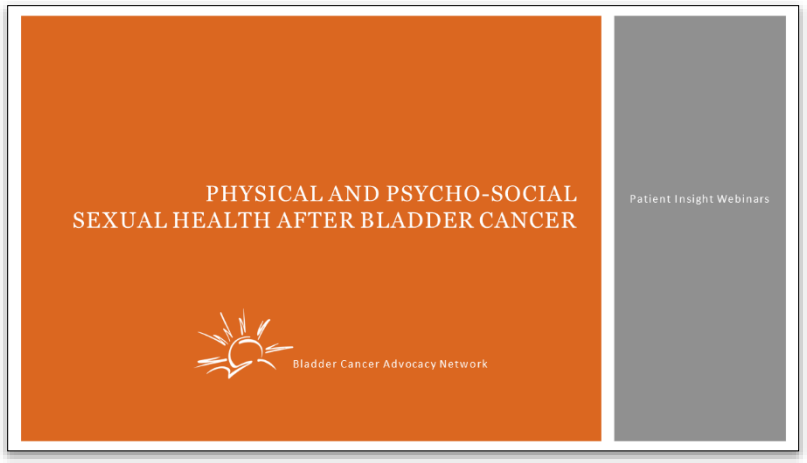
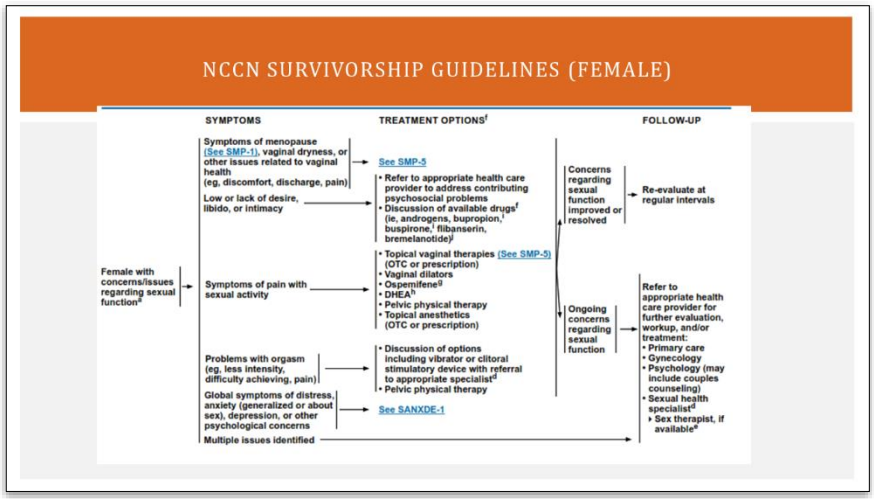


Stephanie Chisolm:

Excellent. That was fabulous. Really, you made so many points that I think the bladder cancer patient, the criticism and critique of their bodies is such a big, important factor in addition to any changes that might be a result of their treatment or their disease. There's just so many other things. And I'm sure there are a lot of good questions out there. So don't forget, drop your questions into the Q&A box at the bottom. And Dr. Svetlana Avulova is here with us. We're excited that she's here to talk more about the physical aspect of it and some of the changes that can occur with treatment.

Dr. Svetlana Avulova:

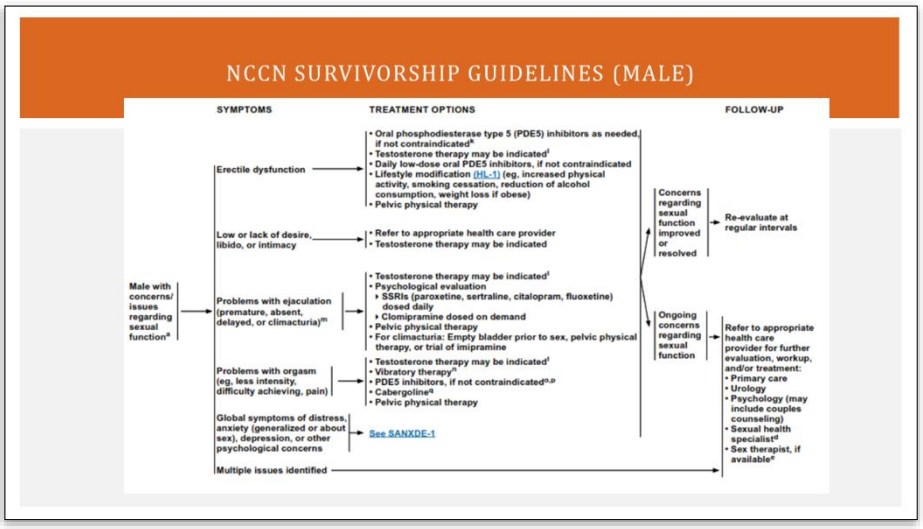
Thank you, Stephanie. And thank you Melissa, I really enjoyed your talk and your tips and tricks. I think allowing for us to kind of understand exactly what is available is really important, so then we can refer patients to you. So we'll start with the next slide. So first of all, I just want to point out that the NCCN, this is the National Cancer Network, they're very, very in tune with survivorship guidelines as it relates to sexual function. And there are very detailed sort of guidelines to follow for both female and male.



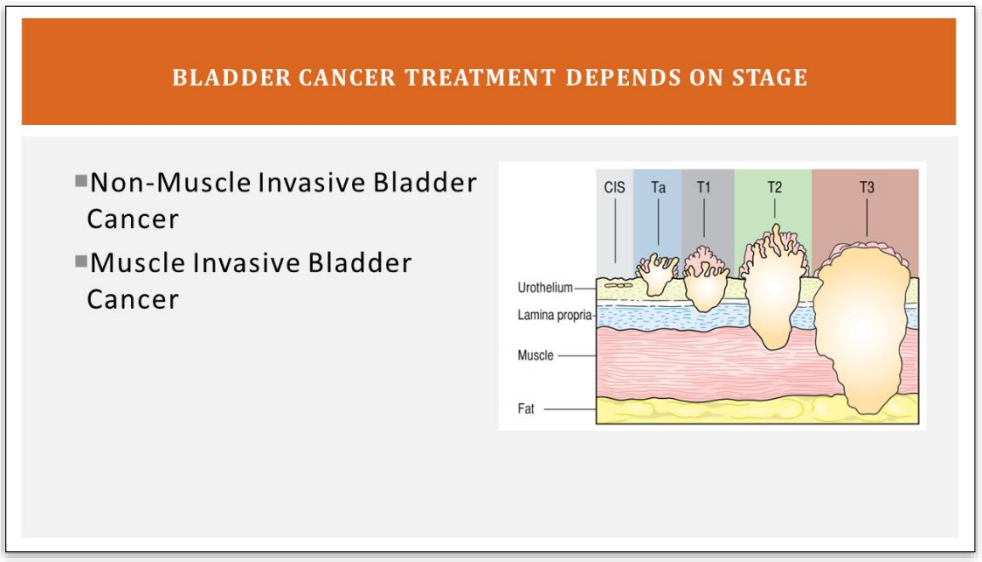
So we'll start with female. So even before honing in towards bladder cancer, any cancer, you can have issues with sexual function. And this is why the NCCN finds it important to provide guidelines for providers. So for women, I'm sure Melissa has already alluded to this, but women may be concerned with symptoms of menopause and what does that mean. Well, it could mean vaginal dryness or other issues related to vaginal health, like dyspareunia, which is pain with penetrative intercourse. And then obviously, low libido or lack of desire or low sexual interest. And then, the symptoms of pain with sexual activity. Women can have problems with orgasm. So they can have issues achieving orgasm or pain. And then, they can have symptoms related to anxiety from having a cancer diagnosis, from thinking about cancer coming back. Again, this is just in the setting of having a cancer

diagnosis. It's not even specific yet to bladder cancer, which we'll get into in a moment. So we'll go through some of the treatment options in the next few slides.

Dr. Svetlana Avulova:



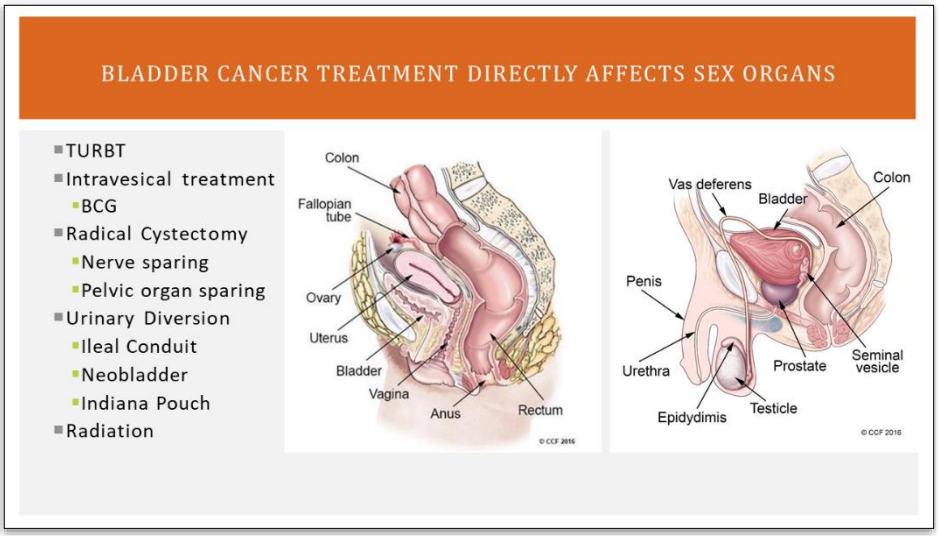
But if you go to the next slide, men obviously have different concerns. So they may have concerns with erectile dysfunction, also with low libido. But then also, they may have problems with ejaculation. So it may be premature, it may be delayed, and it may be absent. Climacturia is when you have urine that comes out with ejaculation. This is really in reference to patients who've had a prostatectomy, because they still have a bladder and they don't have that resistance mechanism of the prostate to hold back the urine. So they have climacturia. And then, they can have issues with orgasm, difficulty achieving orgasm or pain. And again, distress from a cancer diagnosis.



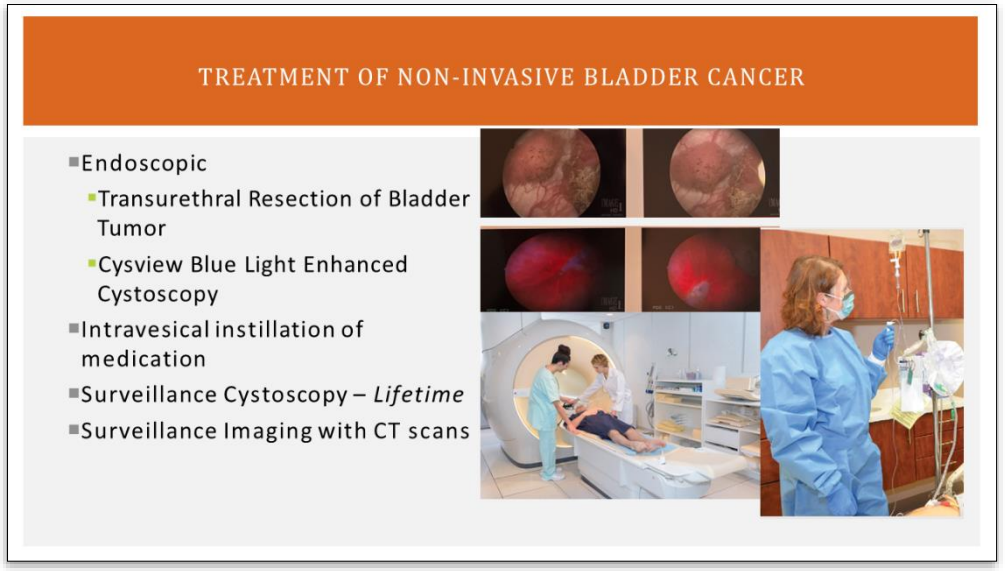
Next slide. So then, when we get into a cancer such as bladder cancer and we talk about the treatments, obviously you have to pause and kind of understand the different types of treatments, whether it's non-muscle invasive treatment or muscle invasive treatment. And this depends on how the tumor invades into the lining of the bladder. Now, the majority of bladder cancer, as most folks on this call know, the majority of bladder cancer that people get is non-muscle invasive, about 75% to 80% of people. And the treatments that non-muscle invasive bladder cancer patients get are vastly different from muscle invasive.

Dr. Svetlana Avulova:

So next slide. But what is important to understand and highlight is that bladder cancer treatment, no matter what it is, it directly affects the sex organs for both men and women. And so, you can see here, the side profile views of the male and female sex organs, and the bladder sits right behind the pubic bone, right in front of the uterus and the anterior vaginal wall. In the anterior vaginal wall and alongside the vaginal canal, there are pelvic nerves that help with vaginal engorgement, as well as they help innovate the clitoris, which helps with the sexual response. For men, obviously the prostate makes the ejaculate fluid. That fluid then gets stored in the seminal vesicle. So that's all part of the sexual response. And then, the pelvic nerves also sit on top and on the side of the prostate. And when we disrupt those, you can have erectile dysfunction. And when we remove the whole bladder and the prostate, you can have changes in ejaculation. But before we even get into that, when we get into non-invasive treatments like the TURBT or intravesical treatment, you can have changes related to sexual function as well. And we'll go through those.

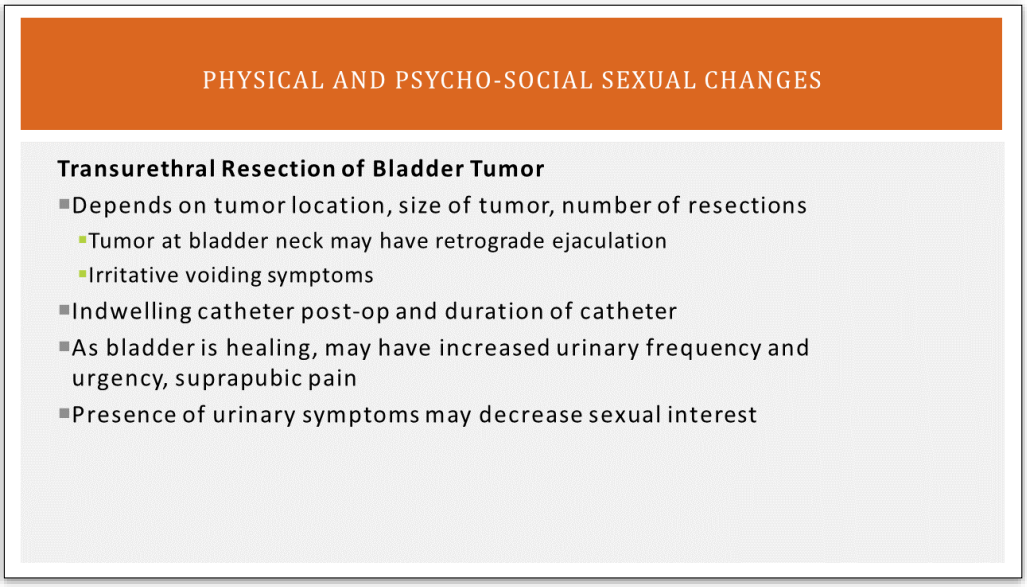


So next slide. So TURBT, as many of you know, is trans urethral resection of bladder tumor. So what does that entail? Well, that entails having a scope or a cystoscope that goes directly into the urethra, and using energy, the tumor gets scraped off the lining of the bladder. Now, we often counsel patients and tell them that, "The bladder doesn't really have any nerve ending, so you're asleep for this procedure, and most of the time you don't have any scars. And so, it's minimally invasive." But the symptoms, they can follow these resections. They can be very debilitating. And oftentimes, patients complain about frequency of urination, urgency, sometimes incontinence, burning with urination. And that is all just potentially from just having a scope inside. But then, when you combine that with the scraping of the bladder lining, the bladder lining could be healing and can produce all of those symptoms.



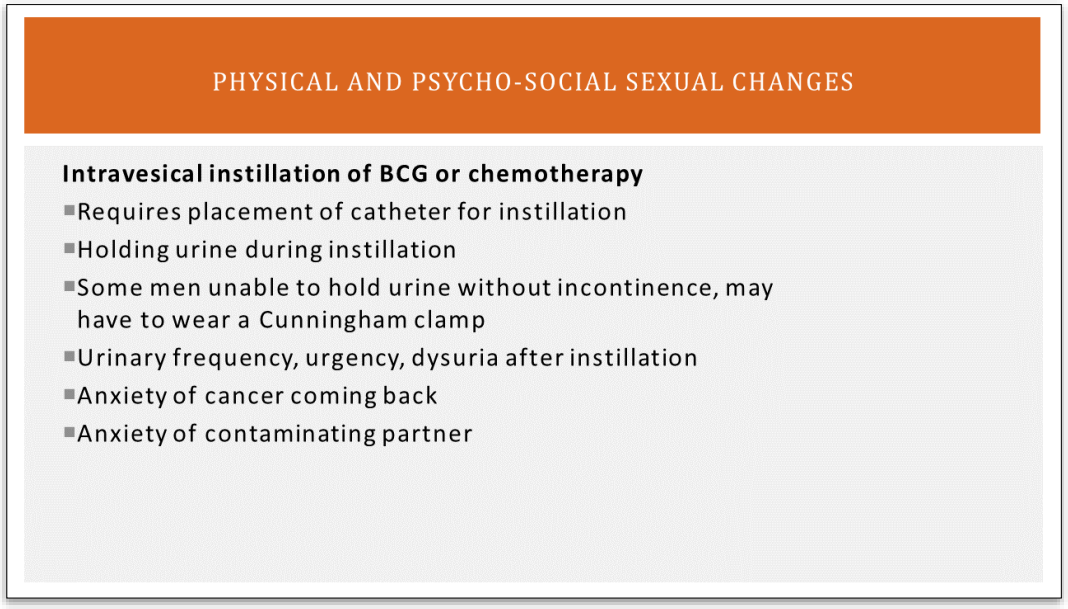
Dr. Svetlana Avulova:

If you go to the next slide, and then if you have multiple scrapings... And bladder cancer, especially non-invasive bladder cancer is known to come back and to recur. And it's a multifocal disease. And so, you can have multiple tumors in the bladder and you can have multiple scrapings. So a lot of this depends on the size of the tumor and the number of resections, as well as the tumor locations. So tumors that are located at the bladder neck, which is the opening of the bladder into the urethra, they can cause even worse symptoms of dysuria, burning with urination, urinary frequency, urinary urgency. And for men, you can have retrograde ejaculation because during a normal physiological ejaculation, the bladder neck actually closes, so that the ejaculate fluid can go forward into the urethra. But when you have a bladder tumor at the bladder neck, that bladder neck can potentially be scraped and that could leave the bladder neck permanently open. Now, you still have the sphincter in the prostate, but you could have a little bit of retrograde ejaculation and then may complain of not having as much ejaculate fluid.



So in addition, after these scrapings, you can have a catheter afterwards. And depending on how deep the scraping was, will determine how long the catheter will stay in. And as the bladder is healing, like I said, you can have these irritative voiding symptoms. And obviously, these symptoms can decrease sexual interest. We have a lot of general studies on quality of life and bladder cancer. And by a lot, I mean at most like 10 in the last 10 years. But we really don't have granular data on exactly what happens with sexual interests or exactly what happens with orgasm function or with retrograde ejaculation or with erections or with pelvic pain that may be related to this and how that can in turn affect sexual interest. We really don't have granular studies looking at this. So it's really difficult to counsel patients beyond saying, "Yes, you will have these symptoms. They will get better with time. We can give you medications to control the urinary symptoms, which may in turn, can help with the sexual side effects that can follow."

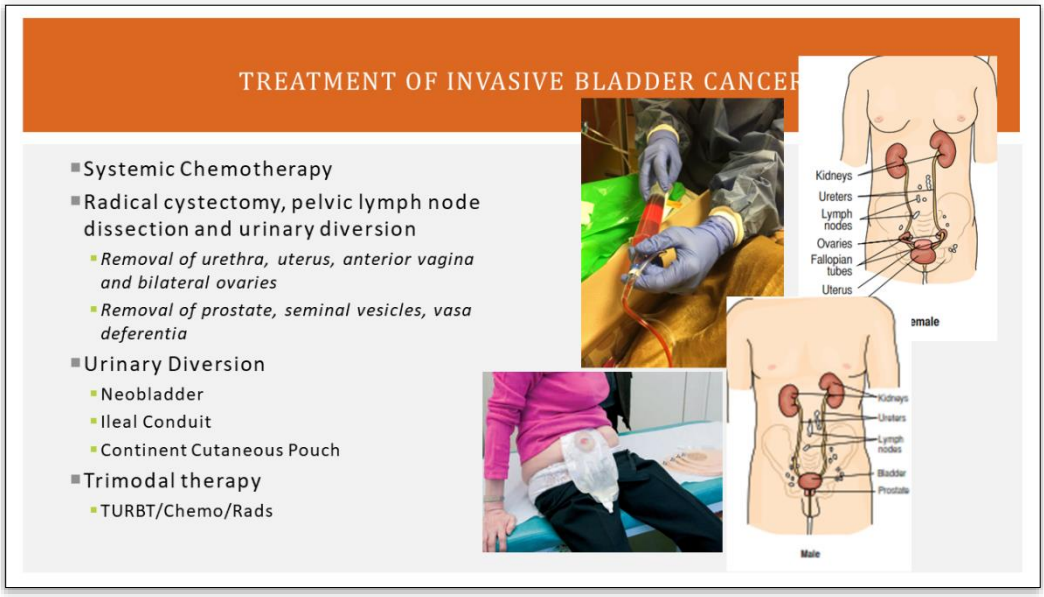
Dr. Svetlana Avulova:



Next slide. And then, if you've had these scrapings and the doctor orders for you to have intravesical treatment, so you would have medicine instilled into your bladder. Now, this requires placement of a catheter, holding the urine during the installation. Some men, they're not able to hold urine without having incontinence. So they may have to wear a Cunningham clamp, which is an external clamp that goes over the penis. I can't imagine anybody feeling sexy after that. And then oftentimes, we know a marker of intravesical therapy working is actually producing these irritative voiding symptoms, like urinary frequency and urgency and burning, because if it is specific to BCG, it's a marker of your immune system going to that site to kind of fight whatever cancer cells that may still be remaining.

And then, with these repeated intravesical therapies, every time you have a scope and you go in for that scope, there's the anxiety of the cancer potentially coming back. And so, every time with the surveillance scopes, there's that anxiety. And then, there's the anxiety of contaminating the partner with either the intravesical BCG or with the chemotherapy we put inside the bladder. And so, there are a few studies highlighting the anxiety related to that. But again, they're about six years old and we really don't have anything new beyond that.

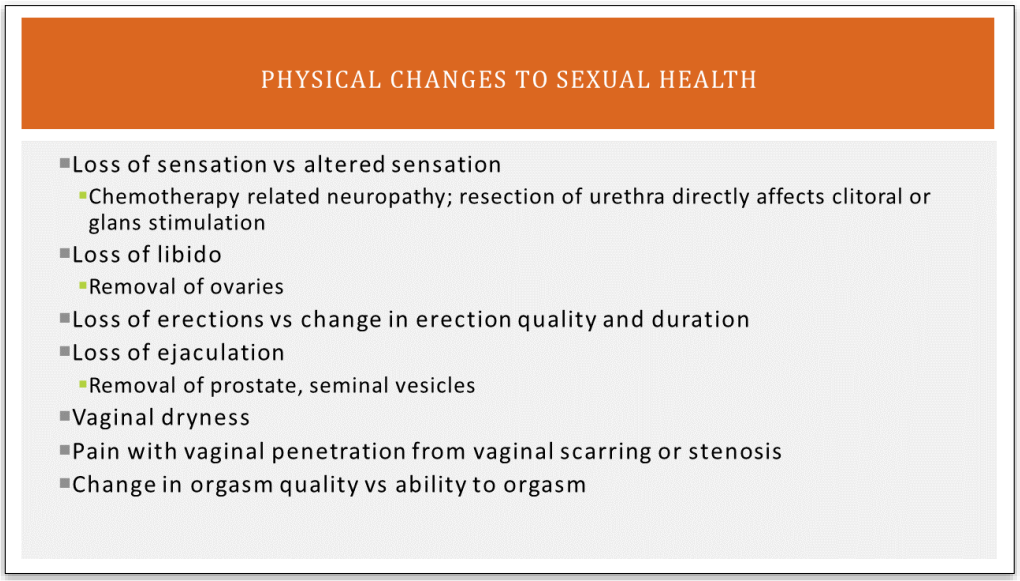
Next slide. And so, for the unfortunate 20% that end up having invasive bladder cancer, well, the road to treatment ends up being much longer. And so, they may undergo systemic chemotherapy. And then, eventually removal of the bladder. And for men, as I alluded to, that involves removal of also the prostate, the seminal vesicles, which store the



ejaculate fluid and the vas deferens on both sides. For women, classically, it involves removal of the urethra, the uterus, the anterior vagina, and bilateral ovaries, as well as fallopian tubes. And then, you need the urine to go somewhere. So you have to create a urinary diversion. And this could either be a pouch on the inside that's connected to your own urethra, like a neobladder, or it could be an ileal conduit, which is a loop of intestine that's connected to the skin. And you would have a bag over that stoma or a continuous cutaneous pouch, which is a pouch on the inside that you would catheterize. And then, sometimes trimodal therapy. So more scrapings, more chemotherapy, and more radiation to the bladder.

Dr. Svetlana Avulova:

Next slide. And all of those treatments can produce different physical changes to your sexual health. So loss of sensation or altered sensation. So for example, chemotherapy, you can have related neuropathy. Now oftentimes, we say you most likely will have peripheral neuropathy in your fingers and toes, but sometimes people may have genital neuropathy and different sensations related to that. Now, resection of the urethra in the very unfortunate few that do have urothelial cancer that extends into the urethra, whether they're men or women, we would have to resect the urethra. Which for women would affect their clitoral stimulation, obviously. And for men, that would include removal of the glans, which, as we know, is the most sensitive part of the male penis.



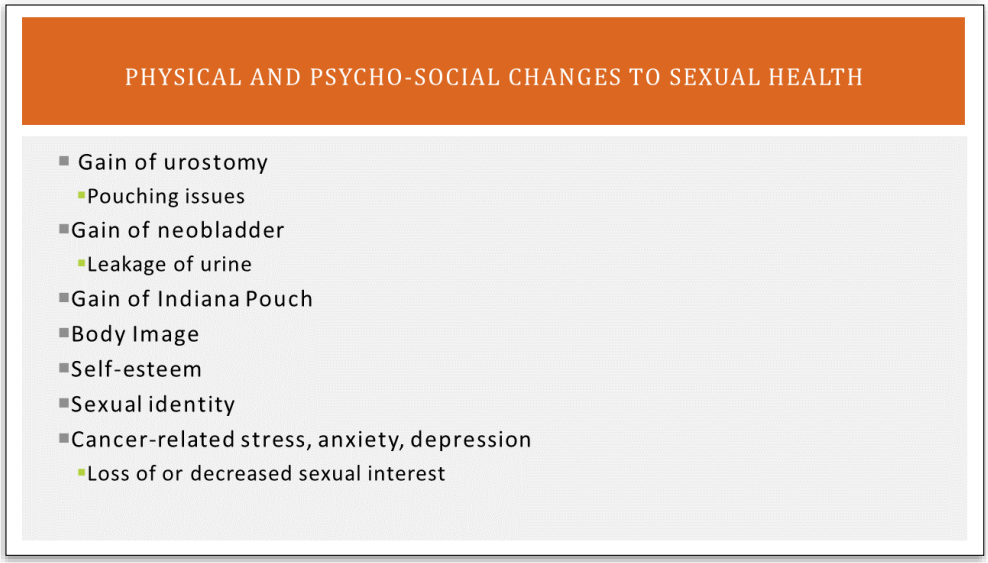
And then, loss of libido. So removal of ovaries, we are now finding evidence that ovaries do contain some lower amounts of potentially testosterone, that can help with libido. And so, removal of them can lead to loss of libido. And then for men, obviously we can check their testosterone level. And anybody who's experiencing symptoms of low libido, it's important to check a morning testosterone to make sure it's not less than 300. And if it is, we can provide testosterone supplementation. And then, loss of erections or change in erection quality and duration.

Now with bladder cancer, you get automatic loss of ejaculation, because you're removing the prostate and the seminal vesicles. For women, vaginal dryness can become even worse. So if women are already battling genital urinary syndrome or menopause, well, you're definitely going to make that worse with surgery, because you're removing the ovaries and that could lead to even more vaginal dryness. Or if you are removing the anterior vaginal wall or reconstructing it, the scar that can form from that can lead to dryness. And then, pain with vaginal penetration. Again, from scarring or even stenosis, that could be related to pelvic radiation.

Dr. Svetlana Avulova:

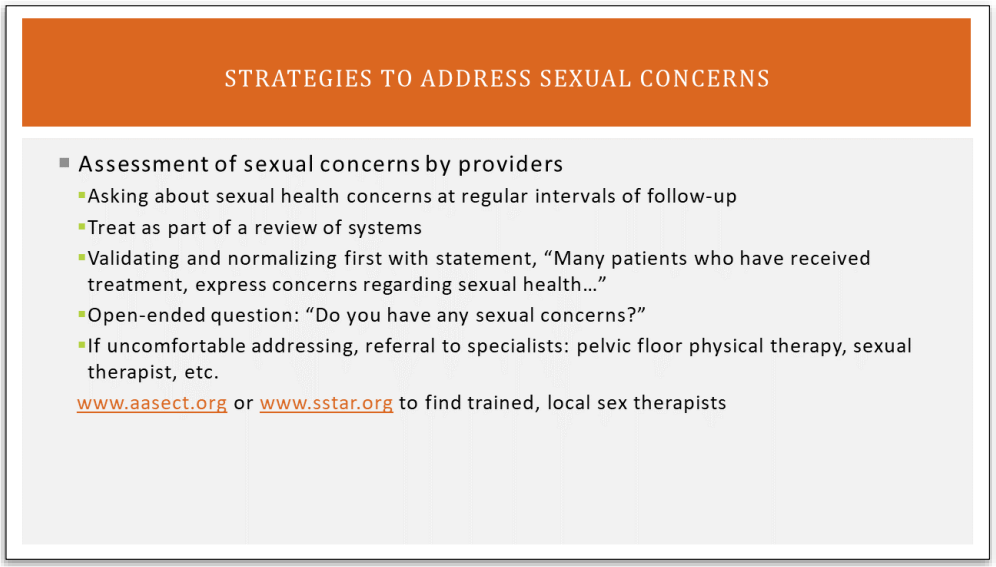
And then, change in orgasm quality or even the ability to orgasm. We really don't have a good idea of how those things are affected. We say that the sensation is intact because we don't resect those pelvic nerves. Usually, the pelvic nerves that we spare in a nerve sparing procedure, they, for men, help with erections, and for women, they could help with vaginal engorgement and lubrication. We really don't know. There's some limited data in the gynecologic oncology literature, where they do perform nerve sparing radical hysterectomies. More often though, they do that procedure to preserve bladder function. But they do have some studies that show that improves their vaginal engorgement and blood supply.

Next slide. And then, when you talk about the urinary diversion, you are losing a lot of your sex organs. But then, you're gaining new things. So you're gaining a urostomy. So you're going to have pouching issues with leakage of urine. You're gaining a neobladder, so that doesn't mean you have a completely perfectly functional bladder. You're gaining potentially having to deal with catheterizing yourself to empty your neobladder or leaking urine if your neobladder hasn't gotten to the appropriate volume where it can hold a certain amount of urine.



Having an Indiana pouch, that's that continent cutaneous pouch. It's continent, but sometimes it could leak also, and you may have to wear a stoma over that as well. And all of those things, they can lead to changes in body image and self-esteem, as well as sexual identity, that can definitely be affected. And if your sexual identity was struggling before this surgery, I can't even imagine what could happen after this surgery. And it's definitely something that needs to be studied further. And then, we all understand that the cancer related stresses and anxiety and depression can lead to loss or decreased sexual interest. And so, all of those things really are part of the physical and psycho-social changes that are as a result of treatment of muscle invasive bladder cancer.

Next slide. And so, what can we do as providers? Well, the first thing we can do is provide an appropriate assessment. And so, this is one of the things that the NCCN really stresses, which is ask about sexual concerns at regular intervals of follow-up. And just as Melissa said, treat

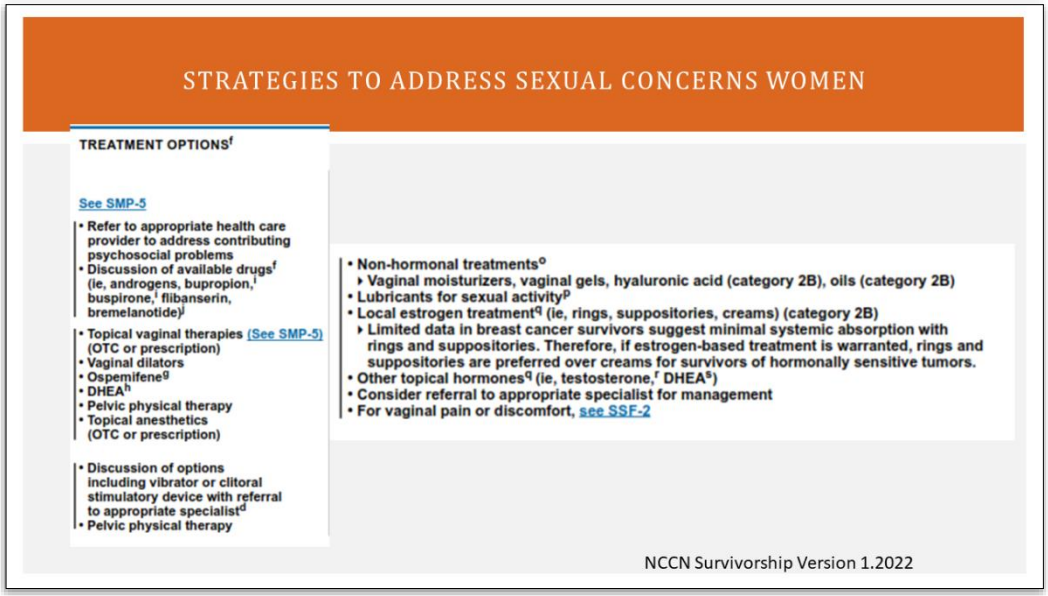


it as part of a review of systems. So just like you ask them, "Have you had any weight loss? Do you have trouble eating? Are you having any sexual concerns?" And one of the ways to sort of break the ice is validate and normalize it first with a statement saying, "Many patients who are receiving the treatment you receive, they express concerns about sexual health." And then, ask them an open ended question.

Dr. Svetlana Avulova:

And obviously, if you're uncomfortable addressing it, referring to specialists, such as a sexual therapist or even pelvic floor physical therapist could be helpful. And I provided those websites to AASECT as well as SStar to find trained local sex therapists. And I would love to hear Melissa's thoughts about the SStar website as well in the Q&A.

Next slide. And so, for women, these are the treatment options. And most of the treatment options are really dealing with treating vaginal dryness, vaginal atrophy. And so, those are the topical vaginal therapies you see there. And if there are issues with vaginal penetration or stenosis, then options for vibrators or vaginal dilators. If there are issues with orgasmic dysfunction, so vibrators or clitoral stimulating devices may be appropriate.

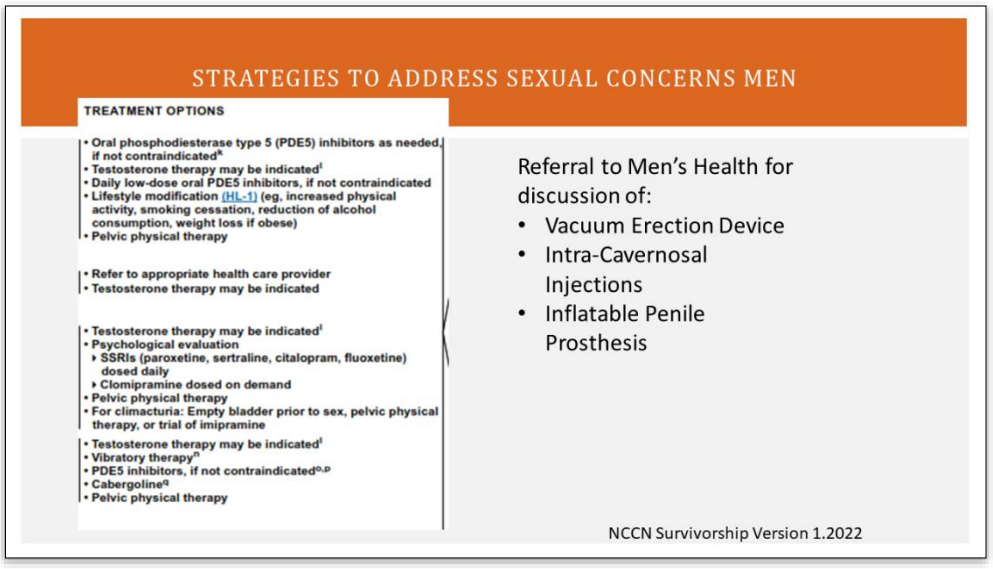


And then, the other box of treatments is really kind of highlighting the non-hormonal treatments that are available. Some women get very nervous about starting a hormonal therapy for risk of having yet another cancer potentially. And so, there are vaginal moisturizers that contain hyaluronic acid, are available, as well as water based lubricants. And for the most part, although there is a very small amount of systemic absorption, if you actually go to the next slide, the vaginal estrogen formulations that are available, they are pretty safe. And if there is a concern for a hormone positive breast cancer, this really good review by Goldman and Abel in urologic clinics of North America, they provide the dosing and formulation of different estrogen based vaginal topical creams or rings or inserts that are available. And one of the things they say is that if there is a concern for hormone positive breast cancer, then you just don't give them the loading dose. But it should be pretty safe to do the maintenance dose.

And the other treatments that are available, and I think Melissa touched upon this, is really to treat the hyposexual disorder, where you have low desire, low libido, low interest. And we have really good medications that have become available, like Addyi or Vyleesi, as well as some even antidepressants. And off-label, some have reported use of Viagra before sexual activity.

Dr. Svetlana Avulova:

Next slide. And for men, most of the treatments are aimed, again, at improving their erections, and that's what that box is. That's directly from the NCCN and guidelines. Now, unfortunately for the men that have bladder removal, even with the best nerve sparing, most of the time the PDE5 inhibitors like Viagra or Cialis, they really don't work anymore. And you would have to move to intra-cavernosal injections of medicine that would bring blood flow to the penis, as well as a vacuum erection device that can basically manually bring blood flow to the penis, and these devices are available. Obviously, ask a men's health expert for different brands that they would recommend.



And ultimately, some men decide to proceed with an inflatable penile prosthesis, which is surgically implanted. Now, we don't have something like that available for women. Where if they do have vaginal stenosis, or at least I'm not aware of us performing these surgeries for recalibrating the vaginal opening. And I think this is where the field of urology has led with improving a man's erection, and we've had this experience from prostatectomy patients, and we just don't have a similar corollary with women because other providers like gynecologists may be treating female sexual dysfunction. And so, we really don't have other surgical treatments available for women.

So that's all I had for you, and I hope that was informative.