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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-

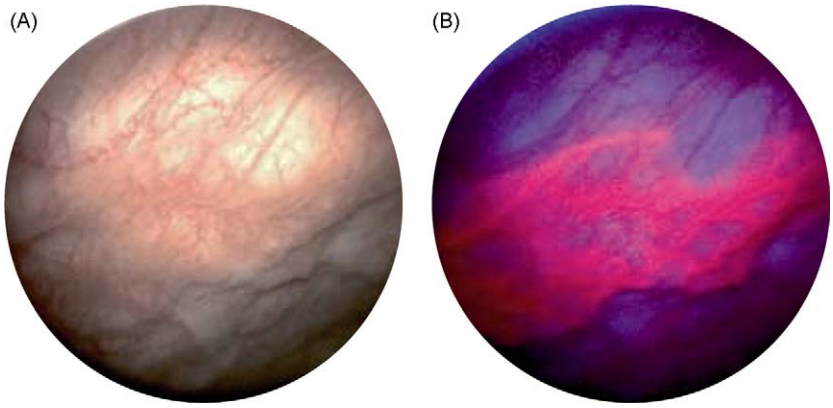

Fig. 1 – Introduction to hexaminolevulinate.
Indication: Detection of bladder cancer, such as CIS, in patients with known or high suspicion of bladder cancer.
Mechanism of action: Photosensitiser—following instillation, hexaminolevulinate causes photoactive porphyrins to accumulate selectively in rapidly 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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Table 1 – Current European guidelines and their recommendations, by country

Country*	Guideline	General recommendation made in line with licensed indication	Specific indication cited				
			To monitor initial TURBT	To aid diagnosis in case of (suspicion) of CIS	To assess multifocal lesions	To assess tumours >3 cm	To assess patients following early recurrence	To follow up T1G3 and CIS
Europe	European Association of Urology [32]	Yes	–	–	–	–	–	–
Czech Republic	Babjuk et al. [33]	Yes	–	Yes	–	–	–	–
France	French Association of Urology [34]	Yes	–	–	Yes	Yes	Yes	Yes
Germany	German Society for Urology [35]	Yes	Yes	Yes	–	–	–	–
Holland	Dutch Urological Association, multidisciplinary guideline [36]	Yes	–	Yes	–	–	–	–
United Kingdom	British Association of Urological Surgeons/British Uro-oncology Group [37]	Yes	Yes	–	–	–	–	–
	Scottish Intercollegiate Guidelines Network [38]	Yes	–	–	–	–	–	–

CIS = carcinoma in situ; T1G3 = tazarotene-induced gene 3; TURBT = transurethral resection of bladder tumour. * Only those countries represented by the authors are included.

derived photosensitiser hexaminolevulinate or its precursor 5-aminolevulinic acid (5-ALA) have been shown to improve the visualisation of bladder tumours, to reduce residual tumour rates by at least 20%, and to improve recurrence-free survival [17–28]. Its ubiquitous use, however, is limited by cost arguments. Due to between-country variations, a cost analysis for Europe as a whole is not feasible; however, numerous model-based analyses have been done across the continent to try to determine the cost effectiveness of PDD versus white-light cystoscopy. These analyses indicate that use of PDD is at least cost neutral [29–31].

Fig. 1 provides a brief introduction to hexaminolevulinate for those readers not familiar with it. Of note, like white-light cystoscopy, PDD is an operator-dependent technique.

Guidelines have been published across Europe advocating the use of hexaminolevulinate and offering relatively uniform advice at a general level (Table 1) [32–38]. There is currently no overall European consensus, however, outlining specifically where hexaminolevulinate is or is not indicated. A group of bladder cancer experts from across Europe met to review the data and discuss and debate, in view of their clinical experience, the role of hexaminolevulinate-guided PDD in the diagnosis and management of NMIBC. This article outlines the evidence base discussed and the recommendations made by the European expert panel.

2. Evidence acquisition

The PubMed MESH database was searched with the search term *5-aminolevulinic acid hexyl ester* [Substance Name] OR *Aminolevulinic Acid* with no restrictions in terms of date or language. The expert panel reviewed the primary articles (including systematic reviews and meta-analyses) retrieved and identified the key papers. Data based on abstracts presented at major meetings of relevance were also reviewed.

3. Evidence synthesis

Hexaminolevulinate has been used in Europe for more than a decade. It is licensed for the detection of bladder cancer in patients with known bladder cancer or a high suspicion of bladder cancer, based on, for example, screening cystoscopy or positive urine cytology. The licence notes that blue-light fluorescence cystoscopy should be used as an adjunct to standard white-light cystoscopy as a guide for taking biopsies. An abundance of data supports its use in this indication [39], as discussed in brief below.

Where possible, only data relating directly to hexaminolevulinate are discussed in this article. Occasionally, however, data for 5-ALA are presented; the expert panel believes, and a recent study has shown, that data for hexaminolevulinate and 5-ALA are generally transferable [40]. Importantly, hexaminolevulinate is the only product licensed for use with PDD anywhere in the world.

Hexaminolevulinate-guided PDD has a comparable safety profile to white-light cystoscopy, with no additional

adverse events noted; observed adverse events are predominantly mild and reversible and related to the TURBT or patient comorbidity [17–21,28,32,41].

3.1. Detection of tumours and subsequent resection

Review of the available literature indicates that hexaminolevulinate-guided fluorescence cystoscopy offers considerable benefits over white-light cystoscopy in the detection of NMIBC (Table 2) [17–21,41]. The benefits are particularly remarkable for CIS [17,19–21,41]. Overall, CIS lesion detection rate is approximately 20% higher with the addition of PDD to white-light cystoscopy versus white-light cystoscopy alone [22,23,25,42]. The clinical benefit of an improved tumour detection rate has been demonstrated by Jocham et al. [20]. Their European multicentre study found that PDD resulted in more complete treatment in 17% of patients ($p < 0.0001$).

3.2. Tumour recurrence

In theory, improved detection and resection of tumours should result in reduced recurrence rates. The findings of a recently presented systematic review of the effectiveness of PDD at the time of primary TURBT indicate that the technique facilitates more complete resection of the tumour(s) and therefore prolongs recurrence-free survival compared with white-light cystoscopy [43]. This conclusion is supported by large prospective randomised studies, most recently a multicentre international study by Stenzl et al. [41] (Table 3) [24–28]. Reported tumour-free recurrence rates at 1 yr range from 66% to 90% with PDD to from 39% to 74% with white-light cystoscopy, and the difference in outcome between the two techniques extended over 8 yr [24,25,32]. It is noteworthy that patients with multifocal or recurrent tumours appear to benefit most from PDD-guided operations [25,41].

3.3. Flexible fluorescence cystoscopy

Flexible cystoscopy is currently the method of choice when outpatient cystoscopy is undertaken. Studies have shown that flexible PDD cystoscopy is possible, and although not as convenient for the investigator and as effective in the detection of bladder cancer as rigid PDD cystoscopy, it is still superior to rigid white-light cystoscopy (Table 4) [44,45]. However, it is widely acknowledged that improvement of flexible PDD equipment is likely to further improve these results. Although with flexible scopes small mucosal biopsies can be taken to confirm the presence of CIS in the outpatient setting, rigid PDD is likely to remain the standard of care pending improvements in the tools available.

3.4. The issue of false-positive biopsies

Historically, PDD has been associated with a higher rate of false-positive biopsy results than white-light cystoscopy, although considerable numbers of false positives are also

Table 2 – Tumour detection rate for hexaminolevulinate-guided photodynamic diagnosis versus white-light cystoscopy alone

Study (tumour grade)	Tumour detection rate (hexaminolevulinate-guided PDD), %	Tumour detection rate (white-light cystoscopy alone), %	Additional tumour detection rate, %	Proportion of patients in whom diagnosis or stage would not be correct without PDD, %
Jichlinski et al. [21] ($n = 52$)				
All tumours	76	46	30	23
CIS	49	5	44	69
Schmidbauer et al. [17] ($n = 211$)				
All tumours	97	78	19	–
Dysplasia	94	53	41	–
pTa	97	88	9	–
CIS	97	58	39	28
Jocham et al. [20] ($n = 146$)				
All tumours	96	77	19	18
Dysplasia	93	48	45	41
pTa	96	85	11	12
CIS	95	68	27	34
Grossman et al. [18] ($n = 108$)				
pTa	95	83	12	–
pT1	95	86	9	–
Fradet et al. [19] ($n = 58$)				
CIS	92	68	24	26
Stenzl et al. [41] ($n = 402$)				
Dysplasia	82	64	18	–
pTa	91	90	1	–
pT1	90	91	1	–
CIS	91	59	32	–

CIS = carcinoma in situ; PDD = photodynamic diagnosis.

Table 3 – Tumour recurrence rates after resection guided by white-light or photodynamic diagnosis

Study	Interval since resection	Rate of recurrence-free survival	
		White light, %	PDD (hexaminolevulinate/5-ALA), %
Filbeck et al. [24] (*n* = 191)	1 yr	74	90 (5-ALA)
	2 yr	66	90 (5-ALA)
Babjuk et al. [25] (*n* = 122)	10–15 wk	68	92 (5-ALA)
	1 yr	39	66 (5-ALA)
	2 yr	28	40 (5-ALA)
Daniltchenko et al. [26] (*n* = 102)	2 mo	59	84 (5-ALA)
	1 yr	39	57 (5-ALA)
	3 yr	27	41 (5-ALA)
	5 yr	25	41 (5-ALA)
Denzinger et al. [27] (*n* = 46)	4 yr	69	91 (5-ALA)
	8 yr	52	80 (5-ALA)
Denzinger et al. [28] (*n* = 301)	2 yr	73	88 (5-ALA)
	4 yr	64	84
	6 yr	54	79
	8 yr	45	71
Stenzl et al. [41] (*n* = 402)	9 mo	54	64 (hexaminolevulinate)

5-ALA = 5-aminolevulinic acid; PDD = photodynamic diagnosis.

seen with white-light cystoscopy [17–20]. However, this gap is closing, with the latest study showing only a 1% difference in the rate of false positives between arms and a marked fall overall [41].

This drop in the number of false positives between PDD and white-light cystoscopy is likely to be due to the increase in experience with PDD and the evolution of the technical equipment.

Of note, although the rates of false positives have improved overall, there are some instances where rates remain high (irrespective of whether white or blue light is used), for example, following recent TURBT or bacillus Calmette-Guérin (BCG) instillation or after a recent or during a concomitant urinary tract infection because of possible scarring or inflammation. On the basis of recent evidence [46], it is recommended that PDD be postponed by 9–12 wk after TURBT or BCG instillation if clinically feasible. Of note, this may not be necessary in patients receiving a single BCG instillation within 12 wk, which probably does not affect PDD specificity. Furthermore, a possible delay of <9–12 wk is supported by data from Ray et al. [47] that indicate after 6 wk there is no association between rates of false-positive biopsies and time since last BCG and that specificity does not improve after 12 wk from the last BCG instillation.

Instillation of mitomycin does not cause inflammation and is not associated with a higher rate of false-positive results [46].

The expert panel members felt that although PDD may be associated with a limited increase in false-positive rates in particular situations, its use is still recommended in view of the associated improved detection rate and better patient management versus white-light cystoscopy.

3.5. *Hexaminolevulinate in clinical practice: recommendations from a European expert panel*

In all countries, hexaminolevulinate-guided PDD is used as an adjunct to white-light cystoscopy. As already noted, guidelines across the continent acknowledge in a general way that PDD has a place in the diagnosis of patients with proven or suspected bladder cancer (Table 1) [32–38]; however, few specific recommendations regarding when PDD should and should not be used exist.

Taking into account the recommendations that have been made in the guidelines from across Europe and from the evidence base, and drawing on extensive clinical experience, the European expert panel made the following recommendations.

3.5.1. *On initial suspicion of bladder cancer*

Use of hexaminolevulinate-guided PDD is recommended for all patients in this indication, where it improves tumour detection rate and staging of all non–muscle-invasive cancers over white-light cystoscopy alone [17–21,28,41,48,49], reducing or negating the need for random biopsies and facilitating fully informed follow-up. Use of PDD for the assessment of all new tumours at the time of primary TURBT also facilitates more complete tumour resection, resulting in a reduced recurrence rate [26,27,41].

Table 4 – Tumour detection rate for flexible and rigid hexaminolevulinate-guided photodynamic diagnosis and white-light cystoscopy [44,45]

Tumour grade	Tumour detection rate (rigid hexaminolevulinate-guided PDD), %	Tumour detection rate (flexible hexaminolevulinate-guided PDD), %	Tumour detection rate (rigid white-light cystoscopy), %	Tumour detection rate (flexible white-light cystoscopy), %
CIS	88	77	63	61
pTa	96	91	91	86
pT1–2	94	91	86	81

Hexaminolevulinate-guided PDD offers particularly great advantages over white-light cystoscopy for the detection of CIS, often doubling the lesion detection rate [17,19–21,36].

Hexaminolevulinate-guided PDD is not recommended in patients for whom cystectomy is indicated because it is unlikely that it would offer any additional useful information.

It is postulated that with improved detection and resection of tumours, less frequent follow-up may be needed. Studies are needed to confirm this hypothesis.

3.5.2. *For assessment at time of tumour recurrences in patients not previously staged with hexaminolevulinate*

If the patient has not been staged previously using hexaminolevulinate-guided PDD, errors may have been made or tumours (particularly CIS) missed; therefore, hexaminolevulinate-guided PDD is recommended for this indication.

3.5.3. *In patients with positive urine cytology but negative white-light cystoscopy*

Hexaminolevulinate-guided PDD is recommended for this indication. The enhanced tumour detection rate seen with hexaminolevulinate-guided PDD over white-light cystoscopy leads to identification of tumours not previously visualised [17–21,28,41,48,49].

3.5.4. *For surveillance*

There are no data on which to base a firm recommendation for the use of hexaminolevulinate-guided PDD for surveillance. It is postulated, however, that the use of PDD is likely to be advantageous in the initial follow-up of patients with CIS or multifocal tumours. Research is needed to determine whether PDD surveillance of this group affects management.

3.5.5. *In the outpatient setting*

Hexaminolevulinate-guided PDD (using a flexible cystoscope) is not currently recommended in the outpatient setting because of difficulties associated with taking biopsies. However, this indication is likely to follow in time as equipment improves [44,45]. The panel believes that mucosal biopsies are possible in an outpatient setting using flexible cystoscopy.

3.5.6. *As a teaching tool*

Hexaminolevulinate-guided PDD is recommended as a teaching tool. It offers clear visualisation of tumours and their margins, thereby facilitating improved TURBT [17–21,41].

4. Conclusions

Improved tumour detection and more complete resection is the best way to decrease tumour recurrence. Both of these goals are achieved with hexaminolevulinate-guided PDD. If the technology is used appropriately, it necessarily affects patient management and follow-up, with benefits for both the patient and, ultimately, the health care economy. The recommendations made in this paper reflect the advantages noted to date for PDD in particular patient subgroups.

Although hexaminolevulinate-guided PDD offers a powerful tool in the diagnosis and management of NMIBC, many clinically relevant questions remain to be answered. If the initial resection with PDD is optimal, one might imagine that a transurethral re-resection could be avoided and the need for a single immediate instillation reduced. Furthermore, if one could resect the areas with CIS completely with the help of PDD, one might hope that the outcome and prognosis of patients with CIS would improve. Further research is warranted in these areas.

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Analysis and interpretation of data: Witjes, Palou, Jacqmin, Sofras, Malmström, Riedl, Jocham, Conti, Montorsi, Arentsen, Zaak, Mostafid, Babjuk.
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Critical revision of the manuscript for important intellectual content: Witjes, Palou, Jacqmin, Sofras, Malmström, Riedl, Jocham, Conti, Montorsi, Arentsen, Zaak, Mostafid, Babjuk.
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