The Role and Structure of a Postradical Prostatectomy Penile Rehabilitation Program

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Erectile dysfunction (ED) is common after radical prostatectomy (RP). ED has a negative impact on health-related quality of life. Penile rehabilitation is defined as the use of any drug or device at or after RP to maximize erectile function recovery. The purpose of penile rehabilitation is the prevention of corpus cavernosal smooth muscle structural alterations not only to maximize the chances of a man having recovery of functional erections but also returning him to his preoperative erectile function level. Appreciating the value of penile rehabilitation requires understanding five concepts: the pathophysiology of ED after RP, cavernosal oxygenation, venous leak, and both the animal and human data supporting this strategy. This paper gives an overview of these factors and attempts to give a common-sense, practical guide to a rehabilitation program.

Introduction

Penile rehabilitation is defined as the use of any drug or device at or after radical prostatectomy (RP) to maximize erectile function recovery. The purpose of penile rehabilitation is the prevention of corpus cavernosal smooth muscle structural alterations to not only maximize the chances of a man having recovery of functional erections but also to return him to his preoperative erectile function level [1].

To appreciate the strategy of penile rehabilitation after RP, a number of concepts need to be understood, namely the pathophysiology of erectile dysfunction (ED) after RP, cavernosal oxygenation, and venous leak.

Pathophysiology of Erectile Dysfunction After Radical Prostatectomy

The pathophysiology of ED after RP involves three factors: neural injury, vascular injury (injury of accessory pudendal artery [2,3]), and smooth muscle damage (Fig. 1). Detailed reviews of pathophysiology have been previously published [4]. It is likely that the experienced, skilled surgeon induces neuropraxia during bilateral nerve-sparing surgery primarily through cavernous nerve stretch. In a recent study, Masterson et al. [5] demonstrated that alteration in technique, whereby the Foley catheter is no longer used as a retraction tool to maximize tension on the lateral pedicles, resulted in a significant improvement in erectile function postprostatectomy. It also has been suggested that exposure of the cavernous nerves alone may be deleterious to their integrity. Mullerad et al. [6] demonstrated in the cavernous nerve injury model that exposure of the cavernous nerves without any direct injury resulted in ED in a rat model. Thus, it appears that even the most minor neural trauma may result in at least short-term erectile problems. Cavernous neuropraxia results in erectile tissue changes, specifically: smooth muscle apoptosis, apoptosis of endothelium, and collagenization of smooth muscle. User et al. [7] have shown that bilateral and unilateral cavernous neurectomy resulted in early smooth muscle apoptosis. In this analysis, apoptosis peaked at 2 to 7 days after nerve injury. Of note, they showed that the smooth muscle apoptosis appeared to be clustered in the subtunical area. The authors suggested that this may in fact be a contributor to development of venous leak postprostatectomy. Another consequence of neuropraxia is alterations in smooth muscle, that is, collagen ratios [2,4,5,8••]. In response to nerve injury, the smooth muscle undergoes collagenization. Neural injury has been shown to be associated with up-regulation of collagen types I and III and up-regulation of fibrogenic cytokines such as transforming growth factor (TGF)-β [9]. Using electron microscopy, Klein et al. [10] showed that cavernous nerve injury results in endothelial cell retraction. Given the importance of corporal smooth muscle and endothelium for the purposes of erection, it can be appreciated how neuropraxia-induced erectile tissue alterations are deleterious to long-term erectile function recovery.

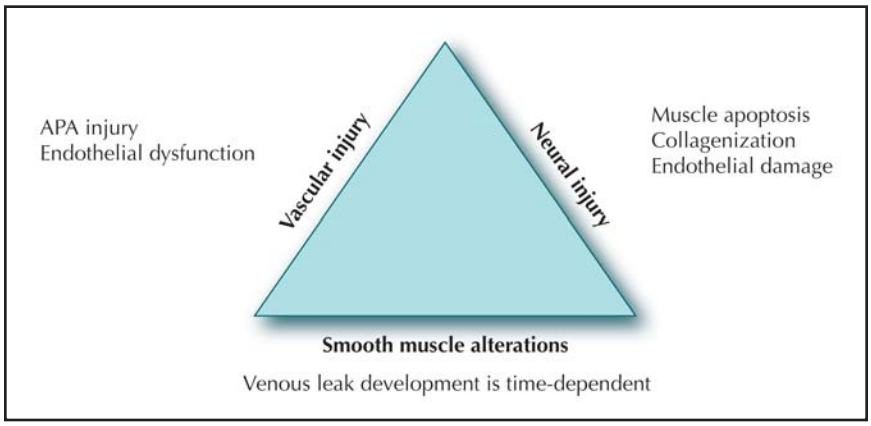

Figure 1. Pathophysiology of erectile dysfunction after radical prostatectomy. APA—aberrant pudendal artery.

It is plausible that these structural changes are amplified by the absence of erections. Given the fact that men obtain three to six erections each night, it is easy to see how going a prolonged period of time without erections may in fact lead to erectile tissue damage. One of the means by which erections protect erection tissue has been purported to be oxygenation of erectile tissue (cavernosal oxygenation). In the flaccid state, the pO_2 is approximately 35 to 40 mm Hg. It has been postulated that this results in up-regulation of fibrogenic cytokines, including TGF-β. TGF-β results in collagen production, which may eventually lead to fibrosis and venous leak. During erection, the penis is oxygenated with pO_2, rising to 75 to 100 mm of mercury. In vitro evidence demonstrates that oxygenation up-regulates production of endogenous prostanoids as well cyclic adenosine monophosphate (AMP) [11]. Moreland et al. [11] have shown in a series of in vitro experiments that exposure of cultured corporal cavernosal smooth muscle cells to low oxygen levels suppress prostaglandin $(PG)E_1$ and cAMP production. Upon returning oxygen environment to normoxia, levels of both normalized. In a further series of experiments the same authors showed that in the in vitro setting, the prostanoids inhibit TGF-β activity and thus reduce collagen production [12]. Therefore, in a healthy male there is an interplay between the flaccid and erect states, and as long as men obtain regular erections, erectile tissue is preserved. However, after RP in a state of unantagonized flaccidity, everything is shifted in favor of fibrogenic cytokine production, leading to structural changes and venous leak development.

The event that leads to the poorest erectile function outcome is the development of venous leak. Positioned between the tunica albuginea externally and the corporal smooth muscle internally are a series of subtunical venules. As the smooth muscle expands in a three-dimensional fashion under nitric oxide control, the subtunical venules are compressed against the tunica. This is the veno-occlusive mechanism. In conditions in which the muscle fails to expand adequately, some or all of the subtunical venules are left in a noncompressed state; this results in the concept we know as venous leak (synonyms: corporovenocclusive dysfunction, venogenic ED). The structural changes previously outlined lead to failure of veno-occlusive mechanism.

Mulhall and Graydon [13] have shown in a series of 16 patients who had preoperative and postoperative hemodynamic assessment that more than half of the men had venous leak after surgery. In a more recent analysis by Mulhall et al. [14], which included men who had partner-corroborated excellent erectile function prior to surgery and who underwent duplex Doppler penile ultrasound after surgery, there was an increase in the incidence of venous leak (based on elevated and diastolic velocities) as time progressed after surgery. The incidence of venous leak less than 4 months after surgery was approximately 10%, and it rose to 35% between 8 and 12 months after surgery and 50% after 12 months. The importance of this information is that in the same series, men with normal erectile hemodynamics were more likely to have recovery of natural erectile function. However, only 8% of men who had venous leak had recovery of natural functional erections after surgery. We also know from other data that men with venous leak are far less likely to respond to phosphodiesterase type 5 (PDE5) inhibitors than men with arterial insufficiency.

Data Supporting the Concept of Penile Rehabilitation

Several published studies demonstrate a positive effect of regular PDE5 inhibitor use after cavernous nerve injury. Three of these studies pertain to tadalafil, two to sildenafil, and one to vardenafil [8••,15–19]. In brief, these studies are uniformly supportive of a beneficial effect of PDE5 inhibitor use after cavernous nerve injury. The results are consistent and demonstrate improved ICP/MAP ratios, reduced incidence and degree of venous leak using cavernosometry, preservation of cavernosal smooth muscle, and endothelial integrity.

The human literature discussing rehabilitation has up until recently been generally positive albeit weak. In 1997, Montorsi et al. [20] published a randomized trial comparing men using intracavernosal injections three times a week for 12 weeks after RP compared with men who used no treatment. Twelve of 15 patients using injection therapy completed the trial, and eight of 12 (67%) had natural erections sufficient for intercourse early after

surgery. This was compared to 20% of men (all 15 finished) in the control arm who had recovery of natural erections. Interestingly, of those patients failing to have recovered erectile function, the majority had venous leak on duplex Doppler penile sound. Although the study was significantly underpowered to address this question, this was the first study to suggest that early erections postprostatectomy are critical for recovery of long-term erectile function. In 2005, Mulhall et al. [21] conducted a nonrandomized study of 132 patients, comparing patients who opted for penile rehabilitation versus those who did not. Rehabilitation patients were told to obtain three erections per week, whether via sildenafil or penile injections. Those in the rehabilitation group averaged 1.9 erections per week; these patients also had significant improvement in natural response, sildenafil response, and intracavernosal injection response. Although short of being definitive, there is a signal from both studies that early erections after RP may be important for long-term recovery and erectile function.

Padma-Nathan et al. [22••] recently published data from a Pfizer-sponsored trial that ended in 2002, in which 76 patients were randomly assigned in a three-way fashion to Viagra (Pfizer Inc., New York, NY), 50 mg or 100 mg, or placebo nightly starting 4 weeks after bilateral nerve-sparing RP and continuing for 36 weeks. Of the patients using Viagra (there was no significant difference between 50 or 100 mg), 27% had recovery of erections similar to their baseline erections compared with 4% of those patients in the placebo group. If we conduct a critical analysis of bilateral nerve-sparing RP patients across all ages, it is likely that we will find that no more than 10% to 20% or so who will have returned to baseline erection rigidity after surgery. Most recently, the Bayer-sponsored REINVENT study has raised questions about the utility of penile rehabilitation [23••]; this study has been critiqued in detail elsewhere [24]. The study was very complicated in its design: Within 14 days of bilateral nerve-sparing RP, patients were randomly assigned in a 1:1:1 ratio to receive either 9 months of treatment with vardenafil, 10 mg nightly (which could be decreased to 5 mg if required), plus on-demand placebo for sexual relations; 9 months of treatment with flexible-dose, on-demand vardenafil for sexual relations (starting at 10 mg with the option to titrate to 5 mg or 20 mg) plus nightly placebo; or 9 months of treatment with nightly placebo plus on-demand placebo for sexual relations. After this, a 2-month single-blind phase was conducted in which all patients received only placebo for sexual relations; this was, in turn, followed by a 2-month open-label phase in which all patients received vardenafil for sexual relations. The inclusion/exclusion criteria were standard for ED post-RP trials. This study failed to demonstrate any difference in natural or vardenafil-assisted erectile function between men using vardenafil on-demand or daily, thus raising questions about rehabilitation as well as the design of the study.

More recently, two other strategies have been explored for the purposes of penile rehabilitation postprostatectomy. Vacuum device therapy has been around for more than a century and has continued to assume a role in the management of men with ED. A number of centers have studied the role of vacuum device therapy for the preservation of penile length postprostatectomy and for rehabilitation. It has been well documented that the pO_2 and pCO_2 levels in the cavernosal sinusoids following the application of a vacuum device remain in the venous range [25]. Indeed, the oxygen saturation is approximately 80%. If one believes that cavernosal oxygenation is critical to erectile tissue health and penile rehabilitation outcomes, this finding would undermine the role of vacuum device therapy as a rehabilitation strategy. A study by Raina et al. [26] included 109 patients who were randomly assigned to vacuum device use daily for 9 months versus observation. Thirty-two percent of patients in the vacuum device rehabilitation group versus 37% in the observation group had recovery of natural erections at 9 months after surgery. Seventy percent of the vacuum device patients and 29% of those not using the vacuum device were able to have sexual intercourse at that time. Dalkin and Christopher [27] studied 39 men with good preoperative erectile function who underwent nerve-sparing RP. Stretched flaccid penile length was evaluated preoperatively and at 3 months postoperatively by a single examiner. The vacuum device was used daily starting the day after catheter removal and was continued for 90 days. In men using the vacuum device on more than 50% of the possible days, only 3% had a decrease in stretched flaccid penile length of greater than 1 cm. Of the three men with poor vacuum device compliance, 67% had a penile length reduction of more than 1 cm. Kohler et al. [28] analyzed 28 men who were randomly assigned to early vacuum device or a control group. The vacuum device group had therapy commenced 1 month after RP, whereas the control group had vacuum therapy instituted 6 months after RP. Postoperative Sexual Health Inventory for Men (SHIM) scores were higher in the treatment group at 6 months (12.4 vs 3.0). Furthermore, in the treatment group, no significant changes in stretched flaccid penile length were measured at 3 or 6 months postoperatively. In the control group, the mean penile length loss at 3 and 6 months was approximately 2 cm. Based on these small studies, there is a solid rationale for the conduct of a large multicenter analysis of vacuum device therapy in a randomized controlled trial as a rehabilitation strategy. In my opinion, the current evidence does not support the role of vacuum devices as monotherapy in penile rehabilitation.

Recently there has been a resurgence in interest in transurethral prostaglandin (MUSE; Vivus, Mountain View, CA) as a treatment strategy for ED as well as a penile rehabilitation strategy. Costabile et al. [29], in a retrospective analysis of all alprostadil clinical trial data, analyzed 384 patients who were postprostatectomy. In this population, 40% had sexual intercourse on at least one occasion at home and 18% of patients had urethral pain and burning.

The limiting factor in the use of alprostadil in the treatment of men postprostatectomy, particularly in the first year after surgery, is penile pain due to PGE_1 hypersensitivity. It is my experience that doses of 500 μg and 1000 μg of alprostadil are associated with penile pain rates in excess of 50%. Raina et al. [30] studied 54 patients using alprostadil post-RP. Of these patients, 55% were capable of having sexual intercourse using alprostadil and 48% continued long-term therapy. The compliance with alprostadil was 63% at a mean follow-up of 2.3 years. Mean SHIM scores went from 19 preoperatively to 5 immediately postoperatively, and this increased to 16 with the use of alprostadil. A score of 16 on the SHIM questionnaire is not normal, although there appears to be a signal that there may be some benefit to alprostadil as a rehabilitation strategy. The same authors studied 91 men who had undergone nerve-sparing RP with a mean follow-up of 6 months. Of these men, 56 were treated with alprostadil, 125 or 250 μg, three times per week for 6 months. Alprostadil was started 3 weeks after surgery. The control group was allowed to use erectogenic agents on-demand for sexual intercourse. Of the alprostadil rehabilitation patients, 50% had sexual intercourse without the use of any aides versus 37% of the untreated patients; 100% had penile pain and 32% discontinued treatment. Once again, given the small number of studies and the small population sizes studied, along with a signal that there may be value to transurethral PGE_1 administration as a rehabilitation strategy, there is a distinct need for a large multicenter, randomized controlled trial to define its role.

The Role of Penile Rehabilitation

The arguments against penile rehabilitation are threefold. It is common for rehabilitation naysayers to talk about the lack of level I evidence-based medicine. Although it is true that there exists only two randomized controlled trials (one of which was likely grossly underpowered and presented inconsistent results), the studies as a whole signal that early erections and PDE5 inhibitors early after surgery is of some benefit. The magnitude of this benefit is difficult to gauge at this time. I believe that many antagonists are somewhat nihilistic in their approach. Indeed, our daily urologic practice is replete with strategies and procedures that do not have level I evidence-based medicine behind them.

The second argument against penile rehabilitation is that animal data do not necessarily always translate into the human model. This is most certainly true; however, we have for two decades now in the field of sexual medicine translated evidence from animal models into humans. Much of the studies assessing the impact of hyperlipidemia on erectile function is based on the hyperlipidemic rabbit model. Furthermore, most of the work conducted on nitric oxide and its role in penile erection has been conducted in eNOS and nNOS knockout mice.

Finally, an argument for both patients and physicians against rehabilitation is cost. Using the Memorial Sloan-Kettering algorithm, we have estimated that the average patient who has no coverage for his medications will pay from $1500 to $2500 over 24 months after RP to accomplish pharmacological penile rehabilitation. For the 55-year-old male who has 25 years of sex ahead of him, this translates into less than $100 per annum for preservation of his future sex life. That is not to say that efforts should not be made to convince the insurance industry or the US Congress to cover medications in this unique population. Indeed, there are many parallels between women who have had a mastectomy for breast cancer who subsequently undergo breast reconstruction and men post-RP who are left with erectile problems and require regular use of medication to preserve erectile tissue to promote recovery of natural erections.

The principal arguments in favor of penile rehabilitation are that ED is associated with a significant reduction in health-related quality of life. Litwin et al. [31] has shown that poor function after RP translates into a high level of distress, whereas good function is associated with a low level of distress. Secondly, in this patient population, venous leak development is time-dependent. It is not known definitively what time period after RP is required to pass before irreparable structural damage to erectile tissue occurs. This is likely related to such factors as age prior to surgery and preoperative erectile function. However, 4 to 6 months after surgery the incidence of venous leak starts to rise sharply; therefore, I and others believe that rehabilitation is ideally instituted within 4 months of surgery, and we start our program immediately following surgery. Again, I believe that the signals from the animal and human studies are clear and robust on the animal side and thought-provoking on the human side. Finally, sexual medicine experts are routinely performing rehabilitation post-RP. When surveyed, 87% of members of the International Society for Sexual Medicine are performing pharmacological rehabilitation after RP.

The data from the REINVENT study are still being digested, but at this time I believe the data infer one of three things: 1) that penile rehabilitation is a waste of time: it is difficult to ignore the robust animal data and several other human studies using sildenafil or injection therapy suggesting a benefit; 2) that the design of this study was inadequate to define such an outcome: the ideal study design is debated, but it is likely that this study was flawed enough so as to make its interpretation difficult; and 3) that vardenafil is inferior to sildenafil in penile rehabilitation: without a head-to-head trial, it is impossible to answer this issue.

Conclusions

Structure of a rehabilitation program

In my practice such patients are divided into two groups (Fig. 2). Group 1 consists of patients who present prior to RP, and Group 2 includes patients who present following RP. These patients are treated in a different manner in the

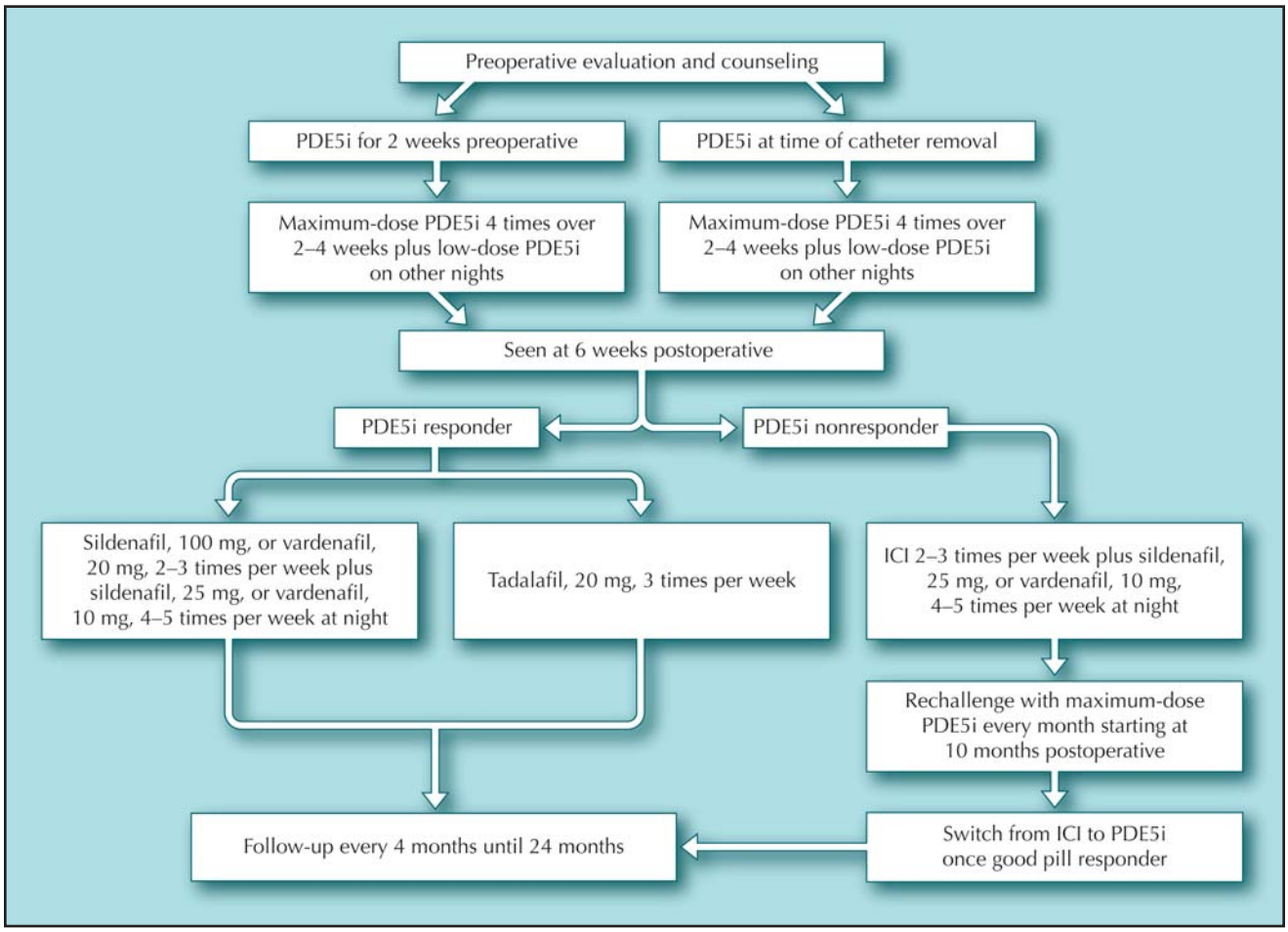

Figure 2. The current Memorial Sloan-Kettering penile rehabilitation algorithm. ICI—intracavernosal injection; PDE5i—phosphodiesterase type 5 inhibitor.

early stages pre- and postsurgery. When patients see me prior to surgery, I encourage them to use low-dose PDE5 inhibitors on a nightly basis for the 2 weeks prior to their operation. This strategy is based on animal data supporting pretreatment (Mulhall, unpublished data). These patients are then told that with the catheter in place they should continue a low-dose PDE5 inhibitor on a regular basis. When they are given permission by their prostatectomist to resume attempts at obtaining erections, they switch to a low-dose PDE5 inhibitor 6 nights a week and a maximum-dose pill 1 night a week. The maximum-dose pill needs to be used in an appropriate fashion with sexual stimulation. The patients are encouraged to return to the office 6 weeks after surgery, which will allow them approximately 4 weeks to try the maximum-dose medication. For patients who have not seen me prior to surgery, the practice nurse will give them a prescription for a PDE5 inhibitor on the day the catheter is removed, and they are told to use a low-dose agent 6 nights a week and a maximum-dose medication 1 night a week with sexual stimulation. Upon return to the office at 6 weeks, patients are asked about their response to the maximum-dose PDE5 inhibitors. If the patient is a responder (defined as penetration hardness), they will use PDE5 inhibitors alone for the purpose of penile rehabilitation: maximum-dose sildenafil or vardenafil 2 nights a week and a low dose on the other 5 nights. Alternatively, they can use tadalafil, 20 mg, three times a week. The patients are encouraged to get at least two erections per week. The major issue with this approach is cost, as a sildenafil responder will use 13 1000-mg pills per month (eight full doses and 20+ quarter pills). A tadalafil responder will use 12 20-mg pills per month. We have not yet explored the tadalafil, 5-mg a day, strategy for this population because after 5 days of continuous use of 5 mg daily, serum levels equivalent to a single 8-mg dose are achieved. This serum level is not likely sufficient for intercourse in the early stages after RP.

Those patients who present at 6 weeks after surgery who have not responded to a PDE5 inhibitor (the majority of patients in my practice) are driven directly to intracavernosal injection therapy. They are encouraged to undergo penile injection therapy training and to use injection therapy at least two times a week. On noninjection nights, they are told to use low-dose PDE5 inhibitors nightly as previously outlined. We discourage patients who are using regular injections from using tadalafil because of its long half-life. Toward the end of the first

year after surgery, if patients are still using penile injection therapy they are encouraged to use a maximum-dose PDE5 inhibitor at least once per month. This is performed in an effort to define if the patient is responding to oral medication, as this will facilitate them ceasing injection therapy. We tell our patients that it usually takes 10 to 14 months after surgery to start seeing some improvement in erectile function, but that it is 18 to 24 months before we see optimization of erectile function recovery. This is also a timeframe for best response to a PDE5 inhibitor.

Penile rehabilitation after RP is a highly labor-, cost-, and space-intensive strategy. It is impossible for an individual physician to run this program alone. A nurse practitioner or physician assistant is critical to the success of the program. The sheer volume of injection patients, and their training, monitoring, and follow-up would be overly burdensome to any given physician. But in multiphysician practices, resources can be shared and a nurse practitioner or physician assistant can cover several physicians' patients, rendering this a more cost-effective program. With the pay-for-performance initiatives looming, I believe that long-term complications of RP will become increasingly focused upon, and the role of penile rehabilitation after this surgery to optimize sexual function outcomes may become critical to this goal.

Finally, it is my personal philosophy that given the devastating consequences of acute onset, long-term ED after RP, we should be giving greater consideration to rehabilitation for these men while we await definitive evidence confirming or refuting its benefit.

Disclosure

Dr. John P. Mulhall has received a grant from Vivus, serves on the Scientific Advisory Board for Auxilium and Fast-Size, and is an investigator for Ethicon and Acorda.

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