Clinical Practice Recommendations for the Management of Non–Muscle Invasive Bladder Cancer

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Abstract

Context: Although the European Association of Urology (EAU), First International Consultation on Bladder Tumors (FICBT), National Comprehensive Cancer Network (NCCN), and American Urological Association (AUA) guidelines all provide an excellent evidence-based background for the management of non–muscle invasive bladder cancer (NMIBC), the four guidelines vary with respect to important issues such as the definitions of risk levels and the appropriate management strategies for patients in these risk categories.

Objective: To build on the existing framework provided by the EAU, FICBT, NCCN, and AUA guidelines and to provide consensus on the definitions of low-, intermediate-, and high-risk NMIBC as well as practical recommendations for the management of patients in each of these risk categories.

Evidence acquisition: A committee of internationally renowned leaders in bladder cancer management, known as the International Bladder Cancer Group (IBCG), identified current key influencing guidelines and published English-language literature related to the treatment and management of NMIBC available as of March 2008. The IBCG met on four occasions to review the main findings of the identified literature and the current clinical practice guidelines of the EAU, FICBT, NCCN, and AUA.

Evidence synthesis: On the basis of a review of the current literature and the EAU, FICBT, NCCN, and AUA guidelines, the IBCG developed a user-friendly treatment algorithm and practical recommendations for the management of patients with low-, intermediate-, and high-risk NMIBC.

Conclusions: A complete transurethral resection of the bladder tumour (TURBT) plus an immediate, postoperative chemotherapeutic instillation is recommended for all patients with NMIBC except those with obvious or suspected bladder wall perforation. For intermediate-risk disease, intravesical induction bacillus Calmette-Guérin (BCG) plus maintenance or intravesical chemotherapy are recommended; for high-risk disease, BCG induction plus maintenance is the recommended management strategy. The appropriate management of recurrences depends on the patient’s level of risk; whereas the management of treatment failures depends on both the type of failure and the patient’s level of risk for recurrence and disease progression.

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1. Introduction

The primary approach to the management of non–muscle invasive bladder cancer (NMIBC) is transurethral resection of the bladder tumour (TURBT) followed by intravesical therapy with either chemotherapy or bacillus Calmette-Guérin (BCG). The instillation of a chemotherapeutic drug immediately after TURBT was originally proposed in the 1970s [1,2] and was based on the assumption that chemotherapy could destroy floating tumour cells and prevent reimplantation in the bladder. Numerous clinical trials have now confirmed the benefits of a single, immediate postoperative instillation of chemotherapy for the prevention of tumour recurrence [3].

Intravesical chemotherapy can also be given as adjuvant therapy for intermediate-risk disease. However, the investigators of a recent systematic review of randomised trials of intravesical chemotherapy could not provide firm recommendations on the use of additional instillations owing to inconclusive results. In fact, short intensive instillation schedules within the first 3–4 mo after an immediate instillation appear to be as effective as longer term schedules [3].

The concept of immunotherapy began in the late 1880s, when the American surgeon Cooley described a bacterial toxin to treat lymphosarcoma. From 1908 to 1921, Albert Calmette and Jean Camille Guérin developed BCG as a vaccine for tuberculosis. This vaccine was sent by the Institute Pasteur to various countries around the globe in the 1920s and 1930s. Because the vaccine was continued as live bacteria, differences developed between the various strains, and collectively these daughter strains are known as BCG. Since the advent of modern lyophilization techniques in the early 1950s, the different BCG strains are grown from stored seed lots and remain essentially unchanged.

It has been recognised for many years that patients with tuberculosis had lower cancer rates than unaffected patients; therefore, the potential application of the BCG vaccine for the treatment of different cancers has been studied by many investigators. In 1966, Coe and Feldman [4] demonstrated that the bladder responded to BCG with a delayed-type hypersensitivity reaction like the skin, and in 1970, Morton in the United States observed regression of malignant melanoma treated with intravesical BCG. Silverstein et al [5] also reported response of melanoma metastatic to the bladder treated with intravesical BCG. In 1975, DeKernion and colleagues [6] found that isolated melanoma in the bladder was treated successfully with cystoscopic injection of BCG vaccine.

In the 1970s, Morales et al [7] described the first human trial using BCG to treat bladder cancer in nine patients. The initial results of the first controlled clinical trial of BCG in bladder cancer were published in 1980 and showed a significant reduction in tumour recurrence with intravesical and percutaneous BCG administration [8]. Similar results were reported in much higher risk patients in a Memorial Sloan-Kettering Cancer Centre study; these results showed that a single 6-wk course of intravesical plus maintenance BCG provided long-term protection from tumour recurrence, and even reduced disease progression [9]. Findings from larger studies by Akaza and colleagues in Japan highlight the direct anti-tumour effects of BCG, with overall complete response rates of 84.4% [10] and 71.8% [11] in patients with carcinoma in situ (CIS) and Ta/T1 disease, respectively.

Although intravesical BCG immunotherapy is now recognised as the treatment of choice for intermediate- and high-risk NMIBC, there are variations among the current key influencing guidelines with regard to the optimal use of BCG in the management of NMIBC. Differences also exist with respect to definitions of levels of risk and other management strategies for NMIBC (see article entitled Current Approaches to the Management of Non–Muscle Invasive Bladder Cancer: Comparison of Current Guidelines and Recommendations in this supplement). Therefore, a committee of internationally renowned leaders in bladder cancer management, known as the International Bladder Cancer Group (IBCG), identified current key influencing guidelines and published English-language literature related to the treatment and management of NMIBC, available as of March 2008. The IBCG met on four occasions to review the main findings of the identified literature and the current clinical practice guidelines of the European Association of Urology (EAU) [12], the First International Consultation on Bladder Tumours (FICBT) [13], the National Comprehensive Cancer Network (NCCN) [14], and the American Urological Association (AUA) [15,16].

After careful review and analysis of the EAU, FICBT, NCCN, and AUA recommendations for the management of NMIBC, the IBCG developed the treatment algorithm in Fig. 1. The goal of this algorithm is to build on the existing framework provided by the EAU, FICBT, NCCN, and AUA guidelines and to provide consensus on the definitions of low-, intermediate-, and high-risk NMIBC as well as practical recommendations for the management of patients in each of these risk categories.
A detailed discussion of each recommendation proposed in this algorithm, along with supporting guidelines and evidence, is provided in this article. It should be noted that upon review of the various guidelines, the IBCG concluded that the EAU guidelines represented best practice with regard to TURBT and the use of intravesical therapy and, as such, were adopted by the group as appropriate recommendations (with some minor modifications and additions) for community urologists.

2. Definitions of levels of risk

Upon review of the definitions of risk levels proposed by the EAU, FICBT, NCCN, and AUA (see article entitled Current Approaches to the Management of Non-Muscle Invasive Bladder Cancer: Comparison of Current Guidelines and Recommendations in this supplement), the IBCG proposed the following practical definitions of low-, intermediate-, and high-risk disease (see Fig. 1):

- Low-risk: solitary, primary low-grade Ta
- Intermediate-risk: multiple or recurrent low-grade tumours
- High-risk: any T1 and/or G3 and/or CIS

3. Transurethral resection of the bladder tumour

3.1. Recommendations

Complete TURBT is recommended for all patients with NMIBC:

1. Appropriate/accepted TURBT techniques should be utilised;
2. Bladder diagram is recommended.
3.2. Supporting guidelines and evidence

The EAU, FICBT, NCCN, and AUA all recommend TURBT as the gold standard for the initial diagnosis and treatment of NMIBC [12,14–19]. After TURBT, the 10-yr disease-specific survival is 85% for Ta tumours and 70% for T1 tumours [20].

Appropriate resection techniques should be used, as the quality of the initial TURBT may have substantial influence on tumour recurrence. Brausi et al., for example, found the recurrence rate at first cystoscopy to range from 3.4% to 20.6% in patients not receiving intravesical treatment and from 0% to 15.4% in those receiving intravesical therapy. In patients with multiple tumours who received adjuvant treatment, the recurrence rate varied between 7.4% and 45.8%. This variability in recurrence rates was attributed to the quality of the TURBT performed by the individual surgeons [21].

The EAU has outlined the following resection techniques depending on the size of the lesion [12]:

- Small tumours (<1 cm) can be resected en bloc.
  - Specimen should contain complete tumour plus part of underlying bladder wall
- Larger tumours should be resected separately in fractions and include:
  - Exophytic part of the tumour
  - Underlying bladder wall with the detrusor muscle
  - Edges of the resection area
- Specimens from different fractions must be referred to the pathologist in separate containers to enable a correct diagnosis.

The IBCG also encourages cold-cup biopsies of the tumour base and emphasizes the importance of avoiding excess cauterisation during resection to preserve the quality of the histologic sample for staging and grading.

A repeat TURBT, 2–6 wk after the initial TURBT, may provide additional diagnostic and prognostic information and is, therefore, recommended in patients with high-grade T1 tumours when the initial resection was incomplete or when the pathologist reported that the specimen contained no muscle tissue [12].

4. Immediate, single, postoperative instillation of intravesical chemotherapy

4.1. Recommendations

Immediate, single, postoperative instillation of chemotherapy is recommended for all patients with NMIBC, except for those with obvious or suspected bladder wall perforation. Choice of chemotherapeutic agent is optional. (Note: Efficacy of single, immediate instillation of chemotherapy has not been studied in high-risk disease.)

4.2. Supporting guidelines and evidence

The EAU, FICBT, NCCN, and AUA guidelines all advocate the use of an immediate, single-instillation of chemotherapy following TURBT [12,14–19]. A meta-analysis conducted by the European Organisation for the Research and Treatment of Cancer (EORTC) showed that a single, immediate instillation of intravesical chemotherapy following TURBT results in a 12% absolute reduction in tumour recurrence (decrease of 39% in odds of recurrence) [22]. The EORTC meta-analysis also found no significant differences in efficacy among the chemotherapeutic agents studied. Therefore, choice of agent is optional.

Timing of the instillation is important. In all studies included in the EORTC meta-analysis, the instillation was administered within 24 h [22]. Kaasinen et al [23] found that the risk of recurrence doubled if the instillation was not given within 24 h of TURBT. However, an immediate, single instillation of chemotherapy should be avoided in cases of overt or suspected intra- or extraperitoneal perforation, as complications have been noted in these patients [24]. Furthermore, it is important to note that there are no studies that have examined the benefits of a single, immediate chemotherapeutic instillation in high-risk disease.

The chemotherapeutic agents commonly used in the management of NMIBC are triethylenethiophosphoramide (thiotepa), doxorubicin, epirubicin, and mitomycin C. Although current evidence suggests that these agents are similar in efficacy, they have been noted to differ in toxicity. Thiotepa, for example, is rarely used in the United States because of its high associated risk of myelosuppression [25]. However, it should be noted that myelosuppression has not been reported when thiotepa is used as a single-dose agent. Furthermore, the intravenous dose is 0.5 mg/kg, providing a safe margin if 30 mg is instilled, even in patients with extensive resection in whom 100% absorption may occur. Moreover, recent studies show that extravasation on cystogram occurs in the majority of patients undergoing TURBT [26]. Thiotepa can be safely administered in the peritoneum and, therefore, may be an agent of choice for immediate postoperative instillation. The side effects of doxor-
ubicin, such as cystitis, decreased bladder capacity, and haematuria, have also hampered its use in some countries [27]. Epirubicin appears to have a better toxicity profile than doxorubicin; associated adverse events are generally mild, with the most common being cystitis, haematuria, or both [28]. The most common side effects noted with mitomycin C include dysuria and urinary frequency [27]. Problematic dystrophic calcification requiring repeat resection may also occur.

A recent study comparing three schedules of intravesical epirubicin in patients with intermediate- or high-risk NMIBC found no difference in the 5-yr recurrence-free period between patients treated with a standard epirubicin schedule (ie, four weekly and five monthly instillations) and those who received standard therapy plus an additional instillation <48 h of TURBT or additional instillations at 9 and 12 mo (maintenance schedule) [29]. It should be noted that epirubicin is not approved for intravesical use in the United States.

Results from studies examining newer chemotherapeutic agents are emerging. Gemcitabine and docetaxel, for example, have minimal toxicity when used intravesically, and they have been found to be effective in intermediate-risk tumours as well as in patients refractory to BCG therapy that refuse cystectomy [30,31]. However, it should be noted that gemcitabine and docetaxel are not currently approved for the treatment of NMIBC. Furthermore, long-term follow-up data with these agents are still lacking.

5. Adjuvant intravesical chemotherapy

5.1. Recommendations

For intermediate-risk disease, intravesical chemotherapy or BCG induction plus maintenance should be initiated following complete TURBT and single, immediate instillation of chemotherapy.

5.2. Supporting guidelines and evidence

Tumour recurrence is the primary concern in patients with intermediate-risk NMIBC. Long-term follow-up studies have shown that >80% of intermediate-risk patients experience a tumour recurrence; even those with solitary G1Ta disease have a long-term recurrence rate of 67% [32]. However, only 1.8% of intermediate-risk patients will progress to muscle-invasive disease [33].

The EAU, FICBT, NCCN, and AUA agree that intravesical chemotherapy or BCG (discussed in the following section) should be offered to patients with intermediate-risk disease following complete TURBT and a single, immediate instillation of chemotherapy [12,14–16,18]. However, the NCCN guidelines state that BCG therapy is preferred over chemotherapy in this patient population [14].

A meta-analysis conducted by the EORTC and the Medical Research Council found that adjuvant chemotherapy after TURBT significantly improves disease-free survival compared to TURBT alone [34]. However, no effect of adjuvant chemotherapy on progression was noted. In a review of controlled trials of intravesical chemotherapies, Lamm et al [32] reported an absolute 14% decrease in tumour recurrence, but found no effect on tumour progression. A meta-analysis conducted by the Japanese Urological Cancer Research Group (JUCRGA) revealed that the prophylactic effect of intravesical chemotherapy after TURBT in patients with intermediate-risk NMIBC continues for a period of 500 d [35].

The beneficial effects of adjuvant intravesical chemotherapy appear to be long-term. For example, a trial comparing two mitomycin C instillation schedules to TURBT alone demonstrated a decrease in the recurrence rate after a median follow-up of 7 yr in those patients treated with chemotherapy [36]. A meta-analysis of seven randomised trials comparing mitomycin C (n = 693) and BCG (n = 834) found that tumour recurrence was significantly lower with BCG only in those patients with high-risk disease. No difference in disease progression or survival was noted between the two groups [37]. A meta-analysis of nine trials comparing intravesical chemotherapy to BCG found an odds ratio for tumour recurrence favouring BCG; however, the investigators suggested that failure to control for prior intravesical chemotherapy in most of the available studies may be related to the greater clinic effect noted with BCG [38]. It should be noted that most of the trials included in these two meta-analyses were of short duration and did not include the Southwest Oncology Group (SWOG) BCG regimen of 3 weekly instillations at 3 and 6 mo, and every 6 mo for 3 yr, which is currently considered the optimal instillation schedule. Meta-analyses may fail to show recurrence, progression, and/or survival advantages owing to lack of BCG maintenance or short duration of follow-up. For example, a meta-analysis by Sylvester et al [39] found that intravesical BCG significantly reduced the risk of progression after TURBT only when maintenance therapy was provided. A recent phase 3 trial comparing the long-term efficacy of epirubicin, BCG, and BCG plus
Fig. 2 – (a) Tumour recurrence (all studies) with odds ratio as effect size. (b) Tumour recurrence (all studies by maintenance) with odds ratio as effect size. (c) Forest plot of tumour recurrence (all studies by maintenance and risk group) with odds ratio as effect size.

Mainten = BCG maintenance regimen; OR = odds ratio; intern = intermediate; Lower, Upper = lower and upper 95% CI of OR; BCG: = bacillus Calmette-Guérin; P = p value (2-sided); NTotal = total sample size; n/N = number of events per number of cases in treatment group; Fixed = fixed effect model; Random = random effect model; MMC = mitomycin C.

Lines indicate 95% CI and squares OR estimates, whereas square size is proportional to sample size, and rhombs meta-analytically pooled OR estimates ±95% CI.

Reprinted with permission from the American Urological Association [44].
isoniazid in patients with intermediate- and high-risk NMIBC found that after a median follow-up of 9.2 yr, time to first recurrence, time to distant metastases, and overall and disease-specific survival were all significantly prolonged in the two BCG arms compared to the epirubicin arm [40].

5.3  Optimal instillation schedule

There is no current consensus on the optimal chemotherapeutic instillation schedule. Randomised studies conducted by the EORTC showed that 1 yr of monthly maintenance chemotherapy was no more effective than 6 mo of monthly maintenance in reducing recurrence rate when the first instillation was given immediately after TURBT [41]. Similar findings were reported in another study that found long-term prophylactic maintenance instillations of epirubicin to be no more effective than short-term instillations at reducing bladder cancer recurrence [42]. However, another randomised trial reported reduced recurrence rates after long-term epirubicin treatment (1 yr) compared to short-term treatment (3 mo) [43].

Results from a recent systematic review of clinical trials examining intravesical chemotherapeutic instillations in NMIBC suggest that a short intensive schedule of instillations within the first 3 to 4 mo after an immediate instillation may be as effective as longer-term treatment schedules. The investigators also concluded that the use of long-term instillations of ≥1 yr be considered only when an immediate instillation has not been provided [3].

6.  Adjuvant bacillus Calmette-Guérin therapy

6.1  Recommendations

For intermediate-risk disease, BCG induction plus maintenance or chemotherapy should be initiated following complete TURBT and a single, immediate instillation of chemotherapy. For high-risk disease, BCG induction plus maintenance should be initiated following complete TURBT and a single, immediate instillation of chemotherapy. (Note: Efficacy of single, immediate instillation of chemotherapy has not been studied in high-risk disease.)

6.2  Supporting guidelines and evidence

The EAU, FICBT, NCCN, and AUA guidelines all agree that in high-risk patients, BCG is the preferred treatment following TURBT and an immediate postoperative dose of chemotherapy [12,14–17,19]. A meta-analysis of seven randomised trials comparing BCG to mitomycin C found BCG to be statistically superior to chemotherapy in reducing disease recurrence in high-risk patients. However, no difference in disease progression or survival was noted [37]. Another meta-analysis of 11 clinical trials found BCG to be superior to mitomycin C for the prevention of tumour recurrences, particularly in the BCG maintenance treatment subgroup, and these findings were irrespective of the actual tumour risk status (ie, intermediate- or high-risk; see Fig. 2a–c) [44].

The most compelling evidence in favour of BCG comes from a large EORTC meta-analysis of 24 trials involving 4863 patients [39]. Five different BCG strains were used, and in 20 of the 24 trials, some form of BCG maintenance was used. In four trials, only a 6-wk induction course was applied. On the basis of a median follow-up of 2.5 yr and a maximum of 15 yr, 260 of 2658 patients (9.8%) on BCG progressed compared to 304 of 2205 (13.8%) in the control groups (TURBT alone, TURBT plus intravesical chemotherapy, or TURBT plus another immunotherapy). Overall, treatment with maintenance BCG was associated with a 27% reduction in the risk of tumour progression. Similar effects were reported in the patients with Ta, T1 papillary tumours, and in those with CIS. Forest plots of tumour progression by treatment method and by disease type are shown in Fig. 3a and b [39].

The results of the EORTC meta-analysis also indicate that maintenance BCG therapy is required for optimal efficacy. No reduction in progression was noted in the four trials in which maintenance BCG therapy was not administered. However, in the 20 trials in which some form of BCG maintenance was given, a reduction of 37% in the risk of progression was observed [39]. A randomised study by the SWOG also found maintenance BCG immunotherapy to be more beneficial than standard induction therapy in patients with CIS and select patients with Ta, T1 bladder cancer. Median recurrence-free survival in patients receiving maintenance BCG was twice as long compared to those not receiving maintenance therapy [45].

Recent data from the EORTC phase 3 trial 30911 confirm the superiority of BCG in intermediate- and high-risk disease. This trial compared the long-term efficacy of six weekly intravesical instillations of epirubicin, BCG and BCG plus isoniazid followed by three weekly maintenance instillations at months 3, 6, 12, 18, 24, 30, and 36 following TURBT in patients with intermediate- and high-risk NMIBC (n = 837).
Median follow-up was 9.2 yr. The investigators found that time to first recurrence ($p < 0.0001$), time to distant metastases ($p = 0.03$), and overall ($p = 0.02$) and disease-specific survival ($p = 0.03$) were all significantly longer in the two BCG arms compared to epirubicin [40].

Given the superiority of BCG over chemotherapy in reducing tumour recurrences and disease progression, the EAU, FICBT, NCCN, and AUA guidelines all advocate a role for BCG in the management of intermediate-risk disease. According to the EAU, in patients with an intermediate or high risk of recurrence and an intermediate risk of progression, one immediate instillation of chemotherapy should be followed by a minimum of 1 yr of BCG or further instillations of chemotherapy [12]. The NCCN guidelines indicate that BCG is the preferred intravesical option for these patients [14].
6.3. **Optimal bacillus Calmette-Guérin maintenance schedule**

The current optimal BCG maintenance schedule is based on the SWOG regimen of three weekly instillations at 3 and 6 mo, and every 6 mo for 3 yr [45,46]. All guidelines and meta-analyses recommend at least 1 yr of BCG maintenance therapy.

6.4. **Optimal dose of bacillus Calmette-Guérin**

Although the optimal dose of BCG is unknown, most clinical studies and meta-analyses have utilised standard dosing, and this remains the global standard of care. Recent evidence suggests that a one-third dose of BCG provides similar results for recurrence and progression as standard-dose BCG [47,48]. However, these results also indicate that standard-dose BCG is likely more effective in patients with multifocal and high-risk tumours [47].

Ojea et al [49] found that one-sixth of the standard BCG dose was significantly less effective than a one-third dose for the treatment of intermediate-risk NMIBC, but was no less toxic, suggesting that a one-third dose is the minimum effective dose of BCG in these patients.

The IBCG acknowledges that full-dose BCG is the standard; however, dose reductions or postponement or cessation of therapy may be considered for patients who are experiencing increased BCG-associated adverse events.

7. **Immediate cystectomy**

7.1. **Recommendations**

Immediate radical cystectomy is recommended for patients with high-grade T1 tumours or high-grade tumours with CIS.

7.2. **Supporting guidelines and evidence**

According to the EAU, immediate radical cystectomy may be offered to the highest risk patients such as those with multiple recurrent tumours, high-grade T1 tumours, or high-grade tumours with CIS [12]. According to the AUA, cystectomy is considered an option for initial therapy in select patients with high-grade Ta, T1, and/or CIS with lamina propria invasion (T1) because of the risk of initially understaged muscle-invasive disease or progression to muscle-invasive disease [15,16].

8. **Device-assisted therapies**

Device-assisted therapies such as thermochemotherapy and electromotive drug administration (EMDA) appear promising for the treatment of NMIBC. The Synergo system, for example, stimulates bladder wall hyperthermia through an energy-delivering unit in the tip of a special catheter equipped with internal thermocouples designed to monitor temperatures, which are maintained between 42 °C and 43 °C. The system is currently used in combination with intravesical mitomycin C and has been shown to be superior to mitomycin C alone. However, the use of Thermochemotherapy is associated with significantly more side effects than mitomycin C alone, although these are generally temporary [30,50].

EMDA has demonstrated efficacy in reducing progression rate when used in combination with BCG. This device-assisted approach temporarily enhances drug penetration through the urothelial barrier of the bladder by using an electrical gradient between the bladder wall and the bladder contents. It should be noted that, although these device-assisted therapies appear promising, they have primarily been used only in small groups of high-risk patients or as second-line therapy [30,50]. Therefore, the IBCG does not make any specific recommendations for the use of device-assisted therapies at this time.

9. **Follow-up schedule**

Although there is currently no agreement on the recommended follow-up schedules for low-, intermediate-, and high-risk disease, the IBCG has proposed the following schedule which is based on the EAU recommendations for follow-up, with minor modifications [12]:

- **Low-risk disease:**
  - Surveillance cystoscopy at 3 mo
  - If negative, subsequent cystoscopies are advised at 9 mo and then yearly for a minimum of 5 yr
  - No upper tract investigations are required.
- **High-risk disease:**
  - Cystoscopy and cytology at 3 mo
  - If negative, subsequent cystoscopies and cytology assessments should be repeated every 3 mo for a period of 2 yr, every 4 mo in the third year, every 6 mo thereafter until 5 yr, and annually thereafter
  - Annual upper urinary tract imaging should also be considered.
10. **Recurrences and treatment failures**

10.1. **Defining recurrences and treatment failures**

To ensure the optimal management of NMIBC, the IBCG emphasizes the importance of distinguishing recurrences from treatment failures and has proposed the following definitions:

- Recurrence—refers to reappearance of disease (any grade, T category, or CIS) after completion of therapy;
- Treatment failure—intravesical therapy is considered to fail when any recurrence or progression occurs during therapy.

The IBCG also acknowledges that defining the type of BCG failure (see Table 1) may be helpful in deciding whether conservative management or cystectomy is required for these patients.

10.2. **Recommendations for the management of recurrences**

The IBCG recommends the following management strategies for recurrences, which are also shown in the algorithm in Fig. 1:

- For recurrences in low-risk patients, treat as intermediate-risk:
  - TURBT plus single, immediate chemotherapeutic instillation
  - Intravesical chemotherapy or BCG induction plus maintenance
- For recurrences in intermediate-risk patients, consider risk category:
  - If still intermediate-risk:
    - TURBT plus single, immediate chemotherapeutic instillation
    - Repeat chemotherapy or BCG induction plus maintenance
  - If high-risk:
    - TURBT plus single, immediate chemotherapeutic instillation
    - BCG induction plus maintenance, or
    - Radical cystectomy

- For high-grade recurrences in high-risk patients:
  - Radical cystectomy (preferred)
  - TURBT plus additional intravesical instillations if patient is not suitable for cystectomy.

(Note: Efficacy of single immediate instillation of chemotherapy has not been studied in high-risk disease.)

10.3. **Recommendations for the management of treatment failures**

According to the IBCG, the appropriate management strategies for treatment failures will depend on the type of failure (ie, chemotherapy or BCG) and the patient’s level of risk. See the following recommendations:

- Chemotherapy failure:
  - TURBT plus single, immediate chemotherapeutic instillation
  - BCG induction plus maintenance, or
  - Additional intravesical chemotherapy
- BCG failure—consider risk category:
  - If intermediate-risk:
    - TURBT plus single, immediate chemotherapeutic instillation
    - Repeat BCG induction plus maintenance, or
    - Radical cystectomy
  - If high-risk, radical cystectomy is recommended

10.4. **Supporting guidelines and evidence**

According to a recent review by Witjes [51], there are no formal studies on patterns of treatment failure available for review; however, the current, best treatment options that will preserve the bladder include repeat resection and repeat BCG. Other options may include cystectomy, intravesical chemotherapy, and combination BCG and interferon-α.

10.5. **Repeat BCG treatment**

According to the results of various studies [52–55], the FICBT suggests that repeat BCG therapy may be appropriate for BCG-resistant and BCG-relapsing disease [17], as long as the recurrence is not T1 disease.

The IBCG acknowledges the role of repeat BCG in certain patients for whom BCG therapy fails and,
therefore, recommends that repeat BCG be provided as an option for intermediate-risk patients for whom BCG therapy fails. Furthermore, low-risk patients experiencing a recurrence following TURBT and an immediate chemotherapeutic instillation should be considered intermediate-risk and, therefore, BCG induction plus maintenance may be an option for these patients.

However, BCG-refractory disease is unlikely to respond to further BCG therapy [56]; therefore, cystectomy is the preferred option in these patients.

10.6. Cystectomy

According to the FICBT, BCG-refractory disease has less of a margin for tolerating treatment-related delays and, therefore, delaying cystectomy in these patients may lead to progression, metastases, and death. In fact, the FICBT recommendations advocate cystectomy for BCG-refractory disease [17]. The EAU, NCCN, and AUA guidelines also recommend cystectomy in patients with high-risk disease failing intravesical therapy.

The IBCG agrees that cystectomy should be the standard for high-risk patients failing BCG or those experiencing a recurrence after completion of therapy; the IBCG also recommends that cystectomy be an option for patients with intermediate-risk disease failing intravesical therapy or in patients with intermediate-risk disease who experience a high-risk recurrence.

The timing of radical cystectomy for high-risk NMIBC is critical to the prognosis and long-term survival of these patients; early cystectomy has been shown to confer better outcomes [57,58]. Patients with refractory T1 tumours or CIS who have evidence of muscle and extravesical involvement and metastatic disease at early cystectomy fare significantly better than those who undergo delayed cystectomy [59,60]. Furthermore, delayed cystectomy and the resulting disease progression dramatically decrease survival. Schrier and colleagues [61] found that patients with muscle-invasive bladder cancer with a history of NMIBC have a worse prognosis than patients with primary muscle-invasive bladder cancer.

Recently, Denzinger and colleagues [62] compared long-term outcomes in patients with initial pT1G3 bladder cancer (n = 105) treated with early or deferred cystectomy for recurrent pT1G3 or muscle-invasive bladder cancer after an initial bladder-sparing approach. All patients were offered early cystectomy: 51% opted for early cystectomy and 49% underwent deferred cystectomy. The 10-yr cancer-specific survival rate was 78% in the early cystectomy group and 51% in the deferred group (p < 0.01). Furthermore, CIS was related to a lower cancer-specific survival rate in deferred cystectomy patients (p < 0.001). The investigators concluded that early cystectomy, as opposed to deferred, appears to prolong the cancer-specific survival rate in high-risk pT1G3 bladder cancer and that patients with CIS should be considered for early cystectomy [62]. However, it is important to note that this study was not a randomised trial and included only those patients who failed or progressed following intravesical therapy.

Cancer-specific survival is not the only consideration and cystectomy is not necessarily the best choice for individuals, even when muscle-invasive disease is present. Herr [63] examined the 10-yr outcome of patients with muscle-invasive bladder

<table>
<thead>
<tr>
<th>Table 1 – Types of bacillus Calmette-Guérin (BCG) failure as proposed by the First International Consultation on Bladder Tumours [17]</th>
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<tr>
<td><strong>BCG-refractory</strong> &lt;br&gt;• Failure to achieve disease-free state by 6 mo after initial BCG therapy with either maintenance or retreatment at 3 mo because of either persistent or rapidly recurring disease &lt;br&gt;• Any progression in stage, grade, or disease extent by 3 mo after first cycle of BCG</td>
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<tr>
<td><strong>BCG-resistant</strong> &lt;br&gt;• Recurrence or persistence at 3 mo after the induction cycle &lt;br&gt;• Recurrence is of lesser degree, stage, or grade and is no longer present at 6 mo from BCG retreatment, with our without TURBT</td>
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<tr>
<td><strong>BCG-relapsing</strong> &lt;br&gt;• Recurrence of disease after achieving a disease-free status by 6 mo &lt;br&gt;Relapse further defined by time of recurrence: &lt;br&gt;- Early: within 12 mo &lt;br&gt;- Intermediate: 12–24 mo &lt;br&gt;- Late: &gt;24 mo</td>
</tr>
<tr>
<td><strong>BCG-intolerant</strong> &lt;br&gt;• Disease recurs after less-than-adequate course of therapy because of serious adverse events or symptomatic intolerance that mandates BCG discontinuation</td>
</tr>
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</table>

Caution: Relapsing disease while on active treatment may qualify as BCG-refractory disease.

TURBT = transurethral resection of the bladder tumour.
cancer treated by TURBT alone. Ninety-six patients with muscle-invasive transitional cell carcinoma underwent repeat TURBT and had T0 disease. With 10- to 20-yr follow-up, 65% of the 23 patients treated with immediate cystectomy were alive compared with 82% of the 73 patients treated with repeat resection, with or without intravesical therapy.

Results from a recent trial by the SWOG also suggest that cystectomy may be an appropriate option for patients with high-risk disease who do not achieve a complete response to induction BCG. This retrospective analysis of 501 evaluable patients randomised to induction BCG, with or without maintenance, found that failure to achieve a complete response after induction BCG was associated with a significant risk of a worsening event and death (hazard ratio [HR]: 0.37, p = 0.017). For those with relapsing disease who required cystectomy, 3-wk maintenance BCG significantly reduced mortality compared with induction BCG, even though cystectomy was delayed [64].

10.7. Intravesical chemotherapy

BCG intolerance occurs in approximately 20% of patients during maintenance therapy. As a result, some of these patients never complete the induction course, meaning they never receive sufficient BCG therapy. In these patients, intravesical therapy with another drug at the time of recurrence may be an appropriate option [51].

Results from various studies suggest that intravesical chemotherapy may be a viable option [65–69]. The IBCG recommends that maintenance intravesical chemotherapy be considered in low-risk patients who fail treatment with TURBT and an immediate single chemotherapeutic instillation. Adjuvant chemotherapy may be considered an option for low- or intermediate-risk recurrences, high-risk recurrences within a clinical trial, or in patients without other options. The use of intravesical chemotherapy post-BCG failure is not well studied and additional investigation in this area is required.

10.8. Immunotherapy after bacillus Calmette-Guérin failure

The combination of BCG and interferon-α appears to be a promising treatment for BCG failures [51]. Small studies, for example, have shown that a one-third dose of BCG combined with 50 million units of interferon-α given intravesically will produce a complete response in 50% of patients who have failed on BCG alone [70–72]. However, these results still need to be confirmed in large, randomised, controlled clinical trials and, therefore, at this time, the IBCG does not make any specific recommendations for the use of BCG and interferon-α in BCG failures.

11. International Bladder Cancer Group recommendations: summary

After careful review and analysis of the EAU, FICBT, NCCN, and AUA guidelines, the IBCG proposed the following recommendations for the management of patients with NMIBC according to risk category:

- For low-risk disease, complete TURBT plus immediate, single, postoperative chemotherapeutic instillation
- For intermediate-risk disease:
  - Complete TURBT plus immediate, single, postoperative chemotherapeutic instillation
  - Intravesical BCG induction plus maintenance or intravesical chemotherapy
- For high-risk disease
  - Complete TURBT plus immediate, single, postoperative chemotherapeutic instillation
  - Intravesical BCG induction plus maintenance
  - Radical cystectomy
- For recurrences in low-risk patients, treat as intermediate-risk
- For recurrences in intermediate-risk patients, consider risk category:
  - If still intermediate-risk:
    - TURBT plus single, immediate chemotherapeutic instillation
    - Repeat chemotherapy or BCG induction plus maintenance
  - If high-risk:
    - TURBT plus single, immediate chemotherapeutic instillation (note: efficacy of single, immediate instillation of chemotherapy has not been studied in high-risk disease)
    - BCG induction plus maintenance or
    - Radical cystectomy
- For high-grade recurrences in high-risk patients
  - Radical cystectomy (preferred)
  - TURBT plus additional intravesical instillations if patient is not suitable for cystectomy
- For intravesical chemotherapy failures
  - TURBT plus single, immediate chemotherapeutic instillation
  - BCG induction plus maintenance or
  - Additional intravesical chemotherapy
These recommendations are built upon the existing framework provided by the EAU, FICBT, NCCN, and AUA guidelines, and they provide practical approaches to NMIBC management that can be used by community urologists throughout the world.

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