Review Article

A Review of Current Guidelines and Best Practice Recommendations for the Management of Nonmuscle Invasive Bladder Cancer by the International Bladder Cancer Group

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Abbreviations and Acronyms

AUA = American Urological Association

BCG = bacillus Calmette-Guérin

CIS = carcinoma in situ

EAU = European Association of Urology

EORTC = European Organization for the Research and Treatment of Cancer

FICBT = First International Consultation on Bladder Tumors

IBCG = International Bladder Cancer Group

IPD = individual patient data

MMC = mitomycin C

NCCN = National Comprehensive Cancer Network

NMIBC = nonmuscle invasive bladder cancer

TURBT = transurethral resection of the bladder tumor

Purpose: Although the European Association of Urology, First International Consultation on Bladder Tumors, National Comprehensive Cancer Network and American Urological Association guidelines all provide an excellent evidence-based framework for the management of nonmuscle invasive bladder cancer, these guidelines vary with respect to important issues such as risk level definitions and management strategies for these risk categories. Therefore, we built on the existing framework provided by current guidelines, and provide consensus on the definitions of low, intermediate and high risk nonmuscle invasive bladder cancer, as well as practical recommendations for the treatment of patients in each of these risk categories.

Materials and Methods: An international committee of experts on bladder cancer management identified and analyzed the European Association of Urology, First International Consultation on Bladder Tumors, National Comprehensive Cancer Network and American Urological Association guidelines as well as the published English language literature related to the treatment and management of nonmuscle invasive bladder cancer available as of April 2010.

Results: Based on review of the current guidelines and literature, the International Bladder Cancer Group developed practical recommendations for the management of nonmuscle invasive bladder cancer.

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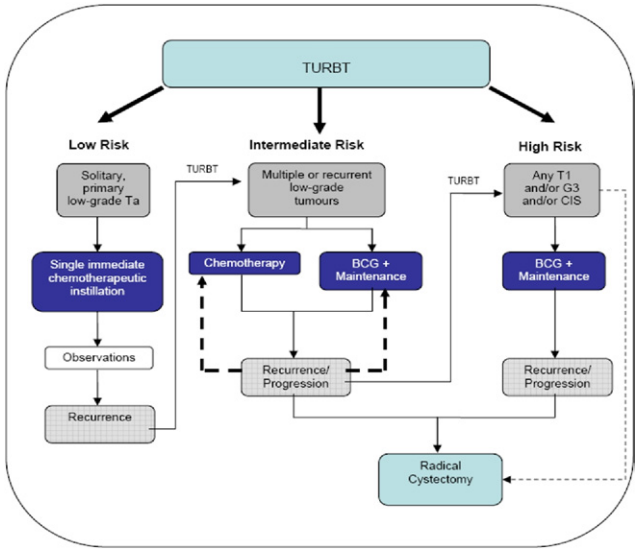
Conclusions: Complete transurethral bladder tumor resection is recommended for all patients with nonmuscle invasive bladder cancer. For low risk disease a single, immediate chemotherapeutic instillation after transurethral bladder tumor resection is recommended. For intermediate or high risk disease there is no significant benefit from an immediate, postoperative chemotherapeutic instillation. For intermediate risk disease intravesical bacillus Calmette-Guérin with maintenance or intravesical chemotherapy is recommended. For high risk disease bacillus Calmette-Guérin induction plus maintenance is recommended. The appropriate management of recurrence depends on the patient level of risk as well as previous treatment, while the management of treatment failure depends on the type of failure as well as the level of risk for recurrence and disease progression.

Key Words: urinary bladder neoplasms; clinical protocols; administration, intravesical; drug therapy; mycobacterium bovis

Currently there is wide variation regarding the management of NMIBC in the community urological setting. Although the EAU, FICBT, NCCN and AUA guidelines contribute to an excellent evidence-based framework for the management of NMIBC,[1–5] there are differences in the recommendations proposed in these guidelines, and contentious areas and gaps in evidence-based knowledge that need to be addressed through expert consensus. Therefore, an international committee of experts on bladder cancer management known as the IBCG was convened to compare these guidelines. Based on this comparison, they developed practical recommendations that would be relevant to community urologists and encourage a more uniform approach to NMIBC management. These recommendations were originally published in *European Urology Supplements* in October 2008.[6] This review provides an update to this publication, taking into account the most recent EAU and NCCN guidelines as well as recent findings regarding the value of BCG maintenance therapy and immediate chemotherapeutic instillations after TURBT for intermediate and high risk NMIBC. In this review we build on the existing framework provided by the 4 guidelines, and 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 (see figure). Note that the IBCG considered the EAU guidelines to represent best practice with regard to TURBT and the use of intravesical therapy and, as such, these were adopted as appropriate recommendations for community urologists (with some minor modifications).[1]

METHODS

The IBCG met in closed sessions on 6 occasions between October 2006 and April 2010. The EAU, FICBT, NCCN and AUA guidelines were presented, and the quality of evidence and strength of recommendations made in these guidelines were reviewed. Although the rigorous methodology applied in the completion of the 4 cited guidelines was not used, a MEDLINE® search was conducted to identify the published English language literature related to NMIBC management. Keywords included "non-muscle invasive bladder cancer," "bacillus Calmette-Guerin," "intravesical chemotherapy" and "transurethral resection of the bladder tumor". Reference lists of review and original articles were reviewed to identify additional applicable literature. Articles with the highest level of evidence were identified with the consensus of all collaborative authors and were critically reviewed. Final preparation and modifications of the recommendations presented in



Algorithm for treatment and management of primary NMIBC proposed by IBCG. Single immediate chemotherapeutic instillation after TURBT is recommended for patients with primary, small, solitary low grade tumors, except those with obvious or suspected bladder wall perforation. Recent evidence suggests no statistically significant benefit from early postoperative chemotherapeutic instillation in patients with large or recurrent tumors (ie intermediate risk) or in those with high risk NMIBC. Recommendations have been simplified for ease of use and will need to be customized to each individual patient. For example, high risk patient with low grade Ta recurrence on maintenance BCG would be candidate for intravesical chemotherapy rather than cystectomy as shown in algorithm. Adapted from Lamm et al.[6]

this article were made by electronic communication. Recommendations are based on consensus interpretation of the current guidelines and literature.

RESULTS

Definition of Risk Levels

Guideline comparison. Although the 4 guidelines agree on the importance of risk stratification for NMIBC management based on patient risk of recurrence and/or progression, there are differences in the definitions of risk as well as in the proposed treatments for each risk category (Appendix 1).[1,3–5,7–10]

IBCG recommendations. Upon review of the 4 guidelines the IBCG proposed the practical definitions of low, intermediate and high risk disease based on risk of recurrence and disease progression (see figure). Low risk was defined as solitary, primary low grade Ta; intermediate risk as multiple or recurrent low grade tumors; and high risk as any T1 and/or G3 and/or CIS.

Transurethral Bladder Tumor Resection

Guideline comparison and supporting evidence. All guidelines recommend TURBT as the gold standard for the initial diagnosis and treatment of NMIBC.[1,3–5,7–10] After TURBT the 10-year disease specific survival is 85% for Ta tumors and 70% for T1 tumors.[11] Appropriate resection techniques should be used. Brausi et al found wide variability in recurrence rates in patients receiving and in those not receiving intravesical treatment, which was attributed to the quality of the TURBT performed by the individual surgeons.[12] A recent retrospective study (sample size of 47) demonstrated that 70% of included patients had an incomplete initial resection.[13] Of these patients 30% had macroscopic residual tumor at the resection site and 70% had at least 1 unresected tumor away from the previous resection site.

The EAU outlined resection techniques depending on the size of the lesion.[1] Small tumors (less than 1 cm) can be resected en bloc and the specimen should contain complete tumor plus part of the underlying bladder wall. Larger tumors should be resected separately in fractions, including the exophytic part of the tumor, the underlying bladder wall with the detrusor muscle and the edges of the resection area. Specimens from different fractions must be referred to the pathologist in separate containers to allow for a correct diagnosis. Cauterization should be avoided as much as possible to prevent tissue destruction.

Based on expert experience, repeat TURBT 2 to 6 weeks after the initial procedure is recommended in patients with high grade T1 tumors, incomplete initial resection or when the specimen contained no muscle tissue.[1] Repeat TURBT should also be considered in referred patients. A recent study of referred patients with bladder cancer revealed substantial differences between initial pathological reports and subsequent review and reinterpretation of TURBT slides that were sufficiently significant to alter management in almost 30% of subjects.[14]

IBCG recommendations. Based on a review of the 4 guidelines the IBCG recommends complete TURBT for all patients with NMIBC using appropriate/accepted TURBT techniques. A bladder diagram is recommended. Repeat TURBT is recommended for high grade tumors if initial resection is incomplete and/or when no muscle is present in the specimen. Repeat TURBT should be considered in referred patients. Pathology slides should be reviewed directly with the pathologist when possible.

Management of Low Risk Disease

Guideline comparison. The EAU, FICBT and AUA recommend TURBT plus an immediate postoperative chemotherapeutic instillation for low risk disease.[1,4,5,7] The NCCN considers TURBT alone the standard for this patient population, and an immediate postoperative chemotherapeutic dose and/or induction intravesical chemotherapy (based on risk of recurrence and progression) should be considered.[3] Guideline recommendations for low risk disease are summarized in Appendix 2.

Additional supporting evidence. An EORTC meta-analysis showed that a single, immediate instillation of intravesical chemotherapy after TURBT results in a 12% absolute reduction in tumor recurrence (a decrease of 39% in the odds of recurrence).[15] No significant differences in efficacy were noted among the chemotherapeutic agents studied, indicating that the choice of chemotherapeutic drug is optional. In an AUA meta-analysis TURBT and single dose MMC resulted in a 17% absolute reduction in recurrence compared to TURBT alone when all patient risk groups were considered.[4]

The timing of the instillation is important. In 1 study there was a doubling in the risk of recurrence if the first of 5 weekly MMC instillations was not given within 24 hours of TURBT.[16] In 2 EORTC trials in which patients received 9 instillations of epirubicin or MMC during 6 months, starting treatment on the day of TURBT was more effective than starting 7 to 15 days later in patients who did not receive further maintenance after 6 months.[17] In another study in which patients received 15 instillations of doxorubicin or MMC during a 1-year period, fewer patients randomized to start treatment within 6 hours had recurrence than did those randomized to start treatment after 7 to 14 days, particularly in the MMC arm.[18] Note that in the major-

ity of these studies the instillations were given within 24 hours, generally immediately or within 6 hours after TURBT. Despite the benefits of an immediate, chemotherapeutic instillation, it should be avoided in cases of overt or suspected intraperitoneal or extraperitoneal perforation because complications have been noted in these cases.[19]

Recent evidence suggests that the benefit of a single, immediate chemotherapeutic instillation after TURBT is limited to patients with low risk disease.[20] In patients with primary, small (less than 5 mm), solitary, low grade tumors, a single early chemotherapeutic instillation after TURBT significantly reduces the risk of recurrence, which is seen in the first 2 years of followup. There appears to be no advantage to an immediate postoperative instillation in recurrent, large (greater than 5 mm) or high grade tumors, or in high risk patients receiving BCG therapy.[21–28] Therefore, the IBCG recommends that a single, immediate postoperative chemotherapeutic instillation be reserved for patients with low risk NMIBC. Although some experts have questioned the ability to accurately diagnose low grade papillary tumors at cystoscopy, evidence suggests that cystoscopic expertise combined with a negative urine cytology accurately identifies low grade tumors in more than 90% of cases.[29,30] Herr et al examined the correlation between cystoscopic appearance and histopathology in 125 patients with 144 recurrent papillary tumors.[29] Of 97 tumors the 90 (93%) considered TaG1 at cystoscopy were confirmed to be low grade papillary lesions at biopsy. Of 86 TaG1s associated with negative cytology, 85 (99%) were low grade papillary tumors histologically. Only 1 of 97 (1%) tumors deemed TaG1 proved to be invasive on biopsy. An EORTC study reported that 5.6% of 501 tumors believed to be noninfiltrating at cystoscopy were under staged compared to histopathology.[30] Tumors appearing superficial that were less than 3 cm in diameter were correctly staged in 96% of cases. No data were available regarding the accuracy of cystoscopy in predicting tumor grade.

IBCG recommendations. Based on comparison of the 4 guidelines and the current literature, for low risk disease the IBCG recommends complete TURBT plus an immediate, single, postoperative chemotherapeutic instillation, except in those patients with obvious or suspected bladder wall perforation (see figure).

Management of Intermediate Risk Disease

Guideline comparison. All guidelines recommend that adjuvant therapy with BCG or chemotherapy is necessary for intermediate risk disease. However, the strength of this recommendation varies and controversy exists about whether induction plus maintenance or induction alone should be used (Appendix 2). The EAU recommends adjuvant BCG with maintenance (1 year or more) or further instillations of chemotherapy (6 to 12 months) for intermediate risk disease.[1] The FICBT recommends intravesical chemotherapy (less than 6 months) as first line and BCG as second line therapy in patients with recurrent, multiple, low grade Ta tumors, or when high risk factors for recurrence are present.[7]

According to the NCCN, options for intermediate risk disease include observation, or treatment with intravesical BCG (preferred) or MMC.[3] The AUA recommends an induction course of BCG or MMC for patients at high risk for recurrence but at low risk for progression (intermediate risk). Although maintenance BCG or MMC is considered optional in these patients, the AUA acknowledges that maintenance is more effective in decreasing recurrence than induction alone.[4,5]

Additional supporting evidence. An EORTC meta-analysis showed that compared to TURBT alone, adjuvant chemotherapy after TURBT significantly improves disease-free survival but has no effect on progression.[31] In a review of controlled trials of intravesical chemotherapy Lamm et al reported an absolute 14% decrease in tumor recurrence but also found no effect on tumor progression.[32]

To our knowledge no consensus currently exists on the optimal chemotherapeutic schedule. Results from a systematic review of intravesical chemotherapy trials suggest that a short, intensive schedule of instillations (3 to 4 months) after an immediate instillation may be as effective as longer term schedules.[33] The investigators concluded that long-term instillations of 1 year or more should only be considered when an immediate instillation has not been provided.

Recent data suggest that BCG with maintenance may be superior to chemotherapy for intermediate risk disease and may be the preferred treatment option for this patient population. The EORTC 30911 trial compared the long-term efficacy of 6 weekly intravesical instillations of epirubicin, BCG and BCG plus isoniazid followed by 3 weekly maintenance instillations at months 3, 6, 12, 18, 24, 30 and 36 after TURBT in patients with intermediate (497) and high risk (323) NMIBC.[34] Median followup was 9.2 years. Time to first recurrence ($p < 0.001$), time to distant metastases ($p = 0.046$), and overall ($p = 0.023$) and disease specific survival ($p = 0.026$) were all significantly prolonged in the 2 BCG arms combined compared to the epirubicin arm. However, no difference in progression was noted between the treatment arms. The investigators concluded that intermediate and high risk patients benefit from BCG therapy. The observed treatment benefit was

at least as large, if not larger, in the intermediate vs high risk patients.

Results from a recent IPD meta-analysis of 9 trials (2,820) further confirm the superiority of BCG when maintenance therapy is provided.[35] This meta-analysis revealed no overall difference in time to first recurrence ($p = 0.09$) between BCG and MMC. However, in the trials using BCG maintenance a 32% reduction in the risk of recurrence with BCG vs MMC was found ($p < 0.0001$), while there was a 28% risk increase ($p = 0.006$) with BCG in the trials without maintenance. BCG with maintenance was more effective than MMC in patients previously treated and in those not previously treated with chemotherapy. No significant differences in progression, overall survival and cancer specific survival were noted between the 2 groups. Note that the majority of patients included in this meta-analysis were intermediate risk (74%), further confirming the value of BCG maintenance in this patient population.[35]

IBCG recommendations. Based on guidelines and supporting evidence, for intermediate risk disease the IBCG recommends the initiation of BCG induction plus maintenance or intravesical chemotherapy after complete TURBT (see figure). Adjuvant chemotherapy should not exceed 12 months.

Management of High Risk Disease

Guideline comparison. All guidelines regard BCG as the standard adjuvant treatment for high risk patients (Appendix 2). The EAU recommends a second TURBT 2 to 6 weeks after the initial resection and adjuvant intravesical BCG for at least 1 year for high risk disease. Immediate radical cystectomy may be offered to the highest risk patients such as those with multiple, recurrent high grade tumors, high grade T1 tumors or high grade tumors with CIS.[1] For patients with CIS the EAU recommends intravesical BCG plus maintenance for at least 1 year.[36]

For high grade Ta the FICBT recommends a 6-week induction course of BCG plus 1 to 3 years of maintenance.[9] In patients with completely resected T1 tumors (based on negative repeat resection) initial intravesical BCG therapy should be considered.[8] According to the FICBT, radical cystectomy at CIS diagnosis constitutes overtreatment in up to 50% of patients. Therefore, intravesical BCG with at least 1 year of maintenance is recommended because it is associated with the highest rate of complete response and the highest long-term disease-free rate among intravesical treatments.[9]

The NCCN advises re-resection for T1 disease. If residual disease is present, BCG (category 1) or cystectomy is advised. If there is no residual disease, intravesical BCG (preferred, category 1) or MMC is recommended.[3] According to the AUA, repeat resection followed by BCG induction plus maintenance is recommended for patients with initially histologically confirmed high grade Ta, T1 and/or CIS with lamina propria invasion (T1) but without muscularis propria in the specimen. Cystectomy is considered an option for initial therapy in select patients due to the risk of initially under staged disease or progression to muscle invasive disease.[4,5]

Note that high grade Ta tumors represent a relatively small subgroup of cases and the histological diagnosis is subject to considerable misclassification. The FICBT recommends repeat TURBT and bladder mapping 2 to 4 weeks later for Ta tumors.[2] Given that the pathologist cannot confirm if muscle is uninvolved unless it is present in the specimen, all guidelines suggest repeat TURBT when there is no muscle in the specimen.[1–5] However, general guidelines and recommendations cannot dictate each individual management decision. Therefore, some experts indicate that re-resection is unnecessary if muscle is not present in the specimen but the lamina propria is clearly uninvolved and the diagnosis of Ta disease is secure.

Additional supporting evidence. EORTC 30911 and the IPD meta-analysis by Malmström et al (discussed previously) highlight the importance of maintenance BCG in intermediate and high risk NMIBC.[34,35] EORTC 30911 showed that time to first recurrence, time to distant metastases, and overall and disease specific survival were all significantly prolonged in the 2 BCG arms combined compared to the epirubicin arm, and the IPD meta-analysis showed a 32% reduction in the risk of recurrence with BCG maintenance vs MMC.[34,35] Although neither study demonstrated a beneficial effect of BCG on disease progression, an EORTC meta-analysis of 24 trials (4,863) showed that BCG maintenance therapy was associated with a 37% reduction in the risk of tumor progression compared to the control groups (TURBT alone, TURBT plus intravesical chemotherapy, TURBT plus another immunotherapy).[37] Another meta-analysis of 9 trials comparing BCG to MMC showed that BCG maintenance was significantly superior to MMC for the prevention of tumor progression.[38]

A meta-analysis of 11 clinical trials demonstrated that BCG was superior to MMC in decreasing tumor recurrence (OR 0.56, 95% CI 0.38 to 0.84, $p = 0.005$).[39] In the subgroup treated with BCG maintenance all 6 individual studies showed a significant superiority of BCG compared to MMC (OR 0.43, 95% CI 0.35 to 0.53, $p < 0.001$). In a single arm AUA meta-analysis of randomized trials in high risk patients the 5-year recurrence rate was 34% in those receiving TURBT and BCG mainte-

nance vs 62% in those on MMC maintenance. A trend toward improvement in overall progression was also noted with BCG maintenance therapy.[4]

Malavaud performed a systematic review of the literature comparing conservative treatment and radical cystectomy, and concluded that immediate radical cystectomy is indicated in young patients with T1 tumors who have at least 1 additional factor associated with a poor prognosis such as multifocality, associated CIS, prostatic involvement or tumor located at a site difficult to resect.[40] Bianco et al performed a multivariate analysis to identify risk factors in patients undergoing cystectomy that influenced cancer specific survival, and found that those with concomitant CIS or those with persistent disease after an initial course of BCG had worse cancer specific survival.[41]

IBCG recommendations. Based on a review of current guidelines and evidence, for high risk disease the IBCG recommends BCG induction plus maintenance after complete TURBT (see figure). Immediate radical cystectomy should be considered for high grade, multiple T1 tumors; T1 tumors located at a site difficult to resect; residual T1 tumors on reresection or high grade tumors with CIS.

Optimal BCG Induction and Maintenance Schedules

BCG instillations are classically given according to the empirical 6-weekly induction schedule of Morales et al introduced more than 30 years ago.[1,8,42] There is currently no agreement on the optimal BCG maintenance schedule. However, according to the FICBT and AUA,[4,5,8] the current optimal schedule is based on the Southwest Oncology Group regimen of 3 weekly instillations at 3 and 6 months after induction, and every 6 months thereafter for up to 3 years.[43] The EAU guidelines recommend at least 1 year of BCG maintenance therapy.[1]

Followup Schedule

The recommended followup schedules for low, intermediate and high risk disease vary among the 4 guidelines. However, all guidelines indicate the importance of regular followup cystoscopy. Although not evidence-based, the IBCG has proposed a schedule based on the EAU recommendations for followup with minor modifications.[1] For low risk disease surveillance cystoscopy at 3 months is recommended. If results are negative, the following cystoscopy is advised at 9 months and then yearly for a minimum of 5 years. No upper tract investigations are required. For high risk disease, cystoscopy and cytology at 3 months are recommended. If results are negative, the following cystoscopies and cytology assessments should be repeated every 3 months for 2 years, every 4 months in the third year, every 6 months thereafter until 5 years and annually thereafter. Annual upper urinary tract imaging should also be considered. For intermediate risk disease the followup schedule should be between that for low and high risk disease, and should be adapted according to individual patient factors.

Management of Recurrence and Treatment Failure

For the optimal management of NMIBC the IBCG emphasizes the importance of distinguishing recurrence from treatment failure and has proposed some definitions. Recurrence refers to the reappearance of disease (any grade, T category or CIS) after the completion of therapy. Failure of intravesical therapy occurs with any recurrence or progression during therapy.

Guideline comparison and supporting evidence. According to the EAU, patients with recurrence after intravesical chemotherapy may benefit from BCG instillations.[1] Patients with a high grade, nonmuscle invasive tumor at 3 months of BCG therapy can receive an additional BCG course as this has been associated with complete response in more than 50% of patients.[44] Although the EAU acknowledges that changing from BCG to chemotherapy can lead to further remission in select patients in whom BCG has failed, in most high risk patients with BCG failure immediate cystectomy is strongly advocated due to the high risk of progression to muscle invasive disease.[1]

The FICBT suggests that repeat BCG therapy may be appropriate for BCG resistant and BCG relapsing disease[8] as long as the recurrence is not T1 disease. Patients in whom induction BCG fails who experience recurrence of high grade disease at 6 months should be offered cystectomy (grade C). For patients with initial induction BCG therapy failure who are unfit, refuse cystectomy, or who have low or intermediate grade disease, an additional course of a BCG containing intravesical therapy is preferred (grade C). In the case of treatment failure before completion of maintenance BCG, cystectomy should be considered if high grade T1 or CIS is present (grade B). For high grade Ta recurrence the FICBT recommends repeat resection and continued BCG maintenance (grade B). If early failure occurs after the completion of maintenance BCG, 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 tumors should be considered for cystectomy if they have had 2 prior induction cycles of BCG (grade D).[8]

According to the NCCN a change in intravesical agent or cystectomy is recommended for patients

with CIS or Ta recurrence after intravesical therapy (no more than 2 consecutive cycles, category 2A). For high grade T1 recurrence, cystectomy is recommended (category 2A). Maintenance BCG therapy is optional in patients with recurrent or persistent disease showing complete response on followup cystoscopy regardless of whether 1 or 2 courses of induction therapy were administered.[3]

The AUA recommends repeat resection before additional intravesical therapy (standard) for patients with high grade Ta, T1 and/or CIS recurrence after intravesical therapy. Further intravesical therapy, particularly with BCG, may also be considered (an option) in these patients and cystectomy as a therapeutic alternative is recommended.[4,5] In fact, earlier cystectomy has been shown to improve the long-term survival of high risk patients in whom BCG therapy has failed.[45] A retrospective analysis of 90 patients with high risk NMIBC who ultimately underwent cystectomy demonstrated improved 15-year disease specific survival in those who underwent cystectomy within 2 years after initial BCG treatment.[45] Improved survival outcomes were also noted in patients who underwent cystectomy for recurrent disease compared to those treated for progression. Therefore, deferring cystectomy until progression to muscle invasive disease may negatively impact survival.

IBCG recommendations for treatment failure. The appropriate management strategies for cases of treatment failure depend on the type of failure (ie chemotherapy or BCG) as well as the risk level. For failure of chemotherapy in intermediate risk patients, TURBT plus BCG induction plus maintenance or additional intravesical chemotherapy is recommended. For high risk patients, TURBT plus BCG induction plus maintenance is recommended, or cystectomy can be considered. For BCG failure in intermediate risk patients, TURBT plus repeat BCG induction plus maintenance or radical cystectomy is recommended, whereas for high risk patients radical cystectomy is recommended.

IBCG recommendations for management of recurrence. The management of recurrence depends not only on previous and current levels of risk, but also on the previous treatment received. For recurrence in low risk patients the IBCG recommends treatment as for intermediate risk patients with TURBT plus intravesical chemotherapy or BCG induction plus maintenance. For recurrence in intermediate risk patients the risk category should be considered. If the patient is still classified as intermediate risk, TURBT plus repeat chemotherapy or BCG induction plus maintenance (depending on previous treatment) is recommended. If high risk, TURBT plus BCG induction plus maintenance or radical cystectomy is recommended (depending on previous treatment). For high grade recurrence in high risk patients, radical cystectomy is preferred, or TURBT plus additional intravesical instillations are recommended if cystectomy is not suitable for the patient.

CONCLUSIONS

Established areas of consensus among the 4 guidelines include the importance of TURBT in all patients with NMIBC and the benefit of adjuvant BCG for high risk disease. However, the guideline recommendations vary with regard to the definitions of low, intermediate and high risk disease as well as the appropriate treatment and followup 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 failure. To address these issues and provide urologists with more practical and unified guidance on the management of NMIBC, the IBCG has proposed the recommendations presented in this article.

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APPENDIX 1

Comparison of risk stratification definitions proposed by the EAU, FICBT, NCCN and AUA[1,3–5,7–9]

	Definitions		
	Low Risk	Intermediate Risk	High Risk
EAU	Low risk of tumor recurrence (EORTC recurrence score = 0) and progression (EORTC progression score = 0)	Intermediate (EORTC recurrence scores ranging from 1–9) or high (EORTC recurrence score ranging from 10–17) risk of recurrence and intermediate risk of progression (progression scores ranging from 2–6)	High risk of progression (EORTC progression scores ranging from 7–23)
	eg G1-2Ta	eg multifocal G2Ta, solitary G2T1	eg multifocal G2T1, G3Ta-T1, CIS
FICBT	Low grade Ta	Low grade Ta with high risk factors for recurrence or recurrent low grade Ta tumors	High grade Ta, all T1, CIS
NCCN	Low grade* Ta	High grade* Ta	All T1 (CIS listed separately)
AUA	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

Adapted from Persad et al.[10]

* Grading refers to the *World Health Organization International Histological Classification of Tumours,* 1973. The majority of grade 2 tumors are high grade. Some grade 2 tumors may be classified as low grade by some pathologists.

APPENDIX 2

Comparison of guideline recommendations for low, intermediate and high risk disease[1,3–5,7–9,32]

Guideline	Low Risk Disease	Intermediate Risk Disease	High Risk Disease
EAU	• TURBT • Single immediate post operative instillation of chemotherapy (grade A)	• TURBT • Single, immediate postoperative instillation of chemotherapy followed by: – Induction BCG plus maintenance (at least 1 year) (grade A), or – Maintenance intravesical chemotherapy (grade A) of 6–12 months (grade B)	• Repeat TURBT 2–6 weeks after initial resection (grade B) • Intravesical BCG induction plus maintenance for at least 1 year (grade A) • Immediate radical cystectomy for highest risk patients (grade C) — Multiple recurrent high grade tumors — High grade T1 tumors — High grade tumors with concomitant CIS CIS: • Intravesical BCG plus maintenance for at least 1 year (grade A) – Assess response at 3 months: ■ If no response: • Continue with 3 weekly boosters (grade B), or • Additional 6-week course of BCG (grade B), or • Cystectomy (grade B) – No complete response at 6 months: radical cystectomy (grade B)

(appendix continued)

APPENDIX 2 (continued)

Guideline	Low Risk Disease	Intermediate Risk Disease	High Risk Disease
FICBT	• TURBT • Single immediate postoperative instillation of chemotherapy (grade A)	Multiple low grade Ta • TURBT • Single immediate postoperative instillation of chemotherapy • Further adjuvant intravesical therapy: — First line: intravesical chemotherapy less than 6 months (grade B) — Second line: BCG (grade A)	High grade Ta • Second look TURBT and bladder mapping biopsies 2–4 weeks after initial resection (grade B) • If residual tumor is found: — Re-resection and 1 immediate instillation of chemotherapy — Followed 2–3 weeks later by 6-week BCG induction and 1–3 years of BCG maintenance (grade A)
		Recurrent low grade Ta • Office fulguration only in select patients with less than 5 small (less than 0.5 cm) low grade recurrent tumors and negative cytology (grade C) • Formal TURBT if clinical doubt that tumor is low grade, cytology positive, or change in tumor appearance has occurred (grade C) • Adjuvant intravesical therapy (see above)	T1 • Repeat TURBT (grade B) • Initial intravesical BCG for patients with completely resected primary and recurrent T1 tumors (based on a negative repeat resection) (grade C) CIS • Intravesical BCG for 6 weeks (grade A) • Maintenance BCG for 1 year or more (grade A)
NCCN	• TURBT • Observe (category 2A), or • Consider single immediate postoperative instillation of chemotherapy (category 2A), and/or • Induction intravesical chemotherapy (category 2A)	• TURBT • Repeat TURBT if incomplete resection or no muscle in specimen (category 2A) • Observe or • Intravesical therapy — BCG (preferred) or — MMC (category 2A)	All T1: Strongly advise re-resection or cystectomy for high grade *Residual disease:* • BCG preferred (category 1), or • Cystectomy (category 2A) *No residual disease:* • BCG preferred (category 1), or • MMC (category 2A) Any CIS/Tis • Complete resection followed by intravesical BCG (category 2A) • Repeat resection if lamina propria invasion without muscularis propria in specimen prior to intravesical therapy (standard)
AUA	• TURBT • Single immediate postoperative instillation of chemotherapy (recommendation)	• TURBT • Intravesical BCG or MMC (recommendation) • Maintenance BCG or MMC (option)	• Induction BCG followed by maintenance (recommendation) • Cystectomy (option)

Adapted from Persad et al.[10]

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