IJIR: Your Sexual Medicine Journal (2021) 33:401–409
https://doi.org/10.1038/s41443-020-00374-8

REVIEW ARTICLE

Prevalence of post-prostatectomy erectile dysfunction and a review of the recommended therapeutic modalities

Thiago Fernandes Negris Lima[1] · Joshua Bitran[1] · Fabio Stefano Frech[1] · Ranjith Ramasamy[1]

Received: 15 June 2020 / Revised: 22 September 2020 / Accepted: 2 November 2020 / Published online: 17 November 2020

Abstract

Radical prostatectomy (RP) represents one of the most commonly used first-line treatment modalities in men with localized prostate cancer. One of the most feared post-surgical complications is erectile dysfunction (ED), usually caused by direct damage to the cavernous nerves or due to neuropraxia. Penile rehabilitation is an emerging concept that was proposed to stimulate and accelerate recovery of erectile function after RP. The goal is to improve blood flow to the penis, increasing cavernous oxygenation and avoiding fibrosis. The most common used modalities include oral phosphodiesterase type 5 inhibitors (PDE5-I), vacuum erection devices (VEDs), intracorporeal injection (ICI) therapy, medicated urethral system for erections (MUSE), and a combination of these treatments. For those patients with severe ED, ED refractory to medical therapy and/or seeking long term reliable results, the penile prosthesis implant remains an excellent alternative. We conducted a broad review of post-prostatectomy ED prevalence with different techniques and the success rates of the different therapeutic approaches.

Introduction

Prostate cancer (PCa) is the second most common cancer in American men. According to the American Cancer Society, about 191,930 patients will be diagnosed with PCa in the US in 2020 [1]. Currently, radical prostatectomy (RP) represents one of the most commonly used first-line treatment modalities in men with localized PCa [2]. For the past twenty years, functional outcomes have gained special importance and have become the means to measure surgical quality. One of the most concerning post-surgical complications is erectile dysfunction (ED) [3]. Post-RP ED is related to the injury of the cavernous nerves, incomplete nerve-sparing surgery, or neuropraxia - stretching, heat, and direct trauma to the nerve [4]. Corroborating this idea, previous studies have shown that erectile function (EF) can improve during long-term follow-up [5, 6].

Some studies posit that the prevalence of ED after robotic assisted radical prostatectomy (RARP) at 12 and 24 months ranges from 10–46% and from 6–37%, respectively [7–9]. In comparison, the incidence of ED after retropubic radical prostatectomy (RRP) was reported to range from 14–82% over varying periods of time [10–16]. Other studies compared potency, EF sufficient for intercourse, in patients after laparoscopic radical prostatectomy (LRP) and RRP and showed varying rates between 34.6–81% (within 1–12 months) and 33.3–72% (within 3–12 months), respectively [17, 18]. Joseph et al. compared LRP and RARP and showed potency rates of 36% and 46% (after 3 months), respectively [19]. These studies thus suggest that there is minimal evidence for choosing a single radical prostatectomy technique for the sole outcome of EF [17–19]. Interestingly, when comparing different nerve-sparing techniques (unilateral and bilateral sparing), potency rates tend to favor bilateral sparing in both RRP and RARP [20]. Studies showed potency rates within 6–18 months after RRP ranging from 0.5–34.4% with no nerve-sparing technique, 5.4–47% with unilateral nerve-sparing, and 15.9–68% with bilateral nerve-sparing [10, 16, 21–23]. In comparison, potency rates within 3–24 months after RARP ranged from 29–80% with unilateral nerve-sparing and 44–93% with bilateral nerve-sparing [7, 24–27] (Table 1). Regardless of the technique used, bilateral nerve-sparing seems to favor increasing potency rates after RRP and RARP.

✉ Thiago Fernandes Negris Lima
thiagofernandesnl@gmail.com

[1] Department of Urology, University of Miami Miller School of Medicine, Miami, FL, United States of America

Table 1 Potency rates comparing RRP/RARP and differing nerve sparring techniques.

Technique	No nerve sparing	Unilateral nerve sparing	Bilateral nerve sparing
RRP	0.5%–34.4%	5.4–47%	15.9–68%
RARP	–	29–80%	44–93%

EF is complex, dependent on central and peripheral mechanisms that include spinal tracts, nerve bundles, vascular compartments, and smooth muscle cells [28]. The spinal pathways involve both parasympathetic and sympathetic communication to promote and maintain a successful erection for intercourse [28]. The pelvic plexus located in the posterolateral wall of the prostate has been shown to be composed of both parasympathetic and sympathetic tracts providing autonomic innervation to the corpora cavernosa [29]. During RP, these cavernous nerves may be transected or damaged [29]. Nerve-sparing RP (nsRP) have provided an amelioration in potency induction post-RP (Table 1). Nonetheless, ED is still evident in many patients even when undergoing bilateral nsRP, suggesting that ED is not only attributed to nerve injury [30]. Interestingly, Mulhall et al. [31] showed that patients undergoing bilateral nsRP may have either arterial or venous insufficiency, proposing a vascular component in the pathophysiology of ED. Maintenance of the appropriate oxygen levels in the corporal environment has been suggested to play a role in the prevention of corporal fibrosis [32]. TGF-Beta has been shown to promote corporal fibrosis in hypoxic states through the induction of collagen deposition in cavernosal smooth muscle cells [33]. Vascular changes associated with RP [31] may theoretically induce a hypoxic environment which may cause cytokine release resulting in cavernosal fibrosis. Additionally, previous studies advocated that neuropraxia can cause long-term low oxygen tension state in the flaccid penis, possibly resulting in smooth muscle apoptosis and fibrosis [33, 34]. These irreversible changes can produce veno-occlusive dysruption [35]. Since this cascade of events is related to an initial nerve injury, the changes are most pronounced with bilateral nerve damage. Therefore, the first step in preserving EF relies on the surgical technique [29] along with new technologies that enhance the surgeon's perception in the operative field [36]. After the procedure, most patients will experience a gradual return of EF and, although it can take over 2 years [6], few patients will return to their baseline EF [37]. For this reason, penile rehabilitation has been proposed to stimulate and assist in the recovery of EF after RP. The main goal is to restore satisfactory EF, based on the enhancement of corpora cavernosa oxygenation and interruption of cavernous nerve injury-induced structural changes of the penile tissue [38]. The most common methods used in penile rehabilitation after RP include oral phosphodiesterase type 5 inhibitors (PDE5-I), vacuum erection devices (VEDs), intracorporeal injection (ICI) therapy, medicated urethral system for erections (MUSE), and a combination of these treatments [39, 40] as summarized in Table 2. Lamentably, limitations and contrasting results from previous studies complicate the elaboration of a guideline for clinical practice. Finally, the surgical approach to implant a penile prosthesis is recommended to patients that have failed medical therapy nor are satisfied with results and delivery routes. The objective of this study is to conduct a broad review to evaluate the effect and success rates of different therapeutic modalities for the management of post-RP ED.

Management

Patient counseling and psychosocial interventions

It is important to discuss the occurrence of post-RP ED with every candidate for RP. In addition, it is crucial to assess EF using available questionnaires, such as International Index of Erectile Function (IIEF) and Expanded Prostate Cancer Index Composite (EPIC), prior to and after the procedure to monitor EF recovery after RP. Patients should be aware that post-RP ED can be permanent or temporary, and although there is a tendency towards better preservation of EF with RARP, there is insufficient evidence to support a specific surgical technique (RRP vs RARP) that promotes better postoperative EF recovery [41, 42]. During the preoperative counseling, patients should also be aware of the relevant predictors of EF recovery, such as younger age, preoperative EF, bilateral nsRP and all penile rehabilitation methods. It is essential that patients are oriented that the recovery of postoperative EF can take many years. Finally, additional sexual changes should be clarified by the urologist, such as reduced libido, changes in orgasm, anejaculation, climacturia, and reduction of penile size [38].

Peer support seems to be positively associated with patient adherence to medical treatments for ED [43]. A randomized controlled trial involving 189 heterosexual couples, where the men underwent RP for PCa, showed that partners in the peer support group had higher sexual adjustment and used sexual aids more often when comparing to men in nurse counseling and usual care groups [43]. Although the main goal of RP is oncological, for many patients restoration of EF is as important. Psychological factors, such as relationship quality, depression or anxiety, are very important for the postoperative couple's sexuality. Canada et al. reported that sexual counseling intervention at 3-month assessment reduced overall distress among men and increased male and female global sexual function, with a return to baseline conditions at 6-month evaluation. As

Table 2 Erectile function recovery after different penile rehabilitation modalities.

Therapeutic modality	Characteristics	3 months	6 months	9 months	13.5 months	18 months
PDE5-I	Taladafil PRN			22.30%	23%	
	Taladafil OaD			11.30%	24.60%	
	Sildenafil (Begun < 6 months)	24%			51%	58%[a]
	Sildenafil (Begun > 6 months)					30%[a]
ICI	Begun < 6 months		67%[a]			52–58%[a]
	Begun > 6 months					30%[a]
VED				17%[a]		
MUSE		26%		55–74%	47%	

[a]Drug-assisted erection.

men regained the confidence to engage in sexual activities, they have reported an increase of ED treatments use from 31% at baseline to 49% at 6-month follow-up [44].

Timing to initiate penile rehabilitation

A study by Mulhall et al. [45], dividing men who started penile rehabilitation early after RP (<6 months) from those who had delayed (>6 months) start in penile rehabilitation, showed significant improvement in IIEF-EF domain score for the early group when compared to the delayed group. Additionally, there was also an increase in the proportion of men in the early group at 2 years after RP who had unassisted erections and PDE5-I-assisted erections when compared to the delayed group (58% vs 30%). Starting penile rehabilitation within 6 months of RP may offer benefits in improving overall EF but must be carried out in an individualized manner to assure patient safety. More recent studies have advocated a more precocious start of penile rehabilitation, starting PDE5-I as soon as the catheter is removed [46].

Therapeutic modalities

PDE5-I

As a response to sexual stimuli, nitric oxide (NO) is released from endothelial cells in the corpus cavernosum. NO activates guanylate cyclase to convert guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). Accumulation of cGMP leads to smooth muscle relaxation in and increased blood flow to the penis. PDE5 converts cGMP to 5′-GMP. PDE5-I competitively inhibits PDE5, enhancing the effects of NO. The increasing levels of cGMP in the smooth muscle cells is responsible for sustaining an erection [47]. Common adverse effects reported for PDE5-I include headache, flushing, nasal congestion, nasopharyngitis, and dyspepsia. Rare but serious reports of priapism have been reported with PDE5-I.

Despite nerve-sparing surgical techniques, PDE5-I are usually not very effective early after surgery, with 12–17% of responders after 6 months, because the cavernous nerves are injured intraoperatively and can take until 2 years to heal [48].

Interestingly, an in vivo study with rats undergoing unilateral and bilateral cavernosal resection showed that long-term PDE5-I administration post-RP significantly decreased the amount of smooth muscle cell apoptosis and collagen deposition in corpora cavernosa, corpus spongiosum, and tunica [49]. Given that PDE5-I administration positively affected rats in both resection groups, this suggests that ED post-RP may not be completely attributed to acute nerve injury, but rather its chronic sequalae [49]. A study involving patients that underwent bilateral nsRP showed that 59% had preoperative cavernosal arterial insufficiency and 26% had venous leakage, of which only 31% and 8% achieved functional erections 12 months post-RP [31]. Additionally, 47% of the patients with normal vascular status were able to achieve functional erections, which suggests that ED pathology involves more complex mechanisms that may be attributed in part to arterial sufficiency, and not solely neurogenic etiologies [31].

Trying to elucidate PDE5 efficacy, Mulhall et al. [50] performed a nonrandomized study using PDE5-I in a penile rehabilitation protocol. Men with functional preoperative erections who underwent RP were treated early post-operatively with oral sildenafil. Non-responders were switched to ICI and instructed to use ICI three times a week. Only patients who presented within 6 months post-RP, who completed the IIEF questionnaire on at least three separate occasions after surgery, and had been evaluated for at least 18 months were included. At 18 months post-RP, men that followed the protocol had higher rates of medication-unassisted intercourse, mean erectile rigidity, and mean IIEF-EF domain scores. Although this study showed remarkable work, the authors did not use a strict definition of EF recovery.

More recently, Mulhall et al. took on this problem in the REACTT trial [51]. The results of this randomized clinical trial suggested that treatment with tadalafil once daily (OaD) started early after bilateral nsRP for PCa may contribute to EF recovery. The authors observed that men receiving tadalafil OaD (22.3%) had achieved "back-to-baseline" IIEF-EF twice as often when compared with tadalafil PRN (11.8%) and placebo (7.8%). Unfortunately, this difference was eliminated after the drug-free washout period. Following the 3 months of open label treatment with tadalafil OaD, the number of men with EF recovery had almost doubled in all 3 groups. These results indicate that treatment with tadalafil OaD started early after nsRP improved drug-assisted EF, but had no effect on unassisted EF following treatment cessation after 9 months.

Vacuum erection device

Vacuum devices provide negative pressure to the penis, creating a passive engorgement of the corpora cavernosa. Men are advised to use a constrictor ring placed at the base of the penis to retain blood within the corpora. Studies in rats undergoing cavernous nerve injury demonstrated that VED therapy encourages EF recovery after RP acting on the preservation of both smooth muscle and endothelial integrity via anti-hypoxia, anti-apoptosis, and antifibrotic mechanisms [25]. In another study, Raina et al. [52] assessed 109 patients who developed ED after nsRP, and showed that 80% of patients that began early use of VED could have sexual intercourse, with a 55% sexual satisfaction rate. After 9 months, 17% of men had spontaneous erections sufficient for vaginal intercourse, compared to 10% of men in the control group [52]. Recently, Basal et al. randomized more than 200 patients treated with RARP to VED, PDE5-I alone, VED and PDE5-I, or placebo [53]. It was demonstrated that PDE5-I or the combination of PDE5-I and VED were the only modalities able to increase EF recovery after surgery. Conversely, VED as single therapy failed to show improvement in postoperative EF recovery. These results were limited by a small sample size and by the heterogeneity in preoperative characteristics, where a significant proportion of the subjects had ED before surgery. An additional benefit that may result with daily use of a VED is the preservation of penile length after RP [54], as some studies suggest that no penile rehabilitation therapy may result in up to a 2 cm penile length reduction [54]. The most common side effects of VED are mild and include numbness, pain, penile bruising, or petechiae. The use of the correct negative pressure should avoid most of these side effects. Men may also complain of lack of spontaneity and the sensation of a "cold" penis [54]. Other rare complications such as leg spasms, testicular migration, and urethral varicosities/bleeding have been reported [55].

ICI

ICI therapy is an important therapeutic option for men with ED. After administrated, the ICI stimulate relaxation of the corpora cavernosa smooth muscle to induce an erection [56, 57]. The most common administered drugs are phentolamine, prostaglandin E1 (PGE1), and papaverine. Phentolamine is an alpha-adrenergic antagonist that causes a decrease in peripheral vascular resistance and vasodilatation [58]. PGE1 is an endogenous prostaglandin that elicits cAMP production and thus decreases the influx of calcium within the penile vascular smooth muscle, leading to relaxation of trabecular smooth muscle, arterial dilation, blood entrapment and erection [59]. Papaverine is a direct-acting smooth muscle relaxant, causing the non-selective inhibition of PDE enzyme and direct inhibition of calcium channels [60]. Among the benefits of ICI, it should be noted that it does not involve irreversible procedures or the use of devices and has reproducible erection responses with tolerable side effects. Despite many advantages, some studies report a 11–31% drop-out rate, especially due to pain (11%) and lack of efficacy (9.7%) [61, 62].

Penile rehabilitation with ICI was initially performed by Montorsi et al. in 1997 [63]. Patients were given ICI of alprostadil three times per week for 6 months and compared to patients without injections. 67% of men that received ICI reported spontaneous erections sufficient for intercourse, while 20% of men in the control group had spontaneous erections. Mulhall et al. [50] also evaluated men that received penile rehabilitation with ICI and compared them to men who did not follow the protocol. The authors described an increase in the proportion of men who were able to have intercourse without the use of medication (52% vs. 19%, respectively); mean erectile rigidity (53 ± 21% vs. 26 ± 43%, respectively); mean IIEF-EF (22 ± 6 vs. 12 ± 14, respectively); and response to ICI (95% vs. 76%, respectively) at 18 months post-RP.

ICI should be used between 4 and 10 min before intercourse and its effects will last for ~2 h after the injection [64]. Before starting the treatment, men should be counseled about possible side effects and complications of ICI. The most feared side effect is having prolonged and painful erections, also known as priapism (1–5%) [62]. Patients should be oriented to seek immediate medical assistance in this situation. Other possible side effects include corporal fibrosis (2%, papaverine), hypotension and tachycardia (phentolamine) [65], and penile pain [66–68].

Intraurethral therapy with alprostadil suppository

The most common drug used in this modality is called medicated urethral system for erections (MUSE) and involves the formulation of alprostadil (PGE1) into a small

intraurethral suppository that can be inserted into the urethra. As previously described, PGE1 acts by increasing the cAMP level and oxygenation by promoting blood flow [59]. At first, MUSE was used to treat males with organic ED and presented decent efficacy, with 69% of men achieving satisfying erections, compared to 11% of patients in the placebo group [69]. Currently, the only available randomized study investigating MUSE for penile rehabilitation compared MUSE with daily sildenafil in 139 patients and showed no difference in EF one year after RP [70]. Unfortunately, this study did not have a placebo or no-treatment group, impairing proper analysis and comparison with other methods of penile rehabilitation. Raina et al. [71] also studied MUSE therapy in 91 men after bilateral nsRP. A total of 56 men were treated with MUSE while the remaining 35 patients received no ED treatment. After 6 months, 37% more men receiving MUSE achieved erections sufficient for intercourse. Also, men in the treatment group had higher Sexual Health Inventory for Men (18.9) when compared to the control group (15.8). Once more, a flaw in the design with improper randomization precluded an unbiased analysis. Furthermore, there was a 32% drop-out rate in the MUSE group due to lack of efficacy, reduced sexual interest and adverse effects.

The most common adverse events of MUSE are local pain (29–41%), dizziness - possibly associated to hypotension (1.9–14%), penile fibrosis, priapism (< 1%), urethral bleeding (5%), and urinary tract infections (0.2%); the last two related to the mode of administration [72].

Penile implant

Penile prosthesis is the most effective therapeutic modality for severe and/or medically refractory ED and provides reliable, on-demand erections, and high satisfaction rates [73–75]. Globally, between 2005 and 2012, more than 63,000 penile implants were performed, with ~85.9% of penile implants performed within the United States. The two most reported indications for the surgery were organic ED (23.7%) and post-RP ED (21.2%) [76]. Although a high number of penile prostheses were performed due to post-RP ED, only a small amount of post-RP patients would proceed with penile implant. In the state of Florida, between 2006 and 2015, only 4.9% patients with PCa treated with RP underwent subsequent prosthesis. The mean time from RP to prosthesis was 2.6 years [77]. Worldwide, however, the rate of penile prosthesis implantation after RP was even lower, varying from 0.8 to 1.9% [78, 79]. Since the recovery from neuropraxia after nsRP is time dependent, penile prosthesis implantation for post-RP ED is usually delayed for at least 1 year following the procedure [79], justifying the elevated mean time between RP and the penile prosthesis implant. A study by Tal et al. [79] evaluating predictors of penile prosthesis implant found that men who had RP for Ca, were of a younger age, African/American/Hispanic race, unmarried, and living in a geographic region other than the Northeast were more likely to proceed with penile prosthesis implantation.

The two currently available types of penile prostheses include malleable and inflatable devices (2- and 3-piece). The malleable device requires a less invasive procedure (no reservoir or pump) and results in a rigid penis, which may be manually concealed by bending the penis when desired [80]. The 2-piece inflatable prosthesis can be an interesting option among patients who are at high-risk of complications with reservoir placement, besides being easier to manipulate. The 3-piece inflatable devices are usually preferred due to the more "natural" erections obtained and excellent rigidity, besides mimicking the flaccid state of the penis, but require higher manual dexterity [80]. Additional attention should be given to the reservoir placement when performing the 3-piece inflatable prosthesis implant in patients with history of RP. The reservoir is usually placed in the space of Retzius, but if the space of Retzius is obliterated due to previous pelvic surgery, the reservoir may be placed in the submuscular space, anterior to the transversalis fascia, using a separated incision or through the inguinal ring [81–83]. Also, retroperitoneal placement of the reservoir can be an option for specific cases when the abdominal wall condition precludes the conventional sites [84, 85].

Satisfaction after a penile prosthesis implant is as high as 80% even when considering all functional aspects of the device, such as inflation, deflation, and rigidity [75]. Other studies reported satisfaction rates with malleable prostheses higher than 90% and slightly higher with inflatable devices [86]. Despite the need for psychological and sexual adaptation after the penile prosthesis implant, patients experience a marked improvement in EF with elevation of libido. Fear regarding the maintenance of an erection during sexual activities is remarkably soothed. In addition to an increase in the regularity of sexual activity and sexual satisfaction, there is also an improvement of mood and anxiety [87], showing the psychological importance of EF to the patient. The most important factors contributing to high level of satisfaction are rapid generation of erection, consistently optimal rigidity, minimal rate of postoperative complications, ease of concealment, cosmetic outcome, device function, ease of use, and partner acceptance [88].

The two most important complications of penile prostheses surgery are mechanical failure and infection [89]. Several improvements of the 3-piece prosthesis resulted in mechanical failure rates of <5% after 5 years of follow-up [75, 90, 91]. Also, surgical techniques that decrease contact with the patient's skin associated with proper antibiotic prophylaxis reduced infection rates to 2–3% with primary implantation in low-risk patients and high-volume centers [88, 90–94].

Additionally, this therapy requires the ability to grasp and visualize the penis for appropriate use; therefore either the patient or the partner needs to have a certain degree of hand dexterity for this therapeutic option to be effective [95]. For men lacking such manual dexterity, a malleable penile device can be offered due to its simpler operability [80].

Penile rehabilitation suggestions

Given that age and baseline EF play a critical role in achieving successful penile rehabilitation [96], it is important to establish a preoperative EF baseline to assess which treatments to offer.

For patients with normal preoperative EF, urologists should consider minimally invasive penile rehabilitation protocols such as concomitant use of PDE5-I and VED as first-line options [97]. More invasive procedures such as ICI and its combination with VED should be offered as second choices [46]. It is important to note that since PDE5-I are the least invasive method, they can be used as early as catheter removal [46, 97]. Due to their more invasive nature, VED and ICI should be started one month after the surgery [63, 98, 99]. The goal for rehabilitation is for the patient to obtain reasonably frequent erections. Therefore, we recommend the penile rehabilitation frequency of at least 3 times a week.

Patients with preoperative ED should be closely monitored after surgery and managed more aggressively. Therefore, ICI can be considered as a first-line option for penile rehabilitation. For men that failed penile rehabilitation measures, or with severe preoperative ED, the penile implant should be offered as an option given their positive success rates [73–75]. Since recovery from neuropraxia is time-dependent, men with undetectable postoperative PSA are candidates for surgery after 1 year [79].

Novel therapies such as shock wave therapy and platelet rich plasma injections should be offered as experimental modalities inside clinical trials. Additionally, due to poor results, we do not offer intraurethral suppository as part of penile rehabilitation therapy [100].

Conclusion

ED is a reality for men in the post-RP follow-up, with a prevalence ranging from 10–82%, and this complication should be addressed in preoperative counseling. The best outcomes for the management of post-RP ED combines adequate pre- and postoperative care, psychosocial support and refined surgical technique, but there is still not enough evidence to support RARP over RRP. One significant obstacle for postoperative care is the lack of a standardized and objective definition to accurately determine baseline EF and postoperative ED. This makes it challenging to tailor treatment, manage expectations, and monitor progress in men who suffer from post-RP ED. Nevertheless, treatment remains unquestionably superior to no intervention, and the maintenance of adequate blood flow to the penis regardless of the chosen treatment should be the focus. Urologists should consider the use of minimally invasive penile rehabilitation protocols such as concomitant use of PDE5-I and VED as first-line options, with the more invasive procedures such as ICI, intraurethral suppository, and penile implant being second-line choices. The process of rehabilitation should be initiated as early as catheter removal or during the first month post-RP. Urologists should expect that patients with previous normal EF will spontaneously recover EF in 22% of cases. When choosing treatment, patients can expect 25% recovery in EF within the first 9 months with PDE5-I, a wide range of 25–75% after 2 years with PDE5-I or with VED, and 67% with ICI. Although MUSE did not show significant difference when compared to PDE-5 inhibitors, the drop-out rate was considerably higher (30%). Additionally, psychological and sexual counseling has shown additional improvements and increased adherence for rehabilitation and treatment strategies of post-RP ED. For those patients with poor preoperative EF, non-responders, and those with non-nerve sparing intervention, the penile prosthesis implant remains a long-term, highly satisfactory intervention.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. American Cancer Society. Facts & Figures 2020. Atlanta, GA: American Cancer Society; 2020.
2. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol. 2017;71:618–29.
3. Borregales LD, Berg WT, Tal O, Wambi C, Kaufman S, Gaya JM, et al. 'Trifecta' after radical prostatectomy: is there a standard definition? BJU Int. 2013;112:60–7.
4. Walz J, Burnett AL, Costello AJ, Eastham JA, Graefen M, Guillonneau B, et al. A critical analysis of the current knowledge of surgical anatomy related to optimization of cancer control and preservation of continence and erection in candidates for radical prostatectomy. Eur Urol. 2010;57:179–92.
5. Masterson TA, Serio AM, Mulhall JP, Vickers AJ, Eastham JA. Modified technique for neurovascular bundle preservation during

radical prostatectomy: association between technique and recovery of erectile function. BJU Int. 2008;101:1217–22.
6. Glickman L, Godoy G, Lepor H. Changes in continence and erectile function between 2 and 4 years after radical prostatectomy. J Urol. 2009;181:731–5.
7. Ficarra V, Novara G, Ahlering TE, Costello A, Eastham JA, Graefen M, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. Eur Urol. 2012;62:418–30.
8. Kim SC, Song C, Kim W, Kang T, Park J, Jeong IG, et al. Factors determining functional outcomes after radical prostatectomy: robot-assisted versus retropubic. Eur Urol. 2011;60: 413–9.
9. Krambeck AE, DiMarco DS, Rangel LJ, Bergstralh EJ, Myers RP, Blute ML, et al. Radical prostatectomy for prostatic adenocarcinoma: a matched comparison of open retropubic and robot-assisted techniques. BJU Int. 2009;103:448–53.
10. Catalona WJ, Carvalhal GF, Mager DE, Smith DS. Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. J Urol. 1999;162:433–8.
11. Fulmer BR, Bissonette EA, Petroni GR, Theodorescu D. Prospective assessment of voiding and sexual function after treatment for localized prostate carcinoma: comparison of radical prostatectomy to hormonobrachytherapy with and without external beam radiotherapy. Cancer. 2001;91:2046–55.
12. Guillonneau B, Cathelineau X, Doublet JD, Baumert H, Vallancien G. Laparoscopic radical prostatectomy: assessment after 550 procedures. Crit Rev Oncol Hematol. 2002;43:123–33.
13. Katz R, Salomon L, Hoznek A, de la Taille A, Vordos D, Cicco A, et al. Patient reported sexual function following laparoscopic radical prostatectomy. J Urol. 2002;168:2078–82.
14. Kundu SD, Roehl KA, Eggener SE, Antenor JA, Han M, Catalona WJ. Potency, continence and complications in 3,477 consecutive radical retropubic prostatectomies. J Urol. 2004;172: 2227–31.
15. Potosky AL, Davis WW, Hoffman RM, Stanford JL, Stephenson RA, Penson DF, et al. Five-year outcomes after prostatectomy or radiotherapy for prostate cancer: the prostate cancer outcomes study. J Natl Cancer Inst. 2004;96:1358–67.
16. Dubbelman YD, Dohle GR, Schröder FH. Sexual function before and after radical retropubic prostatectomy: a systematic review of prognostic indicators for a successful outcome. Eur Urol. 2006;50:711–8.
17. Anastasiadis AG, Salomon L, Katz R, Hoznek A, Chopin D, Abbou CC. Radical retropubic versus laparoscopic prostatectomy: a prospective comparison of functional outcome. Urology. 2003;62:292–7.
18. Roumeguere T, Bollens R, Vanden Bossche M, Rochet D, Bialek D, Hoffman P, et al. Radical prostatectomy: a prospective comparison of oncological and functional results between open and laparoscopic approaches. World J Urol. 2003;20:360–6.
19. Joseph JV, Vicente I, Madeb R, Erturk E, Patel HR. Robot-assisted vs pure laparoscopic radical prostatectomy: are there any differences? BJU Int. 2005;96:39–42.
20. Meuleman EJH, Mulders PFA. Erectile function after radical prostatectomy: a review. Eur Urol. 2003;43:95–102.
21. Geary ES, Dendinger TE, Freiha FS, Stamey TA. Nerve sparing radical prostatectomy: a different view. J Urol. 1995;154:145–9.
22. Schover LR, Fouladi RT, Warneke CL, Neese L, Klein EA, Zippe C, et al. Defining sexual outcomes after treatment for localized prostate carcinoma. Cancer. 2002;95:1773–85.
23. Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. JAMA. 2000;283:354–60.
24. Carlucci JR, Nabizada-Pace F, Samadi DB. Robot-assisted laparoscopic radical prostatectomy: technique and outcomes of 700 cases. Int J Biomed Sci. 2009;5:201–8.
25. Rodriguez E Jr., Finley DS, Skarecky D, Ahlering TE. Single institution 2-year patient reported validated sexual function outcomes after nerve sparing robot assisted radical prostatectomy. J Urol. 2009;181:259–63.
26. Shikanov SA, Zorn KC, Zagaja GP, Shalhav AL. Trifecta outcomes after robotic-assisted laparoscopic prostatectomy. Urology. 2009;74:619–23.
27. Ploussard G, Xylinas E, Salomon L, Vordos D, Hoznek A, Abbou CC, et al. Robot-assisted extraperitoneal laparoscopic radical prostatectomy: experience in a high-volume laparoscopy reference centre. BJU Int. 2010;105:1155–60.
28. Gratzke C, Angulo J, Chitaley K, Dai YT, Kim NN, Paick JS, et al. Anatomy, physiology, and pathophysiology of erectile dysfunction. J Sex Med. 2010;7:445–75.
29. Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. J Urol. 1982;128:492–7.
30. Castiglione F, Ralph DJ, Muneer A. Surgical techniques for managing post-prostatectomy erectile dysfunction. Curr Urol Rep. 2017;18:90.
31. Mulhall JP, Slovick R, Hotaling J, Aviv N, Valenzuela R, Waters WB, et al. Erectile dysfunction after radical prostatectomy: hemodynamic profiles and their correlation with the recovery of erectile function. J Urol. 2002;167:1371–5.
32. Leungwattanakij S, Bivalacqua TJ, Usta MF, Yang DY, Hyun JS, Champion HC, et al. Cavernous neurotomy causes hypoxia and fibrosis in rat corpus cavernosum. J Androl. 2003;24: 239–45.
33. Moreland RB. Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. Int J Impot Res. 1998;10:113–20.
34. Kim N, Vardi Y, Padma-Nathan H, Daley J, Goldstein I, Saenz, et al. Oxygen tension regulates the nitric oxide pathway. Physiological role in penile erection. J Clin Invest. 1993;91:437–42.
35. Lue TF, Tanagho EA. Physiology of erection and pharmacological management of impotence. J Urol. 1987;137:829–36.
36. van Poppel H, Everaerts W, Tosco L, Joniau S. Open and robotic radical prostatectomy. Asian J Urol. 2019;6:125–8.
37. Nelson CJ, Scardino PT, Eastham JA, Mulhall JP. Back to baseline: erectile function recovery after radical prostatectomy from the patients' perspective. J Sex Med. 2013;10:1636–43.
38. Salonia A, Adaikan G, Buvat J, Carrier S, El-Meliegy A, Hatzimouratidis K, et al. Sexual rehabilitation after treatment for prostate cancer-part 1: recommendations from the fourth International Consultation for Sexual Medicine (ICSM 2015). J Sex Med. 2017;14:285–96.
39. Liu C, Lopez DS, Chen M, Wang R. Penile rehabilitation therapy following radical prostatectomy: a meta-analysis. J Sex Med. 2017;14:1496–503.
40. Gandaglia G, Suardi N, Cucchiara V, Bianchi M, Shariat SF, Roupret M, et al. Penile rehabilitation after radical prostatectomy: does it work? Transl Androl Urol. 2015;4:110–23.
41. Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N. Engl J Med. 2008;358: 1250–61.
42. Punnen S, Cowan JE, Chan JM, Carroll PR, Cooperberg MR. Long-term health-related quality of life after primary treatment for localized prostate cancer: results from the CaPSURE registry. Eur Urol. 2015;68:600–8.
43. Chambers SK, Occhipinti S, Stiller A, Zajdlewicz L, Nielsen L, Wittman D, et al. Five-year outcomes from a randomised

controlled trial of a couples-based intervention for men with localised prostate cancer. Psychooncology. 2019;28:775–83.
44. 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.
45. 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.
46. Jo JK, Jeong SJ, Oh JJ, Lee SW, Lee S, Hong SK, 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.
47. Huang SA, Lie JD. Phosphodiesterase-5 (PDE5) inhibitors in the management of erectile dysfunction. P T. 2013;38:407–19.
48. Fode M, Ohl DA, Ralph D, Sønksen J. Penile rehabilitation after radical prostatectomy: what the evidence really says. BJU Int. 2013;112:998–1008.
49. Kovanecz I, Rambhatla A, Ferrini M, Vernet D, Sanchez S, Rajfer J, 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.
50. Mulhall J, Land S, Parker M, Waters WB, Flanigan RC. The use of an erectogenic pharmacotherapy regimen following radical prostatectomy improves recovery of spontaneous erectile function. J Sex Med. 2005;2:532–40.
51. Mulhall JP, Brock G, Oelke M, Fode M, Probst KA, Henneges C, 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;13:679–83.
52. Raina R, Agarwal A, Ausmundson S, Lakin M, Nandipati KC, Montague DK, et al. Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. Int J Impot Res. 2006;18:77–81.
53. 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.
54. Lehrfeld T, Lee DI. The role of vacuum erection devices in penile rehabilitation after radical prostatectomy. Int J Impot Res. 2009;21:158–64.
55. Yuan J, Hoang AN, Romero CA, Lin H, Dai Y, Wang R. Vacuum therapy in erectile dysfunction—science and clinical evidence. Int J Impot Res. 2010;22:211–9.
56. Kim N, Azadzoi KM, Goldstein I, Saenz, de Tejada I. A nitric oxide-like factor mediates nonadrenergic-noncholinergic neurogenic relaxation of penile corpus cavernosum smooth muscle. J Clin Invest. 1991;88:112–8.
57. Rajfer J, Aronson WJ, Bush PA, Dorey FJ, Ignarro LJ. Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, noncholinergic neurotransmission. N. Engl J Med. 1992;326:90–4.
58. National Center for Biotechnology Information. PubChem Compound Summary for CID 5775, Phentolamine. https://pubchem.ncbi.nlm.nih.gov/compound/Phentolamine. Accessed Nov. 13, 2020.
59. Melanie R, Hew VG. Prostaglandin E1. Treasure Island, FL: StatPearls Publishing; 2020.
60. National Center for Biotechnology Information. PubChem Compound Summary for CID 4680, Papaverine. https://pubchem.ncbi.nlm.nih.gov/compound/Papaverine. Accessed Nov. 13, 2020.
61. Linet OI, Ogrinc FG. Efficacy and safety of intracavernosal alprostadil in men with erectile dysfunction. The Alprostadil Study Group. N. Engl J Med. 1996;334:873–7.
62. Virag R, Shoukry K, Floresco J, Nollet F, Greco E. Intracavernous self-injection of vasoactive drugs in the treatment of impotence: 8-year experience with 615 cases. J Urol. 1991;145:287–92.
63. Montorsi F, Guazzoni G, Strambi LF, Da Pozzo LF, Nava L, Barbieri L, et al. Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial. J Urol. 1997;158:1408–10.
64. Zorgniotti AW, Lefleur RS. Auto-injection of the corpus cavernosum with a vasoactive drug combination for vasculogenic impotence. J Urol. 1985;133:39–41.
65. Deveci S, Mulhall JP. Chapter 37 - Male sexual dysfunction. In: Legato MJ, editor. Principles of gender-specific medicine. Second Edition San Diego: Academic Press; 2010. p 408–13.
66. Eardley I, Donatucci C, Corbin J, El-Meliegy A, Hatzimouratidis K, McVary K, et al. Pharmacotherapy for erectile dysfunction. J Sex Med. 2010;7:524–40.
67. Porst H, Burnett A, Brock G, Ghanem H, Giuliano F, Glina S, et al. SOP conservative (medical and mechanical) treatment of erectile dysfunction. J Sex Med. 2013;10:130–71.
68. Lakin MM, Montague DK, VanderBrug Medendorp S, Tesar L, Schover LR. Intracavernous injection therapy: analysis of results and complications. J Urol. 1990;143:1138–41.
69. Williams G, Abbou CC, Amar ET, Desvaux P, Flam TA, Lycklama à Nijeholt GA, et al. Efficacy and safety of transurethral alprostadil therapy in men with erectile dysfunction. MUSE Study Group. Br J Urol. 1998;81:889–94.
70. McCullough AR, Hellstrom WG, Wang R, Lepor H, Wagner KR, Engel JD. 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.
71. Raina R, Pahlajani G, Agarwal A, Zippe CD. The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. BJU Int. 2007;100:1317–21.
72. Shabsigh R, Padma-Nathan H, Gittleman M, McMurray J, Kaufman J, Goldstein I. Intracavernous alprostadil alfadex is more efficacious, better tolerated, and preferred over intraurethral alprostadil plus optional actis: a comparative, randomized, crossover, multicenter study. Urology. 2000;55:109–13.
73. Wilson SK, Delk JR, Salem EA, Cleves MA. Long-term survival of inflatable penile prostheses: single surgical group experience with 2,384 first-time implants spanning two decades. J Sex Med. 2007;4:1074–9.
74. Bettocchi C, Palumbo F, Spilotros M, Lucarelli G, Palazzo S, Battaglia M, et al. Patient and partner satisfaction after AMS inflatable penile prosthesis implant. J Sex Med. 2010;7:304–9.
75. Carson CC, Mulcahy JJ, Govier FE. Efficacy, safety and patient satisfaction outcomes of the AMS 700CX inflatable penile prosthesis: results of a long-term multicenter study. AMS 700CX Study Group. J Urol. 2000;164:376–80.
76. Baas W, O'Connor B, Welliver C, Stahl PJ, Stember DS, Wilson SK, et al. Worldwide trends in penile implantation surgery: data from over 63,000 implants. Transl Androl Urol. 2020;9:31–7.
77. Bajic P, Patel PM, Nelson MH, Dornbier RA, Kirshenbaum EJ, Baker MS, et al. Penile prosthesis implantation and timing disparities after radical prostatectomy: results from a statewide claims database. J Sex Med. 2020;17:1175–81.
78. Stephenson RA, Mori M, Hsieh YC, Beer TM, Stanford JL, Gilliland FD, et al. Treatment of erectile dysfunction following therapy for clinically localized prostate cancer: patient reported

use and outcomes from the Surveillance, Epidemiology, and End Results Prostate Cancer Outcomes Study. J Urol. 2005;174:646–50.
79. Tal R, Jacks LM, Elkin E, Mulhall JP. Penile implant utilization following treatment for prostate cancer: analysis of the SEER-Medicare database. J Sex Med. 2011;8:1797–804.
80. Salonia A, Bettocchi C, Carvalho J, Corona G, Jones TH, Kadioglu A, et al. Management of erectile dysfunction: European Association of Urology; 2016. https://uroweb.org/guideline/sexual-and-reproductive-health/#5.
81. Karpman E, Sadeghi-Nejad H, Henry G, Khera M, Morey AF. Current opinions on alternative reservoir placement for inflatable penile prosthesis among members of the Sexual Medicine Society of North America. J Sex Med. 2013;10:2115–20.
82. Henry G, Hsiao W, Karpman E, Bella AJ, Carrion R, Jones L, et al. A guide for inflatable penile prosthesis reservoir placement: pertinent anatomical measurements of the retropubic space. J Sex Med. 2014;11:273–8.
83. Stember DS, Garber BB, Perito PE. Outcomes of abdominal wall reservoir placement in inflatable penile prosthesis implantation: a safe and efficacious alternative to the space of Retzius. J Sex Med. 2014;11:605–12.
84. Thirumavalavan N, Gross MS, Munarriz R. Techniques of ectopic reservoir placement and their pitfalls. J Sex Med. 2017;14:1451–4.
85. Perito PE, Wilson SK. Traditional (retroperitoneal) and abdominal wall (ectopic) reservoir placement. J Sex Med. 2011;8:656–9.
86. Steege JF, Stout AL, Carson CC. Patient satisfaction in Scott and Small-Carrion penile implant recipients: a study of 52 patients. Arch Sex Behav. 1986;15:393–9.
87. Tefilli MV, Dubocq F, Rajpurkar A, Gheiler EL, Tiguert R, Barton C, et al. Assessment of psychosexual adjustment after insertion of inflatable penile prosthesis. Urology. 1998;52:1106–12.
88. Akin-Olugbade O, Parker M, Guhring P, Mulhall J. Determinants of patient satisfaction following penile prosthesis surgery. J Sex Med. 2006;3:743–8.
89. Serefoglu EC, Mandava SH, Gokce A, Chouhan JD, Wilson SK, Hellstrom WJ. Long-term revision rate due to infection in hydrophilic-coated inflatable penile prostheses: 11-year follow-up. J Sex Med. 2012;9:2182–6.
90. Hellstrom WJ, Montague DK, Moncada I, Carson C, Minhas S, Faria G, et al. Implants, mechanical devices, and vascular surgery for erectile dysfunction. J Sex Med. 2010;7:501–23.
91. Wilson SK, Cleves MA, Delk JR 2nd. Comparison of mechanical reliability of original and enhanced Mentor Alpha I penile prosthesis. J Urol. 1999;162:715–8.
92. Carson CC 3rd, Mulcahy JJ, Harsch MR. Long-term infection outcomes after original antibiotic impregnated inflatable penile prosthesis implants: up to 7.7 years of followup. J Urol. 2011;185:614–8.
93. Darouiche RO, Bella AJ, Boone TB, Brock G, Broderick GA, Burnett AL, et al. North American consensus document on infection of penile prostheses. Urology. 2013;82:937–42.
94. Zargaroff S, Sharma V, Berhanu D, Pearl JA, Meeks JJ, Dupree JM, et al. National trends in the treatment of penile prosthesis infections by explantation alone vs. immediate salvage and reimplantation. J Sex Med. 2014;11:1078–85.
95. Knoll P, Rai S, Talluri S, Bezinque A, Micciche R, Rao G, et al. A survey of usage of penile prosthesis. J Sex Med. 2020;17:2287–90.
96. Salonia A, Castagna G, Capogrosso P, Castiglione F, Briganti A, Montorsi F. Prevention and management of post prostatectomy erectile dysfunction. Transl Androl Urol. 2015;4:421–37.
97. Segal RL, Bivalacqua TJ, Burnett AL. Current penile-rehabilitation strategies: clinical evidence. Arab J Urol. 2013;11:230–6.
98. 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.
99. Köhler TS, Pedro R, Hendlin K, Utz W, Ugarte R, Reddy P, et al. A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. BJU Int. 2007;100:858–62.
100. Porst H. Transurethral alprostadil with MUSE (medicated urethral system for erection) vs intracavernous alprostadil-a comparative study in 103 patients with erectile dysfunction. Int J Impot Res. 1997;9:187–92.