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Photodynamic Diagnosis in Non–Muscle-Invasive Bladder Cancer

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Abstract

Context: Although crucial to optimal management, transurethral resection of the bladder (TURB) techniques and results are highly heterogeneous in Europe, due in part to site-specific variations in the detection of cancer foci.

Optimizing detection is of tantamount importance. Techniques were designed that took advantage of the ubiquitous observation that cancer cells exhibit abnormal heme metabolism resulting in increased intracellular concentrations of protoporphyrin IX (PPIX) after topical or systemic application of heme precursors. In the bladder, the excitation of PPIX by blue light (380–450 nm) induced a faint red (640-nm) fluorescence of cancer cells that gave rise to the concept of photodynamic diagnosis (PDD) in non–muscle-invasive bladder cancer (NMIBC).

Evidence acquisition: This paper is based on a presentation at the 2010 meeting of the European Society of Oncological Urology. A structured comprehensive literature review was performed. The latest version of the European Association of Urology (EAU) guidelines on NMIBC was also accessed.

Evidence synthesis: Current diagnosis of NMIBC is based on white light (WL) cystoscopy. The current literature on NMIBC suggests that there is significant room for improvement in that setting. One solution was to augment the signal-to-noise ratio of suspicious lesions versus normal mucosa by highlighting cancer cells either indirectly, through the alteration in their stromal support such as in narrow-band imaging, or directly, as in Hexvix-based PDD. Hexvix is now available in most European countries and use is steadily increasing.

Recent evidence at the molecular level has confirmed clinicians' suspicions that NMIBC is a very heterogeneous condition. Sylvester et al identified six independent risk factors (number of tumors, tumor size, prior recurrence rate, T category, carcinoma in situ [CIS], and grade), the combination of which was predictive of progression to muscle-invasive state and of recurrence. As recommended by the EAU guidelines, these factors are used to stratify patients into risk groups that drive treatment and follow-up modalities.

In the setting of low-risk NMIBC, three objectives can be addressed by Hexvix PDD—detection, quality control of resection, confirmation of the absence of CIS—with the ultimate objective of reducing the recurrence rate and related costs. Hexvix PDD increases the rate of detection of NMIBC by 20%. It is a valuable tool in controlling the quality of resection at the end of TURB and was recently shown to reduce the recurrence rate at 9 mo by 21%, which is anticipated to offset the supplementary costs for equipment and Hexvix within the first year of follow-up.

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Regarding high-risk NMIBC, Hexvix PDD facilitates the detection of CIS and might improve treatment results by reallocating the case to a higher level of risk, requesting more intensive treatment (eg, bacillus Calmette-Guérin), and by improving the quality of resection. Mixed results were observed in control resection, where Hexvix PDD can be used to detect additional lesions such as associated CIS when the first TURB was conducted under WL.

Five endoscopic criteria (smooth of slightly raised appearance, intensity [mild or intense], homogeneous or irregular fluorescence, well-delineated or indistinct limits, detachment of the fluorescent mucosa by the loop) were prospectively recorded to assess their respective value in detecting CIS among the wide array of flat PDD-positive lesions. We showed that a slightly raised appearance and detachment of fluorescence by gentle stroking with the loop were associated with the diagnostic of CIS. This new semiology could refine the level of suspicion of PDD-positive flat lesions to reduce the number of false-positive results.

Conclusions: In low-risk NMIBC, Hexvix PDD helps to avoid overlooking small preexisting papillary lesions and to optimize resection. It was recently shown to reduce 9-mo recurrence rates by 20%, which is anticipated to be sufficient to offset the supplementary costs in equipment and drugs. In high-risk NMIBC, Hexvix PDD can be of value in restaging TURB to detect additional lesions such as associated CIS when the first TURB was conducted under WL. Finally, the high rate of false-positive results for flat PDD-positive lesions can be controlled by implementing simple semiotic analysis and focusing on CIS-associated characters such as slightly raised appearance and detachment of fluorescence by gentle stroking with the loop (pink veil sign).

1. Introduction

Although bladder cancer-specific mortality is decreasing in Europe due to the recent decline in smoking by European men and to reduced exposure to occupational carcinogens [1], it remains the fourth-leading cause of cancer death in men. In 2004, there were 120 000 incident cases observed in the European Union, and 70 000 new cases were expected in the United States in 2009 [2].

At first diagnosis, most cases do not exhibit invasion of the muscle layer, befitting the definition of *non–muscle-invasive bladder cancer* (NMIBC), for which bladder endoscopy and optimal transurethral resection of the bladder (TURB) are the cornerstones of risk stratification [3]. It is estimated that more than 320 000 TURBs are performed annually in the European Union.

Although crucial to optimal management, TURB techniques and results are highly heterogeneous in Europe, due in part to site-specific variations in the detection of cancer foci [4] that can be made difficult in conventional white light (WL) cystoscopy by the often multifocal character of NMIBC and by flat carcinoma in situ (CIS) lesions. Optimizing detection is of tantamount importance.

In the early 1990s, techniques were designed that took advantage of the ubiquitous observation that cancer cells exhibit abnormal heme metabolism resulting in increased intracellular concentrations of protoporphyrin IX (PPIX) after topical or systemic application of heme precursors. In the bladder, the excitation of PPIX by blue light (380–450 nm) induced a faint red (640-nm) fluorescence of cancer cells that gave rise to the concept of photodynamic diagnosis (PDD) in NMIBC [5].

The present review aims to summarize the relevance of PDD in the modern management of NMIBC in view of the current literature, European Association of Urology (EAU) guidelines [6], and personal experience.

2. Evidence acquisition and clinical series

This paper is based on a presentation at the 2010 meeting of the European Society of Oncological Urology (ESOU, a section of the EAU). A structured comprehensive literature review was performed. The latest version of EAU guidelines on NMIBC was also accessed [6].

From March 2007 to June 2009, we performed 542 TURBs. Of these, 75 procedures (13.8%) met the French Association of Urology recommendations for PDD (high-grade cytology, multifocal papillary lesions on ambulatory WL fibroscopy, size >3 cm) and were conducted under Hexvix PDD (Exera II; Olympus Europa GmbH, Hamburg, Germany). In all cases suspicious lesions visible in WL and blue light cystoscopy were noted on a bladder chart with their corresponding characteristics and harvested by bipolar resection in saline (TURis; Olympus Winter & IBE GmbH, Hamburg, Germany). One hundred and seventy-six lesions were individually retrieved and sent in separate vials for individual pathologic examination to establish rigorous correlation between endoscopy and pathology.