

## **Morgan Stout:**

A bladder cancer diagnosis can be terrifying to a patient and their family. What do you need to know

about muscle invasive bladder cancer, MIBC and the treatment options for it? BCAN is delighted to have Dr. Tracey Krupski, a professor of urology at the University of Virginia today for today's program. Dr. Krupski is a surgeon who's specialty is urologic oncology and her research focuses on health related quality of life and outcomes of robotic versus open surgery for muscle invasive bladder cancer. Welcome Dr. Krupski, I'll turn it over to you.



## Dr. Tracey Krupski:

Thank you, Morgan. That was very nice introduction. And I too would like to thank the sponsors that you can because it really is through their support that we are able to provide educational programs like this so thank you very much. So today we're going to talk about muscle invasive bladder cancer. I am Tracey

Krupski. I originally am from New York and then I went to Virginia, but I did my urologic oncology training at UCLA before I came back here.

And now that I'm at UVA, I predominantly see bladder cancer patients both the non-muscle invasive kind, which is usually how they present and then of course, muscle invasive as we already alluded to. So I have had funding related to bladder cancer through the American Cancer Society and I've been part of some industry sponsored trials for new bladder cancer therapies which are since complete so I have no ongoing disclosures right now.

So what I thought we'd try to talk about today and we may feel like we're jumping around, but I was going to try to take you through the way I think of presenting this to my bladder cancer patients, is first, what are the indications for a cystectomy? There can be several different reasons that somebody is going to undergo a cystectomy, and then along with that, we want to talk about who should potentially consider chemotherapy before having their big surgery.

Then since I'm the surgeon, we're going to touch a little bit on nonsurgical options, but mostly we're going to spend some time talking about preparing for surgery, the expectations during surgery, what happens after surgery immediately and then how this could influence your longer term quality of life. And then I just wanted to tie up with some exciting new things that could be coming along the pike for bladder cancer.

It's been a really exciting time the last maybe five years or so. For 20 years, we hadn't had anything for bladder cancer and now we're just having explosion of information and new treatment options, so it actually is very satisfying. So let's just dive right in. Usually my experience is the BCAN population is quite sophisticated and usually ask me a lot of really poignant questions, but let's all start from same ground level and make sure that we're on the same page, so to speak.

## Dr. Tracey Krupski:

So hopefully you can see my mouth, but if not, I can just kind of walk you through it. The bladder is comprised of three layers, the mucosal layer, which is the surface. And I tell people that's like the mucosa of your mouth, that inner lining that touches, in this case, the food, but here, the urine. Then there's the scaffolding layer, that's this kind of circle, or we call it the lamina propria. But it holds the bladder in an actual circle, then the muscle that does the contracting.



So the depth of invasion, not necessarily

the size is really what's most important. If it's a surface tumor like this, it means it's jutting up off of the mucosa with a little stem and it doesn't go deep. If the root system like a plant is going deeper into the first layer, the laminal layer, it becomes this T1 tumor. If it was just at the surface, it's a Ta tumor. And then if it's going deep into the muscle below that surface that you can see, it's a T2 or T3 and then T4 means it's trying to grow outside the bladder into adjacent organs.

Endoscopically you can't really appreciate whether something's all the way through or not, but you can often on imaging or if the bladder is totally removed, that's when you know if it's gone outside the bladder. So this carcinoma in situ is a little bit different. It is non muscle invasive because it's on the

surface, but by definition, it tends to act a little bit more aggressively so we keep a very close eye on carcinoma in situ.

### Dr. Tracey Krupski:

The focus of this talk is T2 or those deep tumors going into the muscle. So just for you to visualize, endoscopically, we diagnose these by looking through a camera into the bladder, and this is a very frangula little papillary tumor. It looks like a little broccoli flowerette or a sea anemone. This is almost certainly a Ta tumor, low grade, not going to be muscle invasive and tends to keep coming back, but doesn't spread to other organs and become particularly dangerous.



This on the other hand is kind of a representative picture of a tumor that's much more nodular. We kind of call this sessile, meaning it has a broad contact with the bladder base and it just looks a little bit more hefty and aggressive. So for somebody who walks in the door of a urologist's office with bladder cancer, 70 to 80% are going to be this low grade, non muscle-invasive kind. They tend to come back but don't tend to spread.

20% of the time you will come in the door with a bad cancer, a muscle invasive cancer. It's not that these gradually become these. Most of the time, you actually walk in the door with a bad cancer. These unfortunately are dangerous, they can be lethal and so we want to treat them quite aggressively. This is one brief non muscle invasive slide. So for that first papillary type picture this is where you'll hear things like what is the size of the tumor? What is the grade of the tumor? How often does it come back or are there more than one?

When you hear those kind of words or lingo, that's non muscle invasive cancer and we're worried about risk stratifying them in terms of how quickly or how often they'll come back, not necessarily in terms of prognosis like being lethal or spreading to your legs, lungs or lymph nodes, et cetera. So if you hear something like low, intermediate, high risk, this is for a recurrence bladder therapies inside the bladder, all of that is related to non muscle-invasive disease, not muscle invasive disease.

So the obvious reason that we'll see on the next slide is muscle-invasive cancer, that's of common reason to take out someone's bladder, but we can do it in the setting of these non muscle-invasive tumors for certain characteristics. So if it's T1, that means it's going down into that first layer of the bladder, high grade. Grade always refers to how does it look under the microscope? Is it aggressive appearing or not aggressive appearing?

## Dr. Tracey Krupski:

And so if you have a T1 tumor going into the first layer, high grade and it has some of those other features like it keeps coming back quickly, we can't seem to remove it entirely when we do this resections endoscopically or it has any of these funny types of tumors that are a different cell type than the normal lining of the bladder. So the normal lining of the bladder is urothelial cancer. If you have a cancer that's called micropapillary, nested,



plasmacytoid, neuroendocrine, sarcomatoid, these are aberrant or different histologies that tend to act more aggressively.

So we often think of removing the bladder for these or high grade T1 tumors that keep coming back that that could be our window for cure. So there could be an indication other than just being less invasive. Not the focus of this talk but if you've done anything with bladder cancer, you know we often treat BCG, we use non muscle invasive cancer and treat it with BCG. If you have an unresponsive tumor to BCG, you may also undergo a cystectomy.

# Indications for Cystectomy

#### • T1, high grade urothelial cancer

- Chance of understaging of the original tumor
- Diffuse T1, window to cure is before muscle invasion
- Heightened concern if atypical (aberrant histology) Micro



- Highest progression (multi-focal, CIS, rapid recurrence)
- BCG unresponsive
  - Nomenclature has changed but essentially means non-muscle invasive cancer that has not resolved with intravesical therapy

The most common reason is as I showed in those first pictures, you have a bad cancer that's going into that muscle layer or beyond, that's maybe your first tumor ever and that is the main indication to consider removal of the bladder. People ask, can you just remove part of the bladder? Why do you have to take the whole thing? Well, urothelial cells line everything that's in contact with urine so the upper part of the right kidney and the tube to the right kidney, the upper part of the left kidney, the tube to the left kidney and the entire bladder is covered with urothelial cells.

So most of the time it's a field defect and it's going to be another cancer cropping up in the lining of your bladder even if you remove one. So there's a couple times if it's a diverticula, which means there's only cancer in the outpouching, a very large capacity bladder or a small tumor right at the very top, those would be the only times your doctor may discuss with you doing just a partial cystectomy.

## Dr. Tracey Krupski:

If your tumor invades the prostate and you're a man, you have to have the whole bladder removed because that's by definition spread into another organ. And occasionally people have opted for chemo radiation, we're going to talk about that in a second. But if that fails, then you could consider removing the bladder at that time. So those are all the oncologic reasons to remove a bladder. There are other reasons, multiple sclerosis, things like that, spinal cord injuries. We're not talking about those, we're just talking about cancer reasons.

There's lots of different guidelines that you can look up to follow on the internet. There's non-muscle invasive, muscle invasive, nonmetastatic, there's European guidelines, there's the AUA, which is our national organization. And I'm sure you're familiar with the National Comprehensive Cancer Network. They also put out these algorithms and flow sheets to

## Indications for Cystectomy

- Muscle invasive (T2) urothelial cancer
  - Rare instance that can remove only part of bladder
    - Diverticulum
    - Large capacity bladder
  - Adenocarcinoma at the dome
- Invasive disease in the prostate
- Salvage procedure following chemoradiation
- There are benign reasons to have bladder removed but not our focus



help figure out how we should best treat cancer.

So if you have muscle invasive bladder cancer, there is a choice of the two main pathways to be treated. There is surgical removal of the bladder or there is chemo radiation. So this first one is cystectomy, removing the bladder. If you're a man, you remove the prostate along with it. If you're a woman, often part of the uterus, cervix or some portion of the vagina may be removed as well. You have to reroute the kidneys, you have to use intestine for a reservoir. And we traditionally remove lymph nodes, which are near the large vessels to your legs that give you blood flow.

So it's a major operation dealing with a lot of different organs. If you choose to not do that, you may be older, maybe medically you don't think you're going to do well with that big a surgery, you may opt for what we call chemo radiation or trimodal therapy. That means you do an endoscopic surgery to remove all the visible tumor and go as deep as we could to try to get rid of everything that we can see on the inside of the bladder then you get radiation and chemotherapy at the same time.

## **MIBC: Choice**

- Cystectomy is a MAJOR surgery
  - Operating on the bladder and prostate/uterus and vagina
  - Re-routing the kidney
  - Using intestine for reservoir
  - nodes are near large vessels
- Frail or medically unfit (or patient choice)
  - Trimodal therapy is option
  - Maximal TURBT
  - Chemosensitizer (5FU or cisplatinum)
  - Daily Radiation

### Dr. Tracey Krupski:

And that may go on for five weeks while we are treating the bladder cancer and treating your entire bladder with a combination of radiation and chemotherapy. That is kind of represented. I just wanted to show you these national comprehensive guidelines. So if you look, you have stage two. If you can remember back to that original diagram, that means it's the deep going into the muscle, muscle invasive bladder cancer.



And if you're a cystectomy candidate, you would proceed along this side of the pathway. If you don't want to have a cystectomy or you're not medically maybe strong enough for it, we're going to this star part of things. So this little segue here is talking about not doing surgery for muscle invasive bladder cancer, but rather considering chemo radiation. So a few words about chemo radiation. Again, this is what I was alluding to.

It's very important to go under anesthesia, have the urologist scope you, look in through your urethra and remove as much visible tumor as they can. That means going almost all the way through the muscle to the point where they get to the fat around your bladder and then you keep a catheter for a little while while you heal that little hole and then you can consider getting the radiation to both the bladder, as well as some of those lymph nodes that we removed during the surgical part. So the pelvic lymph nodes and the bladder get radiated and we are able to then treat you with chemotherapy, which is sensitizing. What that means is it's making the radiation work better. So we use that in conjunction, they're synergistic, so to speak. Occasionally you'll get some markers put in the bladder to sort help focus where the radiation needs to go. And there's a 5 to 7% chance that after just a really, really aggressive resection in the operating room, you may be able to be rendered tumor free. That's what T0 means, no more cancer in your bladder if you have a really aggressive resection.

## Dr. Tracey Krupski:

Now that's not standard, but that's part of why we call it do all three, a good resection, chemotherapy and radiation. So if you're thinking about this option, it's going to save your bladder, right? You don't have to worry about removing the bladder and what are you going to do for a reservoir, this is a third of the patients are done. They've kept their bladder, their cancer doesn't come back and they don't have to worry about it.

A third go on to have their cancer come back, but it's still within their bladder. So they can go back to that cystectomy option again and then a third of the disease will progress to other organs and there would be no role for moving the bladder anymore. So in a sense, you can think of it as like two thirds respond initially and do well and maybe up to 30 to 40% continue to do well and never need anything else after chemo radiation.

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- Very important to get as complete a resection as possible.
- Some people place gold seed markers in the bladder-not everywhere
- Some patients are T0 after just the TURBT

Repeat resection

UNIVERSITY VIRGINIA HEALTH SYSTEM

UNIVERSITY VIRGINIA HEALTH SYSTEM

- There is level 1 evidence proving that chemoradiation is superior to radiation alone
- Chemoradiation + salvage cystectomy has the same survival as immediate cystectomy in many patients(not level 1)

#### How to think about this regarding cure

- Likelihood of saving the bladder:
- $\sim 1/3$  patients keep their bladder cancer free
- ~1/3 go on to require cystectomy
- ~1/3 die of disease
- ~2/3 respond to chemoradiation at least initially

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So this is a reasonable option. You should not just get radiation alone. Radiation alone is not as curative as chemo radiation. And if you do chemo radiation and you're closely followed and you go on to have recurrence in your bladder, the bladder cancer comes back, then we remove your bladder. That's what salvage cystectomy means, meaning we didn't do it up front, we're going to do it after you had this other therapy, you still do as well. Now that it's not quite as high of level evidence, but it can be done and you can be cured by removing the bladder if chemo radiation did not work. So here's just one little graph, we call these survival curves. So these are overall survival curves. These are people who got radiation only, and these are the people who got chemotherapy and radiation. And when these curves are separated like this, there's a much better chance of being cured with the chemotherapy combined with radiation.

Again, just to emphasize, close follow up. Somebody needs to look into your bladder every three months to see if that



cancer's coming back. CTs or pet scans are not good for this because urine tends to pick up the pet tracers so you can't tell anything that's going on in the bladder. We don't want your kidneys to get blocked, that's what hydronephrosis means. And the ideal patient is one who had a solitary muscle invasive tumor in one spot that's been fully resected.

## Dr. Tracey Krupski:

If it's sort of dotting all over the bladder, encompassing the whole half wall of bladder, those are not going to respond as well as a small tumor, fully resected, one spot, not blocking any kidneys, that type of thing. So chemo radiation.

