

Strategies for Optimizing Bacillus Calmette-Guérin

Jay B. Shah, MD, Ashish M. Kamat, MD*

KEYWORDS

• Superficial bladder cancer • Non-muscle invasive bladder cancer • Bacillus Calmette-Guérin

KEY POINTS

- Bacillus Calmette-Guérin (BCG) is arguably the most effective intravesical treatment option for patients with intermediate-to-high risk superficial bladder cancer.
- A poor understanding of how and when BCG should be used can lead to suboptimal outcomes.
- Careful attention to patient and tumor characteristics can help identify candidates most likely to respond to BCG.
- Specific technical strategies can be employed to optimize BCG outcomes.

INTRODUCTION

As discussed throughout this issue, bladder cancer represents a significant physical and emotional burden to patients as well as a substantial financial burden to society (see the article by James and colleagues elsewhere in this issue). For patients at the extremes of risk, treatment algorithms are relatively straightforward; yet the outcomes are variable. Within the spectrum of non-muscle invasive bladder cancer (NMIBC), for patients with the lowest-risk tumors, the mainstay of treatment is complete transurethral resection (TUR) followed by surveillance (see the article by O'Neil and colleagues elsewhere in this issue); for patients with the most advanced risk tumors, radical cystectomy may be the only viable option (see the article by Daneshmand elsewhere in this issue). Among the areas of greatest uncertainty within the discipline of bladder cancer is the management of patients with NMIBC thought to have a high risk of recurrence and/or intermediate-to-high risk of progression. In this setting, intravesical immunotherapy with bacillus Calmette-Guérin (BCG) is the current gold standard therapy with the highest response rates; however, despite

its frequent use, it remains poorly understood, resulting in usage that is far from optimal.

In this article, the authors review the role that BCG has played in the management of bladder cancer over the last several decades and discuss specific approaches to optimize BCG. They focus on selection strategies to help practitioners identify candidates most likely to respond to BCG as well as on technical strategies to enhance the administration of the drug in such a way as to optimize the response rates, adverse effects, and outcomes (**Box 1**).

HISTORY OF BCG

The history of BCG dates back to the mid-1800s when scientists identified *Mycobacterium bovis* as the causative agent for bovine tuberculosis. Extrapolating from the successful use of the cowpox agent to develop a highly effective vaccine against smallpox in humans, clinical trials were performed in the late 19th century using *M bovis* to prevent tuberculosis in humans. Unfortunately, *M bovis* was proven to be highly virulent in people, and the approach was quickly abandoned.

Conflicts of Interest: Neither author has any relevant financial disclosures.

Department of Urology, MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1373, Houston, TX 77030, USA

* Corresponding author.

E-mail address: akamat@mdanderson.org

Urol Clin N Am 40 (2013) 211–218

<http://dx.doi.org/10.1016/j.ucl.2013.01.012>

0094-0143/13/\$ – see front matter © 2013 Elsevier Inc. All rights reserved.

Box 1
Strategies for practitioners

Tumor Characteristics

High-grade tumors with risk of recurrence/progression

No invasive component

No aberrant histology (micropapillary, small cell)

No T1 on prompt repeated TUR

Patient Characteristics

No active immunosuppression (eg, transplant)

Elderly okay

HIV (+) status okay

Personal history of tuberculosis okay

Technical Aspects

Give induction + maintenance (SWOG8507 protocol)

Minimize fluid intake in the hours before instillation

Start with empty bladder

Inspect voided urine for visible hematuria (routine urinalysis/dipstick not necessary)

Catheterize urethra atraumatically

Minimize lubricant (to avoid BCG clumping)

Avoid lidocaine (acidity degrades BCG)

No need for rotisserie-style turning

Statins/aspirin therapy okay to continue

Use antispasmodics for local symptoms

Use antipyretics for influenza-like symptoms

Give 1 dose of quinolone 6 hours after BCG

Admit suspected BCGosis/BCG sepsis for prompt workup and aggressive therapy

Several decades later, in 1908, a French bacteriologist, Albert Calmette and a veterinarian, Camille Guérin observed that incubation of *M bovis* in a glycerin-bile-potato medium rendered the bacteria slightly less virulent. Over the next 13 years, they serially passaged the bacteria 231 times, and in 1920 ultimately obtained a strain of *M bovis* that was avirulent in both animals and people.¹ This unique strain came to be known as bacillus of Calmette and Guérin (BCG).

Clinical trials using BCG as a vaccine against tuberculosis were initiated in 1921 but were not met with enthusiasm. Several early catastrophic events caused by cross-contamination with pathogenic strains led to public distrust of the agent. In one particularly disastrous situation in 1930 in Lübeck, Germany, 240 infants vaccinated shortly

after birth all developed tuberculosis, and 72 of these newborns died.² After several decades of disuse, widespread BCG vaccination was once again implemented outside of North America to minimize the postwar increase in tuberculosis expected after World War II. In the United States, BCG vaccination has never been widely adopted.

In the last half century, there has been renewed interest in the application of BCG to the management of patients with various medical disorders. As a potent stimulus of the immune system, BCG has been studied as a treatment option for diabetes mellitus, multiple sclerosis, and Parkinson disease.³⁻⁷

In the field of oncology, the first hint that BCG may have a therapeutic role was present in 1929 when Pearl, a pathologist, observed that tuberculosis patients had fewer malignancies than patients who died of other diseases.⁸ In the recent era, BCG has been studied to varying degrees in colorectal cancer, lung cancer, and melanoma.⁹⁻¹¹ Far and away, the most successful reapplication of BCG in the developed world has been in the field of bladder cancer.

The initial work suggesting a role for BCG within the bladder was performed in 1966 by Coe and Feldman, who demonstrated a consistent and potent T-helper type 1 immune response in pig bladders exposed to intravesical BCG.¹² 10 years later, Morales reported that 9 patients with superficial bladder cancer experienced a decrease in rate of tumor recurrence after intradermal and intravesical treatment with the Armand-Frappier strain of BCG.¹³ This led to a prospective, randomized clinical trial in 1980 that confirmed the beneficial findings of the smaller initial report.¹⁴ In this clinical trial, Lamm and colleagues demonstrated that treatment with a single percutaneous injection followed by 6 weekly intravesical administrations of BCG led to a decreased tumor recurrence rate at 1 year.

Since this initial trial, multiple investigators have undertaken larger trials aimed at more clearly identifying the optimal route, dosing, and scheduling parameters of BCG for patients with superficial bladder cancer.¹⁵⁻¹⁸ These refinements form the basis of current guidelines concerning the optimal use of BCG in the management of bladder cancer and are discussed further in the following sections. In fact, when BCG is used optimally, it has a definite role in reducing progression and deaths from bladder cancer.^{19,20}

OPTIMIZING PATIENT SELECTION FOR BCG THERAPY

As with all cancer therapies, successful use of BCG is critically dependent on careful patient selection.

For patients with NMIBC, the 2 main indications for the use of BCG are: adjunctive therapy to reduce the recurrence (and progression) of tumors after complete surgical resection of high-grade T_a or T₁ papillary tumors, and ii) primary treatment of carcinoma in situ (CIS).

Tumor Characteristics

For patients with low-grade papillary tumors, BCG therapy is typically not recommended, because, the most patients can be managed with surgical resection (plus or minus single-shot postoperative intravesical chemotherapy) alone. BCG has been used to treat residual tumor in patients with a high volume of disease within the bladder where surgical resection was deemed unachievable and/or for patients medically unfit for any operative procedures with complete response rates up to 66% and partial response rates up to 21%. In general, however, complete endoscopic control is recommended before BCG instillation.^{15,21,22}

For patients with muscle-invasive disease, there is currently no standard role for BCG; the use of BCG or any other intravesical therapy limited to the mucosal surface should be considered insufficient. In 1 report of 13 patients with muscle invasive bladder cancer treated with BCG, only 1 of 13 patients had neither local nor systemic disease recurrence; 10 of 13 patients developed systemic disease, and 7 patients died from metastases.²³ The delay to removal of the bladder that these intravesical therapies impose can have disastrous consequences for patients.

Similarly, for patients with high-risk histologic variants of bladder cancer, BCG therapy may not be sufficient even if the tumors are superficial at diagnosis. For example, in patients found to have micropapillary architecture, the risk of early spread to regional lymph nodes or distant sites is sufficiently high to make conservative local therapy unsafe.^{24,25} For patients with small cell histology or features of neuroendocrine differentiation, the propensity for early microscopic metastases also argues against the use of BCG and other conservative intravesical therapies.²⁶

Given the efficacy of BCG in superficial urothelial tumors and the danger of BCG in muscle-invasive tumors and high-risk histologic variants, it is critical to accurately establish the true stage of any bladder tumor before deciding on therapy. Current guidelines recommend a repeat TUR for all patients with T₁ bladder cancer.^{27,28} This is discussed in more detail by Ritch and colleagues elsewhere in this issue, but the guiding principle before intravesical therapy with BCG should be removal of all cancerous tissue, where feasible.

From the specific perspective of optimization of BCG, data from repeat TUR can help stratify patients into those at higher and lower risk of response to BCG. For example, data from Memorial Sloan Kettering Cancer Center (MSKCC) suggest that patients with initial T₁ disease found to have no tumor or stage less than or equal to T_a on repeat resection have a 19% chance of progression to muscle-invasive disease within 5 years, whereas those patients with evidence of continued T₁ disease at repeat TUR have an 80% chance of progression to muscle-invasive disease within 5 years.^{29,30} While these data are colored with the particular referral biases (and no use of maintenance), it nonetheless provides an impetus to use the repeat TUR data as 1 variable in discussions with patients.

Given the important prognostic information that can be gained from a second TUR, the authors' practice is to perform repeat TUR at 4 to 6 weeks on all patients with T₁ bladder cancer being considered for intravesical therapy. In those patients who have had a complete TUR at the first setting and yet have T₁ disease at repeat TUR (ie, early recurrence of aggressive disease), the authors counsel the patients on the potential high failure rate of BCG and the benefit of early radical cystectomy. However, this does not apply to delayed repeat TUR or repeat TUR where the quality of initial TUR is suspect.

Location of tumor within the bladder may also help predict response to BCG. Tumors located in the prostatic urethra may not have adequate exposure to BCG during instillation and may thus have worse outcomes.³¹ In these patients, it is the authors' practice to perform a limited TUR of prostate several weeks before initiation of BCG to facilitate surface contact of the medication with the urothelium of the prostatic urethra.

Patient Characteristics

Aside from staging and histologic concerns, patient selection must also be optimized. Because BCG is a live attenuated bacterium that exerts its effects primarily via a T_H1-driven response, the patient's immune status is highly relevant. Patients on active immunosuppressive medications following organ transplantation should be considered for BCG therapy only in select cases. Besides the risk from an infective viewpoint, the intense immunostimulatory cytotoxic response evoked by BCG may place the transplanted organ at risk of rejection.

Patients who are very elderly or have poor performance status may have weakened immune systems, but they are still eligible to receive BCG.^{32,33} Although this immunosenescence is

not a contraindication to BCG therapy, it may blunt the ability of BCG to evoke a sufficient immunostimulatory response. Patients with a history of human immunodeficiency virus (HIV) infection can usually also be safely treated with BCG. Given that most patients with HIV in the current era have intact immune systems, their bladder cancer can be managed the same as other patients, and similar outcomes can be expected.³⁴

Lastly, some practitioners mistakenly exclude patients with a personal history of tuberculosis from consideration for BCG therapy. Although there are no data specifically examining this, the authors and others have successfully treated these patients with BCG therapy. In fact, recent data suggest that pre-BCG priming enhances the response of patients.³⁵ However, given the prior exposure of these patients' immune systems to mycobacterial antigens, clinicians should be particularly vigilant about optimizing delivery with respect to the reduction of adverse effects.

OPTIMIZING ADMINISTRATION OF BCG

Although proper patient selection and use of maintenance therapy can improve overall outcomes with BCG therapy, there are also specific strategies in the administration of the drug that can increase the likelihood of successful intravesical treatment. The following paragraphs discuss aspects that can contribute to enhanced outcomes for patients treated with BCG therapy.

Strains

From the initial avirulent strain of *M bovis* cultured by Calmette and Guérin in 1920, multiple sub-strains of BCG have been isolated, and they have been used clinically to varying degrees. These BCG substrains are generally classified as either evolutionarily early (eg, Japan, Moreau, and Russian) or evolutionarily late (eg, Connaught, Danish, Glaxo, Phipps, and Tice). While the early and late substrains are known to be genetically distinct, the exact differences in antitumor activity, if any, remain unknown.

The wide geographic variation in success rates seen with large-scale clinical trials of BCG vaccination for tuberculosis has been postulated to be due at least in part to the variable clinical efficacy of different BCG substrains available locally around the world.^{36–40} In bladder cancer, recent preclinical investigations suggest that immunomodulatory potential differs between the various BCG substrains, but the clinical impact of these differences remains undefined.^{41,42} This should be kept in mind when comparing the results of

clinical trials of BCG in bladder cancer that have used different substrains of BCG.

Dosing

As with other avirulent bacteria prepared for therapeutic use, the dosing measure of BCG is the colony-forming unit (CFU). CFU varies from strain to strain, and a vial of BCG may contain variable amounts of BCG CFU based on lot date, manufacturer, and other factors. Current data suggest that an intravesical dose between 10^8 and 10^9 CFU is effective, but response has been reported with doses as low as 10^6 CFU. These variations explain the differences in recommended milligram dose between different preparations of BCG (eg, Sanofi-Pasteur 81 mg; Tice, 50 mg; Tokyo, 40 mg; Dutch [RIVM], 120 mg).

Duration

The first randomized trial of BCG therapy for bladder cancer examined the efficacy of a treatment regimen that consisted of 6 weekly intravesical instillations of BCG.¹⁴ Subsequent trials have investigated the effect of additional instillations given to boost the immune response. The initial 6-week treatment regimen is known as induction, and the subsequent instillations are referred to as maintenance therapy. In a large-scale cooperative group trial performed in the United States, Lamm and colleagues¹⁸ demonstrated that routine use of BCG maintenance therapy given as 3 weekly instillations at the 3-, 6-, 12-, 18-, 24-, 30- and 36-month time points decreased both recurrence and progression rates for patients with NMIBC when compared with patients who received induction BCG therapy alone. A European intergroup trial published in 2010 found that routine use of this same 3-week BCG maintenance regimen resulted in improved time to recurrence, disease-specific survival, and overall survival when compared with patients receiving intravesical chemotherapy.¹⁹ While future studies will likely continue to elucidate the specific details of the ideal maintenance regimen, the data currently available all suggest routine incorporation of maintenance therapy (using the SWOG 6+3 regimen) if BCG is to be used optimally.

Technique

It is important to optimize the administration of BCG in such a way that the bacterium has optimal propensity to adhere to the urothelium while at the same time causing the patients the least inconvenience/discomfort. In the authors' practice, patients presenting for treatment are instructed to minimize fluid intake in the hours before their

scheduled BCG instillation and to empty their bladders immediately before BCG instillation. The voided urine specimen is visually inspected to confirm absence of gross hematuria (microscopic hematuria or positive dipstick is not a contraindication to BCG). BCG mixed in 50 mL normal saline is then instilled intravesically via a urethral catheter. Minimizing fluid intake and starting with an empty bladder increase the likelihood of successful retention of the medication for the recommended duration of 2 hours. Other technical tips include minimal use of lubricating jelly (to avoid clumping of bacteria), avoidance of lidocaine (the acidic composition can be deleterious), and, of course, to perform the instillation only in the setting of atraumatic catheterization.

An interesting practice among some urologists is to have patients lie recumbent during the instillation period and to have them rotate every 15 minutes in an attempt to evenly expose the entire bladder surface to BCG. Although well-intentioned, this rotisserie method does not seem to have any basis in the scientific literature. The elastic nature of the compliant bladder suggests that it changes size to accommodate the volume of fluid inside. Therefore, unless the instillation was incorrectly done and a large air pocket was introduced in the bladder, serial turning of the patient is not necessary. It is the authors' practice to have patients lie recumbent for several minutes after instillation of the BCG and then to allow them to ambulate normally during the 2-hour retention period.

Usage of certain medications has been suggested to be a relative contraindication for BCG therapy. Because of the increased propensity for hematuria while on antiplatelet agents such as aspirin or clopidogrel, patients taking these medications are sometimes not considered candidates for BCG therapy or are instructed to discontinue the medications during BCG therapy. Similarly, given the documented ability of statin medications to induce a T_H2 immune response (and therefore limit the ability of BCG to induce a T_H1 response), it has been suggested that patients discontinue statins during BCG therapy.⁴³

The authors believe the risk of treatment-altering hematuria due to antiplatelet agents and the risk of immune steal due to statin therapy are both extremely low. There is even evidence to suggest that aspirin therapy may have a beneficial effect on the efficacy of BCG.⁴⁴ Similarly, since the initial report suggesting the negative effect of statin therapy on BCG efficacy, multiple authors have reported no impact of statin therapy on post-BCG outcomes.^{45,46} It is the authors' practice to have patients continue their usual medications during

BCG therapy. The authors generally do not initiate new medications or discontinue ongoing medications in most patients.

Reduction of Adverse Effects

A common misconception around the administration of BCG is that it is too toxic, and practitioners will often quote the data from the SWOG8507 study and cite that "less than 18% of patients finished 3 years of BCG."¹⁸ Although this is true of that study, it must be recognized that these were results from 2 decades ago, and much has been learned since then about optimal administration of BCG. In fact, now, a diligent practitioner should be able to reduce the BCG discontinuation rate in their patients to less than 15%. This has been borne out by the large-scale study⁴⁷ in which less than 10% of patients receiving a full dose therapy for 3 years discontinued BCG because of toxicity. This section discusses the spectrum of adverse effects that may result from BCG and provides strategies to minimize these effects. Most of these side effects can be prevented or managed with minor interventions without the need for termination of BCG therapy. However, the most serious adverse effects demand immediate recognition and prompt initiation of aggressive measures.

Irritative voiding symptoms (dysuria, frequency, and urgency) and low-grade fever are the most commonly reported complaints immediately after BCG instillation.⁴⁸ In most cases, these resolve within 48 hours and do not need intervention. Many practitioners anecdotally regard the transient local symptoms and influenza-like symptoms as an encouraging sign of the intended immune activation effects of BCG therapy. Antispasmodic medications and over-the-counter antipyretics can be used with good effect to control the symptoms. In the authors' practice, patients who experience moderate or severe irritative voiding symptoms are prescribed antispasmodic medication for the acute episode, and they are also instructed to take the antispasmodic medication before subsequent BCG administrations.

The most serious adverse effects with BCG therapy are seen when the medication is inadvertently absorbed into the bloodstream. This allows the *M bovis* bacteria to access the systemic circulation. Depending on the amount of BCG absorbed and the extent of previous immune priming (eg, personal history of tuberculosis), the sequela of systemic BCG spread can range from prolonged pyrexia (BCGosis) to a severe systemic inflammatory response syndrome (BCG sepsis) to death.⁴⁸ Given these dangerous possibilities, it

is imperative that practitioners employ all means to prevent systemic BCG absorption. For this reason, BCG administration should be postponed for any patient with visible hematuria. For patients with a history of tuberculosis, the authors also routinely perform urine dipstick to assess for microscopic hematuria, as absorption of even small amounts of BCG can incite a cytokine storm from the hypersensitized immune systems of these patients.

In all patients, urethral catheterization should be performed as atraumatically as possible, and BCG administration should be postponed if bleeding is triggered during catheterization. BCG should not be given in the presence of a urinary tract infection. During an episode of urinary tract infection, the risk for BCG intravasation is greater. This is because the urothelium is more permeable, and the surface vasculature is predisposed to bleeding more readily. For the treatment of urinary tract infections in patients receiving intravesical BCG, it was previously suggested that use of quinolone antibiotics was to be avoided because of their antimycobacterial activity.⁴⁹ More recently, several investigators have shown that short-term administration of a quinolone decreases the incidence of moderate-to-severe adverse events (especially grade 3 events) after BCG instillation.^{50,51} For this reason, it is the authors' practice to instruct all patients to take 1 dose of a quinolone antibiotic 6 hours after BCG instillation. In the authors' experience, this practice increases patient comfort and decreases the likelihood of patient dropout from BCG therapy.

FUTURE DIRECTIONS

The integration of BCG into the management of patients with superficial bladder cancer has been among the most important advances in the field over the past several decades. Based on the results of multiple large-scale clinical trials conducted in the United States, Europe, and Asia, BCG therapy is now accepted as having a clear role in reducing recurrence, progression, and death from bladder cancer.

In the coming decades, the authors anticipate there will be increasing emphasis on developing accurate predictors of response to BCG therapy. Although several algorithms based on clinical parameters have been developed,^{52,53} the recent acceleration in technologies for gene expression profiling suggests that future efforts will focus on developing molecular markers that predict BCG sensitivity and that allow for personalized cancer therapy. Multiple avenues are being investigated for use as potential molecular biomarkers of BCG sensitivity. These include tumor-associated markers (pRb, CD68, Bcl-2, Bax markers of gene

expression and methylation), urinary markers (interleukin [IL]-2, IL-8, IL-18, tumor necrosis factor- α) and serum markers (single nucleotide polymorphisms in multiple DNA repair, inflammation, cell cycle, and apoptosis pathways).⁵⁴⁻⁵⁷ At MD Anderson, the authors have recently performed a prospective clinical trial investigating the concept of molecular recurrence using fluorescence in situ hybridization to predict response to BCG therapy.⁵⁸ The authors are hopeful that this approach may help counsel patients undergoing BCG therapy, and it may also provide a role in future clinical trial design.

SUMMARY

For the treatment of patients with superficial bladder cancer and a moderate-to-high risk of tumor recurrence or progression, intravesical BCG has been the key development of the last generation because of its ability to decrease tumor recurrence, progression, and death from bladder cancer. However, because of its bacterial composition and its intravesical route of delivery, BCG has also brought with it a novel set of challenges that require thoughtful planning and vigilant monitoring. An understanding of when, to whom, and how BCG should be given is critical if optimal outcomes are to be achieved. As the ability to better select patients for BCG therapy continues to be refined in the future, outcomes with this unique treatment will only continue to improve.

REFERENCES

1. Guerin C. Early history of BCG. In: Rosenthal SR, editor. BCG vaccination against tuberculosis. Boston: Little Brown; 1957. p. 48-53.
2. Rosenthal SR. BCG vaccination against tuberculosis. Boston: Little, Brown & Company; 1957.
3. Faustman DL, Wang L, Okubo Y, et al. Proof-of-concept, randomized, controlled clinical trial of bacillus-Calmette-Guerin for treatment of long-term type 1 diabetes. *PLoS One* 2012;7(8):e41756. <http://dx.doi.org/10.1371/journal.pone.0041756>.
4. Ristori G, Buzzi MG, Sabatini U, et al. Use of Bacille Calmette-Guèrin (BCG) in multiple sclerosis. *Neurology* 1999;53(7):1588-9.
5. Paolillo A, Buzzi MG, Giugni E, et al. The effect of Bacille Calmette-Guèrin on the evolution of new enhancing lesions to hypointense T1 lesions in relapsing remitting MS. *J Neurol* 2003;250(2):247-8.
6. Rutschmann OT, McCrory DC, Matchar DB. Immunization Panel of the Multiple Sclerosis Council for Clinical Practice Guidelines: Immunization and MS: a summary of published evidence and recommendations. *Neurology* 2002;59(12):1837-43.

7. Yong J, Lacañ G, Dang H, et al. BCG Vaccine-induced neuroprotection in a mouse model of parkinson's disease. *PLoS One* 2011;6(1):e16610. <http://dx.doi.org/10.1371/journal.pone.0016610>.
8. Pearl R. Cancer and tuberculosis. *Am J Hyg* 1929;9: 97–159.
9. Mosolits S, Nilsson B, Mellstedt H. Towards therapeutic vaccines for colorectal carcinoma: a review of clinical trials. *Expert Rev Vaccines* 2005;4(3): 329–50.
10. Miyazawa N, Suemasu K, Ogata T, et al. BCG immunotherapy as an adjuvant to surgery in lung cancer: a randomized prospective clinical trial. *Jpn J Clin Oncol* 1979;9(1):19–26.
11. Lu CY, Lin GC, Gu JZ, et al. A preliminary study of BCG adjuvant therapy in oral and maxillofacial malignant melanoma. *Shanghai Kou Qiang Yi Xue* 1994;3(3):144–5 [in Chinese].
12. Coe JE, Feldman JD. Extracutaneous delayed hypersensitivity, particularly in the guinea-pig bladder. *Immunology* 1966;10(2):127–36.
13. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guérin in the treatment of superficial bladder tumors. *J Urol* 1976;116(2):180–3.
14. Lamm DL, Thor DE, Harris SC, et al. BCG immunotherapy of superficial bladder cancer. *J Urol* 1980; 124:38–40.
15. Brosman SA. Experience with bacillus Calmette-Guérin in patients with superficial bladder carcinoma. *J Urol* 1982;128(1):27–30.
16. Bretton PR, Herr HW, Kimmel M, et al. The response of patients with superficial bladder cancer to a second course of intravesical BCG. *J Urol* 1990; 143:710–3.
17. Catalona WJ, Hudson MA, Gillen DP, et al. Risks and benefits of repeated courses of intravesical BCG for superficial bladder cancer. *J Urol* 1987;137:220–4.
18. Lamm DL, Blumenstein BA, Crismon JD, et al. Maintenance BCG immunotherapy for recurrent TA, T1 and CIS TCC of the bladder: a randomised Southwest Oncology Group Study. *J Urol* 2000;163:1124–9.
19. Sylvester RJ, Brausi MA, Kirkels WJ, et al. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guérin, and bacillus Calmette-Guérin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. *Eur Urol* 2010;57(5):766–73.
20. Herr HW, Schwalb DM, Zhang ZF, et al. Intravesical bacillus Calmette-Guérin therapy prevents tumor progression and death from superficial bladder cancer: ten-year follow-up of a prospective randomized trial. *J Clin Oncol* 1995;13(6):1404–8.
21. Schellhammer PF, Ladaga LE, Fillion MB. Bacillus Calmette-Guérin for superficial transitional cell carcinoma of the bladder. *J Urol* 1986;135(2):261–4.
22. Akaza H, Hinotsu S, Aso Y, et al. BCG treatment of existing papillary cancer and carcinoma in situ of the bladder. *Cancer* 1995;75:552–9.
23. Rosenbaum RS, Park MC, Fleischmann J. Intravesical bacille Calmette-Guérin therapy for muscle invasive bladder cancer. *Urology* 1996;47(2):208–11.
24. Kamat AM, Gee JR, Dinney CP, et al. The case for early cystectomy in the treatment of nonmuscle invasive micropapillary bladder carcinoma. *J Urol* 2006; 175(3 Pt 1):881–5.
25. Kamat AM, Dinney CP, Gee JR, et al. Micropapillary bladder cancer: a review of the University of Texas M. D. Anderson Cancer Center experience with 100 consecutive patients. *Cancer* 2007;110(1):62–7.
26. Lynch SP, Shen Y, Kamat A, et al. Neoadjuvant chemotherapy in small cell urothelial cancer improves pathologic downstaging and long-term outcomes: results from a retrospective study at the MD Anderson Cancer Center. *Eur Urol* 2012 Apr 17. [Epub ahead of print].
27. American Urologic Association. The Management of Bladder Cancer: Diagnosis and treatment recommendations. Available at: <http://www.auanet.org/content/clinical-practice-guidelines/clinical-guidelines/main-reports/bladcan07/chapter1.pdf>. Accessed January 23, 2012.
28. Babjuk M, Oosterlinck W, Sylvester R, et al. European Association of Urology (EAU): EAU guidelines on nonmuscle-invasive urothelial carcinoma of the bladder, the 2011 update. *Eur Urol* 2011;59(6):997–1008.
29. Herr HW. The value of a second transurethral resection in evaluating patients with bladder tumors. *J Urol* 1999;162:74.
30. Dalbagni G, Herr HW, Reuter VE. Impact of a second transurethral resection on the staging of T1 bladder cancer. *Urology* 2002;60:822.
31. Gofrit ON, Pizov G, et al. Prostatic urothelial carcinoma: is transurethral prostatectomy necessary before bacillus Calmette-Guérin immunotherapy? *BJU Int* 2009;103(7):905–8.
32. Joudi FN, Smith BJ, O'Donnell MA, et al. The impact of age on the response of patients with superficial bladder cancer to intravesical immunotherapy. *J Urol* 2006;175(5):1634–9.
33. Shariat SF, Milowsky M, Droller MJ. Bladder cancer in the elderly. *Urol Oncol* 2009;27(6):653–67.
34. Gaughan EM, Dezube BJ, Bower M, et al. HIV-associated bladder cancer: a case series evaluating difficulties in diagnosis and management. *BMC Urol* 2009;31:9–10.
35. Biot C, Rentsch CA, Gsponer JR, et al. Pre-existing BCG-specific T cells improve intravesical immunotherapy for bladder cancer. *Sci Transl Med* 2012; 4(137):137ra72.
36. Colditz GA, Brewer TF, Berkey CS. Efficacy of BCG vaccine in the prevention of tuberculosis. *J Am Med Assoc* 1994;271(9):698–702.

37. Fine PE. Variation in protection by BCG: implications of and for heterologous immunity. *Lancet* 1995; 346(8986):1339–45.
38. Hart PD, Sutherland I. BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life. Final report of the Medical Research Council. *Br Med J* 1977;2(6082):293–5.
39. Comstock GW, Palmer CE. Long-term results of BCG in the southern United States. *Am Rev Respir Dis* 1966;93(2):171–83.
40. Tuberculosis Prevention Trial. Trial of BCG vaccines in south India for tuberculosis prevention. *Indian J Med Res* 1979;70:349–63.
41. Secanella-Fandos S, Luquin M, Julián E. Connaught and Russian showed the highest direct antitumoral effects among different BCG substrains. *J Urol* 2012. <http://dx.doi.org/10.1016/j.juro.2012.09.049>. pii: S0022-5347(12)04880-X.
42. Gsponer JR, Biot C, Bisiaux A, et al. Immunotherapy of bladder cancer using bacillus Calmette Guerin (BCG): generation of cytotoxic T-cells is BCG strain dependent. American Association for Cancer Research 2012 Meeting (abstract # 5386).
43. Hoffman P, Roumeguere T, van Velthoven R. Use of statins and outcome of BCG treatment for bladder cancer. *N Engl J Med* 2006;355:2705–7.
44. Gee JR, Jarrard DF, Bruskewitz RC, et al. Reduced bladder cancer recurrence rate with cardioprotective aspirin after intravesical bacille Calmette-Guérin. *BJU Int* 2009;103(6):736–9.
45. Skolarus TA, Lee EW, Virgo KS, et al. Intravesical bacille Calmette-Guérin therapy for nonmuscle-invasive bladder cancer: effects of concurrent statin therapy. *J Am Coll Surg* 2009;209(2):248–53.
46. Berglund RK, Savage CJ, Vora KC, et al. An analysis of the effect of statin use on the efficacy of bacillus calmette-guerin treatment for transitional cell carcinoma of the bladder. *J Urol* 2008;180(4):1297–300.
47. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette-Guérin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur Urol* 2013;63(3):462–72.
48. Rischmann P, Desgrandchamps F, Malavaud B, et al. BCG intravesical installations: recommendations for side-effects management. *Eur Urol* 2000; 37(Suppl 1):33–6.
49. Durek C, Rusch-Gerdes S, Jocham D, et al. Interference of modern antibacterials with bacillus Calmette-Guérin viability. *J Urol* 1999;163:1959–62.
50. Colombel M, Saint F, Chopin D, et al. The effect of ofloxacin on bacillus Calmette-Guerin induced toxicity in patients with superficial bladder cancer: results of a randomized, prospective, double-blind, placebo controlled, multicenter study. *J Urol* 2006; 176(3):935–9.
51. Damiano R, De Sio M, Quarto G, et al. Short-term administration of prulifloxacin in patients with nonmuscle-invasive bladder cancer: an effective option for the prevention of bacillus Calmette-Guérin-induced toxicity? *BJU Int* 2009;104(5):633–9.
52. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. *Eur Urol* 2006;49(3):466–77.
53. Fernandez-Gomez J, Madero R, Solsona E, et al. Predicting nonmuscle-invasive bladder cancer recurrence and progression in patients treated with bacillus Calmette-Guerin: the CUETO scoring model. *J Urol* 2009;182(5):2195–203.
54. Thalmann GN, Sermier A, Rentsch C, et al. Urinary Interleukin-8 and 18 predict the response of superficial bladder cancer to intravesical therapy with bacillus Calmette-Guerin. *J Urol* 2000;164(6): 2129–33.
55. Saint F, Salomon L, Quintela R, et al. Do prognostic parameters of remission versus relapse after bacillus Calmette-Guérin (BCG) immunotherapy exist? Analysis of a quarter century of literature. *Eur Urol* 2003;43(4):351–60 [discussion: 360–1].
56. Ajili F, Kaabi B, Darouiche A, et al. Prognostic value of Bcl-2 and Bax tumor cell expression in patients with non-muscle invasive bladder cancer receiving bacillus Calmette-Guerin immunotherapy. *Ultrastruct Pathol* 2012;36(1):31–9.
57. Lima L, Dinis-Ribeiro M, Longatto-Filho A, et al. Predictive biomarkers of bacillus Calmette-Guérin immunotherapy response in bladder cancer: where are we now? *Adv Urol* 2012;2012:232609.
58. Kamat AM, Dickstein RJ, Messetti F, et al. Use of fluorescence in situ hybridization to predict response to bacillus Calmette-Guérin therapy for bladder cancer: results of a prospective trial. *J Urol* 2012; 187(3):862–7.