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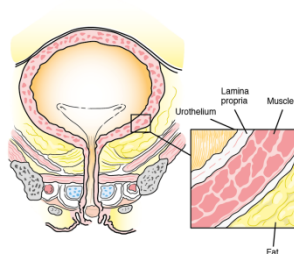


Dr. Matthew Mossanen completed his college and medical school training at UCLA. He is now a Urologic Oncology Fellow at the combined Urologic Oncology Program at Brigham and Women's Hospital in Massachusetts General Hospital. He is also obtaining an MPH from the Harvard T.H. Chan School of Public Health. In July, he will begin working as a faculty member at Brigham and Women's Hospital and Dana-Farber Cancer Institute. One of his main clinical research focuses centers on improving the quality of care for patients with bladder cancer.

Dr. Mossanen: I'm a Urologist and I'm really excited to be here. This is a great opportunity for patients, caregivers, anybody impacted by bladder cancer, to basically have an overview. I'm also joined by Guru Sonpavde and Kent Mouw, so you have three people representing three disciplines that deal with bladder cancer. My hope is that we can go over a little bit of background talking about what the bladder's job is, just some basics. We'll go into a little bit of detail about what bladder cancer is. We'll talk about what a pathology report contains the information inside. We'll talk about how we actually get that diagnosis, which is in the pathology report. And then importantly, kind of the meat of this talk is going to be to go over the specific stages of bladder cancer. And then at the end each of us, a Urologist, a Medical Oncologist, and a Radiation Oncologist will give you sort of a sampling or a brief overview of different treatment options.

What is the bladder's job?

- **Bladder**
 - Function: Store and excrete urine
 - Location: Lower abdomen
 - Structure: Layers
- **Layers of the bladder**
 - Urothelium
 - Lamina propria
 - Muscle
 - Fat



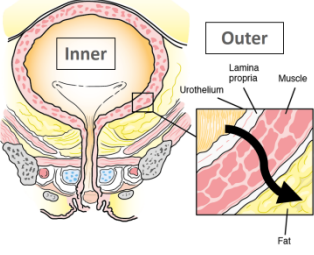
So this is just sort of like a basic introductory slide. What's the bladder's job? So the bladder stores urine, it's located in the lower part of the abdomen under the belly button, and importantly, the structure of the bladder is that it's a wall made of layers. And the wall has basically four layers, you can think of it that way. And if you look at the picture, the innermost layer is called the urothelium. And then behind that, or if you move outward from the center of

the bladder, there's a lamina propria. And then outside of that is a thicker muscle layer. And then the outermost layer is the fat. So again, the innermost layer's the urothelium, the outermost layer is the fat.

And if you understand that, staging will make a little bit more sense. And if you look on that picture, you can see that what we've done here is we've sort of taken this little box, we've blown it up, and this is the inner surface with urothelium and the outer surface with fat.

What is bladder cancer?

- **Bladder cancer**
 - Cells grow "out of control"
 - Usually starts in inner layer
 - Can grow into deeper layers
- Layers help us understand stage
 - Stage is how **deep** the cancer is growing into the bladder wall
 - Urothelium = surface lining
 - Lamina propria = connective tissue
 - Muscle
 - Fat



The diagram shows a cross-section of the bladder wall. The innermost layer is the urothelium, followed by the lamina propria (connective tissue), then the muscle layer, and finally the fat layer. A box labeled 'Inner' highlights the urothelium, and a box labeled 'Outer' highlights the fat. An arrow points from the urothelium towards the fat, indicating the direction of cancer growth.

So what is bladder cancer, then? So bladder cancer is when the cells in the wall of the bladder, usually they start in the inner most layer, they start to grow sort of out of control. And it can grow into the deeper layers. So if we think about the layers, we start to understand stage. And stage is basically how deep the cancer is growing into this wall. And the urothelium, again, is this sort of inner surface lining that goes all the

way in the inner surface of the bladder. Then again, a lamina propria, which is like a connective tissue layer, and then the muscle which is just like muscle that you're familiar, and then fat which surrounds the entire bladder. The graphic here, this arrow's just meant to show that you need to conceptually think of your stage as how deep it goes within this wall.

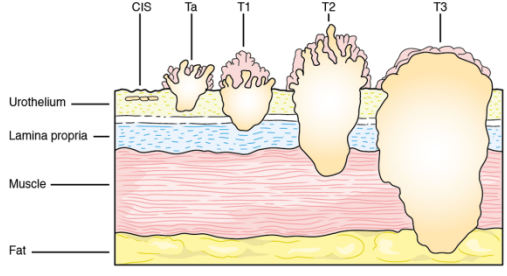
So staging refers to a process where we try to figure out through a variety of different procedures and imaging tests which layer of the wall the cancer's in and if the cancer's maybe spread to other places in the body. It's important to be aware of this because if it's not treated, then the tumor might be able to grow and go into deeper layers or maybe even spread to other places. And so thinking about it, as you go through the stages, the stage increases as the bladder tumor grows through the wall. So the higher the stage, the further the T stage.

So these are some of the different potential diagnoses that you may have when you do your bladder biopsy and get your staging.

So one is we call it CIS and that stands for Carcinoma in situ. And this is a non-invasive, flat, high grade cancer within the urothelium and you can see that sort of represented here in the cartoon.

The next stage of bladder cancer is called Ta and Ta usually refers to papillary tumors which kind of have this papillary shape, almost like a little piece of seaweed, and it's not usually going any deeper than the urothelium layer. And you can kind of see that here depicted in the cartoon.

What are the stages of bladder cancer?



The diagram shows a cross-section of the bladder wall with five stages of cancer labeled: CIS, Ta, T1, T2, and T3. CIS is a flat tumor within the urothelium. Ta is a papillary tumor that has grown into the urothelium but not deeper. T1 is a papillary tumor that has grown into the lamina propria. T2 is a papillary tumor that has grown into the muscle layer. T3 is a papillary tumor that has grown through the muscle layer and into the fat layer. The layers are labeled: Urothelium, Lamina propria, Muscle, and Fat.

Bladder Cancer Stages

Now a T1 is a little bit different now. We

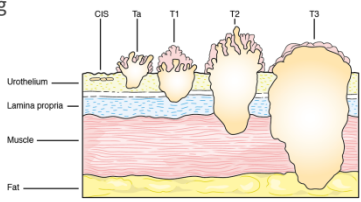
moved from the "a" which represented a papillary tumor, to numbers. So T1 typically means that the tumor's invading the connective tissue underneath the surface lining, or the urothelium. And again, for orientation, this is the innermost layer and the fat is where we have the outermost layer. So T1 again is in the connective tissue.

Now T2 bladder cancer refers to the stage that invades into the muscle layer. And so if you have anything greater than that which is T3 then usually what that means is that the bladder cancer's going all the way through the muscle layer and involving the fat. If you have T4 bladder cancer, what that typically means is that it may be in a nearby structure; a prostate for a man, or a vagina for a woman.

Thinking about the walls of the bladder is how you can understand your stage. And so we'll go through a little bit of how you can anticipate potential treatment options based on your stage.

A side note

- Another way to think about staging
- Bladder cancer is like termites
- If the bladder is a wall in a house
 - Urothelium = in the paint
 - Lamina propria = in the drywall
 - Muscle = in the wooden beams
- Nodes = in the vents
- Metastases = in another room



The diagram shows a cross-section of the bladder wall layers: Urothelium (outermost), Lamina propria, Muscle, and Fat (innermost). Tumor stages are indicated by arrows: CIS (Carcinoma in situ) is on the surface; T0 is a papillary tumor on the surface; T1 invades the lamina propria; T2 invades the muscle layer; T3 invades through the muscle into the fat; and T4 invades through the fat into adjacent structures.

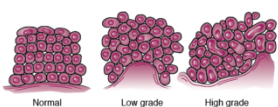
This is a quick side note. So I spend a lot of time talking to patients and explaining their stage to them and there's a lot of confusing terminology here. But one of the analogies that I like to use is thinking of bladder cancer like a bunch of termites. This may be helpful for some people that like to think in analogies, and if this doesn't make sense to you, you can just ignore it. But I'm

going to go through the example anyway because sometimes people find this helpful. So if bladder cancer's like a group of termites and the bladder is like the wall in a house, if the termites are going into the paint of the wall, it's kind of like bladder cancer that's in the urothelium. If the termites are going a little bit deeper, kind of like into the drywall, it's almost like they're in the lamina propria. If the termites are going through the paint, through the drywall, and into the wooden beams that sort of give the room its support, then you can think of that as muscle invasive disease. If they get into the vents it's like you have node involvement and if there's termites in another room of the house you can think of that as metastatic disease. Hopefully this is a useful analogy for just a few people out there. If this is confusing or doesn't make sense, you can totally disregard it.

So another important part of your bladder cancer diagnosis that you get from pathology is the grade. The grade can typically be "low" or "high". The cells in high grade tumors look very different from the normal cells. And so the less normal looking the cell is, the higher the grade.

What is grade?

- Grade can be **low or high**
- The cells in **high grade** tumors look **very different** from a normal cell
- The less normal looking the cell, the higher the grade
- Higher grade tumors are more **aggressive**



The diagram shows three stages of cell morphology: Normal (uniform, organized cells), Low grade (slightly irregular cells), and High grade (highly irregular, disorganized cells).

This is important because higher grade tumors are typically more aggressive or show more risky behavior that makes us concerned.

Imaging is also used in staging

- ✓ It is important to know if bladder cancer may have spread from one part of the body (the bladder) to another
- ✓ CT or MRI used to take detailed pictures of areas inside the body
→ This can give information about lymph nodes or metastasis
- ✓ **Lymph node:** Lymphatic tissue also called a lymph gland. They perform filtering functions in the body.
- ✓ **Metastasis:** The spread of cancer from one part of the body to another.

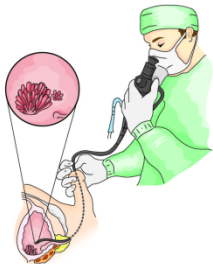
So what else is done in staging? So in addition to the T-stages, it's also important to know if bladder cancer may have spread to another part of the body, so somewhere beyond the bladder. Usually what we do is we get a CT or an MRI and we take some detailed pictures. And the reason we do this is because it gives us information about other areas,

and in particular lymph nodes or metastasis. Now lymph node, for the people that are sort of getting acquainted with bladder cancer that might not know, is an area of lymphatic tissue. It's also called the lymph gland and these are located throughout the body, and the lymph nodes perform filtering functions. And CT or MRI can tell us if we suspect that one of these lymph nodes may be involved in bladder cancer. Metastasis is the spread of cancer to another part of the body, to, for example, another organ.

So we've gone into a little bit of detail about staging that involves the layers of the bladder wall. We've talked a little bit about getting a CAT scan or an MRI to get a little bit more information about staging. But I think it's important to talk just briefly about how this diagnosis is obtained.

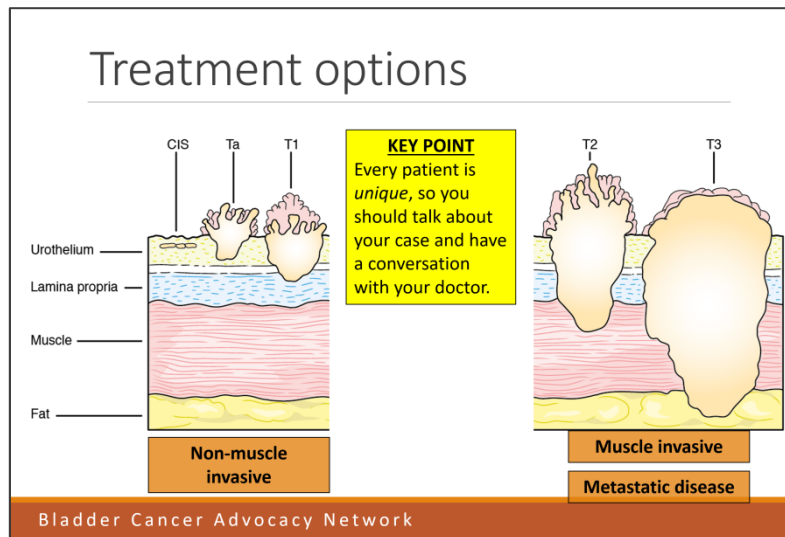
Now many patients will undergo cystoscopy and that is where the Urologist puts a camera inside the bladder and gets a look at the tumor. In order to get the diagnosis, a TURBT is done, and that's sort of like an abbreviation for a term that we use and it means transurethral resection of bladder tumor. And this refers to a procedure where we remove or scrape the tumor. We take it out, usually all of it, sometimes part of it, it really depends. But we remove it so that we can get more information. This procedure, a TURBT, is done by a Urologist, it's done in the operating room, and you need anesthesia for this to be done. The results are usually put in a pathology report and it's important because the pathology report is your roadmap to your diagnosis. It includes the information that we just went into in detail.

Diagnosis

CYSTOSCOPY	TURBT
	<ul style="list-style-type: none">• TURBT – Transurethral resection of bladder tumor• A <u>procedure</u> used to remove (or scrape) the tumor so it can be analyzed under a microscope• Procedure is done by a <u>urologist</u> in the operating room with anesthesia• The results are put into a <u>pathology report</u> and this will be important in figuring out treatment options

So this is a little bit of a summary slide. So after you undergo your TURBT, or the resection of the bladder tumor, you'll get a pathology report and it's important that you sit down and go over this with your team. So the type of cancer is written on the report and in most cases it's called, "urothelial cell carcinoma" or "transitional cell carcinoma". The stage will usually be there. It can also include PTA or CIS and then the grade, and this is usually low or high, but in some institutions this corresponds to grades 1

to 3. Now this is a lot of information, pathology reports are very complex documents. So it's important to highlight that at this point, you really want to talk to your Urologist or your Pathologist. Then based on that discussion, you can figure out if more people need to join the discussion, such as a Medical Oncologist or a Radiation Oncologist. And fortunately today, we have both of those people here who will give a little bit of information about what their involvement might entail. The pathology report is the roadmap to diagnosis.



Now one way to think about your treatment is to think about it as non-muscle invasive disease and muscle invasive disease. There's also a category for metastatic disease. But since every patient is unique, I want to emphasize that you really need to have a conversation with your doctor, with your Urologist, about your specific situation. But one way to think of it is a non-muscle invasive disease, muscle invasive disease, and metastatic disease.

Okay. So treatment options. Now this is where we sort of move from staging to the broad non-specific overview of what potential treatment options might include. This is meant to sort of give you a preview of what could potentially be done to treat your bladder cancer. And remember that the choice will depend on your specific diagnosis. But some of those choices might include things like observation with cystoscopy, and that means that you'll come into the Urologist's office at fixed intervals and they'll look in your bladder with a camera and just kind of monitor things. It's also common for some patients to require repeat procedures, such as another TURBT within a few months after your initial one or even down the road, because as we all know bladder cancer can re-occur. In certain situations, you may also receive intravesical therapy. That word, intravesical, means inside the bladder and what this refers to is a liquid medicine. We usually put a catheter in the bladder, we instill medicine, and we let it sit there. Some commonly medications are mitomycin C and BCG and there are others.

I wanted to put a bullet point here to emphasize that you can discuss this with your provider based on your pathology report and also visit the BCAN website because sometimes there are clinical trials that may be applicable to your specific situation. Those include things like immunotherapy or even radiation.

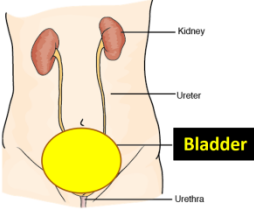
So the next slide. We were just on non-muscle invasive and so the overview for muscle invasive bladder cancer can include a few different things. And it's important to highlight that patients have multiple choices. Again, discussing this with a provider, visiting the BCAN website, which has a lot of great information including other webinars and really concise two-page summaries, to sort of go over some of these topics here. But in the interest of giving you guys a preview, one is a cystectomy with a urinary diversion. This usually involves Urologists that do the surgery. There's also chemotherapy, or immunotherapy, that's done by Medical Oncology. And then there's trimodal therapy which is also

called bladder sparing. And this includes a Radiation Oncologist working together and it's a little bit misleading to only list a Urologist under cystectomy and only a Medical Oncologist under chemotherapy and only a Radiation Oncologist under trimodal therapy because in reality, for many of these treatments, the doctors all work together to be a team and to sometimes even combine these therapies.

Urologic Oncology

BLADDER REMOVAL = CYSTECTOMY

- Urologist performs a radical **cystectomy** = surgery to remove the bladder (open or robotic)
 - Includes prostate in men and uterus in women
- A lymph node removal is also done at the time of surgery
- Large team involved in the preparation for surgery, hospital stay, and healing process



So I'm going to talk a little bit about the Urology side of things which is bladder removal. And that term is cystectomy. A Urologist typically performs a cystectomy, which is a surgery to remove the bladder. And this can be done open or robotic; it will depend on where you get your care and the experience of the surgeon. That's a little bit beyond the scope of this talk. But what's important is that

the bladder is removed and this can also include the prostate in men and the uterus in women. At the time of cystectomy what we also do is a lymph node removal. It's sometimes called a lymph node dissection. For patients that undergo cystectomy it's important to highlight that it's actually a very large team involved in getting patients ready and helping patients while they're in the hospital and in helping patients recover after a cystectomy.

After a cystectomy is performed and the bladder is removed, a urinary diversion is constructed. There are lots of different kinds of urinary diversions. There are things called ileal conduits, neobladders, Indiana Pouches. This is really a complex decision that depends on a lot of factors. There's a nice webinar that goes into detail over some of these choices and satisfaction is usually pretty good as long as patients pick the diversion that's right for them. So I encourage you to talk to your provider, visit the BCAN website, or even talk to other patients that may have gone through a similar experience to you.

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