

EAU Guidelines

EAU Guidelines on the Diagnosis and Treatment of Urothelial Carcinoma in Situ

Adrian P.M. van der Meijden^{a,*}, Richard Sylvester^b, Willem Oosterlinck^c,
Eduardo Solsona^d, Andreas Boehle^e, Bernard Lobel^f, Erkki Rintala^g

for the EAU Working Party on Non Muscle Invasive Bladder Cancer

^aDepartment of Urology, Jeroen Bosch Hospital, Nieuwstraat 34, 5211 NL 's-Hertogenbosch, The Netherlands

^bEORTC Data Center, Brussels, Belgium

^cDepartment of Urology, University Hospital Ghent, Ghent, Belgium

^dDepartment of Urology, Instituto Valenciano de Oncologia, Valencia, Spain

^eDepartment of Urology, Helios Agnes Karll Hospital, Bad Schwartau, Germany

^fDepartment of Urology, Hopital Ponchaillou, Rennes, France

^gDepartment of Urology, Helsinki University Hospital, Helsinki, Finland

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Abstract

Objectives: On behalf of the European Association of Urology (EAU), guidelines for the diagnosis, therapy and follow-up of patients with urothelial carcinoma in situ (CIS) have been established.

Method: The recommendations in these guidelines are based on a recent comprehensive overview and meta-analysis in which two panel members have been involved (RS and AVDM). A systematic literature search was conducted using Medline, the US Physicians' Data Query (PDQ), the Cochrane Central Register of Controlled Trials, and reference lists in trial publications and review articles.

Results: Recommendations are provided for the diagnosis, conservative and radical surgical treatment, and follow-up of patients with CIS. Levels of evidence are influenced by the lack of large randomized trials in the treatment of CIS.

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1. Background

A number of review papers on carcinoma in situ (CIS) have been published [1–8], some of which are based on previous bladder cancer consensus conferences. The problem with many publications investigating the treatment of CIS is that they are based on only a small number of highly-selected patients and on retrospective analyses with different endpoints, evaluation

criteria, and durations of follow-up. It is thus difficult to obtain evidence-based results. The recommendations in these guidelines are based on a recent comprehensive overview and meta-analysis in which two panel members have been involved (RS and AVDM) [9,10]. A systematic literature search was conducted using Medline, the US Physicians' Data Query (PDQ), the Cochrane Central Register of Controlled Trials, and reference lists in trial publications and review articles.

It has been estimated that 5% to 10% of all patients with superficial bladder cancer have CIS [5,11]. However, due to differences in patient selection, the lack of a uniform definition and classification system for CIS,

* Corresponding author. Tel. +31 73 6992407/6162434;

Fax: +31 73 6992373/6162373.

E-mail address: a.v.d.meijden@jzbz.nl (Adrian P.M. van der Meijden).



and inter-observer variability, especially between varying degrees of dysplasia and CIS, the percent of patients with CIS varies from one series to another. For example, Kaasinen et al. [11] reported that 5% of patients with superficial bladder cancer had concurrent CIS as compared to 19% reported by Palou et al. [12].

CIS is a flat, high grade, noninvasive urothelial carcinoma. CIS is classified together with Ta and T1 papillary tumors as a superficial bladder cancer. Unlike low grade Ta and T1 tumors, CIS is a highly malignant entity which, when left untreated, has a much higher progression rate than most Ta and T1 tumors [1] (level 2). The term carcinoma in situ might suggest that CIS is a precursor of cancer. While it may be a precursor of *invasive* bladder cancer, the histological and cytological aspects of CIS make this an overtly malignant entity in itself.

Macroscopically, CIS can be missed at cystoscopy or be considered as an inflammatory lesion if not biopsied. It is often multifocal and can occur in the upper urinary tracts and in the prostatic ducts and urethra [6].

CIS is classified into one of three different clinical types [5]:

- Primary CIS: isolated CIS with no previous or concurrent papillary tumors
- Secondary CIS: CIS detected during the follow-up of patients with a previous papillary tumor
- Concurrent CIS: CIS in the presence of papillary tumors

2. Classification

The 2002 TNM Classification of Malignant Tumors, 6th edition is recommended [13] for the classification of bladder tumors:

T: Primary tumor

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Ta: Noninvasive papillary carcinoma
- Tis: Carcinoma in situ
- T1: Tumor invades subepithelial connective tissue
- T2: Tumor invades muscle
 - T2a: Tumor invades superficial muscle (inner half)
 - T2b: Tumor invades deep muscle (outer half)
- T3: Tumor invades perivesical tissue:
 - T3a: Microscopically
 - T3b: Macroscopically (extravesical mass)
- T4: Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall

- T4a: Tumor invades prostate, uterus, or vagina
- T4b: Tumor invades pelvic wall or abdominal wall

N: Regional lymph nodes

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single lymph node 2 cm or less in greatest dimension
- N2: Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3: Metastasis in a lymph node more than 5 cm in greatest dimension

M: Distant metastasis

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

G: Histopathological grading

- GX: Grade of differentiation cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3–4: Poorly differentiated/undifferentiated

In 1998, the WHO/ISUP consensus classification of urothelial neoplasms of the urinary bladder defined CIS as follows [14]:

“The lesion is characterized by the presence of cells with large, irregular, hyperchromatic nuclei that may be either present in the entire thickness of the epithelium or only a part of it. Mitotic activity is frequently observed, often in the mid to upper urothelium. CIS encompasses lesions which in the past were designated as severe dysplasia or marked atypia.”

By definition, all CIS are high grade lesions. CIS should not be subclassified by grade despite the spectrum of pleomorphism seen within this entity.

3. Diagnosis of CIS

The diagnosis of CIS is made in most cases by a combination of cystoscopy, urine cytology, and multiple bladder biopsies [3]. Of these, the histology of bladder biopsies is determinant in establishing the diagnosis. In CIS, the coherence and adherence of epithelial cells is decreased and this feature often results in denuded biopsies when taken by cold cup or with the resection loop.

Standard (white-light) cystoscopy might reveal no visible abnormalities at all, although multifocal red, velvet-like patches are often visible. Zaak et al. [15] found that under white-light endoscopy 30% of specimens with grade 2 dysplasia and 53% of specimens with CIS were missed.

Fluorescence cystoscopy, which is done with a porphyrin-based photosensitizer, (hex)-aminolevulinic acid (HAL or ALA), will reveal areas in the bladder that are suspicious for CIS and that cannot be seen with white-light cystoscopy. In a group of 83 patients with CIS, HAL cystoscopy detected CIS in 18 patients (22%) that was missed by traditional white-light cystoscopy [16]. Although the use of fluorescence cystoscopy improves the detection rate of CIS to more than 95% [16,17] (level 2), it has not yet been implemented on a regular basis in daily practice.

Although CIS is defined as an overt high grade lesion, consensus on the diagnosis does not always exist when the specimen is reviewed by several pathologists. There is both intra-observer and inter-observer variability, even between severe dysplasia and CIS. For example, Sharkey [18] found a considerable discrepancy between local and review pathology: 15 of 69 (22%) cases of CIS were downgraded to dysplasia while 8 of 27 (30%) reports of dysplasia were upgraded to CIS. In addition, sampling errors may also lead to an incorrect diagnosis.

Both papillary tumors, and especially CIS, shed cells in the urine. Due to a loss of cohesion of cells in the epithelial lining of the bladder in CIS, there is a larger number of floating cells in the urine as well as a high degree of anaplasia. Classic urine cytology will not detect low grade papillary tumors in all cases. However, CIS is a disease that is nearly always detected by urine cytology; both the sensitivity and specificity of urine cytology are over 90%.

During the last decade, many new urine tumor markers have become available such as NMP22, Immunocyt, BTA stat, and telomerase [19]. In a comprehensive literature review and meta-analysis in 348 patients with CIS, Lotan et al. [20] have shown that some urine-based bladder tumor markers may have a sensitivity which is at least as good as cytology, but the specificity of these tests was not reported and the number of patients included in the various studies was small. Markers such as UroVysion, HA-HAase, and BLCA-4 are promising as they all have a high sensitivity to detect CIS [21]. However further studies are required before any of these markers can be recommended to replace classic urine cytology (level 2, Grade B).

Controversy exists, however, whether cytology should be derived from voided urine or from a bladder wash (barbotage). It has been stated that more shed cells are to be expected from rinsing the bladder as compared to voided urine. However, rinsing the bladder requires catheterization, which is a minor but invasive procedure which sometimes leads to urinary tract infection. On the other hand, barbotage fluid can be examined in patients undergoing diagnostic or control cystoscopy.

When high grade cells are found on cytology in the absence of visible tumor on cystoscopy and intravenous urography (IVU), and when biopsies from the bladder and prostatic urethra are normal, CIS in the upper urinary tract should be suspected, even though it is rare [22]. It is possible to detect which renal unit is involved by investigating the urine produced by each unit separately. Sampling is done using a ureteral catheter or ureteroscopy. Brushing and biopsies of suspicious areas are also possible, but in many cases neither imaging nor biopsies will confirm the diagnosis. CIS in the upper urinary tract may thus be diagnosed only by repeated cytology.

3.1. Recommendations

Fluorescence cystoscopy should be considered because it has a greater sensitivity than white light cystoscopy (Grade B). All suspicious areas in the bladder should be biopsied. In patients with concurrent high grade Ta and in all T1 papillary tumors, a second-look TUR should be done (Grade B). In patients with a positive cytology, random biopsies including the prostatic urethra should be taken (Grade B). A bladder diagram should be used to identify the exact location where biopsies have been taken. For a proper pathological assessment of the extent of the disease, it is recommended to submit different types of material to the pathologist in separate, properly labeled containers, for example one container with the exophytic part of the tumor, one with the underlying muscle, another with the random mucosal biopsies, and another with biopsies from the prostatic urethra [23].

The marker of choice for the detection and follow-up of patients with CIS is cytology (Grade B). It is recommended to perform cytology with voided urine unless a bladder wash is done at the time of cystoscopy (Grade B).

4. Treatment of CIS

If concurrent CIS is found in association with a muscle-invasive bladder cancer, the therapy for the

patient is determined according to the invasive tumor. If concurrent CIS is found in association with a non-invasive tumor (Ta or T1), TUR of the papillary tumors is mandatory for correct staging. No consensus exists thereafter whether conservative therapy (intravesical instillations) or aggressive therapy (cystectomy) should be done, especially when there are concurrent high grade papillary tumors. Randomized trials between instillation therapy and early cystectomy as immediate primary treatment are lacking [8]. Tumor-specific survival rates of early cystectomy series in CIS are excellent, but as many as 40% to 50% of patients may be over-treated. Radiotherapy is not a viable treatment option for CIS [5].

In his review of 497 patients, Lamm [5] reported that intravesical chemotherapy produced a complete response rate of 48%: 38% in 89 patients treated with thiotepa, 48% in 212 patients treated with doxorubicin, and 53% in 196 patients treated with mitomycin C (MMC). There was, however, considerable variability with the same drug from one study to the next. In 1496 patients treated with BCG, the complete response rate was 72% (level 2). In 2 recent studies of BCG, complete response rates of 83% and 93% were achieved [24,25].

The classic induction course of BCG consists of 6 consecutive weekly intravesical instillations. Some 40% to 60% of patients not responding after this initial induction course respond to a second cycle of 6 weekly instillations [24–29] (level 2).

There are two important limitations to drawing conclusions based on an overview of complete response rates in different studies:

1. There may be important differences between studies with respect to the definition of CIS, patient characteristics, and assessment of response to treatment.
2. An initial complete response is not always durable. As approximately 50% of complete responders may eventually recur with risk of invasion and/or extravesical recurrence [3,25,29,30], one must take into account the long-term disease-free and progression-free rates.

Treatment recommendations should only be based on the results of randomized clinical trials with long-term follow-up. Unfortunately, there are relatively few randomized trials in patients with CIS alone. Most trials include patients with either papillary tumors or CIS, resulting in only a small number of CIS patients being entered. Thus, the power to detect treatment differences is low and the reliability of the conclusions is limited.

4.1. Randomized trials comparing different chemotherapy regimens

Eleven randomized trials comparing different chemotherapy regimens were identified, however 6 of the studies included less than 25 patients with CIS so no conclusions can be drawn from them [9].

4.2. Randomized trials comparing BCG to chemotherapy

For more than 20 years, intravesical BCG, a non-specific immunotherapy, and intravesical chemotherapy, with drugs such as thiotepa, adriamycin, epirubicin and mitomycin C, have been used in the treatment of CIS. The relevant clinical question is whether intravesical BCG is more effective than intravesical chemotherapy in the treatment of CIS.

Twelve randomized trials including 845 patients with CIS compared BCG to different chemotherapy regimens [26,31–41]. The results of these trials are summarized in Tables 1 and 2, both by type of chemotherapy and overall. In over 600 patients, there was a 68% complete response rate on BCG and a

Table 1

BCG versus chemotherapy: complete response rate in patients with CIS

Reference	BCG	Chemotherapy
BCG versus MMC		
Di Stasi [35]	23/36	11/36
Vegt [34]	26/38	8/12
Witjes [33]	NA/24	NA/16
Lamm [32]	17/31	16/35
Malmstrom [31]	NA/41	NA/42
Total	66/105 (63%)	35/83 (42%)
BCG versus electro MMC		
Di Stasi [35]	23/36 (64%)	21/36 (58%)
BCG versus Adriamycin		
Lamm [36]	45/64	23/67
Martinez-Pineiro [37]	NA/6	NA/6
Total	45/64 (70%)	23/67 (34%)
BCG versus Epirubicin		
De Reijke [26]	55/84	47/84
Melekos [38]	NA/4	NA/3
Total	55/84 (65%)	47/84 (56%)
BCG versus Thiotepa		
Martinez-Pineiro [37]	NA/6	NA/5
BCG versus MMC + ADM		
Sekine [39]	18/21 (86%)	17/21 (81%)
BCG + MMC versus MMC		
Witjes [41]	NA/29	NA/36
Rintala [40]	21/28	20/40
Total	21/28 (75%)	20/40 (50%)
Overall Total	205/302 (68%)	163/331 (49%)

NA: Data not available.

Table 2

BCG versus chemotherapy: disease-free rate in patients with CIS

Reference	BCG	Chemotherapy	Median follow-up (yrs)
BCG versus MMC			
Di Stasi [35]	17/36	9/36	3.6
Vegt [34]	NA/38	NA/12	3.0
Witjes [33]	11/22	7/16	7.2
Lamm [32]	NA/31	NA/35	2.5
Malmstrom [31]	23/41	14/42	5.3
Total	51/99 (52%)	30/94 (32%)	
BCG versus electro MMC			
Di Stasi [35]	17/36 (47%)	17/36 (47%)	3.6
BCG versus Adriamycin			
Lamm [36]	26/64	8/67	5.4
Martinez-Pineiro [37]	4/6	0/6	3.0
Total	30/70 (43%)	8/73 (11%)	
BCG versus Epirubicin			
De Reijke [26]	37/84	16/84	5.6
Melekos [38]	NA/4	NA/3	
Total	37/84 (44%)	16/84 (19%)	
BCG versus Thiotepa			
Martinez-Pineiro [37]	4/6 (67%)	3/5 (60%)	3.0
BCG versus MMC + ADM			
Sekine [39]	16/21 (76%)	6/21 (29%)	3.9
BCG + MMC versus MMC			
Witjes [41]	NA/29	NA/36	
Rintala [40]	20/28	17/40	2.8
Total	20/28 (71%)	17/40 (43%)	
Overall Total	154/302 (51%)	97/353 (27%)	3.75

NA: Data not available.

49% complete response rate on chemotherapy (Table 1). In the complete responders, 68% of patients treated with BCG remained disease-free as compared to 47% of patients receiving chemotherapy based on a median follow-up of 3.75 years. The overall disease-free rates were 51% and 27%, respectively (Table 2). Although the long term benefit of BCG based on the disease free rate was smaller in trials with MMC, BCG was superior to MMC in trials where maintenance BCG was used (OR = 0.57, $p = 0.04$) [10].

As compared to chemotherapy, treatment with BCG thus increased both the complete response rate and the overall percent of patients remaining disease free (level 1).

4.3. Randomized trials comparing BCG plus chemotherapy to BCG alone

In the largest study in CIS, the Nordic trial compared alternating MMC and BCG instillations to BCG alone in 304 patients with CIS [11]. No difference in the complete response rate was seen between the two

treatment groups, however based on a median follow up of 56 months, there was a significantly longer disease-free interval in the BCG monotherapy arm: 80 of 145 (55%) patients were disease-free on BCG alone compared to 72 of 159 (45%) patients on the combination of BCG and MMC. Thus an alternating schedule of MMC and BCG is not superior to BCG alone (level 1).

4.4. BCG meta-analysis of progression

In 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to either intravesical chemotherapy or a different immunotherapy (OR = 0.65, 95%CI 0.36 to 1.16, $p = 0.10$). Twenty-five of 212 (12%) patients on BCG progressed as compared to 31 of 191 (16%) patients receiving these other treatments [42] (level 1).

4.5. Treatment of extravesical CIS

The treatment of CIS in the upper urinary tract consists of rinsing the renal unit with BCG or with chemotherapeutic drugs such as mitomycin C or epirubicin. The watery solutions can be introduced into the upper urinary tract using a ureteral stent or nephrostomy catheter [43,44].

Only anecdotal cases have been reported and experience is therefore limited. Thalmann [45] found that 19 of 22 (86%) patients (25 renal units) with upper urinary tract CIS responded to BCG perfusions. Nine patients (41%) died of their disease after a median follow-up of 50 months (level 3).

Response to the treatment is determined by conversion of cytology in urine derived from the upper urinary tract from high grade to negative. If no response is achieved, a nephroureterectomy should be considered. Before performing a radical cystectomy, the urologist should know whether the prostatic urethra is free of CIS. During cystectomy, the distal ureters should also be investigated for the presence of CIS [3].

If CIS is found in the prostatic urethra, this is an ominous sign [3]. Three different entities might be encountered. CIS may be present only in the epithelial lining of the prostatic urethra. However CIS might also grow in the prostatic tissue following the prostatic ducts. In the worst case scenario, CIS may be found in the prostatic tissue stroma (T4) and this has the worst prognosis of all. Cystoprostatectomy is advised when CIS is found in the stroma. In the other two situations, a TUR of the prostate can be performed followed by intravesical instillations of BCG [3].

Kurth [3] and Lamm [5] further discuss the treatment of CIS involving the ureters and the prostatic urethra.

4.6. BCG toxicity

Because of the more pronounced side effects of BCG as compared to intravesical chemotherapy [26,32,34–37], reluctance still exists about its use. However, with increasing experience in applying BCG, serious side effects are now encountered in less than 5% of patients and can be effectively treated in virtually all cases [46].

In a large randomized SWOG study [29], only 16% of patients completed the entire 3-year maintenance schedule, suggesting that maintenance BCG is too toxic (level 1). In a recent EORTC trial including 487 patients treated with BCG [47,48], about one-third of the patients completed the 3 years of maintenance and 99 (20%) stopped due to adverse events. Local BCG side effects did not increase during maintenance and systemic side effects were more frequent during the first 6 months of treatment, after which time they decreased. Two-thirds of all patients who stopped BCG due to side effects did so during the first 6 months of treatment [48] (level 1).

While BCG-associated cystitis is more frequent than that with mitomycin C, Bohle [49] concluded that it did not differ according to whether BCG maintenance treatment was given or not. Saint [50] and Morgia [51] also concluded that the side effects of BCG were the most prominent during the induction and early maintenance instillations.

Thus the assumption that BCG induced side effects increase with time during maintenance does not appear to be correct (level 1).

4.7. Treatment of BCG failures

For BCG-refractory CIS, Kim [7] presented a review of the role of both radical cystectomy and conservative therapy with valrubicin [52–54], interferon alpha-2b [55–57], BCG plus interferon alpha-2b [58], bropririmine [59–62], and photodynamic therapy [63–66].

Radical cystectomy is the treatment that is offered to most patients when intravesical treatment has failed [67]. The timing of cystectomy remains a challenge and is still controversial. About 70% of patients treated with an initial BCG induction course of 6 weeks will respond, thus a considerable number of patients will require additional BCG instillations before biopsies and cytology become negative. Approximately 40% to 60% of patients not responding after an initial course of 6 weekly instillations will respond to a second cycle of 6 weekly instillations [24–29] (level 2). Additional complete responses have also been encountered if, after the initial induction course of 6 weeks, maintenance cycles consisting of 3 weekly booster

instillations are given [29] (level 1). On the other hand, the likelihood of progression to muscle-invasive disease and the development of metastases increases with the number of unsuccessful courses. Thus doubt remains concerning the best time point to abandon conservative treatment and proceed to cystectomy.

In patients for whom cystectomy is not possible, conservative treatment may be considered [68]. In the largest series of BCG refractory patients with CIS, complete response rates of 19 of 90 (21%) on valrubicin [52], 10 of 22 (45%) on interferon alpha-2b [57], 21 of 65 (32%) on bropririmine [59], and 21 of 36 (58%) and 13 of 27 (48%) on photodynamic therapy [65,64] were observed. In a large phase II study of BCG plus interferon alpha-2b, separate results were not presented for the patients with CIS who had previously failed BCG [58]. A phase I study of intravesical gemcitabine included 18 BCG-refractory patients, 14 of whom had CIS. Seven of the 18 (39%) patients had a complete response [69].

In summary, BCG plus interferon alpha-2b, photodynamic therapy and gemcitabine all warrant further evaluation in order to determine their role in the treatment of BCG-refractory patients (level 3).

5. Recommendations for detection, treatment and follow-up of CIS

Unlike for papillary tumors, few randomized trials on the treatment of CIS have been published. Evidence-based results are thus seriously hampered by the lack of sufficient high quality data. Based on the existing data, the following recommendations are provided:

1. The best marker to diagnose CIS or to assess response to treatment is cytology. None of the other currently available markers have been proven to be superior (Grade B).
2. Radical cystectomy at the time of diagnosis of CIS, instead of instillation therapy, provides excellent disease-free survival but is over-treatment in up to 50% of the patients (Grade A).
3. The treatment of CIS with intravesical BCG is recommended since it provides the highest rate of complete response as well as the highest long-term disease-free rate among intravesical treatments (Grade A).
4. Six weeks only of BCG is suboptimal treatment for CIS. Maintenance BCG treatment is required but the optimal maintenance schedule is unknown. In

- the absence of treatment failure, at least one year of maintenance BCG is recommended (Grade A).
5. The response to intravesical BCG should be assessed 3 months after starting treatment. If no response is seen, one might offer the patient either cystectomy, another 6-week course of BCG or continue with 3 weekly boosters (Grade B). As approximately 50% of patients will respond to a second course of BCG, cystectomy already at 3 months is over-treatment in about 50% of the patients. While failure at 3 months is a poor prognostic factor, the optimal time to abandon conservative treatment and proceed to cystectomy is unknown. Note: response of CIS in the bladder does not influence the course of CIS outside the bladder (upper urinary tract and prostatic urethra).
 6. If a complete response has not been achieved at 6 months, the therapy of choice is radical cystectomy (Grade B). In patients for whom a cystectomy is not possible, one of the conservative treatments mentioned above may be considered (Grade B).

7. Patients with CIS, even complete responders, should be monitored lifelong due to the high risk of recurrence and progression, both within the bladder and extravesically (Grade A).

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