Journal of the Egyptian National Cancer Institute (2016) **28**, 89–94

Cairo University

Journal of the Egyptian National Cancer Institute

www.elsevier.com/locate/jnci
www.sciencedirect.com

Full Length Article

Reducing understaging of bladder cancer with the aid of photodynamic cystoscopy

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Received 27 October 2015; revised 29 February 2016; accepted 9 March 2016
Available online 1 April 2016

KEYWORDS

Bladder;
Cancer;
Photodynamic;
Cystoscopy

Abstract *Background:* The authors evaluated the role of photodynamic cystoscopy in the detection of additional urothelial lesions, mainly carcinoma in situ, that would not be detected solely with white light cystoscopy, leading to disease understaging.
Methods: From 2009 to 2011, 70 patients underwent white light cystoscopy, followed by photodynamic cystoscopy (blue light system, Karl Storz, Tuttlingen, Germany). Preoperatively they were instilled intravesically with 50 ml of Hexvix (Hexaminolevulinate hexylester). We recorded all lesions found with white light cystoscopy and the additional lesions revealed by blue light cystoscopy. Afterward all lesions were removed and sent for pathologic evaluation.
Results: Seventeen patients (24.3%) had primary tumors while 53 patients (75.7%) had recurrent disease. In 53 out of 70 patients (75.7%) white light cystoscopy revealed urothelial lesions. In the rest 17 patients who had no findings with white light cystoscopy, blue light cystoscopy revealed 7 cases of Cis (41.2%) and 8 cases of dysplasia (47%). In the group of patients with visible lesions in white light cystoscopy photodynamic cystoscopy revealed additional carcinoma in situ in 22 patients. Altogether additional carcinoma in situ cases found with the aid of photodynamic cystoscopy were 29 out of 70 cases (41.4%).
Conclusions: Photodynamic cystoscopy is the most efficient diagnostic procedure for flat urothelial lesions and especially for carcinoma in situ. It is significantly more sensitive than conventional white light cystoscopy in Cis diagnosis, thus reducing understaging of the disease and consequently improving recurrence and progression rates.

Introduction

Bladder cancer is a very frequent neoplasm (the fourth most frequent cancer in men and the ninth in women) [1,2]. In 2006 in Europe 104.400 new patients with bladder cancer were diagnosed accounting for 6.6% of all cancers in men and 2.1% in women. Male to female ratio is 3.8–1. Bladder cancer is responsible for 4.1% of deaths due to cancer in men and

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Peer review under responsibility of The National Cancer Institute, Cairo University.

http://dx.doi.org/10.1016/j.jnci.2016.03.002

1.8% in women [3]. During the last 60–70 years a considerable rise in bladder cancer diagnosis was noticed, which, however, was suppressed the last years and in some countries totally disappeared due to well organized smoking cessation programs [4].

The cornerstone of bladder neoplasm diagnosis is cystoscopy, also playing the most important role in the follow-up of patients with bladder cancer history. However very small Ta or T1 tumors can be missed with the rates of unnoticed tumors varying from 3.4% to 20.6% for single tumors and from 7.4% to 45.8% in cases of multiple tumors [5].

The major diagnostic disadvantage of cystoscopy is its low sensitivity for the diagnosis of flat urothelial lesions, especially for carcinoma in situ (Cis). Flat urothelial lesions are not always visible or are very often difficult to distinguish from normal epithelium. According to 2004 WHO classification, flat urothelial lesions are dysplasia, urothelial hyperplasia, reactive atypia, atypia of unknown significance and carcinoma in situ [6]. Among these lesions carcinoma in situ is the most important and most dangerous neoplasm as it is a flat, high grade, non muscle invasive cancer. It is found as a primary lesion in 1%-3% of all urothelial malignancies or it can be found as a secondary cancer during the follow-up of patients with previous exophytic tumors, or simultaneously with other tumors. In the last case it accompanies 5% - 19% of non muscle invasive tumors and 45% - 65% of muscle invasive neoplasms [7]. Patients with Cis have 40% to 83% possibility to develop muscle invasive cancer if left untreated, especially if they have concurrent papillary tumors [8]. The presence of Cis is an independent prognostic factor for recurrence, progression and disease specific mortality [9]. Cystoscopy can diagnose Cis in 38.1–71.4% of cases. This means that a large number of Cis lesions are missed thus worsening prognosis of these patients [10].

Photodynamic cystoscopy came to the fore in order to overcome these drawbacks of classical cystoscopy. This technique is based on the selective concentration of photosensitizing agents in neoplastic cells of bladder urothelium, which then emit fluorescence that can be visualized with blue light, using the proper equipment [11,12].

Materials and methods

This study was approved by the Institutional Review Board of Laiko Athens Hospital. Records of patients with primary or recurrent bladder cancer from 2009 to 2011 to the department of urology, Laiko hospital were retrospectively reviewed. From 2009 to 2011, 70 patients (66 men and 4 women) aged 25 to 82 years old (mean age 66.4 ± 9 years) were enrolled in this study.

Provided they had negative urine culture, 50 ml Hexvix (Hexaminolevulinate Hexylester) was instilled via a 10F Nelaton catheter in patients' bladder 1 h preoperatively. After keeping the solution for 1 h in their bladder, the patients were asked to urinate before they were carried to the surgery room. The time frame between drainage of the drug and inspection of the bladder was 60 min. This particular time frame was important not to be exceeded, to avoid possible distortion of visualization with blue light.

The equipment used was Karl Storz Photodynamic Diagnostic D-Light C (PDD) System. The system includes a D-Light-C light Source and a Fluid Light Cable, a PDD cystoscope, an Endovision Tricam® SL Camera Control Unit and a PDD Camera Head.

In the operating room first cystoscopy was performed with white light and all visible lesions were recorded. Cystoscopy with the blue light system followed and all additional lesions were recorded. Consequently all lesions (visible with white and blue light) were removed and sent separately for pathologic evaluation. A biopsy sample from normally appearing urothelium was taken.

The biopsy specimens were all evaluated by the same pathologist according to 2004 WHO classification of urothelial tumors and 2002 TNM staging system.

Results

The medical records of 70 patients with primary or recurrent bladder cancer who had received surgical treatment from 2009 to 2011 were retrospectively reviewed. Among them were 66 males (91.7%) and 4 females (8.3%), whose age ranged from 25 to 82 years, with an average of 66.4 ± 9 years. Primary tumors were detected in 17 patients (24.3%) while 53 patients (75.7%) had recurrent disease. In those cases of recurrent disease primary lesions were Ta low grade in 29 patients (54.7%), Ta high grade in 5 patients (9.4%), T1 low grade in 4 patients (7.5%), T1 high grade in 14 patients (26.4%) and Ta with synchronous Cis in 1 patient (1.9%). The demographic and clinicopathological data are shown in Table 1.

In 53 out of 70 patients (75.7%) white light cystoscopy revealed urothelial lesions. Namely these lesions were Ta low grade (12 cases, 22.6%), Ta high grade (6 cases, 11.3%), T1 low grade (2 cases, 3.8%), T1 high grade (12 cases, 22.6%), Cis (8 cases, 15.1%), Ta with concurrent Cis (1 case, 1.9%), T1 with concurrent Cis (4 cases, 7.5%), T2 (1 case, 1.9%), dysplasia (6 cases, 11.3%) and denuding cystitis (1 case, 1.9%). The results of positive white light cystoscopy cases are summarized in Table 2.

All subjects who were positive to white light cystoscopy had additional lesions with fluorescence cystoscopy. Additional Carcinoma in situ was detected in 22 patients with photodynamic cystoscopy (Table 3), dysplasia, reactive atypia and denuding cystitis in 21, 3 and 7 patients respectively.

In the rest of the 17 patients with no findings with white light cystoscopy, blue light cystoscopy revealed lesions that would be otherwise missed. More specifically these lesions were Cis (7 cases, 41.2%), dysplasia (8 cases, 47%), denuding cystitis (1 case, 5.9%) and reactive atypia (1 case, 5.9%) (Table 4).

Discussion

As mentioned above cystoscopy may be the cornerstone of bladder cancer diagnosis and follow-up. Nevertheless it can sometimes fail in the diagnosis of urothelial tumors in 3.4% to 45.8% of cases of Ta or T1 tumors [5]. Its diagnostic efficacy is even smaller for flat urothelial lesions and more specifically for carcinoma in situ. Cis diagnosis is based on the combination of urine cytology with cystoscopy and biopsy of the bladder. The diagnosis rate of Cis with conventional cystoscopy (white light) varies in published studies from 38.1% to 71.4% [10], which indicates that conventional cystoscopy may miss a significant number of Cis lesions. This is of major importance,