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Review – Bladder Cancer

Hexaminolevulinate-Guided Fluorescence Cystoscopy in the Diagnosis and Follow-Up of Patients with Non–Muscle-Invasive Bladder Cancer: Review of the Evidence and Recommendations

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Abstract

Context: Compared with standard white-light cystoscopy, photodynamic diagnosis with blue light and the photosensitiser hexaminolevulinate has been shown to improve the visualisation of bladder tumours, reduce residual tumour rates by at least 20%, and improve recurrence-free survival. There is currently no overall European consensus outlining specifically where hexaminolevulinate is or is not indicated.
Objective: Our aim was to define specific indications for hexaminolevulinate-guided fluorescence cystoscopy in the diagnosis and management of non–muscle-invasive bladder cancer (NMIBC).
Evidence acquisition: A European expert panel was convened to review the evidence for hexaminolevulinate-guided fluorescence cystoscopy in the diagnosis and management of NMIBC (identified through a PubMed MESH search) and available guidelines from across Europe. On the basis of this information and drawing on the extensive clinical experience of the panel, specific indications for the technique were then identified through discussion.
Evidence synthesis: The panel recommends that hexaminolevulinate-guided fluorescence cystoscopy be used to aid diagnosis at initial transurethral resection following suspicion of bladder cancer and in patients with positive urine cytology

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but negative white-light cystoscopy for the assessment of tumour recurrences in patients not previously assessed with hexaminolevulinate, in the initial follow-up of patients with carcinoma in situ (CIS) or multifocal tumours, and as a teaching tool. The panel does not currently recommend the use of hexaminolevulinate-guided fluorescence cystoscopy in patients for whom cystectomy is indicated or for use in the outpatient setting with flexible cystoscopy.

Conclusions: Evidence is available to support the use of hexaminolevulinate-guided fluorescence cystoscopy in a range of indications, as endorsed by an expert panel.

1. Introduction

Bladder cancer is a common cancer, with an incidence across Europe of between 3.1 and 12.4 per 100 000 and with almost 45 500 new cases reported in 2006 [1]. Although improvements have been seen in 5-yr survival in some European countries, rates vary widely across the continent [2]. The differences are small, but there are significant socioeconomic and gender-based inequalities in survival, with women and those from more deprived backgrounds at a distinct disadvantage [3,4].

About 90% of bladder cancers diagnosed in developed countries are urothelial carcinomas, and, of those, approximately 75–85% are non–muscle invasive [5–7]. Irrespective of the grade and stage of the tumour at diagnosis, all patients with non–muscle-invasive bladder cancer (NMIBC) require some form of long-term endoscopic surveillance of the bladder after treatment because there is a significant risk of local recurrence [8]. According to risk tables published by the European Organisation for Research and Treatment of Cancer, the calculated probabilities for recurrence of disease range from 15% to 61% at 1 yr to from 31% to 78% at 5 yr; rates for progression range from <1–17% at 1 yr to 1–45% at 5 yr [9].

An important factor predisposing for recurrence is incomplete resection of the original tumour (or missed tumours at initial transurethral resection of bladder tumour [TURBT]). This is documented to occur in >40% of patients initially presenting with multifocal tumours [10] and is due, certainly in part, to the absence of standards for TURBT techniques. Ultimately, identification followed by complete resection and destruction of all cancerous tissue at the time of the initial TURBT is the most desirable outcome and may reduce subsequent recurrence and progression [11,12], with postulated benefits for both patients and the health care economy.

Another key concern is failure to identify the presence of carcinoma in situ (CIS), a tumour entity that is difficult to visualise with standard white-light cystoscopy and carries a considerable risk of both recurrence and progression [11,12].

Random biopsies of normal-looking bladder mucosa to detect CIS used to be undertaken, but this is no longer standard practice. Indeed, studies have shown that random biopsies offer little advantage in terms of detection and can carry an increased risk of implantation of floating tumour cells at sites within the bladder wherever the mucosal barrier has been damaged, potentially leading to tumour recurrence [13–16]. Unquestionably, improved methods of detection are needed.

Compared with standard white-light cystoscopy, photodynamic diagnosis (PDD) with blue light and the porphyrin-

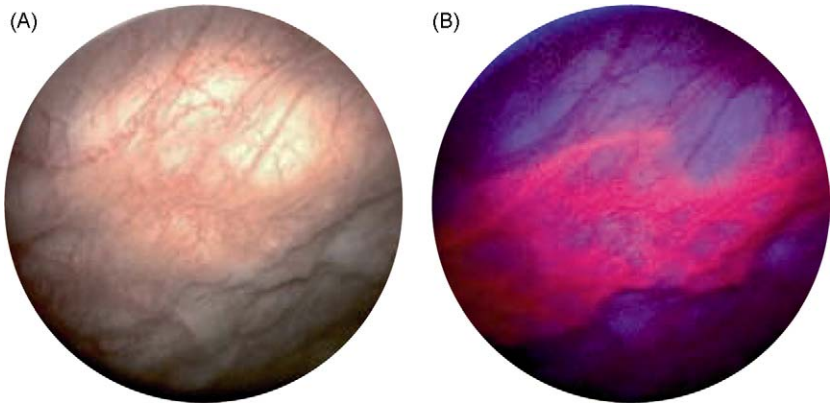

Fig. 1 – Introduction to hexaminolevulinate.
Indication: Detection of bladder cancer, such as CIS, in patients with known or high suspicion of bladder cancer.
Mechanism of action: Photosensitiser—following instillation, hexaminolevulinate causes photoactive porphyrins to accumulate selectively in rapidly proliferating cells (eg, tumour cells). These porphyrins emit red fluorescence when exposed to blue light; hence lesions will be seen as red against a blue background of normal mucosa.
Dosage and administration: (1) Ensure bladder is empty; (2) instill 50 ml of hexaminolevulinate into the bladder; (3) patient should retain solution in the bladder for approximately 60 min; (4) following evacuation of the bladder, cystoscopic examination with both (A) white and (B) blue (wavelength: 380–450 nm) light should begin within 60 min.
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