Question and Answer

Stephanie Chisolm: "Having cystectomy in a few weeks. Is cytology the only way to detect any remaining bladder cancer after surgery?"

Dr. Phil Abbosh: I'll answer that if it's okay. So, cytology is not the only way to determine if there's residual cancer left. It's one way, although I don't think it's really very routinely used. Certain situations or special situations certainly some centers may try to perform a bladder biopsy before cystectomy to determine if there's any residual disease, although that's not really routine, and it's certainly not considered standard of care. Cytology, I imagine, will often be negative in patients maybe, for instance, who have had chemotherapy where there may not be a very high burden of disease left in the bladder or maybe no tumor. Or the tumor might be sort of more into the wall of the bladder rather than interfacing with the urine. And so I don't think cytology is typically used for those reasons.

Stephanie Chisolm: Okay. All right. "Why if after a prostatectomy and then radiation do they not normally do cytology to see, if the radiation has subsided, is not changing into bladder cancer?"

Dr. Max Kates: So, one of the other scenarios I talked about BCG. Radiation to the bladder also can very frequently cause particularly atypia. It will usually cause atypia of the bladder, and that's because it has an inflammatory response. Now, with the question "So, why aren't we doing screening urine tests in patients who have had radiation for prostate cancer?" Well, when you actually look at the data, the rates of bladder cancer after radiation for prostate cancer on a population level are very low. Now, people who treat a lot of bladder cancer like myself and Phil, we tend to see many of those patient. But the point is is it's still certainly single digit percentages, and so if we were to do a screening test, it could also lead, once again, to over treatment because it's just not good enough of a urine test yet.

Stephanie Chisolm: Okay. Here's a unique question in that, "what tests are used with neobladders, or any kind of diversion if they're still checking urine. What are they looking for there at that point in time if there's no bladder material there?"

Dr. Phil Abbosh: Yeah. Good question. So, I routinely do not get cytology tests in patients who have had a cystectomy, whether they had a diversion with a ileal conduit, a continent cutaneous diversion, etc. What ends up happening for patients who have had a cystectomy know you always have this sort of like inflammatory snot that just, it' mucus that comes from your bladder, sorry, from your bowel, which is now integrated into your urinary tract. And so that sort of... There's a lot of bacteria. There's a lot of mucus. It really ends up being nondiagnostic, essentially almost 100% of the time. So, I really do not use, and I think most oncologists don't use cytology routinely after cystectomy.

Dr. Max Kates: Yeah. I would echo that. I do not check cytologies after a cystectomy.

Stephanie Chisolm: Okay, you've already mentioned that you do research with Cxbladder, but somebody was asking about your opinions as a follow up test or used in conjunction with cytology. What are your thoughts on that?

Dr. Phil Abbosh: Well, I guess if you're not comfortable. I mean, I think... So, I don't use Cxbladder very much. I think it's... It has impressive data like from the perspective, observational clinical trials. I think I imagine it might be used maybe to adjudicate as we talked about. I don't know that it replaces cytology. It's probably more sensitive for cytology, especially for lower grade tumors. Max, I'll let you, you are the expert.

Dr. Max Kates: Yeah, yeah. No problem. Every patient is a little different, and they have their own unique circumstances. I think when cytology works well, I have some phenomenal cytopathologists to read our cytology, so I trust them a lot. When it works well, it works very well. And then I use these other tests, notably Cxbladder, to help adjudicate when there's questions, and when there's questions both on my side and when the patient's not comfortable. So, when there's questions on both sides.

Stephanie Chisolm: Well, you brought up a good point, Dr. Kates. You're both affiliated with large academic institutions, so you probably have top notch cytologists there that are looking at all of these things. They see a lot of samples. What about somebody who's being seen in their community practice where they might not be looking specifically for bladder cancer per se. I mean, what are your recommendations there in terms of, what's the general practice that you know of from people who are treating patients in the community not affiliated with the great resources that are at your institutions?

Dr. Phil Abbosh: So, I can comment on that. One of my clinics is kind of an outreach clinic, and some of the urine samples that we get actually are sent to a third party where they don't go to the pathologist where I have clinic, like my academic center. They go to a commercial entity, and that commercial entity gets probably in the thousands of urine samples every week or maybe even every day. I'm not sure. But they certainly have people who are very experienced looking at these things day in and day out. There's probably people who only look at urine cytopathology specimens.

And so that sort of repetition and that familiarity with what they're looking at makes those pathologists very good at what they do. So, if you're in a small community and your sample, for instance, is being sent to third party commercial entities that do urine cytopathology, even if you don't have a high powered cytopathologist in your hospital.

Stephanie Chisolm: Okay, good. Good information to have. Thank you. So, how often should you have urine cytology done while on BCG? How soon after you've had BCG can you have your next cytology?

Dr. Max Kates: I think that what I do is I do a cystoscopy for surveillance, and I get a cytology at the time of cystoscopy. So I typically will do a cystoscopy about four weeks after patient finishes BCG. And I'll get a urine cytology at that same time.

Dr. Phil Abbosh: Yeah, I agree. There definitely needs to be an interval after the BCG before the cytology is obtained because, as Max had said several times, BCG causes a pretty significant inflammatory reaction. A lot of those sample will be atypical, and again, I don't tend to really pursue atypical cytologies unless there's something I see in the bladder that I'm halfway suspicious about and might want to do a biopsy for. But even... Actually, I mean, along those lines I guess, even after BCG, there's a lot of inflammatory lesions in the bladder. A lot of times I'll just kind of watch and wait, and I'll make a note of it on my cysto note. And when the patient comes back three months later for their cysto, I know exactly where to look, and I'll make a note about what it looked like. And so we're able to spare a lot of people anesthesia, biopsies, etc. just by being patient because we know that BCG causes a lot of these inflammatory reactions in the bladder.

Stephanie Chisolm: Thanks. Yeah, and you just answered two questions at once, so I've already knocked the other one off the list. So, here's another question. Polyoma virus, what are the morphologic characteristics, and what is the significance of this finding if you have that reported in your cytology?

Dr. Phil Abbosh: So, polyomavirus is a virus just like many other viruses that can infect cells in your body. One of the cell types it can infect is in your bladder, the urothelial cells. You will often see changes, like atypical changes, of a, that you might see on a cytology. I couldn't tell you the exact changes you'd, like on a microscopic level, but I think they are associated with atypical nuclear shape. You'll often seen chromatin that looks abnormal. And then there may be inclusion bodies. I can't remember from my pathology textbook. Yeah, but it's essentially, it's a benign virus that causes a benign change in what the cytology looks like of the cells that are infected with it.

Stephanie Chisolm: Okay. Here's an interesting question partially related to cytology, but do you have any other suggested workup or expert opinion for persistent undiagnosed microhematuria with negative cystoscopy?

Dr. Phil Abbosh: My practice is actually a lot of general urology, so I see a lot of microhematuria patients. We see a lot of patients with persistent microhematuria. Often those patients after they've had a negative workup including normal cystoscopy, normal CT scan, potentially multiple normal cystoscopies, negative or benign cytologies, often those patients are patients with blood pressure problems, diabetes, cholesterol, metabolic syndrome, etc.

I suspect that a great number of those patients with persistent microhematuria have, where that blood comes from is probably from their kidneys where, because patients with high blood pressure, diabetes, etc., vascular disease, tend to have abnormal kidney function where their kidneys let things through that they're supposed to filter and retain. Rather than filtering and retaining, they filter and those things leach out. And so you get blood in the urine that comes from a kidney source that's really just related to

their other medical comorbidities, rather than a bladder cancer, a kidney stone, an upper tract cancer, etc.

Stephanie Chisolm: Here's a specific one. What do you think of the test Bladder EpiCheck by Nucleix?

Dr. Phil Abbosh: I don't know that one.

Dr. Max Kates: Yeah, so I off hand don't know it or use it.

Stephanie Chisolm: Okay. Here's a little bit of a technical question. Couldn't the role of artificial intelligence, or isn't there a role for artificial intelligence in eliminating all too frequent atypical findings?

Dr. Phil Abbosh: That's an interesting question. I was actually just on artificial intelligence and machine learning with my kids this weekend. So, in theory, the problem, or one of the obstacles I should say, with using machine learning to maybe eliminate the idea of an atypical cytology would be that you have to know the outcome. So if someone has an atypical cytology, what does that mean? And like, because when you do machine learning or artificial intelligence, you have to like... What... Your imagine, your cytological image that you're feeding into the computer has to be associated with an outcome. And if we don't really have a strong connection with an outcome, the information you're putting into the system is... Sorry, the information you get out of the system is only as good as the information you put into the system.

Dr. Phil Abbosh: So, if you don't have good information going in, you're not going to have good information going out. I imagine there's probably a way to do it. It would require I think longitudinal samples from patients with atypical cytology to identify those few percentage of patients that actually end up having a cancer diagnosed so that you could tell the machine, "These are the ones that ended up being positive, and these are the ones that ended up being not positive, or not positive yet." And so I think there's probably a way to do it, but I think it's going to take somebody a lot smarter than me and Max.

Stephanie Chisolm: Here's a general question in terms of, you're a researcher, Dr. Abbosh. How can urine cytology be improved in the future? What pieces do you think it will be helpful to increase the accuracy? How do you think this is going to work. I know you're working on some interesting studies. What can you tell us about the future of urine cytology?

Dr. Phil Abbosh: Sure. So, I think the future, we're sort of seeing the future now. I think with bladder Cx and these other sort of molecular tests where scientists and companies are looking at nucleic acids that are shed by the tumor into the urine, and those things can be measured. I think that's probably where the future of this is going. I don't know if these will ever replace cytology. I mean, they may replace cytology. There's certainly going to be a cost issue, and there's also going to be an issue of where and when do you use each of these tests.

Certain tests will be effective in low-grade tumors, and certain tests may be better in high-grade tumors. Some tests may be better in surveillance when we know someone has a history of bladder cancer. There are certain tests that may be better when we don't know if a patient, when someone just comes in with a fresh diagnosis of hematuria. I personally believe in like the nucleic acid. I think that's... Whether it's

MRNA or DNA, where you're measuring alterations in those nucleic acids which are strongly associated with cancer, I think that's... I mean, that's where our lab has invested a lot of time and effort and certainly where our funding has been.

So, that's what I think. I mean, my hope is that what we're working on is maybe clinically available in, some time in the next five to ten years. That'll be awesome.

Stephanie Chisolm: If you had papillary not carcinoma high-grade bladder cancer, is it also important to get urine cytology to check for cancer return with the papillary type? You were mentioning very heavily the carcinoma in situ.

Dr. Max Kates: Yeah. I mean, all of these scenarios are, urine cytology is helpful. I would say the areas where it's not helpful is a history of low-grade cancer is where it's not helpful. The other scenarios, it's helpful.

Dr. Phil Abbosh: Yeah, I agree with that.

Stephanie Chisolm: Thanks. Have you ever noticed an atypical result patient turned out suspicious or high-grade over time?

Dr. Phil Abbosh: I can't recall one off the top of my head, but it seems very plausible to have something like that happen. As I mentioned, I may sometimes pursue an atypical cytology with like a biopsy, maybe next time they come in for they cysto or in the operating room. But that's not necessarily the same scenario as the person asked the question had. That's more where I'm biopsying someone that has atypical as opposed to watching a cytology become positive over time. I don't know. Max, have you had that?

Dr. Max Kates: Yeah, I mean, the way I would answer it is, typically when I'm getting cytologies, I'm also getting as an adjunct to cystoscopy and to imaging periodically, CT imaging. And so I'm not really concerned about the atypical because usually I'm going to be getting another cytology at another time interval, three months, six months later. And so at some point, a patient can have a recurrence, but it's not clear to me that that meant that they had cancer when they had the atypical cytology.

Stephanie Chisolm: How confident are you about biomarkers-based diagnoses over cystoscopy? Do you think this is really going to be where it's going?

Dr. Phil Abbosh: I'm, right now, I'm more of a seeing is believing person. When I see a tumor, I know what it is. Max sort of mentioned the scenario where you've evaluated someone's urothelium, and they have a positive urine cytology, but it could be a positive urine test of any kind, whether it's a cytology or some other sort of a test. The question I think... I think where that question is going is if someone had... How am I going to make a clinical decision when everything looks normal, but a urine test is abnormal? I don't see myself counseling someone that they need to have their bladder removed on account of an abnormal urine test when everything else looks normal. So, you sort of have to contextualize the abnormal test with what you see. What does the clinical scenario really bring to you?

Dr. Max Kates: I would echo that, and maybe the question was also asking will it replace cystoscopy? And my answer to that is, I'm a data guy, and I want as much data as possible to make a

good decision with the patient. So I view all of these tests as being combined, but I don't love the idea of replacing anything.

Stephanie Chisolm: Okay. Here's a very specific question. What does poorly preserved degenerating cells mean in a cytology report? How do you read that?

Dr. Phil Abbosh: So, this is probably related to what I had mentioned about getting an early morning void. So if... An early morning void will have a very high concentration, which tends to preserve those cells. A urine sample right after you got done drinking a big jug of juice or coffee maybe, where the urine will be a little bit more dilute, may not preserve those cells. It's also possible, say, in the setting of an infection or maybe after a cystectomy or someone has ileal conduit, for instance. Whatever normal urothelium is present may have been eaten up by those bacteria or the yeast or whatever is growing in the conduit.

Dr. Max Kates: That was a great answer. I was going to answer a verbose pathologist, but in all seriousness, that's a perfect example of sort of what can be on pathology reports. And if you don't see the word cancer on there, it usually means it's not cancer.

Stephanie Chisolm: Okay. So, here's another. Related question to post radical cystectomy, wouldn't cytology for a person with a neobladder or in any other type of diversion indicate whether there was a recurrence in the ureters, kidneys, not the urethra, but the, well, possibly the urethra for somebody with a neobladder but not with the other two? But wouldn't this indicate a possible recurrence of the cancer somewhere else in the urinary system?

Dr. Max Kates: Theoretically, yes. But as Phil mentioned, the issue is that the new, whatever the urinary reconstruction is, is sloughing off so much cells that it skews the picture. It makes the test not interpretable.

Dr. Phil Abbosh: Yeah. I mean, it's really almost like a question of dilution. So, if the... Even if someone has a normal bladder before cystectomy, the amount of urothelium that is contributed to your urinary tract by the ureters and the urethra is probably five percent or less. So, even if you have a positive, let's say you have a renal pelvis tumor, still probably a good proportion of the cells that are in your urine cytology are going to come from the normal parts of the bladder. So if you replace the bladder with a ileal conduit or with a neobladder, the amount of cells that are sloughed off by the conduit are now probably tenfold more than they were just when you have a bladder.

So, imagine, there's already very, very few cells in the cytology that will be positive from the urethra or the renal pelvis. Those are drowned out now even more by whatever's coming from the conduit. So it's just, you're kind of trying to find a needle in the haystack with a cytology after cystectomy, in my opinion.

Dr. Max Kates: And in the upper tract and in the renal pelvis, we can identify even subtle tumors with a good CT scan. And this is why we do CT imaging after, or MR imaging, after a cystectomy.

Stephanie Chisolm: Okay. We have time for just one more question to be mindful of everybody's time. How do you grade bladder cancer based on cytology report's findings? Is it you as the urologist

who are grading this? Or is it the pathology report? And what information are they using to grade that type of cell that they're seeing?

Dr. Phil Abbosh: So, the pathologist is the one that assigns the grade. In some of the reports that I get, they actually will put pictures of the cells that are either normal or abnormal. The pathologist scores it, and I'm using that clinical data to guide what comes next for the patient.