INTRODUCTION

Erectile dysfunction (ED) rates after radical prostatectomy (RP) continue to improve as a result of gradual improvements in technique. Despite this, reported rates after bilateral nerve-sparing RP are still significant at 20–60%. Patient selection and precise surgical technique, with strict avoidance of neurovascular bundle damage, are key determinants. However, emerging data also emphasize the role of penile rehabilitation after surgery, with early pharmacological prophylaxis recommended and an emphasis on the use of vacuum erectile devices (VEDs) to improve erectile function. At present the precise mechanism of action of these therapies in patients after RP is unclear and the optimal regimen for penile rehabilitation has yet to be decided. We discuss the recent evidence in an attempt to maximize the outcome for patients undergoing RP.

ED after RP can occur for several reasons: a small percentage of men have arterial insufficiency secondary to damage to the arteries supplying the corpora, but most have sustained injury to the cavernous nerves. This might be a transient neuropaxia, in its mildest form, or a complete transaction in the severest. Injury to the cavernous nerves results in atrophy and degradation of the underlying cavernous smooth muscle and a decrease in penile weight. Histologically, neuropaxia leads to apoptosis of the cavernous smooth muscle and an excessive deposition of collagen within the cavernosa, which clinically results in corporeal veno-occlusive dysfunction (CVD). The key to erectile function in patients after RP is the maintenance of corporeal architecture, with prevention of histological changes of apoptosis and fibrosis of the smooth muscle.

Treatment options available for patients after RP are broadly similar to those in the non-surgical population with ED, and include oral pharmacotherapy with phosphodiesterase-5 (PDE-5) inhibitors, intraurethral or intracorporeal prostaglandin E1 (PGE-1) and VEDs. The mechanism of action of PDE-5 inhibitors implies the presence of nitric oxide within the corporeal smooth muscle cells, and therefore only patients with intact neural regulation would be expected to respond. Therefore, a combined approach might be more suitable, with differing treatments acting through different pathways of erection most suitable.

PDE-5 inhibitors already have a confirmed role in the treatment of ED after RP, with sildenafil, vardenafil and tadalafil all reported to have moderate efficacy. Montorsi et al. [1] conducted a systematic review of the use of sildenafil monotherapy in ED after RP; 11 studies reported an overall response rate of 35% (95% CI 24–48), with the primary endpoint being erection sufficient for vaginal penetration. However, in patients who had undergone nerve-sparing surgery the response rates were significantly higher at 35–75%. Importantly, early treatment failure did not necessarily imply lack of efficacy in the future. Another randomized double-blinded study of 303 men who had all had bilateral nerve-sparing RP examined the role of 20 mg tadalafil vs placebo, taken on-demand [2]; the results showed that patients receiving tadalafil reported a greater improvement in all primary and secondary endpoints, including improvements in the International Index of Erectile Function (IIEF) score, with a mean (SD) increase of 5.3 (0.5), and improvements in the rates of successful penetration.

While precise regimens for oral PDE-5 inhibitor treatment are unclear, experience in the non-surgical population with ED suggest that chronic dosing might offer improvements over on-demand regimens. McMahon et al. [3] reported a significantly higher IIEF erectile function domain score and completion of successful intercourse compared with on-demand tadalafil (P < 0.05). In the only study of its kind, Schwartz et al. [4] took penile biopsies from 40 volunteers before and after RP, to examine the effect of sildenafil on

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Correspondence: Abhay Rane, East Surrey Hospitals, Canada Avenue, Redhill, Surrey, UK. e-mail: a.rane@btinternet.com

OPTIMIZING ERECTILE FUNCTION AFTER RADICAL PROSTATECTOMY Miles A. Goldstraw, Tim Lane, Thomas McNicholas and James Adshead – The Lister Hospital, Wellhouse Lane, Stevenage, UK

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Injury to the cavernous nerves can affect the required cascade for PDE-5 inhibition to be effective, hence this treatment might not be suitable for all patients. Furthermore, a certain subset of men who undergo bilateral nerve-sparing RP do not appear to respond to PDE-5 inhibitors for reasons that are not immediately clear. Agents such as PGE-1 act directly on the trabeculated corporeal smooth muscle, and bind to specific receptors and increase cAMP synthesis, in contrast to PDE-5 inhibitors which regulates cGMP. Thus combined therapy might activate both cAMP- and cGMP-mediated vasodilatation and be more effective. Montorsi et al. [7] provided a landmark study into the impact of early prophylactic intracavernous injection of alprostadil after nerve-sparing RP; they reported that 67% of patients had a return of spontaneous erectile function, vs 20% of men with no treatment. In patients with arteriogenic ED, intracavernous injection also appears to improve penile haemodynamics and the return of spontaneous erections [8]. Therefore, this might be more appropriate in patients with non-nerve-sparing RP. Recently, Mulhall et al. [9] reported that the prophylactic use of intracorporeal injections of alprostadil in patients not responding to oral sildenafil resulted in higher rates of spontaneous erections and erectogenic drug response 18 months after surgery.

Another potential application system is the medicated urethral system for erection or MUSE™ (Vivus Inc, Mountain view, CA, USA). Raina et al. [10] reported a study of 91 men who had undergone nerve-sparing RP and who were either given MUSE three times a week initiated 3 weeks after surgery, or on-demand treatment; 74% of men who remained on MUSE were able to have successful vaginal intercourse, compared with 37% in the on-demand group. However, the treatment groups were small and there was a 32% discontinuation rate in that study for reasons which included lack of effect, urethral pain and reduced sexual interest. While it is generally recognized that injectable agents might be considered more invasive and less tolerable than oral alternatives, there is some evidence that combined therapy might offer additional benefits. A small study from the same group reported that 83% of men noticed an improvement in penile rigidity and sexual satisfaction when MUSE was administered in combination with oral sildenafil [11].

Recently there has been renewed interest in the use of VEDs in men undergoing RP, with the intended aim of reducing corporeal fibrosis, penile shortening and CVOD. Kohler et al. [12], in a randomized control study on early VED use (1 month after RP) vs delayed use (6 months after RP), reported preservation of penile length with early VED treatment vs a significant decrease of >2 cm in penile length in those men using delayed VED. There was no increase in spontaneous erections in the early VED group. The authors concluded that this is an extremely cost-efficient treatment alternative with a very low side-effect profile.

In conclusion, a surgical technique that preserves at least one neurovascular bundle is essential for the spontaneous return of normal erections after RP. However, the evidence is fairly strong that penile rehabilitation can result in a shorter recovery time for the return to spontaneous erections and successful sexual activity. The early use of pharmacological therapies is important, with chronic dosing appearing to offer benefits over on-demand dosing. For men with vasculogenic ED, who have had non-nerve-sparing RP, or in whom PDE-5 inhibitor treatment has failed, then intracorporeal or intrraurethral injection of PGE1 might be more appropriate. Combined treatment might offer the maximum chance of improvement. VEDs appear to facilitate early sexual activity and preserve penile length, and might protect against CVOD. Ultimately, each patient must have an individually tailored regimen.

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**Correspondence:** Miles Goldstraw, Urology, Lister Hospital, Flat 5 Myddleton Hall, 32 Almeida St, Islington, London N1 1TD, UK. e-mail: miles.goldstraw@gmail.com

**Abbreviations:** ED, erectile dysfunction; RP, radical prostatectomy; VED, vacuum erectile device; CVOD, corporeal veno-occlusive dysfunction; PDE-5, phosphodiesterase-5; IIEF, International Index of Erectile Function; PGE-1, prostaglandin E1.