

Efficacy of Hexaminolevulinate Photodynamic Diagnosis of Non-Muscle Invasive Bladder Cancer

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Abstract

Objective: This study evaluated the efficacy of hexaminolevulinate fluorescence cystoscopy as a diagnostic tool for bladder cancer. The study was a case series in the Department of Urology in Hippokratio General Hospital of Athens between October 2008 and May 2012.

Methods: Fifty patients (43 males and 7 females) who were investigated for hematuria were included in the study. White light cystoscopy (WLC) was first performed in all patients and after was performed a fluorescence cystoscopy (BLC-blue light cystoscopy). Biopsies were collected from any suspicious area and resection of the tumors identified (TUR).Whenever no suspicious areas could be seen, a standard random mapping including 8 biopsies overall was completed.

Results: Patients demographic data and clinical history are presented in Table 1. Two-hundred twenty specimens were extracted and bladder cancer was diagnosed in 137. There were 17 CIS lesions all diagnosed with BLC whereas only 11 with WLC. WLC correctly diagnosed 109/140 specimens and the positive and negative predictive values were 77.9% and 65% respectively. The sensitivity and specificity were 79.6% and 62.6% respectively. BLC diagnosed 125/169 specimens and the positive and negative predictive values were 73.9% and 76.5% respectively. The sensitivity of BLC was 91.2% and the specificity 46.9%.

Conclusion: Hexaminolevulinate-guided cystoscopy is a valuable diagnostic method, with considerably improved accuracy and improvement in diagnosis of non-muscle-invasive bladder cancer and especially CIS.

Keywords: Hexaminolevulinate-Guided cystoscopy; Bladder cancer; Transurethral resection

Introduction

Bladder cancer is a very common malignancy of the urinary tract in the Western world, especially in men, three times more than women [1].

North America and Western Europe have very high incidence rates of bladder cancer in contrast with Asian countries and Central Africa where the incidence rates are very low [2,3]. Most (75-85%) bladder cancers incidences are non-muscle invasive at first diagnosis (pTa, pT1, carcinoma *in situ* [CIS]) [4]. In non-muscle-invasive bladder cancer (NMIBC), approximately 70% of patients present as pTa, 20% as pT1, and 10% as CIS lesions [1]. Generally, the prognosis of NMIBC is good, although 30-80% of cases will recur and 1-45% of cases will progress to muscle invasion within 5 yr [1,5]. Early detection of bladder cancer is therefore mandatory in order to reduce the mortality rate. It has been estimated that 10-20% of bladder tumors are overlooked in conventional WLC [6].

Hexaminolevulinate acid (HAL), an ester derivative of 5-ALA (ALA-Aminolevulinic acid) bioavailability is better, thus a higher tissue accumulation of photoactive porphyrins is achieved and this advantage is added to the diagnostic value of WLC [7]. Clinical trials

of phases 1-3 led to the approval of HAL (Hexvix) for the detection of bladder cancer in 26 European countries. The aim of our study was to compare WLC and PDD (photodynamic diagnosis) with HAL in the diagnosis of bladder tumors.

Materials and Methods

The study was a case series and was conducted between October 2008 and May 2012. Fifty patients (43 men and 7 women) with primary bladder cancer were included in the study. All patients have been admitted and investigated for hematuria and/or positive urinary cytology (Table 1) [8-11]. A standard investigative protocol which included general clinical examination, blood tests, urine culture, abdominal ultrasonography, IVP (intravenous pyelography) and eventually a CT scan was applied in all cases. The study was approved by the Hospital Ethical Committee and informed consent was obtained by all patients.

A standard WLC was always performed as a first step of the evaluation and all suspicious areas were accurately described and reported on a bladder map. Thereafter, a fluorescence cystoscopy was accurately performed and any suspicious area was reported on the same map. Biopsies were collected from any suspicious area either under blue or white light and resection of the tumors identified (TUR) [13-16].Whenever no suspicious areas could be seen, a standard

random mapping including 8 biopsies overall was completed. All WLCs and BLCs were performed by the same expert urologist (Table 2) [17].

Characteristic	Value
No. of patients	50
Age (years)	64.8 ± 8.4
Gender (M/F)	43/7
Smokers ratio	41/50
Urinary cytology	
Positive	14
Negative	20
Suspicious	8
Hematuria	39

Table 1: Patients characteristics.

Patients with acute or chronic urinary tract infection, urinary tract lithiasis, multi-drug allergies as well as patients underwent recent BCG installation, radiotherapy and multi bladder catheterizations were excluded [12].

	Presence of Ca	Absence	Total
WLC+	109	31	140
WLC-	28	52	80
BLC+	125	44	169
BLC-	12	39	51
Total	137	83	220

Table 2: WLC and BLC findings and diagnosis.

For BLC, patients received 85mg HAL- Hexvix® bladder instillation (85 mg dissolved in 50 mL phosphate buffer solution), using a 14Ch bladder catheter 1 hour prior to cystoscopy [18-22]. The Storz D-light-C system with a xenon arc lamp as source was used in all cases.

Bladder biopsies were performed in selected cases from bladder mucosa areas considered suspicious at WLC or BLC as well as from normal bladder mucosa [23].

Within six hours after TUR all patients included in the study underwent a postoperative chemotherapy instillation of 50 mg Epirubicin. All patients received an adjuvant intravesical immunotherapy with BCG vaccine as all patients had high or intermediate-risk cancer.

Categorical data were examined by chi-square test, while continuous variables were evaluated by the t-test. Specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with the usual mathematical formulas (Table 3) [24].

Results and Discussion

The study was a case series and was conducted between October 2008 and May 2012. Fifty patients (43 men and 7 women) with

primary bladder cancer were included in the study. All patients have been admitted and investigated for hematuria and/or positive urinary cytology [25]. A standard investigative protocol which included general clinical examination, blood tests, urine culture, abdominal ultrasonography, IVP (intravenous pyelography) and eventually a CT scan was applied in all cases. The study was approved by the Hospital Ethical Committee and informed consent was obtained by all patients.

Patients with acute or chronic urinary tract infection, urinary tract lithiasis, multi-drug allergies as well as patients underwent recent BCG installation, radiotherapy and multi bladder catheterizations were excluded.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
WLC	79.6	62.6	77.9	65
BLC	91.2	46.9	73.9	76.5

Table 3: Sensitivity, Specificity, PPV and NPV of WLC and BLC respectively.

A standard WLC was always performed as a first step of the evaluation and all suspicious areas were accurately described and reported on a bladder map. Thereafter, a fluorescence cystoscopy was accurately performed and any suspicious area was reported on the same map. Biopsies were collected from any suspicious area either under blue or white light and resection of the tumors identified (TUR).Whenever no suspicious areas could be seen, a standard random mapping including 8 biopsies overall was completed. All WLCs and BLCs were performed by the same expert urologist.

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Categorical data were examined by chi-square test, while continuous variables were evaluated by the t-test. Specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) were calculated with the usual mathematical formulas.

Conclusion

Hexaminolevulinatate-guided cystoscopy is a valuable diagnostic method, with considerably improved accuracy and improvement in diagnosis of non-muscle-invasive bladder cancer and especially CIS.

Consent: All patients have given their informed consent for the study. All signed forms are available on request.

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