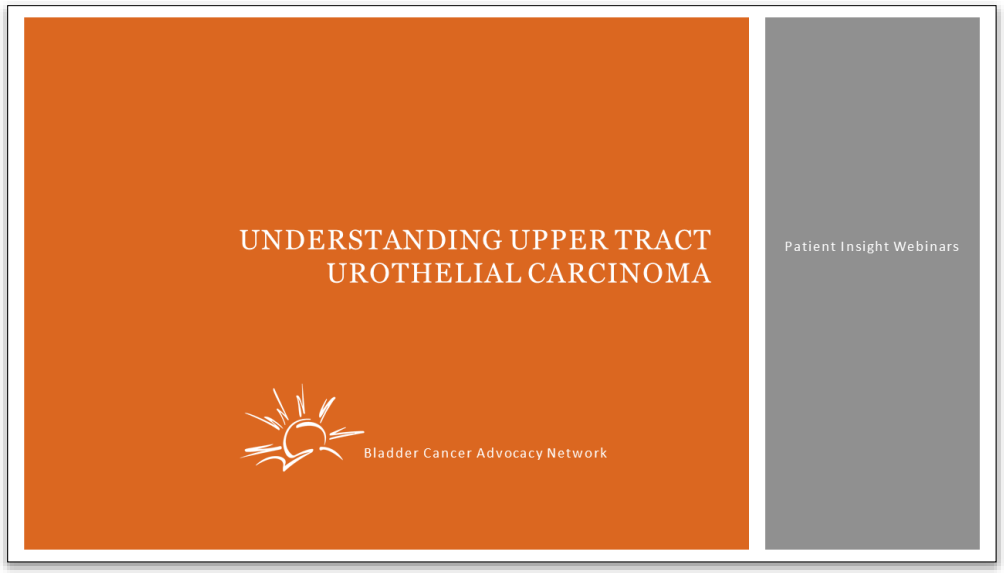


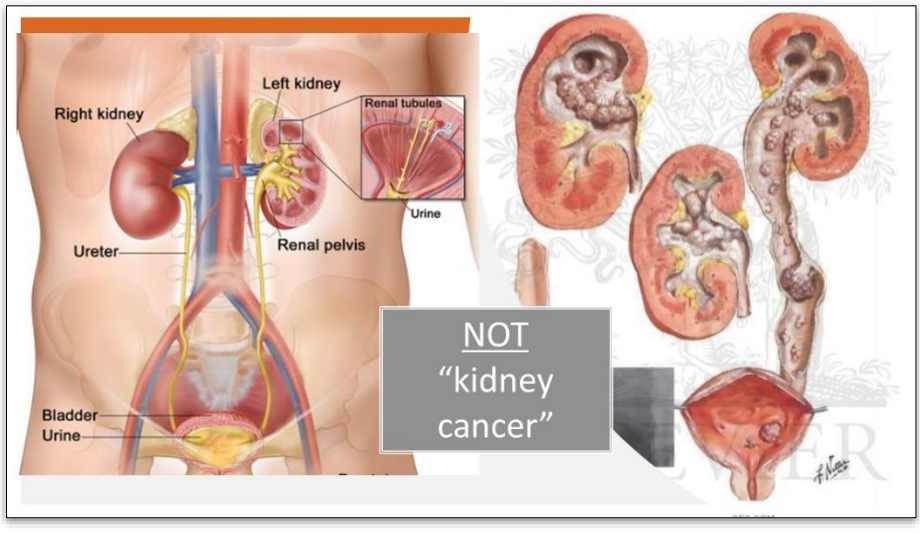
Morgan Stout:

Urothelial cells make up the lining of your bladder and urinary system. Cancer can occur in those cells. Upper tract urothelial carcinoma, or UTUC is a rarer form cancer that impacts the urothelial cells in your kidneys and ureters. It is like other forms of bladder cancer, but UTUC can present additional challenges for treatment because of the location and functions of the upper urinary tract. Beacon is delighted to welcome MD Anderson urologist, Dr. Surena Matin and medical oncologist, Dr. Matthew Campbell and urologist Dr. Kate Murray from the University of Missouri Medical Center for this discussion on how UTUC is similar and different from other forms of bladder cancer in its diagnosis and treatment. With that, I'm going to hand it over to Dr. Matin.

Dr. Surena Matin:

Hello everybody. I'm Surena Matin. I'm very pleased to be here. Thank you for that introduction, Morgan. I'm also very pleased that my terrific colleagues, Dr. Matthew Campbell and Dr. Katie Murray are able to join us as well. I think you should be able to see my screen at this point. What we thought we'd do for today is first of all, keep it conversational. You'd hopefully hear the three of us chatting a little bit, asking each other questions. I'm going to give you a brief introduction and overview, including the anatomy and some disease aspects. Dr. Katie Murray will talk to us about some of the surgical and endoscopic treatments that we have available. Then, Dr. Campbell will talk to us about the role of chemotherapy and immunotherapy for this disease.

Basically, when we talk about upper tract urothelial carcinoma, we're referring to everything being above the bladder. In this figure, you'll see the bladder at the bottom there, and you can see everything that's in yellow essentially reflects the urinary tract and the lining of the urinary tract, as Morgan mentioned, is where these cancers arise. As I'll



show you in the next slide, the majority of the urothelial cancers arise in the bladder and we call it bladder cancer for short. Technically, it's a urothelial cancer because it's arising from the lining of the urinary tract, which we call the urothelium. That same lining extends up the ureters and as you can see the ureters go all the way up to the, what we call the upper retroperitoneal area. Then, these divide up into these multiple channels within the kidney.

That's still all the urinary tract, and it's still lined by this urothelium. Cancers that arise in the ureter or in the renal pelvis or in what we call these calyces, all of these are considered urothelial cancer, but because they're occurring above the bladder, we call it upper tract urothelial cancer. These are some pictures from endoscopy that show you what these look like sometimes when they're smaller. This bottom picture shows you the view from when we're doing ureteroscopy. Now, one thing that I frequently find myself doing with new patients is that I have to explain that this is not kidney cancer. Patients get confused, and quite honestly, even doctors get confused because these cancers, since they're arising within the renal pelvis, which is inside the kidney, people mistakenly think that that might be kidney cancer, and so they look up on the web and get all this information on the internet about kidney cancer, and then they come see us, and then we're telling them all this information that they have not heard and that they've not read about. Then, we have to explain where the confusion may be arising from.

As probably most of you who are tuning in are aware, but some of you may not know, kidney cancer is a completely different cancer that arises from this fleshy part of the kidney. It's genetically completely different and the treatments that we render are different and the way it behaves biologically, also it's very different. Dr. Murray, is there anything here that you want to highlight based on conversations you've had with patients that you think our audience may want to know?

Dr. Kate Murray:

Yeah. I think that you made a great point. Sometimes what I will talk to patients is describe the outer part of the kidney as being the meat of the kidney, of a traditional kidney cancer versus this inside lining. The inside lining of the ureter, the inside lining of these, he was pointing at these yellow calyces in the kidney looking like your fingers would be looking like this. Then, that's also the inside lining of the bladder, and so that's really what we're talking about when we're talking about this upper tract cancer.

Dr. Surena Matin:

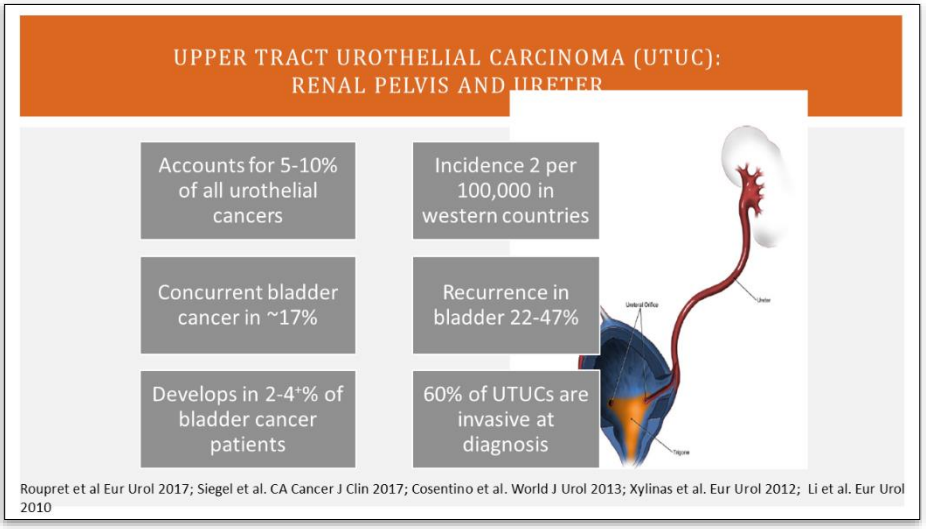
Matt, anything from your end?

Dr. Matthew Campbell:

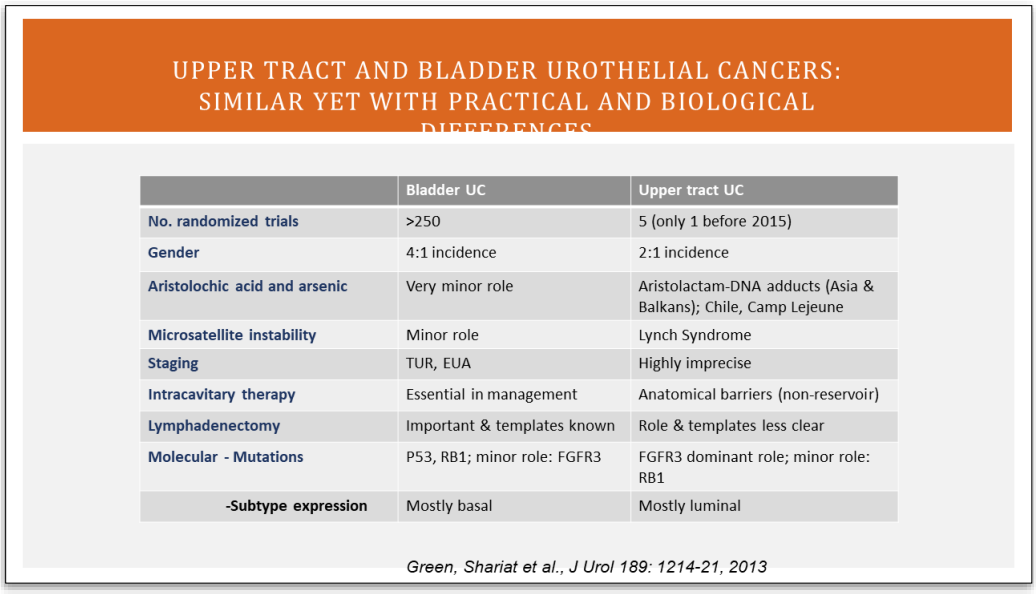
Yeah. I just like to draw it out for my patients, and I basically say that you have this ... the kidney serves as the filter and then you have your funnel system that connects to this tube. This is the delivery system, the bladders, the storage system and the urethras, the elimination, and it's just a waterproof system not intended to secrete or absorb, but just a delivery storage elimination system is how I explain it, and normally, and then I stress again, this is a very different cancer than kidney cancer, which I see in my clinic as well.

Dr. Surena Matin:

Yeah. Thank you both. Great comments. There are some unique aspects about this disease. It is not very common at all. Of all the urothelial cancers we see, of course, most of them are bladder, 5% to 10% are in the upper tract. Overall incidence is two per a hundred thousand in Western countries and I think that one definition of a rare cancer is four in a hundred thousand or less. This meets most of the criteria for being a rare cancer. There's already been a question about whether it can start in the bladder and the answer is yes, and you can see with some of these other boxes. We see them happening, what we call synchronously or at the same time about 17% of the time. On the other hand, about 2% to 4% of bladder cancer patients can develop upper tract disease, so it's not very common, but there are some bladder cancer patients that may be at higher risk than others. In patients who do have upper tract cancer and whom we treat it, there is a higher recurrence rate in the bladder. Mostly, if it helps to think about it, I guess, because the bladder is the most downstream and things can trickle down and seed, but also, the disease can start anew in the bladder as well. Now, this says 22% to 47% with some of the newer methods that we have, which involves giving chemotherapy washes in the bladder during, or excuse me, after treatments. We're able to reduce this to less than 20%, but still have not gotten to a point where we can completely eliminate that risk. Then, one other thing that's different than bladder is that most of these, when they present, are invasive a diagnosis, which is the opposite of what happens with bladder, which is most of them are not invasive.



Then, this table summarizes some of the major differences between bladder and upper tract cancer. In many ways, they're very similar. If you ask a pathologist to look at them under the microscope phenotypically, as we say, or by visual inspection, they look very similar. But when we get down to practical levels and then when we start probing more molecular aspects of it, we find that there actually are some differences. With bladder, we have, for example, tons of evidence and lots of high



	Bladder UC	Upper tract UC
No. randomized trials	>250	5 (only 1 before 2015)
Gender	4:1 incidence	2:1 incidence
Aristolochic acid and arsenic	Very minor role	Aristolactam-DNA adducts (Asia & Balkans); Chile, Camp Lejeune
Microsatellite instability	Minor role	Lynch Syndrome
Staging	TUR, EUA	Highly imprecise
Intracavitary therapy	Essential in management	Anatomical barriers (non-reservoir)
Lymphadenectomy	Important & templates known	Role & templates less clear
Molecular - Mutations	P53, RB1; minor role: FGFR3	FGFR3 dominant role; minor role: RB1
-Subtype expression	Mostly basal	Mostly luminal

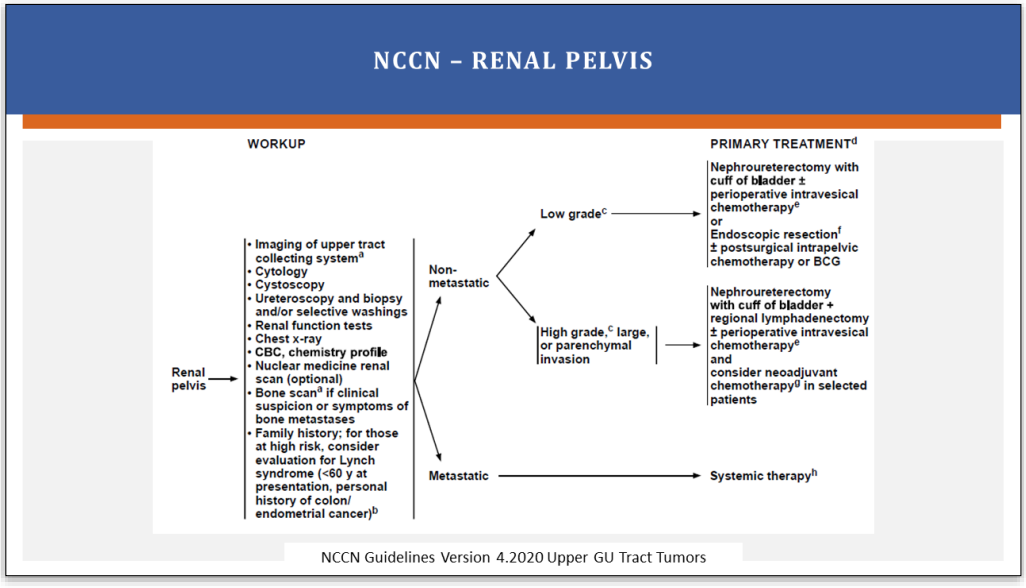
level data, with upper tract disease, we don't. The other interesting thing is that we do see a higher proportion of women with upper tract disease. You'll see with bladder, it's 4:1 male to female ratio. With upper tract, that's 2:1, so it's still mostly males, but overall many more females proportionally than with bladder.

Dr. Surena Matin:

We do see Lynch syndrome, which is an inheritable genetic syndrome, is strongly associated with upper tract cancer and much less so with bladder. We think, overall, maybe about 4% of patients with upper track cancer may have Lynch syndrome, but this is an area that we're still exploring. When we deal with bladder cancer, we can reasonably stage it between a TURBT, which Dr. Murray's going to talk to you about, examining patients under anesthesia or UA and then with CT scans. It is much more imprecise when we're dealing with upper tract disease, because we're looking at such smaller resolution, much smaller organs. Current imaging is at the limit of being able to tell us sometimes things that are happening at the millimeter level, which is sometimes what's going on with this disease. Intra cavitary therapy is treatments that we drip in like for the bladder, and that's essential in a management of bladder cancer like with BCG or chemotherapy. A bladder is perfect because you put something in it, it's a storage organ and it'll sit there. Well, the upper tract is not meant to be a storage organ, it's meant to conduct as Dr. Campbell so nicely worded it and it's a funnel. Things don't necessarily stick around to do their treatment job and that makes it challenging.

We think removing lymph nodes for upper tract disease is important, but there's controversy. If you come to our meetings, you'll hear people argue strongly one way or another, and the role, so the role is still unclear. Then, as I mentioned, from a molecular perspective, what's really interesting is this molecule called FGFR3, which plays a very minimal role with bladder cancer, but in upper track cancer, the majority of them, at least with low grade cancers, have this mutation. Then there's some other details about this that we're finding out in terms of their molecular subtypes, but this is still an evolving area. Matt or Katie. Did you have anything you wanted to add to this? I didn't mention tobacco. That's very similar between both of them. That is, of course, our single, strongest risk factor for both. I didn't include that. It's not necessarily different, but that's still also a risk factor for both diseases.

I wanted to show this guideline from the NCCN, because as you'll notice here, it tells you if it's non-metastatic, you don't see staging. Again, staging for this disease is very difficult. We don't necessarily work hard to talk about staging, although we do more and more talk about risk stratifying patients. But nevertheless, what a lot of people do is really think about it in terms of low grade or high grade disease. The grade is assigned by the pathologist when they look at the cancer under the microscope. Essentially, what I tell



patients is that it's a measure of its aggressiveness. Low grade is low aggressiveness and high grade is high aggressiveness. From that, we can make some assumptions about the possibility of what the stage is. Low grade, for example, almost always is not invasive in its low stage. High grade, on the other hand, has about a 2 out of 3 chance of being invasive to some degree.

Dr. Surena Matin:

As you can see, the treatments are somewhat different. With low grade, we can look at kidney preservation and you're going to hear a little bit more about that in a few minutes. Sometimes, if it's a lot of tumor, we'll have to still do surgery to remove the kidney and the ureter. On the other hand, if it's high-grade, kidney preservation is really not a good option, and not only are we looking at surgery, but sometimes we're also looking at having to add chemotherapy before or after. I just wanted to mention that and the reason for that, again, the grade being such an important part of it is reflected in these charts, which just broadly, if you look all the way to the left, the grade one or low grade, these curves are overall very favorable. Then, if we look over for here for grade three or high grade disease, you can see that the curves, especially the red ones indicate patients who had kidney preservation and endoscopic management, and high grade disease does not do well for that at all. That's why we have to treat these very differently. You're going to be hearing about that over the next several discussions from Dr. Murray and Dr. Campbell. From that, I am actually going to turn it over to Dr. Katie Murray, unless one of the two of you has some comments that you wanted to add at this point.