REVIEW ARTICLE

A contemporary review of the treatments and challenges associated with penile rehabilitation after radical prostatectomy including a proposed optimal approach

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Prostate cancer is one of the most prevalent malignancies affecting men worldwide. Despite advancements in understanding prostate anatomy and minimally invasive approaches to surgical treatment, surgery can have significant adverse effects on sexual function. Penile rehabilitation strategies have emerged as a promising approach to mitigate the impact of prostate cancer treatments on erectile function and improve quality of life. Several methods have been employed for penile rehabilitation, including pharmacotherapy, vacuum erection devices, intracavernous injections, and emerging novel techniques. Yet, there is no consensus on the exact programs or timing of initiation that should be utilized for optimal recovery after surgery. This review discusses various rehabilitation protocols and long-term outcomes and explores the cost-effectiveness of different interventions. Additionally, this review discusses the importance of a multidisciplinary approach to penile rehabilitation which includes patient education, counseling, and the selection of an appropriate rehabilitation strategy tailored to each individual's needs and preferences. Continued research and collaboration among healthcare professionals are essential to refine rehabilitation approaches and ensure optimal outcomes for patients with prostate cancer.

IJIR: Your Sexual Medicine Journal (2024) 36:480–485; https://doi.org/10.1038/s41443-023-00782-6

INTRODUCTION

In 2020, approximately 1.4 million cases of prostate cancer were diagnosed globally, making it the second most frequently detected cancer among men [1]. Prostate cancer was responsible for 268,490 new cancer diagnoses and 34,500 deaths in 2022 in the United States [2]. For men with low and intermediate-risk organ-confined disease, both radical prostatectomy (RP) or radiation therapy, has a curative intent and can be safely recommended to men with a life expectancy of >10 years [3].

Despite advancements in understanding prostatic anatomy as well as minimally invasive techniques, there are significant and life-long side effects associated with surgery [4]. These include, among others, urinary and sexual outcomes, including urinary incontinence, penile shortening, and erectile dysfunction (ED). The potency rate following RP ranges in the literature from 54% up to 94% at 12 and 24 months follow-up, with a single large population-based study reporting 78–87% over a 15-year follow-up [5, 6]. This large discrepancy in ED is attributed to significant variability in defining and reporting erectile function (EF) in the literature. Undoubtedly, ED has a distressing impact on the quality of life for patients, including effects on self-esteem, sexual relationships, and marital happiness [7, 8]. Thus, recovery of EF has become a focus for urologists and oncologists treating prostate cancer and has driven the development of penile rehabilitation (PR) programs.

PR consists of using pro-erectile drugs and other therapies to maximize postoperative EF and reduce recovery time. There is no standardized approach to PR, with significant variability among programs worldwide. This paper aims to discuss the most recent advancements in PR over the past few years, share our experience with the program at our institution, and comment on the future direction for post-RP PR.

CHALLENGES IN REVIEWING AND INTERPRETING THE LITERATURE

Significant advancements in PR have been challenging due to the heterogeneity of data assessment and reporting in the literature. A comprehensive literature review by Mulhall in 2009 brought to light the inadequacies that limit the previously published literature. Many studies on post-RP ED and PR are limited by small sample sizes, variable protocols and unique PR regimens, and conflicting definitions of ED and EF recovery [5]. More recently, Capogrosso et al. performed a methodology data assessment in 280 studies of men undergoing pelvic surgery, primarily RP. They found that only 64% of studies used validated tools to assess postoperative EF [9]. Specifically within the RP cohort, 88% of studies reported baseline EF, 63% described relevant comorbidities, and 39% reported the outcome of ED treatment. They suggested that there should be a more streamlined approach to research on EF following pelvic surgery. This should include perioperative characteristics, surgical intervention details, validated tools to assess EF and specific functional

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Received: 11 June 2023 Revised: 1 October 2023 Accepted: 11 October 2023
Published online: 18 October 2023

postoperative factors that affect EF, including urinary and fecal incontinence and sexual desire [9].

REDEFINING ERECTILE FUNCTION

Defining EF postoperatively remains a challenge. Although there are a variety of sexual health questionnaires available for use, none are specific to post-RP recovery. The International Index of Erectile Function (IIEF) has been used most frequently, with particular interest focused on the six questions that comprise the EF domain (IIEF-EF) [10]. Various (IIEF-EF) scores have been used to define functional erection, which was investigated by Terrier et al. in a quality-of-life assessment of 168 men undergoing RP for a 24-month follow-up [11]. To better define a "functional" erection, they incorporated scores from the intercourse satisfaction domain from the Prostate-Health Related Quality-of-Life Questionnaire to incorporate patient satisfaction and enjoyment. They aimed to determine the optimal (IIEF-EF) score that correlates with intercourse satisfaction. They redefined an EF score of 24 as a functional erection, which is greater than the 22 previously suggested by Briganti et al. [12]. On the contrary, a posthoc analysis of the REACTT study demonstrated creating a stricter definition of EF from 22–25 to ≥26 had no significant impact [13]. However, whether or not the incorporation of "function" or "satisfaction" is necessary is debatable.

ORAL MEDICATION REGIMENS

Since their initial introduction, oral PDE5Is have been used for PR and have been shown to be effective in EF preservation following RP. It is thought to promote blood flow to corporal bodies, prevent cavernosal hypoxia, and enhance smooth muscle preservation [14]. Although commonly used, there is no consensus concerning the timing of initiation, regimen, and duration of therapy.

The REACTT trial previously evaluated daily tadalafil 5 mg, tadalafil 20 mg on demand, and placebo and found that daily tadalafil had superior results with drug-assisted EF [15]. Recently, Jo et al. conducted a randomized controlled trial comparing early versus delayed administration of sildenafil 100 mg. One hundred and twenty men were randomized: the early group received sildenafil 100 mg twice per week beginning immediately following catheter removal for 3 months vs. the delayed group, which began at three months postoperatively. EF was evaluated at 3-month follow-up intervals, and EF recovery was defined as an IIEF-5 score ≥ 17 at 12 months [16]. They demonstrated that full recovery was significantly higher in the early group, 41.4% vs. 17.7% at 12 months. While several studies have demonstrated that early administration of PDE5I may have superior results, the duration of treatment remains unclear.

A recent retrospective review of 95 men evaluated the use of daily tadalafil following robotic bilateral or unilateral nerve-sparing RP for up to 2 years [17]. Penile color duplex ultrasound was performed 1 year following surgery to evaluate the treatment and define ED as venogenic, arteriogenic, or unremarkable. Interestingly, they found no significant difference in EF recovery at 2 years, but patients receiving daily tadalafil had better outcomes at the 1-year mark, suggesting a faster return to a new postoperative baseline function.

Miranda et al. recently published a randomized controlled 3-arm trial of pharmacologic therapy for PR after RP [18]. They studied as-needed sildenafil 100 mg, nightly sildenafil 50 mg with as-needed sildenafil 100 mg for sexual relations, and nightly sildenafil (5 nights/week) with twice weekly intracorporal injections (ICI). The study was interrupted due to the failure to recruit the necessary numbers in each arm, but they saw no difference between the three groups during analysis. A separate meta-analysis of randomized trials performed by Motlagh et al. concluded that across 22 studies, both pelvic floor muscle training and daily 100 mg sildenafil both led to a higher likelihood of EF recovery [19]. They saw no difference from placebo with on-demand PDE5I dosing.

INTRACAVERNOSAL INJECTIONS

ICI also remains a mainstay in the treatment regimen for PR. Montorsi et al. identified 30 patients with good EF prior to RP and randomized them to ICI three times per week for 12 weeks versus observation without treatment [20]. Patients in the ICI group had return of EF in 67% compared to 20% in the observation without treatment group. Notably, 80% of patients completed the ICI treatment regimen. In a study performed by Polito et al., 37% of patients refused to undergo a PR program which included ICI beginning four weeks after surgery [21]. Of those who did begin ICI therapy, 19% dropped out over the first 6 months. Despite the challenges with patient compliance and ICI therapy, 75% of providers surveyed from the International Society of Sexual Medicine stated that they use ICI as part of their primary rehabilitation strategy [22].

VACUUM ERECTION DEVICE TECHNIQUES (VED)

VEDs have also been used and might have a beneficial role in PR after RP. Feng et al. performed a systematic review and network meta-analysis, including 24 studies with over 3500 patients to compare various PR treatments after RP [23]. Overall, they found that VED led to the best effect concerning IIEF scores within the first three months and that combination therapy with VEDs plus 20 mg of daily tadalafil showed the highest mean IIEF scores > 6 months after RP. Additionally, a systematic review evaluating 16 studies utilizing VED after RP found that VED led to improved IIEF scores, conservation of penile length, and satisfactory intercourse compared to controls [24]. VED was often utilized daily in these studies. Despite this, VED still have high drop-out rates due to pain, discomfort and ineffectiveness.

NOVEL TECHNIQUES

Considering the significant variability in the success of PR and poor adherence to the currently available options, several studies have examined alternative techniques, including low-intensity extracorporeal shockwave therapy (LiESWT) and hyperbaric oxygenation therapy.

The role of LiESWT in the treatment of ED has been explored over the last decade, with controversial findings. A recent meta-analysis evaluated seven randomized trials, including 602 participants, and found statistically significant improvement in IIEF-EF scores in men undergoing Li-ESWT versus sham therapy [25]. Recently, Baccaglini et al. published the first randomized trial addressing the role of LiESWT following RP [26]. They evaluated seventy-seven men undergoing bilateral nerve-sparing RP, with preoperative IIEF-5 score > 20, and in a stable heterosexual relationship. Both arms were started on tadalafil 5 mg daily following the removal of the urethral foley catheter, given its common use in clinical practice. The experimental arm received one dosage of 2400 shocks/session weekly for 8 weeks. The primary clinical endpoint was defined as an increase in IIEF-5 > 4 points. This specific cutoff of at least 4 points in the IIEF-EF is the lowest value, implying a minimal clinically important difference (MCID) [27]. They did find a statistically significant difference in the IIEF-5 score between the two groups, but not enough to reach significant clinical significance given the cutoff selected.

It is proposed that postoperative ED following nerve-sparing RP is due to tissue damage and neuropraxia during surgery, but also postoperative hypoxic corporal bodies accelerating penile fibrosis [28]. Thus, it is proposed that promoting increased blood flow and oxygenation, you can alter the structural and functional recovery

of erectile tissues. Previously, Muller et al. demonstrated hyperbaric oxygen therapy (HBOT) preserved EF in a rat model following crush injury [29]. In March 2018, Chiles et al. completed a randomized controlled trial evaluating the effect of HBOT on EF at 18 months following nerve-sparing RP in 109 men [30]. Patients included were potent preoperatively and underwent bilateral nerve-sparing robotic RP. The experimental group completed ten 90-minute sessions of 100% oxygen, while the control group completed five sessions of 90 min of room air, both beginning 1 day following discharge. Both arms received sildenafil 50 mg daily. However, at 18 months of follow-up, there was no significant difference in erectile recovery in the experimental arm.

In 2017, Yiou et al. conducted a pilot clinical trial on stem cell therapy for the treatment of ED following RP [31]. The therapy involved intracavernous injection of bone marrow mononuclear cells. After a span of 6 months, there was an improvement in EF, as indicated by both the IIEF-EFD and IIEF-EF scores. No significant adverse effects were observed throughout a mean follow-up period of 62.1 months in the initial group of 12 patients.

Saltzman et al. conducted a literature review analyzing the methodological approaches and outcome measures of clinical trials that evaluated restorative therapies for ED between the years 2004 and 2021 [32]. They identified a total of 95 trials, with a majority of them focusing on investigating LiESWT and stem-cell therapies. The methodological approaches exhibited significant heterogeneity, and the predominant tool for assessing efficacy was the IIEF. This study holds importance in establishing a foundational framework for future trials, particularly in the pursuit of formulating more objective and standardized criteria for evaluating ED.

PATIENT COMPLIANCE

In addition to the multiple varied PR protocols, adherence to PR therapy presents yet another challenge. Patients undergoing RP face a period of postoperative recovery, urinary incontinence, and discussion regarding disease status with possible further oncologic interventions.

Several studies have sought to elucidate adherence to PR programs better and identify barriers to treatment. A longitudinal cross-sectional study followed 77 men enrolled in a PR program following bilateral nerve-sparing RP with close follow-up [33]. EF parameters were measured with self-reported questionnaires, stretched penile length, and adherence to PR were followed for up to 24 months. They found that adherence significantly declined over time, and only 49 men completed sufficient evaluations to be included in the study at 12 months. Barriers included cost and lack of insurance coverage, lack of perceived benefit of treatment, inconvenience and time constraints, frustration with the recovery process, and partner factors. Interestingly, they found that both those that felt improvement with the PR protocol and those that felt frustrated by the lack of improvement had decreased adherence. Overall, only 28.6% of men with normal preoperative baseline EF returned to their baseline function at 2 years.

Medication costs and insurance coverage are common reasons for non-compliance to PR regimens. PDE5Is are considered first-line treatment in PR but are infrequently covered by insurance companies. A study in Cleveland, Ohio, evaluated 323 pharmacies in the surrounding area to determine trends in cash price for PDE5Is [34]. As expected, they found wide variability in drug prices, specifically by pharmacy type. There was a 10-fold difference in median cost between independent and wholesale versus hospital associate and chain pharmacies for sildenafil. Additionally, a recent cost analysis focusing on direct-to-consumer healthcare companies found a significantly higher cost to patients for oral PDE5Is when purchased through direct-to-consumer companies (tadalafil 20 mg $161 local pharmacy vs. $2888 direct-to-consumer) [35]. In Italy, all Tuscan citizens undergoing nerve-sparing RP received free-of-charge PDE5I and were followed over a 5 year period. As expected, those receiving free PR had higher compliance and adherence and a higher early rehabilitation onset [36].

Penile injection therapy faces its own barriers to adherence given its more invasive nature. A recent pilot randomized controlled trial out of Memorial Sloan Kettering evaluated the impact of Acceptance and Commitment Therapy for Erectile Dysfunction (ACT-ED) on the use of penile injections [37]. The ACT-ED program was delivered by a clinical psychologist and emphasized values regarding EF, acceptance of frustrations associated with ED, and commitment to the program. This was delivered both in person and via telephone, and compared to a single arm comparison of enhanced monitoring. The ACT-ED intervention suggests positive impact on psychosocial barriers to adherence with a 44% adherence rate in comparison to 10% in the comparison arm.

PREOPERATIVE COUNSELING AND MULTIMODAL PENILE THERAPY

Given the significant impact on quality of life, preoperative assessment and counseling can have a powerful impact on patients undergoing RP. Thorough, honest, and accurate preoperative expectations can significantly impact patient satisfaction and perception of side effects. However, preoperative counseling is challenging given the complexity of predicting postoperative outcomes. To this end, Mulhall et al. developed a nomogram to assist with patient counseling and calculate the risk of post-RP ED [38]. They used multivariate logistic regression models to analyze EF recovery with or without the use of PDE5I at three time points: preoperative, 3-months postoperative, and 12-months postoperative. The nomogram includes age, baseline IIEF EF score, and relevant comorbidities. Nerve-sparing status was included in the early postoperative nomogram. The nomogram provides the probability of severe ED (IIEF Ef score ≤ 10), moderate dysfunction, and robust function (IIEF EF ≥ 24). This provides a tool to guide a more accurate and comprehensive discussion regarding postoperative expectations, as well as a tangible resource that patients may reference.

There has been a movement to create comprehensive and multidisciplinary approaches to providing education, psychologic support, and multimodal therapy through comprehensive clinics. Many institutions have instituted prehabilitation in an effort to fully maximize postoperative outcomes. A recent study at UCLA demonstrated that patients who underwent prehabilitation with preoperative pharmacotherapy were five times more likely to report return of EF [39]. The program described included attendance at a comprehensive sexual medicine clinic with a stepwise approach to refractory postoperative ED and lifestyle counseling at each visit. The prehabilitation group began 5 mg tadalafil daily and 1500mg L-citrulline BID two weeks prior to surgery and VED began twice weekly at 1 month follow up. Men with refractory ED began ICI at 3 months. The prehabilitation group had better compliance with oral therapies and VED, with an impressive compliance rate of 90 and 84%, respectively. The strongest predictor of EF was the number of follow-up visits, which reflects the impact of continued contact with patients to offer education and motivation, a multimodal approach with available resources, opportunity to adjust and titrate medications, and encouragement with compliance.

SEXUAL HEALTH NEEDS OF PATIENTS AND PARTNERS

Recently, increasing attention has been given to the sexual health concerns of patients and partners. While the majority of research has focused on optimizing EF outcomes after RP, little has been mentioned regarding the specific sexual needs of both the patient

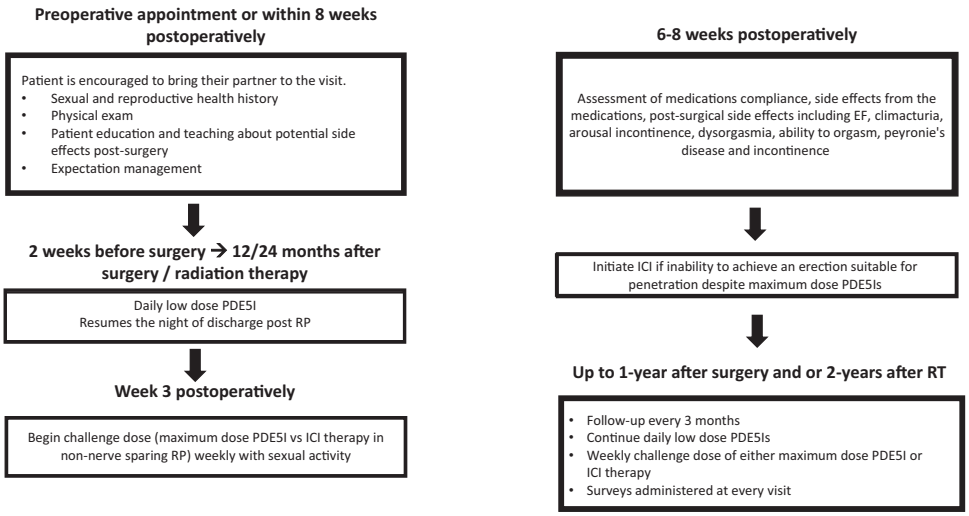

Fig. 1 Penile rehabilitation protocol at Indiana University. Flow diagram of penile rehabilitation protocol as well as timing of treatment initiation.

and their partner. A recent qualitative study from Li et al. looked at over 6000 posts in a prostate cancer online support community and overwhelmingly found that both patients and female partners described a feeling of loss from the sexual changes associated with prostate cancer treatment [40]. A recent study involving 12 prostate cancer patients' female partners found significant lack of physician-led sexual health counseling and support [41]. It also described the experience of prostate cancer related sexual dysfunction as a "couple's disease." The authors highlighted the need to include the patient's partner in the sexual recovery process and to continue to develop programs to address the partners' unmet sexual needs. Additionally, targeted strategies to improve the quality of life for both prostate cancer patients and their partners have been suggested [42]. These include comprehensive education and preoperative counseling to alleviate anxiety and facilitate communication, engaging partners in the treatment decision-making process, and involving both the patient and partner in support groups. This needs to be incorporated into PR programs moving forward.

OUR PROTOCOL AT INDIANA UNIVERSITY

Patients who present to our clinic are typically seen preoperatively or within the first 6- weeks postoperatively (Fig. 1). This visit involves a comprehensive sexual and reproductive health history, physical exam and allows time for patient education and teaching regarding potential side effects post-surgery, treatment protocols, expectation management and our prehabilitation or PR program. Patients are encouraged to bring their partner to the first visit or the second visit, which allows us to involve them in the treatment plan and goals moving forward. They are then encouraged to both come to follow up visits. Patients are started on a low dose PDE5I that they take daily beginning two weeks prior to their surgery and restart the night they are discharged home from the hospital post-RP, continuing through the first 12–24 months post-surgery/post radiation therapy. Beginning around week 3 postoperatively, they are instructed to take a challenge dose (maximum dose PDE5I) weekly with sexual activity. Upon return to the office 6–8 weeks postoperatively, they are questioned about their compliance with medications, side effects from the medication, post-surgical side effects including EF, climacturia, arousal incontinence, dysorgasmia, ability to orgasm, Peyronie's disease and incontinence. If they are unable to achieve an erection suitable for penetration despite max dose PDE5Is, then they are instructed on ICI. Patients continue with once daily low dose PDE5Is and a weekly challenge dose of either maximum dose PDE5I or ICI therapy for 12 months post-surgery. Patients are seen every 3 months thereafter until the 1-year mark following surgery and or 2-year mark following radiation therapy. In addition, they complete several surveys and questionnaires at each 3-month follow-up visit. In our practice we have seen that frequent follow-up and patient education improves patient adherence and compliance leading to better EF outcomes and more empowered patients. Cost is mitigated by recommending patients go through GoodRX.com and other cost-savings programs or compounding pharmacies. If patients undergo a non-nerve-sparing RP, they are immediately started on ICI therapy with weekly low-dose PDE5Is. All patients are also given patient education each visit on the different erection recovery treatments.

CONCLUSION

There remain significant barriers to EF recovery following RP, including patient characteristics, compliance, and cost. There has been a movement to create comprehensive and multidisciplinary approaches to providing education, psychological support, and multimodal therapy through comprehensive clinics. However, there is still no standardized approach to PR, with great variability among programs worldwide. Further research should aim at studies evaluating the optimal approach and treatment methodology to PR post-RP and solutions to overcoming barriers and maximizing patient compliance. In addition, an optimal method should include both patient and partner, if available.

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AUTHOR CONTRIBUTIONS

MB: acquired data and designed the paper, drafted manuscript, approved final version. RTB: helped draft several sections of the manuscript, prepared edits and revised manuscript, wrote final version. TP: helped draft several sections of the manuscript, prepared edits and revised manuscript, wrote final version. HB: designed manuscript and conceived idea for work, revised manuscript, approved final version.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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