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Review article

Reviving intimacy: Penile rehabilitation strategies for men after prostate cancer treatment

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ABSTRACT

There have been considerable advances in the field of penile rehabilitation for upwards of 90% of men adversely affected by either short-term or long-term erectile dysfunction after definitive prostate cancer treatment. Despite the evolving landscape of treatment modalities for penile rehabilitation, there is a lack of consensus in the urologic community on the best therapies due to the level of evidence and efficacies of the current and emerging offerings. This review of current and next-generation interventions provides a practical approach to the myriad of data to make a better-informed decision based on the pathophysiology and highest-quality evidence available.

1. Introduction

Male sexual dysfunction after prostate cancer (PCa) treatment remains an enigma to the urologic community despite several advances in nerve-sparing surgical techniques, hypofractionated radiation, erectile pharmaceuticals, and apparatuses. Penile rehabilitation (PR) is defined as the use of any drug or device at or after radical prostatectomy (RP) or radiation to maximize recovery of erectile function (EF). The concept of PR has been discussed since the inception of the RP and has evolved over the last four decades as integral to PCa survivorship. PR aims to prevent corpus cavernosal smooth muscle structural alterations to maximize recovery of functional erections and return the patient to baseline preoperative EF. While erectile dysfunction (ED) is most targeted and discussed for PR, male sexual dysfunction can be categorized into hypogonadism, ejaculatory complaints, and penile shortening as well. This review will focus on PR for ED in its current state, future directions, and practice preferences within the global urologic community.

2. Overview of the mechanism of ED after cancer treatment

2.1. Pathophysiology of erectile dysfunction after prostatectomy and radiation

Several concepts regarding the pathophysiology of erections after PCa treatment must be understood to fully appreciate the mechanism behind PR interventions. Historically, ED after RP involves neural injury, vascular injury, and smooth muscle damage. The most well-studied intraoperative etiology of ED is a thermal injury to the cavernous nerves, yet Mullerad et al. demonstrated minor injuries such as prolonged traction with a Foley catheter and open exposure without direct insult can also cause the same effect.[1] This damage to the cavernous nerves initiates a cascade involving Wallerian degeneration resulting in disruption of nitric oxide (NO) release, the predominant mediator of erections.[2] NO stimulates guanylate cyclase in the penis, which in turn cleaves guanosine triphosphate into cyclic guanosine monophosphate (cGMP). Increased cGMP promotes protein-kinase-G-dependent smooth muscle relaxation via several downstream effectors.[3] The net result of smooth muscle relaxation is penile tumescence.

Detumescence is achieved via phosphodiesterase type 5 (PDE5), which is the enzyme primarily responsible for the degradation of cGMP in the penis and the inhibition of the NO cascade. Cavernous nerve injury (CNI) from unilateral or bilateral neurotomy results in fibrosis and apoptosis of the smooth muscle tissue in the corpora cavernosa (CC) due to increased reactive oxygen species, profibrotic

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factors, and hypoxia.[4] This damage to the smooth muscle and endothelium inhibits the critical mechanism of vaso-occlusion whereby blood is maintained in the penis and intracorporal pressure is increased to produce penile erection. Several studies have also demonstrated an alternative mechanism for postoperative arteriogenic ED which may be the transection of the accessory pudendal arteries (APAs) described in up to 75% of patients and could lead to penile hypoxia independent of CNI.[5] Thus, changes in compliance of erectile tissues lead to "venous leak," which is then compounded with neuropraxia resulting in the devastating net effect of ED.[6]

While prostatectomy is the highest risk of CNI, radiation-induced injury occurs via a similar molecular mechanism. Several studies showed radiation elevates reactive oxygen species from upregulation of NADPH oxidase activation resulting in chronic oxidative stress causing significant CNI and CC damage.[7-9] Many promising interventions using novel applications of molecules and immunomodulators in animal models have failed to demonstrate significant results in humans, including perioperative erythropoietin, tacrolimus, atorvastatin, and hyperbaric oxygenation.[10-13]

Less is studied regarding the central nervous system's regulation of erections. Of the known literature, there are psychogenic changes in erections, arousal, and psychosocial effects after definitive PCa treatment. One study identified activation of the cerebellar vermis, the bilateral extrastriate cortex, and the right orbitofrontal cortex, suggesting a role of cognition and emotion during erections induced by audiovisual sexual stimuli on positron emission tomography scan.[14] The detrimental impact of ED post-RP on a man's mental health and relationship with a partner is an evolving investigation warranting further study.[15]

3. Patient Selection and Preoperative Counseling

The preoperative assessment for patients planning to undergo RP is the foundation for PR. This baseline assessment not only documents the patient's preoperative EF as a parameter of general health but also evaluates both oncological and functional parameters. Once surgical and oncological risks are assessed, the decision to perform bilateral nerve-sparing radical prostatectomy (BNSRP) can be safely evaluated. Comorbidities such as cardiovascular diseases, diabetes mellitus (DM), and advanced patient age are critical to understanding the outcomes of both EF and overall recovery after surgery. There are several validated tools urologists may use to measure EF, including the Sexual Health Inventory for Men and the International Index of Erectile Function (IIEF), and risk stratification of comorbidities with the Charlson Comorbidity Index (CCI). A study by Rabbani et al. demonstrated the effect of patient age on the probability of EF recovery after surgery, showing rates of recovery of 70%, 45%, and 30% for patients $\leq$60, 60–65, and >65 years of age, respectively.[16] More recently, a study by Briganti et al. found patients after BNSRP with intermediate pre-operative ED risk, defined by age 66–69 years or IIEF-EF scores 11–25 and CCI $\leq$1, significantly benefited more from daily therapy with PDE5 inhibitors (PDE5i) compared with the on-demand PDE5i administration (74% vs. 52%, respectively).[17] Comparable efficacy of the two administration schedules was demonstrated between the low- and high-risk ED groups at 3 years. The 3-year EF recovery rates were 85%, 59%, and 37% for patients in the low, intermediate, and high-risk categories, respectively ($p < 0.001$).[17] In a cohort of 3,241 patients undergoing RALP, Kumar et al. demonstrated men $\geq$70 years old had significantly lower EF recovery rates than a matched subgroup of younger men (33.5% vs. 52.3%, respectively).[18] Similar to predictors of organic ED, Salomon et al. examined the overall burden of comorbidities and patient age, showing that body mass index, type 2 DM, and depression were significantly associated with baseline ED in candidates for RP[19] Thus, preoperative EF status is the main predictor of post-RP EF recovery. Understanding the baseline EF is essential to a complete preoperative assessment. According to a study by Kim et al., the optimal timing for obtaining an IIEF-5 questionnaire was before the prostate biopsy as opposed to one day before RALP, given the prebiopsy scores were in greater agreement with the results 1-month post-RALP.[20]

Setting realistic expectations of achieving preoperative EF after RP should be done in the preoperative visit. Whether or not these discussions are held and measured appropriately at all institutions is not clear per a study by Mulhall.[21] Redefining sexual and overall satisfaction post-RP may be feasible. This was demonstrated in a study by Briganti et al. involving a cohort of preoperatively fully potent (IIEF-EF $\geq$26) patients post-BNSRP assessing postoperative scores of intercourse satisfaction (IS) and overall satisfaction (OS).[22] After a mean follow-up of 2 years, patients with an IIEF-EF of 22–25 had comparable results in terms of IS and OS scores to those with an IIEF-EF $\geq$26. These data suggest IIEF-EF scores $\geq$22 could be a reliable benchmark for defining post-RP EF recovery and setting early realistic expectations critical to successful PR. A flowchart adapted from Capogrosso et al. [Fig. 1] demonstrates a practical preoperative patient assessment when engaging in shared decision-making for NSRP.

4. Penile Rehabilitation Interventions

4.1. Current State of Pharmacologic Therapy

4.1.1. Intracavernosal Injections

Inhibition of corporal and endothelial fibrosis after RP and radiation is critical to EF recovery, which was first initiated with intracavernosal injections (ICI) of alprostadil in 1997.[23] Initially discovered in a study by Moreland et al., prostaglandin E1 (PGE_1) was found to suppress TGF-β1 induced collagen synthesis in an in-vitro culture of human corpus cavernosum smooth muscle cells.[24] Based on this canonical study, Montorsi et al. demonstrated significantly more men post-BNSRP undergoing alprostadil injections

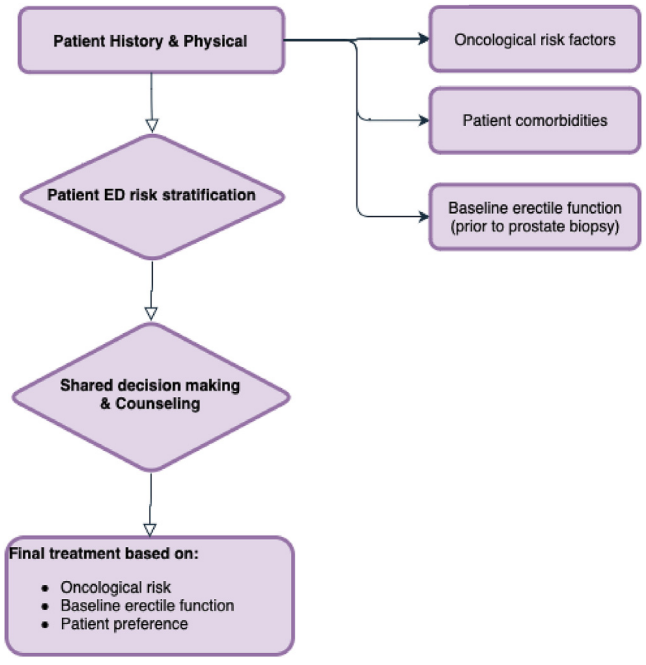

Fig. 1. Preoperative patient assessment flowchart
ED: erectile dysfunction.

three times weekly for 12 weeks reported spontaneous EF recovery sufficient for satisfactory sexual intercourse at 6 months, compared to unassisted controls (67% vs. 20%).[23] These early data were supported by animal models that were then translated into additional randomized clinical control trials (RCT) in humans using PDE5i. Each with its limitations, several RCTs and case-control studies shaped the current landscape of PR [Table 1].

To date, ICI with PGE_1 is the second most commonly prescribed monotherapy following Tadalafil and other PDE5is as first-line monotherapy worldwide.[25] Appropriate patient education about the application and adverse effects of ICI is vital due to the risk of priapism with a mean rate of 3–5.5% in various studies.[26] Despite the risk profile and coaching that is often needed for penile injections, the data show better patient satisfaction rates of up to 94% with minimal systemic side effects with ICI compared to oral PDE5i monotherapies.[26] However, attrition rates are the greatest within 3–6 months of initiation due to penile pain, fibrosis, anxiety, or lack of a sexual partner.[27] Alprostadil is the only FDA-approved ICI medication with an efficacy of up to 80% as monotherapy. Clinical guidelines also recommend combination therapies to potentiate a more vigorous response with "bimix" or "trimix," which may include alprostadil, papaverine, and phentolamine.

4.1.2. Intraurethral Suppositories

Intraurethral suppositories with alprostadil are also successful and used as an expensive alternative to ICI. In the two largest double-blind, parallel, placebo-controlled trials for intraurethral suppositories, the most frequently reported adverse effects include pain in the penis (36%), urethra (13%), testes (5%), or female partner vaginal burning (5.8%).[28] In practice, it is common to prescribe ICI for men with significant ED post-RP, especially without BNS, who desire a robust and rapid erectogenic agent. Attrition rates with ICI are greatest within 3–6 months of initiation due to pain, fibrosis, anxiety, or lack of a sexual partner.[27]

4.1.3. Oral Phosphodiesterase Type 5 Inhibitors

While almost all patients receive NSRP, oral PDE5-inhibitors remain the mainstay of PR today.[29,30] Four PDE5is are FDA approved in the United States: sildenafil, vardenafil, tadalafil, and avanafil. All have comparable efficacy and side effect profiles. Sildenafil and vardenafil have similar half-lives of 4 h, while tadalafil has the longest (17.5 h) and avanafil has the shortest (3 h). Vardenafil should be used with caution in patients with prolonged QT intervals. Several early RCTs studied the use of PDE5i on penile remodeling and preservation of CC compliance. The REACTT trial showed Tadalafil once daily was most effective on drug-assisted EF post-BNSRP men vs placebo (IIEF-EF: $p = 0.016$; Sexual Encounter Profile (SEP-3): $p = 0.019$).[31] However, during a 6-week drug-free washout (DFW), unassisted EF men decreased IIEF-EF and SEP-3 but continued to improve during open-label treatment with Tadalafil daily. At month 9, at the end of double-blind treatment (EDT), penile length loss was significantly reduced versus placebo in the tadalafil once daily group only ($p = 0.032$). These data along with other RCTs with similar results suggest a potential role for tadalafil once daily provided early after surgery in contributing to the recovery of EF after prostatectomy and preserving CC integrity.[32-36] A recent meta-analysis by Liu et al. demonstrated the use of PDE5-inhibitors only showed an increased patient response rate (OR = 2.161, $p = 0.00$) and IIEF score (SMD = 0.922, $p = 0.00$).[30] Although, after the PDE5i washout, there was no significant improvement in spontaneous EF regardless of administration schedule: daily or on-demand (OR = 1.027, $p = 0.61$).[30] Another recent systematic review and meta-analysis by Tain et al. evaluated short (≤6 months) and long-term (>6 months) PDE5is use in PR post-NSRP. This study corroborates earlier data on PDE5i efficacy versus placebo, with no difference in long-term IIEF-EF scores between PDE5i schedules, and redemonstrates their safety without significant severe adverse events.[37] The optimal timing for initiating PDE5i post-RP is conflicting, but data largely supports early administration. One prospective randomized trial by Jo et al. found immediate use of sildenafil 100 mg twice weekly after catheter removal was more likely to achieve full recovery with IIEF-5 >17 (17.7%) at 12 months versus delayed initiation 3 months post-BNSRP.[32] A prior smaller prospective randomized study evaluated the timing of PR after NS radical cystoprostatectomy. Mosbah et al. found significant improvement in EF, intercourse satisfaction, and overall satisfaction ($p = 0.02$, 0.03, and 0.02, respectively) in those without spontaneous EF 8 weeks postoperative who started early sildenafil or ICI 2 months postoperative.[38] The control group started treatment 6 months postoperative. This study also measured penile Doppler ultrasonography (PDU) which found early PR improved IIEF scores versus late although both groups had significantly reduced end-diastolic velocity postoperative.[38] In practice, starting with tadalafil daily after catheter removal post-RP or before radiation with the option of transitioning to on-demand after the first 6 months is not only reasonable due to its proven efficacy and tolerability but also practical given its affordability with internet coupon services for 90-day supplies.

4.2. Current State of the Vacuum Erectile Device

The first concept of the vacuum erectile device (VED) was documented in 1874 to create an artificial erection with tensile force.[27] Studies show this force and shear wall stress may overcome neurovascular injury and fibrosis by dilating the cavernosal vasculature which mediates NO release and activation of the PKA/Akt pathways.[39,40] Yuan et al. discovered EF was improved with VED therapy measured by ICP/MAP ratios by reducing HIF-1α expression, apoptotic indices (AI), and TGF-β1 expression while increasing smooth muscle/collagen ratios with preservation of ASMA and eNOS expression significantly compared to controls.[41] Thus, VED therapy in CNI rat models preserves EF through anti-hypoxic, anti-apoptotic, and anti-fibrotic mechanisms.[41] An earlier study by Dalkin et al. showed that 97% of men post-BNSRP who used VED daily for 90 days after catheter removal were able to maintain their preoperative stretched penile length ($p < 0.001$).[42] One RCT by Kohler et al. demonstrated early use of VED (defined as 4 weeks postoperative) versus control (6 months postoperative) had higher IIEF scores at 3 and 6 months of use.[43]

A worldwide survey conducted by Rubilotta et al. in 2022 found the majority of VED prescribers recommend usage one to three times weekly for 5 min as monotherapy while 10 min of daily use with daily PDE5i was preferred among one-third of responders. Another third of responders also described daily VED or 1-2 times weekly for 10–15 min with concurrent ICI use.[25] While the satisfaction rate was reported up to 90%, the discontinuation rate was up to 30% due to pain and temporary changes to penile sensation due to the rubberized band, ejaculation problems, poor dexterity, anatomical challenges, and bruising from improper use.[26] One study by Kim et al. suggested only a minority of patients use VED as a single therapy long-term.[27]

Restorex PTT (RxPTT) is a novel second-generation traction device developed by Dr. Landon Trost that was found to improve penile length by a mean of 1.7 cm and sexual function (SEP) with use beginning one-month post-RP in a six-month RCT followed by a three-month open-label phase 44. While men did subjective report improvement in EF, there was no statistical difference in IIEF scores. The benefits sustained discontinuation of therapy 9 months after a 6-month trial followed by an open-label phase of 30–60 min daily for 5–7 days per week after starting 1-month post-RP44. The RxPTT

Table 1
Referenced Studies of Pharmacological and Vacuum Erectile Device Treatments

Study	Year	Patients, n	Interventions	Study duration	Study design	Outcomes
Montorsi et al	1997	27	Alprostadil injections 3 times/wk or penile injections	6 mo	RCT	Early postoperative administration of alprostadil injections significantly increases the recovery rate of spontaneous erections after nerve-sparing radical retropubic prostatectomy
Mulhall et al	2005	132	Sildenafil 100 mg and penile injection	18 mo	Case-control	Pharmacologic penile rehabilitation protocol results in higher rates of spontaneous functional erections and erectogenic drug response after RP
Raina et al	2006	95	VED daily	9 mo	RCT	Early use of VED following RP facilitates early sexual intercourse, early patient/spousal sexual satisfaction, and potentially an earlier return of natural erections sufficient for vaginal penetration
Köhler et al	2007	28	VED dailv for 5 months starting 1 month after RP, followed by 6 months OLT with VED or PDE5I (no DFWP)	6 mo	RCT	No difference in IIEF-5 scores between groups following OLT; greater penile length preservation with daily VED therapy
Raina et al	2007	91	Intraurethral alprostadil 125 ug or 250 ug 3 times/wk for 9 mo	9 mo	Case-control	Initiating intraurethral aprostadil shortly after RP is safe and tolerable, and appears to shorten the recovery time to erectile function
Montorsi et al	2008	423	Vardenafil 10 or 5 mg nightly for 9 mo; vardenafil 5, 10, or 20 mg on demand for 9 mo	13.5 mo	RCT	No statistically significant differences among treatment groups in the proportion of patients with an IIEF-EF $\geq$22 or in SEP3 success rates after the washout period. On-demand vardenafil treatment was significantly greater IIEF-EF scores and better SEP3 response rates than placebo over the entire treatment period.
Padma-Nathan et al	2008	125	Sildenafil 50 or 100 mg/d once daily at nighttime vs placebo	48 wk	RCT	Although the study prematurely terminated owing to lack of effect on prospective analysis, meta-analysis demonstrated nightly sildenafil administration for 36 weeks after RP significantly increased (27% vs 4%) the return of normal spontaneous erections
Montorsi et al	2014	423	Tadalafil 5 mg once daily, tadalafil 20 mg on demand	13.5 mo	RCT	At end of EDT, Tadalafil daily significantly improved both IIEF and SEP3. No differences between groups in achieving IIEF-5>22 after DFWP or OLT
Zganjar et al	2023	45	RxPTT after RP vs no treatment for 5 mo followed by 3 mo OLT	9 mo	RCT	Use of RxPTT improved SEP3 and penile length with benefits maintained after discontinuation

VED: Vacuum erectile device; PDE5I: Phosphdiesterase Type 5 Inhibitor; RxPTT: Restorex penile traction therapy; IIEF: International Index of Erectile Function; SEP3: Sexual Encounter Profile; RP: radical prostatectomy; OLT: open-label therapy; DFWP: drug-free washout period; RCT: randomized control trial.

has several improved characteristics including a modified penile clamp, counterbending, stronger mechanical springs, and dynamic adjustment of traction during us.[44,45] Overall, there were no significant adverse events, and men who used RxPTT were satisfied with the treatment and would recommend it to a friend.[44]

4.3. Current State of Therapies Utilizing Physical Energies

4.3.1. Low-Intensity Extracorporeal Shockwave Therapy (LISWT)

Low-intensity extracorporeal shockwave therapy is theorized to induce neovascularization and enhance local blood flow through pressure-induced shear stress on local tissues.[46] Animal models show LISWT promotes progenitor cell activation, proliferation, migration, and differentiation in penile tissue.[47] The differentiation of penile endogenous stem cells toward smooth muscle cells and endothelial cells after LISWT renews CC tissue in rat models of ED with penile fibrosis and impaired vascularization.[48] In similar models with CNI, LISWT induces nerve regeneration by enhancing the recruitment and the activation of progenitor Schwann cells.[47-49]

There currently is no consensus on the types of SW (linear vs. focused) or protocols for LISWT of ED due to limited evidence.[49] A subgroup of a meta-analysis by Man et al. found focused SWs to have a significant improvement in IIEF-EF scores without severe adverse events.[50,51]

One recent RCT by Baccaglini et al. compared the early intervention of Tadalafil daily combined with LISWT (2,400 shocks/session across four penile regions) weekly for 8 weeks to an unassisted control group after BNSRP. This study failed to achieve a significant difference in final IIEF-5 scores between the two groups at 8 weeks.[52] Rho et al. conducted a recent systematic review and meta-analysis of LISWT following RP and reported IIEF scores 3–4 months post-BNSRP were statistically better than the control (weight mean difference = −5.37, p = 0.02).[53] Although, two studies in their analysis found no significant difference at 9–12 months post-LISWT. Despite a low level of evidence among the five studies in their analysis, these data suggest LISWT may have a statistically significant impact on early EF recovery post-BNSRP. Another recent systematic review by Sighinolfi et al. included three RCTs among their nine total studies published between 2015 and 2022 comparing PDE5i's alone versus a combination of LISWT and PDE5i's post-RP. They found some authors demonstrated statistically significant improvement in erectile function with LISWT + PDE5i's with differing starting times ranging from 3 days to 6 months after surgery.[54] To date, there is neither a standardized protocol for LISWT for postprostatectomy ED nor studies directly comparing protocols.[49,54] Albeit contested in other meta-analyses, Man et al.'s study noted an EFD = 0.09 mJ/mm^2 with <6 weeks of treatment was superior, while Clavijo et al. found 18,000 SWs better than 6,000 SWs.[49,50,55] These findings were similar to the European Society of Sexual Medicine 2019 recommendations by Capogrosso et al., although post-RP ED was not specifically reviewed [Table 2]. The main limitations of all the systematic reviews and meta-analyses are the scarcity of studies, small sample sizes, high risk of bias, and high heterogeneity among studies. The available evidence for using LISWT post-RP with or without PDE5i's is insufficient and due to its high cost in the U.S. market, it should not be considered best practice for PR at this time.

4.3.2. Low-intensity pulsed ultrasound (LIPUS)

LIPUS was initially used to deliver pulsed ultrasound to target tissue at intensity <3 W/cm^2 in animal models which is thought to improve erectile function by increasing ICP and reverse CC remodeling.[56] An RCT by Cui, et al was conducted in mild to moderate ED evaluating the effect of low-intensity pulsed ultrasound (LIPUS) over a 12-week follow-up period. This study demonstrated significantly increased IIEF and SEP scores compared to the sham group after three months of treatment (67.5% vs 47%, p < 0.05 and 73.08% vs 28.95%, p < 0.05, respectively).[57] No adverse effects were reported, but additional high-quality clinical studies are necessary.

4.4. Current State of Penile Prosthesis Implantation

The penile prosthesis is a surgically implanted device for ED treatment in practice for over 40 years. There is a diversity of penile prostheses, including malleable and inflatable devices. The malleable device contains two semi-rigid cylinders that are implanted into the penile corpora. This is often the best option for patients who are physically handicapped with poor hand dexterity or failed inflatable penile prosthesis (IPP). The malleable device has poor concealment and lower mechanical failure rates due to its minimal components.[32] There are two types of inflatable penile prostheses both providing full rigidity regardless of the two or three pieces-including a reservoir. IPPs are considered a better option than the malleable prosthesis producing better penile rigidity and more flaccidity that closely replicates a normal erection.[26] The patient satisfaction rates of IPP are 86% which is higher than oral medication or ICI. The 5 and 10-year overall survivals of modern prosthetics are estimated to be 90.4% and 86.6%, respectively.[26,58,59] Given IPP placement to be a more invasive treatment, there are several adverse effects including severe infection, device erosion or extrusion, mechanical failure, and changes in penile length. A penile prosthetic is considered an irreversible procedure typically reserved for patients who fail pharmaceuticals and VED.

In 2019, a novel physiologic penile prosthesis was introduced by Le, et al that uses shape memory alloy properties to mimic the transition between a flaccid and erect penis using magnetic induction instead of hydraulic pressure.[60] The authors used a handheld magnetic inductor to successfully activate the small metal alloy penile prosthesis without direct contact under 45 seconds and negligible temperature changes in animal and cadaveric tests.[60] While this merits future in-vivo investigation for safety, efficacy, and endurance, industry leaders like Coloplast and Boston Scientific are also undergoing prototypes for hands-free IPP activation.

4.5. Current State of Regenerative Technologies

4.5.1. Low-intensity Electrostimulation (LIES)

A recent and promising study by Burnett et al. demonstrated a novel use of low-intensity electrostimulation (LIES) on cavernous nerves. LIES uses bipolar microelectrodes to deliver electrical impulses at a physiologic neuronal firing frequency with an intensity that enhances peripheral nerve regeneration.[61-63] This study divided rats into Sham, bilateral CNI (BCNI), and BCNI + LIES for one hour per day for seven days. Compared to BCNI, LIES increased EF based on ICP, normalized the increased intracavernosal reactive oxygen species (DHE), normalized the increased protein expressions of TGF- b1, IL-6, and CRP, normalized the decreased a-SMA and/or total collagen ratio, increased the basal protein expression ratio of p-ERK/ERK and p-AKT/AK, normalized the decreased myelination and number of nNOS positive cells in the CN, and reversed the elevated apoptotic nerve cells within the dorsal penile nerve.[64] There were no differences in eNOS expression in the penis between groups. Of note, no erectile response was observed at an intensity lower than 2V, confirming that the LIES parameters are under the threshold necessary to induce penile erection in rats.[64] Despite these encouraging findings in an animal model, this study had several limitations, including a lack of translational evidence and a brief seven-day follow-up given spontaneous molecular recovery begins at 4-24 weeks post-CNI. The authors suggest

Table 2
Referenced Studies of Regenerative Technologies Restoring Erectile Function

Regenerative technology	Study	Year	Patients, n	Interventions	Study duration	Study design	Summarized outcomes
Immunomodulator (tacrolimus)	Mulhall et al	2018	124	Tacrolimus 2–3 mg daily vs placebo post-RP	27 wk	RCT	No significant difference
Stem cell therapy	Yiou et al	2016	12	Intracavernous injection of bone marrow-mononuclear cells post-RP	12 mo	Phase I clinical trial	Significant dose dependent improvements in intercourse satisfaction, IIEF, and EHS; no significant side effects
Stem cell therapy	Haahr et al	2018	15	Intracavernous injection of adipose-derived regenerative cells post-RP after failed conservative therapy	12 mo	Phase I clinical trial	Intracavernous injection of adipose-derived regenerative cells is safe with efficacy starting at 6 mo and sustained at 12 mo
Gene therapy	Melman et al	2006	11	A single-dose intracavernous injection of hMaxi-K, a "naked" DNA plasmid carrying the human cDNA encoding human slow-poke (hSlo) at doses ranging from 500 - 7500 ug	24 wk	Phase I clinical trial	Clinically significant sustained IIEF improvements over 24 wk at the two highest doses of hMaxi-K (5000 and 7500 ug)
Low intensity extracorporeal shockwave therapy	Frey et al	2016	16	Six treatments with a Duolith® SD1 T-Top machine over 6 wk	12 mo	Case-control	Significant improvement in IIEF scores from baseline (+3.5 and + 1) at 1 mo and 12 mo, respectively. No severe side-effects were reported
Low-intensity extracorporeal shockwave therapy	Baccaglini et al	2020	77	Both arms started tadalafil 5 mg/day post-RP: the experimental group received 2,400 shocks/session-week on 4 different penile regions for a total of 19,200 impulses across 8 weeks	12 mo	RCT	No clinically significant difference in erectile function using shockwave therapy
Low-intensity pulsed ultrasound (LIPUS)	Cui et al	2019	104	LIPUS or sham treatment was applied to bilateral corpora and crus for 5 min, twice a week for four weeks	12 wk	RCT	Significant improvement in IIEF and SEP3 without adverse effects

IIEF: International Index of Erectile Function; EHS: Erection Hardness Scale; SEP3: Sexual Encounter Profile; RP: radical prostatectomy; RCT: randomized control trial.

extending a trial for at least three weeks in-vivo may show continued and durable benefits. Though finite, several studies also explore the use of intra-operative direct electrostimulation of the CN via the prostatic plexus.

A study by Burnett et al. stimulated the neurovascular bundle (NVB) after radical retropubic prostatectomy using a temporarily placed electrode array of an implantable neurostimulation system (20 Hz frequency, 260 m seconds pulse width, 5 mA– 60 mA amplitude up to 10 minutes) and found six of twelve men had measurable increases in penile circumference (mean 5 mm) with adverse effect or changes in oncological outcome.[65] A follow-up study by Skoufias et al. used a novel 2-dimensional flexible electrode array capable of covering the entire pelvic plexus (prostatic and pelvic sidewall) without the need for intraoperative NVB direct visualization.[66] They found a clinically significant increase in tumescence in 75% of the 24 patients with a mean 6 mm increase in circumference. The study also demonstrated a potentiated erectile response when the plexus was stimulated bilaterally, though patients with pre-operative IIEF <22 presented a reduced response.[66] Further investigation is warranted of this promising technology, especially given its decades of successful use in other peripheral nerve injury treatments.

4.5.2. Nerve Grafting

The restoration of EF by the augmentation of the CNs with nerve grafts was reported in several animal studies, but the largest RCT to date reported less clinically insignificant results.[67] It is clear the restoration of the neural conduit in the pelvic plexus intraoperatively remains complex despite the advances in surgical techniques with autologous vein or nerve grafts and end-to-side nerve grafting.[67] Further investigation is needed to establish the proper technique, identify the appropriate grafting conduit, and the overall efficacy and durability of nerve grafting on EF and CC restoration.

4.5.3. Stem Cell Therapy (SCT)

There is growing interest in using multipotent stem cell therapy to treat ED due to their self-renewing capacity. Embryonic stem cells could potentially promote regeneration via replacing existing damaged nerve cells or probably by stimulating host factors to promote nerve growth. Gu et al. have shown that human placental stem cell treatment significantly increased in vivo erectile responses and markers of nerve, endothelial, and smooth muscle cells at the end of the 6th and 12th week in rats.[68] Due to ethical concerns, further translational research has yet to be studied in an RCT. Several positive studies for post-RP ED include intracavernous bone marrow-mononuclear cells and adipose-derived stem cells (ADSC) via ICI.[67] Both studies found a clinically significant improvement in IIEF, EF, and erection hardness with or without PDE5i either at 6 months or 4 weeks after CNI, respectively.[67,69,70] A follow-up study found a single dose of ADSC could improve IIEF scores at a six-month duration with 53% of men able to have penetrative intercourse without PDE5i which was sustainable after 12 weeks.[67,69,71] Potential mechanisms include the dispersion of the transplanted cells to the injured area, providing neuroprotection, and preventing neuropraxia. In an animal study, ADSC-derived exosomes and bone marrow-derived, and MSC-derived exosomes reduced pathological alterations in neural anatomy, smooth muscle atrophy, endothelial injury, and collagen deposition.[68] Combining ICI of marrow-derived MSCs and oral-long term administration of PDE5i tadalafil seems to be superior in preserving the CC and endothelial tone while maintaining EF after CNI. Given a low-risk safety profile, SCT and PDE5i suggest a potential role for this dual strategy in the management of PR.[58] All studies thus far have yet to report severe adverse reactions during their brief

follow-up periods. SCT in ED is a rapidly evolving field that is limited in its current evidence by ethical concerns, methodologies, mechanism and timing of delivery, optimal dose and cellular concentration, safety, efficacy, and choice between autologous and allogenic injection. It is promising PR will likely exponentially grow as more multicenter db-RCTs with SCT are published over the next decade.

4.5.4. Current status of gene therapy

Melman et al. administered a single-dose cavernosal injection of hMaxi-K, a 'naked' DNA plasmid carrying the human cDNA encoding the gene for the alpha subunit of the human smooth muscle Maxi-K channel in the first Phase I trial evaluating PR. No adverse events were noted in the 11 patients who received this therapy over the 24-week study. Patients reported sustained improvements in erectile function as indicated by improved IIEF domain scores over the length of the study.[58,72] COX-2-10aa-PGIS is a newly engineered protein that is considered a potent smooth muscle relaxant.[68] Lin et al., demonstrated Ad-COX2-10aa-PGIS via ICI had a beneficial effect on improving EF in BCNI rats after 28 days.[68] This improvement appears to be related to its antifibrotic and antiapoptotic mechanisms. Several other studies report positive effects on CC integrity and preservation of EF when using viral capsid-mediated gene transfer of various biologics including Smad7, ADSCs, and myocardin.[68]

4.5.5. Summary

One retrospective, single-institution, cohort study by Mulhall et al. identified several trends that suggest PR has yet to show demonstrable improvement in ED despite significant changes to surgical techniques, optimizing pharmaceuticals, and advances in medical devices.[73] Findings from these data detailing the historic and latest advances in PR prove more efforts are needed to deliver more effective, durable, and satisfactory results for men undergoing definitive PCa treatment. It is important to note the multimodal approach that must take into consideration the patient's mental and physical challenges along with his partner's support. It is time to be more realistic regarding EF recovery if emerging data suggest EF improvement extends beyond two years post-BNSRP and age is predictive of greater recovery.[74] Contrasting these findings with previously discussed advanced age at surgery with increased risk of comorbidities, the promise of full unassisted EF recovery at the widely acknowledged 2-year milestone is becoming more misleading. On the horizon, there are still numerous and exciting opportunities to grow and shape PR for men seeking to recover their erectile function and sexual satisfaction after definitive prostate cancer treatment.

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