

## Contemporary Strategies for Treating Erectile Dysfunction Following Radical Prostatectomy

a report by

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### Introduction

Prostate cancer is the leading solid-organ cancer among adult men in America and the second leading cause of cancer deaths. Radical prostatectomy is a major option for the treatment of clinically localized prostate cancers. For men with low-grade, organ-confined disease, tumor control and long-term survival are achievable with this approach. For this reason clinicians have begun to focus on optimizing lifestyle outcomes for men treated for prostate cancer. With radical prostatectomy this essentially means recovery of urinary continence and erectile function.<sup>1,2</sup> Several studies have demonstrated acceptable continence rates following surgery.<sup>3-5</sup> Walsh<sup>3</sup> showed that by performing an anatomical bilateral cavernous nerve-sparing radical retropubic prostatectomy, the majority of men who are potent prior to surgery will experience the return of erectile function to a degree that is satisfactory for intercourse; however, most men will still report decreases in penile rigidity and penile length.<sup>2,6</sup> Recent advances in the understanding of post-prostatectomy erectile dysfunction (ED) have led to promising new strategies in the treatment of this serious issue.

### Risk Factors for Post-prostatectomy Erectile Dysfunction

The ultimate goal in treating prostatectomy-related ED in men who are potent prior to surgery should be the return of spontaneous erections to a degree sufficient for sexual intercourse. Although this is probably not achievable in every patient, it is possible to predict whether erectile function will be recovered on the basis of certain risk factors. The factors predictive of recovery of erectile function after radical prostatectomy include age less than 60 years, absence of vascular disorders (e.g., diabetes, hypertension, coronary artery disease (CAD), and dyslipidemia), non-smoking status, ideal nerve sparing, low pre-operative stage of disease, and motivated partner. An assessment of a patient's pre-operative erectile function is essential when counseling patients prior to surgery to appropriately inform them of the risk of ED.<sup>7,8</sup> This is particularly important with men who use phosphodiesterase type 5 inhibitors (PDE5-Is), which place them at risk of worsening ED

after surgery. Using a validated questionnaire such as the International Index of Erectile Function (IIEF) may help determine the severity of the patient's pre-operative ED during the initial patient assessment.<sup>9</sup>

### Pathophysiology of Post-prostatectomy Erectile Dysfunction

Erectile function becomes impaired immediately following radical prostatectomy and is thought to be secondary to damage to the cavernous nerves, which is known as neuropraxia. Even in the most meticulous nerve-sparing dissection some degree of neuropraxia is unavoidable because of the close proximity of the nerves to the prostate gland. These nerves tend to recover slowly; it may take as long as three years for them to reach a new baseline functional status.<sup>5</sup> Lack of post-operative erection is thought to lead to poor oxygenation of the corporal bodies, eventually progressing to cavernosal fibrosis, and ultimately causing a venous leak seen clinically as ED.<sup>10</sup> A reduction in arterial inflow has also been reported by several authors. This is thought to be related to the ligation of accessory internal pudendal arteries during prostatectomy.<sup>11,12</sup> These insults may ultimately lead to apoptosis or programmed cell death, which has recently been linked to the pathophysiology of post-prostatectomy ED. Montorsi et al.<sup>4</sup> suggested that this combination of reduced inflow, increased venous leak, and corporal fibrosis likely accounts for the post-prostatectomy penile hemodynamic changes, as well as a decrease in penile length. Subsequently, several studies have demonstrated that the capacity for sexually-stimulated erections and nocturnal erections are decreased following radical prostatectomy.<sup>13,14</sup>

### Penile Rehabilitation Following Radical Prostatectomy

In 1997, Montorsi et al.<sup>15</sup> pioneered the concept of penile rehabilitation following radical surgery. Their goal was to decrease the time to recovery of spontaneous erections. In a randomized trial of two or three times weekly injections of intracavernosal prostaglandin E1, started one month after surgery, compared with no treatment, 67% of men who

received the injections had recovery of unassisted erections at six months compared with 20% of the men who received no treatment. This study prompted further interest in an early intervention to ensure the recovery of penile erections.

The next logical step was to look at restoring nocturnal erections as another way to increase oxygenation of the cavernosal bodies, preventing tissue damage and fibrosis. In a study, the results of which were presented at the 2003 annual meeting of the American Urological Association (AUA), 76 men with normal erectile function pre-operatively who had undergone bilateral nerve-sparing radical prostatectomy were randomly assigned to receive sildenafil or placebo nightly. Treatment began four weeks after surgery and consisted of sildenafil at 50mg or 100mg or placebo every night for 36 weeks followed by two months without therapy. At the end of the trial 27% of men in the sildenafil group compared with 4% in the placebo group reported return of spontaneous normal erections. Additionally, there was a progressive increase in the duration and amplitude of nocturnal erections in the sildenafil-treated group.<sup>16</sup> Although the results of this study are modest, it is the first study to correlate the return of nocturnal erections with the return of spontaneous sex-stimulated erections that are sufficient for intercourse. Multicenter clinical trials are needed before declaring the cost-effective and therapeutic benefits of daily use of the currently available PDE5-I class of drugs to restore spontaneous penile erections.

### Treatment Modalities

Prophylactic treatment to restore erectile function should be a part of every patient's recovery plan following prostatectomy, but early return of erectile function is not always possible. For men who do not recover erections early, the literature has consistently shown that without some intervention spontaneous erections sufficient for intercourse are unlikely to begin more than one year after surgery. However, there are several other options available to these patients.

PDE5-Is have been shown in several studies to be efficacious following prostatectomy and represent first-line therapy. Men younger than 60 years of age, who undergo a bilateral nerve-sparing surgery, and who have return of some spontaneous erections are most likely to benefit from these medications. Sildenafil, owing to the fact that it has been on the market longer, is the most widely studied of the PDE5-Is. It is common practice to take sildenafil at the highest available dose, but good results with 25mg or 50mg doses have been observed. Outcomes have been shown to improve over time post-operatively, with the best responses beginning after one to two years.<sup>17-22</sup> Both vardenafil and tadalafil have also

been tested in large multicenter trials of patients with ED following bilateral nerve-sparing prostatectomy – the success rates and tolerability profiles were similar to those of sildenafil.<sup>23-25</sup>

Men who do not respond adequately or are not candidates for PDE5-I monotherapy can often be managed with second-line pharmacotherapy such as intracorporeal or intraurethral prostaglandin E1. Intracavernosal injection will work for the majority of patients post-prostatectomy regardless of the degree of nerve preservation.<sup>26</sup> Gontero et al.<sup>27</sup> recently demonstrated that the best clinical and hemodynamic responses to prostaglandin E1 injection occurred one month after surgery; however, the drop-out rate in their study was high when this approach was started so early after surgery. The authors recommended beginning therapy three months after prostatectomy to optimize long-term success. The authors recently demonstrated that intracavernosal injection therapy is therapeutically effective and probably the most cost-effective treatment for patients who undergo radical prostatectomy without bilateral nerve sparing.<sup>28</sup> Intracavernosal injection can be used as first-line therapy for ED in this unique group of patients because the majority of them will fail PDE5-I therapy. The authors prefer to use a combination of prostaglandin E1, papaverine, and phentolamine because it is associated with a low rate of penile pain and maintains a high success rate.<sup>29</sup> The primary disadvantage of a combination injection is that it is not available on the market, so the urologist or pharmacist must prepare and distribute the solution.

Vacuum erection devices (VEDs) have also been shown to be efficacious following radical prostatectomy with achievement of erections that are satisfactory for intercourse; however, their need for a motivated patient and partner may have kept them from becoming a primary choice of therapy.<sup>26</sup> For patients receiving maximum dosages of sildenafil with less than optimal results with their ED, VEDs can be added to enhance the erectile effect. Both intraurethral and intracavernosal prostaglandin E1 in combination with sildenafil have been shown to salvage a large number of PDE5-I monotherapy failures.<sup>30,31</sup> Despite these advances in non-invasive therapy, some patients will still find the currently available non-surgical treatments unsuccessful or unacceptable. These patients should be considered for implantation of a penile prosthesis. Penile prosthesis implantation has been found to be more effective against ED than sildenafil or intracavernosal injection;<sup>32</sup> however, due to the risks associated with prosthetic surgery, it will remain the third-line treatment option.

Several investigators have reported on the loss of penile length following radical prostatectomy. Munding et al.<sup>33</sup> reported a decrease of penile length greater than 1cm in

48% of patients evaluated three months post-operatively, and Savoie et al.<sup>34</sup> reported a 15% or greater decrease in penile length in the same time-frame. The authors have recently begun a penile rehabilitation program in conjunction with a cavernosal nerve interposition graft protocol. Cavernous nerve reconstruction with the use of sural nerve grafting has been reported to be beneficial in restoring spontaneous erections.<sup>35</sup> A previous study from their institution revealed that 72% of patients were able to engage in sexual intercourse with or without taking sildenafil at the 23-month follow-up examination after non-nerve-sparing prostatectomy and bilateral sural nerve grafting.<sup>36</sup> In their recent study, patients were started on daily use of a VED, bi-weekly injection of combined prostaglandin E1, papaverine, and phentolamine and patient-directed use of PDE5-Is following unilateral nerve resection and grafting. Patients were evaluated pre-operatively, six weeks post-operatively, and at four-month intervals thereafter for up to two years for rehabilitation regimen compliance and penile length. Their preliminary data showed that penile length was significantly shorter six weeks after surgery compared with the pre-operative length. At four months, patients with good VED compliance had a 0.4cm increase in penile length compared with a 0.3cm decrease in length in those with poor VED compliance relative to their six-week measurement. At eight months, patients who received a sural nerve graft had a mean increase of 1.1cm compared with a decrease of 0.4cm in patients who did not receive a graft.<sup>37</sup> This finding clearly needs to be studied in a larger trial, but it seems to suggest that combination therapy, given as prophylaxis, may allow recovery of both spontaneous erections and penile length. The authors also found that compliance with their rehabilitation regimen was better in patients older than 57 years of age than with those

who were younger. This factor highlights the need to counsel all patients about treatment compliance, but particularly younger men who may be more likely to neglect therapy.<sup>38</sup>

### New Horizons

Current and future studies of post-prostatectomy ED are being directed at improving penile rehabilitation, enhancing nerve regeneration, and preserving penile length. Investigators are currently looking at different nerve regeneration regimens for applicability in treating post-prostatectomy ED. An on-going multicenter, placebo-controlled trial of neuroactive molecules offers a positive option for the future. The updated information regarding this neuroprotection clinical trial will be presented at the upcoming AUA annual meeting in May 2005 in San Antonio, Texas. Currently, multicenter clinical trials are evaluating the benefits of scheduled use of intraurethral prostaglandin E1 in the recovery of erectile function after prostatectomy. A similar study on the use of VEDs is also on-going – the results were not published at the time of press.

While outstanding surgical techniques clearly play a large role in preventing post-prostatectomy ED, early counseling for the patient and his partner about realistic expectations and treatment possibilities should be a key component of clinical practice. Due to the fact that no strategy has been proven to be the most effective in all patients, it is important to let patients know early that a period of trial and error is often needed. Some form of penile rehabilitation should be the standard of care to prevent damage to the corporal bodies during resolution of cavernosal nerve neuropraxia. ■

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