystoscopy, due to the improved tumor detection rate [13].

In his editorial emphasizing a cost-effectiveness analysis upon new urologic procedures, Colombo underlines the fact that currently, the most obvious clinical impact of PDD has been proved regarding the management of any form of CIS, T1G3 patients during follow-up after TURB, as well as multifocal disease during TURB or follow-up [14].

Jichlinski and Guillou examined the sensitivity and specificity of Hexvix fluorescence cystoscopy in patients with superficial bladder cancer. HAL cystoscopy was
well tolerated, with no definite drug related adverse events, with an increased sensitivity, improved detection of bladder tumors, and a particular usefulness in finding CIS [15].

Most of the adverse events considered to be related to HAL instillation are mainly limited to local symptoms such as dysuria, hematuria, bladder spasm and bladder pain. Regarding these side effects, there is no difference between patients undergoing fluorescence endoscopy and standard WLC, respectively [5].

**Conclusions**

Hexaminolevulinate (HAL – Hexvix) fluorescence cystoscopy is a powerful diagnostic method in superficial bladder cancer, with more effective imaging, higher detection rates and improved sensitivity by comparison to WLC.

Patients with Ta, T1 and especially CIS are the main beneficiaries of this technique, as it provides them with better chances for a complete TURB.

According to significant studies, the reduced recurrence rate in cases diagnosed with BLC represents the main advantage of the procedure.

Further studies need to establish the impact of Hexvix-BLC upon the prognostic and the survival rates in patients with superficial bladder tumors.

Also, large and multicenter studies, comparing the outcome of patients with primary and recurrent cancer following PDD are still warranted [8].

In the future, the impact of Hexvix – PDD upon the recurrence rates in superficial bladder tumors in our series remains to be evaluated.
References


