

Canadian Guidelines for Treatment of Non-Muscle Invasive Bladder Cancer – A Focus on Intravesical Therapy

Wassim Kassouf MD*, Ashish M. Kamat MD, Alexander Zlotta MD, Bernard H. Bochner MD, Ronald Moore MD, Alan So MD, Jonathan Izawa MD, Ricardo A Rendon MD, Louis Lacombe MD, Armen G. Aprikian MD

McGill University (WK, AGA), University of Alberta (RM), UT M.D. Anderson Cancer Center (AMK), Memorial Sloan Kettering Cancer Center (BB), University of Toronto (AZ), Laval University (LL), Dalhousie University (RR), University of British Columbia (AS), University of London Ontario (JI)

*Corresponding Author: Wassim Kassouf, MD, FRCS(C).
Division of Urology,
McGill University Health Center
1650 Cedar avenue, Rm L8-315,
Montreal, Quebec H3G 1A4, Canada.
Phone: 514-934-8246
Fax: 514-934-8297
E-mail: wassim.kassouf@muhc.mcgill.ca

Key words: non-muscle invasive bladder cancer, superficial, guidelines, intravesical therapy, cystectomy, transurethral resection

Potential conflicts of interest for authors: None

1. Introduction

In 2008, bladder cancer is estimated to be the fourth most common male cancer accounting for 6% of all cancers and the eighth highest cancer-related mortality rate in Canadian men. The most common type is urothelial carcinoma (>90%), followed by adenocarcinoma, squamous cell, and small cell carcinoma. Risk factors that have been associated with bladder cancer include smoking, chronic inflammatory changes in the bladder (due to persistent bladder stones, recurrent urinary tract infections, indwelling catheters, or Schistosomiasis), and chemotherapeutic exposure such as cyclophosphamide.¹⁻⁶ Other risk factors include pelvic irradiation, occupational exposure to chemicals from the aromatic amines family, and chronic phenacetin use.⁷⁻¹⁰ Non-muscle invasive bladder cancer (NMIBC) accounts for approximately 75-80% of all bladder cancer cases;¹¹ Ta accounts for the majority of NMIBC (60%) where T1 and Tis (carcinoma in situ, CIS) account for 30% and 10%, respectively. The actual prevalence of non-muscle invasive bladder cancer is ten times its incidence creating a major economic burden on health care systems.¹² As measured on the basis of cumulative per patient cost from diagnosis until death, bladder cancer is the most expensive human cancer to treat.¹³ The management of NMIBC has significantly changed over the last decade. Canadian guidelines on the treatment of NMIBC are lacking. This manuscript provides a Canadian consensus on the management of NMIBC with an emphasis on intravesical therapy after a comprehensive review of the literature, as well as review of the guidelines from the EAU, AUA, and NCCN.¹⁴⁻¹⁶

2. Prognostic factors for recurrence and progression of NMIBC

The overall rate of recurrence for NMIBC is 60% to 70%, and the overall rate of progression to a higher stage or grade is 20% to 30%.^{17, 18} The two most important prognostic factors in NMIBC are stage and grade. Ta tumors (which are usually low grade) rarely progress to a higher stage but tend to recur frequently. On the other hand, T1 tumors (which are usually high grade) have the potential to be more aggressive, with higher rates of progression to muscle invasion and even metastasis. Heney and colleagues have shown that the risk of disease progression to muscle invasion is strongly associated with tumor grade.¹¹ The risk of progression for Ta tumor was 2%, 11%, and 45% for grades 1, 2, and 3 respectively. When stratified by stage, tumor grade continues to correlates with progression and mortality as stage increases. Most subsequent studies also suggested that grade is a better prognostic indicator of progression and mortality than of recurrence.¹⁹⁻²² However, recurrence is still a significant problem in the management of superficial bladder cancer. As many as 60-90% of NMIBC will recur if treated by TUR alone.²³ Using 6 clinicopathologic parameters (grade, stage, tumor size, prior recurrence rate, presence of concomitant CIS, and number of tumors), the probability of recurrence and progression of NMIBC can be calculated with risk tables provided by the EORTC, that were developed and based on individual patient data from 2596 patients diagnosed with Ta/T1 tumors who were randomized in seven EORTC trials

(www.eortc.be/tools/bladdercalculator). In general, patients with NMIBC can be stratified into low risk disease (solitary, low grade Ta lesion, <3cm), intermediate (\geq 3cm, multiple, or multi-recurrent low-intermediate grade tumors), and high-risk (high grade Ta, T1 tumors, or CIS).

3. TURBT

Transurethral resection of bladder tumor (TURBT) is the first and gold standard treatment option for NMIBC. Complete resection of the tumor should be performed including all areas of suspected CIS and abnormal areas in the prostatic urethra and bladder neck. If extensive CIS is present, mapping biopsies should be obtained, and all visible papillary lesions resected. TURBT should be made sure to include detrusor muscle (muscularis propria) in the specimen in an attempt to rule out T2 disease and minimize the risk of under-staging (**Grade A**). TURBT not only eradicates all visible tumors, it also provides tissue for pathological analysis and determination of histological type and grade together with detecting the presence, depth, and type of invasion. The quality of the initial TURBT specimen is extremely important.²⁴ Several studies demonstrate that the quality of the TURBT can be improved using fluorescent cystoscopy. Integration of fluorescent cystoscopy during TURBT has been shown to reduce recurrence rates (**level 2**).^{25, 26} However, false positives with fluorescent cystoscopy can be increasingly induced by inflammation, recent TUR, or intravesical instillations. Although fluorescent cystoscopy reduces recurrence rates, it is not certain if the long-term recurrence-free survival is affected. Furthermore, it is unclear whether fluorescent cystoscopy improves progression-free and overall survival in patients with NMIBC. At the present time, the use of combined fluorescent and white light TUR is optional (**Grade C**).

4. Second TURBT

Restaging TUR provides more tissue for pathologic examination and better staging as well as insight into the biology of the disease (**level 2**). In patients with T1G3/T1HG, re-TUR upstaged tumors to T2 disease in 49% of patients if muscularis propria was not present in the specimen compared to 14% upstage if the initial TUR showed benign muscularis propria.²⁷ Restaging TUR is also associated with better local control of tumor (**level 3**). Herr previously reported that 75% of patients who underwent repeat TURBT in 2 to 6 weeks after initial resection have residual tumor. Forty four percent of them were found to have T1 or muscle invasive tumor. Furthermore, 17% of patients who had TURBT of primary cancers actually have histological evidence of cancer at previous resection site despite a normal cystoscopic examination.²⁸ After 5 years of follow-up in 124 patients, Grimm et al found that 63% of those who underwent a repeat TURBT had tumor-free bladders compared with 40% of those who did not.²⁹ Similarly, a recent study demonstrated that a restaging TUR improved initial response to intravesical immunotherapy.²⁴ We recommend that a second TUR should always be performed 4 to 6 weeks after the initial resection when the initial TUR is incomplete or a T1 tumor is detected in the absence of muscularis propria in the specimen (**Grade A**). A second TUR is also recommended for any high grade tumors or T1 tumors with benign muscularis propria in the specimen (**Grade C**). Collectively, removing all residual tumors in a second therapeutic TURBT allows for more accurate staging, improves

patient selection (and thus response) to BCG therapy, reduces the frequency of recurrence, and potentially delays tumor progression (**level 2**).²⁹

5. Follow-up

All patients are recommended to undergo a cystoscopy at 3 months following TURBT as cystoscopic findings at 3 months has been shown to be a prognostic factor of recurrence and progression of disease (**Grade A**).³⁰ Prospective studies to better refine the surveillance schedule are sorely needed. Although there is no consensus for surveillance strategies, our general recommendation is to perform a follow up cystoscopy with urine cytology (or other urine marker) every 3-4 months for 2 years, then every 6 months for the second 2 years, then yearly thereafter (**Grade B**). Patients with a primary, solitary, low-grade Ta tumor may have less frequent cystoscopic examination (3 and 9 months then annually thereafter) (**level 3**). Any recurrence resets the clock in the follow up schedule. Annual upper tract imaging is recommended for patients with intermediate and high-risk NMIBC (**Grade C**).

6. Intravesical Therapy

Intravesical therapy can be either chemotherapy or immunotherapy and is either therapeutic (treatment of CIS or residual non-visible tumor), prophylactic (prevention of recurrence and progression of disease) or adjuvant in the immediate postoperative setting.

6.1 Chemotherapy

6.1.1 Single immediate post-operative instillation

High proportion of patients with NMIBC will develop recurrences with a significant number recurring 3 months following TURBT. Incomplete TUR or tumor cell implantation post-TUR has been implicated to be responsible for the high recurrences at 3 months. As such, several studies have evaluated the role of a single postoperative intravesical instillation of chemotherapy. The commonly used intravesical chemotherapeutic agents are doxorubicin, epirubicin, and mitomycin C (MMC). Sylvester and associates performed a meta-analysis of seven randomized trials (n=1476) on the outcome of TUR alone versus TUR plus one immediate postoperative instillation of intravesical chemotherapy.³¹ Over a median follow-up of 3.4 years, patients who received one immediate instillation had recurrence rate of 37% compared with 48% of patients who had TUR alone. The benefit was more pronounced for those with single low grade papillary tumor compared with patients with multiple tumors. Efficacy of the immediate postoperative instillation is within 6 hours from time of TUR and significantly decreases if given beyond 24hrs (**level 2**).³² Immediate postoperative instillation of chemotherapeutic agent is recommended for all patients with NMIBC after TURBT (**Grade B**); patients who are planned to be treated with BCG, the use of an immediate postoperative instillation of chemotherapy is optional as its benefit in this situation is less clear (**Grade D**). Overall, long-term recurrence reduction is similar between the different chemotherapeutic agents, being in the range of approximately 15%.

The most commonly used intravesical chemotherapeutic agent in Canada is MMC. Since the molecule has a high molecular weight, absorption and myelosuppression due to MMC is uncommon. Patients with suspected bladder perforation should not receive an immediate instillation as severe complications have been reported in this setting.³³⁻³⁵ Efficacy of MMC is dependent on the concentration at which the drug is administered. The dose commonly used is 40mg in 40ml of saline or water (with some using 40mg in 20ml). Recently, Au et al published a phase III, randomized trial that showed superiority and prolonged median time to recurrence with an 'optimized' MMC administration which consist of a period of dehydration (no fluids for 8 hrs prior to treatment), urinary alkalization, confirmation of complete bladder drainage prior to instillation, and a higher MMC concentration (40mg in 20ml of water).³⁶

6.1.2 Multiple adjuvant instillations

Patients with low grade Ta disease will benefit from induction chemotherapy followed by maintenance therapy. There are no published trials that directly compared induction course of MMC to MMC induction with maintenance therapy; however a current meta-analysis suggests that long-term maintenance therapy enhances the effectiveness of MMC induction in preventing recurrences.¹⁶ Two meta-analysis assessing the impact of intravesical chemotherapy in primary and recurrent NMIBC demonstrated reduction in recurrences with the use of chemotherapy; the benefit appeared to be more significant when at least 1-2 years of maintenance therapy was used.^{37, 38} Optimal maintenance dose, schedule, and duration remain unclear. Importantly, none of the studies incorporated the 'optimized' administration of MMC which has been shown to significantly influence the drug's efficacy in a phase III trial. Furthermore, none of the trials directly compared MMC maintenance therapy to a single immediate postoperative instillation. Patients with low-risk disease that develop recurrent low-grade Ta lesions may receive an induction followed by maintenance course of intravesical chemotherapy (**Grade C**). Meta-analysis of 22 randomized, prospective studies evaluating the role of intravesical chemotherapy for NMIBC did not show any benefit in reduction of progression rates compared to TURBT alone (**level 1**).³⁹ Intravesical gemcitabine and docetaxel have been studied but there is insufficient evidence to support its superiority over the currently used intravesical chemotherapeutic agents.

6.2 Immunotherapy

6.2.1 BCG

The US Food and Drug Administration approved BCG for the treatment of CIS of the bladder in 1990. Since then, BCG immunotherapy has emerged as the standard against which all new therapies are compared. Six controlled trials carried out from 1985 – 1996 showed that BCG decreases recurrence rates from 67 to 29%.⁴⁰⁻⁴⁶ Six meta-analyses compared BCG with intravesical chemotherapy; all of them except one⁴⁷ showed superiority of BCG over chemotherapy in terms of decreasing recurrence.⁴⁷⁻⁵² BCG following TUR is superior to TUR alone or TUR plus intravesical chemotherapy in decreasing recurrences, particularly in patients with high-risk disease (**level 1**).

BCG is the only intravesical agent that have been shown to affect tumor progression in several randomized trials (**level 1**).^{42, 43, 53} Herr et al evaluated 86 patients with high risk superficial cancer and showed that the disease progression and mortality rates in patients treated with BCG decreased from 35 to 28% and 32 to 14%, respectively.⁵³ This apparent advantage is less significant over long term follow up at 15 years.⁵⁴ Among several series, BCG induces a complete response rate to CIS in over 70%.⁵⁵ In a recent meta-analysis involving 24 randomized trials on 4,863 patients treated with TUR plus intravesical BCG, TUR alone or TUR plus treatment other than BCG, Sylvester et al demonstrated a statistically significant decrease in progression rates (27% reduction) for patients who received BCG compared with the control group (9.8% versus 13.8% respectively).⁴⁸ A subset analysis demonstrated that the reduction in progression rate was significant only when BCG maintenance was administered. In 2005, Sylvester and colleagues reported their analysis on 12 different randomized trials that included patients with CIS. They compared BCG with different intravesical chemotherapy regimens.⁵⁶ There was 68% versus 48% complete response rate with BCG versus chemotherapy respectively. The overall disease free rates over a median follow up of 3.75 years were 51% versus 27% for BCG versus chemotherapy respectively. Similarly, another meta-analysis of 9 randomized trials showed similar results.⁵² Takenaka and colleagues found that the overall response rate to BCG in patients with primary, concomitant, or secondary CIS was 86.6%, with a 5 year progression free survival rate of 78.5%.⁵⁷ The majority of recurrences or progression occur within the first 5 years.⁵⁸ BCG is the standard of care following TUR for high-risk NMIBC (**Grade A**). Patients with intermediate risk NMIBC are recommended to receive either intravesical induction course with chemotherapy or BCG followed by maintenance (**Grade B**). Patients with NMIBC who fail intravesical chemotherapy may benefit from BCG induction and maintenance (**Grade B**).

6.2.2 Treatment schedule

BCG is given after 2-4 weeks following TURBT to avoid systemic side effects. Treatment schedules have not been established, but there is a universal agreement that 6 weekly induction only is not enough.⁵⁹ A second induction has been shown to have additional benefit of approximately 25% when used for prophylaxis and 30% when used for CIS (**level 3**).^{59, 60} However, there is sufficient evidence that BCG maintenance in addition to induction confers reductions in both recurrence and progression (**level 1**). Lamm and associates randomized patients with intermediate/high risk NMIBC to receive 6 weekly inductions with BCG versus 6 weekly inductions followed by maintenance (3 weekly cycles at 3 months and 6 months then every 6 months up to 36 months).⁶¹ Patients receiving maintenance compared to those who did not showed improved median recurrence-free and progression-free survival. In a meta-analysis of 24 trials with 4863 patients, Sylvester et al showed a proven superiority of BCG over intravesical chemotherapy.⁴⁸ Progression-free survival was improved only in the patients that received maintenance BCG. Similarly, Bohle and colleagues had similar conclusions in their meta-analysis of 9 trials where 1328 patients with NMIBC treated with adjuvant MMC were compared to 1421 patients treated with adjuvant BCG.^{49, 51} With a median follow up of 26 months, recurrence and progression rates were 46.4% versus 38.6% and 9.4% versus 7.7%, respectively (p = 0.08, Odds Ratio = 0.77). When only trials using

maintenance were included (5 trials), the difference was significant ($p = 0.02$, Odds Ratio = 0.66). The authors concluded that at least 1 year of maintenance BCG was required to show superiority of BCG over chemotherapy in decreasing recurrence or progression. The optimal BCG maintenance schedule has not been determined. We recommend that all patients planned to undergo BCG therapy to receive a 6 week induction course followed by the Lamm maintenance protocol, if tolerated (**Grade B**). Several European studies have demonstrated that BCG can be reduced to 1/3-1/4 with a reduction in toxicity but comparable efficacy.^{44, 62, 63} However, Morales et al have shown that dose reduction is associated with decreased efficacy in North American patients, hypothesizing that a lower immune response may be induced in patients who do not have previous exposure or inoculation with tuberculosis. As such, we recommend a full dose of BCG to be given to patients who can tolerate intravesical therapy, particularly in high-risk NMIBC with dose reduction reserved for tolerance issues (**Grade B**).

6.3 BCG failure

BCG failure is defined as the presence of high grade NMIBC at 6 months from time of TURBT (or at 3 months if the initial tumor is T1G3/T1HG) or any worsening of the disease (higher grade, stage or # of recurrences, or appearance of CIS) while on BCG therapy despite initial response to BCG (**level 2**).⁶⁴ In patients with NMIBC treated with an induction course of BCG (without maintenance) and then later developed recurrence of disease, a second induction course may achieve up to 30-50% response rates.^{60, 65} Beyond 2 induction courses with BCG is not recommended as there is a 7% actuarial risk of progression with each additional course.⁶⁶ Patients with high-risk NMIBC who fail BCG, the option of radical cystectomy should be recommended and discussed with the patient (**Grade B**). Herr et al compared outcome of patients with NMIBC who received a radical cystectomy due to recurrence of disease within 2 years from initial BCG therapy with patients who received radical surgery after 2 years; early radical cystectomy was associated with significantly improved survival in patients with non-muscle invasive recurrence as well as muscle-invasive recurrence.⁶⁷ After BCG failure, second line intravesical therapy with combined low-dose BCG and interferon alpha 2b (induction followed maintenance therapy) is a viable option with lower toxicity but may be associated with significant oncologic risk (**level 3**). In a recent large multicenter phase II trial, 467 BCG failure patients receiving low dose BCG and interferon alpha 2b in parallel with 536 BCG naïve patients receiving standard dose BCG with interferon alpha 2b.⁶⁸ After a median follow-up of 24 months, 45% of the BCG failure patients and 59% of BCG naïve patients were disease-free.⁶⁹ Immediate radical cystectomy may be offered upfront in patients with T1G3/T1HG tumors, high grade tumors with concomitant CIS, or multiple recurrent high-grade tumors (**Grade C**).

6.4 Device-assisted therapy

Several studies have evaluated the efficacy of device-assisted therapy in the treatment of patients with NMIBC. Two studies have demonstrated that patients with intermediate/high risk NMIBC treated with MMC combined with hyperthermia (thermochemotherapy) had significantly prolonged recurrence-free survival compared to those treated with MMC alone.^{22, 70} Another phase III studies demonstrated improved recurrence and progression rates in 108 patients with T1 disease treated with sequential

BCG and MMC/electromotive drug administration compared to BCG alone.⁷¹ Until more studies are completed to further evaluate device-assisted therapies as first and second line treatment, no recommendations are possible at the present time.

References

1. Kirkali, Z., Chan, T., Manoharan, M. et al.: Bladder cancer: epidemiology, staging and grading, and diagnosis. *Urology*, **66**: 4, 2005
2. Chow, W. H., Lindblad, P., Gridley, G. et al.: Risk of urinary tract cancers following kidney or ureter stones. *J Natl Cancer Inst*, **89**: 1453, 1997
3. Kantor, A. F., Hartge, P., Hoover, R. N. et al.: Urinary tract infection and risk of bladder cancer. *Am J Epidemiol*, **119**: 510, 1984
4. Fioriti, D., Pietropaolo, V., Dal Forno, S. et al.: Urothelial bladder carcinoma and viral infections: different association with human polyomaviruses and papillomaviruses. *Int J Immunopathol Pharmacol*, **16**: 283, 2003
5. Mostafa, M. H., Sheweita, S. A., O'Connor, P. J.: Relationship between schistosomiasis and bladder cancer. *Clin Microbiol Rev*, **12**: 97, 1999
6. Cannon, J., Linke, C. A., Cos, L. R.: Cyclophosphamide-associated carcinoma of urothelium: modalities for prevention. *Urology*, **38**: 413, 1991
7. Kaldor, J. M., Day, N. E., Kittelmann, B. et al.: Bladder tumours following chemotherapy and radiotherapy for ovarian cancer: a case-control study. *Int J Cancer*, **63**: 1, 1995
8. Clayson, D. B.: Specific aromatic amines as occupational bladder carcinogens. *Natl Cancer Inst Monogr*: 15, 1981
9. Droller, M. J.: Alterations of the p53 gene in occupational bladder cancer in workers exposed to aromatic amines. *J Urol*, **160**: 618, 1998
10. Piper, J. M., Tonascia, J., Matanoski, G. M.: Heavy phenacetin use and bladder cancer in women aged 20 to 49 years. *N Engl J Med*, **313**: 292, 1985
11. Heney, N. M.: Natural history of superficial bladder cancer. Prognostic features and long-term disease course. *Urol Clin North Am*, **19**: 429, 1992
12. Botteman, M. F., Pashos, C. L., Redaelli, A. et al.: The health economics of bladder cancer: a comprehensive review of the published literature. *Pharmacoeconomics*, **21**: 1315, 2003

13. Avritscher, E. B., Cooksley, C. D., Grossman, H. B. et al.: Clinical model of lifetime cost of treating bladder cancer and associated complications. *Urology*, **68**: 549, 2006
14. Babjuk, M., Oosterlinck, W., Sylvester, R. et al.: EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder. *Eur Urol*, 2008
15. Montie, J. E., Abrahams, N. A., Bahnson, R. R. et al.: Bladder cancer. Clinical guidelines in oncology. *J Natl Compr Canc Netw*, **4**: 984, 2006
16. Hall, M. C., Chang, S. S., Dalbagni, G. et al.: Guideline for the management of nonmuscle invasive bladder cancer (stages Ta, T1, and Tis): 2007 update. *J Urol*, **178**: 2314, 2007
17. Zlotta, A. R., van Vooren, J. P., Huygen, K. et al.: What is the optimal regimen for BCG intravesical therapy? Are six weekly instillations necessary? *Eur Urol*, **37**: 470, 2000
18. Soloway, M. S.: Overview of treatment of superficial bladder cancer. *Urology*, **26**: 18, 1985
19. Holmang, S., Hedelin, H., Anderstrom, C. et al.: The relationship among multiple recurrences, progression and prognosis of patients with stages Ta and T1 transitional cell cancer of the bladder followed for at least 20 years. *J Urol*, **153**: 1823, 1995
20. Millan-Rodriguez, F., Chechile-Toniolo, G., Salvador-Bayarri, J. et al.: Multivariate analysis of the prognostic factors of primary superficial bladder cancer. *J Urol*, **163**: 73, 2000
21. Flamm, J., Havelec, L.: Factors affecting survival in primary superficial bladder cancer. *Eur Urol*, **17**: 113, 1990
22. van der Heijden, A. G., Kiemeney, L. A., Gofrit, O. N. et al.: Preliminary European results of local microwave hyperthermia and chemotherapy treatment in intermediate or high risk superficial transitional cell carcinoma of the bladder. *Eur Urol*, **46**: 65, 2004
23. Lutzeyer, W., Rubben, H., Dahm, H.: Prognostic parameters in superficial bladder cancer: an analysis of 315 cases. *J Urol*, **127**: 250, 1982
24. Herr, H. W.: Restaging transurethral resection of high risk superficial bladder cancer improves the initial response to bacillus Calmette-Guerin therapy. *J Urol*, **174**: 2134, 2005

25. Filbeck, T., Pichlmeier, U., Knuechel, R. et al.: Clinically relevant improvement of recurrence-free survival with 5-aminolevulinic acid induced fluorescence diagnosis in patients with superficial bladder tumors. *J Urol*, **168**: 67, 2002
26. Danilchenko, D. I., Riedl, C. R., Sachs, M. D. et al.: Long-term benefit of 5-aminolevulinic acid fluorescence assisted transurethral resection of superficial bladder cancer: 5-year results of a prospective randomized study. *J Urol*, **174**: 2129, 2005
27. Herr, H. W.: The value of a second transurethral resection in evaluating patients with bladder tumors. *J Urol*, **162**: 74, 1999
28. Schips, L., Augustin, H., Zigeuner, R. E. et al.: Is repeated transurethral resection justified in patients with newly diagnosed superficial bladder cancer? *Urology*, **59**: 220, 2002
29. Grimm, M. O., Steinhoff, C., Simon, X. et al.: Effect of routine repeat transurethral resection for superficial bladder cancer: a long-term observational study. *J Urol*, **170**: 433, 2003
30. Fitzpatrick, J. M., West, A. B., Butler, M. R. et al.: Superficial bladder tumors (stage pTa, grades 1 and 2): the importance of recurrence pattern following initial resection. *J Urol*, **135**: 920, 1986
31. Sylvester, R. J., Oosterlinck, W., van der Meijden, A. P.: A single immediate postoperative 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*, **171**: 2186, 2004
32. Kaasinen, E., Rintala, E., Hellstrom, P. et al.: Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. *Eur Urol*, **42**: 167, 2002
33. Nieuwenhuijzen, J. A., Bex, A., Horenblas, S.: Unusual complication after immediate postoperative intravesical mitomycin C instillation. *Eur Urol*, **43**: 711, 2003
34. Oddens, J. R., van der Meijden, A. P., Sylvester, R.: One immediate postoperative instillation of chemotherapy in low risk Ta, T1 bladder cancer patients. Is it always safe? *Eur Urol*, **46**: 336, 2004
35. Racioppi, M., Porreca, A., Foschi, N. et al.: Bladder perforation: a potential risk of early endovesical chemotherapy with mitomycin C. *Urol Int*, **75**: 373, 2005

36. Au, J. L., Badalament, R. A., Wientjes, M. G. et al.: Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. *J Natl Cancer Inst*, **93**: 597, 2001
37. Huncharek, M., Geschwind, J. F., Witherspoon, B. et al.: Intravesical chemotherapy prophylaxis in primary superficial bladder cancer: a meta-analysis of 3703 patients from 11 randomized trials. *J Clin Epidemiol*, **53**: 676, 2000
38. Huncharek, M., McGarry, R., Kupelnick, B.: Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. *Anticancer Res*, **21**: 765, 2001
39. Lamm, D. L., Riggs, D. R., Traynelis, C. L. et al.: Apparent failure of current intravesical chemotherapy prophylaxis to influence the long-term course of superficial transitional cell carcinoma of the bladder. *J Urol*, **153**: 1444, 1995
40. Lamm, D. L.: Bacillus Calmette-Guerin immunotherapy for bladder cancer. *J Urol*, **134**: 40, 1985
41. Nseyo, U. O., Lamm, D. L.: Immunotherapy of bladder cancer. *Semin Surg Oncol*, **13**: 342, 1997
42. Herr, H. W., Pinsky, C. M., Whitmore, W. F., Jr. et al.: Experience with intravesical bacillus Calmette-Guerin therapy of superficial bladder tumors. *Urology*, **25**: 119, 1985
43. Herr, H. W.: Transurethral resection and intravesical therapy of superficial bladder tumors. *Urol Clin North Am*, **18**: 525, 1991
44. Pagano, F., Bassi, P., Milani, C. et al.: A low dose bacillus Calmette-Guerin regimen in superficial bladder cancer therapy: is it effective? *J Urol*, **146**: 32, 1991
45. Melekos, M. D., Chionis, H., Pantazakos, A. et al.: Intravesical bacillus Calmette-Guerin immunoprophylaxis of superficial bladder cancer: results of a controlled prospective trial with modified treatment schedule. *J Urol*, **149**: 744, 1993
46. Krege, S., Giani, G., Meyer, R. et al.: A randomized multicenter trial of adjuvant therapy in superficial bladder cancer: transurethral resection only versus transurethral resection plus mitomycin C versus transurethral resection plus bacillus Calmette-Guerin. *Participating Clinics. J Urol*, **156**: 962, 1996
47. Huncharek, M., Kupelnick, B.: Impact of intravesical chemotherapy

- versus BCG immunotherapy on recurrence of superficial transitional cell carcinoma of the bladder: metaanalytic reevaluation. *Am J Clin Oncol*, **26**: 402, 2003
48. Sylvester, R. J., van der, M. A., Lamm, D. L.: Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol*, **168**: 1964, 2002
49. Bohle, A., Jocham, D., Bock, P. R.: Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. *J Urol*, **169**: 90, 2003
50. Shelley, M. D., Wilt, T. J., Court, J. et al.: Intravesical bacillus Calmette-Guerin is superior to mitomycin C in reducing tumour recurrence in high-risk superficial bladder cancer: a meta-analysis of randomized trials. *BJU Int*, **93**: 485, 2004
51. Bohle, A., Bock, P. R.: Intravesical bacille Calmette-Guerin versus mitomycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. *Urology*, **63**: 682, 2004
52. Sylvester, R. J., van der Meijden, A. P., Witjes, J. A. et al.: Bacillus calmette-guerin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: a meta-analysis of the published results of randomized clinical trials. *J Urol*, **174**: 86, 2005
53. Sternberg, C. N., Yagoda, A., Scher, H. I. et al.: M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. *J Urol*, **139**: 461, 1988
54. Cookson, M. S., Herr, H. W., Zhang, Z. F. et al.: The treated natural history of high risk superficial bladder cancer: 15-year outcome. *J Urol*, **158**: 62, 1997
55. Lamm, D. L.: Carcinoma in situ. *Urol Clin North Am*, **19**: 499, 1992
56. Sylvester, R. J., van der Meijden, A., Witjes, J. A. et al.: High-grade Ta urothelial carcinoma and carcinoma in situ of the bladder. *Urology*, **66**: 90, 2005
57. Takenaka, A., Yamada, Y., Miyake, H. et al.: Clinical outcomes of bacillus Calmette-Guerin instillation therapy for carcinoma in situ of urinary bladder. *Int J Urol*, **15**: 309, 2008
58. Herr, H. W., Wartinger, D. D., Fair, W. R. et al.: Bacillus Calmette-Guerin

therapy for superficial bladder cancer: a 10-year followup. *J Urol*, **147**: 1020, 1992

59. Kavoussi, L. R., Torrence, R. J., Gillen, D. P. et al.: Results of 6 weekly intravesical bacillus Calmette-Guerin instillations on the treatment of superficial bladder tumors. *J Urol*, **139**: 935, 1988

60. Bretton, P. R., Herr, H. W., Kimmel, M. et al.: The response of patients with superficial bladder cancer to a second course of intravesical bacillus Calmette-Guerin. *J Urol*, **143**: 710, 1990

61. Lamm, D. L., Blumenstein, B. A., Crissman, J. D. et al.: Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol*, **163**: 1124, 2000

62. Losa, A., Hurle, R., Lembo, A.: Low dose bacillus Calmette-Guerin for carcinoma in situ of the bladder: long-term results. *J Urol*, **163**: 68, 2000

63. Mack, D., Frick, J.: Five-year results of a phase II study with low-dose bacille Calmette-Guerin therapy in high-risk superficial bladder cancer. *Urology*, **45**: 958, 1995

64. Herr, H. W., Dalbagni, G.: Defining bacillus Calmette-Guerin refractory superficial bladder tumors. *J Urol*, **169**: 1706, 2003

65. Bui, T. T., Schellhammer, P. F.: Additional bacillus Calmette-Guerin therapy for recurrent transitional cell carcinoma after an initial complete response. *Urology*, **49**: 687, 1997

66. Catalona, W. J., Hudson, M. A., Gillen, D. P. et al.: Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. *J Urol*, **137**: 220, 1987

67. Herr, H. W., Sogani, P. C.: Does early cystectomy improve the survival of patients with high risk superficial bladder tumors? *J Urol*, **166**: 1296, 2001

68. Joudi, F. N., Smith, B. J., O'Donnell, M. A.: Final results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alpha-2B for reducing recurrence of superficial bladder cancer. *Urol Oncol*, **24**: 344, 2006

69. O'Donnell, M. A., Lilli, K., Leopold, C.: Interim results from a national multicenter phase II trial of combination bacillus Calmette-Guerin plus interferon alfa-2b for superficial bladder cancer. *J Urol*, **172**: 888, 2004

70. Colombo, R., Da Pozzo, L. F., Salonia, A. et al.: Multicentric study comparing intravesical chemotherapy alone and with local microwave hyperthermia for prophylaxis of recurrence of superficial transitional cell carcinoma. *J Clin Oncol*, **21**: 4270, 2003

71. Di Stasi, S. M., Giannantoni, A., Giurioli, A. et al.: Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol*, **7**: 43, 2006

Non-Muscle Invasive UC of Bladder

Low-risk

Intermediate-risk

High-risk

