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Current Approaches to the Management of Non-Muscle Invasive Bladder Cancer: Comparison of Current Guidelines and Recommendations

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Treatment failures

Abstract

Context: The guidelines of the European Association of Urology (EAU), the First International Consultation on Bladder Tumors (FICBT), the National Comprehensive Cancer Network (NCCN), and the American Urological Association (AUA) all provide an excellent evidence-based background for the management of non-muscle invasive bladder cancer (NMIBC). Although there are areas of consensus among the four guidelines, their recommendations vary with respect to important issues surrounding NMIBC.

Objective: To provide community urologists with practical and unified guidance on the management of NMIBC through a comprehensive review of current influencing guidelines.

Evidence acquisition: A committee of internationally renowned leaders in bladder cancer management, known as the International Bladder Cancer Group (IBCG), was convened in October 2006 to review current literature surrounding the management of NMIBC as well as the current clinical practice guidelines of the EAU, the FICBT, the NCCN and the AUA. Following the inaugural meeting in October 2006, the IBCG met on three subsequent occasions (March 2007, September 2007, and March 2008) to critically analyze and compare the EAU, FICBT, NCCN, and AUA guidelines.

Evidence synthesis: The IBCG critically analyzed and summarized the EAU, FICBT, NCCN, and AUA guidelines and identified the key similarities and differences in their recommendations.

Conclusions: Established areas of consensus among the four guidelines include the importance of transurethral resection of the bladder tumour (TURBT) and an immediate, postoperative dose of chemotherapy (agent optional) in all patients with NMIBC, as well as the benefit of adjuvant bacillus Calmette-Guérin (BCG) therapy in high-risk disease. However, the four guideline recommendations vary with regard to the following important issues: (1) the definitions of low-, intermediate-, and high-risk disease, and (2) the appropriate management and follow-up of patients in each of these risk categories. Furthermore, there is currently no consensus on the definition and appropriate management strategies for primary intravesical treatment failures among the four guidelines.

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1. Introduction

The guidelines of the European Association of Urology (EAU) [1], the First International Consultation on Bladder Tumors (FICBT) [2], the National Comprehensive Cancer Network (NCCN) [3], and the American Urological Association (AUA) [4,5] all contribute to an excellent evidence-based framework for the management of non-muscle invasive bladder cancer (NMIBC). However, there are differences in the recommendations made in these guidelines as well as contentious areas and topics that are not addressed.

To provide more practical and uniform recommendations that would be applicable to community urologists, the International Bladder Cancer Group (IBCG) for NMIBC critically analyzed and compared the EAU, FICBT, NCCN, and AUA guidelines. This article summarizes these guidelines and identifies the key similarities and differences in their recommendations.

Before comparing the guidelines, it is important to note the categories of consensus or evidence-based grading systems used by each of the individual guideline panels. The level of evidence and grade of recommendations used in the EAU guidelines are shown in Table 1 [6,7]. The recommendations of the FICBT are based on the International Consultation on Urologic Disease (ICUD) grading system presented in Table 2 [2,8], and the NCCN recommendations are based on the categories of consensus shown in Table 3. All NCCN recommendations are category 2A unless otherwise specified [3]. The AUA Guidelines Panel conducted its own meta-analyses of randomised controlled trials and developed tables that provided outcome estimates for different treatment modalities for NMIBC. Based on evidence in the outcome tables and expert opinion, the AUA guideline statements were graded with respect to the degree of flexibility in their application [4,5]. These three levels of flexibility are defined in Table 4.

The treatment and management of NMIBC ultimately depends on the patient's risk of recurrence and/or progression. The following article compares the EAU, FICBT, NCCN, and AUA risk-stratification definitions and treatment recommendations for each level of risk.

Table 2 – International Consultation on Urologic Disease modified Oxford Center for Evidence-Based Medicine grading system for recommendations used by the First International Consultation on Bladder Tumors [2,8]

Level of evidence
• Level 1: Meta-analysis of RCTs or good-quality RCT • Level 2: Low-quality RCT or meta-analysis or good-quality prospective cohort studies • Level 3: Good-quality retrospective case-control studies or case studies • Level 4: Expert opinion based on "first principles" or bench research, not on evidence
Grades of recommendations
• Grade A: Usually consistent level 1 evidence • Grade B: Consistent level 2 or 3 evidence or "majority evidence" from RCTs • Grade C: Level 4 evidence, "majority evidence" from level 2 or 3 studies • Grade D: No recommendation possible because of inadequate or conflicting evidence

RCT = randomised controlled trial.

2. Definitions of levels of risk

Although the EAU, FICBT, NCCN, and AUA guidelines agree on the importance of risk stratification

Table 1 – Levels of evidence and grade of guideline recommendations used in the European Association of Urology guidelines [6,7]

Level	Type of evidence
1a	• Evidence obtained from meta-analysis of randomised trials
1b	• Evidence obtained from at least one randomised trial
2a	• Evidence obtained from one well-designed controlled study without randomisation
2b	• Evidence obtained from at least one other type of well-designed quasi-experimental study
3	• Evidence obtained from well-designed non-experimental studies such as comparative studies, correlation studies and case reports
4	• Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities
Grade	**Nature of recommendations**
A	• Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	• Based on well-conducted clinical studies, but without randomised clinical trials
C	• Made despite the absence of directly applicable clinical studies of good quality

Table 3 – National Comprehensive Cancer Network (NCCN) consensus categories [3]

Category 1	Uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate
Category 2A	Uniform NCCN consensus, based on lower level evidence including clinical experience, that the recommendation is appropriate
Category 2B	Non-uniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate
Category 3	Major NCCN disagreement that the recommendation is appropriate

Table 4 – Grading of American Urological Association guideline statements according to degree of flexibility in their application [4,5]

Standard	• Health outcomes of the alternative interventions are sufficiently well known to permit meaningful decisions, and • Virtual unanimity about which intervention is preferred
Recommendation	• Health outcomes of the alternative intervention are sufficiently well known to permit meaningful decisions, and • An appreciable but not unanimous majority agrees on which intervention is preferred
Option	• Health outcomes of the interventions are not sufficiently well known to permit meaningful decisions, or • Preferences are unknown or equivocal Options can exist because of insufficient evidence or because patient preferences are divided and may/should influence choices made.

for NMIBC management, there are differences in their definitions of level of risk as well as their proposed treatments for each risk category. Table 5 summarizes the definitions for low-, intermediate-, and high-risk disease proposed by the EAU, FICBT, NCCN, and AUA [1,3–5,9–11].

3. Comparison of recommended management approaches

3.1. *Transurethral resection of the bladder tumour*

All guideline recommendations agree that transurethral resection of the bladder tumour (TURBT) is the gold standard for the initial diagnosis and treatment of NMIBC, regardless of level of risk.

According to the FICBT recommendations, complete tumour resection should be attempted, except in cases of diffuse carcinoma *in situ* (CIS), and bladder perforation should be avoided [12]. The AUA acknowledges that the size and/or multiplicity of tumours or obvious deep muscle invasion may prevent complete resection and that comorbid conditions may occasionally influence a decision about whether to attempt entire endoscopic removal of bladder tumours [4,5].

The EAU recommends that small tumours (<1 cm) be resected in one chip, which contains the complete tumour plus a part of the underlying bladder wall, and that larger tumours be resected in fractions. In the case of larger tumours, the exophytic tumour tissue should be removed first, and then, separately, the underlying bladder wall should be resected into the muscle. The presence of

Table 5 – Comparison of risk stratification definitions proposed by the European Association of Urology (EAU), the First International Consultation on Bladder Tumors (FICBT), the National Comprehensive Cancer Network (NCCN), and the American Urological Association (AUA) [1,3–5,9–11]

	Definitions		
	Low risk	Intermediate risk	High risk
EAU [1]	G1-2Ta Low risk of tumour recurrence and progression (EORTC recurrence score = 0; progression score = 0)	Multifocal G2Ta, G1T1, solitary G2T1 Intermediate or high risk of recurrence and intermediate risk of progression (EORTC recurrence scores ranging from 1–9; progression scores ranging from 1–6)	Multifocal G2T1, G3Ta-T1, CIS High risk of progression (EORTC progression scores ranging from 7–23)
FICBT [9–11]	Low-grade Ta	Low-grade Ta with high risk factors for recurrence or recurrent low-grade Ta tumours	High-grade Ta, all T1, CIS
NCCN [3]	G1-2Ta	G3Ta, solitary G1-2T1	Multifocal T1, G3T1 (CIS listed separately)
AUA [4,5]	Small volume, low-grade Ta	Multifocal and/or large volume low-grade Ta High risk of recurrence, low risk of progression	High-grade Ta, all T1, CIS

CIS = carcinoma *in situ*; EORTC = European Organization for the Research and Treatment of Cancer.

Table 6 – Comparison of guideline recommendations for low risk disease [1,3–5,9]

Guideline	Definition of low risk	Recommendations
EAU [1]	G1-2Ta Low risk of tumour recurrence and progression (EORTC recurrence score = 0; progression score = 0)	TURBT Single immediate postoperative instillation of chemotherapy (grade A)
FICBT [9]	Low-grade Ta (without high risk factors for recurrence)	TURBT Single immediate postoperative instillation of chemotherapy (grade A)
NCCN [3]	Ta, G1-2	TURBT Observe (category 2A) or Consider single immediate postoperative instillation of chemotherapy (category 2A)
AUA [4,5]	Small volume, low-grade Ta	TURBT Single immediate postoperative instillation of chemotherapy (recommendation)

EORTC = European Organization for the Research and Treatment of Cancer; TURBT = transurethral resection of the bladder tumour; EAU = European Association of Urology; FICBT = First International Consultation on Bladder Tumors; NCCN = National Comprehensive Cancer Network; AUA = American Urological Association.

muscle is required to stage the tumour as Ta, T1, or T2. Because CIS may be present, the EAU also advises separate resection of the edges of the resected area in larger tumours [1].

3.2. *Management of low-risk patients*

There is general agreement among the four guidelines on the management of patients with low-risk NMIBC. The EAU, FICBT, and AUA all recommend a single, immediate postoperative instillation of chemotherapy as standard therapy for low-risk disease [1,4,5,9]. The NCCN considers TURBT without intravesical therapy as the standard treatment for this patient population but indicates that an immediate postoperative dose of chemotherapy should be ''considered'' [3]. The AUA also considers an immediate postoperative chemotherapeutic instillation to be an ''option'' in patients with an abnormal urothelial growth who have not yet been diagnosed with bladder cancer [4,5].

A meta-analysis of seven randomised trials conducted by Sylvester et al [13] demonstrated that one immediate instillation of chemotherapy after TURBT results in a 12% absolute reduction in tumour recurrence (decrease of 39% in odds of recurrence). In an AUA meta-analysis, TURBT and single-dose mitomycin C resulted in a 17% absolute reduction in recurrences compared to TURBT alone when all patient risk groups were considered [4,5].

All four guidelines agree that the timing of the chemotherapeutic instillation is crucial. In all studies included in the meta-analysis by Sylvester et al [13], the instillation was administered within 24 h. One study reported that if the first instillation was not given within 24 h, the risk of recurrence increased 2-fold. In fact, the best results were noted when the chemotherapeutic instillation was given within a few hours of TURBT [14]. It is important to note that BCG is never administered as an immediate postoperative instillation.

The EAU, FICBT, NCCN, and AUA also agree that there is no superior chemotherapeutic agent with regard to efficacy and, therefore, choice of chemotherapeutic drug is optional. In addition, all four guidelines indicate that there is no evidence that multiple adjuvant instillations of either bacillus Calmette-Guérin (BCG) or chemotherapy provide additional benefit in patients with low-risk disease [1,3–5,9].

The EAU, FICBT, NCCN, and AUA recommendations for low-risk disease are summarized in Table 6.

3.3. *Management of intermediate-risk patients*

The treatment goals for intermediate-risk patients differ slightly among the guidelines. The EAU, for example, indicates that the treatment goal in these patients is prevention of recurrence and progression [1], whereas the AUA considers prevention or delay of recurrence as the primary treatment goal [4,5]. All four guidelines agree that adjuvant therapy with either BCG or chemotherapy is necessary in intermediate-risk disease; however, the strength of this recommendation varies among the four guidelines and controversy exists about whether induction plus maintenance or induction alone should be used. Furthermore, there is no consensus regarding the frequency and duration of adjuvant intravesical therapy.

For intermediate-risk disease, the EAU recommends complete TURBT followed by an immediate single postoperative instillation of chemotherapy as the standard. Adjuvant intravesical therapy is necessary, but no consensus exists regarding the optimal drug and the optimal schedule: either adjuvant BCG with maintenance of at least 1 yr or further instillations of chemotherapy. Although the ideal duration and intensity of additional chemotherapeutic instillations remains undefined, the EAU suggests that they should probably be given for 6–12 mo. If a chemotherapeutic agent is given, it is advised to use the drug at its optimal pH and to maintain drug concentrations during instillations by reducing fluid intake [1].

The FICBT also recommends an immediate postoperative instillation of chemotherapy followed by further adjuvant therapy in the case of multiple low-grade Ta tumours or when high-risk factors for recurrence are present. Intravesical chemotherapy is recommended as first-line therapy in these patients, and the duration of treatment should be <6 mo. According to the FICBT, intravesical BCG should be reserved as second-line treatment for intermediate-risk disease [9].

The recommendations of the FICBT also indicate that office fulguration alone is not an appropriate treatment for an initial bladder tumour. However, office fulguration may be appropriate in select patients with fewer than five, small (<0.5 cm), low-grade-appearing recurrent tumours in the setting of negative cytology. Formal TURBT is necessary whenever clinical doubt exists about whether a tumour is low-grade, when the urine cytology result is positive, or if there is a change in the appearance of the tumour [9].

According to the NCCN, options for intermediate-risk disease include observation or treatment with intravesical BCG or mitomycin. BCG is the preferred intravesical option. The NCCN guidelines make no mention of the preferred schedule of either adjuvant BCG or chemotherapy [3].

Although the AUA guidelines do not use the specific term ''intermediate risk,'' they do provide recommendations for the management of bladder tumours that have a high risk of recurrence but a low risk of progression. These recommendations are comparable to those of the intermediate-risk category stated in the EAU, FICBT, and NCCN guidelines. According to the AUA, the recommended treatment

Table 7 – Comparison of guideline recommendations for intermediate risk disease [1,3–5,9]

Guideline	Definition of intermediate risk	Recommendations
EAU [1]	Multifocal G2Ta, G1T1, solitary G2T1 Intermediate or high risk of recurrence and intermediate risk of progression (EORTC recurrence scores ranging from 1–9; progression scores ranging from 2–6)	• TURBT • Single, immediate postoperative instillation of chemotherapy followed by: – Induction BCG plus maintenance (at least 1 yr) (grade A), or – Maintenance intravesical chemotherapy (grade A) of 6–12 mo (grade B)
FICBT [9]	Multiple low-grade Ta	• TURBT • Single immediate postoperative instillation of chemotherapy • Further adjuvant intravesical therapy: – First-line: intravesical chemotherapy <6 mo (grade B) – Second-line: BCG (grade A)
	Recurrent low-grade Ta	• Office fulguration only in select patients with fewer than five small (<0.5 cm) low-grade recurrent tumours and negative cytology (grade C) • Formal TURBT if clinical doubt that tumour is low-grade, cytology positive, or change in tumour appearance has occurred (grade C) • Adjuvant intravesical therapy (see above)
NCCN [3]	G3Ta, solitary G1-2T1	• TURBT • Observe or • Intravesical therapy – BCG (preferred) (category 1) or – Mitomycin (category 2A)
AUA [4,5]	Multifocal and/or large volume low-grade Ta or recurrent low-grade Ta High risk of recurrence, low risk of progression	• TURBT • Intravesical BCG or mitomycin C (recommendation) • Maintenance BCG or mitomycin (option)

EORTC = European Organization for the Research and Treatment of Cancer; TURBT = transurethral resection of the bladder tumour; BCG = bacillus Calmette-Guérin; EAU = European Association of Urology; FICBT = First International Consultation on Bladder Tumors; NCCN = National Comprehensive Cancer Network; AUA = American Urological Association.

for these patients is an induction course of intravesical BCG or mitomycin C. Maintenance BCG or mitomycin C therapy is considered optional. The AUA acknowledges that maintenance therapy with BCG or mitomycin C is more effective in decreasing recurrences than induction alone. The AUA's meta-analysis of randomised controlled trials published between 1990 and 2006 demonstrated that, compared to TURBT alone, recurrences decreased by 31% (95% CI, 18–42) with TURBT and BGG maintenance and by 18% (95% CI, 6–30) with TURBT and mitomycin C maintenance. However, the AUA guideline panel considers routine maintenance therapy to be an option rather than a standard in intermediate-risk disease because the side effects and costs associated with treatment may outweigh the benefits in these patients [4,5].

The EAU, FICBT, NCCN, and AUA recommendations for intermediate-risk disease are summarized in Table 7.

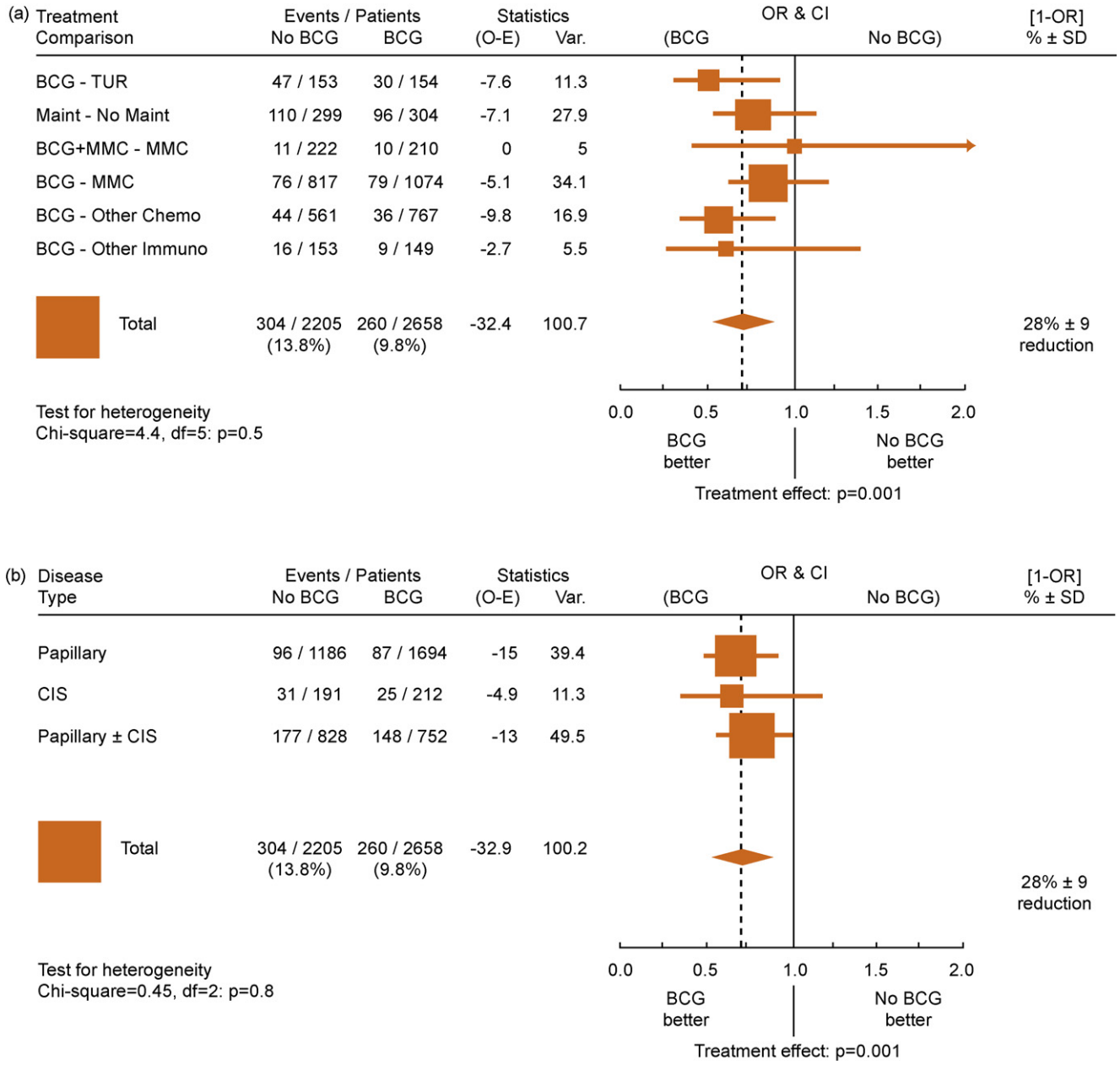


Fig. 1 – (a) Forest plot of tumour progression by treatment method. (b) Forest plot of tumour progression by disease type. BCG = bacillus Calmette-Guérin; TUR = transurethral resection; OR = odds ratio; CI = confidence interval; SD = standard deviation; maint = maintenance BCG therapy; MMC = mitomycin C; CIS = carcinoma *in situ*; O–E = observed number of progressions minus expected number of progressions; Var = variance.
Reprinted with permission from the American Urological Association [17].

Two recently published articles provide further insight into the optimal management of patients with intermediate-risk disease. Results from a recent systematic review of clinical trials examining intravesical chemotherapeutic instillations in NMIBC suggest that long-term maintenance chemotherapy is no more effective than a single immediate instillation following TURBT. In fact, the authors of this review recommend that long-term chemotherapeutic instillations of $\geq$1 yr only be provided when an immediate instillation has not been given [15].

Recent data from the European Organization for the Research and Treatment of Cancer (EORTC) Genito-Urinary Group phase 3 trial 30911 suggest that BCG may be superior to chemotherapy for treatment of intermediate-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 mo 3, 6, 12, 18, 24, 30, and 36 after TURBT in patients with intermediate- and high-risk NMIBC (n = 837). Median follow-up was 9.2 yr. 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 prolonged in the two BCG arms compared to the epirubicin arm. The investigators concluded that both intermediate- and high-risk patients benefit from BCG therapy [16].

3.4. *Management of high-risk patients*

All guidelines agree that the primary goal in patients with high-risk disease is the prevention or delay of disease progression. A large EORTC meta-analysis of 24 trials involving 4863 patients showed that BCG maintenance therapy was associated with a 37% reduction in the risk of tumour progression compared to the control groups (TURBT alone, TURBT plus intravesical chemotherapy, TURBT plus another immunotherapy). See Fig. 1a and 1b for Forest plots of tumour progression by treatment method and by disease type [17]. Another meta-analysis of nine trials comparing BCG to mitomycin C found that BCG maintenance was significantly superior to mitomycin C for the prevention of tumour progression [18].

A meta-analysis of 11 clinical trials comparing BCG and mitomycin C showed that BCG was superior to mitomycin C in reducing tumour recurrence (odds ratio [OR]: 0.56; 95% CI, 0.38–0.84, $p = 0.005$; see Fig. 2a). In the subgroup treated with BCG maintenance, all six individual studies showed a significant superiority of BCG over mitomycin C (OR: 0.43; 95% CI, 0.35–0.53, $p < 0.001$; see Fig. 2b and 2c) [19].

A single-arm meta-analysis of randomised controlled trials in high-risk patients conducted by the AUA confirms the superiority of maintenance BCG to mitomycin C with or without maintenance: the estimated 5-yr recurrence rate was 34% in patients receiving TURBT and BCG maintenance and 62% with mitomycin C maintenance. The meta-analysis of all risk groups found that, compared with TURBT and mitomycin C maintenance, TURBT and BCG maintenance therapy reduced recurrence by 17%. The AUA meta-analysis also found a trend to improvement in overall progression with BCG maintenance therapy compared to mitomycin C plus maintenance [4,5].

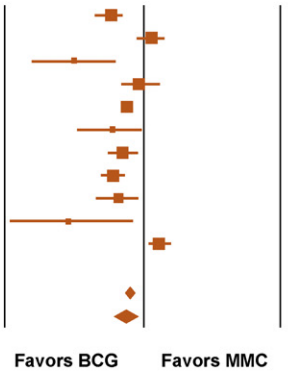
Given these results, the EAU, FICBT, NCCN, and AUA regard BCG as the standard adjuvant treatment for high-risk patients. However, there is no consensus on the optimal BCG maintenance schedule, and differences exist among the four guidelines with regards to other options in high-risk patients.

According to the EAU, the treatment of high-risk disease should consist of a second TURBT 2–6 wk after the initial resection and adjuvant intravesical BCG for at least 1 yr. In fact, the EAU emphasizes the importance of a maintenance schedule for optimal BCG efficacy. 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 [1]. For patients with CIS, the EAU recommends intravesical BCG plus maintenance of at least 1 yr. In these patients, response to intravesical BCG should be assessed 3 mo after starting therapy. If no response is noted, the EAU recommends continuing therapy with three weekly boosters, another 6-wk course of BCG, or cystectomy. If a complete response has not been achieved at 6 mo, then radical cystectomy is recommended [20].

In patients with high-grade Ta, the FICBT recommends one immediate instillation of chemotherapy post TURBT, followed 2–4 wk later by a second-look TURBT and bladder-mapping biopsies. If residual tumour is found, re-resection and one immediate instillation of chemotherapy should be provided. This should be followed 2–3 wk later, once the diagnosis of high-grade Ta has been confirmed, by a 6-wk induction course of BCG and 1–3 yr of maintenance BCG. For patients with completely resected primary and recurrent T1 tumours (based on negative repeat resection), initial intravesical BCG therapy should be considered in those who can tolerate the therapy and who are satisfied with their bladder function [11]. According to the FICBT, radical cystectomy at the time of diagnosis of CIS (rather than instillation therapy) is associated with excellent

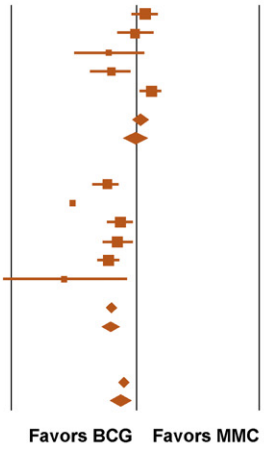
(a)

	Citation	Mainten.	OR	Lower	Upper	P	NTotal	BCG n/N	MMC n/N
	Ayed, 1998	yes	,382	,223	,652	,000	270	72 / 189	50 / 81
	DeBruyne, 1992	no	1,279	,818	2,001	,280	325	66 / 158	60 / 167
	Jauhiainen, 1989	yes	,122	,033	,454	,000	91	3 / 45	17 / 46
	Krege, 1996	no	,935	,508	1,723	,829	214	26 / 102	30 / 112
	Lamm, 1995	yes	,594	,392	,900	,014	363	78 / 182	101 / 181
	Lee, 1992	no	,396	,125	1,250	,109	61	19 / 31	24 / 30
	Lundholm, 1996	yes	,533	,320	,886	,015	250	63 / 125	82 / 125
	Millán, 2000	yes	,395	,271	,578	,000	464	70 / 218	134 / 246
	Nogueira, 2000	no	,438	,213	,900	,022	210	13 / 98	29 / 112
	Pagano, 1987	yes	,094	,012	,729	,006	114	1 / 22	31 / 92
	Vegt-combined, 1995	no	1,616	1,061	2,462	,025	387	137 / 251	58 / 136
Fixed	**Combined (11)**		**,642**	**,547**	**,754**	**,000**	**2749**	**548 / 1421**	**616 / 1328**
Random	**Combined (11)**		**,561**	**,375**	**,841**	**,005**	**2749**	**548 / 1421**	**616 / 1328**



(b)

	Mainten.	Citation	OR	Lower	Upper	P	NTotal	BCG n/N	MMC n/N
	no	DeBruyne, 1992	1,279	,818	2,001	,280	325	66 / 158	60 / 167
	no	Krege, 1996	,935	,508	1,723	,829	214	26 / 102	30 / 112
	no	Lee, 1992	,396	,125	1,250	,109	61	19 / 31	24 / 30
	no	Nogueira, 2000	,438	,213	,900	,022	210	13 / 98	29 / 112
	no	Vegt, 1995	1,616	1,061	2,462	,025	387	137 / 251	58 / 136
Fixed	**no (5)**		**1,084**	**,848**	**1,385**	**,521**	**1197**	**261 / 640**	**201 / 557**
Random	**no (5)**		**,912**	**,558**	**1,490**	**,713**	**1197**	**261 / 640**	**201 / 557**
	yes	Ayed, 1998	,382	,223	,652	,000	270	72 / 189	50 / 81
	yes	Jauhiainen, 1989	,122	,033	,454	,000	91	3 / 45	17 / 46
	yes	Lamm, 1995	,594	,392	,900	,014	363	78 / 182	101 / 181
	yes	Lundholm, 1996	,533	,320	,886	,015	250	63 / 125	82 / 125
	yes	Millán, 2000	,395	,271	,578	,000	464	70 / 218	134 / 246
	yes	Pagano, 1987	,094	,012	,729	,006	114	1 / 22	31 / 92
Fixed	**yes (6)**		**,430**	**,346**	**,533**	**,000**	**1552**	**287 / 781**	**415 / 771**
Random	**yes (6)**		**,419**	**,302**	**,582**	**,000**	**1552**	**287 / 781**	**415 / 771**
Fixed	**Combined (11)**		**,642**	**,547**	**,754**	**,000**	**2749**	**548 / 1421**	**616 / 1328**
Random	**Combined (11)**		**,561**	**,375**	**,841**	**,005**	**2749**	**548 / 1421**	**616 / 1328**



(c)

	Maintenance + risk	Citation	OR	Lower	Upper	P	NTotal	BCG n/N	MMC n/N
	maintenance + high	Jauhiainen, 1989	,122	,033	,454	,000	91	3 / 45	17 / 46
	maintenance + high	Lamm, 1995	,594	,392	,900	,014	363	78 / 182	101 /181
	maintenance + high	Lundholm, 1996	,533	,320	,886	,015	250	63 / 125	82 / 125
Fixed	**maintenance + high risk (3)**		**,507**	**,373**	**,691**	**,000**	**704**	**144 / 352**	**200 / 352**
Random	**maintenance + high risk (3)**		**,452**	**,253**	**,805**	**,007**	**704**	**144 / 352**	**200 / 352**
	maintenance + interm.	Ayed, 1998	,382	,223	,652	,000	270	72 / 189	50 / 81
	maintenance + interm.	Millán, 2000	,395	,271	,578	,000	464	70 / 218	134 / 246
	maintenance + interm.	Pagano, 1987	,094	,012	,729	,006	114	1 / 22	31 / 92
Fixed	**maintenance + interm. risk (3)**		**,366**	**,270**	**,497**	**,000**	**848**	**143 / 429**	**215 / 419**
Random	**maintenance + interm. risk (3)**		**,378**	**,279**	**,514**	**,000**	**848**	**143 / 429**	**215 / 419**
	no-mainten. + interm.	DeBruyne, 1992	1,279	,818	2,001	,280	325	66 / 158	60 / 167
	no-mainten. + interm.	Krege, 1996	,935	,508	1,723	,829	214	26 / 102	30 / 112
	no-mainten. + interm.	Nogueira, 2000	,438	,213	,900	,022	210	13 / 98	29 / 112
	no-mainten. + interm.	Vegt, 1995	1,616	1,061	2,462	,025	387	137 / 251	58 / 136
Fixed	**no-mainten. + interm. risk (4)**		**1,141**	**,887**	**1,469**	**,304**	**1136**	**242 / 609**	**177 / 527**
Random	**no-mainten. + interm. risk (4)**		**1,023**	**,628**	**1,667**	**,927**	**1136**	**242 / 609**	**177 / 527**
	no-mainten. + high risk	Lee, 1992	,396	,125	1,250	,109	61	19 / 31	24 / 30
Fixed	**no-mainten. + high risk (1)**		**,396**	**,125**	**1,250**	**,114**	**61**	**19 / 31**	**24 / 30**
Random	**no-mainten. + high risk (1)**		**,396**	**,125**	**1,250**	**,114**	**61**	**19 / 31**	**24 / 30**
Fixed	**Combined (11)**		**,642**	**,547**	**,754**	**,000**	**2749**	**548 / 1421**	**616 / 1328**
Random	**Combined (11)**		**,561**	**,375**	**,841**	**,005**	**2749**	**548 / 1421**	**616 / 1328**

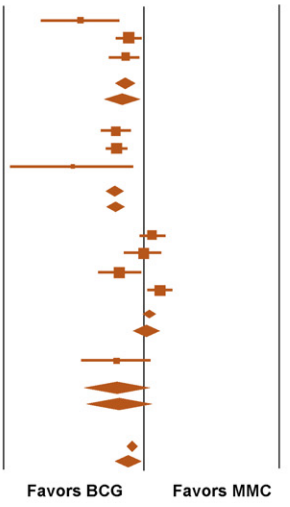


Fig. 2 – (a) Tumour recurrence (all studies) with odds ratio as effect size. (b) Tumour recurrence (all studies by maintenance) with odds ratio as effect size. (c) Forest plot of tumour recurrence (all studies by maintenance and risk group) with odds ratio as effect size.

BCG = bacillus Calmette-Guérin; Mainten = BCG maintenance regimen; interm = intermediate; OR = odds ratio; Lower, Upper = lower and upper 95% CI of OR; *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 indicate OR estimates, whereas square size is proportional to sample size, and rhombs meta-analytically pooled OR estimates ± 95% CI.

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Table 8 – Comparison of guideline recommendations for high risk disease [1,3–5,10,11]

Guidelines	Definition	Recommendations
EAU [1]	Multiple G2T1, G3Ta-T1 High risk of progression (EORTC progression scores ranging from 7–23) CIS	• Repeat TURBT 2–6 wk after initial resection (grade B) • Intravesical BCG induction plus maintenance for at least 1 yr (grade A) • Immediate radical cystectomy for highest risk patients (grade A) – Multiple recurrent high-grade tumours – High-grade T1 tumours – High-grade tumours with concomitant CIS • Intravesical BCG plus maintenance for at least 1 yr (grade A) – Assess response at 3 mo: • If no response: • Continue with three, weekly boosters (grade B), or • Additional 6-wk course of BCG (grade B), or • Cystectomy (grade B) – No complete response at 6 mo: radical cystectomy (grade B)
FICBT [10,11]	High-grade Ta T1 CIS	• Second-look TURBT and bladder-mapping biopsies 2–4 wk after initial resection (grade B) • If residual tumour is found: – Re-resection and one immediate instillation of chemotherapy – Followed 2–3 wk later by 6-wk BCG induction and 1–3 yr of BCG maintenance (grade A) • Repeat TURBT (grade B) • Initial intravesical BCG for patients with completely resected primary and recurrent T1 tumours (based on a negative repeat resection) (grade C) • Intravesical BCG for 6 wk (grade A) • Maintenance BCG for ≥1 yr (grade A)
NCCN [3]	T1, G3 Any CIS/Tis	*Complete Resection:* • BCG preferred (category 1) or mitomycin (category 2A) • Consider cystectomy *Uncertain Resection:* • Repeat resection or cystectomy – If positive: BCG (category 1) or cystectomy (category 2A) – If negative: BCG (category 1) or mitomycin (category 2A) • Complete resection followed by intravesical BCG
AUA [4,5]	High-grade Ta, T1, and/or CIS	• Repeat resection if lamina propria invasion without muscularis propria in specimen prior to intravesical therapy (standard) • Induction BCG followed by maintenance (recommendation) • Cystectomy (option)

EORTC = European Organization for the Research and Treatment of Cancer; TURBT = transurethral resection of the bladder tumour; BCG = bacillus Calmette-Guérin; EAU = European Association of Urology; FICBT = First International Consultation on Bladder Tumors; NCCN = National Comprehensive Cancer Network; AUA = American Urological Association.

disease-free survival but constitutes over-treatment in up to one-half of these patients. Therefore, the FICBT recommends treatment of CIS with intravesical BCG because it is associated with the highest rate of complete response and the highest long-term disease-free rate among intravesical treatments. The FICBT also states that BCG for 6 wk only is suboptimal in CIS and that maintenance BCG therapy is required in these patients. The FICBT acknowledges that the optimal BCG maintenance schedule in CIS is unknown but recommends ≥1 yr of maintenance in the absence of treatment failure [11].

According to the NCCN, a course of BCG, 1–2 wk after complete resection is the preferred option in high-risk disease. If the resection is uncertain because of the tumour size and location, no muscle is shown in the specimen, lymphovascular invasion has occurred, or inadequate staging is speculated, cystectomy or a repeat resection followed by intravesical BCG (preferred, category 1) or mitomycin is recommended [3].

According to the AUA, the standard treatment in patients with initial histologically-confirmed high-grade Ta, T1, and/or CIS with lamina propria invasion (T1) but without muscularis propria in the specimen is a repeat resection before additional intravesical therapy. An induction course of BCG followed by maintenance therapy is also recommended. Cystectomy is considered an option for initial therapy in select patients owing to the risk of initially understaged muscle-invasive disease or progression to muscle-invasive disease [4,5].

The EAU, FICBT, NCCN, and AUA recommendations for high-risk NMIBC are summarized in Table 8.

3.5. *Optimal bacillus Calmette-Guérin administration*

The optimal administration of BCG requires that correct catheterization technique and overall good clinical practice be utilized. BCG should not be instilled for at least 2 wk following a TURBT to minimize the risk of systemic absorption. Furthermore, BCG should not be instilled in patients exhibiting gross hematuria caused by traumatic catheterization, ongoing healing of the epithelium, or infection.

Both the EAU and the FICBT [1,10] indicate that induction BCG instillations are classically given according to the empirical six-weekly induction schedule introduced by Morales et al >30 yr ago [21]. According to the FICBT, induction instillations should begin no sooner than 2 wk after tumour resection (grade B) [10].

According to the FICBT and the AUA [4,5,10], the current optimal BCG maintenance schedule is based on the Southwest Oncology Group (SWOG) regimen of three-weekly instillations at 3 and 6 mo and every 6 mo for 3 yr [18,22]. The SWOG 8507 trial was the first trial to demonstrate the superiority of this regimen over induction alone [18,22]. Numerous meta-analyses have also confirmed that maintenance therapy statistically reduces recurrence and progression rates compared to no maintenance. The EAU [1] suggests that, based on the extent of intravesical immune response, three consecutive weekly instillations give a maximum response [23].

4. Primary intravesical treatment failure

4.1. *Defining treatment failure*

The ability to determine the optimal management strategies for treatment failures has been hampered by the lack of a standard definition for failure. In fact, the EAU, FICBT, NCCN, and AUA all have varying definitions of treatment failure. The EAU, for example, does not define primary intravesical treatment failure but does provide the following definition for BCG failure [1]:

a. Whenever muscle-invasive tumour is detected during follow-up
b. If high-grade non-muscle invasive tumour is present at both 3 and 6 mo
c. Any worsening of the disease under BCG treatment, such as higher number of recurrences, higher T or grade, or appearance of CIS, despite initial response

The NCCN has proposed a very broad definition of treatment failure, which is defined as recurrent or persistent disease at follow-up and varies according to whether the patient has low-, intermediate-, or high-risk disease [3]. The AUA guidelines do not provide a specific definition for treatment failure but do provide recommendations for the management of high-grade Ta, T1, and/or CIS recurrence after prior intravesical therapy [4,5].

The FICBT does not define overall primary intravesical therapy failure but has proposed four types of BCG failure—BCG-refractory disease, BCG-resistant disease, BCG-relapsing disease, and BCG-intolerant disease—in an attempt to provide uniformity in reporting and to assist in the management of these failures. The definitions of each type of failure are shown in Table 9 [10].

4.2. *Management of treatment failures*

4.2.1. *Intravesical chemotherapy failures*

According to the EAU, patients with recurrence of NMIBC following intravesical chemotherapy may benefit from BCG instillations [1]. According to the NCCN guidelines, patients who have recurrent or persistent disease at the 3-mo follow-up can be given a second induction course of intravesical chemotherapy (no more than two consecutive cycles). BCG maintenance therapy is the preferred treatment option for patients who experience a recurrence after a complete response to a second induction course. For patients with a recurrence of Tis or Ta post-intravesical chemotherapy (no more than two consecutive cycles), a change in intravesical agent or cystectomy is recommended. If there is a recurrence of high-risk T1G3 disease, then cystectomy should be performed [3].

According to the AUA, the standard treatment for patients with high-grade Ta, T1, and/or CIS, which has recurred after prior intravesical therapy, is repeat resection before additional intravesical therapy (standard). The AUA [4,5] states that further intravesical therapy may be considered for these patients (option), since there is evidence suggesting that select patients will respond to second induction regimens, particularly with BCG [22,24,25]. Cystectomy as a therapeutic alternative is also recommended for patients with high-grade Ta, T1, and/or CIS that has recurred after prior intravesical therapy (recommendation) [4,5].

4.2.2. *Bacillus Calmette-Guérin failures*

The management of BCG treatment failures is an important issue in NMIBC, particularly in high-risk disease. According to the EAU [1], patients with a

Table 9 – Types of bacillus Calmette-Guérin (BCG) failure as proposed by the the First International Consultation on Bladder Tumours (FICBT) [10]

BCG-refractory	• 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 • Any progression in stage, grade, or disease extent by 3 mo after first cycle of BCG
BCG-resistant	• Recurrence or persistence at 3 mo after the induction cycle • Recurrence is of lesser degree, stage, or grade and is no longer present at 6 mo from BCG retreatment, with our without TURBT
BCG-relapsing	• Recurrence of disease after achieving a disease-free status by 6 mo • Relapse further defined by time of recurrence: – Early: within 12 mo – Intermediate: 12–24 mo – Late: >24 mo **Caution:** *Relapsing disease while on active treatment may qualify as BCG-refractory disease.*
BCG-intolerant	• Disease recurs after less-than-adequate course of therapy due to serious adverse events or symptomatic intolerance that mandates BCG discontinuation

TURBT = transurethral resection of the bladder tumour.

high-grade, non-muscle invasive tumour at 3 mo of BCG therapy can receive an additional BCG course, as this has been associated with a complete response in >50% of patients [26]. The EAU also acknowledges that changing from BCG to chemotherapy can provide further remissions in select patients failing BCG therapy. However, in most cases of high-risk BCG failures, immediate cystectomy is strongly advocated owing to the high-risk of progression to muscle-invasive disease and metastases in these patients [1].

According to the FICBT, patients with induction BCG therapy failure who experience a recurrence of high-grade disease at 6 mo should be offered cystectomy (grade C) [10]. For patients with initial induction BCG therapy failure who are unfit, who refuse cystectomy, or who have low- or intermediate-grade disease, an additional course of a BCG-containing intravesical therapy is the preferred option (grade C). In the case of failure before maintenance BCG has been completed, cystectomy should be considered if high-grade T1 or CIS is present (grade B). For high-grade Ta recurrences, the FICBT recommends repeat resection and continued maintenance BCG (grade B). If early failure occurs after the completion of maintenance BCG therapy, cystectomy should be considered (grade B) for high-grade NMIBC. However, if superficial recurrence occurs later, the FICBT recommends restarting BCG or other instillations as an alternative to cystectomy (grade B). Patients with recurrent T1 tumours should be considered for cystectomy if they have had two prior induction cycles of BCG (grade D) [10].

The NCCN guidelines advocate a second induction course of BCG in those patients who experience a recurrence 3 mo after the initial induction course (no more than two consecutive cycles) [3]. Maintenance BCG is recommended for those patients who experience a recurrence after a complete response to a second BCG induction course. The NCCN acknowledges that the combination of intravesical BCG and interferon-α2b has been shown to be effective in this setting, but that data from the phase 3 randomised trial are not currently available. A change in intravesical agent or cystectomy is recommended for patients who experience a recurrence of Tis or Ta disease post-BCG treatment (no more than two consecutive cycles). Cystectomy is recommended if there is a recurrence of high-risk T1G3 disease [3].

The AUA guidelines recommend repeat resection before additional intravesical therapy as the standard treatment for patients with high-grade Ta, T1, and/or CIS that has recurred after prior intravesical therapy. Further intravesical therapy, particularly with BCG, may also be considered (option) in these patients, and cystectomy as a therapeutic alternative is recommended [4,5].

5. Follow-up regimens

Many urologists perform life-long, frequent follow-up cystoscopies in patients with NMIBC. However, such frequent follow-up is unnecessary, since approximately 50% of these patients have a very low risk of recurrence and a negligible risk of progression [27].

The recommended follow-up schedules proposed by the EAU, FICBT, NCCN, and AUA vary. In low-risk patients, for example, the EAU recommends surveillance cystoscopy at 3 mo. If negative, the following cystoscopy is advised at 9 mo and, subsequently, annually for 5 yr. In high-risk patients, the EAU

recommends cystoscopy at 3 mo. If negative, the following cystoscopies should be repeated every 3 mo for 2 yr, every 4 mo in the third year, every 6 mo thereafter until 5 yr, and annually thereafter. Annual imaging of the upper tract is also recommended in high-risk patients. The follow-up schedule for intermediate-risk disease should be between that for low- and high-risk disease and should be adapted according to individual patient factors [1].

The FICBT advocates cystoscopy at 3 mo in low-risk patients. If negative, the next cystoscopy can be postponed for 9 mo [9]. In patients with high-grade Ta, the FICBT recommends follow-up every 3 mo during the first 2 yr, every 4 mo during the third year, every 6 mo during the fourth and fifth years, and yearly thereafter, as long as there is no evidence of recurrence. For patients with CIS, the FICBT recommends life-long follow-up, even in complete responders, due to the high risk of recurrence and progression in these patients [11].

According to the NCCN, patients with low-risk disease should be followed every 3 mo, with increasing intervals as appropriate. In those with intermediate- or high-risk disease, cystoscopy and urine cytology are recommended every 3 mo for 2 yr, every 6 mo for the subsequent 2 yr, and then annually thereafter. Imaging of the upper tract is recommended every 1–2 yr, and urinary urothelial tumour marker assessment is optional [3].

The AUA does not recommend a specific follow-up schedule [4,5] but highlights that the most common approach has included patient assessment every 3 mo in the first 2 yr after initial diagnosis, followed by every 6 mo for the subsequent 2–3 yr,

Table 10 – Comparison of guideline recommendations for the follow-up of patients with non-muscle invasive bladder cancer [1,3–5,9–11]

Guidelines	Recommendations
EAU [1]	Low risk • Cystoscopy at 3 mo (grade B) • If negative, following cystoscopy advised at 9 mo and, consequently, yearly for 5 yr (grade B) High risk • Cystoscopy at 3 mo (grade B) • If negative, following cystoscopies should be repeated every 3 mo for 2 yr, every 4 mo in the third year, every 6 mo thereafter until 5 yr, and annually thereafter (grade B) • Annual imaging of the upper tract (grade B) Intermediate risk • Schedule should be in between that for low- and high-risk disease and should be adapted according to individual patient factors (grade B)
FICBT [9–11]	Low risk • Cystoscopy at 3 mo • If negative, next cystoscopy postponed for 9 mo; risk of recurrence remains life-long, but most experts propose to stop cystoscopic surveillance when it remains negative for 5 yr (grade C) High-grade Ta • Every 3 mo during first 2 yr (grade B) • Every 4 mo during third year (grade B) • Every 6 mo during the fourth and fifth years, and yearly thereafter, as long as there is no evidence of recurrence (grade B) CIS • Life-long follow-up, even in complete responders, due to high risk of recurrence and progression (grade A)
NCCN [3]	Low risk • Every 3 mo with increasing intervals as appropriate Intermediate or high risk • Cystoscopy and urine cytology every 3 mo for 2 yr, every 6 mo for the subsequent 2 yr, then annually thereafter • Imaging of the upper tract every 1–2 yr (category 2B) • Urinary urothelial tumour marker assessment is optional
AUA [4,5]	No specific follow-up schedule advocated, but the following is mentioned: • Every 3 mo in the first 2 yr • Every 6 mo for subsequent 2–3 yr, and then annually thereafter • Follow-up should include an appropriate history, urinalysis, cystoscopy, and urine cytology

EAU = European Association of Urology; FICBT = First International Consultation on Bladder Tumors; CIS = carcinoma *in situ*; NCCN = National Comprehensive Cancer Network; AUA = American Urological Association.

and then annually thereafter [28,29]. The AUA suggests that clinical follow-up involve an appropriate patient history including voiding symptoms and hematuria, urinalysis, cystoscopy, and urine cytology [4,5].

A summary of the EAU, FICBT, NCCN, and AUA recommendations for the follow-up of patients with NMIBC is provided in Table 10.

6. Conclusions

Through critical analysis and comparison of the EAU, FICBT, NCCN, and AUA guidelines, the IBCG has established areas of consensus on NMIBC management as well as on contentious topics that need to be addressed. Established areas of consensus among the four guidelines include the importance of TURBT and an immediate, postoperative dose of chemotherapy (agent optional) in all patients with NMIBC and the benefit of adjuvant BCG therapy in high-risk disease.

However, the four guideline recommendations vary with regard to the following important issues: (1) the definitions of low-, intermediate-, and high-risk disease and (2) the appropriate management and follow-up of patients in each of these risk categories. Furthermore, there is currently no consensus on the definition and appropriate management strategies for primary intravesical treatment failures.

In an attempt to address the differences and lack of consensus noted in the current guidelines and to provide community urologists with more practical and unified guidance on the management of NMIBC, the IBCG has proposed the treatment algorithm and recommendations in the article entitled, *Clinical Practice Recommendations for the Management of Non-Muscle Invasive Bladder Cancer*, in this supplement.

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References

[1] Babjuk M, Oosterlinck W, Sylvester R, Kaasinen E, Böhle A, Palou J. European Association of Urology guidelines on TaT1 (non-muscle invasive) bladder cancer. Update March 2008. Arnhem, the Netherlands: European Association of Urology; 2008. http://www.uroweb.org/fileadmin/tx_eauguidelines/TaT1%20Bladder%20Cancer.pdf.

[2] Soloway MS, editor. International consultation on bladder tumours. Urology 2005;66:1–125.

[3] National Comprehensive Cancer Network. Clinical practice guidelines in oncology: bladder cancer including upper tract tumors and urothelial carcinoma of the prostate. Version 1. Jenkintown, PA: NCCN; 2007.

[4] American Urological Association. Guidelines for the management of non-muscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update., Linthicum, MD: AUA; 2007 In: http://www.auanet.org/guidelines/bladcan07.cfm.

[5] Hall MC, Chang SS, Dalbagni G, et al. Guidelines for the management of non-muscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. J Urol 2007;178:2314–30.

[6] Stenzl A, Cowan NC, De Santis M, et al. Guidelines on bladder cancer: muscle-invasive and metastatic. Arnhem, the Netherlands: European Association of Urology; 2008. http://www.uroweb.org/fileadmin/tx_eauguidelines/Muscle-invasive%20and%20Metastatic%20Bladder%20Cancer.pdf.

[7] US Department of Health and Human Services. Public Health Service, Agency for Health Care Policy and Research. 1992:115–27.

[8] Abrams P, Grant A, Khoury S. Evidence-based medicine: overview of main steps for developing and grading guideline recommendations. In: Abrams P, Cardoza L, Khoury S, editors. , et al. Incontinence, vol. 1. Plymouth, UK: Health Publications Ltd; 2005. p. 10–1.
[9] Oosterlinck W, Solsona E, Akaza H, et al. Low-grade Ta (non-invasive) urothelial carcinoma of the bladder. Urology 2005;66:75–89.
[10] Nieder AM, Brausi M, Lamm D, et al. Management of stage T1 tumours of the bladder: international consensus panel. Urology 2005;66:108–25.
[11] Sylvester RJ, van der Meijden AP, Witjes JA, et al. High-grade Ta urothelial carcinoma and carcinoma *in situ* of the bladder. Urology 2005;66:90–107.
[12] Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. Urology 2005;66:4–34.
[13] Sylvester RJ, Oosterlinck W, van der Meijden A. A single immediate post-operative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. J Urol 2004;171:2186–90.
[14] Kaasinen E, Rintala E, Hellström P, et al., FinnBladder Group. Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. Eur Urol 2002; 42:167–74.
[15] Sylvester RJ, Oosterlinck W, Witjes JA. The schedule and duration of intravesical chemotherapy in patients with non–muscle-invasive bladder cancer: a systematic review of the published results of randomized clinical trials. Eur Urol 2008;53:709–19.
[16] Sylvester RJ, Brausi MA, Hoelti W, et al. Long-term efficacy results of EORTC GU Group study 30911 comparing epirubicin, bacillus Calmette-Guérin (BCG), and BCG plus isoniazid in patients with intermediate and high risk stage Ta T1 papillary carcinoma of the bladder. Eur Urol Suppl 2008;7:298.
[17] Sylvester RJ, van der Meijden, Lamm DL. Intravesical bacillus Calmette-Guérin reduces the risk of progression in patients with superficial bladder cancer: a combined analysis of the published results of randomized clinical trials. J Urol 2002;168:1964–70.
[18] Böhle A, Bock PR. Intravesical bacille Calmette-Guérin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumour progression. Urology 2004;63:682–6.
[19] Böhle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guérin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. J Urol 2003;169:90–5.
[20] van der Meijden AP, Sylvester R, Oosterlinck W, et al. EAU Working Party on Non Muscle Invasive Bladder Cancer. EAU guidelines on the diagnosis and treatment of urothelial carcinoma *in situ*. Eur Urol 2005;48:363–71.
[21] Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 1976;116:180–3.
[22] Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guérin immunotherapy for recurrent TA, T1 and carcinoma *in situ* transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. J Urol 2000;163:1124–9.
[23] Zlotta AR, van Vooren JP, Huygen K, et al. What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? Eur Urol 2000;37: 470–7.
[24] Catalona WJ, Hudson MA, Gillen DP, Andriole GL, Ratliff TL. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guérin therapy for superficial bladder cancer. J Urol 1987;137:220–4.
[25] de Reijke TM, Kurth KH, Sylvester RJ, et al. Bacillus Calmette-Guérin versus epirubicin for primary, secondary or concurrent carcinoma *in situ* of the bladder: results of a European Organization for the Research and Treatment of Cancer—Genito-Urinary Group Phase III Trial (30906). J Urol 2005;173:405–9.
[26] Herr HW, Dalbagni G. Defining bacillus Calmette-Guérin refractory superficial bladder tumours. J Urol 2003;169: 1706–8.
[27] Oge O, Erdem E, Atsu N, ahin A, Ozen H. Proposal for changes in cystoscopic follow-up of patients with low-grade pTa bladder tumour. Eur Urol 2000;37:271–4.
[28] Messing EM, Catalona W. Urothelial tumours of the urinary tract. In: Walsh AB, Retik AB, Vaughan Jr ED, Wein AJ, editors. Campbell's Urology, 7th ed. Philadelphia, PA: W.B. Saunders; 1998. p. 2327–408.
[29] Sengupta S, Blute ML. The management of superficial transitional cell carcinoma of the bladder. Urology 2006;67:48–54.