Stephanie Chisolm:

Well, that was great. Thank you both so much.

There were a couple of questions that I was just thinking of as you were talking. And going back to almost the very beginning. What is the percentage of low risk patients, if you just wanted to give a vague idea, that have a recurrence, how often do you have to keep going back on patients?

Dr. Eila Skinner:

So the overall percentage is about 50% at three years. You can reduce that a little bit with that immediate post-op chemotherapy. And most of them, as Dr. Lotan mentioned, stay low grades. So they're not any more dangerous than the first one was. But once you've had a recurrence, you have a higher chance of having another one. The bigger question I think is when can you stop doing cystoscopy? And nobody knows the answer to that. It's really not been studied very well.

I usually will kind of start suggesting stopping at about five years for a low-grade patient and about 10 years for a higher risk patient, especially if they had high grade disease. It's really important to get at least an annual urinalysis to make sure there's no blood in the urine. But honestly, there's just no data. And often I find I suggest stopping and the patients are like, "No, no, I want to come every year anyway." But it is an invasive kind of unpleasant procedure to have a cystoscopy. We don't have a urine test yet that's quite good enough to use instead of cystoscopy, but I think we will, and probably fairly soon.

Stephanie Chisolm:

I think that most patients are really eager to find out that they don't have cancer. It's not that they want to find it again, they just want to make sure that what was working still works. I know you mentioned, Dr. Lotan, you were talking about blue light. You don't typically use that for the first time you go in for a cystoscopy to find bladder cancer, the blue light. When do you use blue light? Can you just clarify that?

Dr. Yair Lotan:

Yeah, so I think we should start with, first of all, it's not approved in patients just with blood in the urine. And as I mentioned, how do we find the cancer? We don't even know if you have cancer. So it's really

hard to justify bringing you in, putting something in your bladder, and then looking with blue light when there's a good chance you don't have bladder cancer. Remember, even patients who have visible blood, only about 10% have bladder cancer, so 90% wouldn't benefit from it, and you can do it in the operating room if you find a tumor.

So you're not removing the tumor that day anyway, you're just doing a diagnosis. And so I think it has value for initial resection. I think it's good for patients who have multiple recurrences or multiple tumors. Do I do it religiously and everybody, no, not in everybody and not in every setting. But if they do have recurrences, I'm going to do it. And I'm fortunate because I do have it in clinic, and so patients with carcinoma in situ that I'm monitoring, I will do it quite routinely because I'm concerned that I'm going to miss recurrences. But I recognize that there is a burden both financial and time. And so it's certainly not something that is uniform nationwide.

Stephanie Chisolm:

And you make a really good point. You both are at large academic teaching hospitals and you have access to blue light, but the predominant patient in the community is being seen by a community-based urologist, they might have a big practice. That equipment is very expensive, so they may not have it in their office. They may have access to it at the hospital, at the local hospital, but it's not as easy to...

Dr. Eila Skinner:

There's even a lot of hospitals that can't afford that. It's a little over a hundred thousand dollars equipment.

Stephanie Chisolm:

Just for the machine, right.

Dr. Eila Skinner:

Just for the tower and the scopes and stuff. So you have to have a pretty busy hospital to make that justified.

Stephanie Chisolm:

There's a good question that was submitted because I think this happens often in light of the current shortage, somebody was currently undergoing six weeks of BCG treatment because of the shortage, there have been three treatments canceled. It's a problem that the treatments were not done in the six weeks' time period, or that they only got three treatments.

Dr. Eila Skinner:

I don't think we really know. Because it's an immune treatment, I like to try to stick to the schedule. If we can. If somebody has to be gone one week, we don't panic and we just keep going. But I think most doctors' offices will try to make sure they have enough available and set it aside for those six treatments so that you don't get in that situation. The other thing that we're doing routinely is cutting the dose in half. If we have two patients that are being treated the same day and we can divide the dose up, that means twice as many people are getting treated. And the evidence is not super strong, but suggests that if you have very high risk disease, it's ideal to get full dose if you can, but even half dose is probably better than nothing. If you have intermediate risk, honestly, probably doesn't matter that much whether you use half dose or full dose.

Dr. Yair Lotan:

Yeah, I would say that for us, for intermediate risk, we actually prefer to give chemotherapy because for low grade tumors, we routinely reduce the dose for maintenance, but I think it's important to try to get probably at least five treatments for the induction. And it's okay if you skip a week because of infection, but we know that you need to get at least three or four weeks just to even stimulate the immune response.

The one thing I would say though is that especially for patients who, for some of the newer agents, they really depend on you having had adequate BCG to find out if BCG even works or not. So if you get an inadequate BCG and then you have a recurrence, is it because you didn't respond to BCG, or is it because you didn't get enough? And we have a hard time when we see patients for second opinions. If you didn't get enough BCG, we really struggle. "Should I start you on BCG?" Again, we don't want to waste six weeks of your time by giving you an inappropriate therapy, but we have no way of knowing if you will respond to more BCG because it's still the gold standard for us.

Stephanie Chisolm:

That does make it hard. It is the gold standard. As you mentioned, sometimes even in the clinical trials, they have to have not had any effect or benefit from BCG before they can even enroll in some clinical trials, which does make it a little bit more challenging for patients when they're considering a clinical trial. And you brought up one important point when you said you could split the dose and have two patients be treated at the same time. From what I understand, BCG comes frozen, so if you defrost it, you need to use it at that same time.

Dr. Eila Skinner:

At least that day, yeah.

Dr. Yair Lotan:

But it's a powder.

Stephanie Chisolm:

So, what if somebody doesn't show up?

Dr. Yair Lotan:

It's a powder.

Stephanie Chisolm:

Right.

Dr. Yair Lotan:

So once you put in a solution, then you can't take half the powder out, it will aerosolize. So you actually have to put liquid in and then you can divide it. And people, we divide it routinely to three, but you can't save the powder, can't use half the powder, and you can't save the liquid once it's in liquid. So that's the challenge.

Stephanie Chisolm:

So let me ask a question about intravesical therapy, then. Do you fill the bladder? I'm remembering what you had on your slides. You hold it for two hours. I know holding your bladder for two hours, when it's full, is a challenge. Do you fill it or you just put a little bit in there?

Dr. Eila Skinner:

Most of the time it's a couple of ounces. So we empty the bladder when we first put a catheter in. So you start with an empty bladder, but it is important not to drink a giant Starbucks on the way to the appointment because you don't want to have a huge amount of urine volume, it will dilute the treatment. And the other thing that's one of my pet peeves is some people make patients roll around in the clinic while they have the stuff in their bladder, which seems crazy to me because your bladder, it's not a bowl, it's more like a balloon. So it's collapsed around the treatment and the treatment will get all the edges of the bladder.

But I wanted to make a comment. We didn't include a slide about clinical trials, but there's actually probably 15 agents currently being studied as new approaches to this type of non-muscle invasive bladder cancer, and they really vary. There are some agents that are new immunotherapies, some more gene therapies, virus type treatments. There's some that I have no idea what they do. And so there's a lot, and it's sometimes tricky to find one that's close to home that is available, but hopefully your physician can help you find one or if you can go online and try to see what's out there.

Stephanie Chisolm:

Yeah, remember on our bcan.org website, we have a clinical trials finder.

Dr. Eila Skinner:

That's right.

Stephanie Chisolm:

You enter your state and then you can find all of the clinical trials for your particular diagnosis. So if you have non-muscle invasive disease, higher low grade, you can find the trials that are out there that you might be eligible for. And it's a good way to bring that to your doctor and say, "Hey, should I be in a clinical trial if you can't get me BCG, or if I'm having a recurrence on a regular basis, maybe I should go to a clinical trial and see what else there is." And it's a good question to ask. So I think that's one of those good important things to bring out. Clinical trials are really investigational medicine. They're trying to find new ways to solve the problem of bladder cancer recurrence. And so it would give you access to additional treatments that you might not get in your regular doctor's office. But also you get really good monitoring as well in a clinical trial, because they want to make sure they're checking to see if that new treatment has any kind of an effect. So I'm glad you brought that up. How soon after... I'm sorry.

Dr. Eila Skinner:

I was going to ask Dr. Lotan to comment on, many cancers now you can use sort of personalized medicine to figure out what's the genetics of your cancer and can we pick our treatment based on that? Yair, can you talk about where we stand now with trying to do that for bladder cancer?

Dr. Yair Lotan:

Sure. So for non-invasive cancer right now, the main mutation that people are interested in is fibroblast growth factor FGFR, and the main one is three. So they have a couple of different receptors and they're

inhibitors of those receptors. And there was one trial, at least preliminarily showed a very good response for patients with intermediate risk disease when taken by mouth, but it has a lot of side effects. It can affect your eyes and your nails. So there's actually a new drug that's coming in, a formulation that looks like a little pretzel that will be alluded into the urine, so hopefully avoid some of the systemic side effects.

This is a trial that's called Moonrise by Janssen, and it's this pretzel, it's called TAR-210. And anyway, that's a very exciting trial for us, and that's probably the main targeted therapy because immune therapies and chemotherapies are not targeted, which is good and bad. Now, the drugs, some of the systemic agent, which are checkpoint inhibitors, are looking at different receptors in the immune system. But interestingly enough, even though there are tests to look for those receptor status that hasn't been consistently, the results of the whether or not that marker is abnormal or not hasn't necessarily correlated with a response to the therapy. So theoretically, that could be a target but hasn't been proven yet.

Stephanie Chisolm:

Yeah. So you mentioned the FGFR receptor. So with non-muscle invasive disease, do you typically have a lot of patients that want to have that tumor genomic profile done so that you could determine if they would be eligible for something like that? Or is that something you save more for muscle invasive disease or even advanced disease? When do you do the genetic testing on a tumor?

Dr. Yair Lotan:

Oh, it's an evolving field. So if you have a trial open, we had the trial called THOR2 for these FGFR inhibitors. I did it relatively routinely because I was looking for who might be eligible for the trial. And we're doing it pretty routinely for high risk disease, but I would've to caution that there's not that much you can do with it. We don't use it to tell you if the cancer is more likely to recur, and we don't know that it's going to predict response to therapy. So we do it in part because it's a curiosity and also because once these trials do open, then we at least can tell a patient, look, the drug may not be available right now, but maybe in three, six months if you recur, then I know that you have this mutation and we could enroll you.

Stephanie Chisolm:

Yeah. A quick question. How soon after the initial TURBT is it generally appropriate for a follow-up cystoscopy?

Dr. Eila Skinner:

We pretty routinely do it at three months. And there might be a situation where you do it sooner, but generally the three-month cystoscopy is pretty standard.

Dr. Yair Lotan:

Only if we're resecting do we go back after about four to six weeks, but the reason we wait four to six weeks is because the bladder looks very abnormal right after initial resection, so you wouldn't know what you're looking at it. It's going to look red, it's going to have some irregular tissue. And that's just the healing process.

Dr. Eila Skinner:

Correct.

Stephanie Chisolm:

So you're not normally going right in right away. And I think it's really important to understand that there's a reason why all of these things are paced out, it's based on evidence, iIt's based on all the data, all the studies that it's not just you deciding, but the guidelines are crafted by the American Urological Association and other professional medical associations that bring together leading experts and they discuss the evidence and they weigh the best approach for statistically what's going to be the most beneficial for the patient, and also to make sure that you are doing your job and keeping up with when that tumor might come back. So I think that's important to remember that guidelines are still out there, and we do have them linked on our website. You can visit bcan.org and look for the guidelines. They are in there. We have time for maybe one other question. I know you mentioned that you have BCG at your facilities because they're large institutions. Should they change doctors if their doctor says, "I don't have it," what should people do?

Dr. Eila Skinner:

That's a hard one. I think if you happen to live near enough to a medical center, I think it's worth calling to see if they have BCG available. It's usually going to require getting established with another doctor. But in our area, I think most of the urologists who don't have BCG will offer that to their patients as an alternative. Or, as Dr. Lotan mentioned, if you don't really need BCG and chemotherapy is going to be equally effective, then I think that's also an option. The caveat is that many urologists in small offices don't have intravesical chemotherapy available because there's a lot of regulation that goes with that they may not have in their office. I think if your doctor says there's nothing I can do, then I think it's a reasonable thing to say, could I get another opinion? But on the other hand, if they're busy, and to ask them to call around and figure out who has BCG is probably not appropriate.

Dr. Yair Lotan:

Yeah, I don't know. That change doctor is really the proper thing. I think it's really find another one. You can hold your urologist, but you definitely are going to need to see another one to get to get the treatment. And the fact is, unfortunately, bladder cancer, that's high risk has a lot of significant potential complications to it. And if you don't get the appropriate treatment, it's not just 50 to 70% recur, but 10 to 30% will become muscle-invasive.

If you develop muscle invasive disease, about half the patients will die of their disease within five years. And if you only have noninvasive disease, the chance of dying is only about 10 to 20%. So it's a huge consequence if your disease gets worse. And so unfortunately, I wish everybody had BCG, I wish I could send BCG give you a six-pack and say, "Take it home and have your urologist give it to you." Because the fact is that we're not allowed to do that. Right. And it's unfortunate because I'm in Texas and people drive two hours each way to get BCG with me, and they're not even seeing me, they're seeing my nurse. So it's just access to these medications is just critical and unfortunate that we don't have it more widely available.

Stephanie Chisolm:

So on the opposite extreme, when you do have it available, is there a maximum amount of doses of BCG that a person should have? Do you cut it off after so many rounds of BCG? What is the usual?

Dr. Eila Skinner:

There's not a maximum. I've had patients who have had 20, 30, 40 installations. It doesn't kill you. But generally we recommend for high risk patients, six weeks induction, and then the so called SWOG protocol, which is additional three weeks every three, six, 12, and then every six months after that out

to maybe three years. Nowadays, we often will shorten that down so that we save more BCG for the rest of the world. But the most important is not to keep doing BCG if it's not working. So if you've had two cycles of BCG and you still have cancer there, there's very little evidence that more BCG will help. Sometimes we'll come back to it if it's been many years since you had BCG, but you just don't want to take it if it's not doing anything.

Stephanie Chisolm:

No. Well, I want to thank you both again for taking your time to do this. We're at time right now. I appreciate everybody joining us. So thank you so much Dr. Skinner and Dr. Lotan, and also thank you to UroGen for supporting the Patient Insight Webinar series. We greatly appreciate it.