



Questions & Answers about Sexuality and Intimacy after Bladder Cancer

A Valentine's chat with Dr. Trinity Bivalacqua

Monday, February 13, 2017

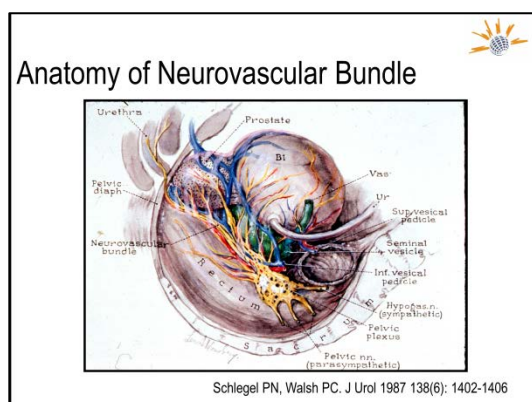
Part III: Causes and Treatments for Sexual Dysfunction

Presented by

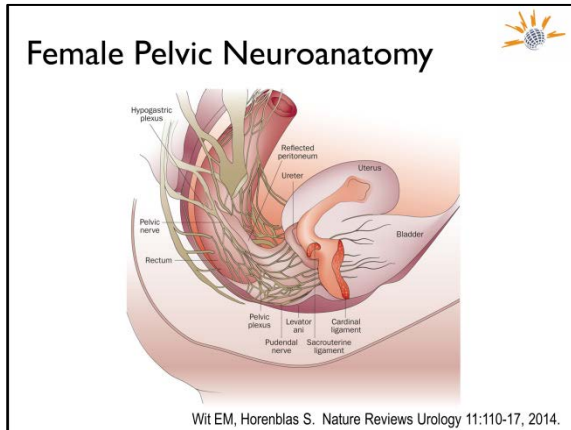


Dr. Trinity Bivalacqua is the Christian Evensen Professor of Urology and Oncology and the Director of Urologic Oncology at the James Buchanan Brady Urologic Institute. He joined the Johns Hopkins Urology Department after completing his general surgery and urology training at Johns Hopkins Hospital. He also completed an American Urological Association (AUA) Foundation Post-Doctoral Fellowship from the AUA Care Foundation. Dr. Bivalacqua has an active clinical practice in Urologic Oncology and Sexual Dysfunction. As a member of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, he participates in multidisciplinary approaches to the treatment of a variety of genitourinary cancers. He has a special interest in cancers of the prostate and bladder with an emphasis on organ sparing therapies, minimally invasive techniques and orthotopic bladder substitution (neobladder). Dr. Bivalacqua has recently been acknowledged for his accomplishments in research with several grants including a Career Development Award from the National Institute of Health (NIH), Greenberg Bladder Cancer Institute, and the AUA "Rising Star" Award.

This is where we're going to get into sort of the causes of both erectile dysfunction and female sexual dysfunction, so you can understand why this is so prevalent in men and women after bladder cancer surgery. Here is the anatomy of the neurovascular bundle. The neurovascular bundle is actually what supplies the innervation to the penis in men. You can see here that it runs laterally to the prostate, and you can see that it runs laterally to the bladder and prostate. You can imagine that during surgery, as your surgeon is coming through and taking the blood supply to



the prostate and the bladder, that these nerves can be damaged very easily. What I will tell you is that a lot of surgeons will not do what we call nerve sparing in patients that undergo a cystectomy or a radical cystoprostatectomy. I'll go over why that is shortly.

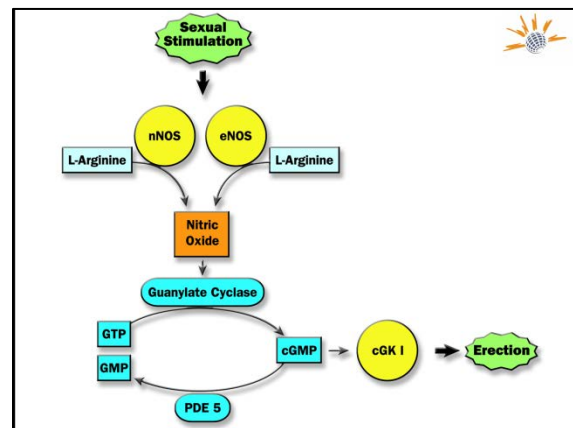


Now, this is a schematic of the female pelvic neuroanatomy. Here's your uterus. Here's your bladder, and those same nerves that are innervating the bladder and then ultimately the vagina and the clitoris are running just adjacent to the uterus and the bladder. You can imagine, once again, that when you're coming through and you're taking the blood vessels, or removing the bladder, these nerves can be damaged very easily. Actually, a lot of surgeons will not even take this into consideration when doing a cystectomy in a woman. I will tell you, back in the

mid-90s, Mark Schoenberg, who used to be here at Johns Hopkins, was one of the first surgeons to actually describe a nerve-sparing operation in women in which the nerves to the clitoris and the vagina that run lateral to the bladder are spared. This is something that needs to be done in women if you want to consider ... If you want to be able to preserve vaginal blood flow as well as innervation to preserve orgasm and arousal.

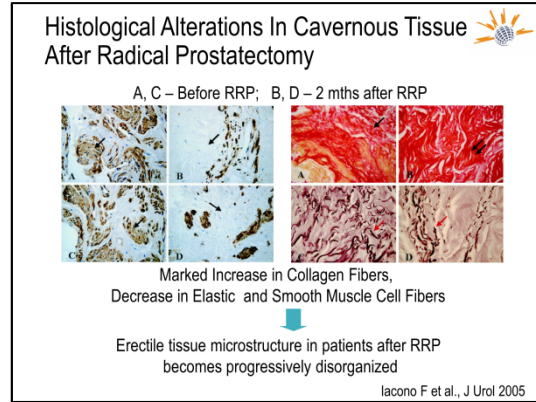
Another thing that I'll point out is that when you are considering a cystectomy as a woman, there are scenarios where the vagina, the anterior portion of the vagina must be removed due to cancer. However, we oftentimes will try to leave the anterior portion of the vagina in place so a woman, if they desire, can have vaginal intercourse.

Now this is where we get into a little bit of the mechanism by which nerve injury can cause both erectile dysfunction and female sexual dysfunction, in that the nerves that are responsible for sending the neural transmitters to the penis and the clitoris and vagina, they can be easily injured. Those nerves release a gaseous molecule called nitric oxide, which binds to the enzyme which increases this second messenger which is cyclic GMP. Viagra, which is the medication used in men, helps keep cyclic GMP around in the penis to promote blood flow into the penis. The reason why I point this out is that if the nerves are removed, if you remove the nerves, or if you injure the nerves, this molecule will not be released and therefore blood flow will not occur in the penis, and thus you will have erectile dysfunction.



Now, this is actually a slide from a man that had a biopsy of the penis prior to a radical prostatectomy. Now I will point out that a radical prostatectomy is different than when we remove both the bladder

and the prostate, but the nerves that innervate the penis are spared during a prostatectomy as well as a radical cystoprostatectomy. This slide is relevant to our bladder cancer patients. You could see here that in this slide, you see nice little big muscle bundles that are here in brown, but as early as two months after an operation in which the prostate removes, if you biopsy the penis, you see this massive decline in the muscle. This is actually the mechanism by which men develop erectile dysfunction. The nerves are injured and therefore the muscle atrophies and they can no longer get an erection.



Some of the things that we know about a cystoprostatectomy or a radical cystoprostatectomy, removal of the prostate and the bladder, or removal of the bladder in a woman, is that we have excellent long-term cancer control rates. What I mean by that is that if you have organ-confined disease that is confined to the bladder or the prostate, we're able to do a great job of controlling the cancer. However,

Radical Prostatectomy (RP) and Radical Cystoprostatectomy (RCP)


- Surgery offers excellent long-term cancer control rates
- Urinary Incontinence largely controlled today
- Erectile dysfunction is a historically known significant complication of the surgery

there are historically very significant complications after the surgery, as it relates to erectile dysfunction or female sexual dysfunction. The thing that most patients don't understand, and honestly are not counseled about this pre-operatively, is that it may take upwards of two to four years to recover their erections, and that when they do get their erections back, they're oftentimes diminished, or their erection quality is not the best, and therefore may affect their relationship, and that erectile aids must be used in the interim, which I'll go over shortly.

The causes of erectile dysfunction after your bladder is removed or prostate is removed, it relates to the surgical trauma, where the nerves are injured or the vasculature or the blood vessels are injured. There are other psychosocial factors such as the depression and anxiety that relate to treatment of their cancer, relationship circumstances, and most importantly, co-morbidities. If a man or a woman has preexisting problems with their blood pressure, if they're smokers or previous smokers, if they have diabetes or advancing age, this will affect erection recovery.

Some of the other realities are that the current treatments are on demand, and they're temporary. The treatments are currently less than satisfying to both the patient and the partner, and we have not come up with today a corrective intervention which prevents this from happening. We can be really wonderful surgeons and we can do our best to preserve the nerves that innervate the penis or the vagina or clitoris, but there's still going to be a large percentage of patients that will suffer from sexual dysfunction. Therefore, you must discuss with the patient and partner the predictability of erection loss,

the timing of erection recovery, as well as the stress that this may have on a couple. This is where it's extremely important that you have this conversation with your surgeon prior to undergoing any treatment, so you can be aware of the problems that you may have postoperatively.



Sexual Dysfunction after RP and RCP


- May take up to 4 years to recover
- May have compromised full erections (diminished erection quality)
- Requires erection aids in the interim (PDE5 inhibitors, intracavernous injections, MUSE, VED)
- Other sexual dysfunctions also associated with RP – climacturia, penile shortening, peyronie's disease, changes in orgasm

Walsh PC, et al. Urology 55:58, 2000
Mulhall J et al. J Sex Med 3:532, 2005

Once again, I'll point out that in men, the most common treatment for erectile dysfunction is the use of PDE5 inhibitors, which is Viagra, Cialis, Levitra, Avanafil. These are all the medications that you can take by mouth, but these are oftentimes not very effective within the first year or two, and therefore most men will move over to what's called intracavernous injections. This is where we teach a man how to inject into the penis a medication that will bypass the nerves and actually induce the blood vessels in the penis to relax, so you can get nice blood flow into the penis.

Other problems after a cystectomy or a prostatectomy are problems with climacturia. Climacturia is actually when a man leaks urine with orgasm after a prostatectomy or a cystoprostatectomy. Now that may not be important for some men that, for example, have an incontinent diversion such as an ileal conduit, but that will be a problem for both men and women that have an orthotopic neobladder. Therefore what I always tell patients is, is that prior to any intercourse or any intimacy, to go ahead and empty your bladder to help prevent that from happening. The good news is, this usually resolves after about a year. Other things that happen in men are penile shortening, where the length of the penis gets less, and you can develop diseases such as Peyronie's disease, which is fibrosis of the penis.

The techniques that we currently use to preserve the erection are preservation of the neurovascular bundle, or you will hear your surgeon talk about a nerve-sparing operation. This is something that should be considered in all men that want to continue to be sexually active. The only way for you to be able to recover your erections is if you undergo a nerve-sparing operation. We've used things like nerve grafting, intraoperative nerve stimulation, neuromodulation, and penile rehabilitation. The problems are that currently none of these have shown to be very effective.



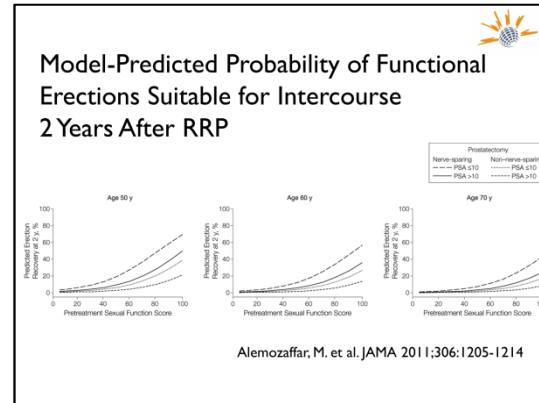
Erectile Function Preservation: Strategies

- Techniques to preserve the neurovascular bundle
- Nerve Grafting (not effective)
- Intraoperative Nerve Stimulation (?)
- Erection Rehabilitation (unknown)
- Neuromodulation (pre-clinical and unknown)

Sopko NA, Hannan JL, Bivalacqua TJ.
Nat Rev Urol. 11:622-8, 2014.

This is something that I think is extremely relevant for our bladder cancer patients that undergo a cystectomy. This is some data from a prostatectomy cohort, but it still pertains to our cystectomy patients. Now this is men that I'm showing here at different ages, decades of life. This is a 50 year old man, a 60 year old man, and a 70 year old man. If you undergo a nerve-sparing operation and you're 50

years of age, and at two years, this is once again at two years, only 60% of men are able to have erections sufficient for intercourse. At 60 years of age, that number is about 40% to 50%, and if you're in your 70s, that number drops down to 40%. If you undergo non-nerve sparing operations, those numbers are less than 20%. This points to the fact that if you are a patient that undergoes a nerve-sparing operation, at best it's a flip of a coin if you're going to regain your erections.



Now, here's actually data from the Cleveland Clinic that was published now over 10 years ago, where they looked at a cystectomy population. Now these were patients that underwent a cystectomy, and this is their erections prior to cystectomy. I want to point out that these numbers just show that the

Erection Recovery after Radical Cystoprostatectomy (RCP) for Bladder Cancer

TABLE 1. SHIM (IIEF-5) analysis: baseline and after radical cystectomy

SHIM (IIEF-5) Domains	Baseline Before RC (n = 49)	After RC (n = 49)
Q15, erection confidence	4.12 ± 0.97	1.39 ± 0.76*
Q2, erection firmness	4.41 ± 0.91	0.97 ± 1.20*
Q5, maintenance ability	4.35 ± 1.09	0.69 ± 1.28*
Q4, maintenance frequency	4.65 ± 0.69	0.69 ± 1.37*
Q7, intercourse satisfaction	4.55 ± 0.87	0.88 ± 1.49*
Total mean IIEF-5 score	22.08 ± 3.96	4.33 ± 5.72*

* Only 7/49 (14%) patients underwent Nerve Sparing.

Zippe C et al, UROLOGY 2004

patients had normal erections. This is what's called the SHIM, or the IIEF score. This is a validated questionnaire to quantify erections. As you can see here just from these numbers, that these are normal. But after a cystectomy, these numbers all show that these men have a severe erectile dysfunction. If you look at why that's the case, only 14% of patients underwent a nerve-sparing operation. You can imagine that only seven of these patients even had an opportunity to regain their erections, and out of these seven patients, only two patients regained their erections.

Now, we looked at this recently in a national database which looked at patients that underwent cystectomy and then what we looked at was the rate of erectile dysfunction therapies after their cystectomy. Unfortunately, what we found was is that the thousand patients in this database that did not have any ED treatments prescribed to them prior to surgery, so what this means is that these are patients that are potent, or have no erectile dysfunction. You can see that only 9% of those patients were actually offered PDE5 inhibitors after cystectomy. If you combine other injection therapy, vacuum erection devices, that only 13% of these patients within the first six months are offered any type of ED treatment. If you look at this exact same table for radical prostatectomy patients, that number is almost 50%. What that tells us is, is that we as bladder cancer surgeons are not doing a very good job of counseling our patients and being able to help them recover their erections. To be honest with you, this is something that we need to change.

Where are our knowledge gaps right now? These are my last couple of slides. We have to educate our bladder cancer physicians about the importance of sexual recovery in both men and women following cystectomy. We have to be able to focus on more disease-specific therapies. Now, Stephanie pointed out sort of what my interest in research. What our interest in research is, is to be able to provide patients, both men and women that undergo a nerve-sparing operation, we want to be able to preserve those nerves after cystectomy, to help them regenerate and to help them innervate the penis and the vagina and clitoris more effectively, to help bring that 50% ED rate to less than 50% in our patients. One

thing that we currently do not know is the impact of intravesical therapy on sexual function, and the overall health-related quality of life in our bladder cancer patients that have non-muscle invasive bladder cancer. We really don't know if intravesical therapy affects their sexual function, and that's something that we're actually studying right now. We need to be able to provide our patients with a pre-surgery navigator that can help with answering simple questions about sexual recovery after cystectomy.

Knowledge Gaps....



- We have to educate bladder cancer physicians about the importance of sexual recovery in both men and women following radical cystectomy.
- Focus on more disease-specific therapies.
- The impact of intravesical therapy on sexual function and overall health-related quality of life.
- Pre-surgery navigator who can help with simple questions about sexual recovery following RC.

What can you do? The first thing you can do is, you could talk to your urologist, your oncologist about sexual dysfunction. During intravesical therapy treatments, ask them questions following surgery or prior to surgery, or if you're undergoing chemotherapy or radiotherapy. It's important that you have this conversation with them, and to be honest with you, if they can't help you, then asked to be referred to a sexual medicine specialist in that practice, so they can speak to you about your options for treatment, and also help educate your surgeon to

come up with a tailored treatment plan. I can tell you right now, a simple thing to do is, is just to ask your surgeon to consider nerve-sparing when undergoing treatment. Then the last thing to point out here is, is that if you are a male or a woman that has sexual dysfunction, there are a number of treatments that we can use. These range from PDE5 inhibitors to intracavernous injection therapies, to lubricants, to hormonal treatment in women, all the way to surgery if you ultimately do not recover erections.

Finally, for women who suffer from female sexual dysfunction, this becomes a little bit more difficult to treat. This is where you really need to speak with a specialist. What I can tell you is that I have patients in my practice that undergo a cystectomy and we'll be able to preserve their vagina, and they're able to have penetrative intercourse, but they can't have orgasms, or their lubrication is less. That's mostly related to impairments in blood flow and innervation, but there are tools that we can use to help with that. Lastly I would tell you, if you're a woman and you need help or

need to speak to someone, please ask to be referred to a sexual medicine specialist. They're going to be the best ones to answer any questions that you may have.



