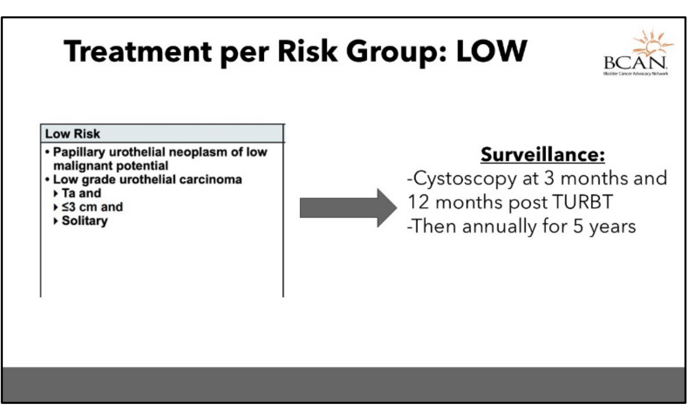
# Walking Through a New Bladder Cancer Diagnosis: Non-muscle Invasive Bladder Cancer

**Guest Presenter:**
**Ava Saidian, MD**

**Dr. Saidian:**

Now, let's get into some of the treatments. Like I mentioned before, the treatments are based on what risk group you're in so that's how we'll go through these treatments.

**Dr. Saidian:**

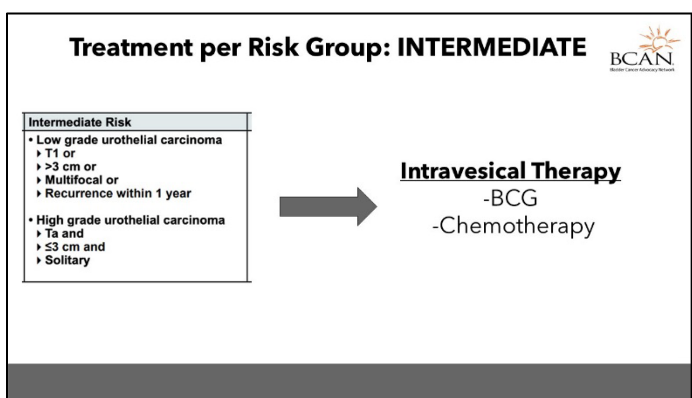



In the low-risk group, so that's the low-grade carcinoma that's not very invasive, it's small, there's maybe just one tumor, our recommendation is that we just watch you. So, once you've had the tumor completely resected out and is for sure a low-risk classification, at three months after your surgery, we'll do another scope in the office, make sure there's no more tumor and again at 12 months. If you've been clear at that 12 months, then we'll just do a cystoscopy once a year for five years and then, after that, only if there's any concern of recurrence. So, if there is a sign of recurrence and you get another TURBT, then we start all over again with our timeline. So, if, at the three-

month one, you have a tumor and we resect it again, then you start back over in the treatment paradigm. Okay?

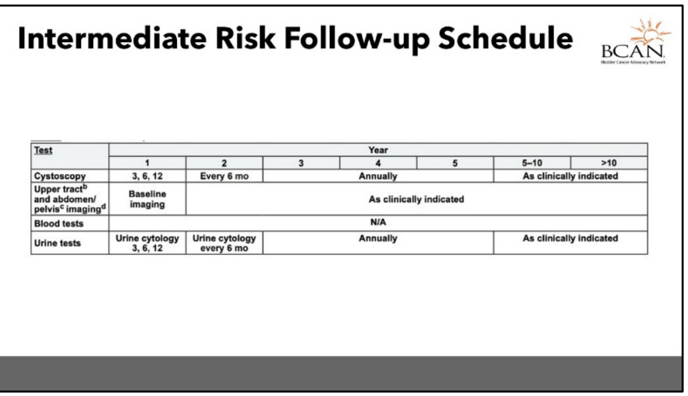
**Dr. Saidian:**

So, excuse me. Next is the intermediate risk group so that's the low-grade but larger, more invasive disease or high-grade but not very invasive. After your TURBT, we recommend intravesical therapy. So, that's essentially immunotherapy or chemotherapy that we put into your bladder. Most commonly, our preferred regimen is BCG which we'll get into the details of that a little later in this talk.




**Dr. Saidian:**

If you have intermediate disease, you will get a cystoscopy three times within that first year of your cancer diagnosis. So, at the three, six and twelve-month mark. If, at any of those cystoscopies we find a tumor, you'll undergo a TURBT and then you'll start that cycle over again at the three, six and twelve-month. For your second year, you'll get a cystoscopy every six months and then annually up to five years and then as needed after that. Your urologist will also do something called urine cytology which is when we do the cystoscopy, we'll collect some of the urine in your bladder and send it off for special testing. It looks at the cells in the urine to see if there are any that are concerning for cancer. So, we might not see the tumor when we do the cystoscope but there could be evidence of it there so that's what that urine cytology is for.

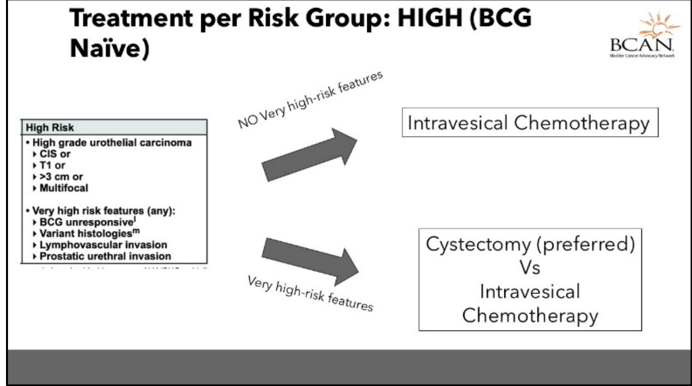


**Intermediate Risk Follow-up Schedule**

| Test | Year | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 5–10 | >10 |
| Cystoscopy | 3, 6, 12 | Every 6 mo | Annually | | | As clinically indicated | |
| Upper tract[b] and abdomen/ pelvis[c] imaging[d] | Baseline imaging | As clinically indicated | | | | | |
| Blood tests | N/A | | | | | | |
| Urine tests | Urine cytology 3, 6, 12 | Urine cytology every 6 mo | Annually | | | As clinically indicated | |

**Dr. Saidian:**

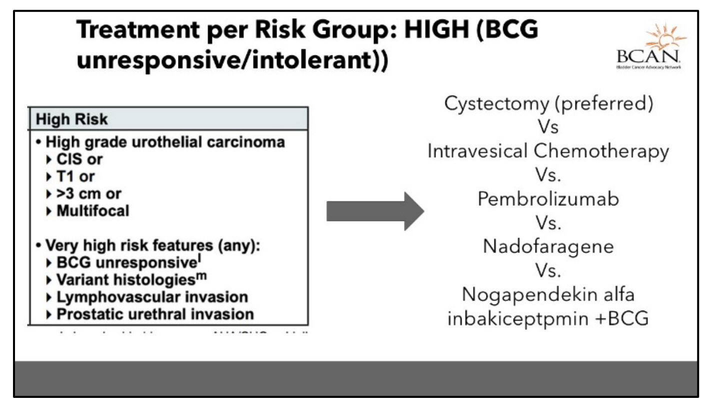
Then our high-risk group so these are the patients with high-grade CIS or invasive disease that's large or anything with high-risk features. So, if you have just the high-risk without any high-risk features, we'll recommend that you get intravesical chemotherapy. If you have any of these high-risk features, so you've already failed therapy, you have any of those variant histologies, invasion into the



lymphovascular system or involvement of your prostate, currently, cystectomy is preferred that's because we know that your disease is going to progress to be muscle invasive and so what we're trying to do is just get rid of it before it gets to a point where it's progressed through and outside your bladder.

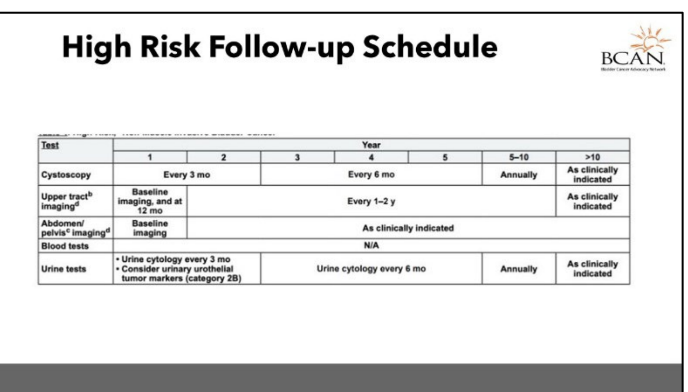
Now, myself and I know a lot of urologists, we are open to doing intravesical chemotherapy for patients with some very high-risk features if they're not a cystectomy candidate or if they want to hold off on cystectomy, which is understandable, it's a very high-risk procedure so we will sometimes try to do the bladder chemotherapy. However, if you have any recurrence, at that point, then we really do recommend that you get a cystectomy.

**Dr. Saidian:**




And then I'm just going to briefly mention this other treatment paradigm. So, if you have high-risk disease and you've tried BCG or you've failed BCG, there are some other treatment options. A lot of these have recently been FDA approved so you might see a lot of ads or commercials for them or pamphlets in your urologist's office which is why I want to mention them. So, currently, these are only FDA approved, these bottom three for patients who have failed therapy or have specific features in their recurrence. So, they're pembrolizumab or KEYTRUDA which you might've seen a lot of commercials for, nadofaragene or NAI plus BCG. Again, these are not necessarily first-line therapies and they're for people who have failed initial therapy but they are becoming more popular and you might hear them talk about which is why I wanted to mention them.

**Dr. Saidian:**




| Test | Year | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 5–10 | >10 |
| Cystoscopy | Every 3 mo | | Every 6 mo | | | Annually | As clinically indicated |
| Upper tract[b] imaging[d] | Baseline imaging, and at 12 mo | Every 1–2 y | | | | | As clinically indicated |
| Abdomen/ pelvis[c] imaging[d] | Baseline imaging | As clinically indicated | | | | | |
| Blood tests | N/A | | | | | | |
| Urine tests | • Urine cytology every 3 mo<br>• Consider urinary urothelial tumor markers (category 2B) | | Urine cytology every 6 mo | | | Annually | As clinically indicated |

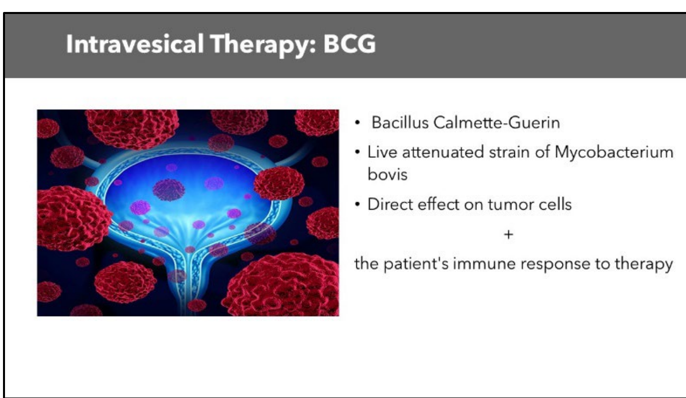
For the high-risk group, as you can imagine, our follow-up is a little bit more aggressive. For the first two years after your initial resection, you'll get a cystoscopy every three months and then every six months for five years and then once a year up to 10 years. So, on top of that, we'll also image your upper tract, so your kidney and your ureter, every one to two years to make sure that there's no disease up in your bladder or ureters.

**Dr. Saidian:**

Okay, so intravesical chemotherapy. So, as you can recall, for intermediate and higher risk, this is our first-line option is putting therapy into your bladder to treat the bladder cancer.

**Dr. Saidian:**

Currently, the preferred regimen for intermediate and high-risk patients is what we call BCG. So, BCG is Bacillus Calmette-Guerin, it is a live attenuated strain of Mycobacterium bovis. So, mycobacterium is bacteria that can cause tuberculosis, this is an attenuated strain so it's like a vaccine. We put it in your bladder, they're not 100% sure how it works but it's been hypothesized that it, not only has a direct effect on killing the tumor cells, but it also stimulates the immune system to fight against the tumor spells by infecting the cancer cells, inducing an immune response and then having antitumor effects.




**Dr. Saidian:**

So, when you get BCG, because it is a live attenuated strain that works by using the immune system, your urologist will usually check your urine to make sure you don't have an active infection before getting the therapy. And on that note, we typically try not to use it in patients who are immune suppressed whether they're a transplant patient or they have any other diseases that suppress their immune system or are on drugs that suppress your immune system for things like lupus or autoimmune disease. This is because it's been found that the BCG doesn't work as well in those patients which makes sense if it uses your immune system to fight the cancer.

**Intravesical Therapy: BCG**

- Urine tested to r/o infection
- Catheter placed
- BCG instilled through catheter into your bladder
- Retained in bladder for 1.5-2 hours.
- Do not have to remain in office during retention time

So, once we know you're a good candidate for it, you'll go into the office and a catheter will be placed, the drug is then inserted through the catheter into your bladder, it's usually about only a 50 to a hundred CC's depending on the dose. The BCG is held in your bladder for about one and a half to two hours. Depending on how the office runs it, how your physician administers it, most of the time, you don't have to stay in the office while you get it, you can go home, you can urinate it into your toilet, we just recommend that no one else uses that toilet until there's been at least three flushes and there's been a cup of bleach poured into the bowl. Also, the catheter does not have to stay in your bladder those whole two hours either.

**Dr. Saidian:**

So, since BCG is based on an immune response, we have to give you an induction course of BCG. So, you'll get one therapy weekly for six weeks and that's to ensure that there's been an immunological response. So, basically, we're hitting your bladder and that cancer with that BCG again and again and again to make sure that we've kicked off that immune response. After your induction BCG, you are now six weeks through induction which has usually started about six weeks out from your last resection. So, now you're three months out from your resection and, as you remember, on most of the protocols, you're going to get a cystoscopy at three months. So, after you finish your induction, you'll get a cystoscopy, we'll make sure there's no more tumor there and then we'll move on to what we call our maintenance BCG.

**Intravesical Therapy: BCG Induction**

- Weekly instillations for 6 weeks
- This is done to ensure an immunologic BCG reaction is achieved

**Dr. Saidian:**

So, maintenance BCG is you get BCG weekly for three weeks at 3, 6, 12, 18, 24, 30 and 36-month intervals.

Now, if you have intermediate risk bladder cancer, we usually only do maintenance for a year versus high risk, you'll be on that maintenance protocol for three years. You'll be getting cystoscopies in between those maintenance sessions to ensure that you don't have any recurrence of your disease. If you do, it's like I mentioned earlier, we start back at the beginning of the timeline with a resection and you then start the whole process over again.

**Intravesical Therapy: BCG Maintenance**

- 3 weekly instillations at months 3, 6, 12, 18, 24, 30, and 36
- Ideally maintenance should be given for 1 year for intermediate-risk and 3 years for high-risk NMIBC

**Dr. Saidian:**

Now, for a very long time, there has been a BCG shortage. It's a very long story why different factories, supply chain, blah, blah, blah but this has been going on way before COVID. So, because there's been a BCG shortage, a lot of really smart people have come together and put out consensus statements on how BCG should be used and what we can use in the absence of BCG. So, it is usually prioritized with patients with high-grade T1 and CIS because those are the patients that are at the highest risk of recurrence and there are some alternative options that are intravesical chemotherapies.

**Intravesical Therapy: BCG Shortage**

BCAN

- BCG prioritized for HG T1 and CIS (high risk of recurrence)
- Alternative options:
  - Gemcitabine/Docetaxel (**BRIDGE Trial**)
  - Mitomycin
  - Gemcitabine alone
  - Split dose BCG (1/3 or ½ dose)

So, gemcitabine and docetaxel, this is the one that I would say most contemporary urologists and urologic oncologists are using. It's currently the treatment of choice in the BRIDGE Trial which is a huge trial. It's actually a really well-designed trial that's going to compare gem/doce directly to BCG. And we haven't really had any trials that have compared any drug directly to BCG so we're all very excited to see what the outcomes of that trial are. But even though the results haven't matured or come out yet, this is what a lot of us are using gem/doce in the absence of BCG.

Other options are mitomycin which is another chemotherapy, gemcitabine alone or even split-dose BCG. So, you can use a half vial or even a third vial and there have been some studies that it can be just as effective as the full dose. However, for example, at one of the hospitals I work at, we have zero BCG so it's not even an option to do a split dose so that's why we've been using the gemcitabine/docetaxel.

So, other than it working to prevent the cancer to come back or recur or progress, the other thing that's going to be most important to the patient is the side effects.

**Dr. Saidian:**

So, what are the side effects of BCG? Well, as you can imagine, we're causing a local immune reaction in your bladder so the most common thing people get is an inflammatory cystitis. So, basically, a really irritated bladder, it might almost feel like you have a UTI, burning with urination, things like that. More rarely, it can be very severe to the point where people cannot tolerate the BCG and we have to choose a different treatment option. You can get some systemic side effects of the immune response. So, your body's kicking up ready to fight so you might feel similar symptoms to when you have a flu like muscle aches, things like that. You can even have a fever.

**Intravesical Chemotherapies:**

BCAN

- Gemcitabine
- Mitomycin
- Docetaxel
- Epirubicin
- Doxorubicin

Now, there is a such thing as BCG sepsis which is where BCG somehow got into your bloodstream and is now causing you to become septic. This is very, very rare but it can be very serious and requires treatment and monitoring. So, even though the fever can be just a response of your immune system kicking into gear, I do tell all my patients, if they do have any fever, that they do need to be seen in the emergency room just to make sure we're not dealing with anything more serious.

**Dr. Saidian:**

So, these are some of the other chemotherapy options, I mentioned some of these. I did add epirubicin and doxorubicin because those are chemotherapy agents that have been around longer or used longer so we do have more data on them. And however, like I mentioned, most contemporary urologic oncologists aren't really using the epirubicin and doxorubicin anymore, we're using gemcitabine and docetaxel.

**Intravesical Chemotherapies:**

- Gemcitabine
- Mitomycin
- Docetaxel
- Epirubicin
- Doxorubicin

**Dr. Saidian:**

A lot of people still use mitomycin and it is very good and very effective, however, mitomycin can have some very serious side effects especially if you have a hole in your bladder from the tumor being resected, that's actually an absolute contraindication. If there's even the slightest concern that you might have a bladder perforation, we cannot use mitomycin because it can cause some severe reactions. Gemcitabine and docetaxel, they have similar local responses. So, urgency, frequency are the most common ones so basically bladder irritation. There can be some pain with urination and blood in the urine as well.

**Intravesical Chemotherapies: Side effects**

- **MITOMYCIN:** Urgency/frequency (30-50%, most mild), Hematuria (5-20%), Pain (15%), Rash & itch (10%), Allergy (5%), Chemical cystitis, severe (1-3%), Encrustation cystitis after TURBT
  - Rare but serious (if systemic absorption): Myelosuppression, Severe skin reaction if spilled on skin
- **GEMCITABINE:** Urgency/frequency (10-20%, most mild). Pain (10%), Hematuria (5%), Rash & itch (5%), Chemical cystitis, severe (1-3%)
- **DOCETAXEL:** Urgency/frequency (20-40%, most mild), Hematuria (10%)
  - Rare but serious (if systemic absorption): Myelosuppression, Hand-foot syndrome, Change in color of nails

**Dr. Saidian:**

So, I think an important thing to think about as a urologist for our patients is how can we make this more tolerable. Because if you can't tolerate these therapies, then we have to talk about being more aggressive and being more aggressive sometimes will mean having to remove your bladder or having to receive more aggressive therapies which we'd like to avoid. So, I have a couple little tips and tricks that I've learned from all my amazing mentors who trained me. So, for one, preventing skin contact. A lot of these might not be labelled as irritative to the skin, however, they are chemotherapeutic agents in the end so I tell all my patients, after they urinate it out, to clean themselves very well, make sure there's

none left on their body anywhere especially women in the vagina around the labia, make sure you wash your hands very, very well.

**Intravesical Chemotherapies: How to make it more tolerable**

- Prevent Skin contact
- Topical estrogen for women (Start before chemotherapy!)
- Men: Avoind penetrative intercourse for ~1 week
- Women: No data, most physicians recommend avoiding intercourse for ~1 week
- Don't have to leave catheter in during therapy IF you can retain in bladder
- Can take anti-bladder spasm medications prophylactically

For women especially, you can imagine, because the urethra is up behind our labia that it can become very irritated. So, women who are good candidates for them, I recommend that they start a topical estrogen. This helps make that tissue a lot healthier, a lot more durable especially because, if you have bladder cancer, you probably already have some irritation with urinating, pain with intercourse, vaginal pain or dryness so topical estrogen can really help with all of that. So, if you think that this might be something you're interested in, I would definitely talk about getting on it with your urologist.

Some other things, men, we counsel for you to avoid penetrative intercourse for about a week. For women, there's no good data on receptive intercourse so most people recommend a week as well but we don't really have good data on it. Some offices will take the catheter out in between your chemotherapy so we'll put in, for example, the gemcitabine, take the catheter out and put another one in to put your docetaxel in. So, if you don't want to sit there with a catheter, you don't have to. However, if you are nervous about being able to hold the chemotherapy in because you just don't think you can tolerate it, you think you're going to pee or leak out on yourself, then we can leave the catheter in. So, based on your urologist office's protocols, you should talk to them about what can be done to make it so that you are able to keep the chemo as long as possible so it's most effective but also stay comfortable.

And then, also, you can ask your doctor about taking a bladder spasm medication. So, basically a medication that calms your bladder down and it keeps it from reacting to the chemo being in there. You can take that before your appointment and this can help a lot of patients tolerate the chemotherapy for a longer period of time which is better for your treatment.