***The Forgotten Cancer: Understanding Bladder Cancer***

**Speaker 1** 00:02

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**Dr. Bill Evans** 00:20

Well, welcome to the cancer assist Show. I'm your host, Dr Bill Evans, and I'm really pleased that we're going to be talking about bladder cancer. You know, I think this is a cancer that hasn't got enough attention. And I'm really delighted that I have two specialists with me today, Dr Lorraine Liang and Dr Ali Khan lilani. Welcome, and I really am appreciative of the fact you're giving up some time. I know you're both extremely busy, and this is a time of year when you're sort of doing a lot of catch up. So thank you so much for being with us now. Lorraine, you're a urologist at the McMaster Institute of Urology located at St Joseph's Hospital here in Hamilton, and you're an assistant professor and you're one of the six urologists working in that institute. So it's quite a team you have put together there. And with you, we have Dr Ali Khan Lalani, who's an Associate Professor and Department of Medicine and the department of oncology at McMaster University and based at the jurors key Cancer Center. And again, I'm delighted you're both here to talk about bladder cancer. Often like to start by maybe asking a little bit about how you got got to be urologist. And so Lorraine to you, why did you choose to get in your own was that your initial idea of what you wanted to be when you grew up.

**Speaker 2** 01:41

I think when I was little, I never thought about what was coming next. I just did what was in front of me. My parents had an ice cream store. Oh, really, yeah. And, you know, I grew up in that store. They took on a lot of, you know, diet products, Atkins, things, sugar free stuff. I became really interested in nutrition, but then I went to school at Columbia and majored in visual arts because the guidance counselor told me, do what you like. So I almost, just almost ended up as as an artist. And then afterwards, I was like, Well, what will I do with my life? Oh, I make a living. Make a living, you know, how do I make a living? How do I get health care. And I looked into, you know, a Master's of nutrition still at Columbia, and I thought to myself, I think if I'm a doctor, people will listen to my advice more than if I'm just a nutritionist. And so that started my long road to go to medical school. In medical school, I found that the medicine folks were a little bit put off by how direct I was, and the surgical folks were a little more comfortable with me. That kind of put me towards the urology surgery path. I did some really great research with some really awesome people in urology. My grades were good, and that's, you know, kind of how I ended up in urology, attracted mostly by robots and lasers and fun things that we get to do. I was

**Dr. Bill Evans** 03:10

gonna say, did you have a role model? And then you mentioned robots and lasers, lasers? Well, that's a very interesting career path, and one of the more interesting ones we've heard about on the podcast. Ali Kai, can you match that?

**Speaker 3** 03:23

Yeah, hard to, hard to top that one. I mean that child of immigrants as well. My all families in business chart of accountants. So absolutely no medicine in my family before I also decided to go into medicine as funny guidance counselors in elementary school said, you know, you you're left handed, you're more artistic, so languages and music and arts will be what you do. And so I enjoy all that. But, yeah, what into medicine? It's funny, I think I started actually being interested in procedural skills, even though, in internal medicine, I thought, I'm going to be a GI doctor. I'm going to be a castronologist, that's it. And then, you know, I remember at the end of first year, I said, you know, I did voluntary call with a fellow, like, who does that? But I decided to do that with a fellow to understand gi better. And I said, this is cool, but at 2am do I want to be scoping someone in the ICU? And I said, you know, I really should broaden my horizons a bit. And then, anyways, oncology happened, I think the mix of personality and science, and so then the rest is kind of history. So, Wow,

**Dr. Bill Evans** 04:22

great. I think you both ended up in a good place, yeah. So thank you. Now, in bladder cancer, I was kind of struck when I did a bit of reading at just how common it is in Canada. Like, like 12,000 plus individuals diagnosed with bladder cancer annually. In Canada, fifth commonest cancer is sort of been flying below the horizon away. We think about the big four cancers, you know, the breast and long colon and prostate. And don't think so much about bladder cancer. So we're way overdue to talk about it on the podcast. And I think it's more important than we've recognized, more common in men than. And women, but tell me a little bit about what are the risk factors for getting bladder cancer?

**Speaker 2** 05:06

So the easiest one is going to be smoking. Modifiable risk factor. Smokers are much more likely than non smokers to have bladder cancer. Also patients who have exposures to aniline dyes. Used to be Tanners or I've had a hot a lot of hairdressers with trouble, patients who have had other cancers and treatments for cancers or chemotherapy and radiation exposures. Unfortunately, a lot of our patients who have worked, done factory work and been exposed to like smelting and smoke and that kind of thing. Also, for some reason, in patients who work in mechanic shops and things like that, just paint thinners and benzene aromatic like smelly chemicals. So

**Dr. Bill Evans** 05:52

Hamilton being the place with a lot of manufacturing, steel smelting and so on, are we seeing more bladder cancer here than in many other places.

**Speaker 2** 06:01

I think everywhere I've been, I've seen a lot of bladder cancer, but I think it's also, you know, a function of what I do. And so there, there is bladder cancer. I think there's probably more here than there would be maybe in Toronto. Sure, you didn't mention

**Dr. Bill Evans** 06:15

age, the thing we can't control, but as we get older, I guess we have greater risk of developing all cancers, practically, but bladder cancer as well. Glad you mentioned smoking being someone who's responsible for the program in the province for smoking cessation. I think a lot of people just think about lung cancer or maybe head and neck cancers with smoking, but there's a dozen other cancers that are associated with smoking, bladder cancer being a prominent one. So it really is an important message to get out that people should stop smoking if they currently are or never start. The ideal situation to try and avoid things like bladder cancer, amongst others, maybe just I ask you Valley COVID, just in terms of presentation, like, how would someone be aware of or suspicious of something wrong that might lead to a diagnosis

**Speaker 3** 07:08

of question and one that someone like Dr Liang would be seeing a lot more as a urologist, but we certainly do hear this when we see them in medical oncology, we go back for the whole story. It often starts with the heme tree or blood in the in the urine. You know, I was always taught in med school painless Hemme tree. And someone over the age of 60s, bladder cancer until proven otherwise, right? And so, you know, you think about where the lesion is and what it can, you know, kind of result as or manifest, and thinking about the whole urothelial track, we're talking about bladder cancer. But obviously the lining in the ureter and the renal pelvis are similar. So I would say, you know, pain, blood in the urine is certainly one of the more common things that I would say in retrospect, we see admittedly, but by the time patients see a medical oncologist, it's muscle invasive or beyond. But these are kind of often times what leads to workup for a patient, where they would see a urologist and have a full kind of view as to what's inside the bladder and beyond. And so these are, unsurprisingly, as you said, part of aging historic issues with smoking, although even on your own podcast, I think people have commented that these rates of smoking are dwindling now, but that population that did that median age of being in the 60s and clinical trials is one thing, but we often see it in the 80s and beyond, even by the time they get to medical knowledge. So it is a an age issue, a smoking issue, then obviously presenting as it might typically. Now,

**Dr. Bill Evans** 08:35

Lorraine Ali Khan mentioned blood in the urine. But how does that appear to a patient, Is it bright red blood they're looking for, or is it something else? Or can it be a mixture?

**Speaker 2** 08:46

So there's, there's going to be a division between patients who actually see the blood in the urine and the patients whose family doctors get their regular annual checkup. And there's just microscopic blood. Admittedly, patients who have microscopic blood have a lower risk, but it does exist. And so we do see a fair number of patients who feel nothing, see nothing, and their doctors are just sending them in because there is blood in the urine. And definitely we do see patients who have bladder cancer come in with only microscopic urine. It is rare, but it does happen patients who have blood in the urine that they can see. So wine colored urine, Rusty colored urine, gross red blood with clots. All of this would be consistent

**Dr. Bill Evans** 09:25

spectrum of color, so just looking for bright red blood wouldn't be the thing. A rusty looking urine is another sign there are little clots.

**Speaker 2** 09:35

Now sometimes you've got patients who say, well, it's in the toilet. I don't know if it's coming from my my bottom end or my middle or my front sometimes I only see it on the toilet paper. The evaluation for bladder cancer is, I think it's such, such that it's not so invasive and painful that it's reasonably worth looking even if you're not sure, especially if there are other risk factors, like we mentioned, to age. Smoking, family history of bladder cancer, that kind of thing. So

**Dr. Bill Evans** 10:03

you touched on looking so how does one look at the bladder?

**Speaker 2** 10:08

So anytime we see a patient who has hematuria blood in the urine, there are a number of tests that we do. We first check the urine itself, look for infection, look for cells in the urine, called a cytology, and that just happens at the lab. And then, depending on whether it's microscopic or gross, if it's microscopic, we'll start with an ultrasound, kidneys and bladder. Look for things like kidney stones, masses in the kidneys, we'll look in the ureters and in the bladder itself. And sometimes you can see a mass on an ultrasound. Sometimes you don't on a CT scan, you would do like a triphasic so without contrast to look for stones, with contrast to see if there are any masses. And then you do a post contrast phase, where it actually waits for the contrast to come into the ureter itself, to see if there are filling defects or things in the ureter itself that you wouldn't otherwise see without that third phase. And the last step would be the cystoscopy, or the camera that goes in the bladder. This is generally done without an anesthetic, but we do put freezing jelly in the urethra. So for a man, that means we put the jelly in the penis. For a woman, it means we put the jelly in the urethra and we put the camera right in where we are at St Joe's, there is a screen where the patient can see what I see. So if I see a bladder cancer, they're able to see it at the same time. We point out different things, anatomical landmarks. And patients are usually quite tolerant of this procedure, maybe one in 100 or so, you know, gets very, very anxious, but we certainly we talk them through it, and it does take less than five minutes. A bladder cancer looks a little bit like a sea anemone, because we're filling up the bladder with fluid, and it kind of waves at you. And they're generally quite popular if they're low grade. And so they're fun to see, less fun to be on, you know, the receiving end

**Dr. Bill Evans** 11:51

of the patient. Maybe not so fun to see, but interesting. But

**Speaker 2** 11:55

they don't they don't mind seeing it if it's there. For the lower grade ones, the 80% of them do end up being lower grade cancers. They're a little bit prettier. The ones that are higher grade or muscle invasive, often quite a bit bigger. There can be some associated bleeding when you're looking at it, sometimes there's got like, little stones on it, so those are a little bit less pretty. But we we identify by looking, how

**Dr. Bill Evans** 12:18

do patients react to seeing things on the screen as you're doing it, like do they feel reassured by visually seeing it? And how did they react when you point out, well, there's actually a cancer here,

**Speaker 2** 12:31

some of them feel relieved that they know why they're having the symptoms that they are a lot of times. And often women get diagnoses later, because sometimes patients go and they say, I blood in the urine, and they're treated again and again for bladder infection, and the cultures come back negative, and the women are like, Well, what's wrong with me? Why does this keep happening? And when you show them a cancer and you tell them what the next steps are, often they're quite relieved, because they think they're not crazy anymore, or they realize they haven't been crazy time. There are some who freak out, but I generally do prepare patients that this is what we're looking for, and if we find this, then we will discuss the next steps. And so usually, if if you're if you're prepared, and you're talking and the patients are engaged, the comfort level is better. And then we just, we go as we take things as they come. Patients generally do quite well.

**Dr. Bill Evans** 13:23

Let's take a situation of very superficial kind of cancer, which I think are the more common things for presentation, right? So what do you do then you've observed it at the same time? Do you go ahead with a procedure? Or is that something you have to prepare the patient for and do it a second

**Speaker 2** 13:40

if the tumors are super, super small, and this is pretty rare, and they're amenable, I can just take a biopsy at the time of the diagnostic system, burn the base, send it off the pathology, and see if we're pretty confident by looking at it that it's going to be like a low grade, superficial I don't have to go much deeper. If it is bigger, like a centimeter or two, or between two and five, we would get them ready. We would consent them for surgery. We would find them a time for surgery, and we would go in, usually you go to sleep, or you get a spinal, and then that's a general anesthetic, or a spinal anesthetic. So it involves an anesthesiologist, and, you know, pre op clinic and that kind of thing. And we go in through the urethra. Again, we use a cautery loop, so it's like this really neat little wire. And you scoop out the tumor, try to take all of it out and get a nice big bite of the muscle to make sure that there's no tumor in it. Then you stop up all the bleeding, and then patient generally goes home the same day.

**Dr. Bill Evans** 14:38

Now, when you scoop up the tumor, do you put it into anything? Or is it just pulled out through the urethra?

**Speaker 2** 14:44

So the camera scope that we use for the resection is a little bit bigger, and that sheath stays in the patient, and then the Luke can come out, so that the tumor can come out through the sheets so it's not touching all the other parts of the patient as it leaves the patient.

**Dr. Bill Evans** 14:57

Now, are you concerned about cancer cell? Cells are broken loose and are floating around in the

**Speaker 2** 15:02

Yeah. So usually we make sure that we get all the pieces out and we burn it all up. Sometimes, if we already know that it's a low grade or if it's multifocal, we can give them a single dose of chemotherapy at the time of surgery, within 24 hours, that would be your post, T, R, B, T, first dose within 24 hours, it would be a Mitomycin that one can sometimes cause you to have a little bit of irritation when you pee. We do drain it out of their bladders before they leave, and they have to be disposed of in a certain way. Sometimes it's a little bit hard to get if you don't prepare in advance, but we do our best, and we're not sure if it's a low grade cancer. If we think that we've resected a bit deep, we generally don't give that post resection dose.

**Dr. Bill Evans** 15:48

Okay, so why do you put chemotherapy in at all?

**Speaker 2** 15:52

Well, we give it so that it doesn't come back as soon or at all,

**Dr. Bill Evans** 15:56

because there is a risk of recurrence, right? Yeah. So fluster cancer,

**Speaker 2** 16:00

I explain to my patients when they're low grade, that while it is cancer, generally it's kind of annoying, like a pimple, and so we remove it, and then we keep an eye on it to make sure it doesn't come back. Generally, they do tend to come back. The sooner they come back, the more we worry, the more other therapies they're offered. If it's just a small tumor, and we've gotten it all, and we look in three months and it's not there, then we continue to look with the hopes that it doesn't return.

**Dr. Bill Evans** 16:25

And the frequency of looking every three months. So for

**Speaker 2** 16:29

the low grade cancers, I like to look three months after the first time, and after that, we space it out between six and 12 months, depending on whether they recur or not. I like to keep them forever. If they start to get kind of antsy, then we can negotiate. What's the negotiation? How frequently we look yeah, I have some patients in their 90s. They're starting to have dementia. The family members are noting that they're getting agitators before coming and then we negotiate. But for healthy people who have reasonable quality

**Dr. Bill Evans** 16:58

of life, you want to make sure it's not coming back. So the frequency is kept more rigid. I guess I like to

**Speaker 2** 17:04

see them once a year, at least once they're three years out. And so

**Dr. Bill Evans** 17:08

those are for the more superficial and and more easily managed, but do tend to recur. But you talked about muscle invasion, so maybe we need to get into that area and what? What's the concern about muscle invasion? What does that portend?

**Speaker 2** 17:24

So muscle invasive bladder cancer is a little bit of a different beast. Once it starts to invade past the Lamar into the muscle, the likelihood of its spreading is much, much higher, and that's where Dr Lalani kind of comes in. When we have muscle invasive bladder cancer, we like to take out the bladder, but generally patients do better with a radical cysto prostatectomy or cystectomy when they've had chemotherapy first.

**Dr. Bill Evans** 17:51

So let's talk about that a bit, because that's now sounding much more challenging when the bladder is coming out and there's chemotherapy beforehand. And so the selection of the patients that you choose, and then what's the chemotherapy look like in terms of side effects

**Speaker 3** 18:08

questions? And I would just say, probably a big theme is that it is truly multidisciplinary care. And I liken it to the baton being passed between the right specialists to help the patient in the time. And as Lorraine mentioned, I mean, these patients have had often a relationship with your oncologist, and we certainly want that to continue, but they are reaching out to say, hey, this patient needs some systemic treatment, potentially before we do something to the bladder. And so just a quick shout out for our multidisciplinary bladder cancer clinic that we have at the driven C Cancer Center. And if you'll permit me just the the lay of this clinic is that every patient with muscle invasive bladder cancer, theoretically, in our in our catchment area or region, can be referred to this clinic, where the patient would see a surgeon if they haven't already. But if they have a Ural oncologist, they would remain the Ural oncologist of record. If it makes kind of the most appropriate sense, they'll see a medical oncologist and a radiation doctor at the same time. And so to your point, at that visit, we get a chance to, you know, three heads kind of come together to revisit the file, start from the whole when it is present with perhaps, but in the urine, how many treatments or things like BCG or other things that they have in the past, and then say, okay, it's now muscle invasive. So let's look at what we can do. And as you've mentioned, the standard of care really is to do chemotherapy, what we call neoadjuvant chemotherapy, or treatment prior to definitive management, before going on to that definitive management. So from a medical oncology perspective, we take the baton at that point. Our job is to make sure the patient is cisplatin eligible, so there's medications like cisplatin and Jim city being given through an IV done for about four rounds or four cycles of treatment, at which point I often book a CT scan at that point to be done after treatment. We make sure it is not the cancer is not spread anywhere, and then the baton goes back. Back to the uron colleges to look inside and say, you know, how are things looking, where we previously saw muscle invasion, and then a critical decision is made for surgery, which is, the majority of our patients do get surgery, or in those who might have been extreme responders and have a very good benefit to get radiation as definitive management with any limitations that come with radiation. But that's where that bladder clinic comes in handy, because the patient can be there. All the principles were there. And of course, there's lots of reasons why a patient might be benefiting from radiation, or unfortunately, some patients aren't surgical candidates or can't get chemotherapy. They go on to radiation. But in general, I think the big takeaway is neoadjuvant chemotherapy and then reassess for a potential surgery. Before

**Dr. Bill Evans** 20:41

we talk a little more about that, I think we'll take a brief break and hear from our sponsors, so to speak, from the cancer Assistance Program, and we'll be right back to talk more about bladder cancer.

**Speaker 1** 20:51

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**Dr. Bill Evans** 21:34

Well, we're back talking about bladder cancer, and we got into muscle invasive bladder cancer, but we want to also go just talk a little bit about the difference between low grade and high grade cancers, because there's a difference in their management. And we meant to talk about that a little earlier, so we'll talk about it now. So Lorraine, that's one of the important things. When you send a specimen off to the lab you're going to be looking at in the report, because that's going to determine whether you do something additional, I think for that particular patient with a higher grade cancer,

**Speaker 2** 22:05

sure. Bill. So when we get the pathology back from the pathologists, the result we're looking to see low grade or high grade. Just as you said, we're looking for depth of invasion, which we kind of touched on before. We can get high grade bladder cancers early, and those can be superficial. So if they're, you know, not quite invading the lamina propria, then they would be considered eligible to have intravesical therapy, or therapy inside the bladder, rather than going to Dr Lalani for something that would go in through an IV to affect the whole body. Generally, what we do is we send people for BCG therapy, and BCG is what they used to use to immunize people against tuberculosis, right? And so instead of injecting you, they put in a catheter, and they put the BCG into the bladder, and it forces the bladder to react, because this is an irritant, and to try to kill any cancers that are there and to prevent the cancers from coming back, it can be pretty irritating to the bladder, and it feels like a UTI. And patients often feel like, you know, they're peeing all the time and urgently. But generally, the people who have that reaction actually have a better response from the BCG from a cancer standpoint. And so if you're miserable, I guess it's worth it, because it's working. What happens when you're getting the BCG is we do monitor you frequently to see has the cancer come back? Is this working? And if it's not working, there are some other intervesco therapies that can be tried. Some of them are available. Some of them are not where we're working. Or we would then send you on to have a talk with Dr lelani's group. Or we would re respect you, and see if there's any sort of depth of invasion that has changed,

**Dr. Bill Evans** 23:44

good. Well, I'm glad we picked that up. Maybe we should also, because we've got people listening who are non medical. When we talk about high grade, what are we really saying? Like, what do we mean when we say high grade versus low grade? What is it the pathologist is seeing? Perhaps, so I

**Speaker 2** 23:59

think they're looking at the numbers of nuclei and how

**Dr. Bill Evans** 24:03

how abnormal cells looks like. They're rapidly growing. If

**Speaker 2** 24:08

they're more abnormal looking or less differentiated, they tend to be more aggressive, and so they use certain markers to identify whether or not patients will likely go on to have metastases, or likely go on to have more depth of invasion compared to a lower grade, which will continue to be like this, this pimple reappearing in the bladder that you just scoop out and move on your way, which is to say, if you ignore the low grade ones, they can grow to be quite large and cause bleeding and obstruction, and then you can't pee. So you shouldn't ignore them, but they're unlikely to kill you,

**Dr. Bill Evans** 24:43

right? That sounds very definitive. Now, what else is definitive? You were talking about preoperative chemotherapy. So we've got preoperative chemotherapy for these muscle invasive cancers that require then a cystectomy. So then they're all. Or to the urologist like yourself, Lorraine, to to do and it isn't just the bladder that's removed at the time of that surgery, as I understand. Is that correct?

**Speaker 2** 25:08

Correct? So I'm no longer doing cystectomies Because I've, I've kind of decided that that's going to be less a part of my practice. Patients who get cystectomy should go to patient to surgeons who are doing them quite often, because they'll get a better outcome. The more you do, the better you are. And so when I decided not to do them, I, you know, decided to support my colleagues who are doing them so that the patients can get a better outcome. But when you hire a man with bladder cancer that needs to be removed, they remove the entire bladder, the prostate. And usually they take a bit of small intestine and either connect it to the the body wall so that the urine can come out into the bag, or they can create a NEO bladder, which is a bit of a sphere. Arts and crafts is actually quite lovely to do. I do miss it and connect it to the urethra so that you can still pee out of it. So it's a very, very big surgery. And then they take, of course, lots and lots of lymph nodes to make sure there's no spread, which is very important. And

**Dr. Bill Evans** 26:08

for a woman, what's the for a woman

**Speaker 2** 26:10

taking the cystectomy? So they're taking the bladder, often, they're taking the uterus as well, as well as a cuff of the vagina. So

**Dr. Bill Evans** 26:19

these are big procedures, and they have, must have some significant morbidity and maybe even risk of death from the surgery.

**Speaker 2** 26:27

So it is, it is a highly morbid surgery, I think 30% complication rate, including things like infection, DVT PE, pulmonary emboli. So clots, clots in the legs, clots in the lungs. You can also get strictures or scarring down in the ureter, where you're connected to two wherever you're putting it. You can get ileus, meaning the bowel is really slow to wake up after surgery. Oftentimes, you know, you can get different things. Well,

**Dr. Bill Evans** 26:59

you made a very good point about having that kind of surgery done where a lot of that surgery is being done, because it is true that in surgery, the more someone does, the better they are at doing it. And so to anyone listening out there who's either in on scheduled to have one or or knows someone who might be scheduled to have one, it really is important to get to a place like the St Joe's urology Institute, where you've got people who are doing them all the time. If you're listening from some other part in the world, then it's important for you to make sure that you get to individuals who aren't just doing one every once in a while, because this isn't important and a big operation, and you need someone who's very competent to do it, and not only the surgeon doing it, but the team behind them that's there to support you, post operatively, make sure you recover properly. So all those things are very important, and when you undergoing major surgery, just as it's important to have a team around you when you're getting systemic therapy and the drugs that we're using these days are increasingly interesting, but complicated and have unique side effects. The not that many people present with what we call stage four bladder cancer, but it's not zero either. I from the stats I saw maybe 8% or something, present with what we call stage four disease, which would be directly, I guess, to a medical oncologist wouldn't. Yeah,

**Speaker 3** 28:23

in general it is, and this is still where our bladder clinic comes in handy. So as mentioned, I know we're going to get to stage four, but for those patients who have had a surgery and they may or may not have had chemotherapy prior, there might be some findings on that pathologic sample. So when they look at the tissue for a size or stage of the of the cancer and lymph node involvement, there might be a reason folks would get adjuvant therapy, which is insurance policy, reduce the chance of it coming back in the form of immunotherapy. So there are patients, and this is where our bladder clinic is super helpful. Who could have the baton go from surgeon to medical oncologist for chemotherapy back to the surgeon, obviously, do that definitive management curative intent, and then back to the medical oncologist to give immunotherapy after surgery, all around a what we call perioperative setting. So I totally echo what you're saying. Make sure, and your team is very experienced in bladder cancer, but is looking after you. Unfortunately, some of those patients, despite all of our best attempts, do, at some point in the future, have cancer come back, or, as you mentioned, might present for the first time, even with bleeding or pain, to found to have a spread cancer. And so that collectively, whether it's grown from local and spread or started spread, is what we'd call kind of advanced or stage four disease. And that has greatly changed. I still think there's a role for all the stakeholders to be involved. Often, these patients have a uro oncologist who can help them, even if complications come along the way or in outstanding responses, which we'll get to the radiation oncologist to help with any pain in an area that might be dealt with. But in general, it's largely the medical oncologist where help. Patients with advanced disease. For many years, we had chemotherapy as the main first tool. That got a bit better a few years ago, when we showed Well, if you get chemotherapy and then the cancer stays stable or shrinks, you could add immunotherapy alongside. And now we've actually kind of totally upended the whole 50 years of bladder cancer by now doing combination immune therapy and antibody drug conjugates as first line treatment. So I

**Dr. Bill Evans** 30:27

have to explain antibody drug conjugate. Sorry, it comes back to in terms of my audience can understand,

**Speaker 3** 30:33

you know, it's, it's really cool. So if you think about kind of the shape of why as an antibody and and that antibody as a few components to it. One, it is seeking a target, right? So it's put in an IV, and it's going to look for something. And in bladder cancer, urothelial cancer, that's nectin Four, which is something that is widely expressed across urothelial cells. It's a kind of protein that's on the cell, exactly you got it. Now, sometimes it overlaps with some skin cells, but in general, it's a very good marker for, let's call it, bladder cancer. So this antibody is seeking out, looking for that in the body. Now, that antibody is linked has a linker to a backpack. That backpack has a drug that, once the target is found, it will drop off that backpack at that cell. And that backpack consists of chemotherapy, you know, in different forms, but you can imagine, and we'll talk about this particular treatment, but you can imagine, there's different targets with different linkers and different backpacks. And then my other hat is drug development. We're thinking about lots of things we can do, but very simply and for the map, bedotin is seeking out nectin For and dropping off some chemotherapy when it finds those cells called MMA. And it's very, very cool. So it's, you know, technically, a form of chemotherapy, but has different tolerance, also given through an IB and importantly, for stage four cancers, combined with immunotherapy called pembrolizumab, which I think probably your listeners and viewers have heard about before, but that is now the first line treatment for a spread bladder cancer. It's

**Dr. Bill Evans** 32:08

a remarkable development all those different component parts, and I love the way you described it to the backpack it contains the chemotherapy it drops. It's a neat explanation, and something that becomes understandable to patients, because this isn't simple stuff for those who are not medical school trained sort of thing. So yeah,

**Speaker 3** 32:28

who are you know it? To understand it and get used to it and then explain it in a term that makes sense to patients, rather than just some handouts, it takes time.

**Speaker 2** 32:38

So does that mean, if it's got that backpack and that tracker that it's not affecting the rest of the body and just the cancer. Yeah.

**Speaker 3** 32:44

So this is where it gets really technical, because, yes, we would say it's better tolerated in the general sense than what we would say cisplatin chemotherapy, which is great, but it kind of, you know, to use a term that some listeners views might might understand, is a little bit like napalm, in the sense that it goes everywhere, and it's fast to fighting right? Whereas this treatment would target those cells, the issue, as I mentioned, is that target is also on skin cells, so it can, unsurprisingly, cause some skin reactions, which can be low grade, but it's the doctor's job who's administering this to understand, hey, it looks like there's a lot of spill in these skin cells. That might actually mean the drug is working quite well, but we need to help the patient to make sure doesn't become a very large grade or spread rash. The other thing that these treatments can can affect is a little bit of neuropathy as well, or kind of pins and needles feeling, but also how well the nurse functions. That's really important. When you think about an age group that might be 70s or 80s, I think about the sensory neuropathy, the motor the function, but also autonomic. When you stand up and you balance yourself, that's really important too. So the skin, I would say, the nerves, and I would say even other things we look for is, how does it metabolize and affects the liver a little bit. So we want to make sure our patients can be diabetic. How is their blood glucose control, and how are their liver function? But in general, I would say is it is better tolerated, but you got to keep an eye for some of these significant side effects, and

**Dr. Bill Evans** 34:09

you're always using the immunotherapy with the antibody drug combination

**Speaker 3** 34:16

when it's the first treatment someone's had for a spread cancer. There's now data for that. But as you well know, the drug development would have started with this antibody drug conjugate. First development was when it everything else had been used, meaning after chemo, after immunotherapy, then the single drug was used, the antibody drug conjugate, called in fortumab. But now it's gotten earlier in the metastatic or stage four setting, to be the first option patients can available. And we're very lucky to have this, you know, approved in many parts of the world, US, Canada, elsewhere, and available. We're using it currently.

**Dr. Bill Evans** 34:50

So you're involved in drug development. So where do you think we'll be in 10 years? Yeah,

**Speaker 3** 34:58

it's, it's cool. So to. Take a whole research program and try and distill it down in a few minutes, I would say there's two areas that are changing. One is how we are understanding the tissue we get from bladder cancer and what's driving someone's cancer is changing. So this is called kind of molecular underpinnings of cancer. So there are sometimes certain receptors, like fibroblast Factor Receptor or fgfr, that is upregulated in bladder cancer. We now have treatments for that. So lock in key mechanism. If we find that lock, we can put a certain key and so we are screening patients for that. That's really important. I think we are looking at bringing other antibody drug conjugates, so different targets, different backpacks in bladder cancer. And then I would say the real evolution might be just, how do we use all of these in the right way earlier on in disease, we talked about muscle invasive bladder cancer, where patients can still be hopefully cured, but we give them some treatment prior, I mentioned chemotherapy. Wouldn't you know it, there's already treatments, looking at chemotherapy plus immunotherapy prior to surgeries. We're waiting on Canadian approval for that, and almost as soon as we get that, guess what, trials are going to read out to show the immunotherapy plus the antibody drug conjugates prior to surgery. So that data is coming out, so you can see how we see the evolution here. And it is very possible that if we have folks that someone like Lorena or colleagues send to us for neoadjuvant treatment, that if we can give very good IV treatments, what if not only there's no spread, but the disease in that bladder were to melt away? How many patients can can experience either a surgery even better or have their bladder maintained. You know, these are all saying, so it's, yeah, it's, I say this the tools in the toolbox we need to get more and then, when do we use those tools? Can we use it earlier in your disease? And that's what's really exciting and, and, you know, my final pitch is even the non muscle invasive setting, where medical oncologists aren't in the mix. Well, wouldn't you know it, there's now data showing subcutaneous or injectable immunotherapy might be helpful for non muscle invasive bladder cancer. We're going to get more data for that at conferences like the American urology Association AUA meetings later this year. So can you imagine if we can get some subcutaneous injectable immunotherapy even earlier, like you can see how everything is moving. And so I think bladder cancer is wonderful to study and to help patients. And I think all of our disciplines are working together.

**Dr. Bill Evans** 37:29

Do you see some changes in the surgical approach or diagnostic approach from your perspective? Lorraine,

**Speaker 2** 37:36

well, I think we still need to get pathology. I mean, you're not gonna

**Dr. Bill Evans** 37:39

be put out of business, but I noticed this technique, we still need

**Speaker 2** 37:44

to identify the cancer before we can treat it, and certainly having that tissue helps them to figure out their lock and key mechanisms and their you know, where to send their backpacks. And so some of it is still tailored to patients. I think, you know, it may be that if we have a really big, aggressive cancer, we just get the bulk of it, and don't go so deep as to potentially perforate the bladder. You don't have to be quite as aggressive with resection. Potentially, if we can get their stuff to be, we

**Dr. Bill Evans** 38:10

rely on some of the drug developments. Herring, man, the other thing

**Speaker 3** 38:14

that's pretty interesting, I agree. I think the you're all oncologist, what they do, what they can see, you know, that's such a cornerstone. But maybe one thing that could add to what the folks are doing is if we can look in the blood and find microscopic cancer cells, so circulating tumor DNA, we're quite interested in that, in trying to bring that into the Hamilton and McMaster ecosystem for these patients. But can we do a blood test after someone has had treatment or even had a surgery, and reassure them that there's nothing microscopic in the blood. Could they avoid adjuvant immune therapy? Because I love giving these drugs, they can cause some side effects. And what if we knew that there was something in the blood before a CT scan showed it? So that's very cool stuff that I think I realize is not ready for prime time use today for our patients, but you know, hopefully they take some hope that it might be on the horizon. Well,

**Dr. Bill Evans** 39:07

I've heard a lot of hopeful things today, and I think it's been really a very useful discussion for people listening to hear about how bladder cancer can be detected, how it's initially managed, and the various stages. But I'm particularly impressed by how quickly it seems to be evolving with use of really exciting drug combinations and immunotherapy. It's really quite fascinating. You're working at a very interesting time. It's a good time to be in medicine looking after a disease like bladder cancer. Want to thank you both for your time and your expertise, and talking to me about this and hopefully helping the people listening to understand better and to get make make sure they get good care, which is a number one thing we're concerned about. So thank you very much for your time. Thanks

39:53

for having us. Thanks for having us.

**Speaker 1** 39:58

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