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Review Article

Management of male sexual dysfunction after cancer treatment

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Background: With an increase in the number of cancer survivors each year, male sexual dysfunction becomes an important topic for discussion between patients and providers who treat cancer. The aim of this article is to review types and mechanisms of sexual dysfunction after cancer therapy and discuss treatment options.

Methods: Contemporary concepts regarding male sexual dysfunction after cancer treatment are reviewed and translated for clinical utility.

Findings: To optimize recovery of erectile capacity after erectile dysfunction causing cancer treatments, a penile rehabilitation protocol involving phosphodiesterase inhibitors, vacuum erection device, intra corporal injections, or a combination is likely to provide some degree of clinically significant benefit. Treating hypogonadism post cancer treatment depends on the type of cancer that has been treated and patient comorbidities. Anejaculation after cancer treatments is typically not successfully or reliably treated due to the mechanism and severity of sympathetic nerve injury. Semen cryopreservation prior to cancer treatments that may injure nerve fibers essential for the ejaculatory response is highly recommended.

Conclusion: Management of post cancer treatment sexual dysfunction requires identification of this problem and referral to a specialist if necessary. There are several management options available that can greatly enhance quality of life in this often overlooked aspect of post cancer treatment care.

Keywords: Cancer; Sexual dysfunction; Erectile dysfunction; Testosterone; Quality of life

1. Introduction

Cancer survivors make up a growing population that is expected to reach an estimated population of 26.1 million [1], representing approximately 5.0% of the population. Given this growing segment of our population that is a result of more effective treatments, more attention has been placed on the quality of life during and after cancer treatment. In 2018, 856,370 men were newly diagnosed with cancer, with prostate cancer being the most common cancer diagnosed (164,690) [2]. Unfortunately, the prostate is in a central pelvic location surrounded by essential structures whose integrity is essential for the maintance of normal sexual function. The resulting erectile dysfunction (ED) after treatment of prostate cancer serves as a prime example of how cancer treatments can affect sexual function [3]. Even in the prostate cancer setting, sexual dyfunction tends to be undertreated and underreported [4]. Thus, it is not surprising that men with cancers whose pathology and treatments are not traditionally associated with sexual dysfunction are often not screened for sexual dysfunction. For the purposes of this review male sexual dysfunction can be broadly categorized into ED, hypogonadism and its associated side effects, as well as ejaculatory complaints.

In this review, we discuss the general pathophysiology of how cancer treatments can affect penile erectile capacity, testosterone production, as well neurologic function as it pertains to ejaculation. We also discuss management strategies for these distressing conditions.

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2. Overview of types and mechanisms of sexual dyfunction after cancer treatment

2.1. ED

ED is defined as the inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse [5]. The etiologies can largely be divided into organic and psychological. Organic causes include neurogenic, vasculogenic or endocrine-related pathology. Although it is likely that there is a psychological component to ED after certain cancer treatments, iatrogenic organic mechanisms are the leading contributors to ED in this population. Surgeries such as radical prostatectomy, radical cystoprostatectomy, and abdominoperinal resection have been associated with injury to post-ganglionic parasympathetic nerves that originate in the inferior hypogastric plexus just lateral to the rectum, and extend into the penis through the cavernous nerve plexus posterolateral to the prostate to facilitate penile erection. Such damage leads to reduction in nitric oxide delivery to the smooth muscles and endothelium lining the cavernous sinuses of the penis, whose integrity is necessary for vasodilation and expansion of the corporal tissue that makes up the 2 corpora cavernosa of the penis [6].

ED as a result of radical prostatectomy/cystoprostatectomy has been extensively studied and improvements in rates of ED after these surgeries largely stems from an understanding of pelvic anatomy. The concept of a cavernous nerve-sparing surgical approach stems from Walsh and his colleagues who used an autopsy specimen to define the pathway of cavernosal nerves which could potentially be preserved during a prostatectomy without entering the prostatic capsule [7]. Several factors have been associated with higher preservation of erectile function in patients who undergo nerve-sparing radical prostatectomy. These include the surgical technique, experience of the surgeon, patient's age, pre-operative sexual function and co-existing medical conditions [8].

The inferior hypogastric plexus can be injured during rectal cancer surgeries, particularly during rectal mobilization and lateral lymph node dissection, and can lead to deterioration of erectile function [9]. Due to this well known postsurgical complication, total mesorectal excision with autonomic nerve preservation has become the gold standard [10]. Studies comparing mesorectal surgery with and without lateral lymph node dissection have found that men who underwent mesorectal excision with lateral lymph node dissection tend to experience significantly higher rates of sexual dysfunction [11].

Radiation is an alternative treatment modality available for prostate cancer and other pelvic cancers that is utilized for curative, salvage, or palliative reasons. It is thought that radiation treatment results in not only damage to the cavernous nerves, but also endothelial damage to the corporal tissue and its arterial supply [12]. Compared to surgical intervention, radiation typically leads to a delayed presentation of ED given the mechanism of action of nerve and vascular injury [13].

2.2. Hypogonadism

Along with surgeries to extirpate the pituitary gland and testicles for oncologic reasons, chemotherapy and radiation can have deleterious effects on testicular and pituitary functions. For example, Imatinib, a tyrosine kinase inhibitor, is known to induce lower testosterone levels likely due to its deleterious effects on testosterone producing Leydig cells [14].

Radiation effects on testicular function is largely dose dependent and, although relatively radio-resistant compared to germ cells. Leydig cells can have a substantial change in metabolism at the molecular level with doses as low as 4 Gy. This is worth noting since pelvic radiotherapy uses total radiation dose significantly greater than 4 Gy [15]. In fact, although it was previously thought that testosterone replacement was likely to be required only at Leydig exposure doses in excess of 20 Gy, more recent literature with long term followup supports significant Leydig cell dysfunction requiring testosterone replacement with doses lower than 16 Gy [16].

Central hypogonadism can also arise due to external cranial radiotherapy for a variety of brain lesions and nasopharyngeal tumors. It has been documented that up to 2 thirds of adult patients who received such radiation treatment developed some form of hypogonadism [17].

2.3. Ejaculatory complaints

The normal male response to sexual stimuli requires complex input from an intact somatic and autonomic nervous system (sympathetic and parasympathetic) [18]. Somatic nerves provide the afferent stimulation pathway via the spinal S2-S4 nerve roots and transmit tactile, pain, and temperature. During the erection phase, it directs contraction of the ischiocavernous and bulbocavernosus muscles [19]. Parasympathetic nerves, derived from spinal S2-S4 nerve roots, also play a central role in tumescence through the cavernous nerve as discussed above. The emission phase, where semen is propelled into the urethra from the seminal vesicles, is marked by a predominant action from sympathetic nerve fibers originiating from spinal nerve roots T11-L2 [20]. The expulsion phase follows and involves propulsion of semen via the urethra through rhythmic contractions of the pelvic striates muscles. During this phase, sympathetic tone signals originating from spinal nerve roots T11-L2 and somatic nerve signals from S2-S4 help keep the bladder neck remain closed and external sphincter stay open, respectively [20].

Therefore, any insults to the autonomic or somatic nervous systems along their signal tracts can invariably lead to ejaculatory dysfunction. The anejaculation resulting from sympathetic nerve fiber injury during retroperitoneal lymph

node dissection for testicular cancer treatment is a prime example.

3. Clinical management of male sexual dysfunction after cancer treatment

3.1. ED

The concept of penile rehabilitation in the setting of radical prostatectomy was first described in the late 1990s. It involved scheduled penile injections of alprostadil post surgery to stimulate strong erections early on in attempts to preserve penile tissue [21]. Both neuropraxia and vasculogenic components are thought to be the main contributors of post surgical ED. In vitro and animal data suggests loss of penile smooth muscle and induction of fibrosis are due to un-inhibited transforming growth factor beta 1. Also, decreased concentrations of available nitric oxide, a critical erectogenic chemical that induces production of cyclic guanosine monophosphate and subsequent smooth muscle relaxation, is thought to lead to smooth muscle fibrosis and atrophy [22].

Phosphodiesterase inhibitors (PDE5i) have been considered to be the first line of therapy for ED since 1998. They promote improved erectile function by inhibiting phosphodiesterase enzyme type 5 leading to downstream effects that relax penile corporal smooth muscle cells [23]. In the setting of ED induced by injury/surgical removal of erectogenic neurovascular structures, PDE5i medications have been shown to counteract deleterious changes by preserving penile smooth muscle and endothelial integrity [22, 24,25]. Despite this basic science data, it is still unclear what the clinical benefits of utilizing PDE5i in humans in penile rehabilitation protocols are. All of the PDE5i medications on the market (vardenafil, sildenafil, tadalafil and avanafil) have been studied in observational and randomized controlled studies utilizing both on demand and regular interval dosing post prostatectomy and prostate radiation. Successful use in penile rehabilitation protocols are reported by most clinical studies in prostatectomy seriesusing validated questionnaires of ED such as the International Index of Erectile Function (IIEF) [26]. It is important to note, however, that a multicenter, placebo-controlled, double-blinded study performed in 2014 in men who had undergone radiotherapy for prostate cancer did not demonstrate improved IIEF score with daily tadalafil use when compared to placebo group at 1 year follow-up [27]. This evidence is balanced by smaller, non blinded studies that have shown a benefit to the use of PDE5i after radiation [28].

Given tadalafil and sildenafil are currently affordable in generic versions, they represent a relatively accessible form of penile rehabilitation that can likely be extended to any post cancer surgery or treatment that results in injury to the cavernous nerves or inferior hypogastric plexus. At present there are no data that define optimal doses for PDE5i. Overall the efficacy of PDE5i and the likelihood of maintaining erectile function after ED causing cancer treatments appears to depend on the patient's age, preoperative erectile function, nerve-sparing surgery and the skill of the surgeon. At our institution, patients are typically started on tadalafil 5 mg daily as soon as it is medically safe post surgery or radiation. Patients are encouraged to trial higher doses of tadalafil or sildenafil intermittently with a minority being able to use PDE5i successfully for penetrative intercourse long term

The concept of applying a device over the penis and creating an artifial erection was first documended in 1874 and is currently achieved by the use of a vacuum erection device (VED) [29]. The purpose of a VED in the penile rehabilitation setting is to overcome the consequence of neurovascular injury by directly dilating the cavernosal arteries and veins and thus preventing fibrosis of the cavernosal muscle [30]. Most notably, it has been shown to help preserve pre-operative penile length [31]. Dalkin et al showed that 97% of men who used VED as instructed were able to maintain their preoperative stretched penile length. Early use of VED (defined as 4 weeks post op) vs. control (6 months post op) showed that the former group had higher IIEF scores at 3 and 6 month post use compared to the latter group, highlighting the notion that early VED use can lead to earlier recovery of sexual function [32]. Contradindications to the use of VED are priapism or other disorders that could lead to intermittent priapism. Concurrent blood thinning product use are relative contraindications. It is our experience that outside of the penile rehabilitation protocol, only a minority of patients use VED as a single therapy long term.

Penile intracavernosal injection (ICI) was first described in 1982 by Drs. Virag and Brindley using papaverine and phenoxybenzamine, respectively [33,34]. In the United States, different combinations of medications are available in the form of erectogenic injectable agents. Alprostadil, a synthetic form of prostaglandin E1, binds to PGE1 receptors and leads to smooth muscle relaxation and perfusion of cavernosal sinusoids. It is FDA approved for monotherapy in the treatment of ED.

Another 2 medications typically used in penile injection formulations are papaverine (a non-selective phosphodiesterase enzyme type 5 inhibitor) and phentolamine (a non-selective alpha-adrenergic antagonist). Bimix is a combined papaverine and phentolamine solution, whereas Trimix consists of Bimix components and alprostadil combined. ICI in any formulation represents a viable option for penile rehabilitation after ED causing cancer treatments given randomized controlled trials have shown increases in recovery rates of spontaneous erections after nerve-sparing radical retropubic prostatectomy and preservation of penile length [35]. However, it should be noted that ICI has not been studied in the setting of penile rehabilitation after other cancer treatments. Because there is a risk of priapism, proper patient education is paramount. The attrition rates are the greatest within 3–6 months of initiation due to pain,

fibrosis, anxiety, and/or lack of sexual partner [36-38]. In our experience, the use of ICI is essential in men with a significant decline in erections after cancer treatments who desire a reliable and potent erectogenic agent that will lead to a "functional" erection soon after their cancer treatment. ICIs are contradicated for use in men who have known allergies to its constituents and in those with medical predisposition for priapism.

Intraurethral alprostadil represents another form of ED treatment that has been utilized in penile rehabilitation protocols. Prospective observational studies have been conducted showing its use has led to enhanced recovery of erections after prostatectomy [39]. Unfortunately, this modality is not only expensive, but also has poor response rates even in those who have not had cancer treatments. Thus, in our experience, very few patients utilize this option.

Of all the treatment modalities, penile implants represent the most invasive option as it requires surgery under anesthesia. Of the complications associated with penile implants, the most devastating for both patient and physician is infection. Luckily changes in implant design over the last decade have led to infection rates lower than 1% in patients without significant comorbid conditions [40]. However, penile implants are known to have extremely high satisfaction rates [41]. Post cancer treatment, it is our experience that patients will typically wait at least 2 years before electing a penile implant given the timeline of erectile recovery as extrapolated from the post prostatectomy data cited previously. However, it should be noted that this treatment option is not well known in certain regions and election of this treatment may depend on provider and patient cultural factors. The 2018 American Urological Association guidelines for ED states that all no-contraindicated treatment options be discussed with the patient during the initial consultation, including penile implant surgery. Thus, when counseling patients it is important to take into account their potential for erectile function recovery after cancer treatment to guide them on decision making regarding the timing and choice of penile implant surgery.

3.2. Testosterone deficiency syndrome treatment

Any significant damage to the hypothalamic pituitary gonadal axis caused by cancer treatments can lead to testosterone deficiency syndrome (TDS). TDS can be a result of primary testicular failure (e.g., such as that caused by bilateral orchiectomy) or hypogonadotropic hypogonadism leading to a loss of luteininzing hormone signaling of the Leydig cells inside the testicles [42]. It may also be incidentally detected after routine care for ED after treatments such as prostatectomy.

There is no exact laboratory or clinical finding to define TDS but many use a constellation of symptoms (e.g., loss of muscle strength, libido, memory, vitality) and a laboratory value (generally total testosterone). The total testosterone cutoff of <=300ng/dL is often utilized to support a diagnosis of TDS, measured on 2 separate occasions. This level has been shown to be the 5th percentile among healthy non-obese patients between 19 and 39 years old [43].

Once the diagnosis is established, a clinician then has several modalities available to address TDS. First, patients must be counseled on the short and long term side effects of testosterone. Although controversial in methodology, 1 prominent study associated testosterone replacement with increased rates of myocardial infarction and stroke in a population of men with history of coronary angiography [44]. However, other studies of equal quality have not made this association and in fact have presented opposite results [45]. It is also important to discuss the expected benefit of testosterone replacement with most contemporary literature suggesting improvemenet in sexual function, particularly libido, and improved bone mineral density [46]. Lastly before initiating testosterone replacement one must advise patients of absolute and relative contraindications including: history of breast or prostate cancer, those planning fertility in the near future, PSA >4 ng/ml, elevated hematocrit, untreated severe obstructed sleep apnea, uncontrolled heart failure, myocardial infarction, or stroke within the last 6 months or thrombophilia [47].

Options for testosterone replacement include: transdermal, injection, intra-nasal, and implantable. A contemporary practical guide on testosterone replacement is referenced below [48]. Post cancer treatment critical considerations include avoiding the promotion of the patient's baseline cancer, especially if there is concern it has not been completely eradicated (e.g., prostate), and the increased risk for thrombotic complications in patients with oncologic histories.

3.3. Ejaculatory complaints

Anejaculation is defined as the inability to ejaculate. Surgical etiologies include retroperitoneal lymphadenectomy, aortoiliac and colorectal surgeries [49]. The first step in treating a patient with anejaculation involves the collection of a post ejaculatory urinalysis to differentiate retrograde ejaculation from failure of emission. Treatment then depends as to whether the patient is seeking fertility treatment. Ideally, patients at risk of developing post cancer treatment anejaculation would have provided a semen specimen for cryopreservation prior. Treatment options include medications such as alpha-1 adrenergic agonists (e.g., midodrine, pseudonephrine) for patients with retrograde ejaculation in an attempt to promote antegrade ejaculation. It should be noted that these treatments are known for their limited efficacy and not considered to be a reliable therapy [50,51]. Failure of emission is much more difficult to treat as it typically requires attempts at electroejaculation or surgical testicular sperm extraction in those seeking fertility treatment.

4. Conclusion

Although commonly overlooked, treatment of male sexual dysfunction after cancer treatment can significantly improve a patients quality of life. For patients with a primary complaint of ED, it has been shown that to optimize recovery of erectile capacity, while preserving penile length and girth, a penile rehabilitation protocol involving PDE5i, VED, ICI, or a combination is likely advantageous. This protocol is likely beneficial during the recovery period that is estimated to be around 2 years for both surgical and radiation pelvic treatments. At our institution a common rehabilitation protocol involves the used of daily tadalafil 5mg and either VED or ICI to obtain maximally rigid erections at least 3 times weekly. Treating hypogonadism is more complex especially in the setting of treatment of androgen sensitive cancers such as prostate cancer. Furthermore, although testosterone replacement has been shown to improve all aspects of sexual function, its positive effect on erections is rarely enough to lead to satisfactory erections given the severity of the mechanisms leading to ED after cancer treatment. Thus, it is difficult to recommend screening for low testosterone in patients presenting solely for post cancer treatment ED although the American Urological Association recommends screening for low testosterone in men with ED in general. Testosterone replacement is less ambiguous in the setting of ablative procedures to the testicles or pituitiary gland where testosterone replacement is essential to maintain quality of life due to extremely low serum levels. Lastly, anejaculation after cancer treatments is typically not successfully or reliably treated due to the mechanism and severity of sympathetic nerve injury. Thus in patients of fertile age it is imperative to promote semen cryopreservation prior to cancer treatments that may injure nerve fibers essential for the ejaculatory response.

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