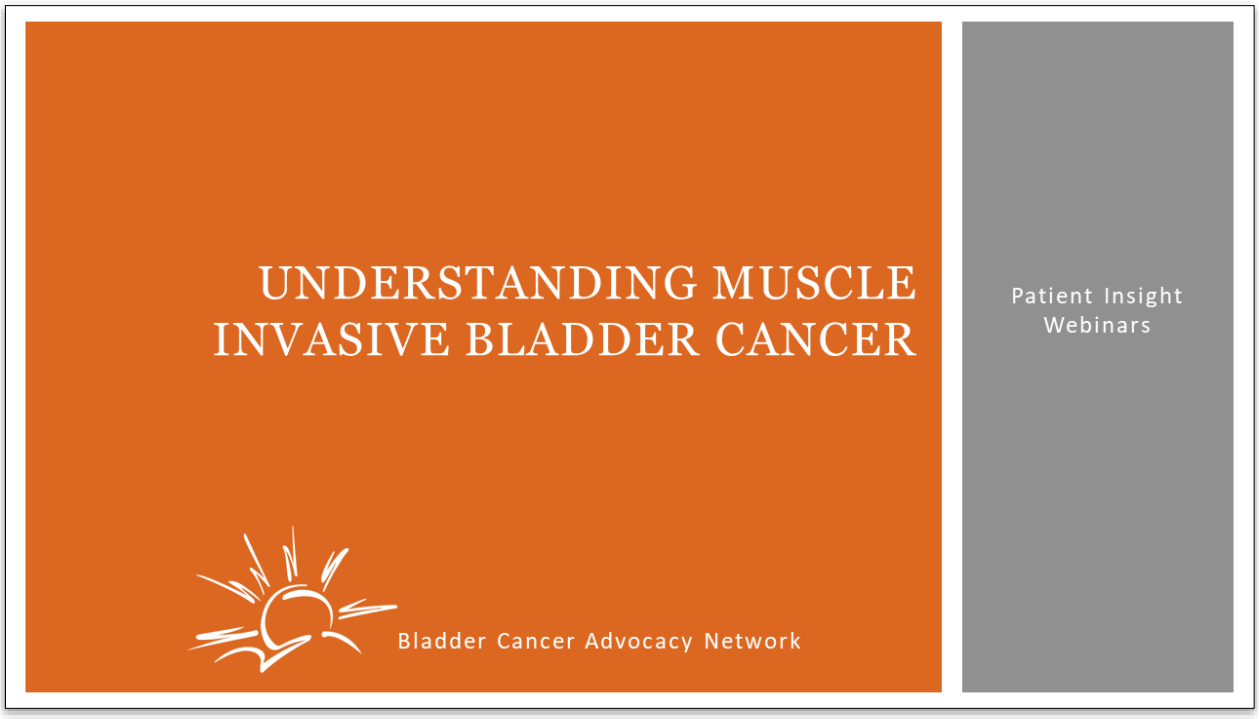
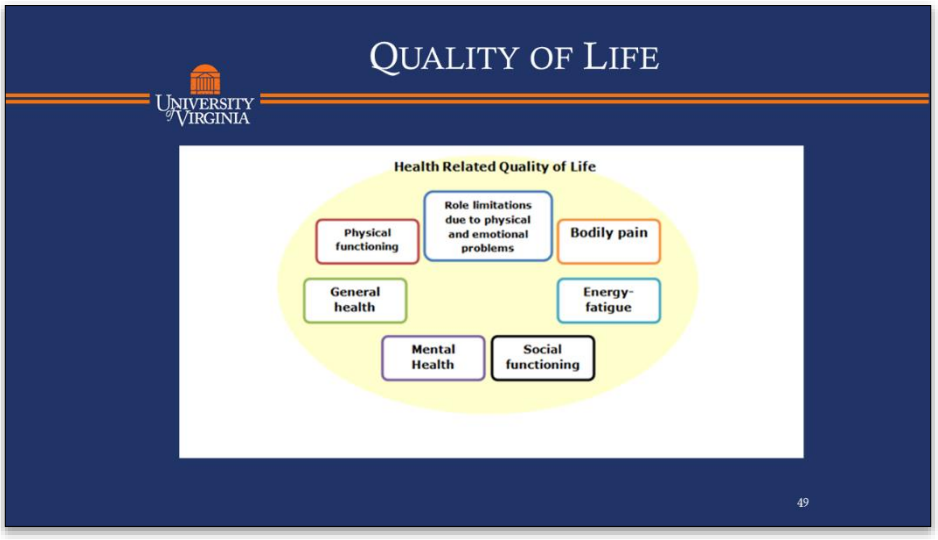



**Dr. Tracey Krupski:**

Quality of life. So what happens after this surgery? So when people talk about quality of life, when I did a lot of health related quality of research in my fellowship, we talk about these domains of health related quality of life. What are your limitations due to your emotional problems from having this surgery or physically you just can't do things anymore. That gets to your mental health, your social functioning.



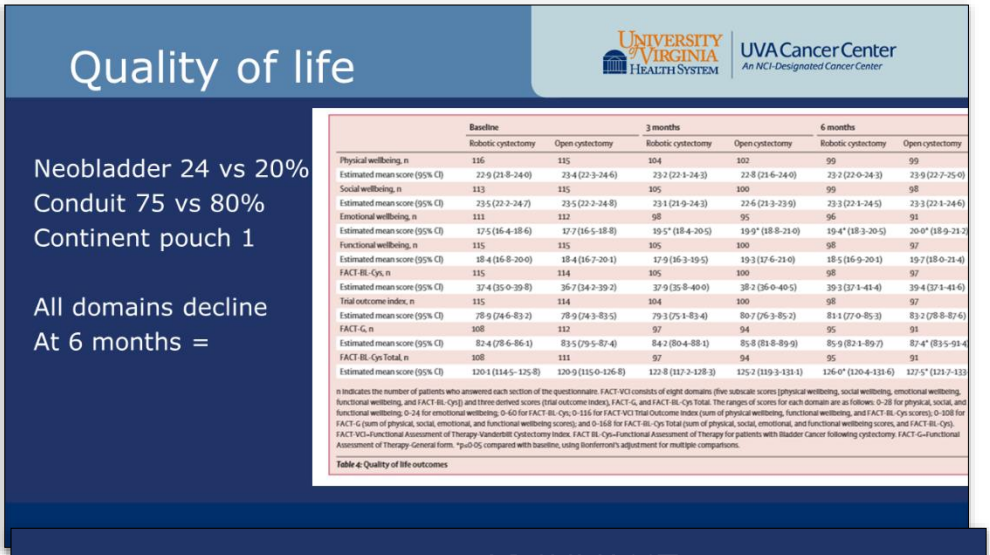
Can you still be a dad? Can you be a wife? Can you be a husband? Can you do those roles that you used to have in your life, a teacher, et cetera? Do you have chronic fatigue? Are you in pain? So these are all health related quality of life and we consider it kind of six or seven domains of quality of life. When we look at this, it's very different. There's no clear best choice that I could tell you everybody with the neobladder has a great quality of life or those people who got a conduit never had any problems.


We have to think about things like your dexterity, arthritis, catheterizations, those things, it's very personal. And going through, this is going to be like a prostate surgery. It's going to change your sexual functioning. It's going to change your orgasm sometimes. You might have incontinence if we build you this new bladder. You'll have incontinence occasionally even if you have the bag. So these are all going to be new life considerations that you probably haven't had to work with right now.

This was that same RAZOR study that we looked at neobladders and conduits and all those different quality of life. There's physical wellbeing, social wellbeing, emotional wellbeing. I'm sure you can't read the slide, but the point of it is all of them declined from baseline over the first six months. So there's a lot of dealing, learning to emotionally deal with getting through the chemo, getting through the surgery, dealing with your new bladder or pouch, however you want to think of it.

## Dr. Tracey Krupski:

And the quality of life changes. We're a little bit more severe for the neobladders than they were for the diversions. But either way, there's a decline in your quality of life and that still hasn't bounced back even six months later so you just have to be ready for that as do your caretakers. Then you might even need extra therapy after cystectomy.

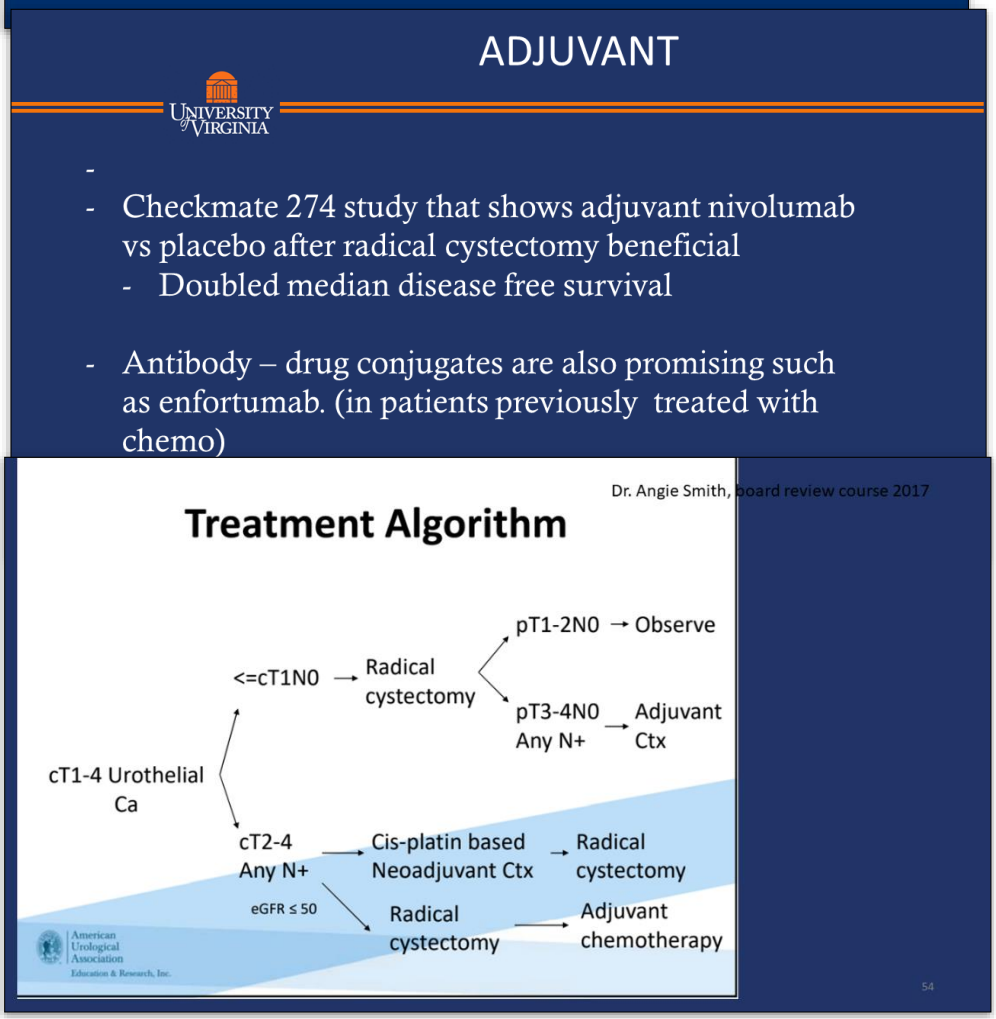



| | Baseline | | 3 months | | 6 months | |
|---|---|---|---|---|---|---|
| | Robotic cystectomy | Open cystectomy | Robotic cystectomy | Open cystectomy | Robotic cystectomy | Open cystectomy |
| Physical wellbeing, n | 116 | 115 | 104 | 102 | 99 | 99 |
| Estimated mean score (95% CI) | 22·9 (21·8–24·0) | 23·4 (22·3–24·6) | 23·2 (22·1–24·3) | 22·8 (21·6–24·0) | 23·2 (22·0–24·3) | 23·9 (22·7–25·0) |
| Social wellbeing, n | 113 | 115 | 105 | 100 | 99 | 98 |
| Estimated mean score (95% CI) | 23·5 (22·2–24·7) | 23·5 (22·2–24·8) | 23·1 (21·9–24·3) | 22·6 (21·3–23·9) | 23·3 (22·1–24·5) | 23·3 (22·1–24·6) |
| Emotional wellbeing, n | 111 | 112 | 98 | 95 | 96 | 91 |
| Estimated mean score (95% CI) | 17·5 (16·4–18·6) | 17·7 (16·5–18·8) | 19·5* (18·4–20·5) | 19·9* (18·8–21·0) | 19·4* (18·3–20·5) | 20·0* (18·9–21·2) |
| Functional wellbeing, n | 115 | 115 | 105 | 100 | 98 | 97 |
| Estimated mean score (95% CI) | 18·4 (16·8–20·0) | 18·4 (16·7–20·1) | 17·9 (16·3–19·5) | 19·3 (17·6–21·0) | 18·5 (16·9–20·1) | 19·7 (18·0–21·4) |
| FACT-BL-Cys, n | 115 | 114 | 105 | 100 | 98 | 97 |
| Estimated mean score (95% CI) | 37·4 (35·0–39·8) | 36·7 (34·2–39·2) | 37·9 (35·8–40·0) | 38·2 (36·0–40·5) | 39·3 (37·1–41·4) | 39·4 (37·1–41·6) |
| Trial outcome index, n | 115 | 114 | 104 | 100 | 98 | 97 |
| Estimated mean score (95% CI) | 78·9 (74·6–83·2) | 78·9 (74·3–83·5) | 79·3 (75·1–83·4) | 80·7 (76·3–85·2) | 81·1 (77·0–85·3) | 83·2 (78·8–87·6) |
| FACT-G, n | 108 | 112 | 97 | 94 | 95 | 91 |
| Estimated mean score (95% CI) | 82·4 (78·6–86·1) | 83·5 (79·5–87·4) | 84·2 (80·4–88·1) | 85·8 (81·8–89·9) | 85·9 (82·1–89·7) | 87·4* (83·5–91·4) |
| FACT-BL-Cys Total, n | 108 | 111 | 97 | 94 | 95 | 91 |
| Estimated mean score (95% CI) | 120·1 (114·5–125·8) | 120·9 (115·0–126·8) | 122·8 (117·2–128·3) | 125·2 (119·3–131·1) | 126·0* (120·4–131·6) | 127·5* (121·7–133 |

n indicates the number of patients who answered each section of the questionnaire. FACT-VCI consists of eight domains (five subscale scores [physical wellbeing, social wellbeing, emotional wellbeing, functional wellbeing, and FACT-BL-Cys]) and three derived scores (trial outcome index), FACT-G, and FACT-BL-Cys Total. The ranges of scores for each domain are as follows: 0–28 for physical, social, and functional wellbeing; 0–24 for emotional wellbeing; 0–60 for FACT-BL-Cys; 0–116 for FACT-VCI Trial Outcome Index (sum of physical wellbeing, functional wellbeing, and FACT-BL-Cys scores); 0–108 for FACT-G (sum of physical, social, emotional, and functional wellbeing scores); and 0–168 for FACT-BL-Cys Total (sum of physical, social, emotional, and functional wellbeing scores, and FACT-BL-Cys). FACT-VCI=Functional Assessment of Therapy-Vandetbilt Cystectomy Index. FACT BL-Cys=Functional Assessment of Therapy for patients with Bladder Cancer following cystectomy. FACT-G=Functional Assessment of Therapy-General form. *p≤0·05 compared with baseline, using Bonferroni's adjustment for multiple comparisons.

Table 4: Quality of life outcomes

So you've done everything we've told you, you've done the neoadjuvant chemo, then you'd get through the surgery, you get through all the complications. And we may still tell you we want to give you extra immunotherapy or these new drugs that are called antibody drug conjugates. So again, there's new data that if your nodes were positive at the time of surgery or we had positive margins, you may want to take an additional therapy to again, extend your survival. And you're like, "Geez, how many more things could I go through?" So it is a journey, that's why I use that word. So this was kind of summarizing the treatment algorithm we've been through.

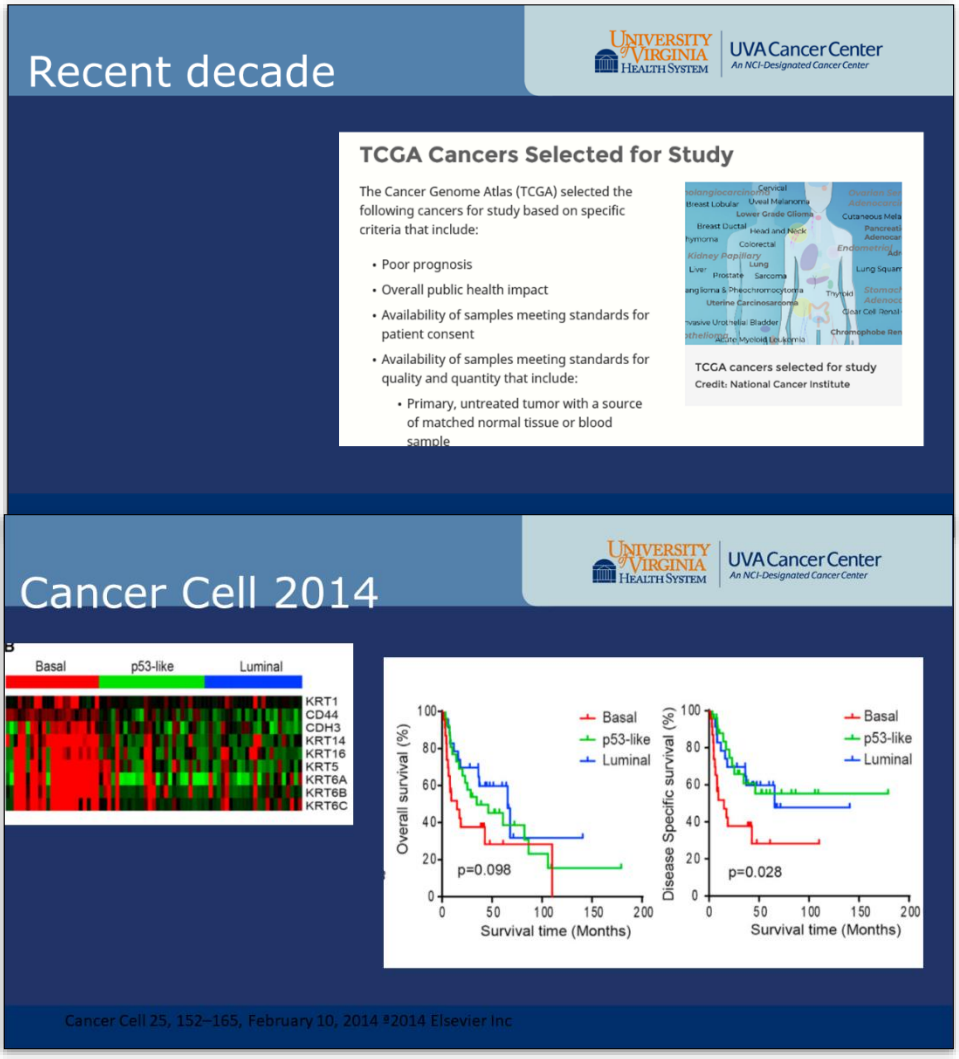



And then the only other thing I just wanted to talk about quickly was you do need to be monitored after this surgery. You need a chest x-ray, CT scans, labs, all that stuff has to be done at six months to 12 months intervals at a minimum for three years, most of us will follow longer if we can. And then if you

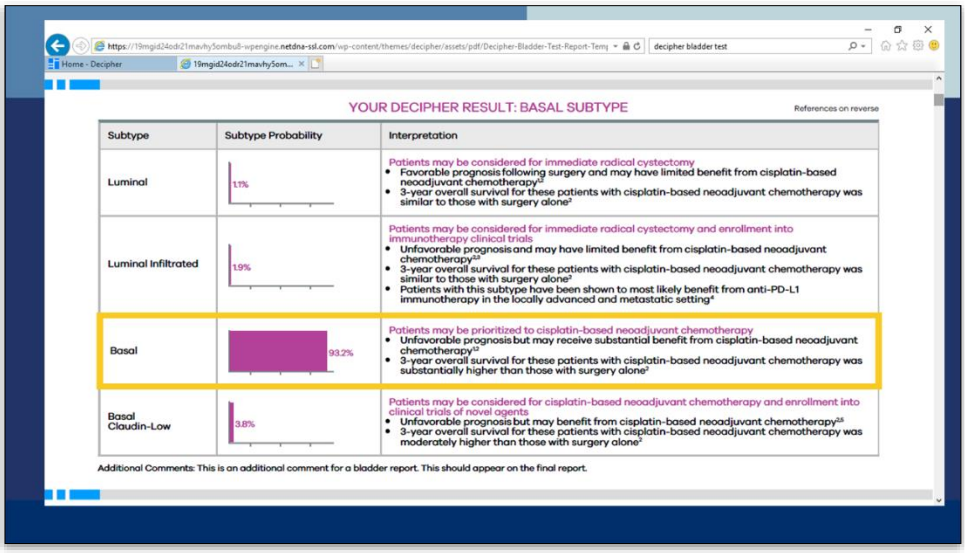
have your urethra still that's in contact with those urine cells so that we may have to have washings done. The newest thing that I wanted to talk a little bit about is the role of genomics.

## Dr. Tracey Krupski:

This was the Cancer Genome Atlas, and I'm just going to speed through. It's one of those huge projects that 2005, the NIH started looking at the genes related to the individual cancers. And around 2010 and 2009, we start to look at urothelial cancers. And we find that urothelial cancers have mutations in 32 different genes and nine of those have never been reported in cancer before. So why that's exciting is it gives us new targets for treatments that might be curative and we can look into their RNA sequences and the proteins that these genes make and again, develop new targets.




And we found that we could classify these cancers into these basal genes that get turned on p53-like or luminal and where this is going now in the modern age is we can use that data to run a bladder decipher test. Like you could do a genomic subtyping of your individual tumor and see which of those genes was turned on which tells us if you're going to respond to chemotherapy potentially. So this hasn't been prospectively validated, but this is the idea, we send the tumor off from your endoscopic procedure and we can say, this person has a basal genomic subtype which would do great with this platinum based

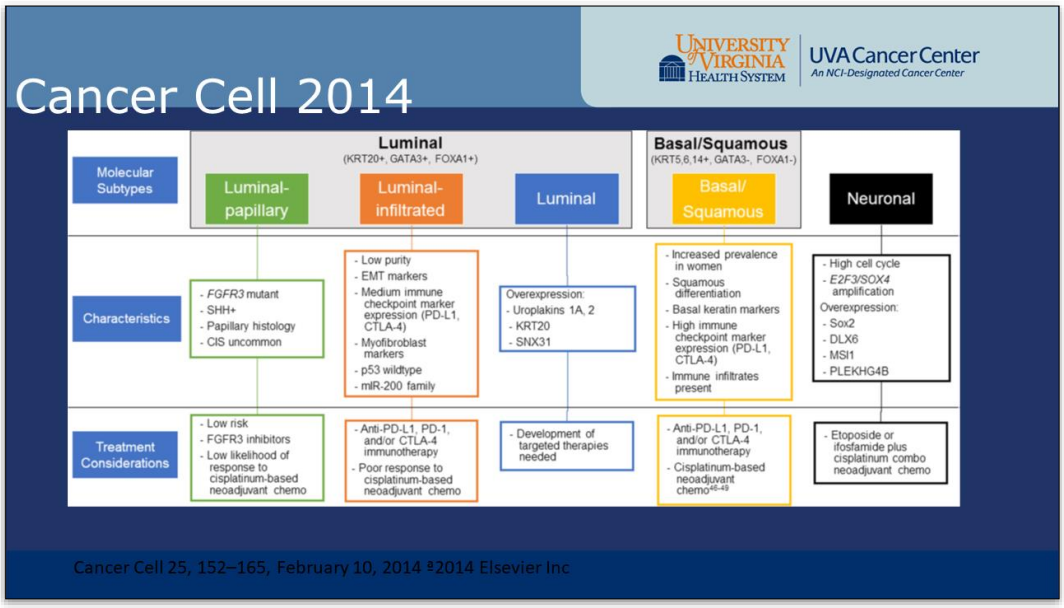


therapy. They should get the chemo because they're totally going to respond.

These would be considered for intermediate immediate surgery because we don't think chemo's going to work as well. So this is sort of brand new stuff that we're working into how we treat people now, and I think it's going to change how we can personalize the medicine for you going down the road. It's not quite prime time, but it's coming. So I just wanted to, again, end on more of a high note.

## Dr. Tracey Krupski:

And again, these are these different subtypes and this shows at the very bottom which of these drug targets there could be. These are good immunotherapy. They don't respond to cisplatin. These look like they would work for ifosfamide. So thank you for your attention.



## Question and Answer

### Morgan Stout:

Thank you so much, Dr. Krupski. That was very thorough and we're so glad that you were willing to do this. We do have a couple of questions. And just as a reminder, if you want to put your questions in the Q&A box. If you put them in the chat box, it's a little harder for us to keep track of so put them in the Q&A. So our first question has to deal with chemotherapy. What are the decision points for a urology team on deciding with a patient whether to do a dose dense MVAC versus GemCis versus straight cisplatin. Can you talk about that a little bit?

### Dr. Tracey Krupski:

Sure. Great question. A lot of that comes down to the medical oncologist preference. Now I will tell you the actual evidence for the neoadjuvant chemo was for dose dense MVAC. So dose dense MVAC was what was done in the trials. And that had the 5 to 8% overall survival, better for T3 disease, that type of thing. However, when they tried to compare the two in the after setting or in other drug combinations or other cancers GemCis, the Gemcitabine with cisplatin seems to be equivalent.

The dose dense MVAC is also much harder on a patient. It has cardiac toxicity. So because we think they're fairly equivalent and there's less toxicity, many oncologists will just give the GemCis. And that's what I see more often in our communities, but by no means would dose dense MVAC be wrong. It's just a little bit harder for the patient to get through.

### Morgan Stout:

Thank you. Thank you for that. Our next question is about going back to that chemo radiation topic. There was a question about confirming chemo radiation that a third of patients will be cured, another third will still need to have their bladder removed and the final third will not have a positive outcome. Can you talk a little bit more about that and just kind of...

### Dr. Tracey Krupski:

Well, to frame that versus surgery, what I will tell people the third, third, third can be a little bit complicated. But if you just walked in the door, I would generally say if you do surgery alone, you have a 65% chance of being cured, meaning your cancer doesn't come back and you don't need any more therapy and we gauge that at the five year time point. If you do chemo radiation, I would quote you 40% chance that you will be alive without cancer in five years with your bladder. If you add chemotherapy to the surgery route, that's where I would prove be more like 70, 75%. So generally, it's 40% of people are cured and they don't need anything else for their bladder cancer if they do chemo radiation. I will say within the first two years is when you fail. So those office cystoscopies that are done after chemo radiation, if we find active bladder cancer, we would recommend then that you go to cystectomy at that time again, if you are a surgical candidate.

So although the third, third, third makes it sound like it's going to progress, the cystectomy people have a third of the cancers coming back too even though you went through all the trouble of getting your bladder removed. So that's where it's a very serious disease. That's where we get that because those numbers are not good. I mean, I don't want to tell any family those numbers, but those are the real numbers.

### Morgan Stout:

Absolutely. And that's super informative. Thank you. So let's talk a little bit about side effects. You had that big long list and this question was dealing specifically with lymphedema after a radical cystectomy with the lymph node excisions. How often does that happen and, or what are the other probably top two most common side effects?

### Dr. Tracey Krupski:

Well, lymphedema would not be one of them. Lymphedema is pretty rare. Usually the pelvic lymph node has enough cross drainage, meaning the inguinal nodes, the ones right under your skin of the groin can usually pick up the slack from the move of the bladder, the prostate, there's sacral lymph nodes, there's other lymph nodes that usually do the job. So I would wonder if there had been either radiation for some other reason that might have impaired those other lymph node, drainage that led to chronic lymphedema or occasionally not usually a nutrition thing, but maybe the surgeon did an extended lymph node dissection, meaning they took a lot more lymph nodes than those ones that I briefly showed in the pictures, those could relate to lymphedema. I think the most common problem after the cystectomy in general, if I'm interpreting the question right, is kidney infections. It's pyelonephritis. It's recurrent kidney infections because the urine is not able to drain quite as quickly as it used to either because there's a little bit of scar tissue where we sewed the intestine to the ureter or sometimes it's just lost the elasticity. There's a peristalsis that gently pushes the urine from the kidney out of the body. And if that's lost, you can have stagnant urine.

And I'd say kidney infections are the most common long term one that we have to be dealing with along with scar tissue. The fortunately slowing down of the bowels is the other big one that keeps people in the hospital. But once you get through those two or three weeks post-op, most of all that you get through it, it's gone, you're just watching for kidney infections and electrolyte abnormalities.

### Morgan Stout:

Absolutely. Another question we had was talking about that genomic testing. What kind of genomic testing do you do and is it covered by insurance?

### Dr. Tracey Krupski:

So I will tell you that the companies are just coming online. The main one I know about is the Decipher, that was the one shown in the slide. I do not work for Decipher, I'm not promoting Decipher. But what those genomic tests will tell you is they will cap it at $200 out of pocket for most patients. So while they might charge insurance X amount, certain insurances will cover it. I don't think Medicare is now, but don't quote me on that. But as far as out of pocket for the patient, it's usually only $200.

### Morgan Stout:

Thank you. This question has to do with adjuvant chemotherapy. If chemotherapy wasn't done after radical cystectomy, can the same type of cancer return or would you see a different type? And can you use chemo and radiation for a different type of cancer that comes?

### Dr. Tracey Krupski:

So couple pieces to that. So we just talked about you could do surgery and a third of the time maybe the cancer, urothelial cancer, meaning bladder cancer will come back. If bladder cancer comes back in a

lymph node or a bone or the liver, you can use the same chemotherapy again that you used pre, so a cisplatin based chemotherapy, again, with the caveats that your body can tell your kidneys are okay.

You also can do immunotherapy now. So those are, you sometimes see it on TV, nivolumab is advertised as KEYTRUDA. Those can be given if the cancer has come back after surgery and then you might use chemotherapy, but you might actually moving towards immunotherapy now, things like ipilimumab, nivolumab, atezolizumab, all these lalamabs, but they're immunotherapy. As far as radiation goes, you can radiate again, but not the same spot. So say somebody had colon radiation, so they had pelvic radiation for a colon cancer. We couldn't radiate the pelvis again because there would be too much radiation toxicity to the tissues. But if you did chemo radiation for your bladder and then you had a spine met way up here, meaning cancer, bladder cancer in your bone, we could radiate that area again to control the tumor or get rid of pain. So yes and no, if that makes sense.

### Morgan Stout:

Absolutely, it does. I think we have time for one more question. And this one just popped out at me. I have a muscle invasive bladder cancer diagnosis, but I haven't started any treatments yet. Why do I feel terrible?

### Dr. Tracey Krupski:

Well, I will say that it's probably because there is tumor. Even though they've resected and we do our best, sometimes there can be tumor underneath the surface, there could be tumor in other parts of the body or other parts of the bladder underneath the surface that the urologist could see. My experience, so there's a couple things, A, you're bummed. I mean, you're not happy. This is not a good disease to be told about. Your body is stressed emotionally because you've been told this diagnosis, and that's hard. I mean, the whole body's responding to bad news, so to speak. Two, your own immune system, whatever microscopic cells underneath the muscle layer that we might not see, whatever tumor is there, your own immune system is spending all its energy trying to keep that in check and you're probably still recovering from this surgery where we scrape out the bladder and that makes you have burning and irritation and blood and frequency and not sleeping well because you're getting up to go to the bathroom all the time and kind of standard urology things, unfortunate, but true.

I have found that when the people start chemotherapy, a lot of people, especially if there's pain, if you're still having pelvic pain with extensive sitting like behind the scrotum or by the vagina, a lot of that will get better with chemotherapy. And honestly, when it gets better with chemotherapy, that is a great sign that the chemo's working, that you're going to do pretty well with surgery that will be able to get rid of everything.

So that could be a long-winded answer to I'm sure it's multifactorial. I mean, there's a couple different things going on. And the biggest thing we could tell people is nutrition, nutrition, nutrition. I mean, the best protein, vegetables, boost instant, Carnation Instant Breakfast, anything that can get you calories that are not just Twinkies or macaroni and cheese, which I like macaroni and cheese like anybody, comfort foods, but getting really good nutrition would be one thing that you could do straight up that you have control over so to speak.

### Morgan Stout:

Absolutely. Well, thank you so much for your time, Dr. Krupski, it was a phenomenal program!

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