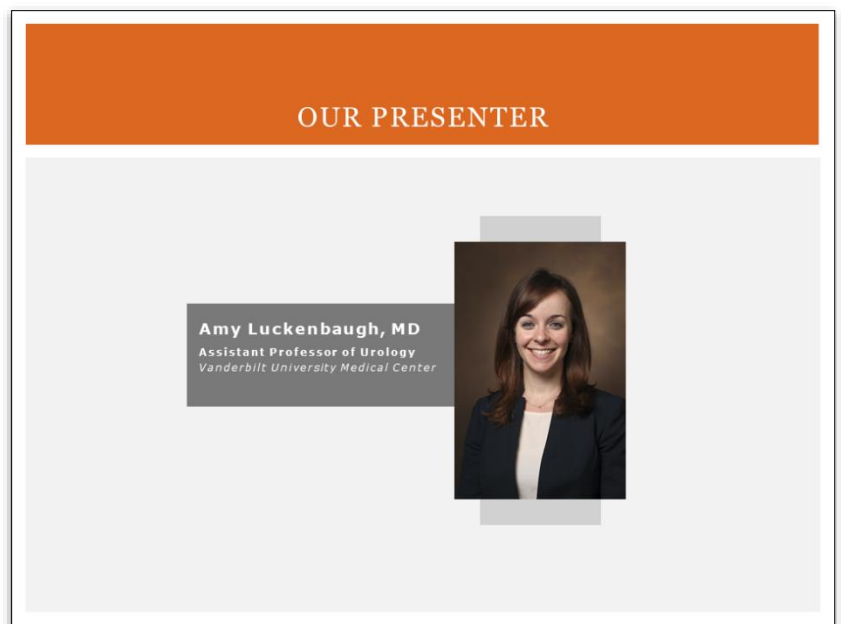


Stephanie Chisolm:

Welcome to understanding non-muscle invasive bladder cancer, a patient insight webinar from the Bladder Cancer Advocacy Network.

A bladder cancer diagnosis can be terrifying to a patient and their family. What do you need to know about non-muscle invasive disease in terms of understanding your diagnosis and your treatment options? Tonight we're really delighted to have urologist, Dr. Amy Luckenbaugh, Assistant Professor at Vanderbilt University Medical Center. Dr. Luckenbaugh is a surgeon whose clinical focus centers around the comprehensive care of patients with neurologic malignancies like bladder cancer. She currently serves as a member of the Society of Women in Urology board. And through her research, she really aims to better understand new options for treating bladder cancer patients.



Really delighted that Dr. Luckenbaugh is here with us. She was one of our 2019 John Quale Travel Fellows, and was able to attend our 2019 Bladder Cancer Think Tank, and be introduced to the community. So it's lovely to have you here, Dr. Luckenbaugh. If you would like to share your slides, you can take it away right now. I'll stop my share.

Dr. Amy Luckenbaugh:

Great. Thank you so much. And thank you so much for having me. So I have no disclosures that are relevant to this talk. And I'm going to try to cover a lot of information, and leave about 15, 20 minutes for questions at the end. And this is kind of the outline of where we'll be going. About the background, diagnosis and evaluation of non-muscle invasive bladder cancer, staging, what it means, the different risk groups and why they're important, and various treatments, as well as emerging therapies.

So, bladder cancer in the United States, there's about 80,000 new cases per year. It's the fourth most common malignancy in the United States among men, and it is not in the top 10 for cancers among women. Risk factors as we know are... Smoking is the number one risk factor, and number one modifiable risk factor for patients to know.

Bladder cancer is the eighth most common cause of death in men. But I think it's important and encouraging to know that most of the cases we find are non-muscle invasive at diagnosis. So, 70% of them are not invasive, and that's very important, and it kind of allows us an area to treat and hopefully prevent them from becoming muscle invasive. 20% are muscle invasive at diagnosis. And 10% present with disease outside the bladder. So, that is just a brief background.

And how about diagnosis and evaluation? So, the way this is often diagnosed is people can present with blood in their urine. And anytime we see blood in the urine, we should be looking inside the bladder with a camera that we put in through the tube that you pee out of. And then if there is a tumor, it is our job to resect the entire tumor and perform upper tract imaging. And what upper tract imaging means is a CT scan to look at the kidneys, the ureter tubes as well. Because those tubes are lined with the same type of cells that the bladder is lined with. And so, it's important to make sure that there's no cancer in that entire tract.

Bladder Cancer

- US: 80,000 new cases per year (M 62,000, F 18,000)
- 4th most common malignancy among men
- Risk factors: **smoking**, chronic bladder irritation, chemical exposure, prior pelvic radiation

Estimated New Cases		
		Males
Prostate	191,930	21%
Lung & bronchus	116,300	13%
Colon & rectum	78,300	9%
Urinary bladder	62,100	7%
Melanoma of the skin	60,190	7%
Kidney & renal pelvis	45,520	5%
Non-Hodgkin lymphoma	42,380	5%
Oral cavity & pharynx	38,380	4%
Leukemia	35,470	4%
Pancreas	30,400	3%
All Sites	893,660	100%

Bladder Cancer - Background

- 8th most common cause of cancer death in men
- **70% are non-muscle invasive at diagnosis**
- 20% are muscle invasive
- 10% are metastatic

Estimated Deaths		
		Males
Lung & bronchus	72,500	23%
Prostate	33,330	10%
Colon & rectum	28,630	9%
Pancreas	24,640	8%
Liver & intrahepatic bile duct	20,020	6%
Leukemia	13,420	4%
Esophagus	13,100	4%
Urinary bladder	13,050	4%
Non-Hodgkin lymphoma	11,460	4%
Brain & other nervous system	10,190	3%
All Sites	321,160	100%

Siegel et al (2020) CA: A Cancer Journal for Clinicians, 70(1):7-30

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Dr. Amy Luckenbaugh:

And then there are some rare cases where we do these cystoscopies and everything looks normal, but we send cells off from the urine, and it can show up as having cancer cells in the urine, and we could not have seen something. When we see that, there are some other places we have to try to look. In a man, that's in the urethra tube that you pee out of, that's in the prostate, as well as up in the kidney and ureter tubes. And when we have those instances where we might have abnormal cells that we see in the urine, but a normal bladder, we sometimes do something called a blue light, or enhanced cystoscopy.

And what that does is we place a catheter, and we put a small amount of medicine in your bladder, we ask that you hold it for 30 minutes, and then we take you to the operating room and look under a special light. And you can see here in the photos of what a tumor under normal light might look like, right here. And then under that special light, what it might look like. And so, it can be challenging to see some of these, and this can add to some utility and help diagnose things. There were some early thought that this might reduce recurrences about one year afterwards, because you can make sure to see things you may not have seen with the normal light.

Diagnosis & Evaluation

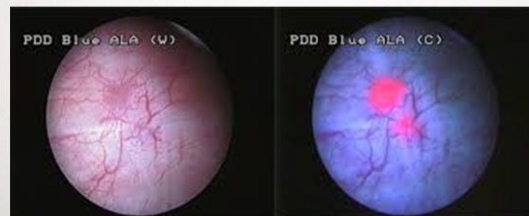
- Cystoscopic examination of the bladder
- Resect all tumor
- Perform upper tract imaging
- Consider bimanual exam under anesthesia
- If normal cystoscopy, but *abnormal cytology* consider:
 - Prostatic urethral biopsies
 - Upper tract evaluation
 - Enhanced cystoscopy

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Blue light cystoscopy

- Utilizes photosensitizer (5-aminolevulinic acid)
- Improves detection of all tumors (AUA Guideline recommendation moderate Grade B):
 - 96% detected vs 77% with white light
 - For Tis lesions: improved detection 95% vs 68%
 - For Ta lesions: improved detection 96% vs 85%
 - Improved detection and treatment led to fewer recurrences at 12 months
 - Increased false positives compared with white light cystoscopy



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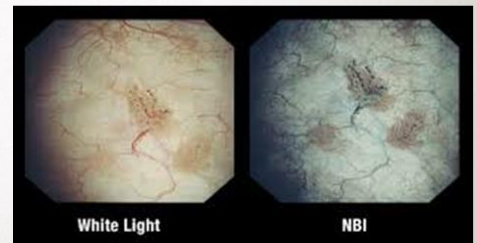
Dr. Amy Luckenbaugh: I currently tend to do this in people who have those cancer cells in the urine that we can't find a reason for. And I also do it in people who I'm looking back in after they've already had a bladder tumor removed, either by an outside urologist, or myself, and we're making sure that there is nothing else there.

This is less common now, but some people still do it. It's called narrow-band imaging. And this basically helps see a bladder tumor based on its vascularity, meaning how many blood vessels there are. This is not quite as useful, in my opinion, as the blue light cystoscopy, but it can certainly help. And you can see again under the normal camera, and then under the special camera. It can help see things that we might miss with our naked eye. So, those are the diagnosis and evaluation.

And now I think the part that is most important and that I'll spend the most time on is the staging and the risk groups. So, these are the types of bladder cancer, as you may already know. And what you can see here is there is something called carcinoma in situ, which is a high grade type of cancer that is growing only on the lining. And this is the lining of the bladder right here. And then there is another type of cancer called TA. And that is when it is on the lining, but it's more on a stalk, and it's not growing in over such a large surface area. And then there is something called T1. And that is something where you may have roots growing into the layer of the bladder, but not

Narrow band imaging

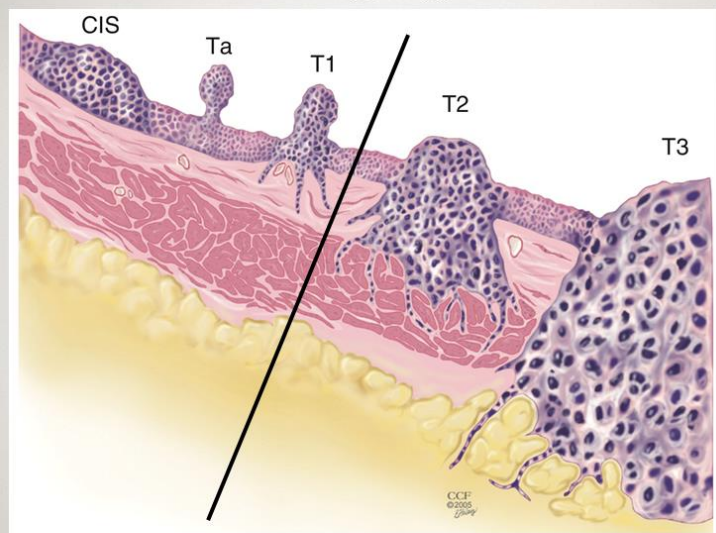
- Enhanced visibility of highly vascular tissue
- AUA Guideline Grade C recommendation
- No intravesical agents required
- Uses 2 wavelengths absorbed by hemoglobin:
 - 415 nm for superficial layers
 - 540 nm for deeper layers



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Staging



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yet into the muscle. And this is the stuff when you start to see things into the muscle. I won't talk about those T2 and T3 today, I'll just be talking about carcinoma in situ, TA, and T1.

Dr. Amy Luckenbaugh: Of people who are diagnosed with non-muscle invasive disease, about 70% will have TA type of cancer, and 20% will have T1, and 10% will have carcinoma in situ. Again, the important thing I think to know is that T1 has those roots that are starting to grow towards the muscle. And so, there is a bit of a higher risk of that becoming muscle invasive. And when it invades the muscle, there's a higher risk of it spreading outside the bladder. And so, that's why we always try to stage these very carefully.

Dr. Amy Luckenbaugh:

What is the difference between stage and grade? When you see your pathology reports online and things like that, what you'll see is a stage and it'll be listed. And then you'll also see a grade, and it will either say low grade or high grade. Grade is what the pathologist sees when they look under the microscope. And it's basically how abnormal the cells are. Low grade cells tend to be closer to normal. They are more likely to come back, but they are not very likely to progress or grow deep into the bladder wall. So, recurrence is tumors coming back. Progression is tumors growing deep into the wall when it was not initially deep into the wall. And low grade is less likely to do that, whereas high grade tumors can both come back and can grow deeper into the wall.

And so, this is kind of a table showing what I was just talking about. You can see in that blue circle, the chance of progression, so growing deep into the wall, for low grade tumors is only around five to 10%. So, it's pretty uncommon. Whereas for high grade tumors, even if it is a stage TA, only in the lining, there's about a 15 to 40% chance it could grow deeper. And so, high grade, we tend to treat a little more aggressively.

Grade

- Low Grade
 - Likely to recur
 - Less likely to progress
- High grade
 - Likely to recur & progress

Progression

TABLE 93-1 Estimates of Disease Progression in Non-Muscle-Invasive Bladder Cancer: World Health Organization/International Society of Urologic Pathology Consensus Classification

TUMOR TYPE	RELATIVE FREQUENCY (%)	PROGRESSION (%)	DEATHS (%)
NONINVASIVE			
Papilloma	10	0-1	0
Papillary urothelial neoplasm of low malignant potential	20	3	0-1
Papillary cancer, low grade (TaG1)	20	5-10	1-5
Papillary cancer, high grade (TaG3)	30	15-40	10-25
INVASIVE			
Papillary cancer (T1G3)	20	30-50	33
CARCINOMA IN SITU			
Primary	10	>50	—
Secondary	90	—	—

From Donat SM. Evaluation and follow-up strategies for superficial bladder cancer. Urol Clin North Am 2003;30:765-6.

Dr. Amy Luckenbaugh:

This is something that I think is really important, and it's a lot of information, but it plays a role in how you personally end up being treated. The AUA came up with these risk groups for bladder cancer based on stage and grade. And what it takes into account is how likely you are either to recur or progress. And it helps guide treatment strategies based on that.

So, for people who have a low risk type of bladder cancer, and it is a small tumor, and it is a low grade tumor, they are the lowest risk type. And so, those type of patients we oftentimes survey. And then there's a second category that's kind of this intermediate risk type of bladder cancer. And that can either be a bigger low grade type of tumor, or any high grade tumor that is under three centimeters and not T1, falls into this category. The high risk category is anyone who has T1, so the cancer that is into the lining, but not yet into the muscle. Any very big high grade TA, any carcinoma in situ, and anyone who has had BCG before without it working successfully, as well as any different type of cells that pathologists saw. And all of these categories really play a role in what treatment we recommend and what treatment you'll receive.

AUA - Risk Groups

TABLE 4: AUA Risk Stratification for Non-Muscle Invasive Bladder Cancer

Low Risk	Intermediate Risk	High Risk
LG ^a solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1
PUNLMP ^b	Solitary LG Ta > 3cm	Any recurrent, HG Ta
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)
	HG ^c Ta, ≤ 3cm	Any CIS ^d
	LG T1	Any BCG failure in HG patient
		Any variant histology
		Any LVI ^e
		Any HG prostatic urethral involvement

^aLG = low grade; ^bPUNLMP = papillary urothelial neoplasm of low malignant potential; ^cHG = high grade; ^dCIS=carcinoma *in situ*; ^eLVI = lymphovascular invasion

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pTa

Low grade

- **Recurrence:** 50%
- **Progression:** 5%
- **Treatment**
 - **Low risk, low grade:** postoperative intravesical chemotherapy (gemcitabine vs. mitomycin) & observe
 - **Intermediate risk, low grade:**
 - Consider 6 weeks of intravesical chemotherapy
 - Consider induction BCG if chemotherapy fails

High grade

- **Treatment**
 - Consider repeat resection
 - Induction BCG + maintenance
 - **Intermediate risk, high grade:** 12 months maintenance
 - **High risk, high grade:** 36 months maintenance

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So, for TA low grade tumor, they can come back about 50% of the time, but they progress only 5% of the time. So I tell people, you're kind of stuck with a urologist for the majority of your life with this, just to keep a close eye on things. For low risk low grade tumors, the treatment options are either to observe, or to give a type of chemotherapy inside the bladder, often at the end of the surgery that you've had.

Dr. Amy Luckenbaugh: And that can be either gemcitabine or mitomycin. And I'll go into more detail about what those are towards the end of that. I tend to favor gemcitabine because it is tolerated just a little bit better.

If there is a low grade tumor, but it is a little bigger, then we will either observe, or we might consider doing a weekly type of chemotherapy in your bladder weekly for six weeks. And so, those are kind of the general options for low grade type of bladder cancer. And I'll again talk more in more detail about each of the medications a little bit later.

For high grade bladder cancer that is still just on that lining, in some cases if it is a large tumor, would consider repeating the TURBT, looking again to make sure that everything is out, to make sure it's not going deeper, and that we got it all. But for high grade cancer, instead of doing a type of chemotherapy in the bladder, that is when we start doing BCG medicine in the bladder. And typically, we do that weekly for six weeks. And if it was something where it is kind of an intermediate risk on those categories I showed you, we may recommend that you get that treatment at three months, six months, and then another six months after that to reduce the risk of it coming back.

And that kind of brings me to the T1. These folks are the people who have the tumor kind of growing into the lining right before the muscles. So, it's the closest to the muscle. The risk of recurrence is quite high in these patients. But the real concern is the risk of progression. So, one out of three people will progress to muscle invasive disease. And so, it's really important that we adequately make sure there's no muscle involvement before we start treating you.

So, anytime there is this T1 type of cancer, we will do what's called a repeat TURBT, where we look back in and we biopsy deeper to really double check that there's no cancer in the muscle. Because about 20 to 40% of the time there can be cancer hiding there that was missed on the first resection no matter how good the first resection was. For these people, because of the risk of progression, not only do we give the six weeks of BCG, but we recommend up to three years total. And that's obviously been changed a little bit because of BCG shortages, but this is in the ideal world.

pT1

- **Recurrence: 50-70%**
- **Progression: 30%**
- **Treatment**
 - Repeat TURBT
 - Induction BCG + 36 months maintenance
 - Repeat TURBT (consider enhanced cystoscopy) 6 weeks after completing induction BCG
 - Consider early cystectomy
 - High volume T1, CIS, variant histology, multifocality, LVI

Dr. Amy Luckenbaugh: And then there is the category of people who have a large volume of this T1 cancer that we might consider early bladder removal. And that's an aggressive option, but it is an option. And specifically for people with a high volume of the T1 tumor, or a special type of histology, meaning the cells that the pathologist reviewed was a little different.

Carcinoma in situ, that is the high grade stuff that kind of grows on the lining in a bigger sheet. This is usually shows up, and is seen in the cytology, which are those cells we send from the urine sample without having to biopsy anything. And for this type of cancer, we treat it like it's high risk. And you would get induction BCG, so the six treatments, and then three years worth. 10 years after diagnosis with carcinoma in situ, there's about 20% of people who could still die from bladder cancer. And so, that's why we're so aggressive about treating this with three years of BCG, if we can.

And these are the special cases I kind of referred to earlier. There's a select few of you who might have what we call a variant histology. That's an uncommon type of bladder cancer that the pathologists look at and they see under the microscope. And some of those uncommon types tend to be more aggressive. And so, even if it is non-invasive, we sometimes consider early removal of your bladder because they tend to be more aggressive.

Carcinoma In Situ

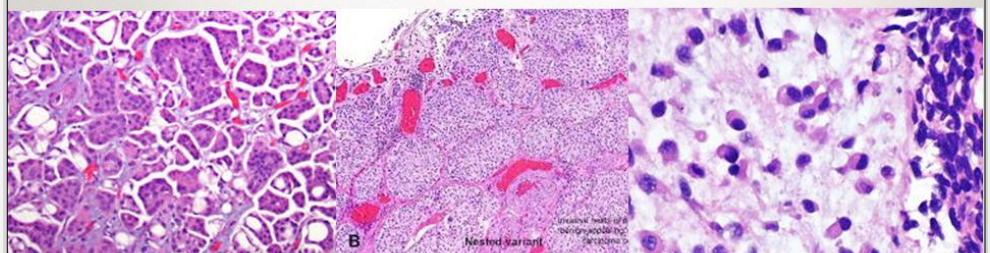
- Majority have positive cytology
- Treatment: induction BCG + 36 months maintenance
 - After iBCG: repeat TURBT, cytology
 - Recurrence after initial complete response to BCG: 30%
 - Progression after initial complete response to BCG: 20%
 - Consider cystectomy if persistent disease after iBCG
- At 10 years, 20% with CIS will die from urothelial carcinoma

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Special Cases

- **Variant histology:** Micropapillary and nested variants (perhaps also plasmacytoid, signet ring, sarcomatoid) are very aggressive and should consider early cystectomy even when NMIBC
- **AUA Guidelines:**
 - Path should be reviewed by experienced GU pathologist
 - If considering bladder sparing, should re-resect within 4-6 weeks
 - Consider early cystectomy due to high rate of upstaging



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