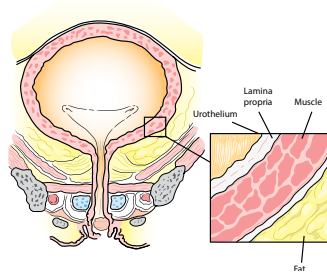


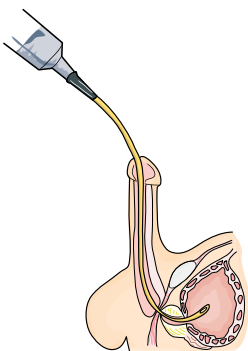
Introduction

A large majority of patients who develop bladder cancer have what is known as ‘non muscle invasive bladder cancer’ or ‘NMIBC’. This terminology comes from the fact that the tumor has not yet invaded into the true muscle layer of the bladder. When detected at this relatively early stage it is often possible, with the appropriate combination of treatments, to save the patient’s bladder.



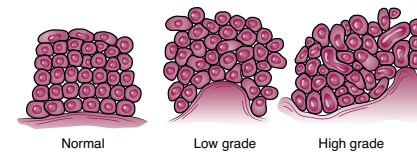
The first step is complete removal of all visible disease within the bladder. This is achieved with a transurethral resection of the tumor, also called TURBT. For some patients, this may require more than one surgery, especially if the tumor is high grade and involving more than the very first layer of the bladder. After this has been achieved and the bladder has healed, the appropriate treatment may be with intravesical instillation of Bacillus Calmette-Guerin or BCG. BCG is a form of the tuberculosis bacteria and originated as a vaccination against tuberculosis. After decades of detailed investigation including large trials in multiple countries that have tested BCG against various other agents, it currently remains the most effective therapy for NMIBC. However, as with any treatment, it works best when used appropriately – i.e for the right patient in the right manner.

It is instilled into the bladder with a urethral catheter (intravesical) in the office for several treatments. BCG works locally in the bladder to stimulate the body’s own immune system to fight off the cancer cells in the bladder. Because it stimulates the immune system, it is considered an immunotherapy (as opposed to chemotherapy). It works to activate the body’s immune system to kill cancer cells without harming the normal cells. In addition, BCG is instilled locally in the bladder cannot reach other cells in the body.



Who is eligible for BCG?

Intravesical immunotherapy with BCG is effective if the tumor is non-muscle invasive. These tumors are often divided into risk groups (low-risk, intermediate-risk and high-risk) based on the risk of recurrence (the likelihood the tumor will return) and the risk of progression (the likelihood the tumor will get worse and potentially become invasive or spread).



[1] There are various factors that your urologist will consider when making this risk assessment – such as on how big the tumor is, if it is a first time tumor or a tumor that has

regrown, the length of time it took for the tumor to regrow, if the bladder cancer is pure urothelial cancer, as well as the location of the tumor and the grade of the tumor.

In general, bladder cancer tumors can be low grade and high grade. Low grade cancers can recur often, but are less likely to progress. Thus the goal of therapy with these tumors is mainly to reduce the frequency of recurrence. The high grade tumors can progress and become muscle invasive or metastasize. In treating this type of tumor the goal is to not only prevent recurrence but especially to prevent progression.

Most patients with the intermediate-risk and high-risk non-muscle invasive bladder cancers will be candidates for immunotherapy with BCG. However, based on individualized risk assessment, other intravesical treatments or even bladder removal (cystectomy) may be recommended.

What are the benefits of BCG for patients?

BCG is relatively non-invasive and used to directly treat the bladder lining. BCG intravesical treatment for non-muscle invasive bladder cancer is the most effective treatment that exists for reducing the recurrence and progression of bladder tumors. [1] In patients who respond appropriately, BCG can be a life-saving treatment that reduces death from bladder cancer. Over half of patients have a complete response to BCG

Intravesical Immunotherapy with BCG

without tumor recurrence for an extended period of time. In order to achieve this, it is crucial that patients received at least one course of induction BCG (6 weeks) and at least one course of maintenance BCG (at least 3 weeks) to allow the immune response to reach its peak.

BCG treatments do not require any additional adjunct medications such as urinary alkalization. Although BCG has some side effects, under the guidance of a diligent urologist the incidence of severe side effects are uncommon and most patients are able to successfully complete their therapy course. When mild BCG side effects do occur, they are often treated with over the counter medications.

After BCG treatment, patients must be followed closely with regular cystoscopy surveillance to detect any cancer recurrence or development of a new primary tumor in the bladder or elsewhere within the urogenital tract (ureters, bladder, urethra).

What are the risks?



BCG often causes some burning with voiding after the treatments. It can also cause some urgency and frequency. These often resolve a few days after the treatment, but the symptoms can increase in intensity after each instillation.

It is important to note that there may be no correlation of side effects with the dose and duration of the BCG maintenance. [2] Most patients do well with BCG and a small minority discontinue treatment because of side effects. [3]

It is normal for patients who receive a BCG instillation to have some transient flu-like symptoms (fever <101.5F, chills, malaise, joint aches, and fatigue). However, if BCG gets into the blood stream it can cause a bad infection or even sepsis. Symptoms of sepsis are flu-like symptoms for greater than 72 hours or a fever greater than 101.5F. With the appropriate precautions, such as delaying instillation if you see visible blood in the urine, making sure there is no trauma during instillation, etc, it is very rare for BCG to get in the blood stream.

BCG can cause infections in the other parts of the genitourinary system that are connected to the bladder such as the prostate and testicles. This can cause prostatitis or orchitis, but these are usually managed conservatively.

The other risk is that the BCG may not work. After BCG other treatments may be needed. If the BCG does work it will often be recommended to continue with maintenance BCG treatments.

What can be done for symptoms associated with BCG?

Make sure your bladder is emptied right before the BCG instillation.

Limitation of fluids before the instillation can be helpful. Limiting fluids will decrease urine production during the time you are holding the treatment in your bladder. This will decrease your discomfort while you are being treated.



You can ask your doctor for antispasmodic medication if you are having a lot of bladder and urethral irritation symptoms known as lower urinary tract symptoms. These symptoms are common, but are an uncommon cause of BCG discontinuation.

If you have a mild fever or flu-like symptoms it is okay to take medication to reduce fever, such as acetaminophen.

What factors can influence BCG effectiveness?

Some antibiotics may weaken effects of BCG. If you are given antibiotics it is recommend you do not take them in the 24 hours before or within 6 hours after BCG unless specifically instructed by your doctor.

Too much lubricating jelly that is used to insert the catheter should be avoided. Excess jelly can trap the BCG and keep it from treating the cancer. [4]

In addition lidocaine and lidocaine jellies should be avoided with the administration of BCG. The lidocaine can degrade the BCG and this can decrease the effectiveness of the BCG. [4]

What is the maintenance schedule for BCG?

In addition to the induction course of BCG, BCG maintenance is important in reducing bladder tumor recurrence and progression. With BCG induction and maintenance 60% of patients with an upfront tumor response will be tumor free for more than 5 years. [1] Also, the addition of maintenance decreases the risk of disease progression by 35%. [5] After the first six weeks of BCG treatments if there is no tumor on the follow up cystoscopy it is likely BCG maintenance treatments will be recommended. The most effective schedule would be BCG maintenance administered at months 3, 6, 12, 18, 24, 30, 36. At each of these time points of BCG is instilled once a week for three weeks (i.e. at 3 months there would be 3 weekly instillations). The table on the next page shows the schedule of BCG induction,



maintenance and the cystoscopies that are needed to stay on the treatment plan. The follow up schedule of treatments is continued based on the risk category of the bladder cancer (for at least 1-year in intermediate-risk patients and the full 3-years in high-risk patients). If you are not offered BCG after the initial 6-week induction period, it is prudent to ask your provider if BCG maintenance would be beneficial in your case.

are advised not to engage in sexual activity for 48 hours after the treatment. At other time points during the treatment it is recommend you use a barrier, such as a condom, be used to prevent BCG transmission to your partner. Women are advised not to become pregnant while on BCG therapy.



Sex after BCG: Is there a risk to my partner? How long should I wait?

Both men and women undergoing BCG treatments

Why do I have to hold it in so long? How long does BCG need to be held in the bladder?

BCG should stay in the bladder for 90 mins to 2 hours after it is administered. This allows time for the BCG to make adequate contact with the tumor cells and initiate the immune response. [5]



Intravesical BCG Treatment/Cystoscopy Schedule

Month	BCG Introduction		
	BCG #1		
	BCG #2		
	BCG #3		
	BCG #4		
	BCG #5		
	BCG #6		
3	Approximately 6-8 weeks from 6th BCG	Cystoscopy	
	BCG Maintenance #1 - start within 0 to 3 weeks		
	BCG #1		
	BCG #2		
	BCG #3		
6	Approximately 9-12 weeks from last BCG	Cystoscopy	
	BCG Maintenance #2 - start within 0 to 3 weeks		
	BCG #1		
	BCG #2		
	BCG #3		
9	Approximately 9-12 weeks from last BCG	Cystoscopy	
12	~3 months from last Cystoscopy	Cystoscopy	
	BCG Maintenance #3 - start within 0 to 3 weeks		
	BCG #1		
	BCG #2		
	BCG #3		

How does changing positions while the BCG is in my bladder help the BCG work?

Rotating positions when BCG is instilled was previously recommended. However, there is no current evidence to support the practice of changing positions with intravesical BCG. [5]

Copy and cut out this Intravesical BCG Treatment/Cystoscopy Schedule to keep track of your treatments.



Note: Your doctor may modify schedule based on your individual needs.

AUTHOR BIOGRAPHIES



Ashish Kamat, MD
MD Anderson Cancer Center

Ashish M. Kamat is Professor of Urologic Oncology (Surgery) and Cancer Research at M.D.

Anderson Cancer Center; Associate Head of the Cancer Center, Reliance Foundation Hospital in Mumbai, and President of the International Bladder Cancer Group (IBCG). He is Associate Editor for European Urology Oncology, served as the Director of the MD Anderson Urologic Oncology Fellowship from 2005-2016 and is a graduate of the AUA Leadership Program.

Dr. Kamat's focus in urologic oncology is on bladder cancer, especially immunotherapy and organ sparing therapies. He maintains an active research portfolio in this area. His research laboratory focuses on identifying and developing predictive markers of response to therapy, and research into mechanisms of inducible cancer stem cells. These findings have been published in high impact journals and he has over 275 publications to his credit. Dr. Kamat has received commendations for his educational efforts, is listed in 'Who's Who in Medicine' and 'Best Doctors in America', and has won the 'Compassionate Doctor Award' from patient groups. He has been involved with BCAN since its inception and is a strong advocate for patients.



Janet Krukeja, MD
MD Anderson Cancer Center

Dr. Krukeja attended the University of Missouri-Kansas City 6-year combined

BLA/MD program. She then completed her residency in Urology at the University of Rochester Medical Center in Rochester, NY. While in residency she was able to earn her MPH from the University of Rochester School of Medicine and Dentistry. She is currently a Urologic Oncology fellow working on clinical trials, health services research and translational research at MD Anderson Cancer Center. She has interest in research for all genitourinary malignancies.

References:

1. Sylvester RJ, van der MEIJDEN AP, Lamm DL. 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* 2002;168:1964-70.
2. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU Cancers Group randomized study of maintenance bacillus Calmette-Guerin 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;63:462-72.
3. Witjes JA, Palou J, Soloway M, et al. Current clinical practice gaps in the treatment of intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC) with emphasis on the use of bacillus Calmette-Guerin (BCG): results of an international individual patient data survey (IPDS). *BJU Int* 2013;112:742-50.
4. Lamm DL, Blumenstein BA, Crissman JD, 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* 2000;163:1124-9.
5. Shah JB & Kamat AM. Strategies for Optimizing Bacillus Calmette-Guerin. *Urologic Clinics of North America*. May 2013; 40 (2):211-218.

Intravesical BCG Treatment/Cystoscopy Schedule

15	Approximately 9-12 weeks from last BCG	Cystoscopy		
18	~3 months from last Cystoscopy	Cystoscopy		
	BCG Maintenance #4 - start within 0 to 3 weeks			
	BCG #1			
	BCG #2			
21	Approximately 9-12 weeks from last BCG	Cystoscopy		
	24	~3 months from last Cystoscopy	Cystoscopy	
		BCG Maintenance #5 - start within 0 to 3 weeks		
BCG #1				
21	Approximately 9-12 weeks from last BCG	Cystoscopy		
	24	~3 months from last Cystoscopy	Cystoscopy	
		BCG Maintenance #5 - start within 0 to 3 weeks		
BCG #1				
30	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #6 - start within 0 to 3 weeks			
	BCG #1			
30	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #6 - start within 0 to 3 weeks			
	BCG #1			
36	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #7 - start within 0 to 3 weeks			
	BCG #1			
36	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #7 - start within 0 to 3 weeks			
	BCG #1			
36	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #7 - start within 0 to 3 weeks			
	BCG #1			
36	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #7 - start within 0 to 3 weeks			
	BCG #1			
36	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #7 - start within 0 to 3 weeks			
	BCG #1			
36	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #7 - start within 0 to 3 weeks			
	BCG #1			
36	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #7 - start within 0 to 3 weeks			
	BCG #1			
36	Approximately 21-24 weeks from last BCG	Cystoscopy		
	BCG Maintenance #7 - start within 0 to 3 weeks			
	BCG #1			

Note: Your doctor may modify schedule based on your individual needs.