

## TREATMENT TALKS

What you need to know about intravesical therapy to treat bladder cancer



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### **Stephanie Chisolm:**

I'm going to open this up. As far as Christina, did you have any particular lessons learned? You said you had flank pain. Dr. Singla, is that a common symptom for patients who have upper tract disease because of the involvement in the ureter or the kidneys? Is that common?

### **Dr. Singla:**

Yeah. When it comes to diagnosing UTUC, most commonly it would be some form of hematuria, in other words, blood in the urine, which may be either microscopic or seen with the naked eye. One thing that is unique to a subset, but not all types of UTUC, is also the possibility of developing flank pain. That usually is in the setting of form of obstruction, so you may recall one of the example CT scans that I showed earlier in the presentation, where there was some dilation of the kidney upstream from the tumor. Sometimes when that occurs on a relatively quicker timeframe, that can actually cause flank pain, but that isn't necessarily the case across the board. There are many cases where there could be obstruction without flank pain, or there may be tumors in the kidney that are not causing obstruction and hence not causing these symptoms.

### **Stephanie Chisolm:**

Great. With superficial high grade upper tract disease, what are the primary methods of discovery diagnosis in the distal ureters of the renal pelvis? How do you get all the way up there to figure that out? I know you talked about it, but can you explain it a little bit better? What sort of tests do you use? Is it CT imaging? Are you just doing a wash to check cytology, see if that cancer's still in there? What are you doing to monitor all the way up there?

### **Dr. Singla:**

Yeah. Yeah, absolutely. For the diagnosis we still do require the use of direct visualization of the ureteroscopy, especially for CIS or carcinoma and CY2, which is a flat form of UTUC, and generally one that tends to be more superficial in nature, but not one that you often will have your classic tumor protruding into the lumen or the inside of the either kidney or the ureter collecting system. And so these are often not seen definitively on imaging because of their nature, and so oftentimes if prompted by one of these other symptoms, often microhematuria, or potentially even gross hematuria, the next step would be to... Oftentimes cytology can be a tip off for the upper urinary tract that may require the use

of then a ureteroscopy for a more definitive diagnosis. But unfortunately for CIS, the sensitivity of cytology is a little bit higher sometimes compared to other forms of UTUC.

### **Stephanie Chisolm:**

And just jump ahead to another question, and I'll come back to the next one in the line, in the queue, but should all patients with upper tract disease be diagnosed, or should be tested genetically for Lynch syndrome? Is that something that you think should happen to all patients that have upper tract disease? Is there any implication of knowing whether or not they have the genetic mutation for Lynch syndrome in their treatment? This is a question for either of you doctors.

### **Dr. Singla:**

Sure. I'm happy to address it. Just very quickly, Lynch syndrome, it's also called HNPCC or hereditary nonpolyposis colorectal cancer, is a... It's a genetic syndrome that has been shown to be associated with a number of different cancer types. Colorectal cancer is most common entity, but also there's a unique association with UTUC as well. The truth of the matter is that more and more we're finding that actually a lot of patients who are diagnosed with UTUC do truly have an underlying Lynch syndrome that was actually undiagnosed, and that the routine genetic testing of patients who present with UTUC may actually uncover this genetic association and may be helpful not just for that patient, but also future progeny as well. And so we're very much in support of testing patients for characteristic mutations called DNA mismatch repair genes that are characteristic of Lynch syndrome for patients who have UTUC.

### **Stephanie Chisolm:**

Okay, great. I'm going to ask another question in terms of staging that I'm going to ask you also to explain exactly what it is for the listeners in this group. What is the role of multiparametric MRI and VI-RADS in staging? Can you explain what those are, and then is this something that's common?

### **Dr. Hoffman-Censits:**

I will attempt to answer this question, and Dr. Singla may have a better answer. In terms of any kind of specialized imaging, for the most part our patients are getting either a CT with contrast or a CT urogram is the most common, and in fact, for most clinical trials we use CAT scans. Depending on the patient and the need, sometimes for renal function issues, a physician may use an MRI instead, or a different form of an MRI, and then less commonly, but often a question that's raised by patients and families is what about PET imaging? PET imaging is tough in urothelial cancer because the tracer is metabolized by the kidneys and then excreted in the urinary system, so it's very hard to see anything on the inside of the urinary system, so from a staging perspective, unless you're looking for metastatic disease, it's not helpful for looking at localized disease.

### **Dr. Hoffman-Censits:**

I think potentially an answer to your question is that there is no, I think, kind of standard imaging, and everyone gets potentially somewhat different imaging, again, most common being a CT scan. Is it perfect? No. Could it be better? Absolutely. And in fact, Dr. Singla and I even had a meeting about this today in terms of optimizing imaging across the board for patients to help us better determine those that may have noninvasive disease, may have invasive disease, determining low grade versus high grade. There's a lot of imaging modalities and some research being done in terms of what's being done with

multiparametric MRI and how to define that better. That's the information I have. I don't know if Dr. Singla, you have any additional information.

### **Dr. Singla:**

Yeah, happy to chat a little bit more. Multiparametric MRI is essentially a special form of MRI. It was actually initially developed in the prostate cancer world, but has been extended to other cancer types as well. That involves the use of gadolinium and there's actually multiple phases that are obtained. When it comes to, just like Dr. Hoffman-Censits said, the current sort of gold standard approach to staging, if you will, is typically the use of a multi-phase CT scan with and without IV contrast. That includes a urography or an expiratory phase to look at the ureter in particular. The problem is that not all patients can receive the IV contrast, and so a subset of patients can also reasonably be diagnosed with use of an MRI, usually an MR urography, to characterize these lesions. Now, the VI-RADS system, this is something that was actually developed for bladder cancer specifically. It's the use of a multiparametric MRI for assessing the depth of tumors that are detectable on imaging.

And so this is... It stands for essentially Vesicle Imaging-Reporting and Data System, but essentially that is limited to those tumors that are actually detected on MRI. It hasn't really been explored for upper tract tumors, and the biggest issue is really sensitivity of these imaging modalities. The problem actually is more whether or not we're able to enhance our ability to detect lesions upfront using CT scans or MRIs, but then the next steps would be, are there alternative approaches such as the use of MP MRI to maybe better ascertain the depth of invasion? And so these are actually great questions that are currently under investigation.

### **Stephanie Chisolm:**

Okay, great. I have another question that's come in and I just want to ask sort of in general, since so many patients that have upper tract disease are at risk for losing their kidneys, and once they have had their kidneys removed, are there special dietary concerns that people should follow, that you can recommend, or questions they should be asking a nutritionist that can help keep that other kidney healthy, since now it's doing double duty on helping? Is there anything you can suggest, Dr. Hoffman-Censits or Dr. Singla?

### **Dr. Hoffman-Censits:**

Yeah, that's a great question, and it's one that a lot of our patients have. For some patients, if they do have an impairment of renal function, just like patients that have two kidneys with an impaired renal function, they may be best served to really review some of these questions with a nephrologist or an internist with a subspecialty in treating medical disease of the kidney. I think of urology as kind of the plumbing portion of that relationship, and then a nephrologist is the one that thinks about the function of the kidney and electrolytes and protecting. Oftentimes, unfortunately it's really about protecting what you have, but a lot of nephrologists will advocate for things like great blood pressure control and avoidance of nephrotoxic agents, so sometimes depending on the kidney function, that may be IV contrast or overuse of non-steroidals.

But for the most part for our patients, we just recommend they still stay well hydrated, recognize signs and symptoms of dehydration. And again, from a dietary standpoint, it's often not until someone has maybe a later stage what we call chronic kidney disease or CKD where dietary modifications come into play, so this isn't really a one-size-fits-all answer, but there are specialists that think about this, and so if someone has a particular question, they may want to be referred to a nephrologist.

### **Stephanie Chisolm:**

Would you regularly just make a referral to a nephrologist? Would they be part of the overall team if somebody did have one kidney removed? Is that something that you would normally do?

### **Dr. Hoffman-Censits:**

I mean, honestly, if someone has one kidney, but has really good kidney function, we don't necessarily do that. Most primary care physicians are able to appropriately manage those patients, and they don't necessarily have a change in their morbidity, meaning like the medical problems. It may happen to them in the future, or mortality based on having one kidney. Sometimes people are born with one kidney, they don't even know. But if someone has a significant change in their kidney function or a new diagnosis of CKD, then that's certainly a time where we will have that conversation. And then depending on the patient and their interests, they may seek care with a nephrologist.

### **Stephanie Chisolm:**

Okay. We have time for just a few more questions, because I know we're at time, but we're going to go over by just a couple of minutes. This is a good question. What is the risk of tumors arising in the bladder after nephroureterectomy for high grade upper tract disease? Is there a risk, is there a warning? Is there something that patients should be aware of if they've had their kidney removed, that worried about bladder cancer showing up in the bladder or in the other kidney?

### **Dr. Singla:**

Yeah. I'm happy to feel that one. So yeah, it's a good question. As we know, there's absolutely an increased risk for patients with UTUC for developing bladder cancer, and likewise for patients with bladder cancer in developing UTUC, and likewise for patients who have UTUC and developing what we call contralateral recurrence, or essentially UTUC in the other kidney or ureter. Just to go over percentages, for patient who have UTUC the risk of developing bladder cancer is actually quite elevated. It's about anywhere from 22% to about 47%. Now, there are maneuvers that we utilize intraoperatively for patients who are undergoing nephroureterectomy to help minimize that risk, both from a technical perspective and then also with the use of, for example, intravesical chemotherapy at the time of surgery.

That risk of developing... You might recall at the beginning of the talk, the question was posed for patients who have bladder cancer, what's the risk of developing upper tract recurrence. That's much lower. It's about 2% to 4%, and there's a number of hypotheses surrounding this, but one of them is the fact that for bladder cancer recurrences after UTUC, urine is kind of flowing in a top down approach rather than the down up approach. And then to just round off the discussion in terms of percentages of the risk of developing UTUC in the other kidney or ureter, if you've already had UTUC on the other side, is about 2% to 6%.

### **Stephanie Chisolm:**

Okay. That also ties into the next question in there is about muscle invasive, about upstream upper tract recurrences after bladder removal. Thinking about, again, the idea that sometimes the genetic changes that could occur in some of the cells in the urothelium are really more of a field effect. Are you seeing this often, or is it a rare occurrence for patients when they've had their bladder removed to end up with a tumor in the upper tract?

### **Dr. Singla:**

Yeah. And we see this again, quoted rates just across the board, again, would be on roughly the 2% to 4% scale. But in large part we don't actually tend to treat these as metastases per se. In large part, there are similar risk factors for developing bladder cancer as there are for UTUC, and so we usually tend to treat this more of as a local recurrence and treat it as a UTUC entity rather than your typical approach to, say metastatic bladder cancer treatment.

### **Stephanie Chisolm:**

Okay. Yeah, that's a good point. Again, the same thing that might have triggered the cancer in the bladder itself could be present in the ureters and the renal pelvis as well, I guess, so that it's just a matter of time if it were to flip over and cause a tumor, so thank you for sharing that. It's really good information. We have time for one last question, and there was one that was... Hang on. I'm looking for... We answered that one. Let's see. What are your thoughts on KEYTRUDA for treatment of upper tract disease, Dr. Hoffman-Censits?

### **Dr. Hoffman-Censits:**

Yeah, thank you for that question. KEYTRUDA or pembrolizumab is in a class of what's called checkpoint inhibitors, and these are kind of revolutionary drugs, FDA approved for advanced urothelial cancer, as well as a multitude of other malignancies, so we're really fortunate to have these tools to treat our patients. For patients with metastatic upper tract urothelial cancer, they are absolutely indicated. There's no line in the sand between bladder cancer and upper tract disease in terms of the studies that show that these drugs are helpful. For a minority of patients, they can lead to responses or shrinkage of tumor, and for a smaller minority of patients, we can sometimes see a long-term durable control. Our ability to use KEYTRUDA, as well as other agents to treat advanced urothelial cancer, is in part predicated upon how these drugs were tested and where they're approved by the FDA.

For instance, if a drug is studied and approved by the FDA and therefore kind of like opens the door for insurance companies to then approve for me as a doctor to write it for a patient, there's only certain circumstances that we can do that. For instance, I couldn't take pembrolizumab or KEYTRUDA and give it to somebody with a low grade localized upper tract tumor. There's not an indication for that. There's not a understanding of what that might do to a tumor, and there's no guarantee that that would be paid for it by an insurance company. But there's two really divergent, what we call disease states.

One of the questions that we oftentimes are faced with are, well, what about for other indications? And I think that the question is important and the research is pending, I would say, so we also have these questions, and I think that utilization of immunotherapy as well as other therapies in earlier stage disease is a path that our entire discipline is working on, but probably not yet ready for prime time in terms of ability to use these medications in clinic. But I think we recognize the questions and the problems that our patients have and are working hard on solving them with that tool and others.

### **Stephanie Chisolm:**

Well, thank you. Yeah, this is all good. There's so much research going on. BCAN is very strongly in favor of research. We support a lot of research. We know that a lot of research is being done at the Greenberg Bladder Cancer Institute, and for that we are always grateful, because that information is getting out and helping all bladder cancer patients, so this has been wonderful. Christina, we'll be thinking about you tomorrow and sending happy thoughts your way when you go in to see Dr. Hoffman-Censits for your next evaluation, so thank you for sharing your store.

**Tony K.:**

Good luck.

**Christina Y.:**

Thank you.

**Stephanie Chisolm:**

Anything else to add that you want to share with our group?

**Christina Y.:**

Just, I just feel very, very fortunate to be in the position I'm in, where there've been so many treatment options available to me as I've gone through the course of this disease. And I'm so thankful to talk Dr. Hoffman and Dr. Singla for taking care of me.

**Stephanie Chisolm:**

Great. How about you, Tony? We'll be thinking about you on the 15th and sending positive thoughts your way.

**Tony K.:**

Yeah, I echo those comments. I mean, very fortunate to be in this region and have the ability to get in the schedule. You think about it, just to add the COVID layer that's affected everybody's life over the last two years, to switch hospitals and do all that and get it accomplished and get the treatment I've had, I'm very fortunate.

**Stephanie Chisolm:**

Yeah, definitely. Thank you so much, Dr. Hoffman-Censits and Dr. Singla for sharing your expertise. I remind everybody that you will be getting an evaluation in your email, so please be sure that you completed your thoughts about today's program, are very important to BCAN, and the success of our Treatment Talks, and there are many other programs that you'll be invited to participate in going from here on. Thank you all so much for joining us for today's program, and I'm going to sign off now.

