Penile Rehabilitation: Current Challenges and Future Perspectives

10

Nicolò Schifano, Paolo Capogrosso, and Francesco Montorsi

Abstract

Radical prostatectomy (RP) represents the treatment of choice to manage clinically-localized prostate cancer (PCa). However, the risk of postoperative functional side effects including urinary incontinence (UI) and erectile dysfunction (ED) remains non-negligible. The pathophysiology of post-RP ED primarily involves three factors which almost inevitably occur after RP: neural damage, vascular damage, and damage to the penile smooth muscle. Due to post-RP neuroapraxia, the penis remains in a condition of unantagonized flaccidity, with the metabolic balance being shifted in favour of collagenisation which eventually exerts a permanent detrimental effect on erectile function (EF). Preoperative EF-levels, the patients' fitness and surgical-technique associated factors represent the main predictors to estimate the likelihood to recover after RP. Penile rehabilitation aims to prevent corporal smooth muscle alterations through the means of obtaining reasonably frequent erections in order to enable the patient to re-engage in sexual activity but also to re-establish his preoperative sexual function. The rehabilitation-protocol should be tailored according to the individuals' features and their estimated likelihood to recover. PDE5Is exert a favourable effect on both the EF-levels during the treatment and on the structure of the corpora cavernosa, even though they have failed to show an improvement of spontaneous EF-recovery vs. placebo. The concomitant use of vacuum erection devices (VEDs) may offer some advantages in terms of patients' satisfaction and compli-

N. Schifano · F. Montorsi (✉)
Università Vita-Salute San Raffaele, Milan, Italy

Unit of Urology; URI; IRCCS Ospedale San Raffaele, Milan, Italy
e-mail: montorsi.francesco@hsr.it

P. Capogrosso
ASST Sette Laghi—Circolo e Fondazione Macchi Hospital, Varese, Italy

S. Sarikaya et al. (eds.), *Andrology and Sexual Medicine*, Management of Urology,
https://doi.org/10.1007/978-3-031-12049-7_10

ance with the rehabilitation vs. PDE5I-monotherapy. Intracavernous Injections (ICIs) present with high and immediate levels of effectiveness, but should be reserved to PDE5I-refractory cases due to their inconvenient modality of administration. A number of novel rehabilitation options, including the use of Low Intensity Extracoroporeal Shock Wave Therapy (LI-SWT) and the use of stem cells, are currently under investigation in both the preclinical and clinical settings. Penile rehabilitation protocols should be initiated as early as feasible after RP. Patients should routinely associate drugs with sexual stimulation, with or without the involvement of the partner. Moreover, the comprehensive sexual well-being of the couple should be considered with a specific attention toward the occurrence of sexual dysfunctions other than ED, thus including low sexual desire and orgasmic dysfunction.

Introduction

Prostate cancer (PCa) represents one of the most frequent diagnosed malignancies in Europe and in the United States [1]. Radical prostatectomy (RP) is the treatment of choice to manage clinically localized PCa, providing indeed excellent oncologic outcomes in the long-term [2].

However, the risk of significant post-surgical side effects has to be taken into account. Even though significant progresses have been made aiming to ensure a minimally-invasive surgical approach, the risk of postoperative urinary incontinence [3] (UI) and erectile dysfunction (ED) remains non-negligible, with a detrimental impact on the patient's well-being [2, 4]. Over the last decades, PCa has been more and more often diagnosed at younger ages, hence the increased importance of focusing on post-operative sexual function.

It is difficult to provide an accurate estimate of the real prevalence of ED after RP based on the existing literature, due to the remarkable heterogeneity of the populations in study, the different modalities of data collection and reporting, and the discrepancies in definitions of a normal erectile function (EF) after RP [5]. Postoperative ED is however a relatively common sequela after RP, with rates ranging between 19% and 78% [6].

In this context, penile rehabilitation has been proposed as a strategy to enhance the recovery of EF after surgery for PCa and reducing the risk of permanent ED.

Pathophysiology

The pathophysiology of post-RP ED pathophysiology primarily involves three different factors: neural damage, vascular damage, and damage to the smooth muscle of the penis [7].

The erection of the penis can be considered a neurovascular event, and this indeed requires the integrity of both the neural and the vascular mechanisms. In the flaccid state the smooth muscles of the corporal sinusoids of the penis are tonically

contracted, allowing only a small amount of arterial flow. The penis receives its innervation from the cavernous nerves which originate from the pelvic plexus. Sexual stimulation triggers the release of neurotransmitters from the cavernous nerve terminals, which initiate the erectile cascade. The endothelial cells in the sinusoidal veins of the corpora cavernosa of the penis produce nitric oxide, which elicits an intracellular pathway resulting in decreased intracellular calcium levels and subsequent corporal smooth muscle relaxation [8]. The relaxation of the smooth muscle of the corpus cavernosum in turn triggers the veno-occlusive mechanisms which maintain the erection [9].

The neurovascular bundle, which contains the cavernous nerves, runs along the anterolateral aspect of the prostate [10]. Due to the anatomical proximity of the neurovascular bundles and prostate, levels of injury to erectile nerves during the RP are unfortunately unavoidable, even when the neurovascular bundle is meticulously dissected during surgery [7]. Cavernous nerves are damaged due to a range of different mechanisms, including: the stretching of the cavernous nerves during prostate mobilisation, the possible thermal injury from electrocautery, the inflammation which inevitably occurs after surgical manipulation, and/or neural ischemia secondary to the damage of the vascular supply to erectile nerves. Erectile dysfunction becomes clinically evident immediately after RP, due to a phenomenon of temporary loss of function of the cavernous nerves owing to blockage of nerve conduction called neuropraxia [11]. The full recovery from neuropraxia may take up to 3 years after the insult [12–14].

It has been widely documented that significant functional and structural/anatomical changes arise from neuropraxia, with the corporal smooth muscle and the endothelium being exposed to the detrimental effect of tissue hypoxia [15]. Penile corporal oxygenation is maintained at adequate and physiologic levels whilst the penis undergoes through the erectile cycle on a regular basis [7]. In the flaccid state, the corporal pO2 is 35–40 mmHg [16], with this resulting in the upregulation of some fibrogenic cytokines such as TGF-b [7]. Increased levels of TGF-b lead to augmented collagenic deposition and alterations in smooth muscle-to-collagen ratios, which is capable of eventually causing penile fibrosis which in turn induces venous leak [7]. Iacono et al. [17] have shown that as early as 2 months after RP there is significant increase of the collagenic deposition in the erectile tissues. Erect penis is oxygenated with a pO2 which is instead typically increased to the 75–100 mmHg range [16]. In-vitro studies have shown that higher oxygenation levels upregulate the production of endogenous prostaglandins as well as cyclic AMP exerting a favourable pro-erectile effect [18].

Due to postoperative neuroapraxia, the penis remains in a state of unantagonized flaccidity, with the metabolic balance being shifted in favour of collagenisation thus causing the impairment of the elasticity of the corpora cavernosa. These inelastic corporal sinusoids fail to exert their compressive action on the subtunical venules, eventually leading to the venous leak (e.g., corpora-veno-occlusive dysfunction, or venogenic erectile dysfunction) development [7].

Mulhall and Graydon [19] have shown that more than half of the men had venous leak after RP. In a similar study, the incidence of early venous leak (e.g., less than

4 months after RP) was about 10% and increased to approximately 35% between 8 and 12 months after RP and thereafter to 50% 12 months after surgery [13].

Vascular injury is another factor that contributes to the occurrence of post-RP ED. Levels of possible damage to the accessory pudendal arteries (APAs) may occur during RP [20]. Although the incidence of these arteries is variable based on literature [20–25], they typically lie above the levator ani where they are prone to surgical damage; their origin may be variable as they may arise from the femoral, obturator, vesical, or iliac artery. Breza et al. [20] described in details the arterial anatomy of 10 cadavers, with the APAs being observed in seven of them where they provided the major source of arterial inflow into the penis.

Factors Influencing the Likelihood to Recover Erectile Function

Briganti et al. described three categories of risk to estimate the likelihood of post-RP ED based on the patient-associated preoperative features [26]. First, those men who present with a good preoperative EF have an high expectancy of preserving it after surgery. Preoperative EF represents in fact the main predictor of ED-risk after RP [26–29]. Second, the younger and healthier individuals show higher recovery rates as compared to their older and sicker counterparts [26–28, 30–33]. The likelihood to achieve satisfactory EF after RP is very low among those patients having a pre-existent severe ED [26–29, 34]. Finally, the modality/extension of the nerve-sparing approach, the surgical technique (open, laparoscopic, robotic-assisted), and the surgical experience of the operator may also have a substantial impact on the likelihood to recover after RP [35, 36]. According to a recent meta-analysis, the preservation of the neuro-vascular bundle is not significantly associated with worse oncological outcomes, whilst it leads to better EF- and urinary continence- (UC) recovery [37]. Another recent meta-analysis [38] has identified that robot-assisted RP (RARP) results in better functional outcomes, thus including EF-recovery, when compared to laparoscopic and open techniques.

Rationale of Penile Rehabilitation

The concept of penile rehabilitation, first suggested by Montorsi et al. [39] in the late 1990s, involves the use of any medication or device after RP to maximize EF recovery. Its main purpose is to prevent corporal smooth muscle alterations through the means of obtaining reasonably frequent erections in order to enable the patient to re-engage in sexual activity but also to re-establish his preoperative EF levels [7]. More recently a more comprehensive definition of this concept has been suggested, describing penile rehabilitation as the use of any drug, intervention, procedure or device to promote male sexual function after any type of insult to the function of the penis [40] (e.g., including also modifications in girth, length, and curvature of the penile shaft). While this most typically happens with RP, any possible insult to the normal physiology of EF, as those associated with Peyronie's disease, penile

fracture, priapism, radical pelvic surgery or trauma, may benefit from an attempt of penile rehabilitation [40].

Penile Rehabilitation Protocols and Their Tailoring to the Patient

Salonia et al. [6] distinguished five main categories of penile rehabilitation treatment: phosphodiesterase type 5 inhibitors (PDE5Is), intracavernosal injections (ICIs), intraurethral and topical alprostadil, vacuum erectile device (VED) therapy, and testosterone therapy. The penile rehabilitation practice patterns among the American Urological Association (AUA) members were analyzed by Tal et al. [41]. They found that penile rehabilitation was adopted in the majority of cases (e.g., 89%) after RP, with PDE5Is being indeed the overall preferred option.

For those younger and fitter patients having a normal preoperative EF, physicians should prefer in the first instance the less invasive penile rehabilitation protocols, such as oral treatment with PDE5Is [42]. Those relatively more invasive protocols such as the use of intracavernosal injections (ICIs) and their combination with VED should be offered as second-line options [43] and reserved to patients with preoperative ED who would benefit from a more aggressive management. For those cases where any available penile rehabilitation strategy has failed or when severe preoperative ED was documented, a penile implant surgery should be offered given their favourable success profile [44]. Novel therapies such as low-intensity shock wave therapy (LISWT) and stem cells' treatments should be offered as experimental modalities [45].

The most commonly used penile rehabilitation protocols are summarized in Table 10.1.

Table 10.1 Penile rehabilitation protocols commonly used in clinical practice

Treatment	Suggested protocol
Sildenafil 50–100 mg	On demand (at least 3 times per week)
Vardenafil 10–20 mg	On demand (at least 3 times per week)
Tadalafil 5–20 mg	Daily (5 mg) On demand (at least 3 times per week—10 to 20 mg)
Intracavernous injection of Alprostadil 5–20 μg	On demand (at least 3 times per week)
Vacuum erection device	On demand (at least 3 sessions per week)
Combination treatments	PDE5is 3 times per week + on demand Alprostadil Alprostadil 3 times per week + on demand/daily PDE5i Daily Tadalafil + on demand higher dosage PDE5i Vacuum erection device + PDE5i/Alprostadil

PDE5is, phosphodiesterase type 5 inhibitors

The Importance of Preoperative Counseling

In the preoperative setting, patients are typically too optimistic regarding their expectation of getting back to their preoperative EF [46]. The occurrence of post-RP ED should be discussed with every RP-candidate, given that levels of temporary EF-loss occur most invariably, and permanent ED may also happen in some. Counseling the patient with regards to the expected timing of EF recovery and to the uncertainty of the extent of recovery is of crucial importance. Patients should also be informed regarding the predictors of EF-recovery and should be aware of all the available penile rehabilitation strategies along with their possible limitations. In order to build realistic expectations, patients should be aware that currently there is no conclusive evidence that penile rehabilitation can facilitate the recovery of unassisted erections after surgery. Finally, the possible occurrence of additional sexual side-effects should be discussed by the physician, thus including anejaculation, reduced libido, orgasmic dysfunction, climacturia, and penile morphometric alterations [47].

Timing to Start Penile Rehabilitation

Penile rehabilitation should be started as early as possible during the postoperative course [36, 48], with some studies supporting to commence the patient on PDE5Is when the catheter is removed [43]. Mulhall et al. [49] showed a significantly more consistent improvement in the International Index of Erectile Function (IIEF)-EF domain score for the early penile rehabilitation group (e.g., rehabilitation started <6 months after surgery) when compared to the delayed group (e.g., rehabilitation started >6 months after surgery). They documented also that more patients in the early group achieved satisfactory unassisted erections and PDE5I-assisted erections vs. the delayed group at 2 years after RP (e.g., 58% vs. 30%). Since PDE5Is are the least invasive option, they can be prescribed early after surgery [42, 43]. VED and ICIs may instead be considered not earlier than one month after RP [39, 50, 51].

Phosphodiesterase Type 5 Inhibitors

In a survey [52] over 95% of the International Society for Sexual Medicine (ISSM) members routinely prescribed PDE5Is to their RP patients. Although the available clinical studies [53–63] reported conflicting results regarding the actual efficacy of rehabilitation protocols based on PDE5Is (Table 10.2), preclinical data [64–75] strongly support the beneficial effects of this strategy.

Indeed, the vast majority of clinical studies presented with significant methodological limitations thus including the lack of randomization, a suboptimal duration of the rehabilitation protocol and significant dropout rates [76]. Among

Table 10.2 Summary of the randomized clinical trials of PDE5Is-based penile rehabilitation protocols

Study	Cases (n)	Study design	Patients' features	Rehabilitation protocol and timing of outcome assessment	Main findings
Padma-Nathan et al. [57]	Sil 50 mg OaD (23), Sil 100 mg OaD (28), placebo (25)	Double-blinded RCT	Age 18–70 y, preoperatively potent, BNS	Started 4 wk after RP, EDT at 36 wk, 8 wk DFW	EF recovery[a] ($P = 0.02$), 27% Sil, 4% placebo
Montorsi et al. [56]	Vard OaD (137), Vard PRN (141), placebo (145)	Double-blinded double-dummy RCT	Age 18–64 y, preoperatively potent, BNS	Started 14 d after RP, EDT at 9 mo, 2 mo DFW, 2-mo Vard OaD OL	IIEF-EF score > 22 at EDT, 48.2% Vard PRN ($P < 0.0001$ vs. placebo), 32% Vard OaD, 24.8% placebo; IIEF-EF score > 22 at DFW ($P > 0.05$ all comparisons), 29.1% Vard PRN, 24.1% Vard OaD, 29.1% placebo
Mulhall et al. [58]	Ava 200 mg (94), Ava 100 mg (90), placebo (87)	Double-blinded RCT	Age 18–70 y, history of ED after BNS	Started _6 mo after RP, EDT at 12 wk	IIEF-EF score change at EDT ($P < 0.01$ all comparisons), 5.2 Ava 200 mg, 3.6 Ava 100 mg, 0.1 placebo
Pavlovich et al. [59]	Sil OaD placebo PRN (50), Sil PRN placebo OaD (50)	Double-blinded RCT	Age < 65 y, preoperatively potent, UNS or BNS	Started 1 d after RP, EDT at 12 mo, 1 mo DFW	Recovery of baseline IIEF-EF score at EDT ($P = 0.4$), 63% Sil PRN, 57% Sil OaD; recovery of baseline IIEF-EF score at DFW ($P = 0.01$), 65% Sil PRN, 47% Sil OaD
Montorsi et al. [55]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score >22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	IIEF-EF score _ 22 at DFW, 20.9% Tad OaD ($P = 0.6$ vs. placebo), 16.9% Tad PRN ($P = 0.7$ vs. placebo), 19.1% placebo

(continued)

Table 10.2 (continued)

Study	Cases (n)	Study design	Patients' features	Rehabilitation protocol and timing of outcome assessment	Main findings
Mulhall et al. [60]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score >22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	Patients' return to baseline IIEF-EF score at EDT (*P* value not provided), 22.3% Tad OaD, 11.3% Tad PRN, 7.8% placebo; patients' return to baseline IIEF-EF score at DFW (*P* value not provided), 12.2% Tad OaD, 9.2% Tad PRN, 11.4% placebo
Moncada et al. [61]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score >22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	Time to EF recovery during DBT (for 25% of patients), Tad OaD 5.8 mo ($P = 0.03$ vs. placebo), Tad PRN 9 mo ($P = 0.01$ vs. placebo), placebo 9.3 mo
Brock et al. [62]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score >22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	Stretched penile length at EDT, Tad OaD -2.2 mm ($P = 0.03$ vs. placebo), Tad PRN -7.9 mm ($P = 0.3$ vs. placebo), placebo −6.3 mm
Montorsi et al. [63]	Tad OaD (139), Tad PRN (143), placebo (141)	Double-blinded double-dummy RCT	Age < 68 y, baseline IIEF-EF score >22, BNS	Started within 6 wk after RP, EDT at 9 mo, 6-wk DFW, 3-mo OL	Predictors for recovery of EF: high preoperative IIEF-SD score, high preoperative IIEF score on item 15, robotic surgery, NS score, Tad OaD

AVA, avanafil; BNS, bilateral nerve-sparing procedure; DBT, double-blinded treatment; DFW, drug-free washout period; ED, erectile dysfunction; EDT, end of study treatment; EF, erectile function; IIEF, International Index of Erectile Function; IIEF-EF, International Index of Erectile Function erectile function domain; IIEF-SD, International Index of Erectile Function sexual desire domain; NS, nerve-sparing; OaD, once daily; OL, open-label treatment; PDE5Is, phosphodiesterase type 5 inhibitors; PRN, on demand; RCT, randomized clinical trial; RP, radical prostatectomy; Sil, sildenafil; Tad, tadalafil; UNS, unilateral nerve sparing procedure; Vard, vardenafil

[a]Defined as a score higher than 8 on questions 3 and 4 of the IIEF and a "yes" response to the question, "Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?"

these studies, those trials with a more robust statistical validity have failed to demonstrate any meaningful advantage of penile rehabilitation with PDE5is in terms of achieving a recovery of unassisted erections as compared to placebo [76]. A recent meta-analysis [77] found that PDE5I-administration is indeed capable of increasing EF-levels during the treatment, even though the analysis of the available evidence did not support the improved recovery of spontaneous EF.

Although PDE5I-rehabilitation protocols were not proven to be effective in facilitating the spontaneous return to the preoperative EF, these medications have been proven significantly effective in preserving both the structure of the corpora cavernosa and the penile length after RP [55]. For these reasons, clinical guidelines still suggest the use of PDE5is in the early post-operative phase since this strategy is in any case considered better than leaving the cavernous tissues untreated after surgery [36, 49, 78]. Nowadays, none of the available randomized controlled trials (RCTs) definitively demonstrated a superiority of the once daily administration of PDE5-Is compared to the on-demand (at least three times per week) administration protocols (Table 10.1) [79]. Tadalafil might have the best profile for its use in the penile rehabilitation setting due to his long half-life [80–82]. Of note, overall discontinuation rates of PDE5Is after RP are as high as 72.6% at 18 months follow-up [83], due to a range of reasons including treatment effect below expectations, loss of interest in sex, psychological factors, EF recovery and concerns about their cardiovascular safety.

Intracavernosal Injections

The use of ICIs with alprostadil was the first proposed protocol to enhance EF recovery after RP. This treatment has been associated with high and immediate levels of effectiveness, especially in terms of penile hardness. Montorsi et al. [39] reported data of 27 post-RP patients who were submitted ICIs of prostaglandin-E1, 2–3 times per week. At 6-month follow up, 67% of treated men showed levels of recovered EF, compared to only 20% in the control group. Similarly, Mulhall et al. [84] showed that performing ICIs 3 times per week after RP could lead to a 52% return of functional erection at 18 months follow-up as compared to only 19% in the control group. However, ICIs have been historically associated with low patients compliance due to their inconvenient modality of administration: in their series Polito et al. [85] observed that out of 430 patients who were offered a protocol of postoperative ICIs for sexual rehabilitation, 157 (36.5%) refused to enter the protocol, and 18.6% dropped out of treatment over the first 6 months.

Two alternative molecules typically used for ICI therapy are papaverine (e.g., non-selective phosphodiesterase enzyme type 5 inhibitor) and phentolamine (e.g., a nonselective alpha-adrenergic antagonist) [86]. Bimix combines papaverine and phentolamine, whereas Trimix consists of Bimix components and alprostadil combined [86].

Intraurethral Alprostadil

Alprostadil can be administered in the form of an intraurethral suppository or in the form of a topical cream [87]. The main limitation with the use of this topical treatment after RP, particularly in the first postoperative year, is the frequent occurrence of penile pain. Raina et al. [88] described their experience with 54 patients using intraurethral alprostadil after RP. Although the treatment showed levels of beneficial effect on their assisted EF, the compliance with the treatment was only 63% after a mean follow-up period of about 2 years. All of the patients reported penile pain being associated with the use of the medication.

Vacuum Erection Device

VED therapy is based on the use of a mechanical device that utilizes a negative pressure of approximately 150–200 mmHg to increase the penile blood inflow in order to obtain on-demand erections [89]. Its use in the penile rehabilitation is however controversial [90], although the European Association of Urology (EAU) guidelines suggest VED as an option to be considered when standard oral PDE5I-treatment fails [91].

Indeed, oral PDE5Is alone are not always effective in the post-RP setting and may be associated with adverse effects and significant dropout rates. The concomitant use of a VED may increase the patient's compliance with the treatment and satisfaction and may offer advantages to monotherapy when dealing with penile shortening after RP [92, 93].

There are several possible drawbacks associated with the VED use, including instability at the base of the penis, a cyanotic appearance and a cooler erection [94]. Vacuum therapy is not suitable for penile rehabilitation purpose before the urethral catheter removal [94].

Novel Penile Rehabilitation Options

Currently, a number of innovative treatments aimed to improve EF recovery after RP are under investigation in both the preclinical and clinical setting.

Low Intensity Extracorporeal Shock Wave Therapy

Pre-clinical studies suggest that LI-SWT may induce cellular microtrauma at the level of the cavernous bodies, which in turn stimulates the release of several cytokines and angiogenic factors including the vascular endothelial growth factor (VEGF) and the endothelial nitric oxide synthase (eNOS), thus promoting tissue-neovascularization [95]. To date, few clinical studies have investigated the effect of LI-SWT in the post-operative setting. Zewin et al. reported data of 128 post

nerve-sparing radical cystoprostatectomy subjects [96]. All patients were allocated to one of three groups: LI-SWT; PDE5i; and control. During the follow-up, 16% more patients in the LI-SWT group showed satisfactory EF recovery levels as compared to the control group. Although the difference was not statistically significant ($P = 0.14$), the results were still considered of clinical relevance. In a second study, Frey et al. [97] reported data of 16 patients with mild to severe ED after 12 months since RP. All patients were treated with a 6-week course of LI-SWT and then re-assessed at 1- and 12-month after treatment with no other erectogenic aids allowed during the study period. Results showed a significant improvement in terms of EF recovery, as assessed with the IIEF-EF. As the authors correctly pointed out, it is possible that even better results could be achieved if the treatment is given at an earlier stage after surgery, thus preventing penile fibrosis.

Baccaglini et al. [98] conducted the first RCT aimed at describing the efficacy and safety related with early PDE5Is-introduction with or without LI-SWT on EF-recovery after RP. The treatment protocol was started 6 weeks after RP for a period of 8 weeks. The median IIEF-5 scores at 4 months after surgery in the intervention group (e.g., PDE5is + LI-SWT) were significantly higher than those in the control group (12.0 vs. 10.0, $P = 0.006$). However, the study failed to reach the primary clinical endpoint considering a 4-point difference between the two treatment arms.

The current guidelines are still cautious regarding the adoption of LI-SWT after RP. Further studies are needed to better identify the efficacy of this approach in this setting, including the definition of the optimal shock wave energy delivery strategies.

Stem Cells

In their landmark study, Bochinski et al. [99] showed that stem cells were able to preserve EF in a rat model of neurogenic impotence when injected into the corpora cavernosa. Kendirci et al. [100] and Albersen et al. [101] subsequently published two milestone studies that validated further these results.

Stem cells are classified according to their differentiation potential in totipotent, pluripotent, multipotent, progenitor or precursor cells [44]. The most convenient method of stem-cell administration for ED-treatment is represented by intracavernosal injection [102].

Adult mesenchymal stem cells (MSCs) are multipotent stem cells which are able to differentiate into specific subtypes of mesenchymal cells. They can release in a paracrine-fashion a wide spectrum of trophic factors and cytokines. They can exert an in-vivo beneficial influence when injected in the corpora cavernosa even if they do not engraft in the target tissue and/or they do not differentiate locally [103, 104]. This conclusion was based on the observations that a partial recovery of EF was observed after injection of cell lysate from adipose-tissue-derived stem cells (ADSC) and the limited presence of stem cells engrafted in the corpus cavernosum [101].

One of the most promising strategies in post-RP penile rehabilitation setting is represented by the intracavernous injection of bone marrow-mononuclear cells

(BM-MNCs). Following a range of preclinical encouraging results, a few phase 1 and 2 clinical trials are currently ongoing [105]. The BM-MNCs are an heterogeneous population of cells, which include mesenchymal stem cells, endothelial progenitor cells, and haematopoietic stem cells. These progenitor cells may exert anti-apoptotic, neurotrophic, and angiogenic effects. Yiou et al. [106] selected 12 post-RP patients with localized PCa and whose ED had proved to be unresponsive to medical treatments. Patients were divided into four groups and were treated with escalating BM-MNC dosages. Compared to baseline levels, a significant improvement in terms of intercourse satisfaction and EF were observed at the 6-month follow up. Interestingly, clinical benefits were also associated with improvement of peak systolic velocity at the level of the cavernous arteries and with increased penile nitric oxide release.

Further, larger randomized studies are needed to better define the real efficacy of the stem cell-based approaches for addressing ED after RP.

Sexual Rehabilitation Beside Penile Rehabilitation

Rehabilitation of post-RP sexual function has primarily been focused on facilitating the recovery of the EF. However, other sexual function domains contribute to a successful sexual recovery.

Non-penetrative Intercourse

In those cases when penetrative sex is not possible due to the erections being not firm enough, the patient and the couple should be invited to engage at least in non-penetrative intercourse through the means of oral sex and mutual masturbation. Couples who identify alternative ways of being sexual in the presence of ED report lower sexual distress and higher compliance with rehabilitation protocols [107].

Ejaculatory Complaints

Besides the recovery of EF, the preservation of a normal orgasmic function (OF) is crucial [108].

Urinary incontinence (UI) during sex (e.g., climacturia), dysorgasmia (e.g., painful orgasm) and anorgasmia can also severely impair orgasmic function following RP [109]. Dysorgasmia has a prevalence ranging from 3% to 18% after RP [110] while climacturia could affect up to 30% of patients after surgery [111]. Treatment options for painful orgasm could include the use of tamsulosin to reduce the contraction of the bladder neck responsible for the painful sensation [110]. Likewise, for climacturia patients may be invited to void before sexual intercourse or to apply penile tension loop during sexual activity; moreover, the optimization of UC with pelvic floor muscle training could reduce the risk of urine leakage [110].

Penile Morphometric Changes

Radical prostatectomy could result in penile shrinkage as documented in both open and robotic series [112–114], with penile length losses of up to 2 cm at 12 months in open RP [112, 113]. Those studies investigating this issue in the RARP setting documented a return to baseline penile length at 1 year after surgery [115, 116].

A treatment/preventative measure option to be considered is the adoption of a PDE5Is-based rehabilitation protocol, especially with the use of tadalafil, which has been proven beneficial in reducing significantly the length and girth-loss in both the flaccid and erect state at 3 and 6 months postoperatively after nerve-sparing RP [55, 62].

Moreover, the post RP patient is exposed to an increased risk of developing penile curvature and morphometric alterations due to Peyronie's disease (PD) [117], which has shown a prevalence of 15.9% after surgery [118].

Psychological Factors

Post-RP ED may typically cause a diminished feeling of masculinity. Moreover, the psychological impact of receiving a PCa diagnosis may also affect a patient's mental state. These factors could significantly affect the couple's sexual functioning after surgery. In this context, a psychological support exerts a favorable effect on patients' adherence to penile rehabilitation protocols. A RCT involving 189 couples showed that, after RP, patients in the peer support groups had higher sexual functioning levels when compared to men attending the usual care groups [119].

Canada et al. reported that sexual counseling intervention at 3-month reduced patients' distress and increased both partners' perceived levels of sexual functioning, with an increase of penile rehabilitation protocol adherence from 31% at baseline to 49% at the 6-month follow-up [120].

Penile Rehabilitation After Surgery Other Than Radical Prostatectomy

Radical Cystoprostatectomy

EF recovery after RC ranged between 14% and 80% [121]. Nerve sparing RC approaches might improve functional outcomes according to literature, although rehabilitation programs remain necessary to optimize recovery [122]. Continent patients receiving orthotopic neobladder reconstructions showed better EF-outcomes when compared to incontinent patients and to those undergoing other forms of urinary diversion [123], even though these findings may be due to the orthotopic diversion being typically offered to generally healthier and younger patients, who have a higher likelihood to recover their pre-existent EF. The

concept of sexuality preserving cystectomy was introduced by Horenblas et al. [124], with a surgical approach characterized by the preservation of the vas, the prostate, and the seminal vesicles. The majority of men undergoing this modified-approach experienced a prompt return of a normal EF after surgery. However, this technique presents with significant oncological concerns in leaving the prostatic urethra in place.

Rectal Surgery

Erecetile dysfunction is also prevalent among patients undergoing rectal cancer surgery, ranging between 10% to 60% [125]. Abdomino-perineal resection (APR) presents with a higher risk of postoperative ED than low anterior resection procedure [126]. The colostomy made after APR may also alter the patients' self-perceived body image and may increase the rate of postoperative sexual dysfunctions [127]. Surgical experience may also influence ED rates with series from high-volume cancer centers reporting lower rates of ED [128]. Rehabilitation protocols often require a multidisciplinary approach for these patients which should comprise psychological support for both the patient and the partner along with the use of pharmacological agents [129]. Among the available medications, the efficacy of sildenafil was demonstrated in a study where 32 patients treated with rectal resection were randomized to medical treatment or placebo [130]. Erectile function improved in 80% of patients receiving sildenafil compared to 17% of patients treated with placebo [130].

Conclusions

Despite the improvements of surgical techniques and of penile rehabilitation protocols, ED remains still a common finding after RP. To date, there is no standardized rehabilitation protocol after RP owing to the controversial evidence regarding the efficacy of any treatment for restoring a baseline spontaneous EF after surgery.

However, the adherence to these rehabilitation treatments has to be encouraged, as they have been proven beneficial in maintaining the penile structure intact. Penile rehabilitation protocols should be initiated as early as feasible after surgery and RP-candidates should receive appropriate preoperative counseling regarding the available penile rehabilitation regimens. The rehabilitation-strategy of choice should be tailored on the patient's specific individual features and likelihood to recover.

Moreover, patients should be carefully counselled regarding the importance to associate drug treatment with sexual stimulation, which should be performed routinely with or without the involvement of the partner. Last, the comprehensive sexual well-being of the couple should be considered with a specific attention toward the occurrence of sexual dysfunctions other than ED and including impaired sexual desire and orgasmic dysfunction.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64:9–29.
2. Schiavina R, et al. Survival, Continence and Potency (SCP) recovery after radical retropubic prostatectomy: a long-term combined evaluation of surgical outcomes. Eur J Surg Oncol. 2014;40:1716–23.
3. Schifano N, Capogrosso P, Tutolo M, Dehò F, Montorsi F, Salonia A. How to prevent and manage post-prostatectomy incontinence: a review. World J Mens Health. 2021;39(4):581–97.
4. Mullins JK, et al. The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. J Urol. 2012;188:2219–24.
5. Salonia A, et al. Prevention and management of post prostatectomy erectile dysfunction. Transl Androl Urol. 2015;4:421–37.
6. Salonia A, et al. Sexual rehabilitation after treatment for prostate cancer—part 2: recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2017;14:297–315.
7. Mulhall JP. Penile rehabilitation following radical prostatectomy. Curr Opin Urol. 2008;18:613–20.
8. Kim N, et al. Oxygen tension regulates the nitric oxide pathway. Physiological role in penile erection. J Clin Invest. 1993;91:437–42.
9. Minhas S, Blecher G, Almekaty K, Kalejaiye O. Does penile rehabilitation have a role in the treatment of erectile dysfunction following radical prostatectomy? F1000Research. 2017;6:1–12.
10. Walz J, Graefen M, Huland H. Surgical anatomy of the prostate in the era of radical robotic prostatectomy. Curr Opin Urol. 2011;21:173–8.
11. Clavell-Hernández J, Wang R. The controversy surrounding penile rehabilitation after radical prostatectomy. Transl Androl Urol. 2017;6:2–11.
12. Wang R. Penile rehabilitation after radical prostatectomy: where do we stand and where are we going? J Sex Med. 2007;4(4 Pt 2):1085–97. https://doi.org/10.1111/j.1743-6109.2007.00482.x.
13. Mulhall JP, et al. Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. J Urol. 2002;167:1371–5.
14. Walsh PC. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. J Urol. 2000;164:242.
15. User HM, Hairston JH, Zelner DJ, McKenna KE, McVary KT. Penile weight and cell subtype specific changes in a postradical prostatectomy model of erectile dysfunction. J Urol. 2003;169:1175–9.
16. Dean RC, Lue TF. Physiology of penile erection and pathophysiology of erectile dysfunction. Urol Clin North Am. 2005;32:379–95.
17. Iacono F, et al. Histological alterations in cavernous tissue after radical prostatectomy. J Urol. 2005;173:1673–6.
18. Moreland RB, et al. O2-dependent prostanoid synthesis activates functional PGE receptors on corpus cavernosum smooth muscle. Am J Physiol Heart Circ Physiol. 2001;281:552–8.
19. Mulhall JP, Graydon RJ. The hemodynamics of erectile dysfunction following nerve-sparing radical retropubic prostatectomy. Int J Impot Res. 1996;8:91–4.
20. Breza J, Aboseif SR, Orvis BR, Lue TF, Tanagho EA. Detailed anatomy of penile neurovascular structures: surgical significance. J Urol. 1989;141:437–43.
21. Benoit G, Droupy S, Quillard J, Paradis V, Giuliano F. Supra and infralevator neurovascular pathways to the penile corpora cavernosa. J Anat. 1999;195(Pt 4):605–15.
22. Droupy S, et al. Assessment of the functional role of accessory pudendal arteries in erection by transrectal color doppler ultrasound. J Urol. 1999;162:1987–91.
23. Polascik TJ, Walsh PC. Radical retropubic prostatectomy: the influence of accessory pudendal arteries on the recovery of sexual function. J Urol. 1995;154:150–2.

24. Rogers CG, Trock BP, Walsh PC. Preservation of accessory pudendal arteries during radical retropubic prostatectomy: surgical technique and results. Urology. 2004;64:148–51.
25. Secin FP, et al. Anatomy of accessory pudendal arteries in laparoscopic radical prostatectomy. J Urol. 2005;174:523–6; discussion 526.
26. Briganti A, et al. Choosing the best candidates for penile rehabilitation after bilateral nerve-sparing radical prostatectomy. J Sex Med. 2012;9:608–17.
27. Briganti A, et al. Predicting erectile function recovery after bilateral nerve sparing radical prostatectomy: a proposal of a novel preoperative risk stratification. J Sex Med. 2010;7:2521–31.
28. Briganti A, et al. Prediction of sexual function after radical prostatectomy. Cancer. 2009;115:3150–9.
29. Gacci M, et al. Original article: clinical investigation factors predicting continence recovery 1 month after radical prostatectomy: results of a multicenter survey. Int J Urol. 2011;18:700–8.
30. Gandaglia G, et al. How to optimize patient selection for robot-assisted radical prostatectomy: functional outcome analyses from a tertiary referral center. J Endourol. 2014;28:792–800.
31. Abdollah F, et al. Prediction of functional outcomes after nerve-sparing radical prostatectomy: results of conditional survival analyses. Eur Urol. 2012;62:42–52.
32. Gallina A, et al. Erectile function outcome after bilateral nerve sparing radical prostatectomy: which patients may be left untreated? J Sex Med. 2012;9:903–8.
33. Teloken PE, et al. Defining the impact of vascular risk factors on erectile function recovery after radical prostatectomy. BJU Int. 2013;111:653–7.
34. Harris CR, Punnen S, Carroll PR. Men with low preoperative sexual function may benefit from nerve sparing radical prostatectomy. J Urol. 2013;190:981–6.
35. Ficarra V, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol. 2012;62(3):418–30. https://doi.org/10.1016/j.eururo.2012.05.046.
36. Salonia A, et al. Prevention and management of postprostatectomy sexual dysfunctions. Part 1: choosing the right patient at the right time for the right surgery. Eur Urol. 2012;62:261–72.
37. Nguyen LN, et al. The risks and benefits of cavernous neurovascular bundle sparing during radical prostatectomy: a systematic review and meta-analysis. J Urol. 2017;198:760–9.
38. Du Y, et al. Robot-assisted radical prostatectomy is more beneficial for prostate cancer patients: a system review and meta-analysis. Med Sci Monit. 2018;24:272–87.
39. Montorsi F, et al. Recovery of spontaneous erectile function after nervesparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. J Urol. 1997;158(4):1408–10. https://doi.org/10.1016/S0022-5347(01)64227-7.
40. Hakky TS, et al. Penile rehabilitation: the evolutionary concept in the management of erectile dysfunction. Curr Urol Rep. 2014;15:393.
41. Tal R, Teloken P, Mulhall JP. Erectile function rehabilitation after radical prostatectomy: practice patterns among AUA members. J Sex Med. 2011;8(8):2370–6. https://doi.org/10.1111/j.1743-6109.2011.02355.x.
42. Segal RL, Bivalacqua TJ, Burnett AL. Current penile-rehabilitation strategies: clinical evidence. Arab J Urol. 2013;11:230–6.
43. Jo JK, et al. Effect of starting penile rehabilitation with sildenafil immediately after robot-assisted laparoscopic radical prostatectomy on erectile function recovery: a prospective randomized trial. J Urol. 2018;199:1600–6.
44. Castiglione F, Ralph DJ, Muneer A. Surgical techniques for managing post-prostatectomy erectile dysfunction. Curr Urol Rep. 2017;18:90.
45. Lima TFN, Bitran J, Frech FS, Ramasamy R. Prevalence of post-prostatectomy erectile dysfunction and a review of the recommended therapeutic modalities. Int J Impot Res. 2021;33:401–9.
46. Symon Z, et al. Measuring patients' expectations regarding health-related quality-of-life outcomes associated with prostate cancer surgery or radiotherapy. Urology. 2006;68:1224–9.

47. Schifano N, Cakir OO, Castiglione F, Montorsi F, Garaffa G. Multidisciplinary approach and management of patients who seek medical advice for penile size concerns: a narrative review. Int J Impot Res. 2021;34(5):434–51. https://doi.org/10.1038/s41443-021-00444-5.
48. Mulhall JP, Bella AJ, Briganti A, McCullough A, Brock G. Erectile function rehabilitation in the radical prostatectomy patient. J Sex Med. 2010;7:1687–98.
49. Mulhall JP, Parker M, Waters BW, Flanigan R. The timing of penile rehabilitation after bilateral nerve-sparing radical prostatectomy affects the recovery of erectile function. BJU Int. 2010;105:37–41.
50. Nandipati K, Raina R, Agarwal A, Zippe CD. Early combination therapy: intracavernosal injections and sildenafil following radical prostatectomy increases sexual activity and the return of natural erections. Int J Impot Res. 2006;18:446–51.
51. Köhler TS, et al. A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. BJU Int. 2007;100:858–62.
52. Teloken P, Mesquita G, Montorsi F, Mulhall J. Post-radical prostatectomy pharmacological penile rehabilitation: practice patterns among the international society for sexual medicine practitioners. J Sex Med. 2009;6:2032–8.
53. McCullough AR, et al. Recovery of erectile function after nerve sparing radical prostatectomy and penile rehabilitation with nightly intraurethral alprostadil versus sildenafil citrate. J Urol. 2010;183:2451–6.
54. Bannowsky A, Schulze H, van der Horst C, Hautmann S, Jünemann K-P. Recovery of erectile function after nerve-sparing radical prostatectomy: improvement with nightly low-dose sildenafil. BJU Int. 2008;101:1279–83.
55. Montorsi F, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: a randomised placebo-controlled study (REACTT). Eur Urol. 2014;65(3):587–96. https://doi.org/10.1016/j.eururo.2013.09.051.
56. Montorsi F, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. Eur Urol. 2008;54(4):924–31. https://doi.org/10.1016/j.eururo.2008.06.083.
57. Padma-Nathan H, et al. Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy. Int J Impot Res. 2008;20(5):479–86. https://doi.org/10.1038/ijir.2008.33.
58. Mulhall JP, et al. A phase 3, placebo controlled study of the safety and efficacy of avanafil for the treatment of erectile dysfunction after nerve sparing radical prostatectomy. J Urol. 2013;189:2229–36.
59. Pavlovich CP, et al. Nightly vs on-demand sildenafil for penile rehabilitation after minimally invasive nerve-sparing radical prostatectomy: results of a randomized double-blind trial with placebo. BJU Int. 2013;112(6):844–51. https://doi.org/10.1111/bju.12253.
60. Mulhall JP, et al. Effects of tadalafil once-daily or on-demand vs placebo on return to baseline erectile function after bilateral nerve-sparing radical prostatectomy—results from a randomized controlled trial (REACTT). J Sex Med. 2016;13(4):679–83. https://doi.org/10.1016/j.jsxm.2016.01.022.
61. Moncada I, et al. Effects of tadalafil once daily or on demand versus placebo on time to recovery of erectile function in patients after bilateral nerve-sparing radical prostatectomy. World J Urol. 2015;33(7):1031–8. https://doi.org/10.1007/s00345-014-1377-3.
62. Brock G, et al. Effect of tadalafil once daily on penile length loss and morning erections in patients after bilateral nerve-sparing radical prostatectomy: results from a randomized controlled trial. Urology. 2015;85:1090–6.
63. Montorsi F, et al. Exploratory decision-tree modeling of data from the randomized REACTT trial of tadalafil versus placebo to predict recovery of erectile function after bilateral nerve-sparing radical prostatectomy. Eur Urol. 2016;70:529–37.
64. Ferrini MG, et al. Vardenafil prevents fibrosis and loss of corporal smooth muscle that occurs after bilateral cavernosal nerve resection in the rat. Urology. 2006;68:429–35.

65. Vignozzi L, et al. Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. J Sex Med. 2006;3:419–31.
66. Ferrini MG, et al. Fibrosis and loss of smooth muscle in the corpora cavernosa precede corporal veno-occlusive dysfunction (CVOD) induced by experimental cavernosal nerve damage in the rat. J Sex Med. 2009;6:415–28.
67. Özden E, et al. Effect of sildenafil citrate on penile weight and physiology of cavernous smooth muscle in a post-radical prostatectomy model of erectile dysfunction in rats. Urology. 2011;77:761.e1–7.
68. Hatzimouratidis K, et al. Phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction: a critical analysis of the basic science rationale and clinical application. Eur Urol. 2009;55:334–47.
69. Kovanecz I, et al. Long-term continuous sildenafil treatment ameliorates corporal veno-occlusive dysfunction (CVOD) induced by cavernosal nerve resection in rats. Int J Impot Res. 2008;20:202–12.
70. Lagoda G, Jin L, Lehrfeld TJ, Liu T, Burnett AL. FK506 and sildenafil promote erectile function recovery after cavernous nerve injury through antioxidative mechanisms. J Sex Med. 2007;4:908–16.
71. Hlaing SM, et al. Sildenafil promotes neuroprotection of the pelvic ganglia neurones after bilateral cavernosal nerve resection in the rat. BJU Int. 2013;111:159–70.
72. Sirad F, et al. Sildenafil promotes smooth muscle preservation and ameliorates fibrosis through modulation of extracellular matrix and tissue growth factor gene expression after bilateral cavernosal nerve resection in the rat. J Sex Med. 2011;8:1048–60.
73. Kovanecz I, et al. Chronic daily tadalafil prevents the corporal fibrosis and veno-occlusive dysfunction that occurs after cavernosal nerve resection. BJU Int. 2008;101:203–10.
74. Mulhall JP, et al. The functional and structural consequences of cavernous nerve injury are ameliorated by sildenafil citrate. J Sex Med. 2008;5:1126–36.
75. Lysiak JJ, et al. Tadalafil increases Akt and extracellular signal-regulated kinase 1/2 activation, and prevents apoptotic cell death in the penis following denervation. J Urol. 2008;179:779–85.
76. Clavell-Hernandez J, Ermec B, Kadioglu A, Wang R. Perplexity of penile rehabilitation following radical prostatectomy. Turk J Urol. 2019;45:77–82.
77. Liu C, Lopez DS, Chen M, Wang R. Penile rehabilitation therapy following radical prostatectomy: a meta-analysis. J Sex Med. 2017;14:1496–503.
78. Kaiho Y, Yamashita S, Arai Y. Optimization of sexual function outcome after radical prostatectomy using phosphodiesterase type 5 inhibitors. Int J Urol. 2013;20:285–9.
79. Gandaglia G, et al. Penile rehabilitation after radical prostatectomy: does it work? Transl Androl Urol. 2015;4:110–23.
80. Smith WB 2nd, et al. PDE5 inhibitors: considerations for preference and long-term adherence. Int J Clin Pract. 2013;67:768–80.
81. Montorsi F, et al. Earliest time to onset of action leading to successful intercourse with vardenafil determined in an at-home setting: a randomized, double-blind, placebo-controlled trial. J Sex Med. 2004;1:168–78.
82. Castiglione F, Nini A, Briganti A. Penile rehabilitation with phosphodiesterase type 5 inhibitors after nerve-sparing radical prostatectomy: are we targeting the right patients? Eur Urol. 2014;65:673–4.
83. Salonia A, et al. Acceptance of and discontinuation rate from erectile dysfunction oral treatment in patients following bilateral nerve-sparing radical prostatectomy. Eur Urol. 2008;53:564–70.
84. Mulhall JP, et al. The use of an erectogenic pharmacotheraphy regimen following radical prostatectomy improves recovery of spontaneous erectile function. J Sex Med. 2005;2(4):532–40; discussion 540–2. https://doi.org/10.1111/j.1743-6109.2005.00081_1.x.
85. Polito M, D'anzeo G, Conti A, Muzzonigro G. Erectile rehabilitation with intracavernous alprostadil after radical prostatectomy: refusal and dropout rates. BJU Int. 2012;110:1–4.

86. Kim P, Clavijo RI. Management of male sexual dysfunction after cancer treatment. Urol Oncol. 2020; https://doi.org/10.1016/j.urolonc.2020.08.006.
87. Hatzimouratidis K, et al. Pharmacotherapy for erectile dysfunction: recommendations from the Fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2016;13:465–88.
88. Raina R, et al. Long-term efficacy and compliance of MUSE for erectile dysfunction following radical prostatectomy: SHIM (IIEF-5) analysis. Int J Impot Res. 2005;17:86–90.
89. Yuan J, et al. Vacuum therapy in erectile dysfunction—science and clinical evidence. Int J Impot Res. 2010;22:211–9.
90. Basal S, Wambi C, Acikel C, Gupta M, Badani K. Optimal strategy for penile rehabilitation after robot-assisted radical prostatectomy based on preoperative erectile function. BJU Int. 2013;111:658–65.
91. Hatzimouratidis K, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. Eur Urol. 2010;57:804–14.
92. Sun L, Peng F-L, Yu Z-L, Liu C-L, Chen J. Combined sildenafil with vacuum erection device therapy in the management of diabetic men with erectile dysfunction after failure of first-line sildenafil monotherapy. Int J Urol. 2014;21:1263–7.
93. Zippe CD, Pahlajani G. Vacuum erection devices to treat erectile dysfunction and early penile rehabilitation following radical prostatectomy. Curr Urol Rep. 2008;9:506–13.
94. Qin F, Wang S, Li J, Wu C, Yuan J. The early use of vacuum therapy for penile rehabilitation after radical prostatectomy: systematic review and meta-analysis. Am J Mens Health. 2018;12:2136–43.
95. Capogrosso P, et al. Low-intensity shock wave therapy in sexual medicine-clinical recommendations from the European Society of Sexual Medicine (ESSM). J Sex Med. 2019;16:1490–505.
96. Zewin TS, et al. Efficacy and safety of low-intensity shock wave therapy in penile rehabilitation post nerve-sparing radical cystoprostatectomy: a randomized controlled trial. Int Urol Nephrol. 2018;50:2007–14.
97. Frey A, Sønksen J, Fode M. Low-intensity extracorporeal shockwave therapy in the treatment of postprostatectomy erectile dysfunction: a pilot study. Scand J Urol. 2016;50(2):123–7. https://doi.org/10.3109/21681805.2015.1100675.
98. Baccaglini W, et al. The role of the low-intensity extracorporeal shockwave therapy on penile rehabilitation after radical prostatectomy: a randomized clinical trial. J Sex Med. 2020;17:688–94.
99. Bochinski D, et al. The effect of neural embryonic stem cell therapy in a rat model of cavernosal nerve injury. BJU Int. 2004;94:904–9.
100. Kendirci M, et al. Transplantation of nonhematopoietic adult bone marrow stem/progenitor cells isolated by p75 nerve growth factor receptor into the penis rescues erectile function in a rat model of cavernous nerve injury. J Urol. 2010;184:1560–6.
101. Albersen M, et al. Injections of adipose tissue-derived stem cells and stem cell lysate improve recovery of erectile function in a rat model of cavernous nerve injury. J Sex Med. 2010;7:3331–40.
102. Lin C-S, et al. Stem cell therapy for erectile dysfunction: a critical review. Stem Cells Dev. 2012;21:343–51.
103. Castiglione F, et al. Intratunical injection of human adipose tissue-derived stem cells prevents fibrosis and is associated with improved erectile function in a rat model of Peyronie's disease. Eur Urol. 2013;63:551–60.
104. Castiglione F, et al. Adipose-derived stem cells counteract urethral stricture formation in rats. Eur Urol. 2016;70:1032–41.
105. Capogrosso P, Montorsi F, Salonia A. Phase I and phase II clinical trials for the treatment of male sexual dysfunction—a systematic review of the literature. Expert Opin Investig Drugs. 2018;27(7):583–93.
106. Yiou R, et al. Safety of intracavernous bone marrow-mononuclear cells for postradical prostatectomy erectile dysfunction: an open dose-escalation pilot study. Eur Urol. 2016;69:988–91.

107. Beck AM, Robinson JW, Carlson LE. Sexual values as the key to maintaining satisfying sex after prostate cancer treatment: the physical pleasure-relational intimacy model of sexual motivation. Arch Sex Behav. 2013;42:1637–47.
108. Du K, et al. Orgasmic function after radical prostatectomy. J Urol. 2017;198:407–13.
109. Barnas JL, et al. The prevalence and nature of orgasmic dysfunction after radical prostatectomy. BJU Int. 2004;94:603–5.
110. Capogrosso P, Ventimiglia E, Cazzaniga W, Montorsi F, Salonia A. Orgasmic dysfunction after radical prostatectomy. World J Mens Health. 2017;35:1–13.
111. Capogrosso P, et al. Orgasmic dysfunction after robot-assisted versus open radical prostatectomy. Eur Urol. 2016;70:223–6.
112. Gontero P, et al. New insights into the pathogenesis of penile shortening after radical prostatectomy and the role of postoperative sexual function. J Urol. 2007;178:602–7.
113. Savoie M, Kim SS, Soloway MS. A prospective study measuring penile length in men treated with radical prostatectomy for prostate cancer. J Urol. 2003;169:1462–4.
114. Carlsson S, et al. Self-perceived penile shortening after radical prostatectomy. Int J Impot Res. 2012;24:179–84.
115. Engel JD, Sutherland DE, Williams SB, Wagner KR. Changes in penile length after robot-assisted laparoscopic radical prostatectomy. J Endourol. 2011;25:65–9.
116. Kadono Y, et al. Changes in penile length after radical prostatectomy: investigation of the underlying anatomical mechanism. BJU Int. 2017;120(2):293–9. https://doi.org/10.1111/bju.13777.
117. Segal R, Burnett AL. Erectile preservation following radical prostatectomy. Ther Adv Urol. 2011;3:35–46.
118. Tal R, et al. Peyronie's disease following radical prostatectomy: incidence and predictors. J Sex Med. 2010;7:1254–61.
119. Chambers SK, et al. A randomised controlled trial of a couples-based sexuality intervention for men with localised prostate cancer and their female partners. Psychooncology. 2015;24:748–56.
120. Canada AL, Neese LE, Sui D, Schover LR. Pilot intervention to enhance sexual rehabilitation for couples after treatment for localized prostate carcinoma. Cancer. 2005;104:2689–700.
121. Schlegel PN, Walsh PC. Neuroanatomical approach to radical cystoprostatectomy with preservation of sexual function. J Urol. 1987;138:1402–6.
122. Miyao N, et al. Recovery of sexual function after nerve-sparing radical prostatectomy or cystectomy. Int J Urol. 2001;8:158–64.
123. El-Bahnasawy MS, Ismail T, Elsobky E, Alzalouey EI, Bazeed MA. Prognostic factors predicting successful response to sildenafil after radical cystoprostatectomy. Scand J Urol Nephrol. 2008;42:110–5.
124. Horenblas S, Meinhardt W, Ijzerman W, Moonen LF. Sexuality preserving cystectomy and neobladder: initial results. J Urol. 2001;166:837–40.
125. Banerjee AK. Sexual dysfunction after surgery for rectal cancer. Lancet. 1999;353:1900–2.
126. Keating JP. Sexual function after rectal excision. ANZ J Surg. 2004;74:248–59.
127. Nishizawa Y, et al. Male sexual dysfunction after rectal cancer surgery. Int J Color Dis. 2011;26:1541–8.
128. Havenga K, et al. Male and female sexual and urinary function after total mesorectal excision with autonomic nerve preservation for carcinoma of the rectum. J Am Coll Surg. 1996;182:495–502.
129. Eveno C, Lamblin A, Mariette C, Pocard M. Sexual and urinary dysfunction after proctectomy for rectal cancer. J Visc Surg. 2010;147:e21–30.
130. Lindsey I, George B, Kettlewell M, Mortensen N. Randomized, double-blind, placebo-controlled trial of sildenafil (viagra) for erectile dysfunction after rectal excision for cancer and inflammatory bowel disease. Dis Colon Rectum. 2002;45:727–32.