

# Upper Tract Urothelial Carcinomas (UTUCs)

## Patient Insight Webinar

### Q & A

With BCAN Expert Panel: Drs. Gary Steinberg, Alon Weizer, Seth Lerner, Karim Chamie, Ahmad Shabsigh, Surena Matin and Jennifer Linehan.



**Q:** After two negative cystoscopies but positive FISH test results, my urologist wants to examine the ureters and kidney. Does positive FISH warrant this? I am an 80 year old male in very good health.

**Dr. Karim Chamie:** The role of upper tract evaluation in the setting of abnormal FISH test is dependent on a number of factors. Upper tract evaluation is warranted in patients with a prior history of bladder cancer, cigarette smoking, blood in the urine, abnormal urinary cytology, or abnormal findings on imaging (CT or MRI scans). This evaluation may include ureteroscopy (evaluation of the ureter and renal pelvis with a telescope). It is an outpatient procedure and is not associated with any significant morbidity. It is beneficial if your doctor identifies a lesion in the early (non-invasive) stage.

**Q:** I had rare presentation of bladder CIS (Carcinoma in Situ). It was very diffuse and invisible primary CIS: all 11 cold cup biopsies were positive for CIS! Does this make me more susceptible to upper tract urothelial carcinoma, over time, than another original presentation of CIS?

**Dr. Karim Chamie:** Patients with multifocal CIS are at increased risk of developing upper tract urothelial carcinoma. The risk of developing upper tract urothelial carcinoma over a 10-year period is approximately 20%. Having invisible CIS lesions (with white light cystoscopy) does not particularly mean you have a more aggressive type of bladder cancer. That said, it may be more difficult to diagnose if the lesions are not readily visible at cystoscopy or upper tract endoscopy. Additionally, it is important that your physician ascertain that you do not in fact have upper tract urothelial carcinoma during your evaluation and staging. This may be accomplished by CT urogram or ureteroscopy.

**Q:** Are there some genetic tests available specifically for UTUCs? Are they offered in all hospitals? How do I request this?

**Dr. Surena Matin:** Currently there are no specific genetic tests for UTUC, but the most common genetic syndrome associated with UTUC, Lynch Syndrome (LS), also called HNPCC, is diagnosed via standard genetic testing. No one test is perfect; however, and usually a combination of genomic tests are required to capture most cases.

One of the tests is based on family and personal cancer history and is called the Amsterdam 2 Clinical Criteria. This is easier to remember as the “3-2-1” test: 3 successive family members with LS-related cancers (listed

below), 2 of them first degree relatives, and 1 of them having been diagnosed before age 50. If all 3 of these criteria are met, there is high suspicion of LS. The most common LS-related cancers are colon, endometrial, any other GI cancer, ovarian, breast, sebaceous, skin.

Another set of tests uses tumor tissue, and are available at most centers with a pathology lab. One of these is called immunohistochemistry for mismatch repair proteins, and is relatively easy to do even with small amounts of tumor tissue. If one of these 4 proteins is missing, it suggests LS. Another tissue test requires both tumor and normal tissue (even if from blood) and uses more sophisticated DNA test called PCR and is a test for “microsatellite instability” or MSI. If this is high, it suggests the possibility of LS.

When any of these tests suggest LS, then a referral is placed to a genetic counselor who can discuss the implications of the testing, insurance coverage and future implications, and obtain blood or a cheek swab in order to perform confirmatory germline DNA testing (meaning a DNA test of your normal tissue genes to confirm the presence of an inheritable mutation). Note that there are cases when LS is very highly suspected but the genetic testing is negative. We consider these likely LS, and probably due to a mutation that has not yet been described/discovered.

**Q: How do you judge whether the cancer origins from upper tract or from bladder if tumors are found in both bladder and ureter/kidney?**

**Dr. Surena Matin:** Sometimes you really never know when they are found simultaneously. In truth it becomes a moot question from a treatment perspective, since both sites would need to be treated, however academically and scientifically we do find these phenomena interesting to study so we can learn more about the disease.

**Dr. Alon Weizer:** It is challenging to know if a tumor in the upper urinary tract seeded the bladder, or tumors in the bladder ascended into the upper urinary tract. There are two models that have been suggested for multifocal disease in the urinary tract. One refers to a “field defect”. This describes the phenomenon where the entire urinary tract has been exposed to the same carcinogens, and accumulates genetic changes that lead to cancer at different rates, and hence you see tumors arising at different time points in different parts of the urinary tract. The other possibility is that there is seeding (the clonal hypothesis) where parts of the original tumor break off and form colonies in other parts of the urinary tract. Ultimately the only way to know for sure is to genetically profile different tumors to see if they are brothers and sisters or separate families.

**Q: If a patient has already received chemotherapy for bladder cancer and has had a radical cystectomy and also has been diagnosed with Lynch Syndrome, what are the chances of that patient developing upper tract disease?**

**Dr. Alon Weizer:** The pattern of disease suggested by this question implies that the patient in question has the type of Lynch Syndrome that may be associated with upper tract urothelial carcinoma. Without knowing the exact details of the bladder cancer, patients who have had a radical cystectomy with a negative ureteral margin have an approximately 2-5% risk of developing upper tract disease. Estimates on the lifetime risk of upper tract urothelial cancer in patients with Lynch Syndrome vary from 0.4-20% (or even higher). The risk in Lynch syndrome is influenced by gender and the specific Lynch syndrome mutation as well as other clinical factors. Overall, I would continue periodic surveillance regarding the upper urinary tract for this patient.

**Q:** I had UTUC in 2013 in right ureter, removal of kidney and ureter followed with cancer in bladder in 2014. I have had 18 BCG treatments and am currently having cystoscopy every six months and scans every year. I have been tested and have Lynch syndrome. Is there anything else I should be receiving for treatment?

**Dr. Seth Lerner:** No, you appear to be receiving standard of care treatment supported by AUA and NCCN guidelines for non-muscle invasive bladder cancer.

**Q:** In the case of prior CIS of the bladder, where it said "at 10 years" [slide #9 from Karim Chamie's presentation] risk up to 20% of UTUC. Does this mean AT ten years after all clear of bladder CIS, or UP TO 10 years, please?

**Dr. Seth Lerner:** Within ten years up to 20-25% of patients with a history of CIS in the bladder may have a new urothelial tumor in the ureter or renal pelvis of the kidney. However, this has not been consistently reported in all series.

**Q:** What is the standard of care for monitoring existing bladder cancer patients for the potential for upper tract cancer?

**Dr. Seth Lerner:** For a patient with a history of high grade bladder cancer, a CT urogram at year 1 and 2 then every other year out to 10 years may be recommended; however, this is expert opinion and not based on any definitive data. There is no need for monitoring for low grade cancers.

**Q:** If chemotherapy (e.g. cisplatin/gemcitabine) is given for locally advanced T3G3 urothelial cancer with a negative PET scan, does the chemotherapy only attack the suspected "micro metastases" or does it also kill potentially invisible budding cancer cells inside the urinary tract?

**Dr. Ahmad Shabsigh:** Chemotherapy may target both micro-metastatic disease and the tumor in the renal pelvis and ureter; however, the target is the microscopic metastatic disease. Some studies report that some primary tumors decreased with systemic chemotherapy. However, due to the difficulty confirming complete resolution by CT scan or ureteroscopy of the primary tumor after chemotherapy; radical nephroureterectomy with lymph node dissection is recommended.

**Q:** Is Mitogel only for high grade patients? Could Mitogel be used to treat bladder cancers in lieu of surgical removal of tumors? Is any research being done on this?

**Dr. Ahmad Shabsigh:** Currently, there is a clinical trial studying Mitogel for low grade non-invasive tumors of the renal pelvis. In addition, there are ongoing studies to define the use of this promising agent for non-muscle invasive bladder cancer.

**Q:** In "descending" spread of UT tumors to the bladder- is the later tumor considered to have arisen spontaneously due to a "field effect" or is it thought of as an implant that has broken off the upstream lesion. Are they genetically homogeneous? How do "ascending" lesions arise? Do they flow upstream?

**Dr. Jennifer Linehan:** About 30-50% of the patients who have upper tract urothelial carcinoma- UTUC will develop cancer "downstream" in the bladder. This is not likely due to "implantation" but because the patient is pre-dispositioned genetically to form urothelial cancers, since all the same cell types line the urinary tract kidney to bladder and prostate in men) to the urethra.

Of patients with urothelial cancer starting in the bladder, only 5% will develop tumor above the bladder in the ureter/kidney if there is no CIS - carcinoma in situ present. If a patient has CIS – carcinoma in situ present in the bladder then there may be up to a 20% chance they will develop tumors in the ureter/kidney. Two percent of patients will have tumors in the ureter/kidney at the same time as the bladder tumor is found. Again this is likely do to “field effect” or the fact that the urothelial lining has the genetic code to mutate into cancer already. When we have studied these tumors, especially urothelial carcinoma found in the ureter then in the bladder later, they are NOT always genetically the same and sometimes will present at a lower grade of cancer.

**Q: My right kidney/ureter was removed without having chemo done prior to the surgery, would a post-op chemo now be helpful?**

**Dr. Jennifer Linehan:** This depends on some additional factors especially the final surgical pathology, especially if the lymph nodes are positive for cancer and then patient’s renal function and or contra-indications for cisplatin based treatment.

There is no well-studied data that suggests giving chemotherapy right after surgery improves outcomes or prevents recurrence. There is currently a study called POUT (<https://clinicaltrials.gov/ct2/show/NCT01993979>) that is looking at this issue directly. Currently, patients are followed closely for recurrence with chest and body CT scan as well as cystoscopy. If recurrence, especially metastases, is found then patients are treated with chemotherapy. BUT if those patients had chemotherapy prior to surgery, and still had lymph nodes positive for cancer after being treated with chemotherapy, then chemotherapy may not be the best option. In this setting another treatment such as immunotherapy may be better.