EAU Guidelines on
Non-muscle-invasive Bladder Cancer (TaT1 and CIS)

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Single installation only vs. SI and further repeat instillations
In one study, further chemotherapy instillations after SI improved RFS in intermediate-risk patients [234] (LE: 2a).

Repeat chemotherapy instillations vs. no adjuvant treatment
A large meta-analysis of 3,703 patients from 11 RCTs showed a highly significant (44%) reduction in the odds of recurrence at one year in favour of chemotherapy over TURB alone [235]. This corresponds to an absolute difference of 13–14% in the number of patients with recurrence. Contrary to these findings, two meta-analyses have demonstrated that BCG therapy may reduce the risk of tumour progression [236, 237] (see Section 7.2.2.1) (LE: 1a). Moreover, BCG maintenance therapy appears to be significantly better in preventing recurrences than chemotherapy [238-240] (see Section 7.2.2.1) (LE: 1a). However, BCG causes significantly more side effects than chemotherapy [240] (LE: 1a).

Single instillation + further repeat instillations vs. later repeat instillations only
There is evidence from several studies in intermediate-risk patients that SI might have an impact on recurrence even when further adjuvant instillations are given [241-244]. A RCT including 2,243 NMIBC patients, which compared SI of MMC with an instillation of MMC delayed two weeks after TURB (followed by further repeat instillations in both treatment arms), showed a significant reduction of 9% in the risk of recurrence at 3 years in favour of SI, from 36% to 27%. The effect was significant in the intermediate- and high-risk groups of patients receiving additional adjuvant MMC instillations [241] (LE: 2a). Since the author's definition of the risk groups differed significantly in the initial publication, they adapted their patient stratification in the second analysis and consistently showed improved efficacy of SI followed by repeat MMC instillations [245]. The results of this study should be considered with caution since some patients did not receive adequate therapy. Another RCT found no impact of SI with epirubicin followed by further chemotherapy or BCG instillations in a cohort of predominant HR BC [246].

The optimal schedule of intravesical chemotherapy instillations
The length and frequency of repeat chemotherapy instillations is still controversial; however, it should not exceed one year [244] (LE: 3).

7.2.1.3 Options for improving efficacy of intravesical chemotherapy
7.2.1.3.1 Adjustment of pH, duration of instillation, and drug concentration
A prospective randomised, multi-institutional RCT showed that intravesical solution reduced the recurrence rate [247] (LE: 1b). Another trial reported that duration of a one hour instillation of MMC was more effective compared to a 30-minute instillation, but no efficacy comparisons are available for one- vs. two-hour durations of instillation [248] (LE: 3). Another RCT using epirubicin has documented that concentration is more important than treatment duration [249] (LE: 1b). In view of these data, instructions are provided (see Section 7.7).

It has been suggested that the efficacy of MMC may be improved by optimising application through the adjustment of urine pH, in addition to the use of alternative maintenance schedules. Neither aspect is reflected in the literature quoted above since most published studies do not support this approach.

7.2.1.3.2 Device-assisted intravesical chemotherapy
Microwave-induced hyperthermia effect (RITE)
Promising data have been presented on enhancing the efficacy of MMC using microwave-induced hyperthermia in patients with high-risk tumours [250]. In one RCT comparing one year of BCG with one year MMC and microwave-induced hyperthermia in patients with intermediate- and high-risk BC, increased RFS at 24 months in the MMC group was demonstrated [251] (LE: 1b).

Hyperthermic intravesical chemotherapy
Different technologies which increase the temperature of instilled MMC are available, however, data about their efficacy are still lacking.

Electromotive drug administration
The efficacy of MMC using electromotive drug administration (EMDA) sequentially combined with BCG in patients with high-risk tumours has been demonstrated in one small RCT [252]. The definitive conclusion, however, needs further confirmation.

For application of device-assisted instillations in patients recurring after BCG treatment, see Section 7.6.3.

7.2.2.7 Summary of evidence - BCG treatment

Summary of evidence	LE
In patients with intermediate- and high-risk tumours, intravesical BCG after TURB reduces the risk of tumour recurrence; it is more effective than TURB alone or TURB and intravesical chemotherapy.	1a
For optimal efficacy, BCG must be given in a maintenance schedule.	1a
Three-year maintenance is more effective than one year to prevent recurrence in patients with high-risk tumours, but not in patients with intermediate-risk tumours.	1a

7.2.3 Combination therapy

7.2.3.1 Intravesical BCG plus chemotherapy versus BCG alone

In one RCT, a combination of MMC and BCG was shown to be more effective in reducing recurrences but more toxic compared to BCG monotherapy (LE: 1b). Using similar BCG schedules in both groups, each BCG instillation in the combination group was preceded a day before by one MMC instillation [292]. In a RCT using MMC with EMDA, a combination of BCG and MMC with EMDA showed an improved recurrence-free interval and reduced progression rate compared to BCG monotherapy [252, 293] (LE: 2). Two meta-analyses demonstrated improved disease-free survival (DFS), but no difference in PFS in patients treated with combination treatment comparing to BCG alone [293, 294].

7.2.3.2 Combination treatment using interferon

In a Cochrane meta-analysis of 4 RCTs, a combination of BCG and IFN-2α did not show a clear difference in recurrence and progression over BCG alone [295]. In one study, weekly MMC followed by monthly BCG alternating with IFN-2α showed a higher probability of recurrence compared to MMC followed by BCG alone [296]. Additionally, a RCT in a similar population of NMIBC comparing BCG monotherapy with a combination of epirubicin and INF for up to two years showed the latter was significantly inferior to BCG monotherapy in preventing recurrence [297] (LE: 1b).

7.2.4 Specific aspects of treatment of carcinoma in situ

7.2.4.1 Treatment strategy

The detection of concurrent CIS increases the risk of recurrence and progression of TaT1 tumours [194, 196]. In this case further treatment according to the criteria summarised in Sections 7.2.1, 7.2.2, 7.5 and 7.6 is mandatory. Carcinoma *in situ* cannot be cured by an endoscopic procedure alone. Histological diagnosis of CIS must be followed by further treatment, either intravesical BCG instillations or RC (LE: 4). Tumour-specific survival rates after immediate RC for CIS are excellent, but a large proportion of patients might be over-treated [205] (LE: 3).

7.2.4.2 Cohort studies on intravesical BCG or chemotherapy

In retrospective evaluations of patients with CIS, a complete response rate of 48% was achieved with intravesical chemotherapy and 72-93% with BCG [205-208, 298] (LE: 2a). Up to 50% of complete responders might eventually show recurrence with a risk of invasion and/or extravesical recurrence [208, 230, 285, 298] (LE: 3).

7.2.4.3 Prospective randomised trials on intravesical BCG or chemotherapy

Unfortunately, there have been few RCTs in patients with CIS only. A meta-analysis of clinical trials comparing intravesical BCG to intravesical chemotherapy in patients with CIS has shown a significantly increased response rate after BCG and a reduction of 59% in the odds of treatment failure with BCG [299] (LE: 1a).

In an EORTC-GUCG meta-analysis of tumour progression, in a subgroup of 403 patients with CIS, BCG reduced the risk of progression by 35% as compared to intravesical chemotherapy or immunotherapy [237] (LE: 1b). The combination of BCG and MMC was not superior to BCG alone [300]. In summary, compared to chemotherapy, BCG treatment of CIS increases the complete response rate, the overall percentage of patients who remain disease free, and reduces the risk of tumour progression (LE: 1b).

7.2.4.4 Treatment of CIS in the prostatic urethra and upper urinary tract

Patients with CIS are at high risk of extravesical involvement in the UUT and in the prostatic urethra. Solsona *et al.* found that 63% of 138 patients with CIS developed extravesical involvement initially or during follow-up [301]. Patients with extravesical involvement had worse survival than those with bladder CIS alone [301] (LE: 3). In the prostate, CIS might be present only in the epithelial lining of the prostatic urethra or in the prostatic ducts [302]. These situations should be distinguished from tumour invasion into the prostatic stroma (stage T4a in bladder tumours) and for which immediate radical cystoprostatectomy is mandatory. Patients with CIS in the epithelial lining of the prostatic urethra can be treated by intravesical instillation of BCG. Transurethral resection of the prostate can improve contact of BCG with the prostatic urethra [128, 303] (LE: 3). However, potential spread of CIS has to be considered; no suprapubic trocar-placed catheter should be used.

In patients with prostatic duct involvement there are promising results of BCG, but only from small series. The data are insufficient to provide clear treatment recommendations and radical surgery should be considered [303, 304] (LE: 3).

7.2.4.5 Summary of evidence - treatment of carcinoma in situ

Summary of evidence	**LE**
Carcinoma *in situ* cannot be cured by an endoscopic procedure alone.	4
Compared to intravesical chemotherapy, intravesical BCG maintenance instillations increase the complete response rate, the overall percentage of patients who remain disease free, and reduce the risk of tumour progression.	1b

7.3 Intravesical chemoablation and neoadjuvant treatment

Older marker lesion studies have shown that chemoablation with a single intravesical chemotherapy instillation can achieve a complete response in a proportion of patients [305]. In addition, hypothesis-generating findings from an older RCT comparing immediate pre-operative device-assisted (EMDA) MMC with post-operative SI with MMC and TURB only, showed improved long-term RFS among patients treated prior to TURB [306], and thus even suggest a long-term effect after neoadjuvant instillations. While this has not been reproduced by other groups, additional neoadjuvant clinical trials were recently published. In recurrent low-risk [307] and recurrent Ta tumours [308], 4 and 6 intravesical MMC instillations achieved complete response in 37% and 57% of the patients, respectively. The former study prematurely stopped recruitment as the anticipated 45% complete response after chemoablation was not achieved. Compared to TURB, less dysuria and incontinence occurred in the intervention arm of the trial. Before routine clinical application, additional high-level evidence with RFS as an outcome measure is required.

7.4 Radical cystectomy for non-muscle-invasive bladder cancer

There are several reasons to consider immediate RC for selected patients with NMIBC:

- The staging accuracy for T1 tumours by TURB is low with 27–51% of patients being upstaged to muscle-invasive tumour at RC [162, 309-313] (LE: 3).
- Some patients with NMIBC experience disease progression to muscle-invasive disease (Table 6.2).
- Patients who experience disease progression to muscle-invasive stage have a worse prognosis than those who present with ‘primary’ muscle-invasive disease [314, 315].

The potential benefit of RC must be weighed against its risks, morbidity, and impact on quality of life (QoL) and discussed with patients, in a shared decision-making process. It is reasonable to propose immediate RC in those patients with NMIBC who are at very high risk of disease progression (see Section 6.3 and Tables 6.1 and 6.2) [66, 159, 194, 196, 316] (LE: 3).

Early RC is strongly recommended in patients with BCG-unresponsive tumours and should be considered in BCG relapsing HG tumours as mentioned in Section 7.7 and Table 7.3. A delay in RC may lead to decreased disease-specific survival [317] (LE: 3).

In patients in whom RC is performed before progression to MIBC, the 5-year DFS rate exceeds 80% [318-320] (LE: 3).

7.5 Individual treatment strategy in primary or recurrent tumours after TURB without previous BCG intravesical immunotherapy

The type of further therapy after TURB should be based on the risk groups shown in Section 6.3 and Table 6.1. The stratification and treatment recommendations are based on the risk of disease progression. In particular in intermediate-risk tumours, the 2006 EORTC scoring model may be used (Section 6.1.1.1) to determine a patient’s individual risk of disease recurrence as the basis to decide further treatment on.

Any decisions should reflect the following principles:

- Patients in the low-risk group have a negligible risk of disease progression. The single post-operative instillation of chemotherapy reduces the risk of recurrence and is considered as sufficient treatment in these patients.

7.6 Treatment of failure of intravesical therapy

7.6.1 Recurrence during or after intravesical chemotherapy

Patients with NMIBC recurrence during or after a chemotherapy regimen can benefit from BCG instillations. Prior intravesical chemotherapy has no impact on the effect of BCG instillations [238] (LE: 1a).

7.6.2 Treatment failure after intravesical BCG immunotherapy

Several categories of BCG failures, broadly defined as any HG disease occurring during or after BCG therapy, have been proposed (see Table 7.2). Non-muscle-invasive BC may not respond at all (BCG refractory) or may relapse after initial response (BCG relapsing). Some evidence suggests that patients with BCG relapse have better outcomes than BCG refractory patients [321].

To be able to specify the subgroup of patients where additional BCG is unlikely to provide benefit, the category of BCG-unresponsive tumour was defined. Further BCG instillations in these patients are associated with an increased risk of progression [209, 322]. The category of BCG-unresponsive tumours comprises BCG-refractory and some of BCG-relapsing tumours (see Table 7.2) [323]. The definition was developed in consultation with the U.S. Food and Drug Administration (FDA), in particular to promote single-arm trials to provide primary evidence of effectiveness in this setting [324].

Non-HG recurrence after BCG is not considered as BCG failure.

Table 7.2: Categories of high-grade recurrence during or after BCG

Whenever a MIBC is detected during follow-up.
BCG-refractory tumour
1. If T1 HG/G3 tumour is present at 3 months [209, 322, 325] (LE: 3). 2. If Ta HG/G3 tumour is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance [302] (LE: 4). 3. If CIS (without concomitant papillary tumour) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in > 50% of cases [45, 298, 302] (LE: 1b). 4. If HG tumour appears during BCG maintenance therapy*.
BCG-relapsing tumour
Recurrence of HG/G3 (WHO 1973/2004) tumour after completion of BCG maintenance, despite an initial response [326] (LE: 3).
BCG-unresponsive tumour
BCG-unresponsive tumours include all BCG refractory tumours and those who develop T1/Ta HG recurrence within 6 months of completion of adequate BCG exposure** or develop CIS within 12 months of completion of adequate BCG exposure [323] (LE: 4).
BCG intolerance
Severe side effects that prevent further BCG instillation before completing treatment [280].

** Patients with LG recurrence during or after BCG treatment are not considered to be a BCG failure.*

*** Adequate BCG is defined as the completion of at least 5 of 6 doses of an initial induction course plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.*

7.6.3 Treatment of BCG-unresponsive tumours, late BCG-relapsing tumours, LG recurrences after BCG treatment and patients with BCG intolerance

Patients with BCG-unresponsive disease are unlikely to respond to further BCG therapy; RC is therefore the standard and preferred option. Currently, several bladder preservation strategies are being investigated such as cytotoxic intravesical therapies [327-330], device assisted instillations [331-333] intravesical immunotherapy [334, 335], systemic immunotherapy [336] or gene therapy [337-339].

A phase III RCT including predominantly high-risk NMIBC patients failing at least a previous induction course of BCG, MMC combined with microwave-induced hyperthermia provided 35% overall DFS at 2 years as compared to 41% in the control arm (treated with either BCG, MMC or MMC and electromotive drug administration at the discretion of the investigator). In the pre-planned sub-analysis, MMC and microwave-induced thermotherapy showed lower response rates in CIS recurrences but higher DFS in non-CIS papillary tumours (53% vs. 24%) [333].

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