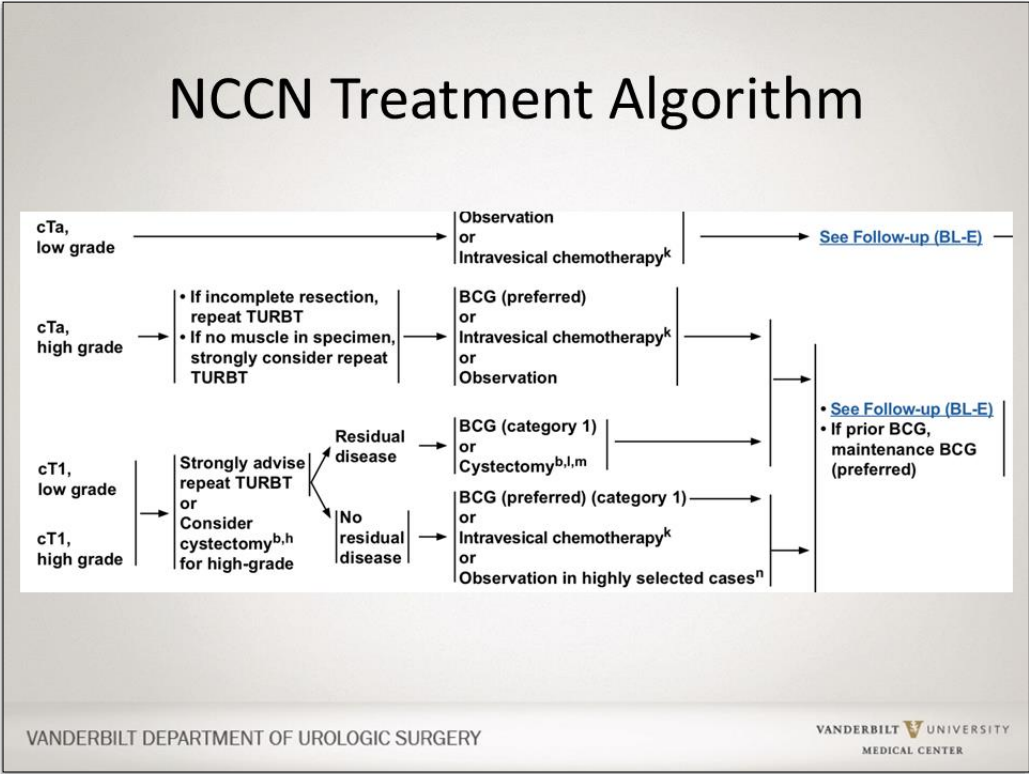


Dr. Amy Luckenbaugh:

These are the National Comprehensive Cancer Center guidelines, kind of outlining what I had just said in those last slides. For low grade, you could either, and it's a low grade low risk, you could do observation, or you could give chemotherapy in the bladder right after the surgery. And that's gemcitabine or mitomycin. If it is still a TA, but it's high grade, you could do BCG, or an alternative option is chemotherapy, or you could observe. And then, for T1 high grade, we would usually look again and repeat the procedure, where we biopsy your bladder, and then go on to do BCG, or in some cases rarely recommend removing your bladder depending on the factors I discussed earlier.



And what about how often do we need to be looking in your bladder? So, if you had low grade, we usually would do look in your bladder three months after we remove that first tumor. And then we would look again somewhere between six to nine months later, and then we would look every year for five years. You wouldn't need additional CT scans in low grade cancer. And then for the intermediate risk people, we would look in three months. And then we would look three months later. And then after that about every six months we do a cystoscopy, just in our clinic, not in the operating room, nothing like that. And then once a year for five years. For the high risk people, we typically look every three months for two years. And then every six months for five years. And then once a year. So, like I said, you're kind of with a urologist for a long time.

Surveillance

Low grade urothelial carcinoma	Intermediate risk, high grade urothelial carcinoma	High risk, high grade urothelial carcinoma
Initial cystoscopy: 3 months	Initial cystoscopy: 3 months	Initial cystoscopy: 3 months
Next cystoscopy: in 6-9 months	Next cystoscopy: in 3 months	Schedule: every 3 months x 2 years, every 6 months through 5 years, annually through 10 years
Schedule: Annual cystoscopy through 5 years	Schedule: every 6 months x 2 years, then annually through 5 years	
Upper tract imaging: as clinically indicated	Upper tract imaging: as clinically indicated	Upper tract imaging: every 1-2 years
Cytology: not indicated	Cytology: at each cystoscopy	Cytology: at each cystoscopy

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Dr. Amy

Luckenbaugh: Those are all the staging and risk groups that we just addressed. And I will now talk about the chemotherapy. This is chemotherapy that is given inside the bladder. So, it is given through a catheter. It's instilled into your bladder, and then we would ask you to try to hold it for around two hours or so. This chemotherapy is given for low grade bladder cancer. And you can see a list of examples. I would say the most common one used today are either gemcitabine or mitomycin, and they directly kill the cells that could be floating in the urine. It reduces the risk of the cancer coming back, but it doesn't reduce the risk of it progressing. It just specifically reduces the risk of cancer coming back.

Here are the ways that this can be given. And one of the common ways is that after you have a bladder tumor removed, while you're still asleep, we put in the catheter, we put the medicine in, and then you wake up and we take the catheter out, and you go to the restroom.

And that can reduce the risk of it coming back if there are multiple tumors by up to 56%. In some cases, if you've had a low grade cancer come back again, or it is a bigger low grade cancer, then we might recommend that you do it weekly for six weeks, and that reduces the risk of it coming back somewhere between 14 and 38%.

Intravesical chemotherapy

- **Indication:** low grade urothelial carcinoma
- **Examples:** mitomycin, thiotepa, gemcitabine, valrubicin
- Direct cytotoxic effect
- Decreases **recurrence**, does not alter progression

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Intravesical chemotherapy

- **Administration options:**
 - Single dose after TURBT – reduces recurrence by 13% and up to 56% for multiple tumors
 - Induction cycle: weekly x 6 weeks – reduces recurrence by 14-38% (for intermediate risk disease)
 - Maintenance: monthly x 1 year – reduces recurrence by 18% (for intermediate risk disease)
- **Side effects:** lower urinary tract symptoms, chemical cystitis, decreased bladder capacity, skin irritation

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Dr. Amy Luckenbaugh: The major side effects of these are feeling like you have to pee more frequently, more urgently. In some cases it can shrink your bladder size, and permanently in some cases. And it can sometimes cause skin irritation if it gets on your skin during the administration.

The two major ones like I spoke about are mitomycin and gemcitabine. Gemcitabine is a newer one, and it seems to be tolerated a little bit better than mitomycin. And so, I tend to favor that if it is available. This is just the article for your reference that kind of tested gemcitabine. And what they did is they tested that medication versus just saline salt water medication. And what they found was a lower risk of recurrence in the group of people who got the gemcitabine, and very few complications, and that it was pretty well tolerated.

That covers the intravesical chemotherapy, so the treatment option for low grade type of cancer. Now we'll talk about BCG therapy. So, BCG is given for high grade tumors, and still remains kind of the gold standard for what we have for this type of cancer. BCG is actually a type of tuberculosis that is given in the bladder through a catheter, and it activates your immune system to basically fight and attack the abnormal bladder lining. And it works well for high grade tumors and carcinoma in situ.

Usually, we wait to give BCG for about four to six weeks after your bladder biopsy, or TURBT, because the bladder wall needs to be healed.

Intravesical chemotherapy

- **Mitomycin C:**
 - Rare systemic absorption due to high molecular weight
 - 40 mg in 20 mL sterile water
 - Reduces recurrence in those with low grade cancer if given post op (not effective for HG or T1)
 - Lower urinary tract symptoms, contact dermatitis
- **Gemcitabine:**
 - decreased recurrence 39-70%
 - 2 gm in 100 mL saline
 - Tolerated better than mitomycin C

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Bacillus Calmette—Guerin (BCG)

- **Indications:** high grade disease, CIS
- **Attenuated live vaccine (Mycobacterium bovis)**
- **Method of action:** Activates the immune system to cause T-cells to attack abnormal urothelium, possible direct inhibition of tumor cell invasion
- **Superior to chemotherapy for high grade tumors & CIS**

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Dr. Amy Luckenbaugh:

And then we would give it once a week for six weeks. And after that six weeks, about a month later, we like to look in the bladder and make sure that everything has stayed, or responded appropriately. If it has not and it is still a not invasive type of cancer, we can try doing an additional six week treatment with BCG. And about 20 to 25% of the time in patients who BCG did not work the first time, BCG actually works 20 to 25% of the time in the second attempt.

And so, it often is worth trying again. And if BCG works, then we would do this therapy three months after your initial treatment, six months after your initial treatment, and then every six months.

This is referring to that maintenance BCG assuming it has worked. We often try to give this for up to one to three years, about every six months. And it would be three treatments those times. This reduces the risk of recurrence, and it also reduces the risk of progression. So both recurrence and progression are affected by this.

BCG is especially effective for carcinoma in situ. And up to 30% of people with carcinoma in situ can have no cancer come back at 10 years after the BCG treatment. And people who don't respond, it is not so good. And so, we need to identify that pretty quickly. And we would do that by looking in your bladder and sending off cells from your urine.

BCG

- Can be given 4 weeks after TUR
- **Induction:** once a week x 6 weeks, re-evaluate with cystoscopy and cytology
- If T1, HG Ta or CIS recurs at 6 weeks can trial an **additional induction course** or consider cystectomy
 - Additional 20-25% response rate
 - 20-50% tumor progression in this group
- If BCG eradicates bladder cancer, consider maintenance therapy

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Maintenance BCG

- Once a week x 3 weeks at 3 and 6 months, then every 6 months for 1-3 years
- Reduces recurrence 30-40%
- Decreased risk of progression 25% (delayed progression)
- SWOG study:
 - 6 week induction course with 3 years of maintenance
 - Median recurrence free survival 76.8 (maintenance) vs 35.7 (control) months ($p < 0.001$)
 - 5-year survival 83% vs 78%
 - Only 16% tolerated the full dose schedule

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Dr. Amy Luckenbaugh: The side effects of BCG. There are a number of them that can occur. Within 48 hours of BCG, the kind of common side effects that you may have, feeling like you have to pee more frequently, urgently, some burning with urination, sometimes blood in the urine. And some people have this feeling like they've had a flu shot, and just kind of feel fatigued. If those are the symptoms, we tend to say that is okay we can continue the BCG medicine, take tylenol, take ibuprofen. And we often can prescribe medications for bladder spasms and burning. If these symptoms don't improve, we can reduce the dosage of BCG. We don't like to go below about a third of the normal dose though.

More severe side effects can happen. And if they are kind of persisting over 48 hours after the BCG, then we would consider checking your urine to make sure you don't have an infection. If you had a high fever, then we would probably recommend you coming into the hospital. And if it is a high fever, you may not be able to receive future BCG, but that's something we would kind of assess on a case to case basis.

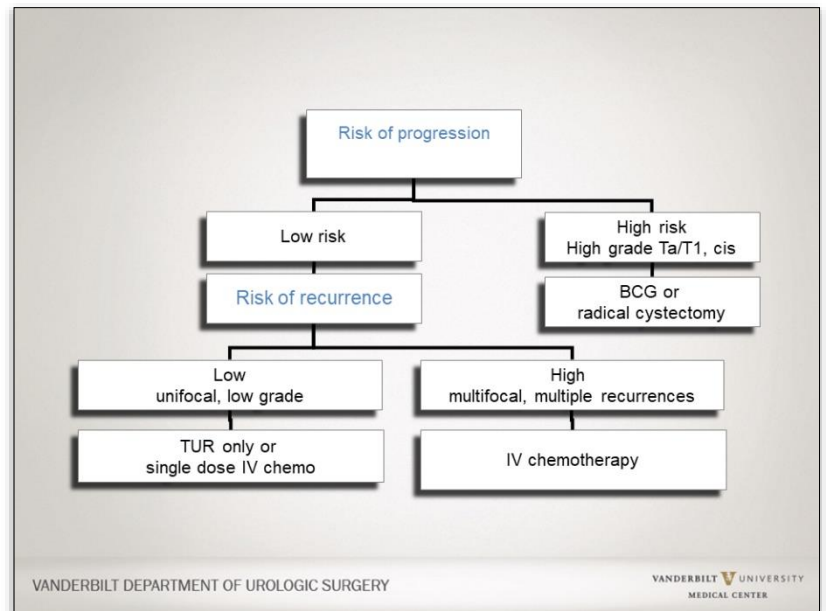
BCG Side Effects

- Within 48 hours of BCG:
 - Cystitis, dysuria, hematuria
 - Urgency, frequency of urination
 - Malaise, fatigue, low grade fever (<38.5)
 - Treat with NSAIDs, reduce dose, medications for bladder spasms
 - Okay to continue BCG

BCG side effects

- >48 hours after:
 - Severe voiding symptoms, hematuria, fever
 - Urine culture, consider blood work, admission if needed
 - Okay to continue BCG once asymptomatic
- BCG Sepsis (0.4%):
 - Fever > 102
 - Typically warrant hospitalization
 - Should not receive future BCG

Dr. Amy Luckenbaugh: This is just a general algorithm of what I have talked about already. So, there's kind of different categories of people. There's people who are low risk to progress, meaning low risk for things to grow deep into the bladder, and those people may have a risk of things coming back. If they only have low grade cancer once, we may just watch, or give medicine in the bladder. If they have something come back multiple times and it's still low grade, then we would do the chemotherapy in the bladder. And if they have a high risk type of cancer, or it's likely to come back and progress, then we'd give the BCG medicine.



So, we've talked briefly about BCG. And next we're going to go to, what if BCG doesn't work? So there are a lot of exciting options for this that are emerging. Truthfully, non-muscle invasive bladder cancer high grade disease can be really frustrating as it tends to come back and it tends to also progress. And so, for people who BCG didn't work even the second course of BCG, we can talk about a bunch of options. One option is to undergo a cystectomy, or bladder removal. And that is kind of the tried and true option, we know it's effective, but there are a number of options that allow you to spare your bladder that are kind of emerging, and these include gemcitabine and docetaxel, BCG plus interferon, pembrolizumab, which is a newer immunotherapy that's given systemically, so in an IV. And then there are a bunch of exciting trials that I'll just briefly touch on a few of them before we end.

Refractory High Grade Disease

- **Cystectomy**
- Single agent chemotherapies: valrubicin, gemcitabine, docetaxel
- Gemcitabine + docetaxel
- BCG + interferon
- Pembrolizumab
- Trial agents

So, why is cystectomy kind of recommended in some of these patients? We know that if you have a high amount of T1, so cancer into the lining right before the muscle, that about 50% of people might actually have muscle invasive disease when we take out the bladder. And so, for people who have recurrent high grade T1, and there's a lot of it, or there's that special type of cell that the pathologist sees that's abnormal, we may recommend removing the bladder, because we certainly don't want to miss a muscle invasive type of bladder cancer.

But there are a number of groups that have looked at giving other medications such as gemcitabine docetaxel. It's a combination of two medicines that's again given in the bladder. And what they found was for people who BCG didn't work, about 60% of patients who were treated with this had no cancer coming back at one year, and 46% had no cancer coming back at two years.

Dr. Amy Luckenbaugh:

Ultimately, about 15% of the people went on to have their bladder removed, but it did allow them a few years before requiring that. And so, this is something that could be done if BCG hasn't worked prior to going into removing the bladder.

Role of “timely” cystectomy

- Significant risk of understaging particularly for T1
 - Up to 50% of those who undergo cystectomy for presumed T1 disease demonstrate muscle invasion
- Consider if:
 - recurrent HG disease
 - LVI
 - deeply invade lamina propria or multifocal T1
 - associated with diffuse CIS
 - located in diverticulum
 - variant histology

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Intravesical gemcitabine/docetaxel

- N=276, median 73 years old, 22.9 months follow up
- **1 year recurrence free survival:** 60% (65% high grade RFS)
- **2 year recurrence free survival:** 46% (52%)
- 3.6% had disease progression
- 15.6% went on to cystectomy (4% had muscle invasion)

Steinberg R, et al (multi institution). Journal of Urology. Dec 10, 2019

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Another mouthful is nadofaragene firadenovec. And that is called in short, astiladrin. And what this is, is it's actually a type of virus that is instilled into the bladder the same way BCG is given. And it was given for people again who BCG did not work. And what they found was quite again a good effect, with about 53% of patients with the carcinoma in situ having a good response, and no cancer at follow up. And then around 72% with the high grade TA or T1 having a good response. Overall, one year out from getting this medication, 30% of people had no cancer that had come back. So, this is another option that is a little harder to find and not quite yet out there as widely available as the gemcitabine and docetaxel.

And lastly, there is pembrolizumab. This is a medication that instead of giving in the bladder, it's actually given through an IV, like it's an immunotherapy. And this was tested in people and evaluated in people with carcinoma in situ and high grade bladder cancer that hadn't responded to BCG. Overall, it was relatively well tolerated, with a complete response rate of 41%. Again, in people who BCG had not worked. But the difference with this, and it's important patients know, is that it's a systemic medication. And so, you have more systemic side effects, like diarrhea, fatigue, rash, and things like that.

Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial

Stephen A Boorjian, Mehrdad Alemozaffar, Badrinath R Konety, Neal D Shore, Leonard G Gomella, Ashish M Kamat, Trinity J Bivalacqua, Jeffrey S Montgomery, Seth P Lerner, Joseph E Busby, Michael Poch, Paul L Crispen, Gary D Steinberg, Anne K Schuckman, Tracy M Downs, Robert S Svatek, Joseph Mashni Jr, Brian R Lane, Thomas J Guzzo, Gennady Bratslavsky, Lawrence I Karsh, Michael E Woods, Gordon Brown, Daniel Canter, Adam Luchey, Yair Lotan, Tracey Krupski, Brant A Inman, Michael B Williams, Michael S Cookson, Kirk A Keegan, Gerald L Andriole Jr, Alexander I Sankin, Alan Boyd, Michael A O'Donnell, David Sawutz, Richard Philipson, Ruth Coll, Vikram M Narayan, F Peter Treasure, Seppo Yla-Herttuala, Nigel R Parker, Colin P N Dinney

- Replication deficient recombinant adenovirus delivers IFN-alpha 2b cDNA into bladder epithelium
- 33 centers, BCG unresponsive NMIBC
 - Single dose w/repeat at 3, 6, 9 months if no recurrence
 - Side effects: fatigue, bladder spasm, urgency

Pembrolizumab

- Human monoclonal antibody that binds to PD-1
- Prevents tumor cells from inhibiting immune mediated cytotoxicity
- FDA approved in January 2020
- **KEYNOTE-057**
 - 98 patients w BCG unresponsive NMIBC analyzed
 - 41% complete response rate
 - 28 month median follow-up, median response duration 16.2 months
 - Fatigue, rash, immune mediated pneumonitis, hepatitis

Pembrolizumab in Bladder Cancer

- Pembrolizumab was approved for treatment of patients with Bacillus Calmette-Guérin–unresponsive, high-risk, non–muscle invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.
- The recommended dose of pembrolizumab in patients with high-risk BCG-unresponsive non–muscle invasive bladder cancer is 200 mg via intravenous infusion over 30 minutes every 3 weeks until persistent or recurrent high-risk non–muscle invasive bladder cancer, disease progression, unacceptable toxicity, or for up to 24 months in patients without disease progression.

Dr. Amy Luckenbaugh: So we just covered the refractory disease. And lastly, I will talk about some ongoing emerging therapies. So one that is ongoing is BCG medicine combined with a special thing that can make BCG work a little better. And it's given similar to BCG in the bladder, and it's administered once a week for six weeks. And then you can continue on maintenance therapy if it has worked. And it is pretty promising, and we're pretty excited about that. So, there are some sites that are still enrolling patients in this, and so that's an option for a disease that it hasn't responded to BCG.

One other trial that is currently enrolling is, again for people who the BCG did not work. And there's three options for this trial, three different things you could receive. One is you could receive a medicine similar to pembrolizumab and an IV to reduce the risk of it coming back and immunotherapy. The other is a medication that is actually given in the bladder, and it's this little pretzel. The pretzel is put in your bladder with a normal cystoscopy like you would have in clinic, and that pretzel contains gemcitabine.

And slowly lets the gemcitabine chemotherapy out over time, rather than having it just given to you once a week for six weeks. And so, that is the other option for treatment in this trial. And then the last option is you could receive that or combine that with an immunotherapy. And again, this is currently enrolling in various places.

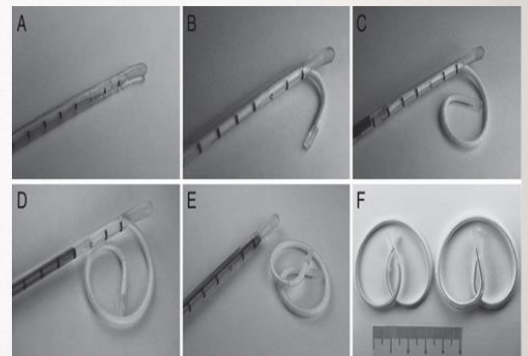
And this is by no means a comprehensive list, just two that I am aware of. So, ask around to your urologist, there are things that are out there for patients who BCG has not worked. And in conclusion, I just think that it's really important that those risk categories of low risk, intermediate risk, and high risk be considered, because that is what goes on, and how we determine how best to treat you. I do think

On-going NMIBC Trials

- **BCG combined with ALT-803**
 - BCG unresponsive
 - ALT 803 – recombinant IL-15 superagonist
 - Administered weekly x 6 weeks, and then maintenance for up to 18 months
 - Currently enrolling

On-going NMIBC Trials

- **TAR 2001**
 - BCG unresponsive
 - Randomizing patients to
 - Intravesical gemcitabine delivered with gemcitabine pretzel (TAR-200)
 - Cetrelimab
 - Intravesical gemcitabine (TAR-200) + cetrelimab
- **Currently enrolling**



there's still the role for timely cystectomy removing the bladder if BCG is continuing to not work. Although it's a big surgery, really does have the best outcomes. And I think the exciting thing is that there are a bunch of options, and that everything is rapidly changing and expanding. So, although BCG may not work in some cases, there are a lot of options that do. Thank you very much, and I'd be happy to take any questions.

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