Review Article

Pharmacologic and surgical therapies for sexual dysfunction in male cancer survivors

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Abstract: The recent recognition that many men experience sexual dysfunction following their diagnosis and treatment of genitourinary cancers, has led to the development multiple varied strategies that attempt to restore or preserve that function. In this manuscript we review the understanding of why it happens, highlight novel management strategies and discuss the concept of penile rehabilitation (PR) following prostate cancer (PCa) treatment, glans preserving strategies among men diagnosed with penile cancer and address the controversial issue of testosterone therapy in men with PCa.

Keywords: Sexual dysfunction; treatment modalities; cancer survivors

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Introduction and classification

Despite rapid advances in diagnosis and therapeutics over the past decade, cancer remains a major public health concern worldwide. The negative quality of life (QoL) impact of cancer and its treatment on sexual function has become more important as greater survival rates and recognition of its impact have been reported (1). Importantly for the clinician, even cancers that do not directly involve sexual organs can result in sexual dysfunction as a consequence of the adverse effects of multi-modal treatment. Cancer related sexual dysfunction in this population of male cancer patients includes erectile dysfunction (ED), structural changes within the penis, ejaculatory dysfunction and hypogonadism among many others (2). While we recognize that additional and important sexual dysfunctions such as climaturia, penile deformities, ejaculatory dysfunction and other concerns develop, given the wide scope of these issues we have limited our discussion to those areas where there exists adequate literature to support therapeutic conclusions.

Materials and methods

A literature search for original and review articles published in the English language was performed using a PubMed database ending October 2014. Search keywords were prostate cancer, bladder cancer, penile cancer, testicular cancer, male cancer survivors, male genital cancer, sexual dysfunction, treatment male cancer survivors, prostate cancer treatment, radical prostatectomy (RP), erectile dysfunction (ED), penile deformities, hypogonadism, ejaculation, orgasmic. The selected articles were reviewed by the authors and their findings/conclusions incorporated into the manuscript.

Prostate cancer (PCa)

PCa remains the most common solid organ nondermatologic cancer in men in the USA. It is estimated that there are nearly 2.8 million men living with a history of PCa in the USA, and more than 90% of all PCas are discovered in the local or regional stages, for which the 5-year relative survival rate approaches 100% (3). Therefore, preservation of continence and erectile function (EF) two factors contributing to long term QoL in this population, are among the most significant interests of patients with local PCa.

Men with PCa often struggle with sexual dysfunction, both before and after treatment. The rates of sexual dysfunction after treatment are quite high despite the development of minimally invasive technology, evolving surgical techniques and a greater understanding of the

anatomy of the pelvis. Following PCa treatment, 70% of men complain of worsening sexual function, which is frequently attributed to RP or radiation therapy (XRT) (4).

Male sexual dysfunction after PCa treatment is truly a diffuse clinical symptom complex, but for simplicity is often divided into three groups: (I) ED; (II) penile deformities; and (III) ejaculatory and orgasmic dysfunctions.

Erectile dysfunction (ED)

The true incidence of ED after PCa therapy is unknown. The contemporary literature reports rates of ED after RP to be around 60-70%, with some robotic and laparoscopic reports citing rates as low as 5-10%. Consensus has been reached on risk factors which include: patients age, preoperative EF status, comorbidities (diabetes, hypertension, hypercholesterolemia), surgical technique (nerves sparing) (5-7). ED after RP is most often attributed to neuronal and/or vascular injury to the cavernous neurovascular bundle at the time of surgery. Subsequent neuropraxia, inflammation and ischemia result in failure of spontaneous erections, which can lead to persistent hypoxia, cavernous smooth muscle apoptosis and ultimately corporal fibrosis. Controversial data exists which support early intervention and penile rehabilitation (PR) strategies attempting to prevent these pathophysiologic changes from becoming established and irreversible (8-10). Age and normal preoperative sexual function parameters emerged as independent determinants of patients' desire to preserve postoperative sexual functioning (11). Briganti *et al*. recently reported a preoperative risk stratification tool aimed to assess the probability of EF recovery after open bilateral nerve-sparing RP (BNSRP), using cardiac risk factors, age and EF as determinants. The resulting tool was able to stratify patients into three groups according to the relative preoperative risk of post-RP ED: low (age ≤65 years, IIEF-EF ≥26, CCI ≤1), intermediate (age 66-69 years or IIEF-EF 11-25, CCI ≤1), and high risk (age ≥70 years or IIEF-EF ≤10 or CCI ≥2). According to the risk-group stratification at 12 months post-operative, EF recovery rate was 82%, 57% and 29% in the low-risk, in the intermediate-risk and in the high-risk group, respectively (P<0.001) (12).

Interestingly, controversy exists concerning another parameter that has been widely reported to affect the rate of post-prostatectomy ED. Given the rapid recent acceptance of minimally invasive approaches to RP, the surgical approach such as open RP (ORP), laparoscopic RP (LRP) or robotic RP (RALP) has been studied in terms of EF outcomes. Tal *et al*. reported that the rate of EF recovery found in open, laparoscopic and robotic RP at 57%, 58% and 73% respectively (13). A cumulative meta-analysis of studies reporting EF in preoperatively potent patients, demonstrated a range of potency rates after LRP *vs*. ORP *vs*. RALP at 48 months were 58-74% and 49-74% and 60-100% respectively (14). Moreover RALP also seems to promote a more rapid EF recovery as compared with ORP and LRP (15). However, conflicting data exists on this topic and no clear statement can be made at this time, clearly demonstrating that robotic compared to laparoscopic or open is truly superior with respect to erectile preservation at this time. There are need randomized controlled study for accurate results (16).

Potvedin *et al*. reported that the outcomes of intrafascial *vs*. interfascial BNSRP techniques for RARP. The recovery rates of EF at 3, 6, and 9 months in the intrafascial group were 24%, 82%, and 91%, respectively, whereas in the interfascial group, they were 17%, 44%, and 67%, respectively. However, the intrafascial technique was associated with higher positive surgical margins rates in patients with pT3 disease (17). Xylinas *et al*. showed that the robot-assisted intrafascial approach provided early satisfactory functional results with respect to postoperative potency (18).

Consequently, preoperative EF appears to be the best independent predictor of postoperative EF, with age, nerve sparing technique and cardiac risk factors also contributing to recovery prediction.

XRT-induced ED is thought to result from neurovascular bundle injury and is related to the amount of radiation given near the penile bulb (19). Two recent prospective trials showed an incidence of ED in 30-40% of the patients treated with external beam XRT (EBRT). Prospective studies have reported an increase of ED between 1 and 2 years after radiotherapy (RT), whereas ED rates did not seem to change after 3 years (20,21). The PCa outcomes study (PCOS) demonstrated that the actual rates of ED between RP and radiation groups are similar at 15 years post treatment. The results showed that 87.0% of patients in the prostatectomy group and 93.9% of patients in the RT group reported an inability to achieve an erection sufficient for intercourse (22,23).

Recent data on brachytherapy indicates that it may provide better preservation of EF compared with EBRT alone or in combination with hormone therapy (24). Vascular comorbidities may have a significant role in ED after XRT. Wang *et al*. recently reported data from 732 patients who treated for CaP with XRT. Patients with three

vascular comorbidities were almost twice as likely (75%) to develop ED at 4 years after XRT, compared with patients with no vascular comorbidities (44%) (25).

Penile deformities (penile length loss and curvature)

Penile shortening (PS) and Peyronie's disease (PD) has been reported after RP. Several studies have shown that penile length decreases after RP, however rates of PS varied between 0-55% depending on whether a subjective or objective method was used for evaluation and on what cutoff value is used to define PS (26-29).

The pathophysiology of PS is clearly unknown. A number of mechanisms have been proposed and include anatomic alterations, neural damage, sympathetic nervous system over activity and histological alterations such as apoptosis (30). PS can be divided into two groups; early phase PS which occurs immediately after RP related to neural damage and sympathetic hyperactivity and late phase PS associated with histological alterations as well as fibrotic accumulation (31). Non-nerve-sparing surgery and ED have repeatedly been shown to be associated with loss of penile length after RP. Contemporary theories place hypoxia and cavernosal smooth muscle apoptosis as the most culpable cause for this length and girth loss. Strategies to reduce length loss and preserve function attempt to mitigate the hypoxia largely through return of early erections with injection therapy or use of PDE-5 inhibitors (PDE5Is) (32-34).

The first long-term prospective study on PS was published by Gontero *et al*. in 2007. They reported that PS after RP peaks at the time of catheter removal and it continues for at least 1 year. Longer preoperative stretched penile length, NS surgery and recovery of EF appeared to be independent protective factors on penile length loss at 1 year (35). Frey *et al*. recently reported that 47% of patients had penile length loss in excess of 1 cm. Patients reported a subjective length loss between 1 and 3 cm, 3 and 5 cm and more than 5 cm was stated at 33%, 11% and 1% respectively. This study showed that a high BMI increased the risk of PS. This finding may be caused by the prepubic fat pad covering the proximal part of the penis, which can be misinterpreted as penile length loss (36). In another study, Briganti *et al*. found no changes in penile length 6 months after NSRP in patients with normal EF before surgery when precise measurements were performed. When the same patients were asked to subjectively estimate if their penis had shortened after the operation, 14% answered affirmatively (26). As a result NS and postoperative EF, strongly correlate with preservation of penile length.

The prevalence of PD (penile curvature) in the normal population is not well established, but prevalence estimates of 3.7-7.1% are widely felt to be reasonable (37). The incidence of penile PD among men with PCa is higher than the normal population and Tal *et al*. found that incidence of PD after RP was 16.7% in 1,161 patients (38). In another study the patients who were referred for ED after RP were asked if they had noticed an altered penile curvature or narrowing. The rate of patients who had clinical fibrosis on their penises was 41% and 24% of those patients having a deformity that resembled a waistband, and 93% patients who had measurable curvatures. Of the patients with clinical fibrosis, 70% reported a subjective shortening of the penis with an average length loss of 24% (39). The pathogenesis of PD is still not clear but some authors have suggested that repetitive micro-trauma of the penile tissue during sexual intercourse can induce PD (31).

Ejaculatory and orgasmic dysfunctions

Although the exact cause of orgasmic dysfunction after RP is unknown, it is clear that removal of the prostate and the seminal vesicles may in itself impact orgasmic pleasure as ejaculation is no longer possible. In addition, the correlation between orgasmic function and postoperative potency, nerve sparing, and urinary control implies that nerve damage may play a role (40).

In a prospective study, Le *et al*. (n=620) showed that the percentage of patients with a "good" or "very good" ability to achieve orgasm was reduced from 65% at baseline to between 25% and 30% postoperatively. Age <65 years, higher levels of education, NS surgery, lack of comorbidities and good EF after surgery were positively correlated with the ability to reach orgasm (41). On the other hand, Tewari *et al*. found that 80% of patients who underwent RP patients had normal orgasmic function (42). This might be because of a high rate of nerve sparing and good postoperative EF in the study. Predictors of good orgasmic function were age <60 years and nerve-sparing surgery (P<0.001). The latest study on orgasmic dysfunction after RP was performed by Frey *et al*. In their study the rate of orgasmic alteration after RP was 5% anorgasmia, 60% reported decreased intensity of their orgasms and for unknown reasons, 6% of the patients in the sexually active group noted an increase in the intensity of their orgasms. The remaining 29% reported no change in their orgasm intensity (36).

Anejaculation after RT is infrequently reported, and the

published data on this issue are scarce. Sullivan *et al*. recently evaluated the effect of RT on ejaculation in patients with PCA. In their study 16%, 69% and 89% of patients reported to have lost the ability to ejaculate in an antegrade fashion after prostate RT at 1, 3, and 5 years respectively. They have found that Age >65 yrs, androgen deprivation therapy (ADT), prostate <40 g, each year post-RT and dose >100 Gy were independent risk factor for anejaculation (43).

Penile rehabilitation (PR) after prostate cancer (PCa) therapy

The optimal treatment modality or rehabilitation strategy for ED after PCA therapy does not exist today. According to a survey by International Society for Sexual Medicine (ISSM), the practice of erectile rehabilitation is commonly performed in the clinical setting and up to 87% of these specialized sexual medicine physicians utilize some form of erectile rehabilitation. The survey showed that 95% used PDE5Is, 75% used intra corporeal injection (ICI), 30% used vacuum device, and 9.9% used intraurethral prostaglandin (44). Since the survey was conducted among ISSM members, it may not accurately reflect the tendencies of the whole urology community. The first clinical study in support of PR was reported by Montorsi *et al*., who showed that intracorporeal alprostadil injection positive effected EF after RP (45). Currently, there are several treatments modalities for ED after PCa therapy such as PDE5Is (sildenafil, tadalafil, vardenafil, udenafil, avanafil), ICIs, vacum erection device (VED) and intraurethral alprostadil (IUA).

PDE-5 inhibitors (PDE5Is) (sildenafil, tadalafil, vardenafil, udenafil, avanafil)

PDE5Is facilitate an erection by locally increasing cGMP levels in the penile tissues through inhibition of metabolism when neural function exists. With adequate preservation of cavernous nerves, PDE5Is reduce cGMP metabolism and thereby increase its concentration, which promotes corporal smooth muscle relaxation and enhanced blood flow. Several animal studies suggests that neuropraxia after RP may lead to hypoxia, apoptosis, venous leak and fibrosis of the corpora cavernosa. The central theme of many rehabilitative strategies is early PDE5Is administration which may reduce hypoxia and the subsequent cascade of events outlined above (46,47). There is no standard regimen for PR, however PDE5Is are widely recommended as first-line treatment for ED after PCa therapy. Typically, response rates to PDE5Is improve as time passes after RP and rates of response range widely from 15% to 80% (48,49).

The first randomized and placebo-controlled trials that assessed the clinical effects of PDE5Is in PR were conducted by Padma-Nathan *et al*. Their study randomized 76 patients after NSRP to double-blind sildenafil (50 or 100 mg) or placebo nightly for 9 months and reported that nightly sildenafil markedly increased the return of normal spontaneous erections (27% and 4% in the placebo group) (50). The second study was a multi-center, placebo-controlled trial by Montorsi *et al*. This study enrolled over 600 patients for a double blind treatment period followed by a washout period and then an open label phase with vardenafil on demand. The patients in their post-prostatectomy period were randomly assigned to use daily vardenafil, on-demand vardenafil, or placebo control. IIEF scores greater than 22 were reported in 24.8%, 32%, and 48.2% of patients for placebo, vardenafil daily and on-demand dosing, at the end double blind phase respectively. This trial showed that the efficacy of on-demand or daily PDE5Is after prostatectomy were similar in terms of EF. The final evaluation of this trial demonstrated efficacy of PDE5Is when taken on-demand in this population of men post RRP, but not a true rehabilitative effect, given that no significant potency advantage was measured among the groups at the end of the open label phase (51).

To date, there is no consensus on the appropriate PDE5Is agent, dose or timing, for post-RP erectile rehabilitation. Pavlovich *et al*. investigated the effect of nightly or on demand 50 sildenafil after NSRP in a double-blind, randomized controlled trial that enrolled a total of 100 men who had IIEF-EF >26, aged <65 years. The patients were randomized to either nightly sildenafil group or the on-demand placebo (nightly sildenafil group), or on-demand sildenafil and nightly placebo (on-demand sildenafil group; maximum on-demand dose six tablets/month) for 12 months. The authors found no significant differences in IIEF-EF scores between nightly and on-demand treatment after RP (52).

Another well designed study was published by Montorsi *et al*. in 2014. This trial investigated the efficacy of tadalafil 5 mg once daily and tadalafil 20 mg on demand versus placebo after RP. The proportion of patients reaching the IIEF-EF >22 was significantly higher in the tadalafil once daily group than in the placebo group while the comparison between tadalafil on demand and placebo was not statistically significant at 9 months after surgery. At 10.5 months, the time point in which the efficacy of spontaneous EF without drug was assessed and was the primary endpoint showed no

statistical difference among the groups (53).

Interestingly however, an important secondary endpoint defining penile length preservation, an index of cavernous smooth muscle preservation, a goal of rehabilitation was found to be statistically superior at 13.5 months post-op in the daily tadalafil group compared to the on-demand group. Additionally at 13.5 months clinically and statistically greater responses were measured in the daily tadalafil arm for SEP question 3. These data indicate that early use of daily tadalafil may preserve cavernous smooth muscle during the critical early phase and results in enhanced PDE5I response at later time points (52). Mulhall *et al*. investigated the efficacy of avanafil 100 mg, and avanafil 200 mg for the treatment ED after BNSRP. Their study showed that patients randomized to 100 and 200 mg avanafil had an improvement in IIEF-EF domain score of 3.6 and 5.2, respectively, compared with 0.1 for placebo (54).

Timing of rehabilitation and choice of treatment remains a major clinical controversy. Several animal studies have clearly shown that early treatment is critical for endothelial and smooth muscle protection and reduction of corporal fibrosis. The current literature suggests that PR should be started as early as possible, indeed should be begin after the day of surgery if possible (55). This means that PDE5Is may be most effective if initiated as early as the diagnosis and surgery date confirmed. Moreover, Moskovic *et al*. instructed their patients to take sildenafil 25 mg nightly as well as to use alprostadil 250 µg urethral suppositories three times per week, beginning one week prior to surgery (56).

The effect of PDE5Is on orgasmic function after RP was investigated by Nehra. In this study, significant improvements in orgasmic function were found with doses of both 10 and 20 mg vardenafil compared with placebo. These improvements were accompanied by significant improvements in satisfaction with EF (P<0.0001 for both groups). In this context, it seems likely that the improvements seen in orgasmic function were caused by improvements in EF (57).

PDE5Is have proved effective in the treatment of ED after RT for PCa. There are numerous well designed randomized controlled trials that address treatment ED after RT. One prospective, placebo controlled study compared tadalafil with placebo taken on demand in patients with PCa after RT treatment. They found that 67% of the patients reported an improvement in EF with tadalafil compared with only 20% in the placebo group (P≤0.0001) (58). Pisansky *et al*. published the effect of tadalafil 5 mg compared to placebo on PCA with ED after XRT. The results for the primary endpoint demonstrated retention of EF in 79% of patients in the tadalafil group *vs*. 74% in the placebo group (P=0.49). The study was not powered to detect a 20% difference between the groups (59). In contrast to these findings, Zelefsky *et al*. designed a similar study where patients received daily sildenafil (50 mg) or placebo. They found that 81.6% of patients on daily sildenafil and 56.0% of those on placebo achieved a functional erection with or without ED medication at 24 months (P<0.045) (60).

Intracavernosal injection (ICI)

ICI with alprostadil alone or in combination with papaverine or phentolamine is an effective option in men who respond poorly to PDE5Is (61). ICIs induced erections result in enhanced cavernosal oxygenation and penile stretch, both of which are known to be protective of erectile tissue structure and function (62). ICI post prostatectomy rehabilitation success rate was investigated by Prabhu *et al*. on 135 men through 8 years and only 44% of those men declared some level of satisfaction as well as pre-operative erectile status was independently associated with use of ICI (63).

Raina *et al*. reported that 68% of patients had sufficient erection for sexual intercourse after ICI therapy. Long-term (>3 years) data have revealed high dropout rates (50%), most often attributed to discomfort, fear, or inconvenience associated with injection (64). Nelson *et al*. investigated injection anxiety and pain in men who used ICI for 4 months after radical pelvic surgery. The study showed that the frequency of ICI use was 29% week, 26% 1/week, 40% 2/week, and 5% 3/week, whereas the IIEF-EF score increased 8 to 22 compared to baseline. They found that injection anxiety on average, was moderately high (score =5.7 on 0-10 point scale) at the first injection training and this significantly decreased at the 4-month follow-up (score =4.1). The result of their study showed that despite the passage of time the rate of anxiety score not changed (65). Moreover, Coombs *et al*. demonstrated RP as an independent risk factor of ICI therapy failure (66).

Vacuum erection device (VED)

The VED is the only non-pharmacologic strategy among the choices for men who do not respond to PDE5Is or for those who have a contraindication (67). Numerous publications have suggested that VED therapy improves EF in 84-95% of patients (68,69). VED therapy uses negative

pressure to distend the corporal sinusoids and to increase blood inflow to the penis. Lin *et al*. found that the mean O_2 saturation of corporeal blood immediately after VED-induced erection was 88.25%. Of the blood in a VED-induced erection, 62% was arterial, and 38% was venous in origin in rats (70). Welliver *et al*. investigated the effect of VED therapy on the penile oxygen concentration in 20 men in a pilot study. They measured penile oxygen saturation before and after VED therapy. They showed that use of VED significantly increased 20% and 55% in both glanular and corporal oximetry compared with baseline respectively (71). Köhler *et al*. designed a pilot study and randomized study to compare early (1 month after surgery) to late (6 months after surgery) use of VED. The results showed that the early use of VED for rehabilitation significantly improves the IIEF-EF scores and preserves penile length compared with control group (EF score: 12.4 *vs*. 3.0) after six months following surgery. However patients did not have adequate erection for spontaneous intercourse at the end of study in either group (72). In a similar study, by Raina *et al*., patients were randomized as either daily VED users or controls for a 9 month period. Although the reduction in penile length and girth were reported in 23% (14) of the VED users and 63% of controls, no statistical difference was found between the two groups (17-29%) in terms of erection adequate for successful intercourse (73).

Penile prostheses

The surgical placement of a penile prosthesis is widely used for ED, particularly in men unresponsive to medical management. Interestingly, according to the SEER-Medicare database only 0.8% of patients who chose a penile implant were after PCa therapy (74). In another study by Menard *et al*. investigating 400 post RP patients who underwent penile prosthesis, while complication rates were less than 5% for infection, revision, mechanical failure, the overall satisfaction rate was reported as 86.1%. In addition, these patients were compared with vasculogenic ED patients who underwent penile prosthesis placement. No significant difference was detected in complications (mechanical failure, infection) or surgical satisfaction rates (86% *vs*. 90%) (75). While penile prosthesis was shown to be superior to PDE5Is in terms of overall improvement at 12, 18, 24 months after the surgery by Megas *et al*., function and satisfaction scores were similar in both groups (76).

Recently an alternative reservoir placement has been suggested for patients with ED and radical pelvic surgery history such as prostatectomy, cystectomy or colon surgery. To date the conventional retropubic reservoir placement has been posterior of transversalis fascia (PTF). Despite the rarity of complications, very grave complications such as vascular or bladder injury may happen during this approach (77). Stember *et al*. investigated the complications of reservoir placement between posterior or anterior to the transversalis fascia (ATF) and demonstrated that no injuries to major blood vessels or bowel occurred in neither of these approaches (78). In a similar study published by Karpman *et al*., AMS 700 conceal or spherical reservoir was used in 747 patients in a prospective, multicenter study. The authors compared satisfaction and complications rates of PTF (n=572) and ATF (n=177) groups and showed that ATF placement approach was as safe and highly satisfactory as PTF (79).

Hypogonadism and testosterone replacement

Hypogonadism is present in more than 20% of men after RP and is often worsened by ADT. Due to prolonged absence of erections, ADT may lead to corporal fibrosis and decreased penile length (80). Testosterone replacement therapy (TRT) in hypogonadal CaP survivors is controversial because TRT may increase the risk of CaP recurrence. However, current evidence supports the safe use of TRT in hypogonadal CaP survivors. Landau *et al*. reported that PCa recurrence was insignificant in those who underwent TRT to treat hypogonadism that occurs before and after RP (81). Most notably, Pastuszak *et al*. recently reported on the use of TRT in 103 hypogonadal men following RP for CaP. Although TRT use did result in slight PSA elevation, there was no associated increase in cancer recurrence at a median of 27 months of follow-up (82).

Bladder cancer

Bladder cancer, the fifth most common cancer in men in the United States, typically presents as a superficial transitional cell carcinoma that is locally resectable and curable. However, in a small minority of men their cancer is muscle invasive requiring more aggressive treatment with a greater risk of sexual dysfunction. Therapeutic options for this population include surgery, radiation and chemotherapy, usually associated with radical cystectomy with urinary diversion (83). The long-term prognosis for those who undergo radical cystectomy continues to improve with advances in technique and earlier diagnosis, regrettably rates of ED and sexual QoL loss remains high (84).

The etiology of ED after radical cystectomy (cystoprostatectomy) is strongly correlated with the peroperative injury to neurovascular bundle. A large number of animal models exit describing the type and extent of this injury which has been classified as traction, percussive, thermal, transection and devascularization injury. Thus, treatment is often associated with the loss of sexual function, the most impactful and frequent of which is ED (85). The high prevalence of post-surgical ED has driven researchers to consider whether NS cystectomy is a safe alternative in the treatment of bladder cancer. Several studies have reported accepted rates of potency after nerve sparing radical cystectomy that range from 42% to 71% (86-88). NS surgery is associated with greater rates of positive outcomes in EF. Most men experience a temporary decrease in function immediately following surgery, which is then followed by a steady return to function (89). Numerous studies showed that age is an important predictive factor of ED after nerve sparing radical cystectomy. Schoenberg *et al*. reported the potency rates of 101 patients after nerve sparing radical cystectomy were 62% in men 49 years and younger and 20% in men 70-79 years old (87). Asgari *et al*. recently investigated the effects of urinary diversion type on sexual function in 41 patients who underwent ileal conduit urinary diversion and 40 patients with orthotropic ileal neobladder substitution who underwent non-nerve sparing radical cystectomy. The baseline total EF scores of the patients were similar for both groups (26.74 *vs*. 26.70). At 12-month following surgery, the mean total EF scores were 5.52±1.24, and 15.60±1.61, in ileal conduit and ileal neobladder groups, respectively (P=0.001). At the post first year, 14 (35.0%) of the ileal neobladder patients were able to achieve vaginal penetration and maintain their erection for intercourse, whereas this rate decreased to 4 (9.8%) in patients with ileal conduit (P=0.006). This study demonstrated the superiority of patients with orthotopic ileal neobladder substitutes to the ones with ileal conduits in terms of EF (90).

Prostate preservation during radical cystectomy provides better postoperative EF. Basiri *et al*. randomized 24 radical cystectomy patients with initial high IIEF scores (>20) into a prostate sparing group (12 patients) and non-sparing group (12 patients). Group 1 [12] had prostate sparing and group 2 [12] had non-sparing cystectomy. After a follow-up time of 39 months, 2 and 10 of the patients lost their erections after the operations in groups 1 and 2 respectively. In addition mean IIEF scores were 19.8 and 5.7 in former and latter groups respectively. This study showed that the patients who underwent prostate sparing surgery had better EF when compared to non-sparing patients (91).

As a result, PR for ED after radical cystectomy is identical to the PCa survivor rehabilitation, PR should be started with PDE5Is as soon as possible after surgery. Early intervention is associated with better sexual functions and satisfaction rates in the light of current literature (92,93).

Penile cancer

Penile cancer is relatively rare (0.58/100,000 men) in the developed countries of the world. However, in some regions of Africa, South America and Asia the incidence of penile cancer can be up to five times higher (94). Penile cancer and its treatment can negative effect sexual function and intimacy, body image, urinary function mental health and QoL. Maddineni *et al*. reported that penile cancer treatment negatively affected well-being in up to 40% of patients with decreased sexual function in up to 60% (95).

Kieffer *et al*. have investigated the impact on QoL, after treatment for penile cancer in 90 patients, 54 with penile sparing surgery and 36 with partial penectomy. The authors found that men treated with penile sparing surgery scored significantly better than those who underwent partial penectomy on the orgasmic function scale. However, there was no statistically significant difference in EF, sexual desire, intercourse satisfaction or overall sexual satisfaction (96). Yang *et al*. recently published a similar study. The authors compared sexual performance between partial penectomy and glans preserving surgery in 135 patients. Patients treated with glans preserving surgery had better performance in all of the IIEF domains score. They also had significantly higher satisfaction (64.4% *vs*. 13.9%) and intercourse confidence (55.6% *vs*. 5.6%) compare to men who underwent partial penile amputation (97).

Recently, brachytherapy have been recommended for initial treatment of invasive T1, T2 and selected T3 penile cancers by consensus guideline (98). Delaunay *et al*. investigated the effect of brachytherapy on sexual function in 47 patients with penile cancer and cancer specific survival rates of 90.7% and 87.6%, were reported at 2 and 5 years respectively. They reported that 58.8% of patients had adequate sexuality after treatment and 47.3% stated that brachytherapy had not affected their sexuality and 15.8% of them had mild changes. Consequently, most patients stated that brachytherapy had little or no influenced on their sexual life (99).

Testicular cancer

Most testicular cancers are diagnosed early and approximately 70% of patients are diagnosed at a localized stage. Typically treatment of testicular cancer begins with inguinal orchiectomy. After inguinal orchiectomy, early stage seminomas are often treated with radiation (45%), however late-stage seminomas (65%) and non-seminomas germ cell tumors (NSGCT) are generally treated with chemotherapy especially at high stages of disease. The 5-year relative survival rates are 99.0% for tumors diagnosed at a localized disease (100).

ED has been reported in 12-40% of men treated for testicular cancer, regardless of cancer treatment method (101). The etiology of ED in these patients is multifactorial depends on how the patient were treated. Psychogenic ED may be attributable to changes in body image after orchiectomy, loss of sense of manhood after orchiectomy, reduced feelings of well-being and other psychosocial changes associated with cancer (102). Pühse *et al*. recently reported on the prevalence of sexual dysfunction in a group of 539 survivors of testicular cancer and found that 35% had reduced sexual desire, 42% had reduced sexual activity and ED was present in 32%, with three-quarters of the latter group having an impaired ability to maintain an erection during intercourse (103). Tal *et al*. investigated the pathogenesis of ED 12 months after the completion of therapy in 76 men with testicular cancer. The study population consisted of, 66% patients had seminoma and received XRT, 79% of had NSGCT and received chemotherapy, 18% underwent primary retroperitoneal lymph node dissection (RPLND) and 20% underwent post-chemotherapy RPLND. The authors found that a total of 26% of patients had total testosterone levels <300 ng/dL and 84% complained primarily of loss of erection-sustaining capability. None of patients had an abnormal Doppler ultrasonography (DUS) finding. Mean (SD) peak systolic and end-diastolic velocities were 48 [16] and 1.2 (2.2) cm/s, respectively. Moreover 88% of patients responded to PDE5Is use, with erections sufficient for penetration. This result suggests that ED in testicular cancer survivors is primarily non-vasculogenic (104).

Anejaculation may be observed in post-chemotherapy patients who underwent RPLND. The anejaculation rate of 7% was reported following nerve sparing RPLD (105). Hsiao *et al*. investigated the effects of pseudoephedrine therapy on patient anejaculation one year after post-chemotherapy RPLND. The anejaculation was a result of retrograde ejaculation or emission failure in 15% and 85% of cases respectively. None of patients with failure of emission responded pseudoephedrine therapy while 50% patients with retrograde ejaculation were responders for sperm retrieval with masturbation (106).

Conclusions

Sexual dysfunctions are common in male patients with cancer and have been shown to vary in intensity and frequency according to treatment modality, age, pre-existing sexual function and many other factors. Management of sexual dysfunction in PCa and bladder cancer survivors can be difficult, but various effective management options exist. The early intervention of rehabilitative strategies may prevent loss of penile length and increased EF score. Despite several preventive and therapeutic strategies being available, there is no evidenced-based specific recommendation on the optimal rehabilitation or treatment regimen at this time. PDE5Is, ICIs, using vacuum constriction devices, after bladder or PCa therapy, have been shown to be useful in achieving EF. The definitive strategy to restore natural erections in this population remains elusive but ongoing research continues to strive towards that goal. Finally penile prostheses should be suggested for the non-responders to medical therapy.

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Footnote

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