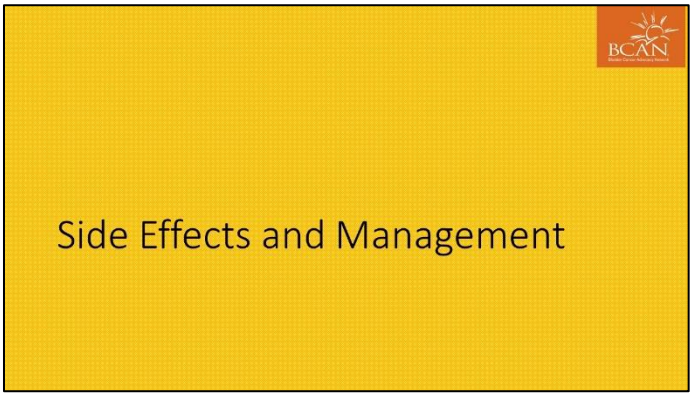
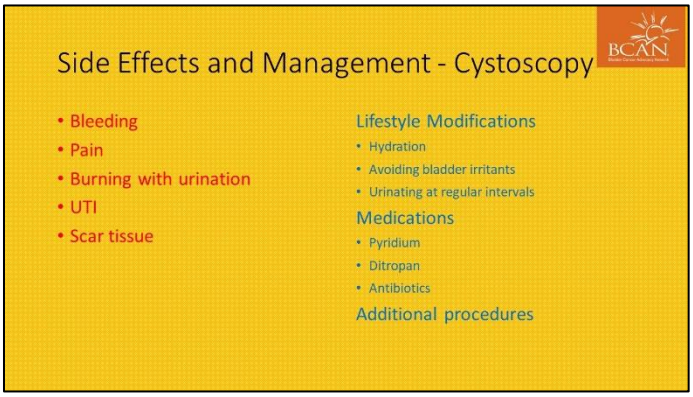
Dr. Kristen Scarpato:

So now let's get into the side effects and management.



Dr. Kristen Scarpato:

Cystoscopy. It's not just a cystoscopy and hopefully no one is ever saying, "Oh, it's just a cystoscopy." It certainly is an invasive and it certainly is uncomfortable and really can cause some significant side effects for some patients. This is why fortunately I think we're seeing so much exploration when it comes to alternatives to cystoscopy, whether it's urine based markers or imaging tests that can cut back on the number of invasive cystoscopic procedures that we need to do for patients who have bladder cancer and certainly making sure that we're not unnecessarily



performing cystoscopy in the evaluation of patients who don't have that diagnosis yet. Most commonly, and this really is with any intravesical management of bladder cancer, whether it's cystoscopy or catheterization or medications into the bladder, most commonly we're seeing things like mild bleeding. So when the scope comes out for a couple of days, patients may notice blood in their urine. Shouldn't be significant, but sometimes it can be significant and come along with clots and certainly we want to know about that.

Pain, so passing even the flexible scope into a urethra can irritate that very delicate lining of the urethra and the lining of the bladder, and that can come along with pain. And typically it's short pain, so for a short amount of time, but not always. Sometimes patients experience pain for quite some time. Burning with urination. So as we're gently scraping the lining of the urinary tract, when you are then going to empty your bladder and urine's going to pass through the urethra, it can certainly burn. There's a risk anytime we introduce any foreign body or foreign material into the body. Not only is your body saying, "What is this and why is this here," but it introduces the risk of infection. And then over time, typically with the more procedures you have, but certainly anytime you have an invasive procedure, scar tissue can form and that scar tissue can make it challenging to urinate afterwards.

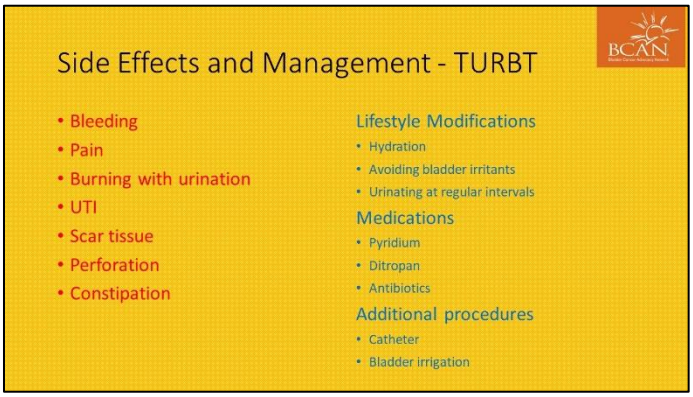
So how do we manage these side effects with cystoscopy, whether it's a flexible cystoscopy or a rigid cystoscopy in the operating room? Well, first in terms of managing the associated bladder symptoms, your urologist or your healthcare provider may recommend what we call some easier things, some lifestyle modifications. We know that hydration, so maintaining a good fluid status can help flush out any blood associated with the procedure. And so drinking plenty of fluids after having a cystoscopy can be important. We know that there are irritants that tend unfortunately to be things that we really enjoy, like coffee, like spicy foods, like any caffeinated beverage or sugary beverage or alcohol, glass of wine. Those things can irritate the bladder, so if you've recently had a procedure avoiding those can make recovery from the procedure easier. Urinating at regular intervals, and we encourage you not to hold your urine if you've had a procedure. Try and go to the bathroom every two, three or four hours to again help flush that out and don't let your bladder get overdistended, which can make it become more sensitive and irritated over time.

In addition to the numbing jelly that we put in, the lidocaine jelly, there are certain medications that we regularly use to help limit the side effects associated with cystoscopy. A common one is peridium, and this is also called AZO over the counter. It's available, but also we can write prescriptions for it. And important to know that this is a medication that can turn your tears orange, your urine orange, sometimes your stool orange. And what it does is it numbs up the lining of the urinary tract and can really help get you beyond the symptoms of the first couple of days. It is not a medication to take long term, but in the short term it is highly effective. Ditropan or more commonly now we're using something called Trospium, because there are fewer cognitive side effects, that can help with spasm.

So when your bladder's saying, "Hey, there's something here that I'm not familiar with or shouldn't be here, I'm going to try and get rid of it, and the way I'm going to try and get rid of it is by spasming," which can be this short burst of really intense pain, then using those medications can be beneficial. But I only recommend those if you're having those symptoms because they can cause dry eyes, dry mouth, blurry vision and constipation. And then certainly if there's any concern for infection, we give antibiotics and send a urine culture. Some patients qualify for antibiotics at the time of their procedure, and so we want to make sure we're practicing good antibiotic stewardship. But if you're a patient who's at risk for infection and your institution should be able to determine that, then we'll give you antibiotics at the time of your cystoscopy. Rarely just after cystoscopy would patients require additional surgical procedures to help manage side effects.

But sometimes in extreme cases, if there's significant scar tissue, then dilation may be necessary to help open up any scar tissue or if there's really significant bladder squeezing, sometimes we can inject things into the bladder wall like Botox to help quiet those symptoms.

Dr. Kristen Scarpato:



TURBT. And again, those same symptoms you'll see on many of these slides, certainly associated with bleeding. So when we're removing tissue, we do cauterize that area, but there's a scab that's in your bladder and that scab can pop off and cause bleeding or there might just be irritation from passing that scope back and forth from the bladder through the urethra in and out, and that can cause some bleeding, pain and burning with urination. Every time we perform a TURBT, you're going to get a single dose of antibiotics to help limit a urinary tract infection. The risk of scar tissue goes up because the scope is bigger, the procedure is more invasive, so we pay attention to that.

Particular to TURBT is a risk of perforation. So what is that? That's making a hole in your bladder. If you have a hole in your bladder, certainly we wouldn't put any medicines into the bladder, intravesical therapies in that setting, because that would be very dangerous. You could reabsorb and have systemic serious side effects related to that, but often it's managed with prolonged catheterization to allow your bladder to heal. So needing to wear a catheter for quite some time and that's uncomfortable and your bladder can scar down from the insult of having a hole made in it. Very rarely do we need to actually make an incision on your belly to repair that hole. If it's at the top and there's urine that's able to get into your abdomen, that can make you quite sick. And so sometimes we have to make an incision to repair that, but not the common or not the norm fortunately. And then I put constipation here because several of you had sent in questions about constipation.

When you have general anesthesia and you have narcotic pain medicine associated at least the time of the procedure and you're not in your normal active routine as you're recovering, you can be prone to constipation. Additionally, there's what I like to call crosstalk between the bladder and the bowel. And so if your bladder is not feeling well, it has been subject to cancer treatments and surgeries, then it might not function as well. And so then your bowel may say, "Hey, I'm not going to function as well either." And that's the nerves and the communication between the two can say, "All right, we're in this together." And so we have to manage those side effects. So how do we do this? Again, lifestyle modification. So staying hydrated to help flush out any of the blood and irritation that has occurred from the TURBT, having healthy regular toileting habits and avoiding those irritants.

We see the same medications used in this space. And then the additional procedures are things like wearing a catheter, as I said, and sometimes bladder irrigation. So if you have significant bleeding with clots afterwards, and I hope this hasn't happened to you, but it's not uncommon where a patient after a TURBT has to come in and be admitted for what we call continuous bladder irrigation. So that's when we put in a larger catheter that has three ports on it and two of them, one is responsible for flushing in fluids, the other is responsible for flushing out and draining those fluids, and that helps clear any of the blood and debris from the bladder. And then after some amount of time you'll be able to turn that off, we'll make sure the bleeding has stopped and then the catheter can come out prior to you going home.

But that is something that we do see and need to manage after TURBT for some patients.

Dr. Kristen Scarpato:

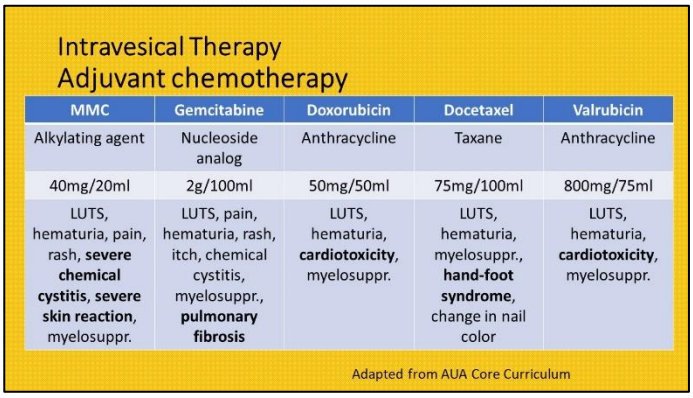
Now we're going to spend a couple minutes here talking about intravesical therapies and there are two broad categories here. They are intravesical chemotherapy, and then immunotherapy. And while many of them have the same risks of bleeding, pain, burning with urination, there are differences in some other aspects of them because they work in different ways. And so when a patient is getting intravesical therapy, we start with again lifestyle modifications and making sure you're maintaining healthy bladder habits. We're utilizing many of those same medications including something I didn't mention before, non-steroidal anti-inflammatory.

So that's Advil, Aleve, medications that can limit the inflammation anywhere in your body including in your bladder. And if there's signs of infection, antibiotics. And then things to limit ongoing inflammation may include interrupting therapy or reducing the dose of the therapy. And that's particularly true with BCG. And as many of you know, there's been a BCG shortage and we have been reducing the dose of BCG to one-half or one-third because of that. And there's mixed data on how that may impact the side effects, but that is certainly something that works for some patients. Bladder irrigations. Bladder irrigations in this case are not the ones that I talked about before to get rid of clots, but we can actually create a mixture that can calm the lining of the bladder.

And so every institution I imagine is different, but here what we use is a combination of Marcaine, which is a narcotic or a numbing medicine, a steroid, Solu-Cortef, bicarbonate, which is something that will make the urine less acidic, and then heparin. So we can put that into the bladder and that can have a calming effect for patients who have significant irritation related to the intravesical therapies that we put in there. And that's something that we use for patients who have benign disease with overactive bladder. You see Botox here on this slide. For patients who really have developed scar tissue and significant urgency and frequency and overactive bladder, we can put in Botox again just like we do for patients who have benign disease but have a hyperactive bladder. Pelvic floor physical therapy. I am so impressed and grateful for the colleagues we have in pelvic floor physical therapy.They can do wonders for patients who have pelvic pain and bladder irritation related to therapies. And so collaborating with them has been very helpful. And then sometimes you just need to change the treatment. Not every treatment is going to work or function or jive with every patient, and so we have to change it up, particularly if there are significant side effects.

Dr. Kristen Scarpato:

So this is really a technical slide here and I just want to highlight that these are some of the agents that we use, mitomycin, gemcitabine, doxorubicin, docetaxel and valrubicin are all medicines we can put directly into the bladder as monotherapy or one agent. And more recently we've been combining agents, for instance, gemcitabine and docetaxel. And all of these you see LUTS, that stands for Lower Urinary Tract Symptoms. All of these agents are going to cause that and cause pain and cause hematuria, but each of them have other much, much less common, rare side effects that can be associated with them as well. And so anytime you're experiencing symptoms related to your therapy that give you pause, I hope that you feel comfortable and I hope that you're able to reach out to your urologist and your care team and say, "Hey, I have this rash," or, "Hey, I have noticed shortness of breath," or, "My skin is really burning here," and we can evaluate further and make sure that there are appropriate therapies for that.



Dr. Kristen Scarpato:

I think one of the most important things about intravesical therapy is managing expectations. And so I just wanted to show this short video to highlight what we give to our patients here that is not totally comprehensive, but it does introduce the process and possible side effects. Here we're going to talk a little bit about BCG that can impact patients. Because whether you're starting intravesical therapy or you're taking a trip to someplace new or you're learning a new anything, there are going to be questions and expectations are important. And understanding what may happen to you, knowing what to look out for, that can really impact the experience during your treatment. If you know you're going to have burning or you know might see blood in your urine, you might be less alarmed, might experience less bother than if no one ever told you, "Oh gosh, you're going to see blood in your urine," or, "You might have constipation after your therapy." And so thorough counseling of expectations is really important. I'm going to show this brief video.

Video Sound:

Really what we're going to start with is talking about the process. So you'll come into our clinic, we'll have you leave a urine sample, you'll go back to the waiting room. We need to check your urine to make

sure you don't have any signs of infection. Once we see that you don't have a urinary tract infection, then we'll mix your treatment. Once the treatment is mixed, we'll get you back to your room and we'll have you undressed from the waist down. Once you're settled in the room, the nurse will come in and she will place the catheter into your bladder. We'll drain your bladder completely so you won't have any urine in your bladder. And then I'll come in and I will put the treatment into your bladder. Then the catheter comes out and we're all done. After your first treatment, we have you get cleaned up and have you sit for about 10 or 15 minutes just to make sure we don't have any reactions that we're not expecting. For the rest of your treatments, it'll be the same process but you won't have to wait for those 15 minutes.

Some things to tell us before we start your treatments or before we give your treatments, we need to know if you're on any antibiotics for any reason, if you're having any signs or symptoms of a urinary tract infection, fevers, chills, burning with urination, any of those things. We also need to know if you have any trouble ever holding your urine. Do you leak urine? Are you incontinent? Do you have to wear pads? Do you have to wear Depends? Those are all really important things for us to know before giving your treatment. After you get your treatment, like I said, "You'll get cleaned up, you'll be good to go." You need to hold the treatment in your bladder for two hours. After two hours you can void, use the restroom. You need to put two cups of bleach into the toilet, let it sit for 15 minutes and then you can flush the toilet.

You'll repeat that same process every time you use the restroom for the first eight hours after your treatment. This is important because we want to make sure we kill any of the treatment before Let's say someone else comes to use the restroom. If we haven't cleaned out or killed the treatment essentially, then that puts that next person at risk for getting a treatment that they don't need. Some common side effects after your treatment that most people experience at some point along the way. Burning with urination, maybe you may even see a little blood in your urine. That's all okay. Frequency, urgency, feeling like you have to run back and forth to the bathroom. A lot of patients will experience a low-grade flu-like symptoms. So a low-grade fever, maybe some fatigue, lethargy. This can last from the first 24 to 72 hours. The best things that we can recommend for this, staying well hydrated and Tylenol and rest. And like I said, after those first 24 to 72 hours, people seem to do just fine.

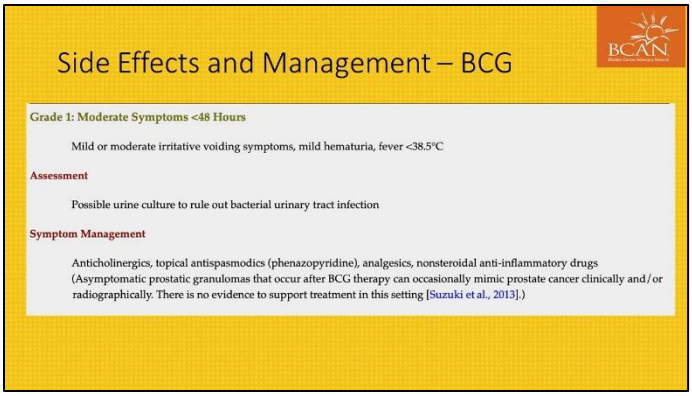
Another very common side effect that we certainly need to know about is if you're not able to hold the treatment for two hours. If you find that you're only holding it for an hour or 45 minutes, important for you to tell us that because there are some tricks and things that we can do to help you to hold the treatment longer. Now, more severe side effects that either requires calling us or a trip to the emergency room. These things are rare, but of course you need to know. Something we call BCG sepsis where you'd get really sick, very high fevers, chills, lethargy, those things, happens in less than one of 1% of patients getting this treatment, but that means calling us and/or a trip to the emergency room.

Untreated urinary tract infections. Urinary tract infections are very common during the treatment. It's not going to mess up your bladder cancer treatment, but we might need you to take a week off, treat the infection and then get back on tract. If a urinary tract infection goes untreated, people can get really sick really quick. And lastly, high fevers. So yes, a low-grade fever is normal, 101 and below all normal. 102 and above, that's a high-grade fever and something we or the emergency room needs to know about. We hope that this helped to clarify some expectations as you start this process and we'll take the best care possible of you while you're undergoing these treatments.

Dr. Kristen Scarpato:

Okay, so we give that to all patients who are undergoing intravesical therapy here to clarify expectations and of course we have an in-depth conversation when you're in the office beforehand. But it is

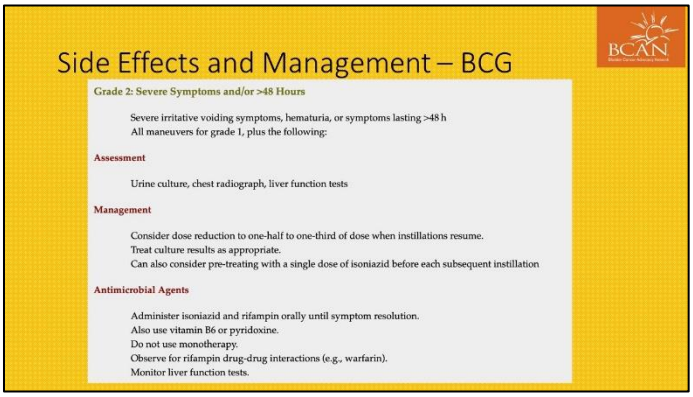
challenging to remember everything. I think it's a lot of new information, a lot of scary information. And having a resource that you can view multiple times and show to other people can be very helpful. A lot of questions about BCG. BCG really has been the standard of care and the best treatment option for patients who have high risk non-muscle invasive bladder cancer. BCG is inactive cow tuberculosis, essentially, it is immunotherapy, it's not chemotherapy and it works by harnessing your body's own immune system to fight off, recognize, prevent cancer recurrence, and in the case of BCG, progression. And while it works better than every other medication we've had to date, it can be challenging to tolerate and it has historically been associated with a lot of treatment related side effects.



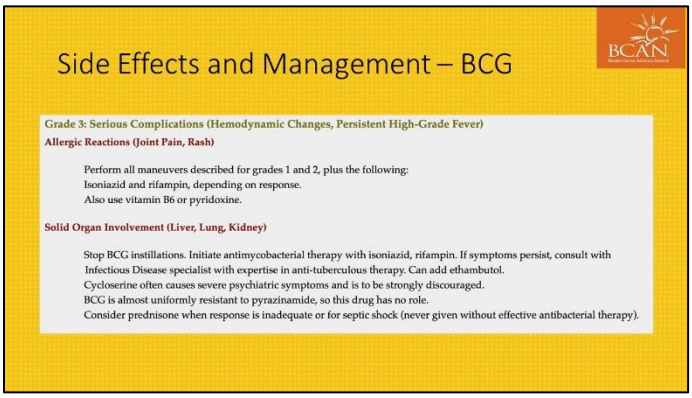
So therefore a lot of questions about BCG. When we're thinking about the side effects of BCG and how to manage them, the things that are important are the degree of symptoms and then the duration of symptoms. And you saw in that video some conversation about that. But generally there are three classes or three grades. Grade one is moderate symptoms. So this is either mild or moderate bothersome urinary symptoms, urgency, frequency, some mild hematuria and a low grade fever. And the time course here is less than 48 hours. So most patients who are getting BCG have this, they experience this. Some don't and tolerate it just fine. Others have these symptoms. And what your doctor may do in this situation is to send a urine culture to rule out infection but then start some of those medicines that we talked about, anticholinergics or the peridium medicine, analgesics like Tylenol or like non-steroidal anti-inflammatories. And that's the norm for most patients getting BCG experience this at some point during their therapy.

Dr. Kristen Scarpato:

A higher grade, so more severe symptoms that last longer can be also indicative of a urinary tract infection. And so we would check a urine culture but also because of the low risk of this progressing to other parts of the body, we investigate other parts of the body. So things like a chest X-ray may be ordered or liver function tests. How do we manage these more severe symptoms associated with BCG? This is when we can see dose reduction to one-half or one third and of course treating urinary tract infections and then pre-treating patients. And honestly, this is not something that I have seen much at all, but using one of the BCG drugs in advance of treatment to see if that improves tolerability, especially if the BCG is working.

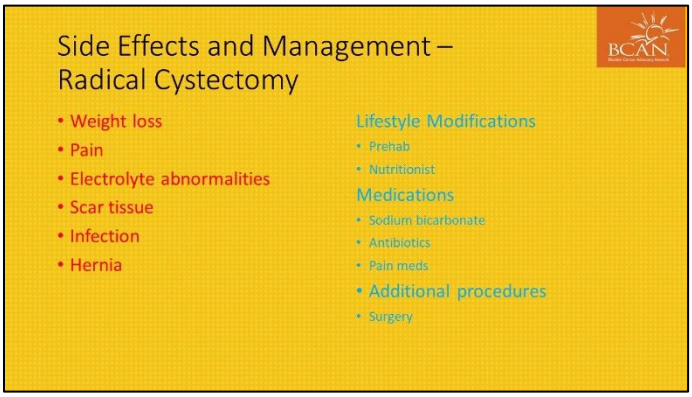


Dr. Kristen Scarpato:



And then the most severe are these allergic reactions or immune reactions that require more significant therapy and hospitalization. And there is a very rare but significant possibility of what's called BCG sepsis or BCG-osis and it occurs in about a half a percent of patients. But if there's any indication that the patient is becoming systemically sick like that, then we stop BCG. The patient's admitted to the ICU for ongoing care and we use these BCG drugs, the tuberculosis drugs to help mitigate, treat, prevent the infection from getting worse. Often in these patients we'll use steroids to limit the side effects here.

Dr. Kristen Scarpato:



So in the last few slides here, I wanted to talk about side effects that you might not immediately think about. We're so focused, we as physicians and sometimes patients and caregivers on the physical side effects that we're not thinking about the emotional and psychological side effects which are real. And I would say particularly for bladder cancer patients, your families. This is really a special patient population and one that we, I would say fortunately get to spend a lot of time together and it's a long-term relationship, but unfortunately, that's because of the close surveillance and the amount of interventions that often bladder cancer patients need. And so managing the emotional and psychological side effects are really important.

Not only the initial diagnosis of, "Hey, there's cancer," but also you have a cancer that has a high rate of recurrence, particularly when we're talking about non-muscle invasive bladder cancer. And even if it's non-muscle invasive, hey, guess what? There's a chance of progression. And while we have these great therapies, they might really impact your quality of life in terms of your urinary and sexual function. It may impact your body image. And also importantly, there's a financial toxicity that can cause significant emotional and psychological stress. And so what are the mitigating factors here? I think we're learning more about this and we're focusing more on this and realizing the importance of it, but asking questions, communicating fully with your care team, asking questions to the community, managing expectations. "Hey, you have bladder cancer, but here's your staging. Here's the treatment that we think you're going to need. Here are the side effects that you may have."

And then talking about your concerns and feelings not only with friends and family and loved ones and your doctor, but sometimes with a psychologist or a support group. And in some instances, particularly if you're feeling really stressed or anxious about it, at least temporarily taking advantage of medications if you need them. So these side effects are important and should not be put by the wayside as you're focusing on the physical side effects of treatment and the diagnosis.

Dr. Kristen Scarpato:

And then along with that, the caregivers. So the caregivers are such a part of this journey and we can't forget about them. Caregivers need a safe space to discuss the stresses and challenges and rewards of caring for loved ones.