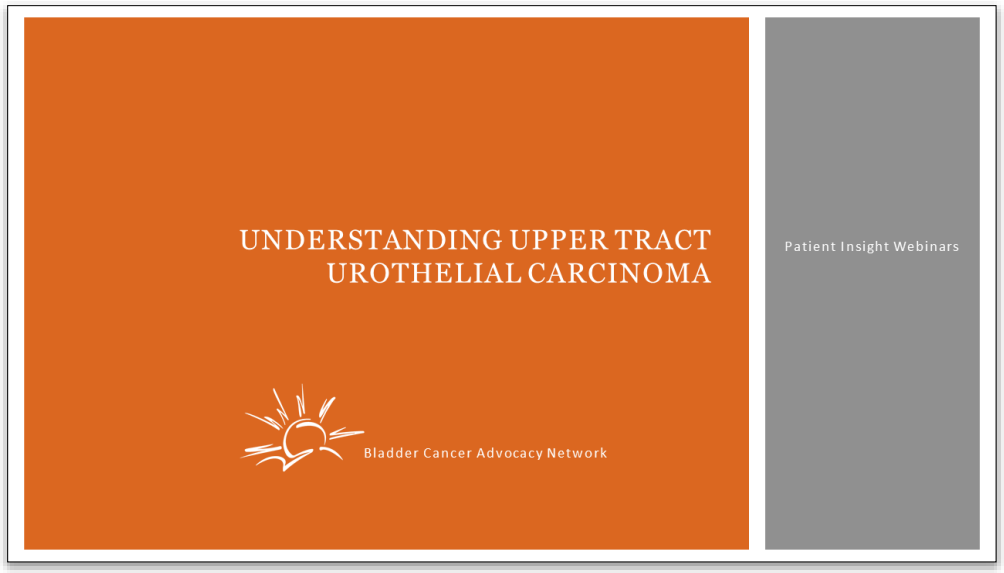
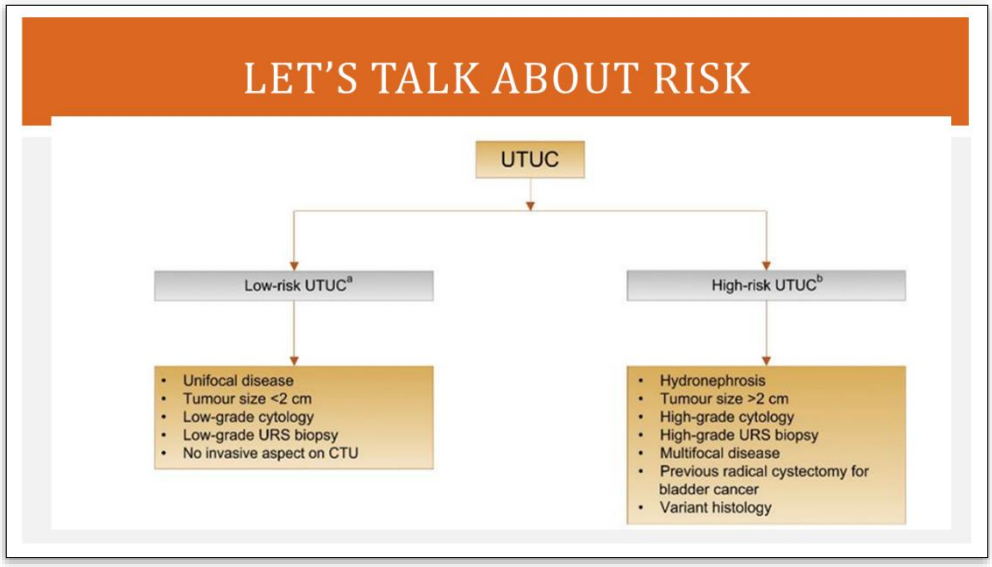



## Dr. Kate Murray:

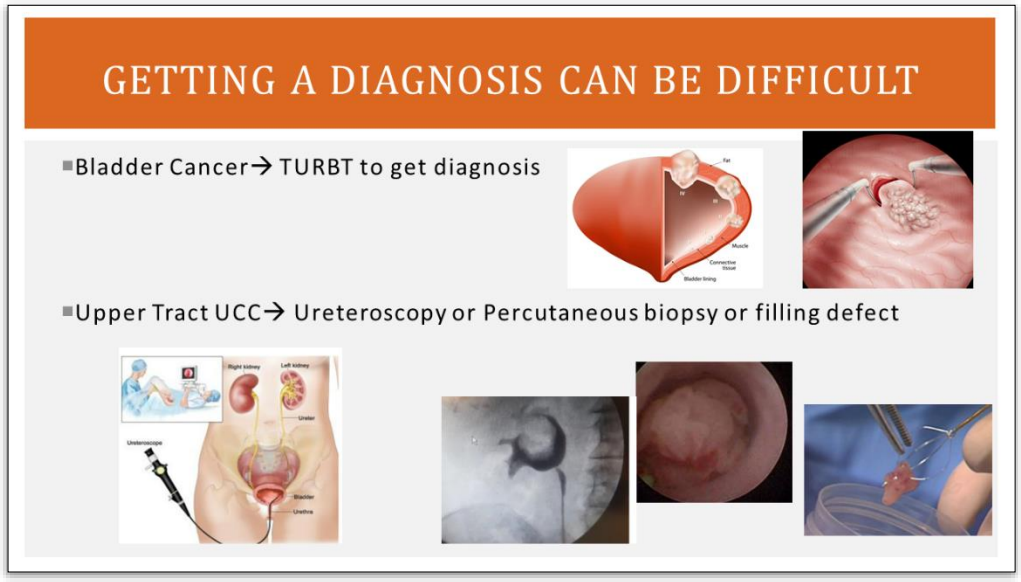
Great. I think everybody can see my slides now, or I hope so. I think Dr. Matin set this up perfectly as a setup to talk about what's next. When I see patients in clinic, this is absolutely what I do, and we do this for all the cancers that we treat. But I think, as we noted, this grade is extremely important to help us risk stratify. Then we say let's talk about risk for patients with UTUC. A big part of that comes in these gradings. We talk about low risk patients. These are the patients that as we go along here, I'm going to talk about trying to save kidneys and not have to do radical surgery on. If these are patients with bladders, we're talking about bladder cancers where we're just removing the tumors and doing things like that. But this low risk for patients with small tumors throughout the ureter or renal pelvis, anything above the bladder, as we talked earlier, a smaller sized single tumors, we do a biopsy, which I'm going to talk about here in a little bit, some of the implications and the difficulties of doing those biopsies. When we look at these patients and we look at CAT scans, we don't see any evidence of invasiveness on it as CT scan for staging. Again, a reminder here is that we always say how important biopsies are. Tissue is so important for us to pass on to our pathology colleagues for them to grade these tumors for aggressiveness and potentially grade these tumors for invasiveness as well. What about these patients that don't fit the criteria? What about these tumors, I should say, that don't fit the criteria for those low risk disease? We're talking about patients with high risk disease. These are patients who already, they may have swelling of the inside



lining of their kidney. We call that hydronephrosis, meaning there's a tumor in that funnel that's blocking off the drainage of the kidney in some way, so urine is not funneling its way out as it would normally. A larger tumor size in the kidney that we may see when we do a biopsy and the pathologist tells us it's high grade, so very aggressive or more aggressive looking tumors, as far as looking at the cells, the tumor cells under the microscope. Multi-focal, meaning this is a tumor that's not located in just one spot in the ureter or just not one spot in the upper, up in the kidney, but maybe in multiple locations up and along that ureter or patients who have had other variants of bladder cancer or have had aggressive interventions or invasive bladder cancer are also patients that we think of as higher risk for upper tract disease.

## Dr. Kate Murray:

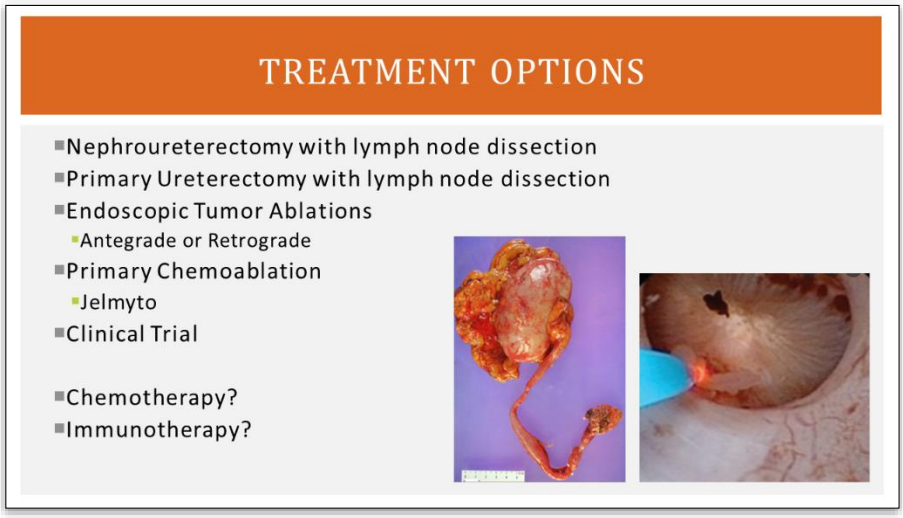
Dr. Matin mentioned this a little bit, and this is something in the daily life of a urologist that we think about and we talk about with our patients, because getting a diagnosis, a true pathologic diagnosis, that's reliable for grading and risk assessment for a patient can be quite difficult. I say this in contrast to bladder cancer, which is urothelial cell carcinoma of the lower urinary tract of the bladder of that urothelium. We do things called, we call it a TURBT, or a trans urethra resection of a bladder tumor. On these pictures here that you can see is, when we see a tumor in the bladder, we have this little hot instrument through a cystoscope when we're looking inside that we're able to scrape that tumor out, as well as some of the muscle wall and some of the bladder wall at the same time, that allows us to have a larger piece of tissue for the pathologist to give us a reliable diagnosis. Upper tract or working in this ureter tube, we often use what we call a ureteroscopy. This is very similar to what urologists use or exactly what urologists use for patients who have kidney stones or obstructing ureteral stones. It's a very common procedure for urologists, where we're taking this scope similar to a cystoscope, but very small. I tell people, as big as the end of my ink pen when it's open and we're going, and we're putting that camera all the way up these ureter tubes up into the kidney. Now, what does that allows us to do? It allows us to directly see that. Dr. Matin had some pictures as well of what these tumors might look like. Here's a picture here of a tumor blocking off a ureter tube. Then, we have to figure out a way to get a biopsy and get it pulled back down that little tiny tube and enough of a biopsy for us to reliably look at under the microscope and say, "This is slow grade, this is high grade, and is it an invasive tumor or not?"



## Dr. Kate Murray:

It can be quite difficult, over here on my far right hand side picture, we use these little baskets oftentimes to do a biopsy of trying to grab a piece of this tumor off, so that we can look at it under the microscope, and so our pathologist can look at it under the microscope for us. We get a diagnosis and I think, one thing that we talk about and Dr. Matin mentioned this as well, is staging as important more so for our patients, obviously, who are high risk with high grade disease. Oftentimes, patients come and they've already had some sort of cat scan or an MRI, or there's a way that we've found this cancer in the first place, but other imaging can be important for staging, looking at the chest, along with that CT of the abdomen, and then, obviously, we're also looking at kidney function and other things that play into what our treatment options may be down the road. I say this as treatment should be based on risk, and this is true for anything that we do. Low-risk disease or low-grade disease should not equal aggressive interventions. Instead, we should save what we call nephrons. Those are ... that's what makes up a kidney. We're wanting to spare kidneys, high risk disease equals aggressive interventions. We need to be doing operations or therapies with curative intent for these individuals, well, but there is some question of maybe there are options for patients that we can still spare nephrons in patients with higher risk disease. Without going in too much detail of high and low and all these different gradings are, in a nutshell, what are our treatment options?

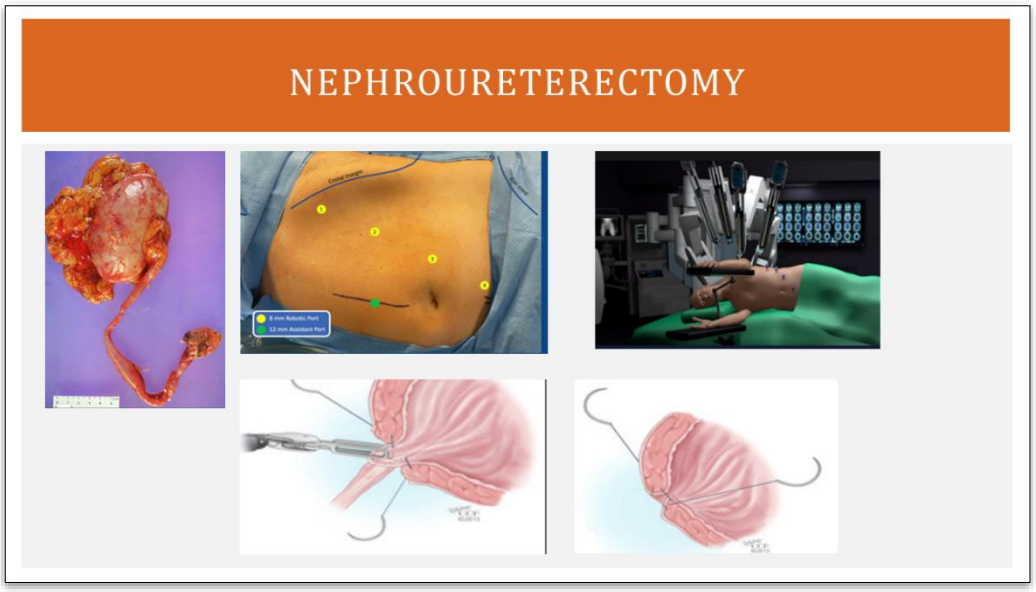

A little bit of this. I flip to the very bottom of this slide first and say, I'm going to rely on Dr. Campbell to answer some of our still unanswered questions about chemotherapies for upper tract disease before and after surgery and now in the era of immunotherapies. Some of our treatment options are things aggressively, such as a nephroureterectomy with a lymph node dissection, a



nephroureterectomy is in contrast to a nephrectomy, which would be nephro means kidney, so removal of the kidney. What's important, when we're talking about upper tract disease, is that we remove that entire system. Here's a pathology, gross picture of a patient's kidney, their ureter, their funnel draining all the way down here into the bladder and there's even a small cuff of bladder that's removed at the same time. There are options for patients to do what we would call ureterectomy if a tumor is located or isolated to a solitary place within the ureter.

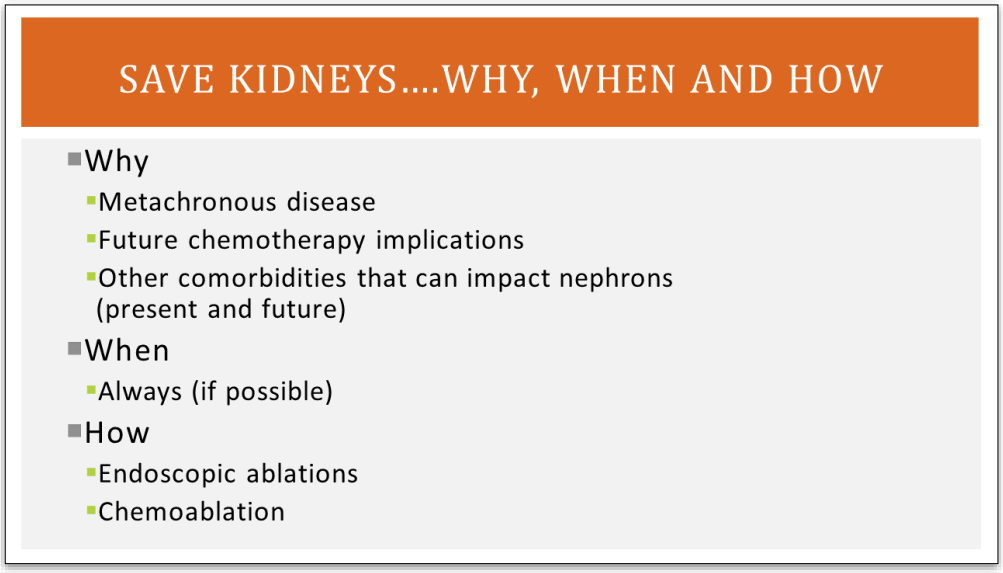
Then, we talk about endoscopic ablations, and that is very similar to what, again, we do this via a ureteroscope that a urologist would use for stones oftentimes, and on my right hand side here, I have a picture of the inside of a kidney. This is in the calyces in one of those fingers of the kidney and there's a tumor here on the bottom, and you can see this blue with a red light on the end of it being a laser fiber and we're ablating or lasering off this tumor. Then, of course, discussions of chemotherapies that are put intra-cavitary or directly into the kidney similar to what we've historically thought about putting BCG or chemotherapy into the bladder. Then, of course, I've not put on their option of a clinical trial for patient for treatment options.

## Dr. Kate Murray:




I'm going to just show a couple of more pictures for each of these different treatments that we would be doing for patients that come to see us for these disease process. Therefore, ureterectomy is, I have the same picture showing that it's the kidney, the entire ureter tube that comes out. It can be done in many different ways. It can be done in an open approach through an incision in the abdomen done robotically. It can be done laparoscopically just as long as that kidney, that ureter, that little piece of bladder is removed all at once, and then a lymph node dissection as well. Here's some pictures of what that would look like robotically and then really, what you're seeing here is this circle on the bottom is our bladder. We're seeing a ureter tube that's coming in and have taken just enough of a piece of bladder to get that entire ureter out and not leaving anything behind, and then we sew up that small hole in the bladder that we've made for a nephroureterectomy.

Next, I'm just going to focus on little bit more on saving our kidneys and the ablations, the biopsies, the chemotherapeutics that we may use as urologists in today's world of 2022. Why do we want to save kidneys? Why? Because, Dr. Matin showed us in that one of his very first slides that recurrence rates happen. We've talked about the risk factors of smoking and other risks for upper tract disease and disease can come back metachronously. That means at a later time. That can happen in the same kidney, it can happen in another kidney, it can happen within the bladder. Taking out kidneys can impact a patient's overall life, so that is impactful in potential future therapies. It can be impactful for, removing kidney also have a great part in blood pressure control in our diabetes, and so we're really trying to help with that.

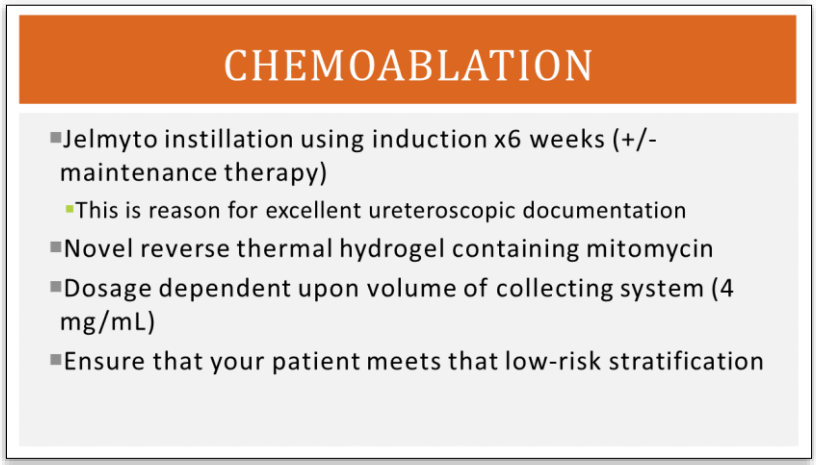


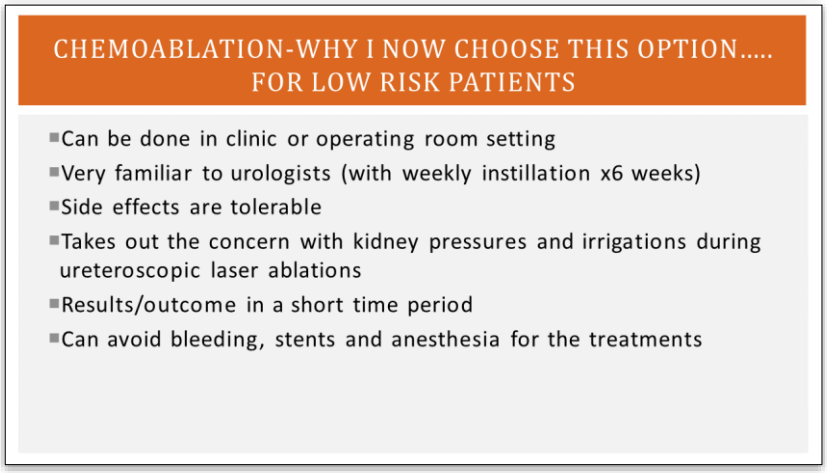

I say, when do you save kidneys always is a good answer if possible? That always comes with a tongue-in-cheek "if possible", and how do we do that? We do that often with these ablations, as I showed you in the first picture, and in now since 2020, talking about some chemoablations at the same time. I showed you those pictures, ablations with or without chemotherapy that can be done in today's world. We talked about this intraluminal chemotherapies and how the bladder is a storage location. It makes sense that you can put a chemotherapy in there and it stays. The kidney, on the other hand, it doesn't stay. Everything drains right back out of the kidney, but there is, newly in 2022, an approval for what's called Jelmyto. It uses a reverse hydrogel technology for installation of a mitomycin C chemotherapy within the upper urinary tract within the renal pelvis.


### Dr. Kate Murray:

It's very, very well-known to urologists. It's six weeks of a weekly installation is what it's FDA approved. The dosage is dependent on what we find at the time of a patient's ureteroscopy when we're looking and doing that biopsy. The reminder that I have here is this is for patients with low risk disease. One of my final slides is I really like to save kidneys if possible and some of these things can be done in multiple

settings, in clinic settings and operating room settings. It's familiar to us as urologists. It's quite tolerable for the patients, and it can avoid repetitive surgeries, repetitive anesthetics for our patients, if possible.




My last take home point from a urology aspect is based on one of those first slides that recurrences happen and they can occur in the same kidney, if it's still there, it can happen in the other kidney and it can happen in the bladder. I think that's something really important for us, is that we definitely need that ongoing management, documenting so that up to 40% of patients could have a bladder cancer after a urothelial of the upper urinary tract, and so we do need ongoing management of the bladder. We need it of the upper urinary tract, we need it of the lymph nodes of everything else, and of course, we're monitoring a patient's kidney function at the same time. Any comments from Dr. Campbell, because he sees these patients after, often after their seeing us as urologists or Dr. Matin if anything different that he does in his practice, or any good points.

## Dr. Matthew Campbell:

I'm just very lucky to have a chance to work with Dr. Matin with a lot of these patients, because I think best care really is a team effort for a lot of patients and trying to figure out best strategies to help maintain kidney function as much as possible and to give patients every chance to treat cancer while it's still localized and before it has spread. Again, I really lean on Dr. Matin's expertise in helping understand when treatments are best given locally versus when I can Linda helping hand with a treatment to make surgery either more feasible or more reasonable for patients.

## Dr. Surena Matin:

Thanks, Matt, for those comments. The only thing, I guess, that I would add is, and it's something that I think we, even in our very detailed conversations at our conferences, we sometimes don't really talk about at all, which is how much disease is there? Kidney preservation is so easy when there's very little disease. On the other hand, when there's a high volume disease and there's a lot of it, even if you think it's all low grade, it's a real challenge. As someone who is and still eager to preserve kidneys when you can, I think there's still indications for surgery to remove the kidney in the ureter if it's a low grade, because it's just so much to put the patient through sometimes to get all the disease and preserve the kidney when there's a lot of it there. Quite honestly, I'm not sure it's really worth it. Hopefully, they have a normal opposite kidney that's going to function well. Of course, in those cases, we have a conversation

about that, but I do think it's something that we need to start highlighting a little bit when we go to conferences and have these conversations and maybe even in the guidelines trying to be a little bit precise about how much disease is actually there, because there's just, it's just that practical factor of there's only so much we can do with our kidney preserving techniques.

### Dr. Kate Murray:

Great points. I think now it looks like we've got a screen share from Dr. Campbell and we will pass it on to him.