

Upper Tract Urothelial Carcinomas (UTUCs)

Part IV: Questions & Answers

November 14, 2017



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



Surena Matin, MD
MD Anderson Cancer Center



Jennifer Linehan, MD
City of Hope



Ahmad Shabsigh, MD
Ohio State University



Seth Lerner, MD
Baylor College of Medicine

Question #1: Is there a way to send intra-vesical BCG to the ureter/kidney for high grade cancer?

Dr. Linehan: So there are two ways you can try to get BCG to the kidney or the ureter. Again, you'll run into some of the similar problems that because it's a liquid it's very difficult to keep it in one place for treatment of tumors within the kidney, or tumors within the ureter. So you can put a stent in, which is a tube that goes from the bladder up to the kidney, and you can put the BCG into the bladder, and that tube can allow the BCG to go back up into the kidney and try to treat the tumor. But, again, if you want to get it all the way up into the kidney, and you want to have the BCG sit in where the actual tumor is, it's very difficult. In some cases I've also had to put a tube through the back into the kidney called a nephrostomy tube. In those cases you can do some very slow infusions of the BCG where you're running it through the tube in the back into the kidney. But again there's always the problem with tumors in the kidney or the ureter of being able to baste the tumor, essentially, in the BCG. Ahmad, do you have anything to add to that?

Dr. Shabsigh: That was well said. I think there's ... you know, in the past I used to put a stent in the ureter and infuse the bladder with BCG. With some limited studies, especially animal models, and some

experience, I switch now to actually bringing the patients to the office every week for six weeks in a row and doing exactly what we do for the mitogel clinical trial, where I actually pass a stent, a catheter, from outside the patient all the way to the pelvis, and then slowly drip the BCG. I think that's probably ... give the tumor more exposure to the chemotherapy. But, again, you know the results are mixed for that.

Dr. Steinberg: One of the things that I think that both of our speakers emphasized is slowly. BCG is an organism that's alive, and while it's been altered to decrease it's infectious capabilities, if BCG gets into your bloodstream it can cause a serious, even potentially life threatening, infection. One of the concerns about putting BCG into the upper urinary tract, in addition to not being sure that it's actually getting to where it needs to go and staying there to be absorbed, but that it can get into the bloodstream of the ureter, or of the kidney, and if it does you could have a significant infection. So I think that for the patients out there that are looking for types of treatment for upper tract disease, including medications, that is a real, true, unmet need and that's what the whole basis of the mitogel program, as well as using, potentially, stents with drugs in them that can slowly be delivered to the tumor, that's really a major focus for the bladder cancer and urologic, urothelial cancer community.

Question #2: Should a patient suspected of upper tract disease see a regular urologist or a urothelial specialist and how would they identify someone who really knows how to treat this rarer form of bladder cancer?

Dr. Lerner: I suppose it would be a little self-serving to say that patients should always see, you know, an expert in urothelial cancer, but to be honest with you, I think most of our residents from all of our programs are trained, certainly in the state of the art ureteroscopy, which means being able to pass a tube up and get direct vision and do biopsies. I think it gets a little complicated when say a patient is having frequent recurrences, or certainly high grade disease, or difficulty in making a diagnosis, and I think that's where we would certainly encourage the community urologist to reach out to, you know, an expert in say a medical center close to them. There's gonna be, in virtually every certainly major city and most states, access to someone with a higher level of expertise. Then, of course, just to put a plug in for BCAN for the listeners that BCAN is an excellent source of when someone is looking for an expert in their community to identify someone in ... any of us. We've got a large scientific advisory board, and BCAN really has their hand in, and knows who the experts are in all of the communities. So that's a good resource if someone's looking for an expert.

Question #3: Is there any particular genetic test available for upper tract? And in particular, what testing is available for Lynch Syndrome? One of our participants and their mother both have been diagnosed with upper tract disease, so how would they find out about Lynch Syndrome?

Dr. Lerner: So, if I may, I think Dr. Matin is the perfect person to answer that question. He's done some really extraordinary research in the last year or two, you know, testing this, in a continuous group of patients. I think it, Surena, it was over 100, maybe 150, and has really worked out the ideal testing strategy. And so I think we're really fortunate to have him on the webinar today.

Dr. Matin: Sure, I'd be happy to speak about that. There's been some laboratory and database studies that suggested there's a fair amount of undiagnosed Lynch patients who present with upper tract cancer. That had never really been sort of evaluated in the clinical setting with, if you will, you know, living, breathing patients. So several years ago we started screening every single upper tract patient that was coming through my clinic, and I do see about the overwhelming majority of these cases that come through our center. What we actually found was a roughly 6% case of confirmed previously undiagnosed Lynch Syndrome in patients who present with upper tract cancer, and about a 14% rate of possible Lynch Syndrome, and it's possible because those were not confirmed by a genetic germ line testing.

What we found in the process of this is that there are two tests that seem to capture all of these cases. One is called the Amsterdam 2 Criteria, and quite honestly, it's a good history from the patient, and as well as their family history. So particularly family history of colon cancer, endometrial cancer, skin cancers, any other form of gastro intestinal cancer, like esophageal or stomach, for example. And then there's a few others that are not quite as strongly associated but could be, such as ovarian, breast, and prostate and kidney cancer. So that's one is just getting a good history and seeing if the patient's history and their family history fits a particular pattern of what we call the 3-2-1, three successive generation, two of them being primarily related, and one of them having been diagnosed before the age of 50, particularly if it was colon or endometrial cancer.

The second test that we found captured, along with the history, every patient is actually a test that already exists at pretty much every center, and this is a test of the tumor tissues called immunohistochemistry, and this is the ability to stain with specific markers these tumor tissues. So there's four proteins that they can test for, and they're already available because this is something that already is done, or should be done, on colon cancer cases and, as well, endometrial cases. So physicians can request for their upper tract tumors to have this staining done and if, by chance, one of those four proteins does not show up in the tumor, that suggests the possibility of Lynch Syndrome and would justify sending the patient to a genetic counselor to have confirmatory testing.

That answers, I think, only part of the question which is, you know, could the patient have Lynch Syndrome. The second one is what happens if you see a patient with diagnosed Lynch Syndrome and upper tract disease. You know, this is an area where we're still learning a lot. We have a lot more to learn. So, you know, I think on the panel there's probably a lot of experience with this, and I think it's something we need to just keep learning about over time.

Question #4: We talked earlier about the descending and ascending tumors, and a descending that spread from an upper tract tumor into the bladder. Is the latter 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 homogenous? Are they the same? Or do ascending tumors lesions arise, they go upstream? How does this happen?

Dr. Weizer: So one of my colleagues at the University of Michigan, a pathologist by the name of Scott Tomlins, he does a lot of genomic sequencing ... what he did, you probably saw this paper a few years

ago, is sequence tumors in patients who had multi focal disease throughout their entire urinary tract. The take home message is what they found, or what he found doing the profiling is that, [inaudible 01:02:04] that some of the tumors within the urinary tract are cousins of each other, meaning that they share the same genomic signature or DNA signature, and some of them are different, you know, they're not from the same family. We often, you know, think that tumors that are arising in the upper urinary tract drop tumor down into the bladder, and oftentimes what you'll see in patients who we've removed the kidney and ureter from, they have roughly about a 25% or 30% chance of recurrence in their bladder that we often see within three to six months after surgery. So that, certainly, would suggest that there is a seeping of the urinary tract, but likely, you know, because of prior exposures that patients have had, or underlying genetic abnormalities, there's likely both at play. Ultimately it just requires us as urologists and [inaudible 01:03:17] to keep a very close eye on people's urinary tract.

One thing that we do try to do in patients who are undergoing surgery to have their kidney and ureter removed, there is level one evidence that supports instilling a single dose of chemotherapy into the bladder around the time of the surgery to try and reduce the risk of people developing tumors within their bladder afterwards. It does seem to reduce the risk although there is obviously some risk of putting chemotherapy in the bladder around the time of the procedure.

BCAN would like to thank our sponsors

**EMD
SERONO**

Pfizer

AstraZeneca

Genentech
A Member of the Roche Group

Incyte

for their support