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Designing the Rehabilitation of Men with Post-Prostatectomy Erectile Dysfunction Using a Pre- and Post-Operative Approach

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Introduction

Men with clinically localized prostate cancer are offered a variety of treatment choices, including active surveillance (AS), surgery in the form of radical retropubic prostatectomy (RRP) or robotic-assisted laparoscopic prostatectomy (RALP), radiation in the form of external beam radiotherapy (EBRT), brachytherapy or a combination, as well as newer techniques such as cryotherapy and high intensity focused ultrasound (HIFU). From a urologic perspective, radical prostatectomy (RP) with or without pelvic lymphadenectomy has been considered the gold standard for treatment. This has traditionally been accomplished by the open technique, but RALP is increasingly being utilized [1]. However, RP is associated with significant post-operative complications, including erectile dysfunction. Rabbani et al. were the first researchers to demonstrate that preoperative erectile function (EF), along with age and intraoperative neurovascular bundle preservation, was a key determinant in predicting postoperative EF [2].

In the current paper, we present a systematic medical literature review and recommendations for both preoperative and postoperative evaluations of erectile function as well as intraoperative techniques to preserve function.

Definition and Diagnosis of ED

Erectile dysfunction (ED) is defined as the constant or recurrent inability of a man to achieve and/or maintain a penile erection adequate for sexual activity [3]. While ED is primarily diagnosed through patient reporting, collateral information from a partner or patient completed questionnaire may aid in the diagnosis. ED can occur at any age after puberty and usually requires duration of 3 months for the establishment of a diagnosis. However, in instances of trauma or surgical induced ED (e.g. after RP), the 3-month minimum is not required for diagnosis [4,5].

Preoperative Evaluation

According to the International Consultation in Sexual Medicine (ICSM), it is recommended that for the clinical assessment and diagnosis of ED, all patients receive a basic evaluation with specialized testing reserved for special cases [5]. We have adopted these guidelines and included additional measures to evaluate patients based upon a medical literature review regarding EF prior to radical prostatectomy. This compilation allows for a standardized examination of a patient's sexual health prior to surgery and therefore aids in predicting EF following surgery [2,6].

Sexual function history

Preoperative sexual function assesses erectile insufficiency, sexual desire, ejaculation and orgasms. As described in Rabbani et al. and Meuleman et al. pre-operative EF is one of the most important predictors in determining postoperative EF [2,6]. Scales and questionnaires are valuable instruments in deciphering a patient's EF and both articles indicate the use of such tools.

IIEF and SHIM: The International Index of Erectile Function (IIEF) is a self-administered, multidimensional 15-item questionnaire that ascertains relevant domains of male sexual function [7]. Established by Rosen et al. in 1997, the IIEF measures participants' responses using a five and six point Likert scale. While the IIEF has become a widely accepted tool for screening and diagnosing ED, it has also served as a catalyst for other questionnaires including the Sexual Health Inventory in Men (SHIM) or IIEF-5 [8]. Both questionnaires rank the severity of ED as no ED, mild ED, moderate ED and severe ED via numerical cutoffs.

SEP: The Sexual Encounter Profile (SEP) [9] is another cost-efficient method of evaluating EF. This 5-question patient diary is completed after every sexual encounter and allows both the patient and his partner to evaluate their sexual occurrence. The questions aim at unveiling the patient's ability to achieve an erection, penetrate his partner, maintain an erection long enough for successful intercourse, and decipher satisfaction of erectile hardness and sexual experience.

EPIC: Unlike the previous listed questionnaires, the Expanded Prostate Cancer Index Composite (EPIC) focuses on the quality of life of prostate cancer patients. The 50-question survey is a derivative of the UCLA Prostate Cancer Index and contains 13 items that focus on sexual domain, including bother [10]. While the EPIC does not offer the ability to gauge ED severity, it does offer a screening tool for prostate cancer specific patients.

EHS: The Erectile Hardness Score (EHS) is a single item patient reported survey that poses the question, 'How would you rate the hardness of your erection?', Patients can respond with a score of zero to four, corresponding to responses of penis does not enlarge to penis is completely hard and fully rigid, respectively. Mulhall and Goldstein et al. have validated the EHS scoring system for the assessment of erection hardness and exposed its clinical use in determining successful sexual intercourse rate [11,12].

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Medical history

Documenting a detailed medical history may expose concomitant factors for a patient's EF. Numerous primary risk factors for the development of ED have been well established including heart disease, diabetes, dyslipidemia, hypertension, certain medications and depression [4,13,14]. In addition, medical illnesses such as renal or hepatic dysfunction, endocrine disease, neurological disease, pelvic or penile trauma and surgery and pelvic radiotherapy can contribute to sexual dysfunction. A patient's medical history might also unveil modifiable lifestyle factors such as obesity, diabetes control, smoking and alcohol consumption [4]. Through obtaining a comprehensive medical history, one can better assess a patient's pre-surgical EF and possible modifications to improve post-surgical sexual function.

Psychosocial history

Psychological and interpersonal factors are potential etiologies for sexual dysfunction and a detailed assessment is essential in every case of ED. It is important that the physician begin the history with broad questions, as every patient is not involved in a heterosexual, monogamous relationship. Further assessment of marital status, sexual orientation and current sexual practices will assist the physician in making patient-specific recommendations. For example, men who engage in anal sexual activity may require firmer erection than for vaginal intercourse, thus their assessment will need to be tailored to approach this issue. The physician should also determine if there were particular times of change in the patient's sexual activity that might be related to a life event, such as recent or past trauma, change in medication,or significant depression/anxiety. Also, it is important to explore interpersonal facets such as occupational status, financial security, family life, and social support [4,5].

Focused physical exam

The focused physical examination in men undergoing pelvic surgery allows the physician to assess the genital anatomy and detect possible comorbidities and associated abnormalities. The ICSM recommends a general assessment of male secondary sex characteristics, cardiovascular system and neurological system with a focused examination of the genito-urinary system [5].

The focused urologic examination begins with inspection of the penis for size, scars, lesions and position of meatus. The scrotum should be evaluated for size and consistency. Prostate size and character are assessed through digital rectal examination. If any abnormalities are detected, further diagnostic evaluation should be undertaken.

Laboratory testing

Laboratory tests allow the physician to further assess the role of potential medical comorbidities for a patient's EF. The general laboratory evaluation should include fasting glucose or hemoglobin A1C, lipid profile and a hormone profile, including a morning testosterone. Research has shown diabetes mellitus occurs in up to 25% of ED patients and up to 70% of ED patients have concurrent dyslipidemias [13,14]. Additional laboratory tests, including prolactin and thyroid function tests, can be obtained at the physician's discretion based on the patient's medical history and clinical presentation [5].

Specialized tests

In general, the use of specialized tests to evaluate initial EF does not contribute new information to the data acquired from questionnaires, medical history, physical examination and laboratory testing [5]. These tests include dynamic infusion cavernosometry and cavernosography (DICC), penile arteriography, computed tomography (CT) and magnetic resonance imaging (MRI), nuclear imaging, vibrometry, bulbocavernosus reflex latency, cavernosal electromyelogram (EMG) and somatosensory evoked potential testing, pudendal and sphincter EMG. The use of such tests should be limited to special circumstances requiring further evaluation of the ED.

The exceptions to this recommendation include the measurement of nocturnal penile tumescence (NPTR) and pharmaco-penile duplex ultrasound. These diagnostic tests allow for an objective measurement of a patient's erectile function. In 1995, Zimmern et al. evaluated different diagnostic techniques for evaluating baseline potency in men undergoing RRP [15]. In a group of 45 potent men, biothesiometry, NPTR and color Doppler ultrasound were performed preoperatively. Their data showed duplex Doppler scanning was the best objective test used to correlate patients' potency (93%) as determined by detailed questionnaires. Similarly, Kawanishi et al. evaluated EF pre- and post-RP, using both aforementioned tests. Out of 123 patients, they discovered 21 patients (17%) were having normal EF prior to surgery. Of this 17%, only 9 out of 21 patients had preserved EF as determined using Doppler ultrasonography and NPTR [16].

Timing and usage of exams

While NPTR and pharmaco-penile duplex ultrasound are excellent tools for evaluating the etiology of ED, certain challenges still remain. With regards to NPTR, the examination is both time consuming and expensive, thereby making it an unlikely test to perform on every preoperative patient. Similarly, while Doppler ultrasound can be easily performed, its expense may limit its usage in a clinical setting. Despite the aid of both tests, the timing of their usage in evaluating pre-operative EF has yet to be determined. Herein, we outline a methodical evaluation in order to stratify which patients require further diagnostic tests in determining their EF.

Assuming the patient's medical history, psychosocial history, physical examination and laboratory results are acceptable and do not appear as a primary etiology of ED, the physician's attention can focus on the sexual history. As stated above, the IIEF is commonly used to assess several domains of ED; namely erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction. Although the IIEF and SHIM provide adequate ED screening questions, we suggest corroborating patients' responses with the erection hardness scale (EHS). This allows the physician to capture patient discrepancy.

Through the comparison of IIEF or SHIM to EHS, the preoperative patient population can be stratified into four groups: 1) No ED as noted by IIEF and validated by EHS, 2) mild to moderate ED as determined by IIEF and corroboratedby EHS, 3) severe erectile dysfunction on IIEF and verified on EHS, and 4) patients with incongruous IIEF and EHS categorical scores. Patients with no ED noted on exam do not require further evaluation. Likewise, patients with severe ED do not need additional testing, however we advise that these patients be counseled on the extremely poor likelihood of attaining an erection after surgery. We propose all patients with mild to moderate ED, or

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conflicting scores, be offered further diagnostic testing. It is at this point in the preoperative evaluation that color Doppler ultrasound, office administration of vasoactive agents, or NPTR can become useful in diagnosing the patient. Through the combination IIEF or SHIM and EHS screening, physicians are better able to stratify their patient population and judiciously use further diagnostic tools for EF evaluation. In addition, patients with conflicting IIEF and EHS results should be asked additional questions to ascertain the source of the discrepancy, such as orgasmic dysfunction.

A supplementary assessment of patient ED that is often not utilized is partner corroboration. By openly discussing EF, expectations and satisfaction with both the patient and his partner, the physician can evaluate additional patients with inconsistent assessments using the aforementioned methods.

Through using this preoperative evaluation approach, the physician can attain subjective and objective measurements of a patient's EF status, and can assess and counsel patients on their risk factors for postoperative erectile function.

Pathophysiology of ED after Radical Prostatectomy

In order to appreciate the intraoperative techniques used to preserve erectile function, it is essential to understand the underlying pathophysiology of ED post-RP. Burnett et al. demonstrated normal EF is dependent upon the relaxation of corporal smooth muscle in the penis via neuronal and endothelial derived nitric oxide (NO) [17]. When NO is released from the cavernous nerves of the neurovascular bundle (NVB), penile smooth muscle relaxes and the hemodynamic changes of penile erection ensues. Interference with the NVB is hypothesized to be the major culprit causing post-RP ED.

Although the mechanism of neuropraxia during RP is not completely clear, hypotheses include idiopathic surgical severance of the NVB, nerve stretching during prostate retraction, electrocautery damage during NVB dissection, ischemic effects and local inflammation in response to surgical trauma [18]. As demonstrated in animal model studies, the resulting neurapraxia associated with cavernosal hypoxia, apoptosis of the penile smooth muscle and endothelium, loss of NO signaling, and penile smooth muscle fibrosis through the increase of transforming growth factor-β, a cytokine marker of chronic inflammation and fibrosis [19-22]. It is postulated that the penile fibrosis causes corpus cavernosum insufficiency and venous leakage.The resulting tissue hypoxia, penile fibrosis, and damage to cavernosal structures manifest themselves as ED.

While neurologic damage is thought to be an important determinant of postoperative ED, other studies have demonstrated a possible arteriogenic etiology due to the accessory pudendal arteries (APAs) [16,23,24]. In 2004, Rogers et al. reported that out of 84 men with the APA, 93% had preserved potency following nerve sparing RP and sparing of one or both pudendal arteries, while only 70% of men had preserved potency when both arteries were sacrificed [23]. Similarly, building off the concept of nerve sparing RP, Mulhall et al. introduced artery-sparing RP in 2008 [24]. Through a medical literature review, they determined that approximately 1 in 4 patients undergoing laparoscopic RP had pudendal arteries of different calibers, supporting the concept that the pudendal arteries have a role in EF and its recovery after RP [24].

In contrast, Blander et al. presented data indicating that APA was not of significance in the maintenance of erections in the post-RP patient [25]. More recently, Box et al. reported no correlation between the presence or absence of APAs and preoperative sexual function, nor any correlation with potency return, time to return of potency, or quality of erection after sacrificing all APAs in RALP [26].

Currently the preservation of the accessory pudendal artery in contributing to post surgical ED is not entirely clear and remains an ongoing source of controversy, however surgeons should be aware of its possible involvement.

Intraoperative Techniques to Preserve EF

Neurovascular bundle preservation

The loss or decline of EF after RP is mostly due to injury to the autonomic cavernous nerves, as demonstrated by Walsh and Donker in 1982 [27]. Walsh went on to develop a technique for RRP based on identifying autonomic nerves and other anatomic structures surrounding the prostate [28]. Numerous studies have reported recovery of erectile potency after NVB sparing RP.

In 1991, Quinlan et al. determined potency recovery was quantitatively related to the preservation of nerves and identified three factors associated with post RP recovery of potency: age, clinical and pathological stage, and preservation of the NVB [29]. Kundu et al. reported out of 3477 patients, 76% of patients with bilateral NVB sparing and 53% of patients with unilateral nerve sparing RP claimed potency after surgery [30]. However, not all reports of NVB sparing have been favorable. In 2002, Noldas et al. performed a study on 289 patients and found erectile potency rates of 51.7% after bilateral NVB sparing RP and 16.1% after unilateral nerve sparing [31].

Despite the different reports on NVB preservation and its correlation to EF after RP, most urologists agree there is a direct link between nerve sparing and potency post RP. This can be appreciated by the meta-analysis performed by Tal et al. on the recovery of EF when comparing unilateral and bilateral NVB sparing RP. Their review showed a sexual potency recovery rate of 47% after unilateral nerve sparing and 60% after bilateral nerve sparing [32].

Intraoperative cavernous nerve stimulation

Identification and localization of the NVB during surgery is often times difficult due to anatomic variations and poor exposure of the surgical field because of blood, body habitus, etc. Lue et al. demonstrated the feasibility of intraoperative electrostimulation of the cavernous nerves in order to produce an erection [33].

With the use of cavernous nerve stimulation (CaNS) during surgery, one would expect intraoperative identification of the NVB would aid in its preservation and thereby, EF. However, the remains uncertainty and controversy regarding this approach.

The surgical tool CaverMap (Alliant Medical Technologies, Norwood, MA) was marketed as a device that detects minor, visually imperceptible changes in penile circumference when applied to the NVB. Using this platform, Klotz and Herschorn performed a pilot study and reported a 31% recovery rate of EF in men 1 year after undergoing bilateral nerve sparing surgery using CaNS [34]. In 2001, Chang et al. prospectively determined intraoperative tumescence response to CaNS after RP positively correlated with postoperative sexual function in 80% of patients [35].

While some studies have reported success with using intraoperative CaNS, many others have described unsatisfactory

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potency retention despite intraoperative erectile tumescence. A study done by Kim et al. suggested intraoperative CaNS was poorly predictive of EF recovery in that potency was recovered in 0% of patients in whom neither NVB were stimulated, 22% of patients in whom only one NVB could be stimulated, and only 27% of patients in whom both NVB could be stimulated [36]. Walsh et al. reported a lack of specificity in the Cavermap locating NVB as identified by experienced surgeons. In nearly half of the recorded response, the stimulated location did not represent the NVB [37].

Currently, the use of intraoperative cavernous stimulation remains a controversial discussion as the specificity and value of stimulation to predict recovery of sexual function has yet to be determined.

Interposition of sural nerve grafts

The idea of NVB preservation has sparked several analyses of cavernous nerve grafts after RP. Theoretically, nerve grafting would provide neurological support after wide excision of NVB. In 1991, Quinlan et al. solidified this theory when they reported positive results in restoring EF in rats via genitofermoral nerve grafting [38].

It was not until 1999 that research showed application of the sural nerve graft to the clinical arena. Kim and Scardino et al. identified 9 patients who required wide NVB removal secondary to high grade prostate cancer. After removal of the prostate, but prior to the vesicourethral anastomosis, an autologous sural nerve graft was interposed between the ends of the cavernous nerves bilaterally [39]. Their study revealed early spontaneous partial erections in their patients and one patient who endorsed an erection sufficient for penetration at 14 months post surgery [39].

Other studies have also reported success: Chang et al. noted a 43% potency rate with bilateral grafting at a mean of 23 months follow up [40], and Anastasiadis et al. reported a 33% success rate with unilateral grafting at an average of 16 months follow up [41]. Although these studies have assessed a limited number of patients, their findings support the potential value of cavernous nerve grafting for restoring EF in men undergoing RP.

Post Operative Evaluation

For nearly all patients undergoing RP, sexual dysfunction begins immediately after surgery. Patients experience a loss of nocturnal, morning and psychogenic erections due to the result of intraoperative neuropraxia as outlined above. Most physicians assess and treat post-surgical ED based on patients' IIEF, SHIM or SEP responses. Herein, we delineate a proposed postoperative evaluation of erectile dysfunction.

It is important to realize having a detailed preoperative evaluation allows for postoperative comparison, and proper diagnosis and treatment. As mentioned previously, similar steps should be taken in the postoperative EF evaluation of a patient, namely; sexual history, medical history, psychosocial history and focused physical examination. In particular, the use of IIEF or SHIM with EHS questionnaires to assess postoperative sexual function allows for an accurate diagnosis of ED and the ability to streamline patients based on the severity of dysfunction.

Following the comparison of pre- and postoperative history and examination, further evaluation should focus on the major etiologies of post-RP ED, specifically neurogenic, arteriogenic, or venogenic complications, or the combination of any two. In regards to neurogenic causes of ED, the best postoperative predictive factor is the intraoperative sparing of the NVB as outlined above. However, unlike neurogenic etiologies, arteriogenic and venogenic causes to post-RP ED can be evaluated using pharmaco-penile duplex ultrasound.

In 2002, Mulhall et al. demonstrated the correlation between post-RP hemodynamic profiles and the recovery of EF [42]. Postoperative vascular evaluation consisted of cavernosometry or penile ultrasonography. In a group of 96 patients, they determined normal vascular status, arterial insufficiency and venous leakage in 35, 59, and 26% or men, respectively. A return to EF with vaginal intercourse at 12 months postoperatively was noted in 9% of men with venous leakage, 31% of men with arteriogenic insufficiency and 47% of men with normal vascular status [42]. Zelefsky et al. [43] also evaluated post RP penile blood flow using duplex ultrasonography and intracavernosal injections. Out of 60 men with post-RP ED, they showed cavernosal dysfunction (defined as abnormal distensibility of the corpora cavernosa) in 31 (52%) men, arteriogenic insufficiency in 19 (32%), neurogenic dysfunction in 7 (12%), and mixed vascular dysfunction in 3 (5%) men[43]. Unfortunately, unlike Kawanishi et al. [16], neither of these studies evaluated the preoperative vascular status of patients.

Since the introduction of early postoperative prophylactic vasoactive therapy in 1997 by Montorsi et al. [44], the concept of penile rehabilitation post-RP has become recognized as a viable treatment strategy. The early treatment of patients may produce better long-term results with regards to recovery of EF and ED treatment modalities. Despite its usage, there remains controversy on what is considered appropriate versus insufficient rehabilitation, as well as a standard protocol to treatment strategy. The ICSM committee has listed five different types of rehabilitative approaches: 1) PDE5 Inhibitors, 2) intracavernosal injections, 3) intraurethral alprostadil, 4) vacuum therapy and 5) neuromodulatory agents [45]. It is important to note that the committee did not offer a specific optimal rehabilitation regimen [45]. In a recent literature review of treatments to improve EF recovery following RP, Mulhall et al. explore and delineate current treatment options [46]. Their research demonstrated the following: 1) There are only a few studies of phosphodiesterase-5 inhibitors in humans post-RP, 2) daily sildenafil showed significant improvement in erection recovery compared to placebo or no rehabilitation, 3) nightly vardenafil compared to on demand and placebo showed no difference in erection recovery, 4) intracavernosal injections have no definitive supporting role in rehabilitation, 5) there is no current data to support vacuum erection devices as monotherapy following RP, and 6) no superiority was found when intraurethral alprostadil was compared to sildenafil in a multicenter, randomized trial [46].

As there is no current optimal rehabilitation regimen, we contend having postoperative evaluation of vascular disease with duplex Doppler ultrasound can theoretically aid in assessing a patient's postoperative EF and can guide the physician to choosing a better rehabilitation approach and possible adjunct therapy. Also, if the patient underwent a preoperative Doppler ultrasound as part of his evaluation, secondary to IIEF/SHIM and EHS discrepancy, there will be a baseline ultrasound evaluation to compare with his postoperative treated ED.

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As with the preoperative evaluation, we recommend that further invasive diagnostic procedures only be employed if they will influence therapeutic decision.

Discussion and Conclusions

The management of ED after RP is fervently advancing; however, the evaluation of stated dysfunction appears to be mostly subjective with no standard procedure. It has been shown that key factors for postoperative erectile function include age at surgery, preoperative erectile function and degree of intraoperative neurovascular bundle preservation [2,6].

We recommend every patient undergoing prostatectomy receive a full preoperative and postoperative evaluation using subjective and objective measures. Evaluations should include sexual history via questionnaires (i.e IIEF, SHIM, SEP, EHS), medical history for concomitant risk factors, psychosocial history for interpersonal complications, sexual orientation and practices, physical examination for anatomical variances, laboratory studies for medical comorbidities, and NPTR or pharmaco-penile duplex ultrasound for patients with conflicting EHS and IIEF/SHIM responses. We suggest that further invasive diagnostic techniques should only be performed if they will influence diagnosis or treatment choice.

The intraoperative technique of NVB sparing can assist in determining the probability of erectile function return of a patient. Other intraoperative practices, such as cavernous nerve stimulation and sural nerve grafting, continue to be controversial and needs further investigation.

Through attaining a detailed preoperative evaluation, utilizing particular intraoperative techniques and attaining a standardized postoperative assessment, physicians can better counsel patients' on their post-surgical EF probability and provide more specific penile rehabilitation therapies.

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