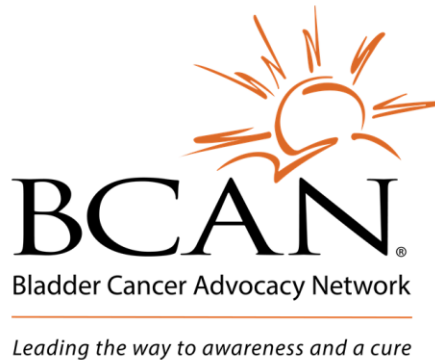


## TREATMENT TALKS

What you need to  
know about  
maintenance therapy  
for bladder cancer



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### Introduction

**Morgan Stout:** Maintenance therapy is a treatment of cancer with medication typically following an initial round of treatment. Maintenance treatment may include chemotherapy, immunotherapy, hormonal therapy, or targeted therapy. Maintenance therapy is used to prevent or delay the cancer's return if the cancer is in complete remission after the initial treatment. Complete remission means that the doctors cannot find any cancer, and you have no symptoms. Another use of maintenance therapy is to slow the growth of advanced cancer after initial treatment. This can help shrink the cancer, which is called partial remission, in this situation maintenance therapy is not used to cure the cancer, but it can lengthen a person's life. You can have maintenance therapy for a long time in either of these situations.

We're delighted to have two leading experts with us today from the University of Washington in Seattle, urologist Dr. Jonathan Wright, and medical oncologist Dr. Petros Grivas. I'm also joined today by two patient advocates, Joseph King and Gail Dykstra, who you will meet after the doctors' presentations. They will share their experiences with their maintenance therapies. I'm going to turn it over to Dr. Wright now.

## Maintenance for NMIBC

**Dr. Jonathan Wright:** Thank you very much, Morgan, appreciate it, and thanks so much for BCAN for putting this together. I'm going to talk about maintenance therapy for non-muscle invasive bladder cancer. As Morgan mentioned, it's important to know the distinction between what we call induction treatment for bladder cancer non-muscle invasive, and maintenance intra-vesical therapy. Induction therapy for non-muscle invasive bladder cancer is weekly installations for six weeks following the primary resection of the bladder tumor. Then the maintenance therapy is given to help keep the cancer from coming back after it has disappeared following the initial induction therapy. So after we look back in, we see no evidence of recurrence after completing the six week induction treatment, we then talk about doing maintenance therapy afterwards to help prevent the risk of recurrence, because certainly we know that with non-muscle invasive bladder cancer recurrences are quite common.

### What is Maintenance Therapy?

#### Induction vs. Maintenance Intra-vesical Therapy

For patients with non-muscle invasive bladder cancer (NMIBC), we talk about **induction** and **maintenance** intra-vesical therapies

- > **Induction:**
  - Weekly installations for 6 weeks following bladder tumor resection
- > **Maintenance:**
  - Treatment that is given to help keep cancer from coming back after it has disappeared following the initial induction therapy



This is a schedule that is put together by BCAN, you can download this on their website. It is an outstanding layout for what most of us do for maintenance therapy. You can actually print it out, cut this part out from the sheet, and take it to your doctor if you're receiving maintenance therapy. I'm going to spend a couple of minutes just walking through the general principle of it. Again, here is the induction BCG done for six weeks, and then you have, at about the three month point they call it, about six

to eight weeks after finishing these six weeks, six weeks and six weeks makes three months, you have the cystoscopy done, assuming that's negative, the maintenance program starts in. Typically, within a week or so or up to three weeks of having the cystoscopy you'll get three weekly treatments, so next three weeks of the first round of maintenance, then about three months later you have your next cystoscopy done, and then the second round of maintenance starts, again in three weekly installations.

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	
6	Approximately 9-12 weeks from last BCG	
	BCG Maintenance #2 - start within 0 to 3 weeks	
	BCG #1	
9	Approximately 9-12 weeks from last BCG	
	BCG Maintenance #3 - start within 0 to 3 weeks	
	BCG #1	
12	-3 months from last Cystoscopy	
	BCG Maintenance #4 - start within 0 to 3 weeks	
	BCG #1	
15	Approximately 9-12 weeks from last BCG	
	Cystoscopy	
	BCG Maintenance #5 - start within 0 to 3 weeks	
18	-3 months from last Cystoscopy	
	Cystoscopy	
	BCG Maintenance #6 - start within 0 to 3 weeks	
21	Approximately 9-12 weeks from last BCG	
	Cystoscopy	
	BCG Maintenance #7 - start within 0 to 3 weeks	
24	-3 months from last Cystoscopy	
	Cystoscopy	
	BCG Maintenance #8 - start within 0 to 3 weeks	
30	Approximately 21-24 weeks from last BCG	
	Cystoscopy	
	BCG Maintenance #9 - start within 0 to 3 weeks	
36	Approximately 21-24 weeks from last BCG	
	Cystoscopy	
	BCG Maintenance #10 - start within 0 to 3 weeks	

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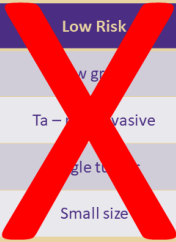

At this point, we then transition to getting the BCG maintenance on a six month schedule typically. So for patients that are getting cystoscopies every three months they'll start having a cystoscopy that doesn't basically followed with maintenance, and then a cystoscopy that is followed with maintenance. You can see this continuing out, cystoscopy three months later, a cysto, maintenance BCG, a cysto, another cysto three months later, and typically the goal of continuing it out to about three years of maintenance BCG, each time with three weeks. These are two of the authors that put this together along with BCAN, and I think it's important to recognize that we do modify the schedule based on your individual needs, and I'm going to come back to that concept later on, because this is a guide for what we do for patients.

So who with non-muscle invasive bladder cancer needs maintenance therapy? Not all patients with non-muscle invasive disease need maintenance therapy. We try to put people in to a different risk category, which then drives whether or not they get maintenance therapy. A low risk individual is one that has a low grade tumor, it's Ta, it's non-invasive, it's single, and it's small, less than two or three centimeters. This is a low risk individual as far as non-muscle invasive bladder cancer. These patients need neither induction nor maintenance therapy.

**NMIBC Risk Categories**

Guides who needs maintenance therapy

Low Risk	Intermediate Risk	High Risk
Low grade	Low grade	High grade
Ta – non invasive	Ta – non invasive	T1 – invading 1 <sup>st</sup> layer
Single tumor	Multiple tumors	CIS
Small size	Large size	
Don't need induction or maintenance therapy	May receive maintenance therapy	Recommend maintenance therapy

Intermediate risk group, they're still a low grade and Ta tumors, non-invasive, but in this time they have multiple tumors, more than one, and a larger tumor. It can also be recurrent tumors, and in some cases we consider small high grade Ta's in this group too, but this is the general intermediate risk category. These patients may receive maintenance therapy, and I say may receive because the data are not quite as strong as those in the higher risk, but a lot of us will give up to a year of maintenance in this setting.

Then finally the high risk, where we're going to focus most of this discussion, those are patients with non-muscle invasive bladder cancer that are high grade, it could be At or it could be high grade T1 or have carcinoma inside too present as well. There are other nuances to becoming high risk too, but in general I'm keeping with the more simpler stratification, and in this case it's recommended that we do maintenance therapy for the higher risk patients after receiving induction therapy. We do this because maintenance BCG improves outcomes. Those that receive maintenance compared to those that receive induction alone are more likely to be free from recurrence of five years, and there have been a couple of studies that have shown this.

I just show one, what we call recurrence curve, that shows in the top line those that got maintenance, and the bottom line those that didn't get maintenance. How this graph works, everyone starts out here at times zero, so months around the bottom, two years, four years, six years, everyone starts out without a recurrence, and then over time people have a recurrence and the curve drops down. So if we look at the five year point in this US study, the SWOG study looking

at BCG induction versus BCG induction plus maintenance, at the five year point those that received only induction about 60% had had a recurrence, as opposed to those that received maintenance only 40% had had a recurrence. So a significant improvement in remaining free from recurrence if you receive maintenance therapy. But again, we have to highlight that recurrences are common in this setting, and we need to then treat that recurrence and adjust our plan after that.

What do the guidelines say? I think we really try to follow guideline care when we're taking care of our patients, and you can look up these guidelines as well. If we take and look at high risk non-muscle invasive bladder cancer patients, and we look at the American Urologic Association, the AUA, they teamed up with the Society of Urologic Oncology, the SUO, and in their guideline in a high risk patient who completely responds to induction BCG, first cystoscopy no tumor, a clinician should continue maintenance BCG for three years as tolerated. We'll talk about that too.

How about the National Comprehensive Cancer Network, the NCCN, were there comments on maintenance intra-vesical BCG? Ideally maintenance should be given for one year for intermediate risk, and three years for high risk non-muscle invasive bladder cancer. Again, with the caveat ideally, because there are nuances to this. I will say I do sit on this panel for full disclosure.

The European Urology Association, in high risk tumors full dose intra-vesical BCG for one to three years, with the three weekly installations, as I showed, is indicated. They have added an additional comment here that I think is timely considering the BCG shortage that we've been dealing with over the last

### Maintenance BCG improves outcomes

- > Those receiving maintenance, compared to induction BCG alone, are more likely to be free from recurrence at 5 years
  - Shown in both US and European studies of BCG

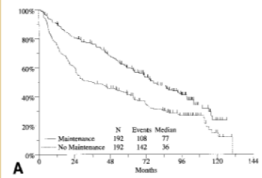


FIG. 1. Recurrence-free survival (A), worseni  
SWOG 8507

### High Risk NMIBC Maintenance Therapy is in the Guidelines

**American Urological Association/Society of Urologic Oncology (AUA/SUO)**  
In a high-risk patient who completely responds to induction BCG, a clinician should continue maintenance BCG for three years, as tolerated.

**National Comprehensive Cancer Network (NCCN)**  
**Maintenance Intravesical BCG**  
• Ideally maintenance should be given for 1 year for intermediate-risk and 3 years for high-risk NMIBC.

**European Urology Association (EUA)**  
In patients with high-risk tumours, full-dose intravesical BCG for one to three years (induction plus 3-weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months), is indicated.  
The additional beneficial effect of the second and third years of maintenance should be weighed against its added costs, side-effects and problems connected with BCG shortage.

several years. Now the additional benefit of the second and third years should be weighted against cost, side effects, and problems with connected with the BCG shortage. An ongoing dialogue with your urologist on the various aspects of it, depending on what is available to you.

I highlight this because not everybody can finish all of the three years of treatment because of the side effects, BCG does cause significant local bladder side effects, and can cause systemic side effects as well too. It's rare to have really severe side effects, but the bothersome ones that can really impact a patient's quality of life do sometimes lead to us stopping. People often ask me, "Well, how

many patients can't finish it?" If we look at these three large randomized controlled trials, and you can see one was published was 20 years ago, one 10 years ago, and one about seven or eight years ago, the percentage stopping due to side effects in this older study, almost 30% stopped due to side effects, more recent study is 19%, and the most recent one only 9% stopped due to side effects. Why the decline? Maybe part of it is that the original earlier study used a different strain of BCG, potentially this one caused a lot more side effects being felt by patients that necessitated stopping. TICE is what we are using now today in the United States, is what we have available, so potentially we're doing a ... it has fewer side effects, people can tolerate it better. Why an improvement over this? I'm not sure. I think probably the answer is somewhere between 8% to 20% of patients have to stop due to side effects.

What can be done to help with these side effects? Again, this is a discussion with your urologist about things, commonly we'll use as bladder medications anticholinergic to stop bladder spasms, pyridium to help with burning. We might give Tylenol for the stomachaches or low grade fevers.

There are data that a quinolone antibiotic, which is a cipro or levofloxacin, the study was actually done with ofloxacin showing that it helped to reduce the side effects of BCG without impacting the efficacy of BCG. BCG is a, we're giving a bacteria in your bladder, and these quinolone class do have some anti-tuberculosis aspects to them, so this has been shown to help, again improve the side effects without negatively impacting the efficacy. Then we can reduce the BCG dose as well too, you can cut the

### Some patients have to stop treatment due to side effects

- > Rare to have severe side effect
  - But significant bothersome side effects lead many to stop before completing full 3 years
- > Randomized clinical trials of BCG Maintenance

Clinical Trial	Publication date	BCG Strain	% of patients stopping due to side effects
SWOG 8507	April 2000	Connaught	28%*
EORTC 30911	May 2010	TICE	19%
EORTC 30962	March 2013	TICE	9%



### What can be done to help with side effects

- > Bladder medications
  - Anti-cholinergics
  - pyridium
- > Quinolone antibiotics
- > Reduce BCG dose



dose in half, and go to a third if you're having significant side effects needing to reduce, it's something else to talk about with your physician.

I really want to come back to this point, is that maintenance is a schedule, it's a guide, it's not rigid. Again, most of us use this protocol which is the SWOG protocol. There are other protocols as well, they have not been compared head to head, so if your urologist is doing a slightly different one that does not mean it's wrong at all, it's just different, and there are just different ways to do this. Sometimes you have to delay a dose. You're coming in and you pee and there's blood that we see in your urine, not microscopic, but then when your urine looks red we're not going to give treatment that day. You're going to have to skip a treatment. If your urinalysis is suspicious for a bladder infection we're not going to give the treatment, we're going to delay that dose.

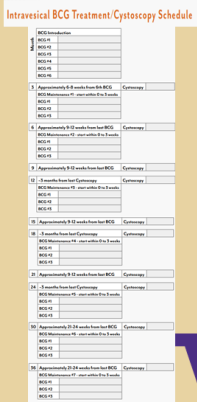
I put here you take a trip. This is mapped out for the next three years of your life, sometimes you got a trip planned, or a wedding, or an anniversary, and it's okay to modify and skip a treatment, or delay it a week. It's okay to do so. Then if we see something on one of these cystoscopies over the three years, we're going to take you back to the operating room to do a biopsy. Then those that you've been treated, you have to wait a few weeks after the biopsy before we're going to put the BCG in, so it's going to shift us around and that is okay.

What are my conclusions? For high risk non-muscle invasive bladder cancer, guideline show us improved freedom from recurrence if we receive maintenance. Most of us use this three year SWOG protocol given every three weeks, every three to six months after three years, not everybody can complete the full three years, that is okay. We try to do it, but not everyone can, it's okay to be flexible with the schedule. It's not rigid. Just keep an open dialogue with your urologist in how you're doing, and what's going on. I think that's so important for every aspect of our care. So with that, I'll turn it over for the next talk, but thank you so much for allowing me to be here with you today.

### What to know about the maintenance schedule


*It is a guide – it is not rigid!!*

- > Most use the SWOG protocol
  - There are other protocols as well
  - The best protocol is not known
- > Sometimes you delay a dose
  - You see blood in the urine before treatment
  - Your urinalysis is suspicious for a UTI
  - You take a trip!
- > If you have to have a biopsy of a suspicious lesion, this will push everything back weeks
  - **THAT IS OK!**



### Conclusions about Maintenance BCG

- > For high risk NMIBC, maintenance treatment is preferred
  - Most use SWOG protocol with 3 years of maintenance treatments
- > Not everyone can complete the full 3 years
- > Its OK to be a little flexible with the schedule
- > Keep an open dialogue with your Urologist



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