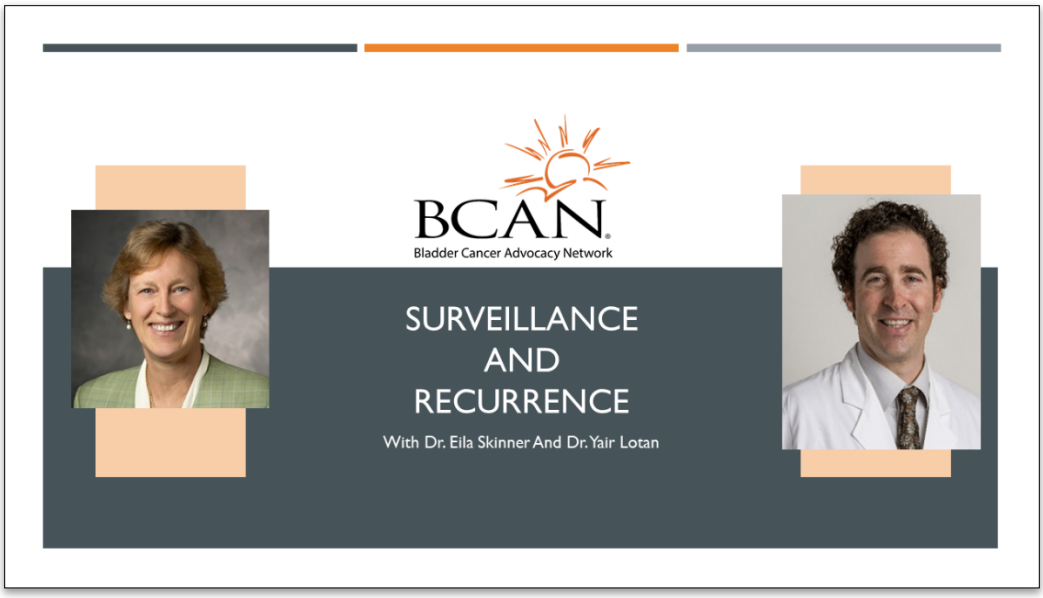

Questions and Answers

Can the bladder tolerate BCG mitomycin treatment indefinitely, or what other methods could or should be used?

Dr. Yair Lotan: I haven't seen any data on how long you can tolerate BCG. Most people don't recommend it. If you, after two or three years, if you've had a very good response and no recurrences, we usually will stop the intravesical therapy and monitor you. In fact, if you recur more than a year after you got BCG, we can restart the BCG, and most people think you have nearly the same benefits, but it's not currently recommended to do more than two to three years of BCG just because there's no trial that has really ever looked at doing it for much longer than that. There's really no reason to think that it causes any harm to the bladder, but it certainly can cause irritative symptoms. If there's no demonstrated benefit, why would you continue to do it since you could always resume it later if you were fortunate enough to be disease-free for a long time?

Dr. Eila Skinner: Can I just add that, in most of the series using all different types of intravesical treatment, there's been about a 10% chance of bad bladder symptoms after initial treatment or multiple treatments, and so, every once in a while, there's a patient who really has a lot of bladder irritation or small bladder capacity. Fortunately, it doesn't happen very often, but that's one reason we don't just give these drugs to everybody. If we don't think it's necessary, we don't want to take that risk.

What is the definition of BCG failure?

Dr. Yair Lotan: This is an area that even is a little confusing for urologists at times because there are a lot of different definitions. There is a condition where you still had cancer. We gave you six weeks of BCG and, at three months, we looked, and you still have cancer. Those patients are considered BCG refractory. We know that for about 30 to 40% of those patients, if we give additional BCG, they will have a good response at six months. Unless you show signs of progression where your cancer got worse or you have invasion of the lamina propria or a lot of disease, we typically will give people additional BCG. However, if at six months, you've had six treatments plus three treatments, or maybe you didn't get all six or all three, but you got close, maybe five and two, and, at six months, you still have carcinoma in situ or recurrent bladder cancer, you're consider BCG unresponsive, and that's an important time point because, if at six months after BCG you still have disease, you're unlikely to respond for more BCG and you should change your treatment.

Dr. Yair Lotan: Six months is really a critical time point for most of us in deciding is BCG working for you or not because, if it's not, there's no reason to waste more time. You really should either have your bladder removed or go into a clinical trial or try another therapy, because giving more BCG is almost never going to help you.

The urologist would like to withhold BCG in the case of recurrence. She thought it would be more effective as opposed to having BCG every two years following five years of being cancer-free, which is Dr. Lamm's protocol. What do you think about that?

Dr. Eila Skinner: Dr. Lamm has a theory that we should keep doing BCG in patients who have responded and basically doing it infrequently, but do it forever. So far, that's not really been tested in any kind of clinical trial. Dr. Lamm is a pioneer in BCG treatment, but those things really need to be tested before they're set out as a standard. So most urologists, I don't think have adopted that approach.

Would you mind just doing a quick brief disclosure on anything that you are working on that might be related to our topic tonight?

Dr. Eila Skinner: I will tell you that I occasionally do work with the Cysview people that do Blue Light. I don't have a formal relationship with them and I've never gotten any money from them, but I've worked with them some, and I have worked on one of the clinical trials that Dr. Lotan mentioned, which is with Genentech's Checkpoint Inhibitor, using that for BCG unresponsive bladder cancer. Finally, I did a course with in a company called Olympus

that makes another scope where we did a course teaching young urologists how to resect bladder tumors, and I was paid for that.

Dr. Yair Lotan: I worked doing research with about four different urine marker companies. I've done research with Abbott, Pacific Edge, Cepheid, MdxHealth. This is research on looking at urine markers to help detect bladder cancer. Some of them are in hematuria. I've also consulted for two of those companies in how to design trials and some of the health economics involved with that. I was involved with Photocure on the phase three trial for the Flexible Blue Light, and I've consulted with them on some health economic type issues. I think those are probably my relevant bladder things. I worked with GenomeDx, on more advanced disease, looking at tissue markers, and then I've worked also in metastatic disease and trial design with AstraZeneca and Merck for checkpoint inhibitors, but not specifically for noninvasive.

Is there any place for radiation or chemotherapy, or radiation and chemotherapy in treating muscle invasive disease?

Dr. Eila Skinner: I would say mostly no. One of the clinical trials that's currently being developed is actually using radiation to make the checkpoint inhibitor work better. Basically, they irritate the immune system to get the checkpoint inhibitor to be able to work.

Dr. Eila Skinner: I think there was also a recent clinical trial with patients with lamina propria invasion, so T1 disease, using radiation, but that's not considered standard of care at this point. That trial has been completed, but there's no results yet. I would say generally no, unless there's a very unique situation where that would be the approach. We don't generally use systemic chemotherapy for that disease either.

What is a checkpoint inhibitor?

Dr. Yair Lotan: We know that the way cancers trick the immune system is that they show them certain antigens which are like flags on cells that tell the immune system, "Hey, we're part of the body. Don't attack us." This is a way that cancer cells use to mask themselves, so the immune system, which is supposed to get rid of cells that are abnormal as well as bacteria and viruses and other things that are attacking us, the immune system is unable to fight the cancer because the cancer is basically hiding in plain sight.

The checkpoint inhibitors are basically ways to unmask the immune system. They basically block these flags or these antigens that the cancer is trying to show the immune system, so the immune system now doesn't see this friendly flag and says, "Oh, now I can see that you're an abnormal cell and I'm going to fight you." This has been a very successful treatment for metastatic disease, for example, in melanoma. It works in some of the

combinations for more than half of the patients when, previously, we had no treatment. It's being used in almost every cancer now it's being tested, but certain cancers like kidney cancers, which are very immune responsive, it's been successful.

In bladder cancer, it is approved. It's success rate is in the 20 to 25% for patients with metastatic disease. That disease spreads throughout the body. There's a variety of trials being done in non-muscle invasive disease. There was one trial that was presented at a meeting that suggested about a third of patients had the response at three months, which I'd have to say is not overly encouraging because the FDA requires that you have at least a 30% response in a year, and you can only assume that some of those 30% that responded at three months might have a recurrence between three months in a year. So it's still very early in assessing these agents, and some of them might be very important combinations, but that's what we're talking about.

When treatment and surveillance protocol vary from hospital to hospital, how does the typical patient find statistics on what the best protocol is? When should they ask for a second opinion about their treatment?

Dr. Eila Skinner: Even though there's some variation from doctor to doctor, there now are guidelines that are written by the American Urologic Association and by the European Urology Association. Those are available for anybody to look up. You can go to auanet.org and look for guidelines and they're in there, and I helped work on those, and so I think they're pretty good.

Dr. Eila Skinner: I think it's fair to always ask your doctor if they're not following the guidelines, why they're not? I don't think anybody should ever be afraid to ask for a second opinion if you don't feel like you're getting the answers that you want from your doctor.

As doctors, do you ever feel offended if somebody is going to ask for a second opinion, do you?

Dr. Eila Skinner: I don't.

Dr. Yair Lotan: That's not a thing to be offended because we're seeing patients all the time for second opinion, but I would say the same thing. If your doctor is very sensitive, then maybe you need a new doctor anyway, because I think most urologists in America are so busy anyway because there's a lot of patients that they're not going to feel offended if you want to get another opinion. In fact, they'll either confirm their judgment or maybe they'll learn something as well, but I certainly haven't had any qualms about sending my patients for another opinion if they're hesitant about what I recommended because, if they didn't like what I had to say, I didn't think they were going to be very compliant with my recommendation anyway. They might as well see if they can find an opinion that they would follow more likely.

Can you talk a little bit about some of the influence of these other exposures on recurrence?

Dr. Eila Skinner: Most of that has not really been tested. I think, for smoking, I showed that one slide that showed that, if you quit, you could actually reduce your risk of recurrence. We think, for bladder cancer, that what causes the cancer could have been something that happened 20 or 30 years before, and we know that, from smoking, that a lot of patients who have a history of smoking, but quit many years ago and still are at an increased risk, so that's probably a very long process to go from smoking until the cancer cell actually starts to develop. For example, there was a lot of press about hair dye and that patients that were particularly hair dressers who used a lot of hair dye on their skin would be at increased risk, and that I think since then has actually been debunked largely, so that I don't think patients have to go around with gray hair necessarily who have bladder cancer, but many of the other things are really mysterious. I mean, we know that there's plenty of people that never smoked who get bladder cancer. In fact, in women, it's as high as half of women never smoked and still get bladder cancer. There's a lot we don't know about those environmental causes.

Steph Chisolm: If you go to www.bcan.org and look on our Patient Insight Webinars, we did one a couple of months ago that was specifically focused on the environmental risk factors and bladder cancer, so it went beyond smoking, although they talked about that, and it featured some experts from the National Cancer Institute that have been studying bladder cancer and the environmental exposures for many, many years. I invite you to go take a look at that.

I was wondering if age affects treatment approach. Are you more or less aggressive when you have a 30-year-old with a T1 high grade in CIS, for example?

Dr. Yair Lotan: It certainly affects it. Thank God, we don't have so many 30-year-olds with bladder cancer, but I think of age a little differently. I think of life expectancy as the more important parameter because, if you have a patient who has a relatively short life expectancy, you're really thinking about recurrence and progression a little differently because they may not have very much time for cancer to really do something very bad in terms of progression.

If you have a patient in his mid-50's with a 30-year life expectancy if they didn't have bladder cancer, I might be more aggressive in terms of treatment because I'm starting to think, "Will I be able to keep them disease-free for 30 years?" It becomes something in the back of my mind. Especially if they're not responding to initial treatment, I'm asking myself, "Why did they get cancer so young, and should I just take out their bladder sooner rather than wait and do every single treatment with a concern that, if I'm wrong, they've lost lot of potential life expectancy?"

If you have a patient in their late 80's, you certainly are not going to be as aggressive. The only other caveat I would say is that, unfortunately, there are some studies that suggest that BCG as an immunotherapy did not work as well in octogenarians, and maybe it's because their immune system is not quite as robust, and so, in some of those cases, I might consider, especially for intermediate risk patients, I'll stay with chemotherapy rather than BCG as my first line therapy with the thought that maybe they'll have less risk of infection and maybe the BCG is not going to be that much better than chemotherapy in those patients.

Is there any significance to having no side effects at all after induction BCG and maintenance BCG?

Dr. Yair Lotan: That's a very good question. A lot of people used to think that if you had more reaction, you'd have a better response, and it seems to make sense. It says, "Well, your immune system came and you had a lot of inflammation and, hence, you have a good response," but I haven't seen very good data to support that. In fact, I've had plenty of patients who've had almost no side effects and very good responses, so I think the jury is out on that. I don't know, Eila, if you've seen any reports on that.

Dr. Eila Skinner: No. I agree. When patients get a bad reaction, we tell them that's good news because it means they're reacting to the BCG, but I don't think you can say that the converse is true.

What are the statistics for recurrence of cancer for patients who've had a radical cystectomy?

Dr. Eila Skinner: The best predictor for recurrence is actually how extensive the cancer was at the time of surgery, so what we call the pathologic stage. For example, the kinds of patients we've been talking about today who have non-muscle invasive cancer, somebody has carcinoma in situ and BCG has not worked and they're going to go to cystectomy. If they have carcinoma in situ on their final pathology and the lymph nodes are negative, then their cure rate is very, very high, probably close to 90%. It never quite gets to 100%, but it's very good. They occasionally will get recurrences in the ureter or the collecting system or the urethra, but, generally, not. On the other hand, if somebody who has even non-muscle invasive disease at the time of surgery has positive lymph nodes, then we know our cure rate is down around 30%, and then we'll generally talk about using chemotherapy or other treatments in addition to surgery to try to improve on that. We're always trying to guess the exact right time point to do a cystectomy so we don't wait so that the cancer is in the lymph nodes, but we don't necessarily pull the trigger too early when we still might be able to treat the patient with intravesical therapy.

Is a high grade TA with 5 to 10% high grade cells considered intermediate or high risk, and what should they be doing?

Dr. Yair Lotan: Are you talking about somebody who has low grade with local high grade primarily? Technically speaking, any high grade, they're at a minimum intermediate risk.

Dr. Eila Skinner: We would generally recommend intravesical therapy for that patient.

A patient has CIS and they've been cancer-free for the past three years, although the last three urine cytologies showed suspicious cells for high grade TCC/CIS, no treatment was administered. The doctor said he can't treat it unless it's a confirmed cancer. What should they be doing? What should they be asking their doctor?

Dr. Yair Lotan: I think, first, the question is what evaluation that they have, because carcinoma in situ is notorious that they can go to different parts of the urinary tract, so, for high risk patients in general, we recommend upper tract imaging like a CT urogram or MRI urogram or retrograde pyelograms once a year. I would be concerned. Are they missing cancer cells somewhere else in the urinary tract? The other place they can hide, if it's a man, is the prostatic urethra. If it was me, I would do Blue Light Cystoscopy, biopsy the prostatic urethra, and then also evaluate the upper tract. It gets suspicious for cancer cells, mostly a positive type finding, and you worry that there might be cancer cells somewhere else in the urinary tract. I would say that if it was persistent, I would even consider whether

or not to go back on BCG therapy because the upside maybe higher than the downside because, if I was really concerned that they might have cancer, and most likely it still would be in the bladder, if they had BCG before, resuming BCG really is not a high risk proposition, and it certainly might make everybody feel a little bit better about the situation, even though it would be nice to know where it's located before I started any treatment.

Steph Chisolm: Thank you both so much for doing this. We took this picture at the Society of Urologic Oncology meeting, and I thought it was a nice way to close down tonight's presentation. Dr. Lotan and Dr. Skinner, thank you so much for sharing your knowledge and time with us this evening.