Chapter 8

Preventing Erectile Dysfunction after Radical Prostatectomy: Nerve-Sparing Techniques, Penile Rehabilitation, and Novel Regenerative Therapies

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Additional information is available at the end of the chapter

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Abstract

Erectile dysfunction is a known and much-dreaded functional consequence of radical prostatectomy. Dr. Patrick Walsh pioneered the nerve-sparing radical retropubic prostatectomy in the early 1980s, which has mitigated the morbidity of this surgery. Postoperative potency rates range widely from 20 to 80%, however, and depend on myriad factors including age, preoperative potency, and degree of nerve-sparing during surgery. Over the past four decades several developments have continued to offer hope to patients and clinicians alike, including refined understanding of cavernosal nerve neuroanatomy, beneficial modifications in surgical technique, as well as the advent of robotic surgery. Furthermore, multiple pre- and post-operative penile rehabilitation techniques using mechanotherapy and pharmaceuticals have also improved functional recovery. This paper examines erectile dysfunction as a consequence of radical prostatectomy, including the physiology of erections, the pathophysiology of post-operative erectile dysfunction, novel surgical techniques to enhance neurovascular bundle preservation, and penile rehabilitation strategies involving hyperbaric oxygen, neuroprotective pharmaceuticals, dehydrated human amnion-chorion membrane allografts, and mesenchymal stem cell therapy.

Keywords: erectile dysfunction, nerve-traction injury, nerve-sparing radical prostatectomy, penile rehabilitation, amnion-chorion membrane therapy, stem cell therapy

1. Introduction

Erectile dysfunction is a known and much-dreaded functional consequence of surgery for prostate cancer. Although surgeons may cite oncologic control as the paramount component of the

"Trifecta" (i.e. cancer cure, continence, and potency), many patients cite recovery of erectile function as the true measure of treatment success. In the early days of radical prostatectomy, post-operative potency rates were poor, and in fact largely non-existent. With the advent of nerve-sparing anatomic radical retropubic prostatectomy, a surgical approach pioneered by Dr. Patrick Walsh, the prospect of post-operative recovery of potency became not only a possibility but a reality for many men. The myriad factors that influence a patient's likelihood of sexual function recovery after both open and robotic radical prostatectomy have been examined and published in the literature. Also, there has been much investigation into the pathophysiology of iatrogenic erectile dysfunction (i.e. neurapraxia and nerve-traction injury) in the form of in vitro, pre-clinical animal studies and even translational studies with randomized human subjects. Given the pivotal importance of erectile function in a patient's perceived post-operative quality of life, there is much interest in the optimization of perioperative techniques to spare the integrity of the cavernous nerves and to develop efficacious mechanical and pharmacologic penile rehabilitation programs. Such programs employ an increasingly sophisticated arsenal of medical technologies such as pluripotent stem cell therapy, cytokine-rich human amnion-chorion membrane allograft, and even reappropriation of pharmacotherapies traditionally used for other disease states that have been found to have neuroprotective properties. This chapter will examine the evolution in the understanding of erectile dysfunction as a consequence of radical prostatectomy and examine novel strategies for prevention and amelioration of this condition.

2. Physiology of erections

2.1. Anatomy

The central role of smooth muscle dynamics in the corpora cavernosa in the development of erections was first elucidated in the 1980s [1]. Identification of nitric oxide (NO) as the principle neurotransmitter for tumescence and phosphodiesterases for detumescence were also major milestones with well-known pharmacologic ramifications. Anatomically, beneath the Buck's fascia, the corpora cavernosa are surrounded by the two-layered tunica albuginea, a reticulated network of collagen and elastin fibers that provides structural support during tumescence. The outer layer serves to compress the obliquely oriented emissary veins during tumescence that results in the "bottle-neck" effect of slower outflow than inflow that is essential for maintenance of an erection (**Figure 1**) [2]. The penile arterial supply arises from internal pudendal artery, which then gives rise to the common penile artery that branches into the dorsal, cavernous, and bulbourethral arteries. The cavernous arteries are responsible for the engorgement of the corpora cavernosa during tumescence. Accessory pudendal arteries may also be present in up to 4–25% of patients and these arise from the external iliac, obturator, vesical, and femoral arteries. Their preservation has been shown to be important for recovery of erectile function after radical prostatectomy [3, 4].

2.2. Neuroanatomy

The vasomotor tone of the cavernous arteries is regulated by the autonomic cavernous nerves. They are the nerves that are being described during "nerve-sparing" techniques during radical

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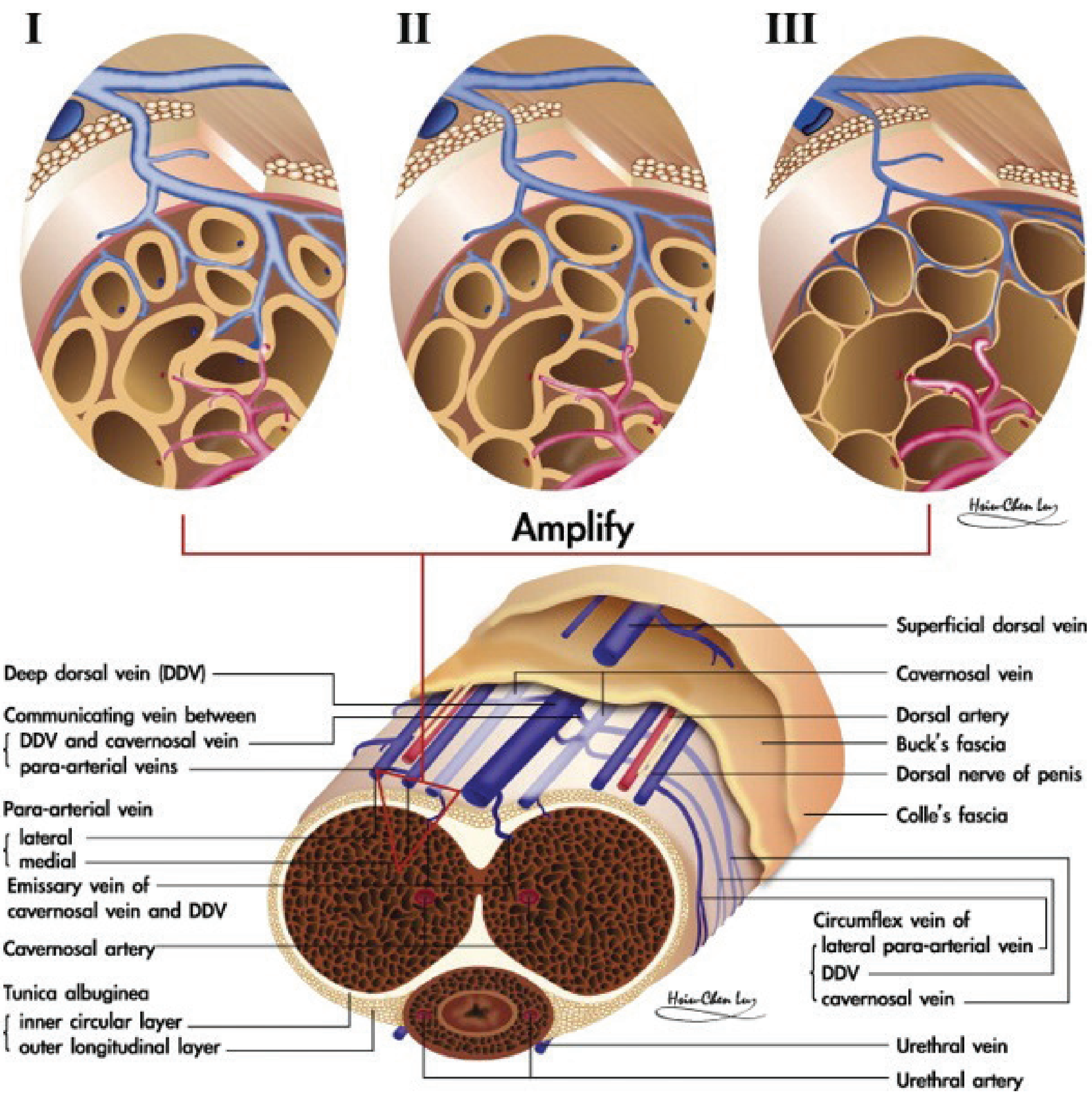

Figure 1. Anatomy of subtunical emissary veins as the basis for tumescence. Reprinted without changes from Molodysky et al. [2] https://creativecommons.org/licenses/by-nc-nd/3.0/.

prostatectomy. These nerves arise as an extension from the parasympathetic pelvic splanchnic nerves that originate from the pelvic plexus (S2–S4) located on either side of the rectum (**Figure 2**). These nerves innervate the endothelium of the cavernous sinuses and release acetylcholine which inhibits adrenergic neurons and stimulates NO release from endothelial cells [5]. NO increases intracellular production of cGMP with resultant decline in intracellular calcium and relaxation of the cavernous smooth muscle. Phosphodiesterase 5 is responsible for the degradation of cGMP and is the target of the well-known medications for erectile dysfunction.

Since Walsh and Donker pioneered the nerve-sparing radical prostatectomy in 1982, there has been much debate about the nature and trajectory of these nerves [6, 7]. These nerves have been found to travel as a latticework of delicate fibers principally along the posterolateral and lateral aspects of the prostate, but with some fibers coursing ventrally as well. Invaluable work in human cadavers by several investigators has elucidated precise position and orientation of these nerves to optimize their preservation during radical prostatectomy.

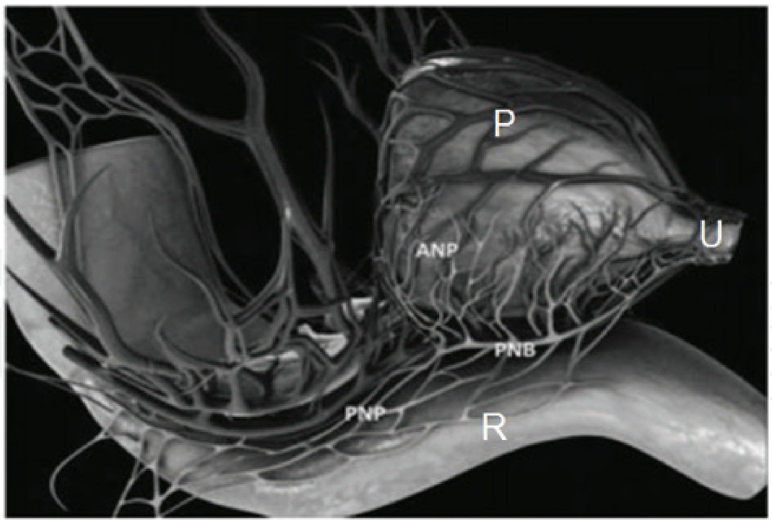

Figure 2. Pelvic plexus and cavernous nerve anatomy. P = prostate; U = urethra; R = rectum; PNP = proximal neurovascular plate; ANP = accessory neurovascular plate; PNB = predominant neurovascular bundle. Reprinted from Tewari et al. [12].

Costello et al. used cadaver models to identify three functional domains of the neurovascular bundle (NVB): the posterior and posterolateral component runs within the Denonvilliers' fascia and the pararectal fascia and innervates the rectum; the lateral component supplies the levator ani, and the cavernosal nerves lie along the posterolateral surface [8, 9]. Furthermore, Lunacek et al. showed that the cavernous nerves are displaced more anteriorly and splay along the lateral aspect of the prostate like a curtain [10]. These findings inspired the "curtain dissection" technique of high anterior release as well as the technique of preserving the lateral prostatic fascia within which the neurovascular bundle travels known as the "Veil of Aphrodite" technique to maximize the number of nerve fibers preserved [10, 11]. Dr. Ashutosh Tewari has conceptualized the neuroanatomy as consisting of a tri-zonal neural architecture, comprised of the proximal neurovascular plate (PNP), predominant neurovascular bundle (PNB), and accessory neural pathways (ANP) [12]. The PNP is synonymous with the pelvic plexus and the PNB is the traditionally described NVB, which is enclosed within the layers of levator fascia and/or lateral pelvic fascia. The nerves are situated in a "hammock-like" distribution rather than a distinct, isolated structure (**Figure 2**).

Further anatomical studies have demonstrated that a significant proportion of the nerves are situated on the anterior surface of the prostate, 21.5–28.5% [13] and 19.9–22.8% (**Figure 3**) [14]. Structural configurations range from round and bundle-like to more widely distributed splay-like [15]. Ganzer et al. employed computerized planimetry software to analyze the topography of the nerves on whole-mount pathologic sections obtained during non-nerve-sparing radical prostatectomy [16]. Total nerve surface area was most concentrated dorsolaterally (74.5–84.1%), but up to 39.9% of nerve surface area was found ventrolaterally. These correspond to the ANPs described by Dr. Tewari's group, who found them in 41% of the cadavers [12]. It is possible that all of these nerves are not responsible for erections. Subsequent studies in electrophysiologic stimulation have shown cavernosal pressure responses with stimulation at all positions of the midprostate between the 1:00 and 5:00 positions for all patients, suggesting their role in potency [17]. The precision vs. degree of electrical spread of such electrical stimulation may represent a limitation of this testing. Conversely, Costello et al. reported that

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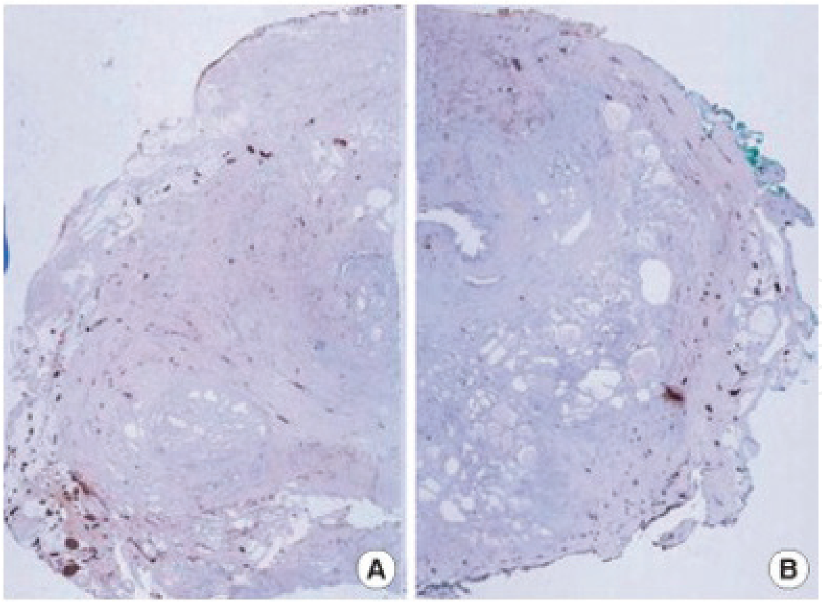

Figure 3. Whole-mount anatomy of neurovascular bundle (NVB) topography on the prostate. A. NVB concentrated at posterolateral aspect of prostate (S-100 stain) B. NVB are more widely distributed to ventral aspect of prostate (S-100 stain). Reprinted from Lee et al. [14].

significantly parasympathetic nerve fibers only account for 4–6.8% of nerves on the anterolateral aspect of the prostate [18]. These findings were corroborated by Ganzer et al., who used immunohistochemistry to distinguish between parasympathetic and sympathetic nerves. They reported that only 14.6% of the parasympathetic nerves resided above a horizontal line drawn at the prostate base and only 1.5% above a horizontal line at the apex [19].

How these anatomical findings impact the functional outcomes of the various nerve-sparing approaches described below, some of which advocate for high anterior release of the prostatic fascia, is interesting to consider (see Section 5.2).

3. Pathophysiology of post-prostatectomy erectile dysfunction

There are several acute and chronic factors that contribute to decline in erectile function after surgery for prostate cancer. These factors may be classified as vasculogenic, neurogenic, and even psychological. The burden of cancer diagnosis, treatment, and need for long-term PSA monitoring, along with recovery from surgery, implications on self-image, awareness of mortality, and perceived or actual reduction in penile length represent a constellation of psychosocial factors that may contribute to ED.

The role of accessory pudendal arteries in vasculogenic erectile function has been described above. Chen et al. has also implicated the veins that travel longitudinally within the layers of the tunica albuginea. His group have reported that ligation of the DVC during prostatectomy results in dilatation of these veins which results in veno-occlusive dysfunction [20].

The vascular sequelae of radical prostatectomy were investigated by Mulhall et al., who reported cavernosometry and/or penile duplex ultrasonography [21]. They found arterial insufficiency in 59% and venous leakage in 26% of men after bilateral nerve-sparing RRP who had excellent pre-operative erectile function. Normal vascular status was found in 35% of men. Return to penetrative function was correlated with the vascular status, with 47% return if normal status, 31% in arteriogenic insufficiency, and only 9% with veno-occlusive dysfunction at 12 months. They also reported that the longer the duration of erectile dysfunction, the higher the risk of venous leakage. Zelefsky et al. reported venous leakage in 52%, arterial insufficiency in 32%, and neurogenic dysfunction in 12% [22]. Montorsi et al. found a higher proportion of patients with veno-occlusive disease in their randomized study of intracavernous alprostadil after open RP: 67% veno-occlusive dysfunction, 17% arterial insufficiency, 17% normal vascular dynamics [23].

3.1. Neurapraxia

The neurogenic basis for erectile dysfunction implicates the cavernous nerve architecture. Preservation of these architectural substrates may not be sufficient alone to engender recovery of post-operative function, as suggested by the well-documented latency period between surgery and functional recovery. This latency ranges from 6–24 months and has been suggested to be the result of nerve-traction injury from the physical manipulation/handling during surgery and resultant neurapraxia and axonotmesis [1, 24, 25].

Intraoperative manipulation and injury to the cavernosal nerves results in hemodynamic and histologic changes within the penis, which manifest clinically as erectile dysfunction. This injury may result from mechanical or thermal sources. Iatrogenic traction on the delicate neurovascular tissue can cause-stretch induced nerve injury and resulting dysfunction. Neuropathies may be classified into three histologic groups: neurapraxia, axonotmesis, and neurotmesis. Neurapraxia is the least severe and is characterized intact neural structural elements, but there may be ischemia and/or demyelination which leads to signal conduction block. Functional deficits in peripheral nerves manifest as motor, proprioceptive, and soft touch deficiencies, but these usually resolve in a few weeks (up to 12 weeks) [26]. The next level of injury is axonotmesis in which axons and their myelin sheaths over long segments of nerve are disrupted, while supporting structures such as the endoneurium are left intact [27]. There is consequent Wallerian degeneration distal to the level of injury and proximal axonal degeneration to the next node of Ranvier. Since the endoneurial tubes remain intact, recovery should be complete after a matter of several months but may not be complete. Frank transection of the nerve is termed neurotmesis, in which the endoneurial tubes and connective tissue components are disrupted. Intraneural fibrosis develops and impairs axonal regeneration and thus inhibits nerve functional recovery. Peripheral nerve regeneration is mediated by multiple factors including neurotrophic factors, extracellular matrix, and intact cellular components of the nervous system (i.e. endoneurium) [28]. Tissue trauma from surgery also generates an inflammatory response and oxidative stress around the degenerating axons with results in chromatolysis (degradation of the protein synthesizing infrastructure of the neuronal cell body) [29].

Nerve injury may have a vasculogenic etiology as well. Nerve ischemia may be a result of direct compression injury or stretch (“traction”) injury, which produces a reduction in cross-sectional area and resultant compression of the vasculature [27]. Traction disrupts and occludes small-sized arteries traveling with the nerves (vasa nervorum) which supply pelvic tissues as well as the nerves themselves. Biochemically within the cavernosal smooth muscle cells, hypoxia induces production of superoxide which initiates oxidative reactions and attacks surrounding molecules to produce more free radicals. Oxygen free radicals in the setting of a nitric-oxide containing environment tends to combine to form peroxynitrite (O=NOO-) which is highly neurotoxic. Exposure of nerves to this compound leads to rapid excitation, excitotoxicity, and degeneration in the acute setting. Nitric oxide bioavailability is thereby reduced in this setting, which further impacts penile smooth muscle relaxation and exacerbates the hypoxic conditions.

3.2. Thermal injury

The importance of athermal dissection has been reinforced as classic teaching during nerve-sparing radical prostatectomy. The precise functional deficits induced by monopolar or bipolar cautery has been investigated in a canine model [30]. A total of 12 dogs were divided into four groups of neurovascular bundle dissection: Group 1, suture ligatures; Group 2, monopolar electrocautery; Group 3, bipolar electrocautery; Group 4, ultrasonic shears. Peak intracavernous pressures in response to distal cavernous nerve stimulation immediately post-op and at 2 weeks showed an attenuated response compared to controls (74–91% decrease and 93–96% decrease, respectively). In the dogs where electrocautery was employed, there was in fact almost no rise in the intracavernous pressure in response to stimulation. The findings in this study were presented in the context of having spared the contralateral neurovascular bundle from any dissection. Their results may have been even more dramatic if thermal energy had been used bilaterally. The follow-up was also admittedly short in this series at 2 weeks post-op only. Much longer durations at 6-, 12-, and even 24 months would be helpful to determine the long-term impact of thermal energy on recovery of potency (see Section 5.6).

This very objective was explored in humans after robotic prostatectomy, demonstrating delayed recovery after 12–18 months, but with 68% of bilateral nerve-sparing patient ultimately recovering function at 24 months [31] (see Section 5.3).

3.3. Chronic cavernosal tissue changes

In the chronic phase of injury, the persistent loss of nerve signal conduction results in loss of spontaneous nocturnal erections and relative cavernosal ischemia. The pathophysiologic consequence is cavernosal smooth muscle apoptosis, upregulation of TGF-beta and collagen deposition within the corpora [32–35]. Cavernous neurotomy studies in rats have demonstrated that corporal smooth muscle apoptosis begins 1 day after injury and peaks within the first week [34]. This fibrotic reaction impairs full expansion of the venous sinuses within the tunica and failure to adequately compress the emissary veins against the tunica. The result is "veno-occlusive dysfunction" in which the venous outflow occurs with the same velocity as arterial inflow. In this setting, tumescence is unable to be achieved or maintained. Furthermore, there is anatomical loss of penile length and girth as a result of the cavernosal smooth muscle fibrosis.

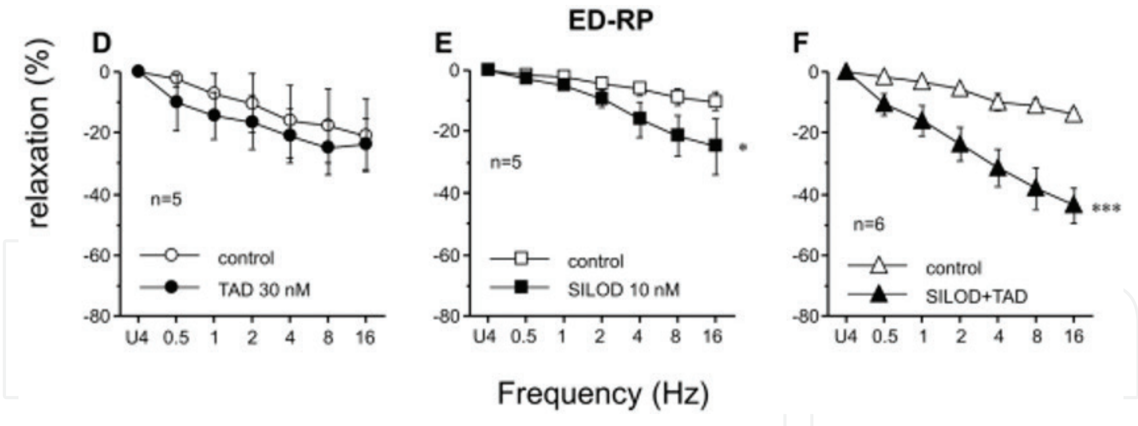

Figure 4. Effects of tadalafil, silodosin, or their combination on neurogenic relaxations induced by electrical field stimulation in human corpus cavernosum strips obtained from patients with erectile dysfunction after RP (ED-RP). *$P < 0.05$, *** $P < 0.001$. Reprinted from Martinez-Salamanca et al. [41].

3.4. Sympathetic disinhibition

Erectile function is not only the result of parasympathetic input, but a dynamic interplay between enhanced parasympathetic and inhibited sympathetic function. The role of adrenergic, sympathetic signals in ejaculation and detumescence have been well-established [36]. The adrenergic system essentially inhibits tumescence via the release of presynaptic norepinephrine (NE) that binds to postsynaptic α1- and α2-adrenergic receptors that induce penile arterial and cavernosal smooth muscle contraction. Also, the activation of presynaptic adrenergic receptors on the parasympathetic nerves inhibits release of NO [37]. The α1 receptor subtype is predominant in human erectile tissue, and furthermore α1A and α1D are more common than α1B in humans [38, 39]. Neurogenic contractile responses have been shown to be increased in the corpus cavernosum from rats after cavernous nerve injury and in cavernosal tissues from men with post-prostatectomy ED [40].

Recent animal studies have elucidated the role of adrenergic function on the contractile dynamics of cavernosal smooth muscle [41]. After bilateral crush injury to the cavernosal nerves rats were administered phentolamine (non-selective alpha-blocker), silodosin (α1A-selective alpha-blocker), or tap water only for 4 weeks and intracavernosal pressure (ICP) was monitored after (1) electrical stimulation of the cavernosal nerve proximal to the region of injury and (2) IV administration of tadalafil (phosphodiesterase 5 inhibitor). A significantly greater increase in ICP was observed for the silodosin group compared to the phentolamine or tap water groups after both electrical stimulation alone and co-administration with IV tadalafil. These findings suggest therapeutic benefit to alpha blockade for recovery of erectile function after RP. The authors translated their experiments to humans by obtaining strips of cavernosal smooth muscle at the time of inflatable penile prosthesis insertion. The response to electrical stimulation ex-vivo was enhanced by pretreatment of the muscle strips with both silodosin and tadalafil compared to tadalafil alone (**Figure 4**) [41].

4. Epidemiology of erectile dysfunction

The prevalence of erectile dysfunction in the general population has been reported by two large surveys: the Massachusetts Male Aging Study (MMAS) and the National Health and

Social Life Survey (NHSLS). According to the MMAS the rate of complete, moderate, and mild ED for the study of n = 1709 community-dwelling men in their 40–70 seconds was 5.1–15, 17–34, and 17%, respectively [42]. The NHSLS examined n = 1410 community-dwelling men and women in 1992 and reported rates of ED by age: 7%, 18–29 years; 9% 30–39 years; 11% 40–49 years; 18%, 50–59 years [43]. The definition of ED in this study was not quantified with validated questionnaires. International studies have reported rates of 20–40% for men 60–69 years [44]. ED is therefore an age-dependent disease. Other established risk factors include diabetes mellitus, hypertension, hyperlipidemia, psychiatric/psychologic disorders, history of pelvic trauma, chronic disease states (i.e. hypogonadism, thyroid disease, chronic kidney disease), and socio-demographic status.

There are multiple validated questionnaires to accurately assess various aspects of a patient's baseline sexual function. These questionnaires are integral in the patient workup as both a quantifiable measure of their function and a method of realistic prognostication of their likelihood of meaningful recovery. These elements comprise an important aspect of patient preoperative counseling and informed consent. The International Index of Erectile Function (IIEF) consists of 15 items and five domains and was developed by an international panel of experts for uses in determining treatment efficacy in clinical trials [45, 46]. Given its high sensitivity for detecting clinically significant treatment effects, it is regarded as the gold standard treatment outcome measure. Administration of this long questionnaire is somewhat cumbersome in a routine clinic setting, however. The National Institutes of Health's Consensus Panel on ED lead the development of an abridged five-item version of the IIEF, called the IIEF-5 or the Sexual Health Inventory for Men (SHIM). The SHIM is a powerful grading system and easily-administered patient reported tool [47]. It has high sensitivity and specificity and has been shown to be more reliable than a single item self-assessment of severity of ED [48]. Each question is rated on a Likert scale from 1 to 5, and consists of: "Over the past 6 months":

1. How do you rate your confidence that you could get and keep an erection?
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
5. When you attempted sexual intercourse, how often was it satisfactory for you?

Based on response to the questions, men may be categorized into one of five grades of ED severity: no ED (SHIM 22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), severe (1–7). Although there have been multiple other questionnaires published—the Quality of Erection Questionnaire, the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS), the Self-Esteem and Relationship questionnaire (SEAR); the Erection Hardness Score (EHS), the Sexual Experience Questionnaire—the IIEF and SHIM are the most widely employed, and have indeed been translated into over 30 languages [49, 50]. Another popular health-related quality of life (HRQoL) questionnaire specific to prostatectomy patients is the

Expanded Prostate Cancer Index Composite (EPIC), which examines urinary, bowel, sexual, and hormonal domains [51]. Some of these validated instruments have been used to measure outcomes in the randomized penile rehabilitation studies (see below).

Studies of ED prevalence among men prior to undergoing radical prostatectomy report potency rates ranging from 43 to 84%; the 43% value was obtained through interrogation with the IIEF [52–54]. The landmark prospective Prostate Cancer Outcomes Study (PCOS) included n = 3533 men from the Surveillance, Epidemiology and End Results (SEER) cancer registries diagnosed with prostate cancer in 1994–1995. A total of n = 1288 men who underwent radical prostatectomy had completed a baseline questionnaire were included. Baseline erections firm enough for intercourse was 81%, with 49% reporting a least "little/some" difficulty in maintaining erections [52, 53]. A limitation of these figures, however, is the fact the FDA approval of sildenafil only occurred in 1998 and "baseline" function was assessed through post-hoc recall within 6 months after treatment in 90% of patients, thereby introducing recall bias.

4.1. Incidence of erectile dysfunction after radical prostatectomy

Recovery rates after bilateral nerve-sparing open RRP ranges from 31 to 86% of sexually active men with organ-confined disease [55]. The recovery rates for unilateral nerve-sparing range from 13 to 56%, and for non-nerve sparing 0–17% [56–60]. The CaPSURE database of community-based Urology practices has reported that only 20% of men return to preoperative baseline potency at 12 months after RP [61]. The metric for assessment has an impact on the incidence of ED, and the use of validated questionnaires such as the IIEF tends to expose higher incidence of ED [55]. The long-term outcomes of the PCOS study demonstrated [53] worse erectile function in men after RP compared to radiation therapy at the 2- and 5-year evaluation time points, odds ratio 3.46 and 1.96, respectively. There was no significant difference at the 15-year follow-up time point, however. Defining sexual function as "erections in sufficient for intercourse" produced absolute rates of ED at 2, 5, and 15 years of 78.8, 75.7, and 87%, respectively (**Figure 5**). Of note, only 14.5% of men underwent bilateral nerve-sparing surgery in this series.. Among men who had bilateral nerve-sparing, 5-year erectile function firm enough for intercourse was reported in 40% of men vs. 23% and 23% for unilateral nerve-sparing and no nerve-sparing, respectively. Age was a significant predictor on multivariable analysis. Some limitations were the late approval of sildenafil in 1998 and the fact that RP was performed in an open manner, which limits applications to modern series. During the 3 years prior to the 5 year evaluation, only 43% of men had tried sildenafil.

Contemporary robotic prostatectomy series demonstrate 12 month potency rates ranging from 70 to 80% [62]. A systematic review and meta-analysis of 15 case series totaling n = 3491 patients reported 12- and 24-month potency rates ranging from 54–90% to 63–94%, respectively [63]. Among patients who had bilateral nerve-sparing, 12- and 24-month potency rates were 74 and 82% respectively. There may be a learning-curve effect with the robotic prostatectomy outcomes as well. The impact of surgeon experience/learning has been reported, but did not demonstrate statistical significance for potency rates between cases 1–300, 301–500, and 501–700 (61, 63, 65%, respectively) [64].

Outcomes stratified by specific nerve-sparing approach are presented below (see Section 5.3 below).

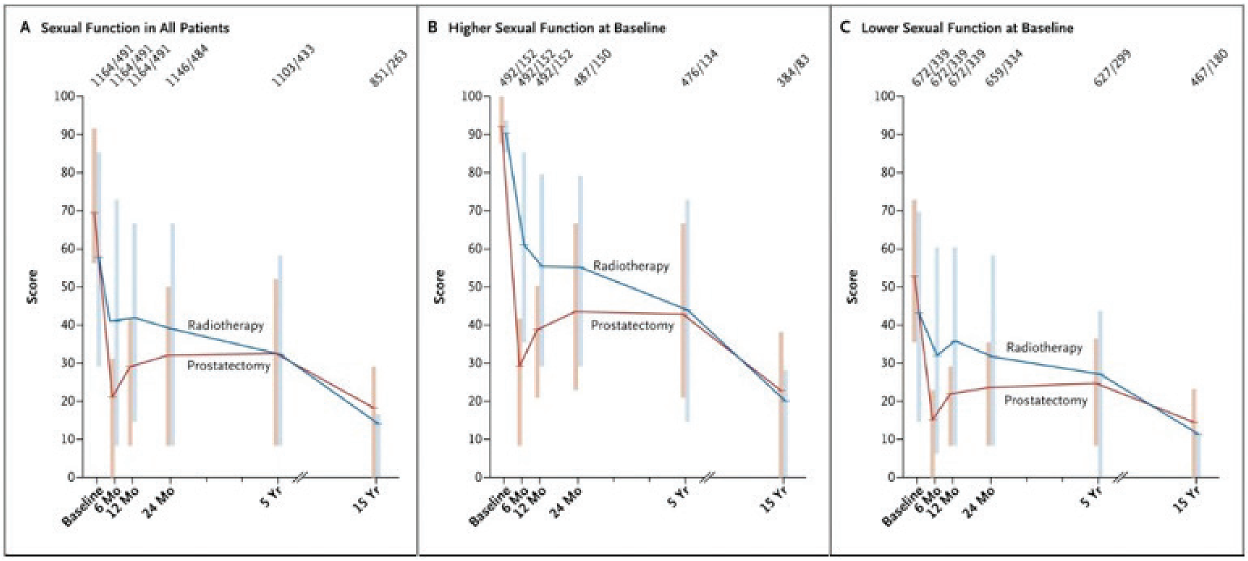

Figure 5. Sexual function over 15 years after treatment for prostate cancer. A. In all patients. B. Higher sexual function with International Index of Erectile Function (IIEF) score > or = 80; C. Lower sexual function, IIEF < 80. Numbers represent total of patients in radical prostatectomy (RP) group/radiation group. Reprinted from Resnick et al. [53].

4.2. Prognostic factors for recovery of erectile function post-prostatectomy

Factors for successful recovery of erectile function have been examined for patients after both open radical retropubic prostatectomy (RRP) and robotic prostatectomy in the modern era. A systematic review post-RRP identified age <60 years, completeness of nerve-sparing, and pre-operative sexual function [55]. Indeed, in the PCOS study a significantly higher proportion of men <60 years reported satisfactory response to sildenafil compared to older men ($p = 0.01$) [52]. The systematic review of robotic prostatectomy by Ficarra et al. cited age, baseline potency status, comorbidities index, and extent of nerve-sparing as predictors of postoperative recovery of potency [63]. There may be a learning-curve effect with the robotic prostatectomy outcomes as well. As discussed below, since nerve-sparing may be performed in an incremental manner rather than an "all-or-none" phenomenon, grade of nerve sparing has shown an influence on recovery [12, 65, 66] (see **Techniques of Nerve Sparing** below).

The impact of surgeon experience/learning has been reported [67], but did not demonstrate statistical significance for potency rates between cases 1–300, 301–500, and 501–700 (61, 63, 65%, respectively) [64]. As mentioned previously, lack of electrocautery during neurovascular bundle dissection portends earlier recovery of erectile function [31]. While other factors have been cited, the previous predictors are the most consistent throughout the medical literature.

Post-operative potency rates may be influenced by the time point of assessment. Studies typically report 12 and 24 month outcomes as the longest follow-up. Although recovery typically occurs within the first 2 years after surgery, delayed recovery is also possible. A series of n = 1003 men who underwent either open or robotic RP between 2007 and 2013 reported on the achievement of "good erectile function" as defined by IIEF-6 score ≥ 22 [68]. Among men with poor function at 12 months, the probability of recovering erectile function at 24, 36, and 48 months was 22, 32, and 40% on Kaplan–Meier analysis. The 12-month functional score and patient age were the only significant predictors of delayed recovery on multivariable analysis.

Also, very interestingly, the degree of nerve-sparing was not a predictor of delayed recovery; perhaps nerve-sparing only impacts early recovery at the 12-month time point. Surgical modality (open vs. robotic) was not explored. Similar findings of delayed recovery have been published in other reports [69, 70]. Such findings may be tempered by the gradual decline in erectile function after year 5 observed in the Prostate Cancer Outcomes Study [52].

5. Methods to improve nerve-sparing

5.1. Preoperative planning with multi-parametric MRI

Multiparametric magnetic resonance imaging (mpMRI) has gained widespread use in the workup of elevated PSA and diagnosis of prostate cancer via MRI-transrectal ultrasound (TRUS) targeted fusion biopsy. This technique has been shown to increase the detection rate of high-grade (i.e. Gleason 4 + 3 = 7) prostate cancer by 30% and result in lower detection of low grade prostate cancers by 17% [71]. The recently published PROMIS trial evaluated the performance of mpMRI to the reference standard template prostate mapping (TPM) biopsy and reported superior sensitivity for mpMRI compared to TRUS biopsy (93% vs. 48%, $p < 0.001$) and negative predictive value (89% vs. 74%, $p < 0.001$), allowing 24% with negative MRI to safely avoid having to undergo biopsy [72].

The utility of MRI may be applied to the domain of pre-surgical planning as well. The aggressiveness of nerve-sparing is not solely based on surgeon experience, but also on the anatomical location of the tumor and the presence of locally advanced (i.e. pT3a-b) disease that may be invading the neurovascular bundle. In the setting of pT3 disease (i.e. extraprostatic extension (EPE) and seminal vesicle invasion (SVI)), aggressive nerve sparing may result in a positive surgical margin (PSM), which has been associated with increased rates of biochemical recurrence, systemic metastasis, and prostate cancer-specific mortality post-prostatectomy, especially for high grade disease (i.e. Gleason Score 8–10) [73]. Even with careful adherence to surgical technique and the use of intraoperative frozen section analysis, microscopic positive margins may be imperceptible during surgery. A meta-analysis of 75 studies comprising 9796 patients who underwent mpMRI between 2000 and 2015 demonstrated high specificity for the detection of EPE (90%) and SVI (95%) [74]. However, sensitivity for these endpoints in the best performing series was 71–73%. Therefore, mpMRI may be limited in detecting microscopic EPE and SVI, which surely impacts the safety of nerve-sparing, especially in high risk patients.

Despite these limitations, there is level one evidence published by a single center in Norway suggesting that preoperative mpMRI does indeed reduce the rate of positive surgical margins at robotic radical prostatectomy and influences the rate of nerve-sparing in patients who otherwise might not have been considered for a nerve-sparing approach [75]. Among the n = 438 men randomized in this study to preoperative MRI vs. no MRI, sensitivity and specificity for detection of pT3 disease was 73 and 65%, respectively. The mpMRI information altered surgical approach in 27% of patients. Bilateral nerve sparing was performed 6.7% less frequently in the mpMRI group. The positive margin rate was reduced in the mpMRI group for cT1c patients (16% vs. 27%, $p = 0.035$). Among the patients found to have pT3 disease, 89% of them had only unilateral nerve sparing or no nerve sparing. This group did not have improvement in positive margin rate with the mpMRI, however. Perhaps, even wider excision is required to render these patients free of positive margins, which has implications for post-operative potency. Further study is surely needed to clarify the role of mpMRI for pre-surgical planning.

5.2. Intraoperative nerve-sparing techniques

Refined understanding of the neuroanatomy of the cavernous nerves informs the surgical approach to and completeness of nerve-sparing. The endopelvic fascia is a multilayered sheath that encloses and buttresses the prostate and bladder and attaches these organs to the pubic bone via the puboprostatic ligaments. This fascia fuses as the arcus tendineus fascia pelvis just lateral to these organs. The fascial investments of the prostate may be further divided into the prostatic "capsule," periprostatic veins with their fascia, the lateral pelvic fascia (prostatic fascia), levator fascia, and levator ani muscles (**Figure 6**) [76]. Lepor and Walsh described nerve sparing in 1983, with the approach beginning at the prostate apex and proceeding in a retrograde fashion toward the prostatic vascular pedicle [6, 7]. In the modern era of minimally invasive and robotic techniques, the nerve-sparing is usually performed in an antegrade manner after first controlling the prostatic vascular pedicle. Initial experiences with robotic prostatectomy employed monopolar or bipolar electrocautery to control the pedicle until the detrimental role of thermal injury was fully appreciated.

Classical approaches to nerve-sparing have been described as "interfascial" vs. "intrafascial" techniques, as well as the "extra-fascial" approach when nerve-sparing is not performed (**Figure 7**). Interfascial dissection follows the plane lateral to the prostatic fascia, which may render the NVB prone to partial resection. The intrafascial technique follows the plane directly on the prostatic capsule, medial to the prostatic fascia and anterior to the Denonvilliers' fascia, especially at the 5:00 and 7:00 positions. Dissection is typically performed with both blunt and sharp dissection in an athermal manner to reduce transmission of heat and electricity to the proximal NVB.

Refinements in the understanding of the neuroanatomy have resulted in more sophisticated classifications of nerve-sparing. An important concept is the ability to perform incremental nerve sparing, not just as an "all-or-none" phenomenon. It has been suggested that optical magnification and the extended degree of freedom afforded by robotic surgery facilitates

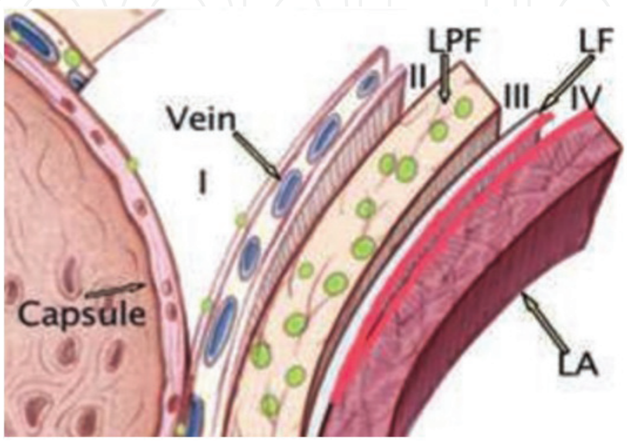

Figure 6. Planes for dissection of nerve-sparing based on prostatic fascial layers. LPF = lateral pelvic fascia (prostatic fascia); LF = levator fascia; LA = levator ani. Reprinted from Tewari et al. [76].

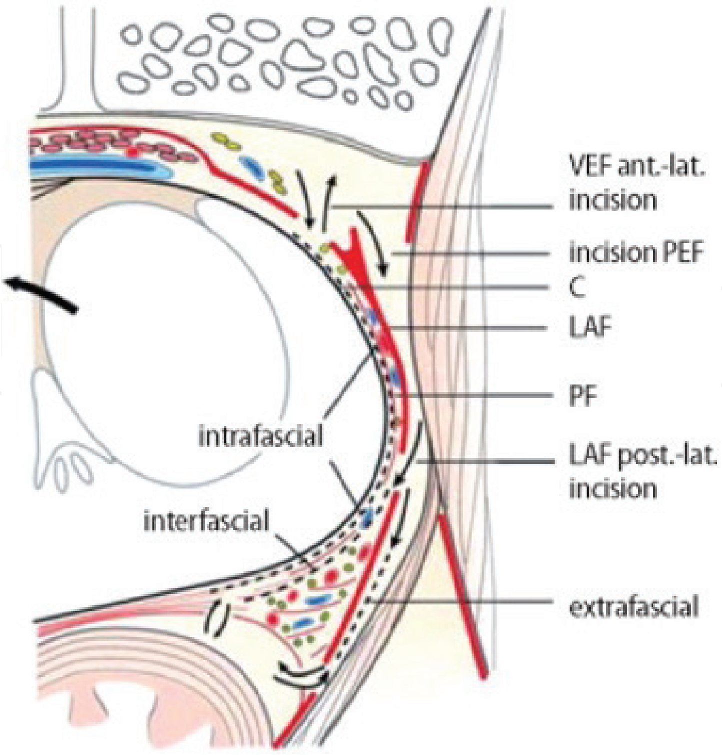

Figure 7. Intrafascial, Interfascial, Extrafascial dissection planes as the basis for nerve-sparing. VEF ant.-lat. = visceral endopelvic fascia anterior-lateral; PEF = parietal endopelvic fascia; C = capsule of prostate; LAF post.-lat. = levator ani fascia posterior-lateral; PF = prostatic fascia. Reprinted from Walz et al. [9].

development of dissection planes within the NVB itself to perform partial nerve sparing in the setting of concern for pT3 disease [12, 77]. This concept is illustrated in **Figure 6**. Dr. Tewari's series of n = 2317 patients was published in 2011 [76]. This approach relies on a risk-stratified approach to the "neural-hammock" as defined by the periprostatic veins and based on preoperative risk stratification based on Gleason score, PSA, digital rectal examination (DRE) findings, cancer volume, and mpMRI findings. The plane of dissection follows one of the grades illustrated in **Figure 6**. A similar grading system based on periprostatic arterial anatomy, rather than venous anatomy, has been proposed by Schatloff et al. (**Figure 8**). In their smaller series of n = 132 patients, they cite a landmark periprostatic artery to define grades as: 1, no nerve sparing; 2, <50% nerve-sparing; 3, 50% nerve sparing; 4, 75% nerve-sparing; 5, ≥95% nerve sparing [78]. The Menon et al. series reported on n = 2652 patients for whom nerve-sparing was initiated by incising the prostatic fascia anteriorly, termed "high anterior release" or the "Veil of Aphrodite" technique (**Figure 9**) [79]. The authors originally reported the development of a plane between the prostatic capsule and prostatic fascia cranially at the base of the seminal vesicles. This plane is propagated deep to the periprostatic venous sinuses with careful blunt and sharp dissection. For patients with significant periprostatic fibrosis after biopsy that impairs development of this plane, the authors recommend initiation of the dissection at the 2:00 or 10:00 position [79].

5.3. Outcomes of nerve-sparing techniques

Comparison of potency rates after the various surgical techniques is not straightforward, as there may be differences in patient demographics such as age and baseline potency,

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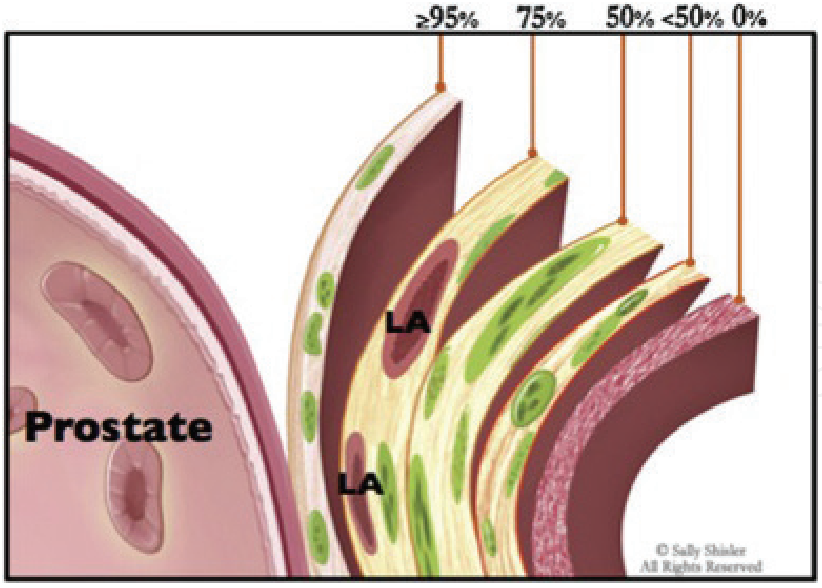

Figure 8. Grades of nerve-sparing based on anatomic landmark of periprostatic artery. LA = landmark artery. Reprinted from Schatloff et al. [78].

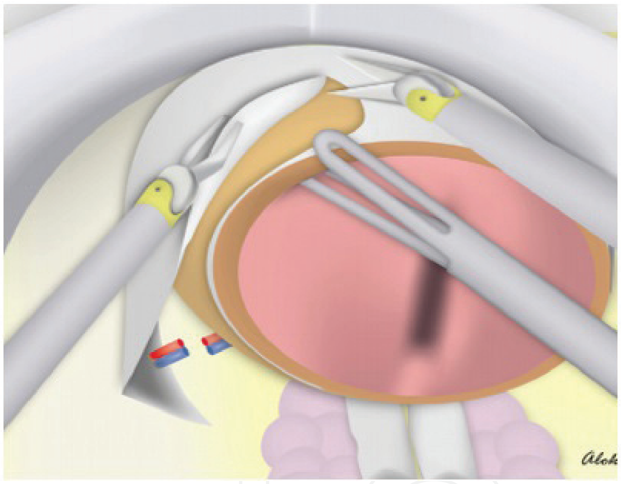

Figure 9. Plane of dissection for Veil of Aphrodite nerve-sparing technique. Reprinted from Menon et al. [79].

as well as tumor characteristics such as stage and grade that may influence the ability to perform bilateral nerve-sparing. Furthermore, based on the aforementioned variations in neuroanatomy among different patients, perfect execution of a given surgical technique may not be enough to accommodate a particular patient's anatomy, resulting in the variability of erectile function recovery. Definitions of potency also vary, with some studies reporting percentage return at a given time point or "return to baseline." The most robust series employ the validated questionnaires (IIEF, SHIM, EPIC), but precise cut-offs for restoration of function may vary. To add the possibility of subjective satisfaction beyond the numbers of the questionnaires, some studies also define potency as "erections suitable for intercourse" that are "satisfactory."

In the setting of these limitations, a recent systematic review and meta-analysis of six studies (only one randomized and three prospective; 4/6 minimally invasive approach) of n = 1663 patients reported improved erectile function at 6 months (RR 1.49) and 12 months (RR 1.40) for intrafascial vs. interfascial nerve-sparing.

Erectile function is not the only component of the Trifecta directly affected by nerve-sparing. Oncologic control with regard to the presence of positive surgical margins is also very important. Given the increased rates of biochemical recurrence and possibility of increased rates of metastasis and prostate-cancer specific mortality associated with the presence of a positive surgical margin, nerve-sparing outcomes must be understood within the context of margin status. Overall, the rates of PSM are around 15%, with rates ranging from 6 to 38% and influenced by pathologic stage, grade, and D'Amico risk category [80]. There have also been reports that bilateral vs. unilateral nerve-sparing in the setting of pT2 disease is associated with a higher rate of PSM, as demonstrated in a series of n = 9915 patients who underwent robotic prostatectomy at two institutions, with relative risk 1.52 [81]. Other studies have not corroborated an increased positive margin rate for intrafascial vs. interfascial nerve-sparing techniques (rate of 9% vs. 9.5%) [82]. The grades of nerve-sparing proposed by Dr. Tewari have been associated with excellent PSM rates, likely owing to preoperative risk stratification based on Gleason score, PSA, digital rectal examination (DRE) findings, cancer volume, and mpMRI findings. The rates of PSM for patients with nerve-sparing grades 1, 2, 3, and 4 were 9.9, 8.1, 7.2, and 8.7%, respectively ($p = 0.636$). The Schatloff series also reported their PSM rate, which was 9% overall. Although the rate of PSM for grade 1 NS was 0%, there was otherwise no consistent correlation between grade of NS and PSM rate (0, 5.7, 16.7, 7.5, 3.6% for grades 1, 2, 3, 4, and 5, respectively), perhaps reflecting good presurgical planning based on patient risk factors [78]. The Veil of Aphrodite technique by the Vattikuti Urology Institute reported a positive margin rate of 13%, which declined to 1.5% for pT2 disease after modification of approach to include en face oversewing of the DVC after apical transection [79].

Regarding the potency rates, it is necessary to standardize the definition of potency, which usually incorporates routine use of oral PDE 5 inhibitors. Furthermore, there is a distinction between restoration of penetrative sexual intercourse vs. return to baseline functioning. There are several contemporary series reporting erectile function outcomes after robotic prostatectomy. Tewari's risk-stratified approach to neural-hammock sparing in n = 2317 men resulted successful intercourse (score of ≥4 on question two of the SHIM and total SHIM >21) of 90.9, 81.4, 73.5, and 62% for nerve-sparing grades 1, 2, 3, and 4, respectively [76]. Regarding return to baseline function: grade 1, 81.7%; grade 2, 74.3%; grade 3, 66.1%; grade 4, 54.5%. Of note, this group also reported earlier return of continence associated with the higher grades of nerve-sparing, which has been controversial [83]. Incidentally, a recent systematic review and meta-analysis of 27 longitudinal cohort studies totaling n = 13,749 patients, however, reported that early urinary continence (at 6 months post-RP) was improved for patients undergoing nerve-sparing vs. non-nerve-sparing surgery (88.9% vs. 69.8%) [84].

Tewari's technical modification of adding real-time penile oxygen monitoring demonstrated that at 6 weeks postoperatively, a larger proportion of patients in the O_2 monitoring group had no ED (24.5% vs. 10.4%, $p < 0.05$) and at 52 weeks this difference was persistent (84% vs. 68%, $p < 0.05$). Furthermore, using the Sexual Health Inventory for Men (SHIM) validated questionnaire at 1 year, a greater number proportion of patients reported minimal to no ED (94% vs. 78%, $p < 0.05$). In this report, the authors did not sub-stratify by grade of nerve sparing [85] (see Section 5.4).

The Schatloff series on grade stratification based on periprostatic arterial anatomy did not report functional outcomes [78]. The Vattikuti Institute series included n = 1142 patients with minimum follow-up of 12 months and among men with normal preoperative function (i.e. SHIM >21) potency rates were 68% in the standard bilateral nerve-sparing patients and 93% in the bilateral Veil nerve-sparing patients [79]. Return to baseline rates depended on preoperative function, and for those without preoperative dysfunction, return to baseline was 39% for standard nerve-sparing and 73% for the Veil technique. Despite these very favorable results, the authors disclosed that only 50% of these patients attained normal SHIM score without medication. Although these findings suggest that the Veil offers improvements in recovery of erectile function, there may be a bias of surgeon experience, as the Veil technique was employed later in the learning curve of this single-surgeon series. This series also demonstrated 84% total urinary control, and 95% social continence (one pad or liner per day) at 12 months follow-up. The role of nerve-sparing in earlier recovery of continence has been corroborated by many series [86–88].

Some limitations of these studies are that they are single institution and often single-surgeon series and there is no direct comparison among different techniques to be able to assess superiority. Furthermore, there may be shortcomings with translation of these techniques into the larger urologic community compared to the immensely high-volume centers where these techniques were invented.

5.4. Intraoperative penile oxygen monitoring

The real-time impact of neurovascular bundle tension on cavernosal ischemia was investigated by Tewari et al. in n = 64 patients [85]. During robotic prostatectomy, these patients underwent real-time penile oxygen monitoring with the Odissey Tissue Oximeter probe placed 2 cm from the base of the penis. Surgical dissection was altered whenever the O_2 alarm sounded until oxygenation was restored to 85%. Functional outcomes were compared to a propensity-matched historical control group of n = 192 patients (matched for age, preoperative prostate specific antigen (PSA), baseline erectile function, comorbidity status, and extent of nerve-sparing). Steps in the operation associated with significant decline in tissue oxygenation included opening the endopelvic fascia, all of the nerve-sparing, excessive traction on the Foley catheter, seminal vesicles, or prostate during the apical dissection, and control of the dorsal vein complex (DVC) prior to apical dissection. Of note, control of the DVC if done after apical transection was not associated with significant penile ischemia. At 6 weeks postoperatively, a larger proportion of patients in the O_2 monitoring group had no ED (24.5% vs. 10.4%, $p < 0.05$) and at 52 weeks this difference was persistent (84% vs. 68%, $p < 0.05$). Furthermore, using the Sexual Health Inventory for Men (SHIM) validated questionnaire at 1 year, a greater number proportion of patients reported minimal to no ED (94% vs. 78%, $p < 0.05$). These findings provide clinical evidence for the importance of minimizing neurovascular bundle manipulation during robotic prostatectomy as a means of preventing neurapraxia/axonotmesis.

Similar evidence comes from a well-designed prospective, randomized, single-blinded study of n = 61 with normal preoperative erectile function from 6 centers [89]. Patients underwent robotic prostatectomy with traditional bilateral nerve sparing compared to nerve-sparing using the Cavermap Surgical Aid. A 12 months post-op, the Cavermap group had mean 15.9 minutes of greater than 60% nocturnal tumescence vs. 2.1 minutes as measured by the

RigiScan. The sexual function inventory questionnaire (SFIQ) scores at 12 months were not significantly different, however. Among those patients with intact response to nerve stimulation after nerve-sparing, 68% of those with bilateral response had recovery on SFIQ vs. 27% with unilateral response, and 0% with no response [89]. A subsequent multi-institutional study utilizing the Cavermap by five experienced surgeons demonstrated limited specificity to identify the precise location of the cavernous nerves, thus limiting its routine application during radical prostatectomy [90].

5.5. No countertraction technique

The detrimental impact of nerve traction injury may also be limited. A series emphasizing nerve-sparing with a lack of countertraction has been published (**Figure 10**). Kowalcyzk et al. reported statistical significantly different erectile function at 5 months post-robotic prostatectomy (24.9% vs. 18.4%, $p = 0.004$), which was confirmed in the multivariable regression model. These differences were no longer present at 12 months (34.7% vs. 33.5%, $p = 0.849$), independent of preoperative erectile function, laterality of nerve sparing, and inter- vs. intrafascial approach [91]. Therefore, "tractionless" surgery may accelerate functional return.

5.6. Minimizing use of electrocautery/thermal energy

In the early experience of robotic prostatectomy, many centers performed dissection of the neurovascular bundle with electrocautery. Ahlering et al. demonstrated slower return of erection function as measured by the IIEF-5 and two questions on the EPIC questionnaire. Of the $n = 125$ patients, only 36 met their inclusion criteria, (age < 66 and IIEF-5 score 22–25), with $n = 3$ having had monopolar electrocautery and $n = 33$ having had bipolar cautery. Of note men with Gleason 7–10 and high volume disease had ipsilateral wide excision of the NVB. Although there was no comparison group, erectile function recovery was modest especially when compared to modern historical series. Among those who had bilateral nerve-sparing, recovery at 15 months was 44.4% and at 24 months was 67.9% [31]. These findings help to support the clinical principle of avoidance of thermal energy during dissection of the neurovascular bundle.

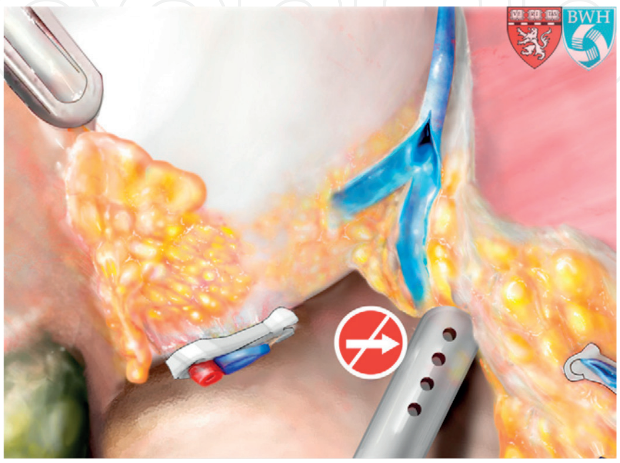

Figure 10. Technique of nerve-sparing with assistant suction neurovascular bundle countertraction which is avoided in the Kowalcyzk et al. technique of nerve-sparing. Reprinted from Kowalczyk et al. [91].

5.7. Seminal vesicle preservation

Building on several observational studies [92, 93], Gilbert et al. reported a randomized controlled, Phase II trial of n = 140 men who underwent radical prostatectomy [94]. Seminal vesicle-sparing approach was employed in 71 men. At 6 and 12 months post-operatively, sexual and urinary function scores were similar on the EPIC questionnaire (erections firm enough for intercourse in 67.7% vs. 56.3%, p = 1). In addition, positive surgical margin status and 12-month biochemical recurrence rates were similar. This approach has understandably not been widely adopted.

5.8. Hypothermic robotic radical prostatectomy

Finley et al. reported the potential benefit of regional hypothermia/cold dissection of the neurovascular bundle in a case–control study of n = 115 who underwent robotic prostatectomy [95, 96]. The rationale for the endeavor mirrors developments in neurosurgery and cardiac surgery that have established significant benefits in randomized studies. Hypothermia was employed to minimize iatrogenic tissue inflammation and consequent cellular edema, lactic acidosis, nerve conduction blockade, free radical damage, and apoptosis that characterizes damage to muscle and nervous tissue. Cold intracorporeal irrigation was employed along with an endorectal cooling balloon cycled with saline at 4°C. Potency rates at 12-months were favorable. Patients subjected to hypothermia were compared to a historical cohort of n = 667 patients. Temperature probes monitored the endorectal and intracorporeal temperatures, which declined to mean 18.7 and 25.6°C, respectively. Potency was assessed during validated questionnaires and defined as "erections adequate for penetration" and "were the erections satisfactory." Potency at 3 months was similar, but at 15 months, the hypothermic group had significantly better function (83% vs. 66%, p = 0.045). There were no differences in oncologic outcomes and no complications related to the technology [97]. These results need further multi-institutional investigation.

5.9. Clipless antegrade nerve preservation

Rather than perform the nerve-sparing in the conventional antegrade (base to apex) fashion, some centers have described a medial to lateral approach. After division of the posterior bladder neck, the posterior plane along the prostate is developed toward the prostatic apex in the midline. The dissection proceeded laterally to release the vascular pedicles and neurovascular bundles in a medial to lateral direction, with sparing use of bipolar cautery. No monopolar cautery or clips were used. Chien et al. reported their series of n = 56 patients who underwent robotic prostatectomy using this approach between 2003 and 2004 [97]. Their outcome metrics relied on the Rand Medical Outcomes Study 36-Item Health Survey, version 2, as well as the University of California, Los Angeles, Prostate Cancer Index up to 12 months postop. Return to baseline potency (allowed use of oral phosphodiesterase inhibitors) among patients with bilateral nerve-sparing occurred in 69%. The positive surgical margin rate in this series was similar to other published techniques at 10.7% [97].

5.10. Intraoperative frozen section analysis

There have been multiple reports of the utility of intraoperative frozen section to allow for more aggressive nerve-sparing in patients whose risk factors may have otherwise prompted a non-nerve sparing surgical approach. In an open series of n = 608 patients who underwent RP, 83 patients were found to have a palpable lesion close to the prostatic capsule [98]. A 4 cm wedge of tissue was excised in the suspicious area for intraoperative frozen section (IOFS). A total of 93% of these IOFS were positive for carcinoma, and 36% of these were pT3. Final positive margin rate overall was 16%. This real-time decision-making allowed for ipsilateral nerve-sparing in 52% of the cases without a negative impact on PSM. Of note, there was a false positive PSM rate of 17%. The applicability to the modern era of robotic prostatectomy may not be lost, but would be based on gross visual suspicion of tumor violation during nerve-sparing.

Another center has pioneered the Neurovascular Structure-Adjacent Frozen-section Examination ("NeuroSAFE") approach to nerve sparing [99]. In this technique, a bilateral nerve-sparing procedure is performed and then the prostate gland is promptly extracted from the surgical field and whole gland circumferential frozen section analysis is performed. The original series consisted of n = 11,069 who underwent open RRP from 2002 to 2011, n = 5392 of whom had the NeuroSAFE technique. When a margin was found to be positive, the ipsilateral neurovascular bundle was resected, including the rectolateral component of the Denonvilliers' fascia, prior to the vesicourethral anastomosis. The sensitivity and specificity of this approach was 93.5 and 98.8%, respectively, with accuracy of 97.3%. Of the 25% found to have PSM initially, 85% of these were converted to final negative margin. False negatives occurred in 2.5% and all of these margins were < 0.5 mm. There were significant reductions in PSM rates within each pathologic tumor stage (except for pT3b) and an increase in the rate of nerve-sparing for all stages. Of note processing time took about 35 minutes and there was no delay in surgery, as hemostasis, bladder closure, lymph node dissection, and posterior reconstruction could be performed during this time (**Figure 11**) [99].

This technique has been translated into robotic surgery in n = 1570 patients from 2004 to 2012, in whom n = 1178 had the NeuroSAFE technique. Intraoperative blood loss was equivalent and nerve-sparing rate increased significantly (overall 97% vs. 81%; pT2 99% vs. 90%; pT3a 94% vs. 74%; pT3b 91% vs. 30%). Furthermore, rate of PSM improved with NeuroSAFE (overall 16% vs. 24%; pT2 8% vs. 15%; pT3a 22% vs. 39%; pT3b 49% vs. 67%; $p < 0.05$) [100]. These findings have contributed to the development of the "Safe-R score," a composite measure of margin status and laterality of nerve sparing [101].

5.11. The influence of surgical modality on nerve-sparing success

It has been postulated that the loss of haptic feedback renders traction-free nerve-sparing difficult during robotic prostatectomy. Conversely, the optical magnification and seven-degrees of freedom afforded by robotic surgery may allow for superior delineation of the neuroanatomy, precision of dissection, and even performance of partial or incremental nerve sparing for patients with concern for locally advanced disease. Such patients may have otherwise been subjected to a non-nerve-sparing technique. Tewari et al. reported earlier return of 50% erectile function (as reported on the EPIC questionnaire) after robotic prostatectomy vs. RRP (mean 180 days vs. 440 days, $p < 0.05$) and earlier return to intercourse (340 days vs. >700 days, $p < 0.05$) Interestingly, these findings were shown even in the setting of a greater number of patients post-RRP using sildenafil (65% vs. 42%) [102]. Such findings were also corroborated by a prospective, non-randomized trial of robotic prostatectomy vs. RRP in n = 208 patients from 2006 to 2007. At

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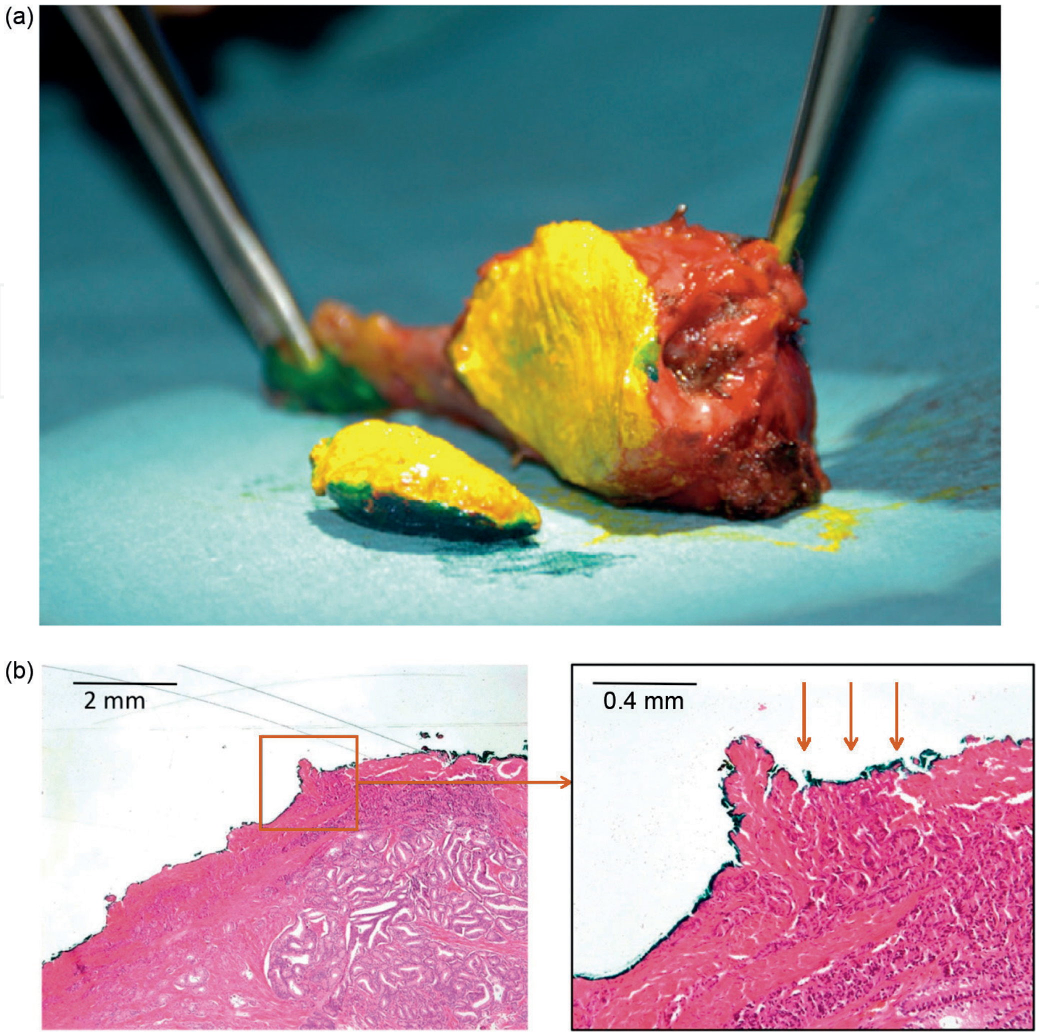

Figure 11. A. Intraoperative picture of NeuroSAFE technique. B. Intraoperative frozen section with tumor contact at linked surface. Reprinted from Beyer et al. [100].

12 months follow-up, of the patients with bilateral nerve-sparing, those who underwent the robotic procedure had superior recovery of erectile function on the IIEF-5 questionnaire (81% vs. 49%, $p < 0.001$) [62]. Further contemporary evidence comes from a systematic review and meta-analysis of 31 studies published between 2008 and 2011 totaling n = 3491 patients [63]. Outcome measures of erectile function were heterogeneous, with some studies employing SHIM > 21 and others using "erections sufficient for intercourse." Cumulative analyses of the six studies with suitable follow-up demonstrated better 12-month potency rates after robotic surgery vs. RRP (24.2% vs. 47.8%; odds ratio 2.84, $p = 0.002$). Absolute risk reduction was 23.6%. Furthermore, 24-month potency was 84% vs. 47% (odds ratio 6.01; $p < 0.001$) Comparison between robotic and laparoscopic approaches was not significant (39.8% vs. 55.6%, $p = 0.21$).

These comparisons may be hampered by different definitions and metrics for erectile dysfunction, patient selection for surgery, and variations in post-operative penile rehabilitation at different institutions. Further evidence is forthcoming from the first randomized controlled phase 3 study of robotic vs. open prostatectomy conducted by Yaxley et al. out of Australia [103]. Although the study randomized n = 326 men and plans to report on urinary and sexual function outcomes (via the EPIC and IIEF questionnaires) at 6 and 12 weeks, as well as 24 months, published results are immature at 12 weeks only. There were no significantly different urinary or sexual function scores at 6 and 12 weeks, nor were there differences in health reported quality of life.

A counterargument to the benefits afford by robotic surgery, however, states that more aggressive nerve sparing, although technically feasible, may not be oncologically safe, given the risk of positive margins. Indeed, the Preston et al. study revealed that positive margins were more likely in patients treated with robotic surgery (relative risk 1.76) compared to open surgery, while there was no difference between lap and robotic surgery [81]. These findings were not corroborated in a very large, albeit retrospective, multi-institutional, multi-national study of n = 22,393 patients, however, which found the lowest rate of positive margins in robotic prostatectomy (13.8%) vs. laparoscopic (16.3%) vs. open (22.8%) [104]. A recent systematic review and meta-analysis by Novara et al. of 21 studies totaling n = 19,238 patients reported similar PSM rates among robotic, laparoscopic, and open surgery, both overall and when sub-stratified into pT2 patients (mean 15%, range 6.5–32% [105]. More recent evidence to mitigate this controversy comes from the previously referenced randomized Phase 3 trial of open vs. robotic prostatectomy by Yaxley et al. Oncologic outcome were equivalent between the two groups, including PSM overall, and for pT2 and pT3 patients (15% vs. 10%, 3% vs. 2%, 11% vs. 8%, respectively) [103].

One notable difference between the open and robotic approach is the use of a retrograde vs. antegrade approach to the dissection of the neurovascular bundle. There is a theoretically reduced risk of placing a clip across the neurovascular bundle with the retrograde approach, which releases the bundle from the prostate prior to obtaining vascular control [106]. These different approaches were compared in a propensity-matched series of n = 344 patients undergoing robotic prostatectomy. Using validated questionnaires at 3,6, and 9 months, the potency rate was significantly higher after the retrograde approach (92.9% vs. 72.1% at 9 months), and this finding was maintained with multivariable analysis. Of note, the PSM rate was similar between groups (11.6% vs. 7%, $p > 0.05$) [107]. Of note, this was a single-surgeon series and the approaches were performed in an interfascial manner, which may not reflect the most current understanding of the cavernous neuroanatomy. Also, the retrograde approach was generally performed more recently in the series with possible artifactual enhancement in outcome from being later in the learning curve. Furthermore, the seemingly excellent results from either approach in this series are likely a consequence of the permissive definition of erection function (erections firm enough for penetration in >50% of attempts).

Of note, although intriguing to consider if there are any technical advantages to nerve sparing with an extraperitoneal vs. transperitoneal approach to robotic prostatectomy, the extant literature has thus far focused exclusively on perioperative rather than functional outcomes [108, 109].

6. Penile rehabilitation

Several options for penile rehabilitation have been proposed and investigated, including pharmacotherapy with oral phosphodiesterase inhibitors or penile intracavernosal injection, as well as use of a vacuum erection device and penile constrictive ring. Often a multimodality approach is advocated. Compliance with these recommendations depends on myriad factors, including physician counseling, patient motivation, and even socioeconomic status—as many of the therapies are not covered under health insurance. The PCOS trial reported that 43% of men tried sildenafil, 25% tried a vacuum erection device, and 17% tried intracavernous injections [52]. Admittedly, the denominator of men who were actually offered these treatments is not known.

The rationale for these treatments has been investigated in preclinical models. There is indeed precedent for treatment success in animal models of chronic low-dose tadalafil administration, with increased cavernosal smooth muscle, decreased fibrous tissue, and functional enhancement of erectile function [110–112]. Similar findings have been reported for sildenafil after bilateral cavernosal nerve damage in a rat model. Nerve damage resulted in elevation in several pro-inflammatory cytokines (interleukin-1β, transforming growth factor β) and markers of oxidative stress (nicotinamide adenine dinucleotide phosphate [NADPH] oxidase, myeloperoxidase, inducible nitric oxide synthase, tumor necrosis factor receptor superfamily member 5 [CD40]), which then normalized after administration of sildenafil in the drinking water. Levels were measured by polymerase chain reaction (PCR) and proteome expression of pelvic ganglia neurons [113].

6.1. Mechanotherapy

The vacuum erection device often in conjunction with penile constrictive ring are routinely recommended for use to assist with recovery of potency after radical prostatectomy. This therapy not only allows for tumescence and penetration, but also cavernosal sinus expansion, smooth muscle “stretching,” and mitigation of hypoxia when used on a regular basis [114, 115]. Compared to pharmacotherapies—which are often not covered by the patient’s health insurance—VED may be more cost-effective, with a decreased side effect profile and the opportunity for the patient and his partner to take an active role in convalescence. In addition, the mechanism of action does not require intact cavernous nerves for success. There have been multiple retrospective studies examining the impact of the VED [115–117]. These suggest improvement in return of spontaneous erections. In particular, a retrospective study of n = 203 patients who underwent robotic radical prostatectomy between 2007 and 2011 investigated whether PD5I alone, VED alone, or a combination of the two yielded the highest improvement of the SHIM questionnaire, substratified into three groups of baseline EF (SHIM 8–16, SHIM 17–21, SHIM 22–25). For each of the baseline EF groups the combination therapy resulted in the highest proportion of successful potency (erections suitable for penetration) and with the shortest latency period [118].

Randomized evidence comes from Raina et al., who reported on n = 109 patient who underwent open RP (both NS and non-NS) randomized post-op to daily VED therapy vs. observation. Compliance with the device was 80% with 55% partner satisfaction rate. After 9 months of treatment IIEF-5 score was significantly increased for both the NS and non-NS patients compared to the no treatment group. Furthermore, decreased penile length was reported in 63% of the control group vs. 23% among patients who responded to VED treatment [115].

Regarding timing of therapy, earlier initiation of 10 minutes daily VED therapy (1 month post-op vs. at 6 months) has been shown in a small randomized trial of n = 28 men to be superior in terms of 1. IIEF score at 3- and 6-months, and 2. preservation of stretched penile length (vs. 2 cm mean decrease observed in the delayed therapy group) [119].

6.2. Pharmacotherapy

The majority of penile rehabilitation studies incorporate early post-op therapy. Phosphodiesterase type 5 inhibitors have been demonstrated to be effective for the treatment of erectile dysfunction through their inhibitory effect on the enzyme that degrades cGMP. These medications augment the nitric oxide-mediation erectile response through increased relaxation of the cavernosal sinus smooth muscle [120]. The commercially available medications have different half-lives of activity, with Tadalafil being the longest ($T_{1/2}$ sildenafil 3–5 mg; vardenafil 4–5 hours; tadalafil 17.5 hours) [121]. There is also experience with both intraurethral and intracavernosal prostaglandin E, which act via a cAMP-related mechanism to effect cavernosal smooth muscle dilatation [122]. Montorsi et al. published the first randomized, placebo controlled trial in 1997, involving intracavernosal injection of alprostadil three times per week × 12 weeks beginning 1 month after open RP [23]. Newer formulations of intracavernosal therapy include Trimix (prostaglandin, phentolamine—a non-selective alpha-blocker—and papaverine—a non-selective PDE5 inhibitor—and Bimix (papaverine and phentolamine). Given the invasive nature of ICI—as well as the putative higher complication rate regarding pain, hematoma, penile plaque formation, and priapism—this therapy is not universally accepted by patients. Therefore, there is much interest in the oral PDE5 inhibitors as a mechanism of increasing intracavernosal cGMP to promote smooth muscle relaxation and mitigate of the post-RP hypoxic state.

6.2.1. Oral PDE 5 inhibitors

There have been several prospective, randomized studies in this domain, which are summarized **Table 1**. Rationale for these trials was based on findings that daily sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy [123]. The studies tended to exclude men with high grade prostate cancer (i.e. Gleason 8) and those who required adjuvant radiation therapy. Latency of medication initiation is also variable, ranging from time of catheter removal to 4 weeks post op. Based on the cavernous neurotomy rat models in which post-injury cavernous smooth muscle apoptosis begins in 1 day and peaks at 1 week, earlier initiation of treatment has definite clinical rationale [34]. Furthermore, the study end-points are not identical. Some examine the impact on erections during an active treatment phase and others examine the rate of return of spontaneous erections (that is, without the need for pharmacotherapy). The proportion of open vs. robotic RP are also variable (open RP: 39.7–100%). The Jo et al. study out of South Korea is the only study comprised exclusively of patients who underwent robotic prostatectomy, and showed more complete return of erectile function at 12 months with immediate post-catheter removal initiation of 100 mg sildenafil twice weekly compared to waiting until 3 months after surgery [124]. The concomitant use of VED in these studies is not clear, which adds another limitation to their interpretation. Also of interest is a follow-up study to the study by Pavlovich et al. [172] suggesting poorer EPIC scores with nightly sildenafil 50 mg compared to PRN dosing, largely in the urinary irritative and bother subscales of the questionnaire [125]. Further study is required to clarify the implications of this report.

Author	Patients	Study drug	Study schema	F/U	Outcome metric	Findings	Conclusion	Limitations
Montorsi et al. [23]	30; mean age 62, "reported satisfactory intercourse preop;" bilateral nerve-sparing	Alprostadil TIW × 12 weeks	Dose titrated for efficacy (2–14 μg) vs. no injection	3 months	"Recovery of spontaneous erections"	80% compliance with injections; 67% recovery vs. 20%	Early ICI with alprostadil increases recovery of spontaneous erections	No sham injection group; no IIEF standardized questionnaire; waited 1 month short f/u; 17% complication
Montorsi et al. [110]	445 (18–64 years); IIEF-EF ≥ 26; bilateral NS; mean age 57.1	Vardenafil × 9 months	10 mg nightly vs. 10 mg PRN within 2 weeks postop	12 months	IIEF-EF ≥ 22 after 2-month washout; then open label PRN	Double blind period: IIEF > 22: 24.8, 32, 48.2% (placebo, nightly, on demand); After 2 months washout and open label PRN no difference	On demand dosing is effective	Did not limit frequency of on demand dosing; dose up to 20 mg
Padma-Nathan et al. [171]	76 (18–70 years) s/p RRP; 8 on Q3 and Q4 of IIEF; mean age 55.5	Sildenafil × 9 months	Nightly 50 mg, 100 mg, placebo within 4 weeks	12 months	IIEF after 8 week washout; plethysmography	IIEF Q3 + Q4 ≥8 and "satisfactory": 4, 26, 29% (placebo, 50 mg, 100 mg)	Sildenafil improved erectile function, but no dose dependence	Closed early for lack of treatment effect; very low rate of EF in placebo arm; waited 4 weeks
Pavlovich et al. [172]	100 (<65 years) s/p MIS RP; IIEF-EF ≥ 26, uni-/bilateral NS; mean age 53.9	Sildenafil × 12 months	50 mg nightly vs. PRN (max 6 per month) immediately after RP	13 months	IIEF, EPIC after 1-mo washout	IIEF-EF > 21: 33.2, 50% (nightly, on demand)	No difference in nightly vs. on demand	No pure placebo arm
Montorsi et al. [173]	423 (≤68 years; IIEF-EF ≥ 22; PSA <10 ng/mL; GS < 8. Bilateral NS; mean age 57.9 years	Tadalafil × 9 months	5 mg daily vs. 20 mg PRN; 6 week washout, then 3 months open-label 5 mg daily	13.5 months	IIEF-EF ≥ 22 after 6-week washout; penile length loss	20.9, 16.9, 19.1% IIEF-EF ≥ 22 (daily, on demand, placebo) after washout—non-signif; 5 mg daily better IIEF-EF vs. placebo	"Unassisted EF was not improved after cessation of active therapy for 9 month." Reduced penile length loss in 5 mg daily (difference 4 mm)	Binary definition of success limited power; patients with mild ED (IIEF-EF 22–25) were included

Author	Patients	Study drug	Study schema	F/U	Outcome metric	Findings	Conclusion	Limitations
Canat et al. [174]	129; mean age 63 years; IIEF-6 no or mild ED; bilateral NS	Tadalafil × 12 weeks	20 mg TIW vs. 20 mg PRN vs. placebo at time of catheter removal	6 weeks, 12 months	IIEF-6 score at 6 weeks and 12 months	6 weeks no diff; 12 months, higher IIEF for TIW group (19.9 vs 15.8 vs. 13.47; TIW, PRN, none)	20 mg TIW is effective and well-tolerated	Lack of placebo
Kim et al. [175]	97; SHIM ≥ 21 and RigiScan >60% × 10 minutes nocturnal erection; b/l NS (robo-, open); mean age 54 years	Sildenafil × 12 months	50 mg starting night after surgery vs. placebo; all patients received 6 tabs × 100 mg/months PRN	13 months	IIEF; RigiScan	RigiScan 40% potency at 13 months for both groups; IIEF > 21 29% vs. 32.4%, non-significant	No difference for 50 mg nightly sildenafil vs. 100 mg PRN	76% compliance; under accrual; lack of true placebo arm
Jo et al. [124]	120; >50 years; IIEF-5 ≥ 17; NS-eligible but not always performed; s/p RALP (~82%);mean age 63.7 years	Sildenafil × 12 months	Sildenafil 100 mg 2×/week after catheter removal × 3 months; delayed group started at 3 months post-op; then PRN 12 months therapy	12 months	IIEF ≥ 12 months	IIEF ≥ in 41.4% vs. 17.7% (early vs. late); PRN usage similar between groups	Early sildenafil improved full EF recovery during 12 months post-RP	Early group younger (61.7 vs. 65.6); small study

TIW = three times per week; RCT = randomized controlled trial; ICI = intracavernosal injection; f/u = follow-up; NS = nerve sparing; IIEF = International Index of Erectile Function; EF = erectile function; PRN = pro re nata (“on demand”); RRP = radical retropubic prostatectomy; MIS = minimally invasive surgery; RP = radical prostatectomy; EPIC = Expanded prostate cancer index composite; EF = Erectile function; PSA = prostate specific antigen; REF = Residual Erection Function; RALP = robotic-assisted laparoscopic prostatectomy.

Table 1. Randomized controlled trials of post-prostatectomy pharmacologic penile rehabilitation.

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A majority of these trials for ED after radical prostatectomy examine daily vs. on-demand dosing schedules. Of note, a randomized, double-blind trial (RESTORE study) in men with mild to moderate ED (IIEF-EF 15–20; *not post-prostatectomy*) of 10 mg vardenafil daily vs. PRN showed no differences in increase of IIEF-EF score [126]. Similar findings appear to be borne out in the post-RP series as well (*see below*). Side effect profiles of the treatment groups were largely favorable and usually without the need for drug discontinuation. Furthermore, daily vs. on demand schedules did not have significantly different adverse effects in a recent meta-analysis, and absolute rates of side effects were not substantially different between treatment and placebo groups overall (59.6% vs. 48.4%) [127]. Side effects generally reported included headache, flushing, dyspepsia, and rhinitis, none of which are severe.

6.2.2. Intraurethral prostaglandin

Intraurethral alprostadil (Medicated Urethral System for Erection, *MUSE*™) has also been developed for use in erectile dysfunction. Experience with this drug for non-post-RP erectile dysfunction has been limited by lack of efficacy and penile pain/dysuria in a large number of patients. Early experience with MUSE after 6 months of post-RP ED showed 55% of the n = 54 patients able to achieve erections suitable for penetration, although only 48% continued long-term therapy (57% of men discontinued therapy for inefficacy) [128]. The author's experience with application of the therapy at 3 weeks post-op for a duration of 6 months showed erections firm enough for penetration in 74% of patients compliant with treatment. All patients reported mild penile pain or urethral burning and 32% of patients discontinued treatment [129].

6.3. Pelvic floor PT

The role of pelvic floor physical therapy (PFMT; "Kegel" exercises) on return of urinary continence has been well understood, as evidenced by meta-analyses demonstrating earlier return of continence with preoperative PMFT and biofeedback [130, 131]. The impact of such therapy on recovery of sexual function has also been explored. Physical therapy efforts focus on the bulbocavernosus (bulbospongiosus) and ischiocavernosus muscles. Contraction of the ischiocavernosus muscle may compress the proximal aspects of the corpora cavernosa and increase intracavernosal pressure during erection [132]. Also, muscle contraction has been shown to increase levels of brain-derived neurotrophic factor in muscle cells, which may have a role in promoting neuronal growth after nerve injury [133]. A trial of n = 55 men with ED for ≥6 months randomized one group to PFMT with biofeedback + lifestyle changes vs. lifestyle changes alone [134]. Lifestyle changes consisted of alcohol intake reduction, smoking cessation, increasing exercise, and avoiding bicycle riding. Outcomes were assessed with IIEF and anal pressure measurements. At 3 months follow-up, the PFMT group had greater improvement in IIEF than the lifestyle changes alone group ($p < 0.001$). Other concomitant therapies for ED (i.e. PDE5 inhibitors or vacuum erection device) were not disclosed by the authors, limiting the strength of the results. Also, there were no post-prostatectomy patients in this cohort.

With regard to prostatectomy, the timing is such physical therapy is also interesting to consider and there is no established consensus of whether pre- and postoperative physical therapy is superior to postoperative therapy alone. Perez et al. examined the use of biofeedback preoperatively to strengthen the levator muscles prior to radical prostatectomy [135]. Their methods employed a device that provided visual feedback based on intra-anal pressures. In this prospective cohort study, a total of n = 20 patients completed 10 sessions pre-RP and n = 32 patients proceeded directly to surgery. Potency outcomes were assessed using the IIEF-5, although follow-up time was not clear. The erectile dysfunction rate in the physical therapy group was 5% vs. 48.6% in the control group $< p < 0.001$). There are likely variations in physical therapy technique and not all methods are standardized.

The impact of PFMT on erectile function after radical prostatectomy has also been examined. Prota et al. studied n = 52 patients who underwent open RP and randomized them to PFMT + biofeedback weekly × 3 months (beginning at time of catheter removal) vs. verbal instructions only [136]. Nerve-sparing was performed in a similar proportion of patients in each group (64.7% vs. 68.8%). There was earlier recovery (IIEF >20) in the treatment group which persisted at 12 months post-op (47.1% vs. 12.5%). The authors report an absolute risk reduction of 34.6%, with number needed to treat (NNT) of 3. These results are even more encouraging given that oral PDE5 inhibitor therapy was withheld during the study. This study provides level 1b evidence supporting the use of post-operative PFMT for erectile function recovery [136]. Optimal schedule and intensity has yet to be determined.

Additional randomized controlled trials are needed to further assess the utility of PFMT in the restoration of potency.

6.4. Novel therapies

6.4.1. Hyperbaric oxygen

The role of hyperbaric oxygen (HBO) in Urology for treatment of radiation-induced hemorrhagic cystitis is well known. Application of this technology to post-RP erectile dysfunction is controversial. There have been preclinical studies in rats with cavernous nerve injury undergoing HBO that demonstrate higher intracavernosal pressure/mean arterial pressure ratio, increased levels of penile nerve growth factor (NGF) and endothelial nitric oxide synthase (eNOS) compared to the controls. Tissue studies on smooth muscle to collagen ratio, however, did not show a significant difference after HBO [137]. Exposure to 100% oxygen at 2 atm pressure induces stem cell differentiation and neovascularization, as well as vasoconstriction that attenuates tissue edema [138]. These findings underlie the rationale for translational studies. Chiles et al. published the first randomized, double-blind controlled trial of HBO vs. air for men after RP [139]. Although the authors were unable to demonstrate significant difference in IIEF score at 18 months, uncertainty about the proper regimen for therapy (total number and frequency of treatments) and lack of a true “sham” group may have limited their ability to detect a clinically relevant difference in outcome.

6.4.2. Neuroprotective agents

There is a growing body of literature on drug therapy to preempt or mitigate the post-cavernosal nerve injury pro-inflammatory environment. The immunophilin ligand FK506 (tacrolimus)—traditionally thought of as an immunosuppressive agent and widely used in for solid organ transplant—has been implicated in a neuroprotective role when administered as early as 1 day following partial nerve-crush injury in a rat model [140]. Further work has demonstrated improved intracavernous pressure/mean arterial pressure ratio, restoration of inducible nitric oxide synthase (iNOS) staining, reduced apoptosis, preservation of cavernosal architecture, and upregulation of glutathione peroxidase (GPX) with resultant decrease in oxidative-stress-induced tissue damage [141, 142].

Pioglitazone, a thiazolidinedione used for the treatment of diabetes mellitus, may enhance neuronal survival and regeneration and decrease inflammation, and has been shown to be neuroprotective in models of sciatic nerve ischemia and optic nerve crush injury, as well as BCNI [143–145]. Furthermore, a small randomized controlled trial has shown efficacy of this agent for erectile dysfunction refractory to sildenafil [146]. A study by Katz et al. investigated the impact of pioglitazone on pelvic ganglion neurons after bilateral cavernosal nerve injury (BCNI) in Sprague-Dawley rats [147]. Four groups were examined: sham surgery, BCNI, BCNI + post-operative pioglitazone, BCNI + pre- and post-operative therapy. Gene expression profiles of neuronal nitric oxide synthase, neurturin, glial cell line-derived neurotrophic factor family receptor alpha-2 (GFRα2), and β-III tubulin were upregulated in the pre-operative therapy group [147]. Further work is necessary to fully explore the utility of this therapy.

6.4.3. Amnion-chorion membrane

Dehydrated human amnion-chorion membrane allograft (dHACM) is a source of implantable neurotrophic factors and cytokines which promote neural survival and facilitate axonal regeneration. Its application has been examined in a rat model of axonal regeneration after spinal cord injury [148]. Clinically, it has been applied in the treatment of burns, corneal injuries, chronic venous ulcers, and chronic wounds [149]. There has been preliminary work in the placement of this membrane after bilateral nerve-sparing robotic RP to accelerate erectile functional recovery after surgery [150]. A single-surgeon propensity-matched analysis of preoperatively potent (SHIM >19) and continent (American Urological Association Symptom Score < 10) patients (n = 58) demonstrated earlier return of continence (1.2 months vs. 1.8 months, p = 0.033) and potency (1.34 months vs. 3.39 months, p = 0.007) with the wrap. (AmnioFix; *MiMedx Group, Marietta, GA, USA*) Some limitations of this series include the small size, lack of randomization, and short mean follow-up of 4 months, which limits conclusions about oncologic safety vis-à-vis risk of biochemical recurrence (BCR). Furthermore, functional recovery rates appear much higher than other series in the literature, and may be a consequence of the recall bias used to assess level of function. These preliminary results are certainly encouraging.

The dHACM allograft wrap was recently examined in a series of n = 940 patients (preoperative SHIM > 20) who underwent robotic RP with bilateral nerve-sparing [151]. A total of n = 235 had bilateral dHACM placement and these were propensity matched in a 1:3 proportion to non-dHACM patients (n = 705). Potency recovery rates were higher in the dHACM group at all time points except 12 months. Time to potency was significantly shorter in the dHACM group after bilateral NS (2.2 months vs. 2.8 months, p = 0.029) and partial NS (3 months vs. 3.9 months). After 12 months follow-up, erections sufficient for penetration were similar. Of note, the recovery rates in this study were higher than what is generally reported in the literature. Also, although the rate of biochemical recurrence at 12 months was similar between groups, longer follow-up is certainly needed to demonstrate the oncologic safety of this application of technology.

A recent pre-clinical study of the role of hemostatic tissue sealing sheets has also investigated the impact on erectile function recovery in a series of 21 Sprague-Dawley rats [152]. The TachoSil (CSL Behring, Tokyo, Japan) is a collagen sponge coated on one side with fibrinogen and thrombin and is approved for achieving hemostasis during surgery. Contact between the sheet and blood or serosanguinous fluid results in deposition of a fibrin clot. Compared to sham surgery, the rats who underwent cavernous nerve dissection and had the TachoSil placed demonstrated similar intracavernous pressure/mean arterial pressure ratios at 4 weeks post-op. Furthermore, PCR-measured expression of inflammatory and oxidative markers (internleukin-6, tumor growth factor beta1, and heme-oxygenase-1) in the major pelvic ganglion was significantly reduced in the sheet group ($p < 0.05$).

6.4.4. Stem cell therapy

Stem cells may be harvested from growing embryos (embryonic stem cells) or as allografts from bone marrow or adipose tissue (mesenchymal stem cells). This technology has been applied to rat models of bilateral cavernosal nerve crush injury and shown considerable promise. Bochinski et al. [153] conducted a study of embryonic stem cells induced along the neuronal cell line with brain-derived neurotrophic factor [153]. These stem cells were then injected into the major pelvic ganglion (MPG) (group 3) and into the corpora cavernosa (group 4) of rats after BCNI. The study was well controlled with sham surgery (group 1) as well as a BCNI group with injection of culture media only (group 2). Volume of stem cells injected was 500 μL of a 10,000 cells/mL solution. Erectile response was assessed by electrostimulation of the cavernosal nerve at 3 months. Immunohistochemistry was also performed of the penile tissue to assess levels of nitric-oxide synthase-containing fibers and neurofilament concentration. Intracavernosal pressure in response to electrostimulation was greatest for sham surgery and lowest for group 2, which was also significantly lower than groups 3 and 4. The neurofilament stain of tissue taken from the MPG and the corpus cavernosum was also greater in groups 3 and 4 compared to group 2 (**Figure 12**). Such neurofilaments are involved in establishing tensile strength and putatively intracellular transport guidance to axons and dendrites [154]. The authors conclude that preservation of the neuronal architecture may promote/facilitate nerve regeneration after nerve injury.

There have been several more studies investigating the role of stem cells in BCNI in rats, either alone [155] or in combination with PDE5 inhibitors [156, 157]. Furthermore, Lin et al. reported that adipose-derived stem cells (ADSCs) injected into the corpora cavernosa migrated within days to the bone marrow and then to the MPG [158]. Subsequent work has been reexamined in multiple systematic reviews and meta-analyses, reiterating the efficacy of these methods in 12 studies, n = 319 rats and 20 studies, n = 248 rats, respectively [159, 160]. The combination of stem cells + PDE5 inhibitor therapy appears to have the greatest effect [159]. Consistent outcomes among the studies were increase in the ICP/MAP ratio, levels of neuronal nitric oxide synthase, cavernous smooth muscle content, ratio of cavernous smooth muscle to collage, and cGMP levels [160]. Furthermore, stem cells modified by growth or neurotrophic factors

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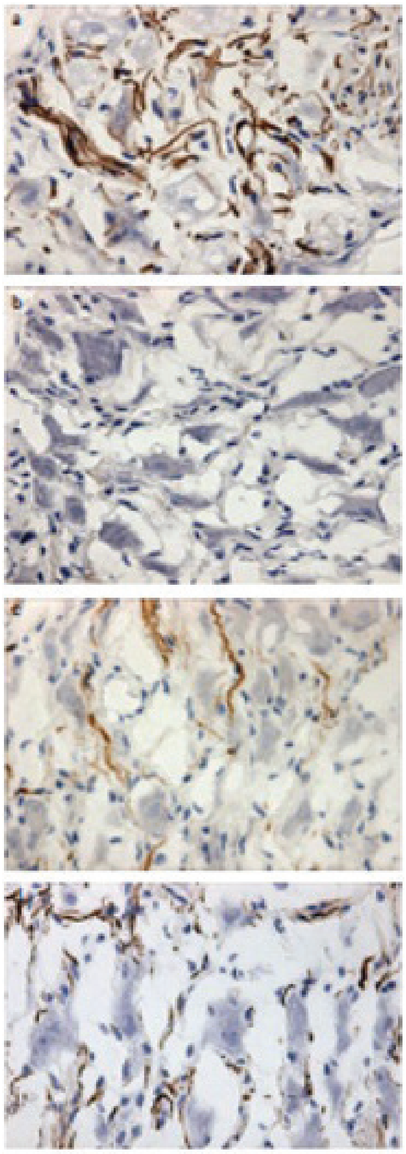

Figure 12. Neurofilament staining in major pelvic ganglion (MPG) of rats after bilateral cavernosal nerve crush injury (BNCI). A. Sham surgery. B. BCNI alone C. BCNI + neuronal stem cells injected into corpora cavernosa. Reprinted from Bochinski et al. [153].

prior to implantation appeared to exert the greatest benefit [160]. Although there are many processing steps to refine and standardize, this approach remains a riveting endeavor in the arena of penile rehabilitation.

7. Penile prosthesis implantation

Despite these advances in the restoration of endogenous erectile function after radical prostatectomy, some men will have dysfunction refractory to the above treatments. The final line treatment option for such patients is insertion of a penile prosthesis, which may in fact be conceived as a type of mechanotherapy. This procedure eliminates the possibility of any spontaneous erectile function in the future and has many potential complications, including pain, erosion, extrusion, infection, mechanical failure, need for revision, and altered penile sensation. There have been a number of surgical improvements that have reduced the infection rate, including the "no touch" technique, standardized protocols for perioperative antibiotics, and the development of antibiotic-impregnated and hydrophilic devices [161–164]. Although the technique of 3-piece penile prosthesis insertion is beyond the scope of this chapter, there are a number of considerations with regard to radical prostatectomy. The cavernosal smooth muscle fibrosis and penile shortening can have an impact on the size of the cylinders able to be accommodated by the corpora, leading to actual or perceived reduction in penile length. Furthermore, the lack of glans tumescence with cylinder expansion may exacerbate the perceived loss of size. After appropriate dilation of the corporal bodies with the dilators, fibrosis should not preclude placement of a three-piece inflatable prosthesis, which has been reported to have the highest satisfaction rates and lowest rate of mechanical failure [165]. Some models of the 3-piece prosthesis (i.e. American Medical Systems, AMS 700 CX) allow for cylinder axial expansion to allow girth. This is important for men with penile plaques/Peyronie's disease and penile curvature that must be corrected during placement of the prosthesis [164]. Although not previously discussed, Peyronie's disease is another "sexual" complication of radical prostatectomy, thought to be from repetitive "buckling" injury to the phallus as a result of intercourse in the setting of an incomplete erection.

Reservoir placement during the three-piece prosthesis surgery also deserves consideration, given the previous dissection of the space of Retzius during the prostatectomy. Given the increased risk of bladder perforation, bowel and vascular injury in this setting, some authors favor ectopic reservoir placement just posterior to the rectus muscle and anterior to the transversalis fascia [166, 167]. Single-institution series have reported excellent outcomes with this approach [166, 167].

Satisfaction with this treatment appears favorable, as exemplified in a recent study of n = 71 patients who underwent penile prosthesis implantation after radical prostatectomy [168]. Pillay et al. employed the EDITS and SEAR questionnaires, as well as the Prostate Cancer-Related Quality of Life Scale and Patient Health Questionnaire-9 (PHQ-9) for both patients and their partners. They reported good sexual function (EPID score > 60) in 77% of men and treatment satisfaction in 94% (EDITS score > 50). Other studies have actually reported improved satisfaction for men undergoing early penile prosthesis insertion compared to those receiving sildenafil or intracavernosal injection therapy 6 months after radical prostatectomy [169, 170]. Such studies did not employ early aggressive pharmacologic penile rehabilitation programs, however. Certainly, for the appropriately selected patient, penile prosthesis implantation has a very high level of success and satisfaction for patients and their partners alike.

8. Conclusions

There have been many advances in the understanding of erectile dysfunction as a result of radical prostatectomy since the initial pioneering work by Walsh & Donker almost 40 years ago. Refined understanding of neuroanatomy, beneficial modifications in surgical technique,

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the advent of robotic surgery, and the exploration of pre- and post-operative rehabilitation techniques using mechanotherapy and pharmaceuticals have improved the prognosis for potency recovery after this once morbid surgery. Further developments in the realm of local and systemic therapies for cavernous nerve neuroprotection and regeneration may mitigate the cascade of cavernosal smooth muscle apoptosis, fibrosis, and veno-occlusive dysfunction that jeopardizes further erectile function recovery after the period of post-operative neurapraxia. Achievement of the Trifecta is extremely important to patients and clinicians alike, and will surely inspire the future waves of investigations that continue to elucidate this field.

Conflict of interest

I have no conflicts of interest to disclose.

Notes/Thanks/Other declarations

None.

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References

[1] Nandipati K, Raina R, Agarwal A, et al. Erectile dysfunction following radical retropubic prostatectomy: Epidemiology, pathophysiology and pharmacological management. Drugs & Aging. 2006;**23**(2):101-117

[2] Molodysky E, Liu SP, Huang SJ, Hus GJ. Penile vascular surgery for treating erectile dysfunction: Current role and future direction. Arab Journal of Urology. 2013;**11**(3):254-266. Available from: https://creativecommons.org/licenses/by-nc-nd/3.0/

[3] Rogers CG, Trock BP, Walsh PC. Preservation of accessory pudendal arteries during radical retropubic prostatectomy: Surgical technique and results. Urology. Jul 2004; **64**(1):148-151

[4] Mulhall JP, Secin FP, Guillonneau B. Artery sparing radical prostatectomy—Myth or reality? The Journal of Urology. 2008;**179**(3):827-831

[5] Saenz de Tejada I, Goldstein I, Azadzoi K, et al. Impaired neurogenic and endothelium-mediated relaxation of penile smooth muscle from diabetic men with impotence. The New England Journal of Medicine. 1989;**320**:1025-1030

[6] Walsh PC, Donker PJ. Impotence following radical prostatectomy: Insight into etiology and prevention. The Journal of Urology. 1982;**128**:492-497

[7] Walsh PC, Lepor H, Eggleston JC. Radical prostatectomy with preservation of sexual function: Anatomical and pathological considerations. Prostate. 1983;**4**:473-485

[8] Costello AJ, Brooks M, Cole OJ. Anatomical studies of the neurovascular bundle and cavernosal nerves. BJU International. 2004;**94**(7):1071-1076

[9] 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. European Urology. 2010;**57**:179-192

[10] Lunacek A, Schwentner C, Fritsch H, et al. Anatomical radical retropubic prostatectomy 'curtain dissection' of the neurovascular bundle. BJU International. 2005;**95**:1226-1231

[11] Menon M, Shrivastava A, Bhandari M, et al. Vattikuti institute prostatectomy: Technical modifications in 2009. European Urology. 2009;**56**:89-96

[12] Tewari A, Takenaka A, Mtui E, et al. The proximal neurovascular plate and the tri-zonal neural architecture around the prostate gland: Importance in the athermal robotic technique of nerve-sparing prostatectomy. BJU International. 2006;**98**(2):314-323

[13] Eichelberg C, Erbersdobler A, Michl U, et al. Nerve distribution along the prostatic capsule. European Urology. 2007;**51**:105-110

[14] Lee SB, Hong SK, Choe G, et al. Periprostatic distribution of nerves in specimens from non-nerve-sparing radical retropubic prostatectomy. Urology. 2008;**72**(4):878-881

[15] Takenaka A, Murakami G, Soga H, et al. Anatomical analysis of the neurovascular bundle supplying penile cavernous tissue to ensure a reliable nerve graft after radical prostatectomy. The Journal of Urology. 2004;**172**:1032-1035

[16] Ganzer R, Blana A, Gaumann A, et al. Topographical anatomy of periprostatic and capsular nerves: Quantification and computerized planimetry. European Urology. 2008;**54**(2):353-360

[17] Kaiho Y, Nakagawa H, Saito H, et al. Nerves at the ventral prostatic capsule contribute to erectile function: Initial electrophysiological assessment in humans. European Urology. 2009;**55**:148-154

[18] Costello AJ, Dowdle BW, Namdarian B, et al. Immunohistochemical study of the cavernous nerves in the periprostatic region. BJU International. 2011;**107**:1210-1215

[19] Ganzer R, Stolzenburg JU, Wieland WF, et al. Anatomic study of periprostatic nerve distribution: Immunohistochemical differentiation of parasympathetic and sympathetic nerve fibres. European Urology. 2012;**62**:1150-1156

[20] Chen SC, Hsieh CH, Hsu GL, et al. The progression of the penile vein: Could it be recurrent? Journal of Andrology. 2005;**26**:56-63

[21] Mulhall JP, Slovick R, Hotaling J, et al. Erectile dysfunction after radical prostatectomy: Hemodynamic profiles and their correlation with the recovery of erectile function. The Journal of Urology. 2002;**167**:1371-1375

[22] Zelefsky MJ, Eid JF. Elucidating the etiology of erectile dysfunction after definitive therapy for prostate cancer. International Journal of Radiation Oncology, Biology, Physics. 1998;**40**:129-133

[23] Montorsi F, Guazzoni G, Strambi LF, 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. The Journal of Urology. 1997;**158**:1408-1410

[24] Stanford JL, Fend Z, Hamilton AS, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: The prostate cancer outcomes study. Journal of the American Medical Association. 2000;**283**:354-360

[25] Kilminster S, Muller S, Menon M, et al. Predicting erectile function outcome in men after radical prostatectomy for prostate cancer. BJU International;**110**:422-426

[26] Parvizi J, Kim GK. Nerve injuries related to orthopaedics. High Yield Orthopaedics. 2010;**154**:317-219

[27] Nakata DA, Stoelting RK. Postoperative peripheral neuropathy. In: Complications in Anesthesia. 2nd ed. Vol. 221. 2007. pp. 881-884

[28] Gonzalez-Perez F, Udina E, Navarro X. Extracellular matrix components in peripheral nerve regeneration. International Review of Neurobiology. 2013;**108**:257-275

[29] Navarro X, Vivo M, Valero-Cabre A. Neural plasticity after peripheral nerve injury and regeneration. Progress in Neurobiology. 2007;**82**(4):163-201

[30] Ong AM, Su LM, Varkarakis I, et al. Nerve sparing radical prostatectomy: Effects of hemostatic energy sources on the recovery of cavernous nerve function in a canine model. The Journal of Urology. 2004;**172**(4 Pt 1):1318-1322

[31] Ahlering TE, Eichel L, Skarecky D. Evaluation of long-term thermal injury using cautery during nerve sparing robotic prostatectomy. Urology. 2008;**72**:1371-1374

[32] Klein LT, Miller MI, Buttyan R, et al. Apoptosis in the rat penis after penile denervation. The Journal of Urology. 1997;**158**:626-630

[33] Moreland RB. Is there a role of hypoxemia in penile fibrosis: A viewpoint presented to the Society for the Study of impotence. International Journal of Impotence Research. 1998;**10**:113-120

[34] User HM, Hairston JH, Zelner DJ, et al. Penile weight and cell subtype specific changes in a post-radical prostatectomy model of erectile dysfunction. The Journal of Urology. 2003;**169**:1175-1179

[35] Hatzimouratidis K, Burnett AL, Hatzichristou D, et al. Phosphodiesterase type 5 inhibitors in postprostatectomy erectile dysfunction: A critical analysis of the basic science rationale and clinical application. European Urology. 2009;**55**(2):334-347

[36] de Groat, WC and Booth, AM. Neural control of penile erection. In: The Autonomic Nervous System, Vol. 3, Nervous Control of the Urogenital System, ed. CA Maggi. Chur, Switzerland: Harwood Academic Publishers, pp. 467-524

[37] Cellek S. Nitrergic-noradrenergic interaction in penile erection: A new insight into erection dysfunction. Drugs Today. 2000;**36**(2-3):135-146

[38] Saenz de Tejada I, Kim NN, Goldstein I, et al. Regulation of pre-synaptic alpha adrenergic activity in the corpus cavernosum. International Journal of Impotence Research. 2000;**12**(Suppl 1):S20-S25

[39] Dausse JP, Leriche A, Yoblonsky F. Patterns of messenger mRNA expression for alpha-1 adrenoceptor subtypes in human corpus cavernosum. The Journal of Urology. 1998;**160**:597-600

[40] Martinez-Salamanca JI, La Fuente JM, Fernandez A, et al. Nitrergic function is lost but endothelial function is preserved in the corpus cavernosum and penile resistance arteries of men after radical prostatectomy. The Journal of Sexual Medicine. 2015;**12**:590-599

[41] Martinez-Salamanca JI, La Fuente JM, Martinez-Salamanca E, et al. α1A-adrenergic receptor antagonism improves erectile and cavernosal responses in rats with cavernous nerve injury and enhances neurogenic responses in human corpus cavernosum from patients with erectile dysfunction secondary to radical prostatectomy. The Journal of Sexual Medicine. 2016;**13**(12):1844-1857

[42] Johannes CB, Araujo AB, Feldman HA, et al. Incidence of erectile dysfunction in men 40-69 years old: Longitudinal results from the Massachusetts Male Aging Study. The Journal of Urology. 2000;**163**:460-463

[43] Laumann EO, Gagnon JH, Michael RT, Michaels S. National Health and Social Life Survey. Ann Arbor, MI, United States: Inter-university Consortium for Political and Social Research [distributor]; 1992 [Apr 17, 2008]. DOI: 10.3886/ICPSR06647.v2

[44] Lewis RW, Rugl-Meyer KS, Bosch R, et al. Epidemiology/risk factors of sexual dysfunction. The Journal of Sexual Medicine. 2004;**1**(1):35-39

[45] Rosen RC, Riley A, Wagner G, et al. The international index of erectile function (IIEF): A multidimensional scale for assessment of erectile dysfunction. Urology. 1997; **49**(6):822-830

[46] Rosen RC, Cappelleri JC, Gendrano N. The international index of erectile function (IIEF): A state-of-the-science review. International Journal of Impotence Research. 2002; **14**:226-244

[47] Rosen RC, Cappelleri JC, Smith MD, et al. Development and evaluation of an abridged, 5-item version of the international index of erectile function (IIEF-5) as a diagnostic tool for erectile dysfunction. International Journal of Impotence Research. 1999;**11**(6):319-326

http://dx.doi.org/10.5772/intechopen.79398

[48] Cappelleri JC, Siegel RL, Glasser DB, et al. Relationship between patient self-assessment of erectile dysfunction and the sexual health inventory for men. Clinical Therapeutics. 2001;**23**(10):1707-1719

[49] Althof SE, Corty EW, Levine SB, et al. EDITS: Development of questionnaires for evaluation satisfaction with treatments for erectile dysfunction. Urology. 1999;**53**(4):793-799

[50] Cappelleri JC, Stecher VJ. An assessment of patient-reported outcomes for men with erectile dysfunction: Pfizer's perspective. International Journal of Impotence Research. 2008;**20**(4):343-357

[51] Wei JT, Dunn RL, Litwinn MS, et al. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. Urology. 2000;**56**(6):899-905

[52] Penson DF, McLerran D, Feng Z, et al. 5-year urinary and sexual outcome after radical prostatectomy: Results from the prostate cancer outcome study. The Journal of Urology. 2005;**173**:1701-1705

[53] Resnick MJ, Koyama T, Fan KH, et al. Long-term functional outcomes after treatment for localized prostate cancer. New England Journal of Medicine. 2013;**368**:436-445

[54] Salonia Z, Zanni G, Gallina A, et al. Baseline potency in candidates for bilateral nerve-sparing radical retropubic prostatectomy. European Urology. 2006;**50**:360-365

[55] Dubbelman YD, Dohle GR, Schroder FH. Sexual function before and after radical retropubic prostatectomy: A systematic review of prognostic indicators for a successful outcome. European Urology. 2006;**50**(4):711-718

[56] Kundu SD, Roehl KA, Eggener SE, et al. Potency, continence and complications in 3477 consecutive radical retropubic prostatectomies. The Journal of Urology. 2004;**172**:2227-2231

[57] Geary ES, Dendinger TE, Freiha FS, et al. Nerve sparing radical prostatectomy: A different view. The Journal of Urology. 1995;**154**:145-149

[58] Walsh PC, Marschke P, Ricker D, et al. Patient-reported urinary continence and sexual function after anatomic radical prostatectomy. Urology. 2002;**55**:58-61

[59] Tsujimura A, Matsumiya K, Miyagawa Y, et al. Relation between erectile dysfunction and urinary incontinence after nerve-sparing and non-nerve sparing radical prostatectomy. Urologia Internationalis. 2004;**73**:31-35

[60] Rabbani F, Stepleton AMF, Kattan MW, et al. Factors predicting recovery of erections after radical prostatectomy. The Journal of Urology. 2000;**164**:1929-1934

[61] Hu JC, Elkin EP, Pasta DJ, et al. Predicting quality of life after radical prostatectomy: Results from CaPSURE. The Journal of Urology. 2004;**171**:703-707

[62] Ficarra V, Novara G, Fracalanza S, et al. A prospective, non-randomized trial comparing robot-assisted laparoscopic and retropubic radical prostatectomy in one European institution. BJU International. 2009;**104**:534-539

[63] Ficarra V, Novara G, Ahlering TE, et al. Systematic review and meta-analysis of studies reporting potency rates after robot-assisted radical prostatectomy. European Urology. 2012;**62**(3):418-430

[64] Zorn KC, Wille MA, Thong AE, et al. Continued improvement of perioperative, pathological, and continence outcomes during 700 robot-assisted radical prostatectomies. The Canadian Journal of Urology. 2009;**16**:4742-4749

[65] Moskovic DJ, Alphs H, Nelson CJ, et al. Subjective characterization of nerve sparing predicts recovery of erectile function after radical prostatectomy: Defining the utility of a nerve sparing grading system. The Journal of Sexual Medicine. 2011;**8**:255-260

[66] Levinson AW, Pavlovich CP, Ward NT. Association of surgeon subjective characterization of nerve sparing quality with potency following laparoscopic radical prostatectomy. The Journal of Urology. 2008;**179**:1510-1514

[67] McCullough AR. Prevention and management of erectile dysfunction following radical prostatectomy. The Urologic Clinics of North America. 2001;**28**:613-627

[68] Lee JK, Assel M, Thong AE, et al. Unexpected long-term improvements in urinary and erectile function in a large cohort of men with self-reported outcomes following radical prostatectomy. European Urology. 2015;**68**(5):899-905

[69] Abdollah F, Sun M, Suardi N, et al. Prediction of functional outcomes after nerve-sparing radical prostatectomy. Results of conditional survival analysis. European Urology. 2012;**62**:42-42

[70] Glickman L, Godoy G, Lepor H. Changes in continence and erectile function between 2 and 4 years after radical prostatectomy. The Journal of Urology. 2009;**181**:731-735

[71] Siddiqui MM, Rais-Bahrami S, Turkbey B, et al. Comparison of MR/ultrasound fusion-guided biopsy with ultrasound-guided biopsy for the diagnosis of prostate cancer. Journal of the American Medical Association. 2015;**313**(4):390-397

[72] Ahmed HU, Bosaily AES, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (Promis): A paired validating confirmatory study. Lancet. 2017;**389**:815-822

[73] Yossepowitch O, Briganti A, Eastham JA, et al. Positive surgical margins after radical prostatectomy: A systematic review and contemporary update. European Urology. 2014;**65**(2):303-313

[74] De Rooij M, Hamoen EHJ, Aitjes JA, et al. Accuracy of magnetic resonance imaging for local staging of prostate cancer: A diagnostic meta-analysis. European Urology. 2016;**70**(2):233-245

[75] Rud E, Baco E, Klotz D, et al. Does preoperative magnetic resonance imaging reduce the rate of positive surgical margins at radical prostatectomy in a randomized clinical trial? European Urology. 2015;**68**(3):487-496

[76] Tewari AK, Srivastava A, Huang MW, et al. Anatomical grades of nerve sparing: A risk-stratified approach to neural-hammock sparing during robot-assisted radical prostatectomy (RARP). BJU International. 2011;**108**:984-992

[77] Ficarra V, Cavalleri S, Novara G, et al. Evidence from robot-assisted laparoscopic radical prostatectomy: A systematic review. European Urology. 2007:45-55

[78] Schatloff O, Chauhan S, Sivaraman A, et al. Anatomic grading of nerve sparing during robot-assisted radical prostatectomy. European Urology. 2012;**61**:796-802

[79] Menon M, Shrivastava A, Kaul S, et al. Vattikuti institute prostatectomy: Contemporary technique and analysis of results. European Urology. 2007;**51**:648-658

[80] Yee DS, Narula N, Amin MB, et al. Robot-assisted radical prostatectomy: Current evaluation of surgical margins in clinically low-, intermediate-, and high-risk prostate cancer. Journal of Endourology. 2009;**23**(9):1461-1465

[81] Preston MA, Breau RH, Lantz AG, et al. The association between nerve-sparing and a positive surgical margin during radical prostatectomy. Urologic Oncology. 2015;**33**(1):18.e1-18.e6

[82] Stolzenburg JU, Kallidonis P, Do M, et al. A comparison of outcomes for interfascial and intrafascial nerve-sparing radical prostatectomy. Urology. 2010;**76**(3):743-748

[83] Srivastava A, Chopra S, Pham A, et al. Effect of a risk-stratified grade of nerve-sparing technique on early return of continence after robot-assisted laparoscopic radical prostatectomy. European Urology. 2013;**63**:438-444

[84] Reeves F, Preece P, Kapoor J, et al. Preservation of the neurovascular bundles is associated with improved time to continence after radical prostatectomy but not long-term continence rates: Results of a systematic review and meta-analysis. European Urology. 2015;**68**(4):692-704

[85] Tewari A, Srivastava A. Sooriakumaran, et al. technique of traction-free nerve sparing robotic prostatectomy: Delicate tissue handling by real-time penile oxygen monitoring. International Journal of Impotence Research. 2012;**24**(1):11-19

[86] Choi WW, Freire MP, Soukup JR, et al. Nerve-sparing technique and urinary control after robot-assisted laparoscopic prostatectomy. World Journal of Urology. 2011;**29**:21-27

[87] Ko YH, Coelho RF, Chauhan S, et al. Factors affecting return of continence 3 months after robot-assisted radical prostatectomy: Analysis from a large, prospective data by a single surgeon. The Journal of Urology. 2012;**187**:190-194

[88] Gandaglia G, Suardi N, Gallina A, et al. Preoperative erectile function represents a significant predictor of postoperative urinary continence recovery in patients treated with bilateral nerve sparing radical prostatectomy. The Journal of Urology. 2012;**187**:569-574

[89] Klotz L, Heaton J, Jewett M, et al. A randomized phase 3 study of intraoperative cavernous nerve stimulation with penile tumescence monitoring to improve nerve sparing during radical prostatectomy. The Journal of Urology. 2000;**164**(5):1573-1578

[90] Walsh PC, Marschke P, Catalona WJ, et al. Efficacy of first-generation Cavermap to verify location and function of cavernous nerves during radical prostatectomy: A multi-institutional evaluation by experienced surgeons. Urology. 2001;**57**(3):491-494

[91] Kowalcyzk KJ, Huang AC, Hevelone ND, et al. Stepwise approach for nerve sparing without countertraction during robot-assisted radical prostatectomy: Technique and outcomes. European Urology. 2011;**60**:536-547

[92] Sanda MG, Dunn R, Wei J. Seminal vesicle sparing technique is associated with improved sexual HRQOL outcome after radical prostatectomy. The Journal of Urology. 2002;**167**:151

[93] John H, Hauri D. Seminal vesicle sparing radical prostatectomy: A novel concept to restore early urinary continence. Urology. 2000;**55**:820

[94] Gilbert SM, Dunn RL, Miller DC, et al. Functional outcomes following nerve sparing prostatectomy augmented with seminal vesicle sparing compared to standard nerve sparing prostatectomy: Results from a randomized controlled trial. The Journal of Urology. 2017;**198**:600-607

[95] Finley DS, Osann K, Chang A, et al. Hypothermic robotic radical prostatectomy: Impact on continence. Journal of Endourology. 2009;**23**:1443-1450

[96] Finley DS, Chang A, Morales B, et al. Impact of regional hypothermia on urinary continence and potency after robot-assisted radical prostatectomy. Journal of Endourology. 2010;**24**(7):1111-1116

[97] Chien GW, Mikhail AA, Orvieto MA, et al. Modified clipless antegrade nerve preservation in robotic-assisted laparoscopic radical prostatectomy with validated sexual function evaluation. Urology. 2005;**66**:419-423

[98] Eichelberg C, Erbersdobler A, Haese A, et al. Frozen section for the management of intraoperatively detected palpable tumor lesions during nerve-sparing scheduled radical prostatectomy. European Urology. 2006;**49**(6):1011-1018

[99] Schlomm T, Tennstedt P, Huxhold C, et al. Neurovascular structure-adjacent frozen-section examination (NeuroSAFE) increases nerve-sparing frequency and reduces positive surgical margins in open and robot-assisted laparoscopic radical prostatectomy: Experience after 11,069 consecutive patients. European Urology. 2012;**62**(2):333-340

[100] Beyer B, Schlomm T, Tennstedt P, et al. A feasible and time-efficient adaption of NeuroSAFE for da Vinci robot-assisted radical prostatectomy. European Urology. 2014;**66**(1):138-144

[101] Becker A, Coelius C, Adam M, et al. Safe-R. A novel score, accounting for oncological safe nerve-sparing at radical prostatectomy for localized prostate cancer. World Journal of Urology. 2015;**33**(1):77-83

[102] Tewari A, Srivasatava A, Menon M, et al. A prospective comparison of radical retropubic and robot-assisted prostatectomy: Experience in one institution. BJU International. 2003;**92**(3):205-210

[103] Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: Early outcomes from a randomized controlled phase 3 study. Lancet. 2016;**388**(10049):1057-1066

[104] Sooriakumaran P, Srivastava A, Shariat SF, et al. A multinational, multi-institutional study comparing positive surgical margin rates among 22393 open, laparoscopic, and robot-assisted radical prostatectomy patients. European Urology. 2014;**66**(3):450-456

[105] Novara G, Ficarra V, Mocellin S, et al. Systematic review and meta-analysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. European Urology. 2012;**62**(3):382-404

[106] Coughlin G, Dangle PP, Palmer KJ, et al. Athermal early retrograde release of the neurovascular bundle during nerve-sparing robotic-assisted laparoscopic radical prostatectomy. Journal of Robotic Surgery. 2009;**3**:13-17

[107] Ko YH, Coelho RF, Sivaraman A, et al. Retrograde versus antegrade nerve sparing during robot-assisted radical prostatectomy: Which is better for achieving early functional recovery? European Urology. 2013;**63**:169-177

[108] Brown JA, Rodin D, Lee B, et al. Transperitoneal versus extraperitoneal approach to laparoscopic radical prostatectomy: An assessment of 156 cases. Urology. 2005;**65**(2): 320-324

[109] Phinthusophon K, Nualyong C, Srinualnad S, et al. Laparoscopic radical prostatectomy: Transperitoneal laparoscopic radical prostatectomy versus extraperitoneal endoscopic radical prostatectomy. Journal of the Medical Association of Thailand. 2007; **90**(12):2644-2650

[110] Montorsi F, Brock G, Lee J, et al. Effect of nightly versus on-demand vardenafil on recovery of erectile function in men following bilateral nerve-sparing radical prostatectomy. European Urology. 2008;**54**:924-931

[111] Mostafa ME, Senbel AM, Mostafa T. Effect of chronic low-dose tadalafil on penile cavernous tissues in diabetic rats. Urology. 2013;**81**:1253-1260

[112] Park K, Ryu KS, Li WJ, et al. Chronic treatment with a type 5 phosphodiesterase inhibitor suppresses apoptosis of corporal smooth muscle by potentiating Akt signaling in a rat model of diabetic erectile dysfunction. European Urology. 2008;**53**:1282-1289

[113] Garcia LA, Hlaing SM, Gutierrez RA, et al. Sildenafil attenuates inflammation and oxidative stress in pelvic ganglia neurons after bilateral cavernosal nerve damage. International Journal of Molecular Sciences. 2014;**15**(10):17204-17220

[114] Colombo F, Cogni M, Deiana G, et al. Vacuum therapy. Archivio Italiano di Urologia e Andrologia. 1992;**64**:267-269

[115] Raina R, Agarwal A, Ausmundson S, et al. Early use of vacuum erection device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function. International Journal of Impotence Research. 2006;**18**:77-81

[116] Turner LA, Althof SE, Levine SB, et al. External vacuum devices in the treatment of erectile dysfunction: A one-year study of sexual and psychosocial impact. Journal of Sex & Marital Therapy. 1991;**17**:81-93

[117] Cookson MS, Nadig PW. Long term results with vacuum construction device. The Journal of Urology. 1993;**149**:290-294

[118] Basal S, Wambi C, Acikel C, et al. Optimal strategy for penile rehabilitation after robot-assisted radical prostatectomy based on preoperative erectile function. BJU International. 2012;**111**:658-665

[119] Kohler TS, Pedro R, Hendlin K, et al. A pilot study on the early use of the vacuum erection device after radical retropubic prostatectomy. BJU International. 2007;**100**(4):858-862

[120] Burnett AL. Phosphodiesterase 5 mechanisms and therapeutic applications. The American Journal of Cardiology. 2005;**96**:29M-31M

[121] Carson CC, Lue TF. Phosphodiesterase type 5 inhibitors for erectile dysfunction. BJU International. 2005;**96**:257-280

[122] Wilke RJ, Glick HA, McCarron TJ, et al. Quality of life effects of alprostadil therapy for erectile dysfunction. The Journal of Urology. 1997;**157**(6):2124-2128

[123] Schwartz EJ, Wong P, Graydon RJ. Sildenafil preserves intracorporeal smooth muscle after radical retropubic prostatectomy. The Journal of Urology. 2004;**171**:771-774

[124] Jo JK, Jong JO, Lee SW, et al. Effect of starting penile rehabilitation with sildenafil immediately after robot-assisted laparoscopic radical prostatectomy on erectile function recovery: A prospective randomized trial. The Journal of Urology. 2018;**199**(6):1600-1606

[125] Hyndman ME, Bivalacqua TJ, Feng Z, et al. Nightly sildenafil use after radical prostatectomy has adverse effects on urinary convalescence: Results from a randomized trial of nightly vs. on-demand dosing regimens. Canadian Urological Association Journal. 2015;**9**(11-12):414-419

[126] Zumbé J, Porst H, Sommer F, et al. Comparable efficacy of once-daily versus on-demand vardenafil in men with mild-to-moderate erectile dysfunction: Findings of the RESTORE study. European Urology; 2008;**54**(1):204-210

[127] Tian D, Wang XY, Zong HT, et al. Efficacy and safety of short- and long-term, regular and on-demand regimens of phosphodiesterase type 5 inhibitors in treating erectile dysfunction after nerve-sparing radical prostatectomy: A systematic review and meta-analysis. Clinical Interventions in Aging; 2017;**12**:405-412

[128] Raina R, Agarwal A, Zaramo CE, et al. Long-term efficacy and compliance of MUSE for erectile dysfunction following radical prostatectomy. SHIM (IIEF-5) analysis. International Journal of Impotence Research. 2005;**17**(1):86-90

[129] Raina R, Rahlajani G, Agarwal A, et al. The early use of transurethral alprostadil after radical prostatectomy potentially facilitates an earlier return of erectile function and successful sexual activity. BJU International. 2007;**100**(6):1317-1321

[130] Chang JI, Lam V, Patel MI. Preoperative pelvic floor muscle exercise and postprostatectomy incontinence: A systematic review and meta-analysis. European Urology. 2016;**69**(3):460-467

[131] Hsu LF, Liao YM, Lai FC, et al. Beneficial effects of biofeedback-assisted pelvic floor muscle training in patients with urinary incontinence after radical prostatectomy: A systematic review and metaanalysis. International Journal of Nursing Studies. 2016; **60**:99-111

[132] Lavoisier P, Proulx J, Courtois F, et al. Relationship between perineal muscle contractions, penile tumescence, and penile rigidity during nocturnal erections. The Journal of Urology. 1988;**139**:176

[133] Matthews VB, Astrom MB, Chan MH, et al. Brain-derived neurotrophic factor is produced by skeletal muscle cells in response to contraction and enhances fat oxidation via activation of AMP-activated protein kinase. Diabetologia. 2009;**52**:1409

[134] Dorey G, Speakman MJ, Feneley RC, et al. Pelvic floor exercises for erectile dysfunction. BJU International. 2005;**96**(4):595-597

[135] Perez FS, Rosa NC, Rocha AF, et al. Effects of biofeedback in preventing urinary incontinence and erectile dysfunction after radical prostatectomy. Frontiers in Oncology. 2018;**8**:1-10

[136] Prota C, Gomes CM, Ribeiro LH, et al. Early postoperative pelvic-floor biofeedback improves erectile function in men undergoing radical prostatectomy: A prospective, randomized, controlled trial. International Journal of Impotence Research. 2012; **24**(5):174-178

[137] Muller A, Tal R, Donohue JF, et al. The effect of hyperbaric oxygen therapy on erectile function recovery in a rat cavernous nerve injury model. The Journal of Sexual Medicine. 2008;**5**:562-570

[138] Thom SR. Hyperbaric oxygen—Its mechanisms and efficacy. Plastic and Reconstructive Surgery, Supplement. 2011;**127**:131S

[139] Chiles KA, Staff I, Johnson-Arbor K, et al. A double-blind randomized trial on the efficacy and safety of hyperbaric oxygenation therapy in the preservation of erectile function after radical prostatectomy. The Journal of Urology. 2018;**199**:805-811

[140] Sezen SF, Hoke A, Burnett AL, Snyder, et al. Immunophilin ligand FK506 is neuroprotective for penile innervation. Nature Medicine. 2001;**7**:1073-1074

[141] Mulhall JP, Muller A, Donohue JF, et al. FK506 and erectile function preservation in the cavernous nerve injury model: Optimal dosing and timing. The Journal of Sexual Medicine. 2008;**5**:1334-1344

[142] Lagoda G, Jin L, Lehrfeld TJ, Liu T, Burnett AL. FK506-binding protein localizations in human penile innervation. BJU International. 2008;**101**:604-609

[143] Rahimian R, Fakhfouri G, Rasouli MR, et al. Effect of pioglitazone on sciatic nerve ischemia/reperfusion injury in rats. Pediatric Neurosurgery. 2009;**45**:126-131

[144] Zhu J, Zhang J, Ji M, et al. The role of peroxisome proliferator-activated receptor and effects of its agonist, pioglitazone, on a rat model of optic nerve crush: PPARγ in retinal neuroprotection. PLoS One. 2013;**8**(7):e68935. DOI: 10.1371/journal.pone.0068935

[145] Aliperti LA, Lasker GF, Hagan SS, et al. Efficacy of pioglitazone on erectile function recovery in a rate model of cavernous nerve injury. Urology. 2014;**84**:1122-1127

[146] Gholamine B, Shafiei M, Motevallian M, et al. Effects of pioglitazone on erectile dysfunction in sildenafil poor-responders: A randomized, controlled study. Journal of Pharmaceutical Sciences. 2008;**11**:22-31

[147] Katz EG, Moustafa AA, Heidenberg D, et al. Pioglitazone enhances survival and regeneration of pelvic ganglion neurons after cavernosal nerve injury. Urology. 2016;**89**:76-82

[148] Liang H, Liang P, Xu Y, et al. DHAM-BMSC matrix promotes axonal regeneration and functional recovery after spinal cord injury in adult rats. Journal of Neurotrauma. 2009;**26**:1745-1757

[149] May F, Vroemen M, Matiasek K, et al. Nerve replacement strategies for cavernous nerves. European Urology. 2005;**48**:372-378

[150] Patel VR, Samavedi S, Bates AS, et al. Dehydrated human amnion/chorion membrane allograft nerve wrap around the prostatic neurovascular bundle accelerates early return to continence and potency following robot-assisted radical prostatectomy: Propensity score-matched analysis. European Urology. 2015;**67**:977-980

[151] Ogaya-Pinies G, Palayapalam-Ganapathi H, Rogers T, et al. Can dehydrated human amnion/chorion membrane accelerate the return to potency after a nerve-sparing robotic-assisted radical prostatectomy? Propensity score-matched analysis. Journal of Robotic Surgery. 2017 [E-pub ahead of print]

[152] Yamashita S, Fujii S, Kamiyama Y, et al. Impact of tissue sealing sheet on erectile dysfunction in a rat model of nerve-sparing radical prostatectomy. The Journal of Sexual Medicine. 2016;**13**:1448-1454

[153] Bochinski D, Lin GT, Nunes L, et al. The effect of neural embryonic stem cell therapy in a rat model of cavernosal nerve injury. BJU International. 2004;**94**:904-909

[154] Al-Chalabi A, Miller CC. Neurofilaments and neurological disease. BioEssays. 2003; **25**:346-355

[155] Piao S, Kim IG, Lee JY, et al. Therapeutic effect of adipose-derived stem cells and BDNF-immobilized PLGA membrane in a rat model of cavernous nerve injury. The Journal of Sexual Medicine. 2012;**9**:1968-1979

[156] Jeong HH, Piao S, Ha JN, et al. Combined therapeutic effect of udenafil and adipose-derived stem cell (ASDC)/brain-derived neurotrophic factor (BDNF)-membrane system in a rat model of cavernous nerve injury. Urology. 2013;**81**:1108.e7-1108.e14

[157] Martinez-Salamanca JI, Zurita M, Costa C, et al. Dual strategy with oral phosphodiesterase type 5 inhibition and intracavernosal implantation of mesenchymal stem cells is

superior to individual approaches in the recovery of erectile and cavernosal functions after cavernous nerve injury in rats. The Journal of Sexual Medicine. 2016;**13**(1):1-11

[158] Lin G, Qiu X, Fandel T, et al. Tracking intracavernously injected adipose-derived stem cells to bone marrow. International Journal of Impotence Research. 2011;**23**:268-275

[159] Shan H, Chen F, Zhang T, et al. Stem cell therapy for erectile dysfunction of cavernous nerve injury rats: A systematic review and meta-analysis. PLoS One;**10**(4):e0121428. DOI: 10.1371/journal.pone.0121428

[160] Hou QH, Ge MY, Zhang CD, et al. Adipose tissue-derived stem cell therapy for erectile dysfunction in rats: A systematic review and meta-analysis. International Urology and Nephrology. 2017;**49**(7):1127-1137

[161] Carson 3rd CC. Efficacy of antibiotic impregnation of inflatable penile prostheses in decreasing infection in original implants. The Journal of Urology. 2044;**171**:1611-1614

[162] Garber BB, Marcus SM. Does surgical approach affect the incidence of inflatable penile prosthesis infection? Urology. 1998;**52**:291-293

[163] Eid JF. Penile implant: Review of a "no-touch" technique. Sexual Medicine Reviews. 2016;**4**(3):294-300

[164] Montague DK. Penile prosthesis implantation for end-stage erectile dysfunction after radical prostatectomy. Revista de Urología. 2005;**7**(Suppl 2):S51-S57

[165] Wilson SK, Delk JR, Salem EA, Cleves MA. Long-term survival of inflatable penile prostheses: Single surgical group experience with 2384 first-time implants spanning two decades. The Journal of Sexual Medicine. 2007;**4**:1074-1079

[166] 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. The Journal of Sexual Medicine. 2014;**11**(2):605-612

[167] Ziegelmann MJ, Viers BR, Lomas DJ, Westerman ME, Trost LW. Ectopic penile prosthesis reservoir placement: An anatomic cadaver model of the high submuscular technique. The Journal of Sexual Medicine. 2016;**13**(9):1425-1431

[168] Pillay B, Moon D, Love C, et al. Quality of life, psychosocial functioning, and treatment satisfaction of men who have undergone penile prosthesis surgery following robot-assisted radical prostatectomy. The Journal of Sexual Medicine. 2017;**14**:1612-1620

[169] Megas G, Papadopoulos G, Stathouros G, et al. Comparison of efficacy and satisfaction profile, between penile prosthesis implantation and oral PDE5 inhibitor tadalafil therapy, in men with nerve-sparing radical prostatectomy erectile dysfunction. BJU International. 2013;**112**:E169-E176

[170] Rajpurkar A, Dhabuwala CB. Comparison of satisfaction rates and erectile function in patients treated with sildenafil intracavernous prostaglandin E1 and penile implant surgery for erectile dysfunction in urology practice. The Journal of Urology. 2003; **170**:159-163

[171] Padma-Nathan H, McCullough AR, Levine LA, 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. International Journal of Impotence Research. 2008;**20**:479-486

[172] Pavlovich CP, Levinson AW, Su LM, 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 International. 2013;**112**:844-851

[173] Montorsi F, Brock G, Stolzenburg JU, et al. Effects of tadalafil treatment on erectile function recovery following bilateral nerve-sparing radical prostatectomy: A randomized placebo-controlled study (REACTT). European Urology. 2014;**65**:587-596

[174] Canat L, Bayram G, Gurbuz C, et al. Effects of three-times-per-week versus on-demand tadalafil treatment on erectile function and continence recovery following bilateral nerve sparing radical prostatectomy: Results of a prospective, randomized, and single-center study. The Kaohsiung Journal of Medical Sciences. 2015;**31**:90-95

[175] Kim DJ, Hawksworth DJ, Hurwitz LM, et al. A prospective, randomized, placebo-controlled trial of on-demand vs. nightly sildenafil citrate as assessed by RigiScan and the international index of erectile function. Andrology. 2016;**4**:27-32