

Upper Tract Urothelial Carcinomas (UTUCs)

Part I: What is UTUC?

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Moderated by:



Gary D. Steinberg, MD
University of Chicago Medical Center

Presented by:



Karim Chamie, MD, MSHS
UCLA Department of Urology



Alon Weizer, MD
University of Michigan Medicine

Dr. Steinberg: Thank you very much, and I'm thrilled to be participating in this outstanding program tonight. It's gonna be a great educational experience. We've got some super outstanding speakers who are experts in their field who, I think, are gonna shed some very important information and light on this important topic.

Dr. Chamie: Well, I'm absolutely honored to give a brief introduction going over the definition, epidemiology, staging and diagnosis, for patients with upper tract urothelial carcinoma. Now, when I talk about upper tract urothelial carcinoma I'd like to first back up and talk about urothelial carcinoma. Now urothelial carcinoma is a cancer that can occur any way from the inner linings of the kidney, down the ureter, in the bladder and down the urethra. Now most of the time patients often assume that bladder cancer is urothelial carcinoma. Now it's true about 92% of all urothelial carcinomas occur in the bladder, but about 7-8% of urothelial carcinomas can occur in the upper lining of the kidney, which we call the calyx and renal pelvis, it could occur in the ureter, or it could occur in the urethra.

Definition

- Definition: Cancer of the lining of the urinary tract
 - ▣ Lining of the kidneys (5%)
 - ▣ Ureters (2%)
 - ▣ Bladder (92%)
 - ▣ Urethra (1%)

The diagram shows the urinary tract from an 'Outside view' and an 'Inside view'. The 'Outside view' shows the kidneys and ureters. The 'Inside view' shows the internal structure of the kidneys, ureters, bladder, and urethra. Labels include 'Kidneys', 'Ureters', 'Bladder', and 'Urethra'. Lines connect the text in the list to the corresponding parts of the diagram.

Now how common is urothelial carcinoma? Now it's ... every year we diagnose 79,000 new cases. And we talk about incidence, these are new cases, 60,000 of them occur in men, 19,000 occur in women. Approximately 17,000 patients die every year from urothelial carcinoma, 12,000 of those are men and 5,000 are women. The good news for women is that the incidence, which is the number of new cases being diagnosed, and the number of deaths due to urothelial carcinoma have actually decreased over recent years. For men the incidence, the number of new cases, has decreased, but the deaths have stabilized. Part of that may be attributed to, you know, fruition of prior smoking tobacco use that's come of age.

Epidemiology: UTUC

- Mean age: 73 years
- 3% involves both upper tracts
- 17% concurrent with bladder cancer
- Ascending tumors:
 - New UTUC in patients with prior bladder cancer is 2–4%
 - New UTUC in patients with prior CIS of the bladder is 20–25% at 10 years
- Descending tumors:
 - New bladder cancer in patients with prior UTUC 22–47%

Urothelial carcinoma accounts for 5% of all new cancers in the United States. It's the fourth most common cancer in men, but less common in women. Now, when we talk about upper tract urothelial carcinoma the mean age, which means the average age, of a patient diagnosed is 73 years. 3% of the time it can occur in both upper tracts, which means that it can occur in both ureters or both renal pelvis, 17% of the time it occurs concurrently with bladder cancer. Now that's a little different than what I'll be

talking about in a minute as far as ascending tumors and descending tumors. Ascending tumors are when patients have upper tract urothelial carcinoma, meaning cancer in the renal pelvis or in the ureter, and then over time they will develop cancer in the bladder. Now if you look at all patients, sorry, that's descending. Ascending tumors occur when patients have tumors in the bladder and ascends up into the ureter or renal pelvis. If you look at all patients that have bladder cancer, 2-4% of those patients will develop upper tract urothelial carcinoma.

Now, if patients actually have carcinoma in situ, which is a high grade tumor in the bladder, 20-25% of those patients will develop upper tract urothelial carcinoma if you follow these patients out to 10 years.

Now descending tumors are tumors that occur in the renal pelvis, or in the calyx, or in the ureters, and it actually feeds down into the bladder. And for those patients we find that 22-47% of those patients will develop bladder cancer some time down in the future.

Dr. Steinberg: I just want to reiterate for the audience that the numbers that Dr. Chamie is speaking about are all urothelial cancers. So the incidence numbers that he spoke about, the majority of those patients have bladder cancer and do not have upper tract disease, but he is including all of those patients that have urothelial cancer, again, predominantly bladder cancer. But as Dr. Chamie's pointed out, there are a significant number of patients that also have the same type of cancer that they had in the bladder, that they also can have in the upper tracts.

Dr. Chamie: That's right. Now as far as staging, what do I mean by staging? Staging is just level of invasion. Now 56% of patients that are diagnosed with upper tract urothelial carcinoma are diagnosed with non-muscle-invasive upper tract urothelial carcinoma, and then 44% of patients diagnosed with upper tract urothelial carcinoma are diagnosed with invasive, or more locally advanced, or metastatic, upper tract urothelial carcinoma.

Staging

- Non-Muscle-Invasive UTUC
 - ▣ Ta: 26%
 - ▣ Tis: 5%
 - ▣ T1: 25%
- Muscle-Invasive UTUC
 - ▣ T2: 14%
 - ▣ T3: 24%
 - ▣ T4: 6%

Let me kind of go over a brief depiction of what I mean by staging. So a stage 0, or stage TA or TIS, is a tumor that is just involving the mucosa, the yellow lining on the top. Now when we see these tumors in the real world it's not yellow, but this is just a depiction here. This occurs in 31% of patients with upper tract urothelial carcinoma. Stage 1 occurs in 25% of patients, and that is when the tumor not only invades the mucosa, but the lamina propria. The lamina propria is a basement membrane, and there are some lymphatics and blood supply there where the tumor, if it sits there long enough, or if it's aggressive, may actually spread.

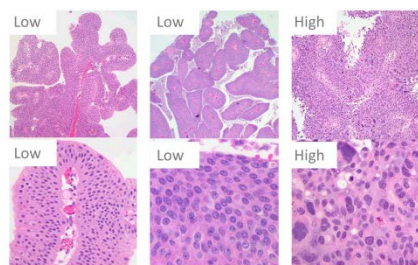
Now we're talking about muscle-invasive upper tract urothelial carcinoma. Again, these tumors not only invade the mucosa, not only invade the lamina propria, but they also invade the muscle lining of the ureter or the renal pelvis. This occurs in 14% of patients, and in stage 3 cancers this occurs in 24% of patients. It involves the mucosa, the lamina propria, the muscle. In the kidney, it can actually grow from the renal pelvis into the kidney or the fat around the renal pelvis or ureter.

Now stage 4 upper tract urothelial carcinoma can involve surrounding organs or, if it spreads to lymph nodes in the lung or in the retroperitoneum, it would also be considered locally advanced or stage 4 upper tract urothelial carcinoma. This occurs in about 6% of patients.

Now oftentimes you'll hear the words low grade and high grade. When we talked about stage that tells us the level of invasion. But when we talk about grade we're talking about the aggressiveness of the tumor. Now oftentimes they go hand in hand. Less aggressive tumors tend to have a lower risk of invading, but not necessarily. Sometimes patients may have less aggressive tumors, but if they sit there long enough they will gain the capacity of invade. Meanwhile, you may have high grade tumors, which are very

Grade

- Low Grade: 35%
- High Grade: 65%



The image displays six histological sections of urothelial carcinoma, arranged in a 2x3 grid. The top row shows low-grade (left and middle) and high-grade (right) tumors. The bottom row shows low-grade (left and middle) and high-grade (right) tumors at a higher magnification. The low-grade images show well-organized, uniform cells, while the high-grade images show disorganized, pleomorphic cells with increased mitotic activity.

aggressive, but if it's caught early it may be non-invasive. As far as low grade and high grade, upper tract urothelial carcinomas 35% of the time have low grade, which means non-aggressive tumors, and 65 of the times are high grade which tells us they're aggressive. Now how we define aggressiveness is based on a pathologist who looks at the tumor under the microscope. And you could see, on the left hand side, it looks more frondular, it looks like a leaf, and it looks more organized on the bottom. But as you start going from left to right you'll notice it starts to look more disorganized, less homogenous, starts to look ugly. That's why we call it high grade because it looks ugly under the microscope, and the cells are rapidly dividing.

Signs and Symptoms

- Blood in the urine (gross and microscopic): 70–80%
- Flank pain: 20–40%
- Palpable mass: 10–20%

- Symptoms suggestive of metastatic disease
 - Anorexia
 - Weight loss
 - Malaise
 - Fatigue
 - Fever
 - Night sweats

Now what are some of the signs and symptoms for patients with upper tract urothelial carcinoma? The most common is blood in the urine. Now not always do you have to see it with your own eyes, sometimes it's picked up by having an abnormal urine test on a routine urine analysis. Your primary care physician may note some blood in the urine. Oftentimes, patients may be assumed to have urinary tract infections. If there are bacteria growing, if your patients are having symptoms that may be the

case. However, it is not uncommon that patients have been treated with antibiotics in the past that may actually harbor tumors in the upper tract, or in the bladder.

20-40% of the time patients may have flank pain. This occurs because patients actually have a little bit of bleeding from the tumor which then obstructs the kidney, acts almost like a kidney stone, and may cause symptoms, and that's how we may pick it up in about a third of patients. Or if the tumor's very locally ... if it's locally advanced it may grow large enough where we can actually palpate and feel the mass in the flank. Now if patients are actually having severe symptoms, oftentimes that may be due to the fact that the cancer has already metastasized. So if patients actually have symptoms such as anorexia, you know, not having much of an appetite, weight loss, fatigue, malaise, fevers, night sweats, that may indicate that the tumor may have spread to other places.

Now what are some of the risk factors for upper tract urothelial carcinoma? We know tobacco increases your chances of getting all urothelial carcinoma, not just the upper tract, and patients are two to three times at increased risk of developing urothelial carcinoma, occupational exposure, such as analane dyes. Balkan endemic nephropathy, these are patients that are born or grew up in the Balkans, so Croatia, Bosnia Herzegovina, Romania, that have been exposed to a certain type of plant which is often used with wheat to make bread, but it's European Birthwort, and increases their chance of not only renal failure, but increases their chance of actually getting upper tract urothelial carcinoma. Some actually use

that same herb to make some of these Chinese herbs in Chinese medicines. Arsenic exposure. Now arsenic exposure is quite high in places like Taiwan, or in Bangladesh, but it may also be elevated in Canada or the upper North West. Genetics. When we talk about Genetics we talk about Lynch Syndrome.

Genetics: Lynch Syndrome

- Lynch Syndrome most common inherited cancer syndrome
 - ▣ Upper tract urothelial cancer is the third most common cancer seen in this syndrome (1st is colon cancer)
- As many as 21% of upper tract urothelial cancers may be associated with Lynch syndrome
- Consider Lynch syndrome in:
 - ▣ Women
 - ▣ Younger age of onset (mean age 62)
 - ▣ Ureteral location
 - ▣ Bilateral disease
- Suspicion includes personal or family history, tissue confirmation, and genetic evaluation

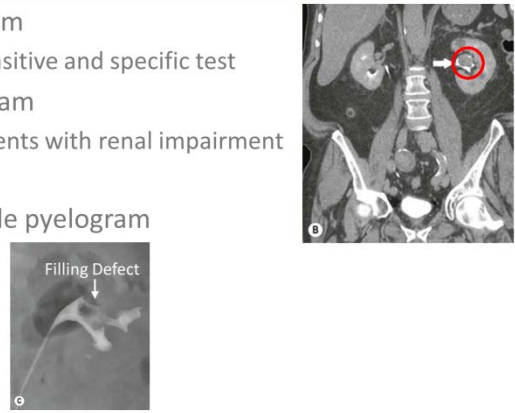
Patients with Lynch Syndrome have an increased chance of developing upper tract urothelial carcinoma. Lynch Syndrome is one of the most common inherited cancer syndromes. Urothelial carcinoma is the third most common type of cancer of that syndrome, the most common being colon cancer. We estimate that 21% of patients with upper tract urothelial carcinoma may, in fact, have Lynch Syndrome, and we tend to identify these patients as being high risk, meaning women, younger age of onset, finding tumors in the ureter, or having bilateral

disease. These patients tend to have ... it's a little uncommon, that's why we'd think it may be associated with the Syndrome because we often think that patients who develop urothelial carcinoma tend to be men who are older, who may have tumors in their renal pelvis. So all these oddities tend to point to Lynch Syndrome. So patients who have a family history, or tissue confirmation, may actually in fact be proved to have the disease.

Now how do we diagnose upper tract urothelial carcinoma? The most common test that we use is a CT urogram, and on the top right hand corner you'll see a CAT scan. You'll see a red circle around the left kidney and, specifically, around the left renal pelvis. You'll see the white. The white is the contrast that is flowing from the kidney out the ureter, and you'll see this black filling defect. This is a very sensitive and specific test for upper tract urothelial carcinoma. If patients have impaired renal function they may not be able to

Diagnosis

- CT urogram
 - ▣ Very sensitive and specific test
- MR urogram
 - ▣ For patients with renal impairment
- Retrograde pyelogram



tolerate the contrast dye from a CT scan. In those instances patients may benefit from getting an MR urogram, which is just as sensitive and specific as a CT urogram. Moreover if patients may have a pacemaker, and they have renal deficiency, the diagnosis may be made by a Retrograde pyelogram. A

Retrograde pyelogram is where a urologist takes the patient to the operating room and under cystoscopy places a very small catheter into the ureter and squirts some contrast which then fills up the collecting system. An area that doesn't fill up here, you'll see that filling defect that I'm pointing to on the bottom image, you'll see that is a sign that's suggestive of a urothelial carcinoma. Now if a patient's been taken to the operating room the urologist may, at that point, place a small scope up the ureter, visualize the tumor and biopsy it all in one setting.

Diagnosis

- Urine Cytology
 - ▣ Very specific test
- Ureteroscopy

Now we also diagnose upper tract urothelial carcinoma with something called a urine cytology. This is a very specific test. Basically it's kind of like a pap smear, but instead of the cervix it's over the urinary system, and we take some cells and a pathologist looks under ... a cyto pathologist looks under the microscope and tells us that these are cancerous cells that are coming from the urinary system. It's not a very sensitive test but it is a specific test. And obviously, the most definitive approach of diagnosis is in at least biopsying an upper tract urothelial

tumor is with something that we call ureteroscopy. That means using a camera and a very small scope to go and look at the ureter and the renal pelvis. You'll see the scope here on the bottom image. It's a very small tube that goes through the urethra into the bladder and up the ureter. Here you'll see two images of a tumor. One is a solitary tumor, here on the left, and on the right you'll see a multi focal tumor, almost looks like a carpet rug pattern, occupying the renal pelvis. The urologist at that point may biopsy this tumor. The urologist may use a basket, or may use a laser fiber to take a snippet of some of this tumor and send it off to the pathologist to look under the microscope.

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