Standard Operating Procedure for the Preservation of Erectile Function Outcomes after Radical Prostatectomy

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ABSTRACT

Introduction. Prostate cancer is common, and, thus, more men are being treated surgically. Long-term functional outcomes are of significant importance to the patient and their partners. Erectile function (EF) preservation (rehabilitation) has gained significant traction worldwide, despite the absence of definitive evidence supporting its use.

Aim. To review the effectiveness of specific pharmacological therapies and other erectogenic aids in the treatment of post-radical prostatectomy (RP) erectile dysfunction.

Methods. A systematic literature review of original peer-reviewed manuscripts and clinical trials reported in Medline.

Main Outcome Measure. This review focused on the evaluation of interventions that aimed to improve EF recovery following RP.

Results. Although well documented in animal models, studies supporting the rehabilitation with phosphodiesterase type 5 inhibitors in humans are scarce. Daily sildenafil has been used in trials (only one randomized placebo-controlled trial) with a significant improvement in erection recovery when compared to placebo or no rehabilitation but with a low return to baseline rates (27% vs. 4% placebo). Nightly vardenafil vs. on demand vs. placebo has been studied in the Recovery of Erections: INtervention with Vardenafil Early Nightly Therapy trial with no difference in erection recovery following RP. Intracavernosal injections, although widely used and attractive from a rehabilitation standpoint, does not yet have definitive supporting its role in rehabilitation. Vacuum erection devices use following RP has been reported, but there are no data to support its role as monotherapy. Intraurethral alprostadil was also studied vs. sildenafil in a multicenter, randomized, open-label trial, and no superiority was found.

Conclusions. At this time, we are unable to define what represents the optimal rehabilitation program in regard to strategies utilized, timing of intervention, or duration of treatment. **Mulhall JP, Bivalacqua TJ, and Becher EF. Standard operating procedure for the preservation of erectile function outcomes after radical prostatectomy. J Sex Med 2013;10:195–203.**

Key Words. Radical Prostatectomy; Erectile Dysfunction; Prostate Cancer

Magnitude of the Problem

Prostate cancer is the most common noncutaneous malignancy in men in the United States and the second leading cause of cancer death in American men, behind only lung cancer. In 2011, the American Cancer Society estimated that 241,740 new cases of prostate cancer were diagnosed and about 28,170 men will die of prostate cancer [1]. Additionally, about one man in 36 with prostate cancer will die from his disease. With the increased number of men being diagnosed with clinically localized prostate cancer and the multiple surgical and nonsurgical options available for definitive treatment, an emphasis on quality of life after treatment has become a substantial factor in

patient's decision making about therapy. Erectile dysfunction (ED) is a potential adverse quality-of-life outcome with prostate cancer treatment [2]. Improved understanding of the anatomic relationships between the prostate and cavernous nerves (CN) of the neurovascular bundle (NVB) has led to the evolution of the anatomic radical retropubic prostatectomy (RP), allowing preservation of the NVB with decreased risk of ED [3].

Despite numerous surgical modifications including the anatomic nerve-sparing (NS) RP, ED rates in contemporary RP series range between 30% and 87% [4–6]. Although anatomic NS radical prostatectomy (RP) promises a high likelihood of postoperative recovery of erectile function (EF), many men will require as much as 2 years or longer to recover satisfactory EF [7]. Recent evidence strongly supports the notion that sexual function is the health-related quality-of-life domain most commonly impaired after prostate cancer treatment [4]. Validated tools have been developed to predict recovery of EF after RP and radiation therapy which include NS status, patient age, preoperative EF, and systemic comorbidities [4,6,8]. Post-prostatectomy ED and overall changes in the quality of erection is highly prevalent in men who undergo prostate cancer surgical and nonsurgical treatment.

Pathophysiology of ED after RP

Advances in the neurobiology of erection have shown that relaxation of corporal smooth muscle in the penis is essential for normal EF, and neuronal- and endothelial-derived nitric oxide (NO) are the principal mediators of corporal smooth muscle relaxation [9]. NO released from the axonal end plates of the CNs within the corpora causes relaxation of penile smooth muscle, thus initiating the hemodynamic changes of penile erection. Accumulating evidence suggests that a return to functional erections following injury to the CNs is dependent, in part, upon axonal regeneration in the remaining neural tissues and upon successful functional reinnervation of the penis [10].

Well-defined pathobiological changes are observed in animal model studies of the penis following CN injury which leads to severe neuropraxia and associated lethal axonal damage including apoptosis of the smooth muscle and the endothelium of the penis, reduced nitric oxide synthase nerve density, pathobiological signaling responses which favor vasoconstriction, upregulation of fibroproliferative cytokines such as transforming growth factor-beta, and penile smooth muscle fibrosis or loss [11–15]. Animal studies and clinical observations support functional, morphological, and metabolic consequences following penile denervation associated with cavernous nerve injury (CNI). The chronic absence of erection secondary to CN neuropraxia during the prolonged recovery phase is thought to increase the potential for further end-organ failure of the penis as a result of corporal smooth muscle structural deterioration and endothelial dysfunction. Iacono et al. reported results from 19 men who underwent sequential corpora cavernosa biopsy at the time of prostatectomy and 2 and 12 months after surgery [16]. In this study, trabecular elastic fibers and smooth muscle fibers decreased and collagen content significantly increased as early as 2 months after RP. These results demonstrate that CN injury during prostatectomy produces profound downstream changes in the architecture of the penis, which influence penile hemodynamics. Therefore, due to the extended period of time required for maximal nerve recovery, it is possible that even under ideal nonenhanced conditions for nerve regeneration, functional recovery cannot be completely restored as post-injury tissue alterations of the penis may be permanent (Figure 1).

Prevalence of ED after RP

The proximity of the CN to the prostatic capsule, positioned as a diffuse, poorly visualized nerve plexus in contact to the lateral aspect of the prostate, represents the major surgical obstacle. Additionally, the CN's small size as well as their dependent location within the male pelvis make visualization and thus preservation difficult [17,18]. A review of the existing medical literature demonstrates a large discrepancy in reported rates of ED following RP [19–24]. There are many reasons why this occurs, including: intrinsic patient factors, surgical factors, and reporting biases.

At present, no precise and generally agreed upon time points post-treatment have been defined as the optimal interval post treatment to determine EF outcomes, but most authorities suggest assessment at 2 years or later as being ideal. After surgery, it appears that the nadir in function occurs at approximately 3 months post-RP and that continued EF recovery may occur out to 24 months after surgery. Indeed, some