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The sensitivity of fluorescent-light cystoscopy for the detection of carcinoma *in situ* (CIS) of the bladder: a meta-analysis with comments on gold standard

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- A literature search was conducted to identify peer-reviewed study reports on the sensitivity of fluorescent-light cystoscopy (FLC) for the detection of carcinoma *in situ* (CIS) of the bladder.
- Data from 16 original studies comprising 1503 patients were pooled.
- The claimed sensitivity of FLC for detecting patients with CIS using the most commonly reported intravesical agents 5-aminolevulinic acid or hexaminolevulinic acid was 92.4%, while that of white-light cystoscopy (WLC) was 60.5%. The two agents did not differ significantly for sensitivity.
- It must be pointed out that a 'gold standard' is lacking in FLC studies.
- The occurrence of CIS of the bladder can only be established by the pathological examination of whole bladders. The true sensitivities of various modes of cystoscopy for detecting CIS can be revealed if patients scheduled for cystectomy are first examined with WLC, FLC, and optionally random biopsies.
- The absolute sensitivity of FLC for detecting CIS of the bladder is not yet known.

What's known on the subject? and What does the study add?
Fluorescent-light cystoscopy has a high sensitivity, relative to that of white light cystoscopy, for carcinoma in situ of the bladder. However, this systematic review reveals that the absolute sensitivity is unknown due to the absence of proper gold standard which is microscopic examination of whole bladders.

KEYWORDS

review, bladder neoplasia, carcinoma in situ, cystoscopy, photodynamic diagnosis, meta-analysis

INTRODUCTION

The purpose of this review was to examine evidence on the sensitivity of fluorescent-light cystoscopy (FLC; alternative term photodynamic diagnosis) for urothelial carcinoma *in situ* (CIS) of the bladder, and to offer a discussion from a histopathology standpoint. Attention was called to the absence of a 'gold standard' in FLC sensitivity analyses in a 1999 publication by Schneeweiss *et al.* [1] entitled '*Is everything all right if nothing seems wrong*'? Recent FLC research reports and systematic reviews do not clearly address this issue. A statement in a FLC publication by Jeon *et al.* [2] exemplifies the hazard of claiming that all CIS are detected by a combination of FLC and white-light cystoscopy (WLC): '*no CIS went undetected*'. Happily though, a recent study by Gudjónsson *et al.* [3] that examined the diagnostic performance of five-biopsy bladder mapping did use cystectomy specimens as gold standard.

According to the WHO, CIS is the condition in which cells with nuclear anaplasia identical to high-grade urothelial carcinoma are present in flat urothelium without invasion. The diagnostic accuracy of general pathologists for CIS has been examined in a study by Isfoss *et al.* [4] indicating low-to-moderate sensitivity (56–69%) but no false positives.

The first mention of CIS concomitant with papillary or invasive bladder cancer was made by Melicow [5] Melamed *et al.* [6] found that CIS does not regress, and that it progresses to invasive disease in 42% of cases. Koss *et al.* [7,8] showed that all cystectomy specimens with bladder cancer not controllable by transurethral resection also contain areas of CIS. They suggested that recurrence and invasion most often occurs from CIS rather than from papillary urothelial neoplasia (PUN). Brawn [9] found that most patients with invasive carcinoma neither have nor had PUN, also suggesting CIS as the origin of most invasive bladder cancers. A Mayo Clinic investigation into the clinical course of 486 patients concluded that CIS still persisting after 6–9 months of intravesical treatment should be treated with cystectomy [10].

Bush *et al.* [11] presented an early form of non-WLC in 1967, and in 1970 this method was suggested by Utz *et al.* [12] to be of significant value in the management of CIS. In 1996 a study of FLC on >100 patients was presented by Kriegmair *et al.* [13].

Gene-expression profiling indicates clusters that separate CIS from PUN, as reported in a study by Sanchez-Carbayo *et al.* [14]. In 2009, Zieger *et al.* [15] reported chromosomal instability in most CIS lesions. *FGFR3* mutations that are found in most non-invasive PUN lesions (pTa), reported by Vallot *et al.* [16], are not found in CIS [17]. Loss of heterozygosity and epigenetic abnormalities present in 77% of morphologically normal bladder mucosa

samples from metachronous bladder cancer suggest multifocal pathogenesis of bladder cancer [18]. Similarly indicating multifocal pathogenesis, microarray expression profiling of PUN with adjacent CIS is similar to CIS and similar to normal appearing mucosa from the same bladders [19]. There is also epigenetic evidence that CIS has common features with muscle-invasive bladder cancer, in that most muscle-invasive tumours are affected by multiple regional epigenetic silencing (MRES) among seven specific chromosomal regions, and that MRES tumours exhibit a CIS-associated gene expression signature [16].

A study published by Wolf *et al.* [20] reported that about half of patients with concomitant CIS progress in ≤5 years. Sylvester *et al.* [21] reported in a study of 2596 patients that concomitant CIS is the most important prognostic factor for patients with T1 grade 3 tumours, with a 2.6-times increased risk of progression at 5 years. Shariat *et al.* [22] reported in a study of 713 cystectomy patients that concomitant CIS is an independent predictor of recurrence.

Although CIS may be revealed during WLC as an erythematous or velvety area, CIS is frequently missed. A recent bladder mapping study of 308 patients by Gudjónsson *et al.* [3] based on five biopsies from unremarkable bladder mucosa indicates a sensitivity of 46% using cystectomy specimens as gold standard. A recent population-based study of 538 patients with bladder cancer by Thorstenson *et al.* [23] reported that patients with non-muscle-invasive bladder cancer have a significantly better cancer-specific survival if examined with random biopsies.

However, the AUA Guideline for the management of non-muscle-invasive bladder cancer does not advocate random biopsies. Similarly, the European Association of Urology Guideline for non-muscle-invasive bladder cancer does not advocate routine random biopsies, although the text recognises concomitant CIS as the strongest risk factor for PUN progression. The shift of urology practice away from random biopsies has occurred more or less simultaneously with the rapid adoption of FLC in standard patient care.

TABLE 1 Selection of publications

Exclusion criteria: publication format, subject, quality of data	Excluded	Remaining
Publications considered		579
1. Non-English	94	485
2. Review, editorial, comment, or case report	126	359
3. Pre-clinical, pharmacological, physiological, or radiological study	68	291
4. Cell line study	52	239
5. Animal model study	75	164
6. *In vitro* laboratory study	73	91
7. Non-urothelial study	9	82
8. Non-bladder urothelial study	1	81
9. Treatment or patient outcome study	17	64
10. Biostatistics, epidemiology, or economics study	4	60
11. WLC and FLC not performed on same patients	10	50
12. Insufficient or non-interpretable data	20	30
13. FLC applied to <31 patients	11	19
14. Intravesical agent other than 5-ALA or HAL	3	16
Publications incorporated		16

MATERIALS AND METHODS

Four separate literature searches were performed in January 2011 in the PubMed database provided online by the USA National Library of Medicine (http://www.pubmed.gov), using the following search strings: '*photodynamic diagnosis*', '*fluorescence cystoscopy*', '*hexaminolevulinate*', and '*aminolevulinic acid*'. Publications not found through these searches were not included in the analysis, but were retained for discussion purposes.

In all, 14 criteria of exclusion were applied (Table 1).

All admissible publications were read, and the following data were retrieved:

I. Intravesical agent(s) used for FLC.
II. Random biopsies guided by WLC routinely obtained, or not.
III. Number of patients examined by FLC, and evaluable in efficacy analysis.
IV. Total number of CIS lesions and/or CIS patients detected.
V. CIS detected by random biopsies, if applicable.
VI. CIS detected by WLC.
VII. CIS detected by FLC.
VIII. CIS detected by FLC and not by WLC.
IX. CIS detected by WLC and not by FLC.
X. CIS detected by both WLC and FLC.

E-mail addresses of corresponding authors were obtained from the original publications. These were verified or modified according to searches on PubMed and the World Wide Web. In cases of non-verifiable corresponding author e-mail addresses, first or last author e-mail addresses were sought in the same manner. The resulting selected author of each publication was sent a request to proofread data as read from the publication. Information obtained through communication with authors was compared with data originally read from the publication.

RESULTS

In all, 579 publications were identified from the searches. Application of exclusion criteria resulted in 16 admissible publications (Table 2) [2,13,24–37]. These comprised 10 studies examining the performance of FLC using 5-aminolevulinic acid (5-ALA), and six studies using hexaminolevulinic acid (HAL). The 5-ALA studies were published in 1996–2009 (mean 2001), and the HAL studies were published in 2003–2010 (mean 2006). The authors of four publications (25%) responded to e-mail, all confirming the data entered through this author's reading of publications.

The patients admitted to the original studies largely included those with symptoms of

TABLE 2 Data from publications

Publication	Agent	Unit of analysis	No. of patients	CIS detected, *n*	CIS detected by random biopsies, *n* (%)	CIS detected by WLC, *n* (%)	CIS detected by FLC, *n* (%)
Kriegmair *et al.* [13]	5-ALA	Patient	104	6	n/a	4 (67)	6 (100)
Riedl *et al.* [24]	5-ALA	Patient	52	7	n/a	2 (29)	7 (100)
Landry *et al.* [25]	5-ALA	Patient	50	6	0 (0)	5 (83)	6 (100)
Grimbergen *et al.* [26]*	5-ALA	Patient	160	21	3 (14)	8 (38)	20 (95)
Draga *et al.* [27]	5-ALA	Patient	306	66	8 (12)	19 (29)	58 (88)
Jichlinski *et al.* [28]	HAL	Patient	52	13	12 (92)	3 (23)	12 (92)
Schmidbauer *et al.* [29]	HAL	Patient	169	83	1 (1)	64 (77)	80 (96)
Loidl *et al.* [30]	HAL	Patient	45	17	n/a	11 (65)	15 (88)
Jocham *et al.* [31]	HAL	Patient	146	29	n/a	17 (59)	27 (93)
Fradet *et al.* [32]†	HAL	Patient	196	58	5 (9)	49 (84)	51 (88)
Geavlete *et al.* [33]	HAL	Patient	223	23	n/a	17 (74)	22 (96)
Koenig *et al.* [34]	5-ALA	Lesion	49	6	0 (0)	4 (67)	5 (83)
Filbeck *et al.* [35]	5-ALA	Lesion	120	7	n/a	4 (57)	7 (100)
Cheng *et al.* [36]	5-ALA	Lesion	41	7	2 (29)	0 (0)	5 (71)
Jeon *et al.* [2]	5-ALA	Lesion	62	20	n/a	1 (5)	20 (100)
Grimbergen *et al.* [26]*	5-ALA	Lesion	160	42	3 (7)	10 (24)	38 (90)
Zumbraegel *et al.* [37]	5-ALA	Lesion	108	14	n/a	9 (64)	12 (86)
Fradet *et al.* [32]†	HAL	Lesion	196	113	5 (4)	77 (68)	104 (92)

**Same study appears twice, with patient- vs lesion-based data; †Same study appears twice, with patient- vs lesion-based data.*

TABLE 3 Meta-analysis

Agent(s) used in studies	No. of studies	No. of patients	CIS detected, *n* (%)	CIS detected by WLC, *n* (%)	CIS detected by FLC, *n* (%)
Patient-based data:					
5-ALA studies	5	672	106 (15.8)	38 (35.8)	97 (91.5)
HAL studies	6	831	223 (26.8)	161 (72.2)	207 (92.8)
5-ALA and HAL studies combined	11	1503	329 (21.9)	199 (60.5)	304 (92.4)
Lesion-based data:					
5-ALA and HAL studies combined*	7	736	209	105 (50.2)	191 (91.4)

**Breakdown not possible due to low number of HAL studies (n = 1).*

bladder cancer, and those with established diagnosis of bladder cancer many of whom had undergone endoscopic and/or intravesical therapy. Information on the patient mix was in some cases less than satisfactory, causing this category to be omitted from the preparation of the meta-analysis.

All the publications presented calculations of sensitivity using a gold standard consisting of the total number of CIS detected by cystoscopy (WLC and FLC), while none used subsequent cystectomy as a gold standard. Eight studies (50%) also entered into the gold standard CIS diagnoses derived from biopsies from unremarkable mucosa (random biopsies). The reported number of standard random biopsies varied from one to six, but was in some cases not adequately disclosed, causing this category to be omitted in the final analysis.

The results were presented in various ways in the publications. The units of analysis were CIS positive/negative patients (nine publications) or CIS positive/negative lesions (five), or both (two) (Table 2). All studies were based on histologically confirmed CIS. The data often specified the number of CIS identified by WLC only, or FLC only, or additional cases identified by either method. When other information was available from the publication this could be added up to the measures of sensitivity selected for the present analysis, i.e. the percentage of CIS found by WLC, and those found by FLC. Thus all admitted publications enabled retrieval of complete data.

Information from all incorporated studies was gathered into a pool comprising 1503 patients, sorted by patient- or lesion-based units of analysis, and by intravesical agent (Table 3). The pooled data indicated presence of CIS in 21.9% of patients. The reported patient-based sensitivity of WLC for CIS was 60.5%, while that of FLC was 92.4%.

Lesion-based sensitivity was 50.2% for WLC, 91.4% for FLC.

DISCUSSION

The literature search was designed to capture the majority of relevant publications, although it was not as exhaustive as those performed for recent systematic reviews by Mowatt *et al.* [38] and Kausch *et al.* [39] using Cochrane Collaboration methods. The present review was limited to publications in the English language *('the Latin of modern times')* as it appeared unfair to limit the review to the handful of languages incidentally within this author's lingual skill set. It is conceivable that a bias was caused by the use of only one observer performing the search and extracting the data. However, authors were invited to proof read entered data, and the responses (although few) were confirmatory.

Not all the studies applied random biopsies, nor were all relevant data entirely clear, thus this could not be reliably analysed. The reported sensitivity of random biopsies for the detection of CIS ranged from 0% to 92%. The largest study by Draga *et al.* [27] indicated that 12% of patients with CIS were diagnosed by random biopsies.

Pooled analysis of all patient-based data (unit of analysis: patients i.e. not individual lesions) indicated a WLC sensitivity of 60.5%. However, there was a considerable difference between the study pool using 5-ALA (35.8%) and the study pool using HAL (72.2%). This difference cannot be explained by the use of different intravesical agents, as this has scarcely any bearing on WLC performance. Another possible explanation is that the HAL studies were performed more recently than the 5-ALA studies (on average 5 years later). This suggests a positive development with regard to WLC technology and/or skills, resulting in better (in fact doubled) CIS detection by WLC.

The overall sensitivity of FLC was 92.4%, obviously very superior to that of WLC. The sensitivities of the study pools using 5-ALA and HAL were almost identical, which is congruent with results from a study that compared the performance of these two agents for CIS detection [40].

CIS concomitant with PUN is a condition with adverse prognosis. The treatment of it results in fewer recurrences. It should therefore be reliably detected. FLC finds significantly more CIS than WLC does.

In all the reviewed studies, the gold standard used for sensitivity analyses was CIS detected by WLC and FLC combined, and including random biopsies in one-half of studies. However, it is unlikely that *all* CIS were found in *any* of the studies. Random biopsies detect <50% of CIS when the gold standard used is CIS found in subsequent cystectomy specimens (Gudjónsson *et al.* [3]). Schneeweiss *et al.* [1] pointed out in 1999 that the most acceptable gold standard for FLC sensitivity is CIS in whole bladders after cystectomy. This can be realized in an experiment in which WLC and FLC is performed before scheduled cystectomy. Such a study would contain a high proportion of pT2+ patients, thus raising concerns that the study subjects are not representative for the non-muscle-invasive patient population in which CIS diagnosis is relevant. However, patients with non-controllable pT1 and pTis are indeed treated with cystectomy when all else fails, which may contribute to a reasonably diverse patient population in such a study. We should acknowledge the advances in diagnosis and treatment that FLC has offered, but we must also be honest enough to admit that the whole truth is not on the table yet.

In conclusion, the sensitivity of FLC for the detection of CIS in the bladder is unknown. Further studies are needed, and must include WLC and FLC, and optionally random biopsies, on patients scheduled for cystectomy.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: **FLC**, fluorescent-light cystoscopy; **CIS**, carcinoma in situ; **WLC**, white-light cystoscopy; **PUN**, papillary urothelial neoplasia; **MRES**, multiple regional epigenetic silencing; **5-ALA**, 5-aminolevulinic acid; **HAL**, hexaminolevulinic acid.