Stephanie Chisolm: Stephanie Chisolm:

Welcome to Treatment Talk, what you need to know about treating upper tract urothelial carcinoma. It's a presentation from the Bladder Cancer Advocacy Network. The objectives of the Treatment Talks are to increase patient understanding of existing and new treatments for the spectrum of bladder cancer diagnoses, to showcase patient questions and ask about empowering patient communication with your healthcare team. How do you talk to your healthcare team about your diagnosis? And then also to highlight current treatment advances for bladder cancer.

In today's program we're going to introduce Dr. Jeannie Hoffman-Censits and Dr. Nirmish Singla, both of Johns Hopkins Greenberg Bladder Cancer Institute and patient advocates, Christina and Tony, who will share their experience with low and high grade upper tract urothelial carcinoma. It's a delight to have you here. Thank you so much. Dr. Hoffman-Censits is a medical oncologist and Dr. Nirmish Singla is a urologist, so we're really thrilled to have you. And we know that upper tract urothelial carcinoma is a rare form of bladder cancer, so can one of you just tell me, how often do you find bladder cancer in the upper tract in your general population? Dr. Singla, do you know how what's the percentage of upper tract patients?

Dr. Singla:

Yeah. Absolutely. We'll talk about this a little bit more, you'll see in the coming slides, but in general, about 5% to 10% of all patients with urothelial carcinomas are found in the upper tract, and about 2% to 4% of patients who have had a history of bladder cancer may develop upper tract urothelial carcinoma at some subsequent point.

Stephanie Chisolm:

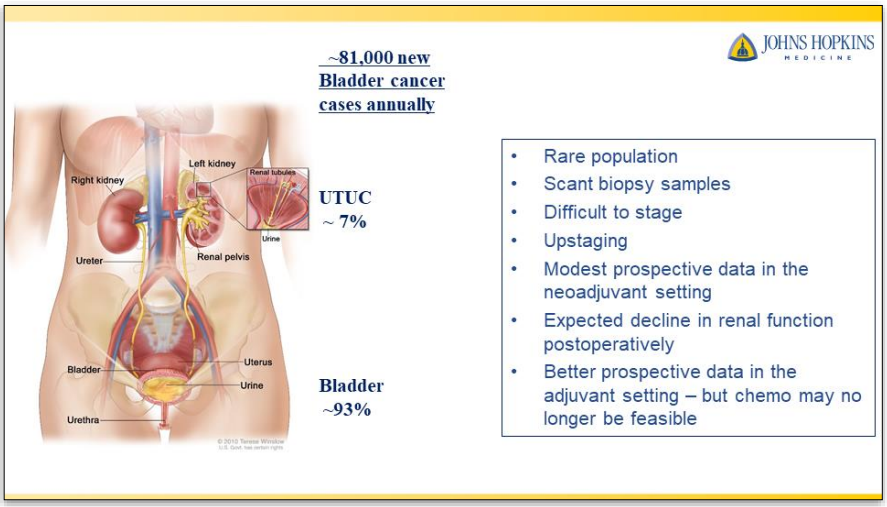
Great. We're going to be talking about some of the challenges of diagnosing and treating this particular rare form of bladder cancer as we go on. And we're going to ask them to turn their screens off, and then Dr. Singla, if you want to share your screen?

Dr. Singla:

Great. Thank you so much, Stephanie. And thank you all for joining this afternoon. It's truly our privilege and honor to be able to talk to you today about treatment options for UTUC, or upper track urothelial carcinoma. And so together, both myself and Dr. Hoffman-Censits are more than happy to initially talk a little bit about what UTUC is, and some of the background information surrounding this relatively rare

entity, and then get into the weeds of some of the treatment nuances as it pertains to low risk or low grade disease, and then the higher grade and higher risk disease states.

Dr. Singla:



All right. And so just to begin, urothelial cancer on the whole is actually relatively common. It accounts for approximately 81,000 new cases annually in the United States. That being said, the overwhelming majority of urothelial cancer cases tend to be of the bladder cancer flavor, or the essentially lower urinary tract cancers, accounting for the overwhelming majority of urothelial carcinomas. On the other hand, as I said earlier, only about 5% to 10% of urothelial cancers come in the upper tract flavor, if you will, or UTUC. Now, UTUC, it's a relatively much harder population of patients to study and to treat for a number of reasons. First and foremost, again, because of its relative rarity, it makes it rather challenging to come up with well-designed prospective clinical trials that allow for the generation of level one evidence to guide the management of this disease state.

Dr. Singla:

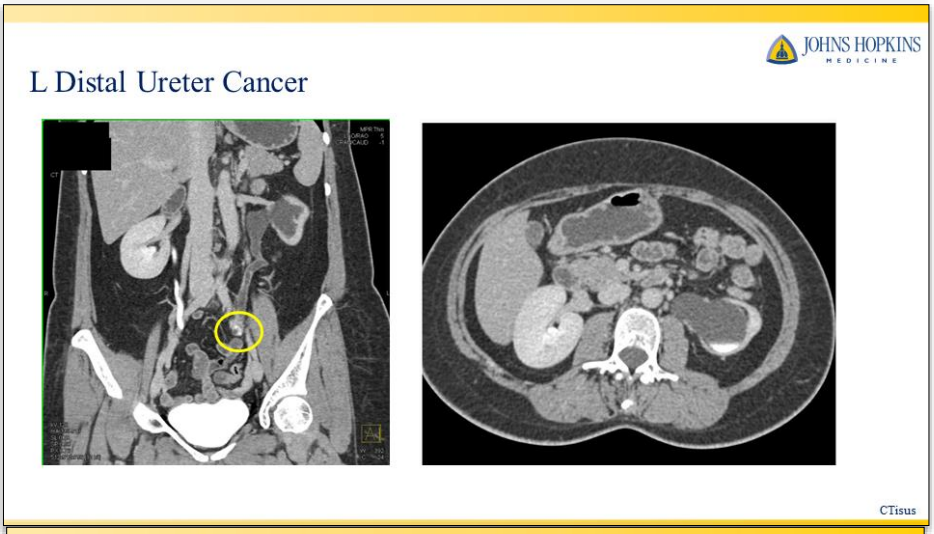
Furthermore, whereas for bladder cancer, we have larger instruments that we can endoscopically introduce into the bladder to get good biopsy samples and help guide management in that way, for the upper urinary tract we're limited with our working channels through ureteroscopes, often with a very limited diameter, to allow us to get good quality biopsy tissue that would then allow us to direct the management accordingly. Furthermore, in terms of staging this disease, we currently rely on cross-sectional imaging, typically a four phase CT scan, as the gold standard approach. However, there are many inaccuracies related to staging with contemporary technology, and so this is certainly an important area of need, and one that I think would start to play a more important role as we start to better tailor individualized treatment strategies for patients. Now, I mentioned again that because of its relative rarity, it becomes a challenging state to design well-controlled clinical trials.

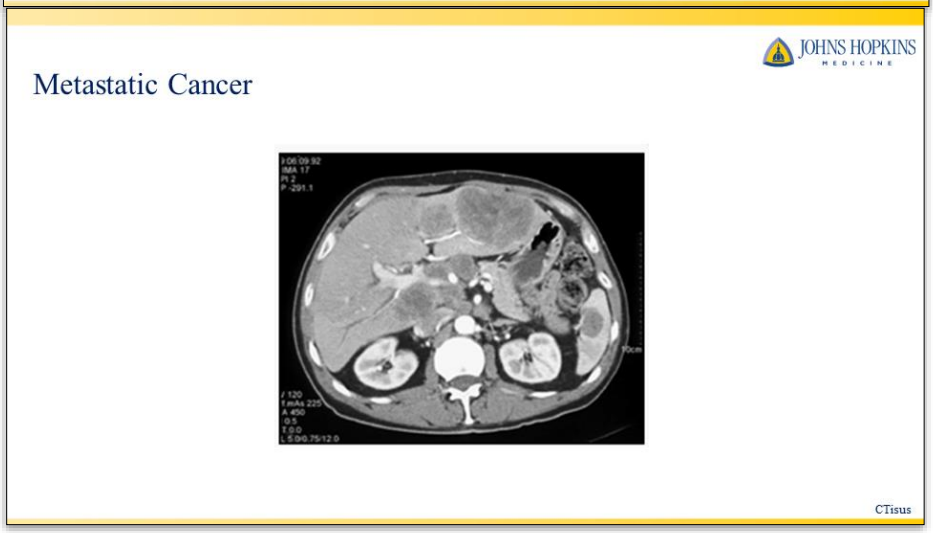
In bladder cancer we have lot have one evidence that supports the use of neoadjuvant chemotherapy followed by a cystectomy, for example, in patients with muscle invasive disease. In the setting of UTUC initially in large part, our management had been extrapolated from bladder cancer literature. Now we are starting to have more prospective evidence emerging, and Dr. Hoffman-Censits will talk a little bit more about this in the second half of this talk, but both for the neoadjuvant and the adjuvant, or the pre-op and postoperative use of systemic therapies surrounding a definitive surgery, the gold standard of which is called a nephroureterectomy. But there is one additional component to managing UTUC that's also not seen so much in bladder cancer, and that's also the fact that the gold standard treatment approach involves the removal of a renal unit. Again, a radical nephroureterectomy, which also has implications, because as you can expect, the overall kidney function may also decline after removing

that kidney, and so that also has implications for the ability of a patient to receive chemotherapy following surgery.

Now, I wanted to talk a little bit about the staging of this disease, because when we approach patients with UTUC, there are two pieces of information that are important to us to come up with a treatment strategy. The first is the cancer stage, and so that essentially entails the understanding of is this entirely a localized disease or potentially a locally advanced disease that could be managed either with procedural means or some multimodal type of an approach, or is this a metastatic setting in which there are other sites that are also involved? And then the other important piece of information, particularly for localized disease, is the grade of the tumors, this low or high grade. And so just by way of example, I wanted to just show some CT scan images just to highlight the types of the spectrum that we can see when it comes to UTUC.

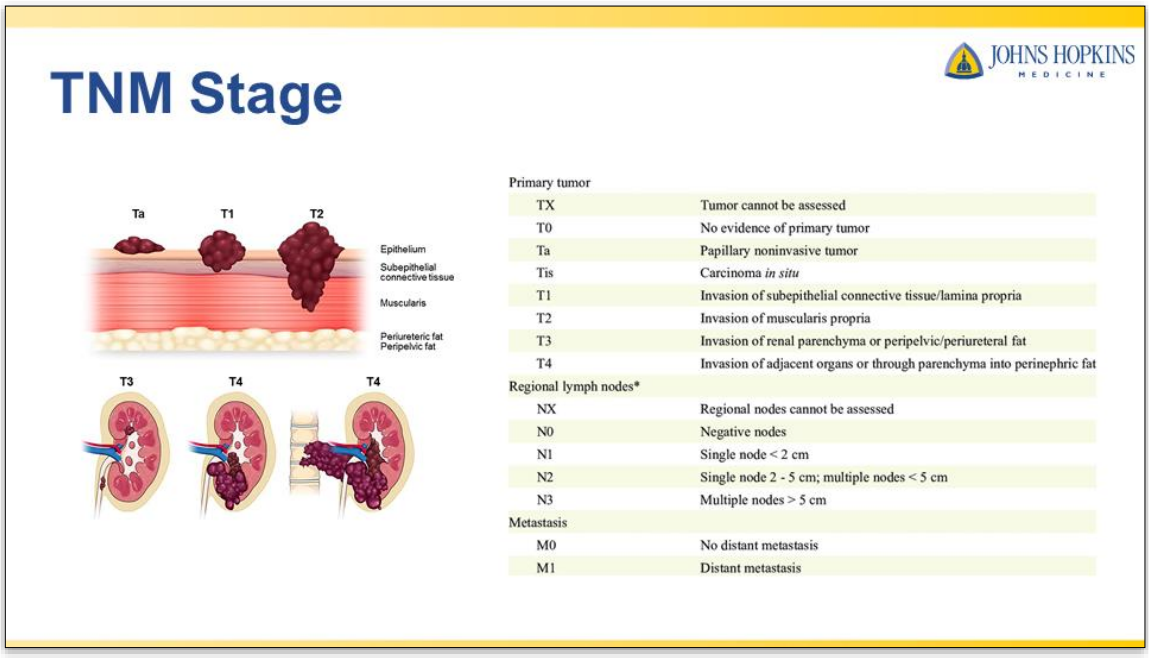
This is an example of a patient who had a ureteral cancer in the distal of the last part of the ureter, which is the tube again that drains the kidney to the bladder. Circled in yellow you can see that tumor. He had no other sites of disease involvement, and so he essentially classified as a localized disease and someone who actually ultimately went on to receive a multimodal approach with systemic therapy followed by a definitive surgery. On the other end of the spectrum, here's an example of a patient who actually presented with metastatic cancer, and so this patient had multiple sites outside of the kidney and ureter that were involved with disease. And so you can see, for example, here in the liver, if you can see my cursor here, there are multiple dark spots that are shown on the CT scan, consistent with metastatic deposits from his urothelial carcinoma, and there's also an additional one here in the spleen.





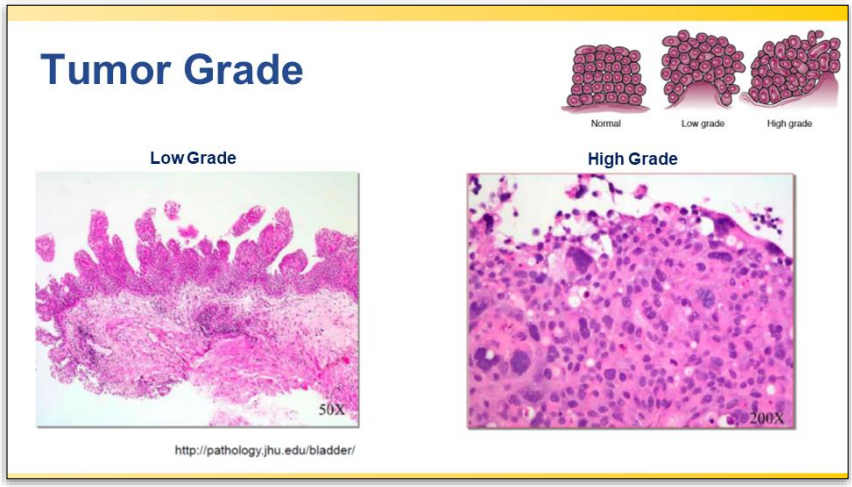
Dr. Singla:

And so this is a patient for whom surgery often will play a more limited role and upfront systemic therapy would typically be the next course of action. Again, when we talk about stage, the classic approach that we use is using this TNM staging system. And what that means is essentially we look at the primary tumor, the lymph nodes, and then the involvement of distant sites. In looking at the primary tumor, we're most interested in assessing the degree of invasion into the lining or the urothelium, as well as into the deeper tissue layers, including the muscle, and sometimes even the fat surrounding the ureter or within the kidney itself, and so we assign something called the T grade, based on the depth of invasion. And again, this is usually based on a CT scan or an MRI that gives us this type of information.

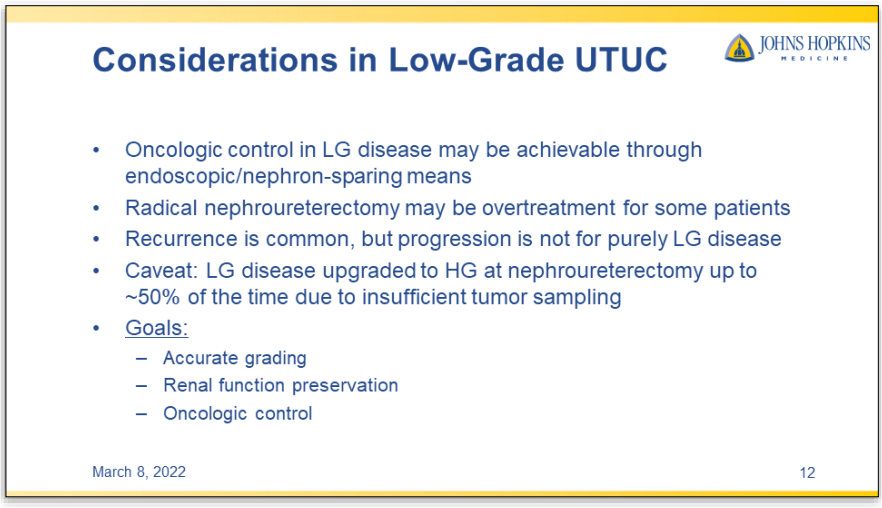


We next look at the involvement of any lymph nodes, and so we have something called the N stage, which is based on the number of nodes involved and also the size of the nodes involved. And then finally we have an M stage, or a metastasis stage, to help us understand if there are other sites of involvement, distance sites of involvement as well. Now, I mentioned the use of grade, and the reason why this plays an important role is because again, as I had mentioned earlier, we are limited in our ability to get a lot of tissue when we do biopsies on patients with ureteroscopy. We often in particular may not get an adequate sense of how deep the tumor is going, simply because there can be sometimes risks to attempting to get particularly deep samples, especially within the ureter.

And so what our management approach has largely been predicated on is understanding what the grade of one's tumor is, and specifically this is based on the appearance of these tumors under the microscope, and it's a piece of information that we can often garner from these biopsies. And so in particular we either have tumors that are low grade or tumors that are high grade, and this will actually serve as the crux of our discussion today, we're going to actually divide... I'll talk a little bit more about the low grade UTUC flavors and the types of management approaches that we use here while Dr. Hoffman-Censits will then talk in the second half of our presentation on high grade UTUC. Specific to low grade UTUC, the good news is that in general, even though recurrences tend to be common, in other words, these tumors could certainly pop up despite attempts at treatment in other parts of the urinary tract, the fortunate aspect is that they often tend to have a low risk for progression.



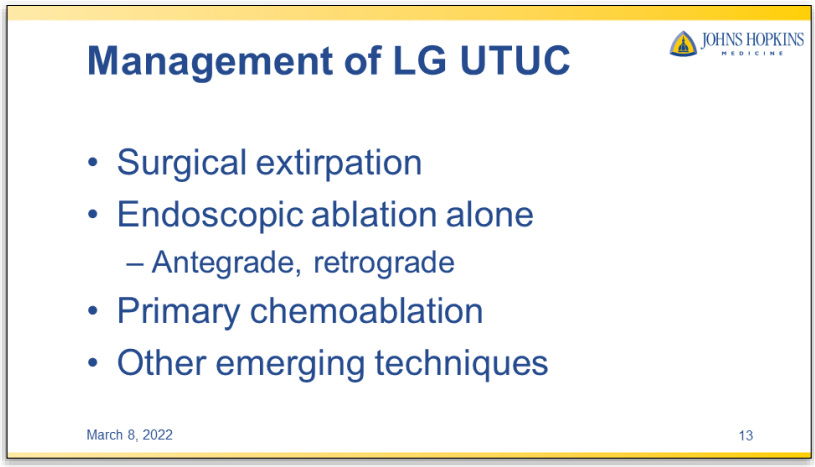
The likelihood of a purely low grade tumor to invade deeply, or to spread to other parts of the body, or in some cases, even to advance to a higher grade state often tends to be limited. And so as a result, whereas in the past a radical nephroureterectomy was considered the gold standard, now we have increasing interest in managing these patients through a nephron-sparing approach, or basically an approach in which we can avoid the need to remove one's kidney and hopefully protect their kidney function overall. And so we often will try to achieve control of the cancer using endoscopic means, or basically using your ureteroscope, often with a laser, to ablate these tumors. And that's in large part because taking out the kidney and ureter may be considered overtreatment and subject patients to unnecessary nephrotoxicity or kidney morbidity from having to undergo that type of a surgery.



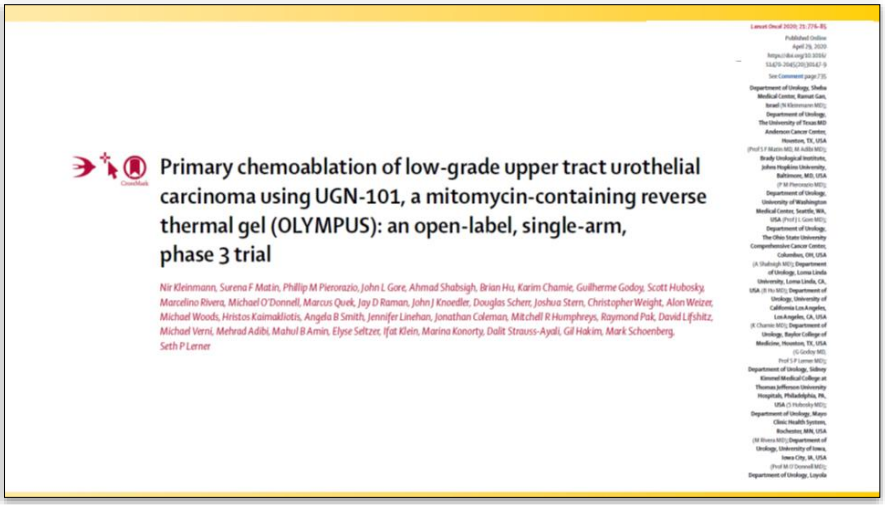
One caveat to note is that again, due to the limitations in our ability to sample these tumors endoscopically, if you look at some series, there's actually a risk of upgrading tumors to a higher grade disease state if you were to undergo an nephroureterectomy for every single patient who was diagnosed initially with low grade disease. And so that's why the main goals of approaching a patient in

whom you suspect low grade disease would be first and foremost trying to ascertain, to the best of our ability, an accurate sense of what the true grade of the cancer is, followed by a balance between preserving kidney function on the whole, but then also making sure that we are able to attain oncologic or cancer-based control.

Dr. Singla:

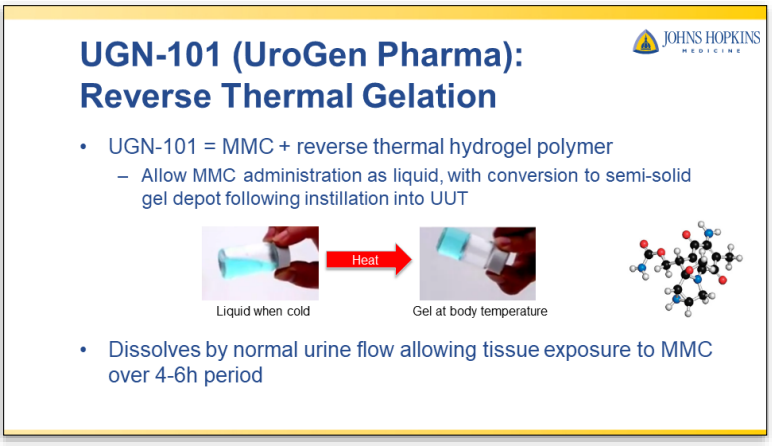


And so in terms of treatment options for low grade UTUC, again, the classic approach had been to perform surgical extirpation, which would either be a radical nephroureterectomy, or in a subset of patients, even a partial ureterectomy with sparing of the kidney, depending on the location of the tumor. And then we also talked about endoscopic means, so this would be via usually a ureteroscope in either a retrograde or an antegrade fashion. A retrograde fashion being that the scope would be introduced from below through the bladder, up the ureter, up to the site of involvement, and typically with the use of some form of an ablative strategy, often with a laser fiber to ablate or essentially kill the tumor cells. Or even via an antegrade approach, which involves accessing the kidney from the back and then going down through the kidney, and plus or minus the ureter, to the destination site and treating the tumor that way.

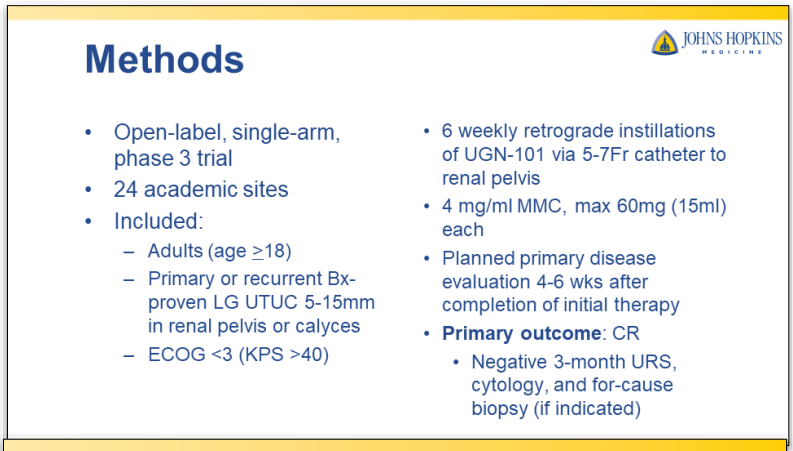


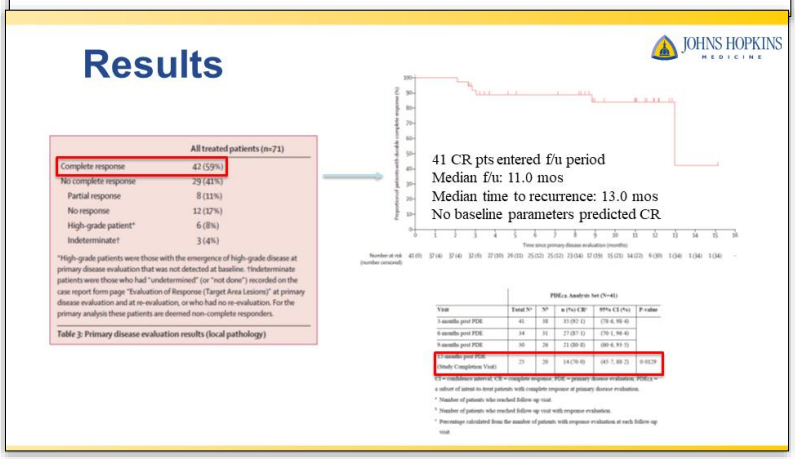
Now, there is one strategy that recently got FDA approved that involves the use of a topical installation of a chemotherapy agent, and this is the strategy I'll talk a little bit more about, referred to as primary chemoablation. And then there are also indeed a number of other investigational strategies that are currently being explored for this disease state as well, with the goal, again, of achieving adequate cancer control while minimizing the need to remove one's kidney. I just wanted to briefly highlight without going too much into the details of the study, but there was essentially an open-label single-armed phase three trial referred to as the OLYMPUS trial that was published a couple years back, and led to ultimately to the FDA approval of a mitomycin containing reverse thermal gel that now is marketed by UroGen pharma as JELMYTO. And the way that this agent works is whereas for bladder cancer we have the benefit of having this gravity dependence where you can apply these topical therapies into the bladder and allow for chemotherapy to have contact with the lining of the bladder for prolonged duration.

In the upper urinary tract the main concern is that if you were to instill a fluid into the kidney, it would likely go down the ureter and into the bladder within a very short timeframe, and that would limit how much contact there would be, the duration of contact between the agent instilled and the lining of the kidney at the ureter. And so this concept of reverse thermal gelation was then combined with a chemotherapy agent commonly used for bladder cancer, mitomycin C, and they essentially developed this reverse thermal hydrogel polymer that means at colder temperatures it would be in a liquid form, but then with heated conditions, such as at body temperature, it would actually form a gel. And so this idea was found to allow for gelation of the mitomycin C for a period of about to six hours in the human body.



And so, as a result, this would actually allow for contact between the mitomycin C and the urothelium for a much longer duration of time compared to just a liquid instillation alone. And so when applied in humans in this phase three study, they actually found that for among 71 patient who are treated using this approach, 59% of patients achieved a complete response, which was actually quite remarkable. And of those patients, 41 had entered into a follow-up period, and of those patients by 12 months, 70% of patients had exhibited a durable response. And since then, there's actually been a recent publication that has updated this experience as well. But based on the data shown here, and the fact that it was a relatively safe agent to receive with a main side effect being the development of usually transient ureteral stenosis that could often be managed conservatively, this ultimately led to the FDA approval for this agent in patients with low grade UTUC.





Dr. Singla:

And this was actually very, very exciting in our field, simply because this is a very challenging disease to study by virtue of its rarity, and to be able to conduct a phase three trial that ultimately led to the first FDA approval of an agent for its effective management to help spare kidneys, especially in those who have higher volume disease that are harder to treat using endoscopic means alone, this allowed for an

extra tool in our armamentarium to treat these patients. And so on that note, I wanted to just shift gears here. I'll hand it over to Dr. Hoffman-Censits next, who will discuss high grade UTUC.