Erectile Function Outcomes in the Current Era of Anatomic Nerve-Sparing Radical Prostatectomy

Arthur L. Burnett, MD

Department of Urology, The Johns Hopkins Medical Institutions, Baltimore, MD

The contemporary use of anatomic nerve-sparing radical prostatectomy, which entails preserving the autonomic nerve supply to the penis required for penile erection, has led to improved erectile function outcomes compared with what has been seen historically. However, delay of postoperative recovery of erection for as long as 2 years is common, such that dysfunctional erection status lingers as a major postoperative problem. Several possible strategies to improve overall recovery rates and to hasten postoperative recovery of erectile function are currently being advanced. These include pharmacologic rehabilitation therapy and neuromodulatory therapy. Rigorous basic scientific investigation and clinical assessment of these new strategic approaches are critically important to establish their actual therapeutic benefits.

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The early descriptions of the course of the cavernous nerves surrounding the prostate and supplying the penis represented a historic advance because they enabled the performance of radical prostatectomy with a decreased risk of erectile dysfunction, a well-known complication of the surgery.[1,2] The discovery, made approximately 2 decades ago, highlighted the importance of the cavernous nerves as the autonomic neuroregulatory requirement for penile

erection, and it revealed that injury inflicted upon these nerves at the time of radical prostatectomy contributed significantly to postoperative erectile dysfunction.[1-3] Walsh and Mostwin[4] subsequently developed modifications of the surgical approach for radical prostatectomy, including maneuvers to preserve the cavernous nerves structurally, which have enabled many men to recover erectile function after undergoing this surgery. Anatomic radical prostatectomy involves an improved understanding of the surgical anatomy of the prostate and its surrounding structures in the deep pelvis and the rational plan of surgical dissection based on the circumstances of the oncologic presentation.[5] Accordingly, for early-stage prostate cancer, which is associated with minimal risk for local cancer spread beyond the prostate, maximal structural preservation of the cavernous nerves might be pursued; conversely, local cancer spread beyond the prostate would contraindicate such objectives.

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With the adoption of anatomic radical prostatectomy with cavernous nerve preservation by many surgeons,[6] the rate of postoperative recovery of erectile function sufficient for sexual intercourse has improved dramatically from that of the previous era. At major academic centers staffed by highly experienced surgeons, reported rates of erectile function recovery range between 60% and 85%.[7-9] Contemporary results generated elsewhere might differ. The cohort study of the Cancer of the Prostate Strategic Urologic Research Endeavor, comprising 29 academic and community-based sites across the United States, established a 75% potency rate after radical prostatectomy among men aged less than 65 years.[10]

These results, taken together, affirm that modifications to radical prostatectomy technique in general have resulted in improved postoperative erectile function outcomes. This conclusion is accepted by many authorities in the field, although controversies persist regarding the exact level of erectile function recovery achieved with surgery as currently performed. Surgeon experience and the volume of surgeries performed are conceivably the dominant factors governing outcomes. More than likely, methodologic factors, such as imprecise documentation of presurgical erectile function status, nonuniform use of outcome instruments for assessing potency, insufficient follow-up intervals after surgery to assess outcomes, lack of prospective assessment, flawed data accrual (including circumstances of investigator bias), and failure to differentiate erection response with and without use of erection-enhancing medication, have all contributed to variations in reported erectile function recovery outcomes after the surgery.

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Modifications of the surgery have indeed resulted in improved erectile function outcomes, but a reality pertaining to this matter warrants increased attention. Although anatomic nerve-sparing radical prostatectomy might be performed with expert precision, promising a high likelihood of postoperative recovery of erectile function, many men will nonetheless require as much as 2 years or longer to recover satisfactory functional status.[7,8] In a recent prospective series, Walsh and colleagues[7] found that 18 months elapsed after surgery before a maximal level of erection recovery was observed among preoperatively potent men who underwent anatomic bilateral nerve-sparing radical prostatectomy. The delayed recovery of erection is relevant because substantial improvements have occurred in other areas of functional recovery after this surgery: the majority of patients who have undergone the surgery recover continence within 6 months, and many patients return to an overall unlimited physical activity level within several weeks of surgery. Thus, dysfunctional erection status lingers conspicuously as a major postoperative problem.

A number of possible explanations have been proposed for the phenomenon of delayed recovery of erectile function after anatomic nerve-sparing radical prostatectomy. These include mechanical nerve stretching that might occur during prostate retraction, thermal damage to nerve tissue caused by electrocoagulative cautery during surgical dissection, ischemic injury to nerve tissue during attempts to control surgical bleeding, and local inflammatory effects associated with surgical trauma.[11] In accordance with current neurobiologic concepts of major axonal injury,[12,13] injured cavernous nerve fibers undergo a process of Wallerian

degeneration, such that normal nerve tissue connections to the corpora cavernosa are lost. This occurrence immediately implies absent neuroregulatory function required for penile erection. It is consistent also with an induction of penile neuropathy resulting in cavernosal tissue degeneration and atrophy.[14] Recent clinical studies correlate cavernous nerve injury during the surgery with an irretrievable reduction of veno-occlusive function required for penile rigidity.[15,16] The fact that erections are eventually recovered in many men who undergo anatomic nerve-sparing radical prostatectomy supports a predominantly neurogenic pathogenesis for the disorder; in contrast, direct vascular injury (eg, accessory pudendal artery ligation) that could occur during the surgery can be expected to produce a permanent defect. Postoperative recovery of erectile function varies from patient to patient, depending on the extent of cavernous nerve functional recovery and preservation of erectile tissue function.

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Because men undergoing anatomic nerve-sparing radical prostatectomy today often experience incomplete or delayed recovery of erectile function, it is imperative that new directions for facilitating improved postoperative erectile function outcomes be considered. The precipitousness and extent of erection loss in many men who are relatively young and possess intact erectile function before surgery, the predictability of erection loss after the surgery, and the implication that its cause is entirely iatrogenic all fuel the demand for corrective intervention and even prevention. There are continuing efforts to develop and apply surgical techniques that optimally reduce damage to the cavernous nerves; still, there is great enthusiasm for generating new ways to improve erection outcomes in this group of patients. New advances would aim to surpass conventional management options (erectile aids), which generally produce only temporary, repetitive means for an erectile response or are artificial. Such options include both pharmacologic and nonpharmacologic interventions (Table 1). In keeping with the notion that ideal therapy achieves spontaneous, natural erectile function, the goal in managing erectile dysfunction after radical prostatectomy is to recover this exact level of functional ability. Among medical and surgical approaches fitting this concept, cavernous nerve interposition grafting, pharmacologic rehabilitation therapy, and neuromodulatory therapy have thus far been considered.[17] The latter 2 approaches are discussed below.

Pharmacologic Rehabilitation

Pharmacologic rehabilitation has rapidly emerged as a clinical strategy to reduce the incidence of erectile dysfunction after radical prostatectomy. The strategy is based on the concept that early-induced sexual

Table 1
Pharmacologic and Nonpharmacologic Interventions for Erectile Dysfunction

Treatment Option	Role	Efficacy (%)	Comment
Oral PDE-5 inhibitors	First line	70–80 (nerve-sparing) 0–15 (non–nerve-sparing)	Function of "nitric oxide-producing" penile nerves essential; sexual stimulation required
Intraurethral medications (penile suppository)	Second line	20–40	In-office instruction and titration recommended
Intracavernosal injections	Second line	85–90	In-office instruction and titration recommended
Vacuum constriction devices	Second line	90–100	Basic instruction sufficient
Penile implants (malleable and inflatable)	Third line	95–100	Surgical expertise required

PDE-5, phosphodiesterase-5.

stimulation and blood flow in the penis might facilitate the return of natural erectile function and resumption of medically unassisted sexual activity. In this respect, early postoperative intracavernous injection therapy has been viewed as a plausible intervention. Montorsi and colleagues[18] are credited with proposing this mode of intervention with the use of alprostadil, reporting in a small series of patients that this intervention led to early postoperative recovery of erectile function. However, the precise role of these therapies remains undefined. Additional controlled trials are needed to fully establish a therapeutic benefit. Such trials are being planned and might soon be completed, but several investigators have already begun to evaluate the feasibility of these clinical pharmacotherapeutic strategies, exploring practical therapeutic regimens.[20,21]

Additional basic scientific investigation might also reveal mechanisms for the supposed beneficial effects associated with such applications. It is presumed that vasoactive pharmacotherapy opposes harmful hypoxemic changes that occur in the penis after radical prostatectomy,[22,23] although definitive evidence for this hypothesis is awaited. An additional protective mechanism associated with alprostadil might be that it reduces collagen deposition in the corpora cavernosa by opposing the actions of the profibrotic cytokine transforming growth factor β1.[24] The mechanistic basis for a protective effect exerted by PDE-5 inhibitor therapy after radical prostatectomy also remains unclear. Proposed explanations include the promotion of the actions of cyclic guanosine monophosphate (a biochemical product of the nitric oxide signaling pathway). This cyclic nucleotide has been established as having effects on neurogenesis, angiogenesis, and smooth muscle growth and differentiation.[25-27]

Early postoperative intracavernous injection therapy has been viewed as a plausible intervention.

ever, this application has not gained popularity. Factors limiting its use have included reluctance by patients to insert needles into the penis on a regular basis, local discomfort associated with the injectable agent alprostadil, and concern that penile scarring complications might occur with this strategy.

More recently, there has been interest in the use of oral phosphodiesterase-5 (PDE-5) inhibitors as a rehabilitative strategy. This interest is not surprising: these oral medications have appeal because they are noninvasive, convenient, and highly tolerable. In a pioneering study that has received significant attention, Padma-Nathan and associates[19] described a curative benefit associated with the use of sildenafil in a placebo-controlled clinical trial involving preoperatively potent men undergoing anatomic bilateral nerve-sparing radical prostatectomy. The Montorsi and Padma-Nathan studies have both generated great enthusiasm for the application of pharmacologic therapies for erection rehabilitation or even prophylaxis in men undergoing cavernous nerve-sparing radical prostatectomy.

Neuromodulation

Neuromodulation has recently gained interest as the next likely prospect in clinical management related to cavernous nerve functional preservation after radical prostatectomy. The therapy consists of neuroprotective and neurotrophic interventions and conceivably would apply to a host of pelvic surgical procedures, including radical prostatectomy, radical cystoprostatectomy, and proctocolectomy, all of which are known to be associated with postoperative erectile dysfunction.[28]

This therapeutic strategy derives from the basic science of neurotrophic growth factors, neural development, neuroprotection, neural regeneration, and prevention of neuronal cell death. Its application to pelvic surgery implies an understanding of the cavernous nerves supplying the penis as having a behavior consistent with peripheral nerve biology, including response to injury.[29] Consistent with axonal injury of a peripheral nerve resulting from axotomy or other trauma, cellular and molecular mechanisms are activated in line with the events of neuronal cell death and recovery.[12,13] Many of these mechanisms are being actively investigated as they apply to penile innervation and possibly penile neurogenesis after cavernous nerve injury.[30] As this understanding evolves, neurogenic approaches would potentially range from the exogenous supply of trophic factors, which might improve axonal regeneration and accelerate target reinnervation, to technologies that protect the penile nerve supply in the face of injury.

Many molecular mechanisms are being actively investigated as they apply to penile innervation and possibly penile neurogenesis after cavernous nerve injury.

Several therapeutic prospects are currently being considered as neuromodulatory therapeutic interventions having potential use in this clinical arena. These include neurotrophins, immunophilin ligands, poly(adenosine diphosphate-ribose) polymerase-1 inhibitors, atypical neurotrophic factors, nerve guides, tissue engineering/stem cell therapy, and gene therapy. Neurotrophins (eg, nerve growth factor) have received a great deal of interest for their potential utility, in view of the emphasis they have received in the biology of peripheral nerve injury. The feasibility of neurotrophic growth factor candidates has been investigated clinically outside of the urologic field; preliminary clinical trials have been conducted using nerve growth factor for diabetic polyneuropathy and human immunodeficiency virus–related neuropathy.[31,32] However, these trials showed questionable efficacy in ameliorating symptoms and painful side effects in clinical trial subjects. Such results call into question the applicability of neurotrophins for facilitating erectile function recovery after radical prostatectomy. In addition, concerns exist regarding the possible cancer-promoting effects of neurotrophins in this setting.[33] Further investigation is needed before the adjunctive use of neurotrophins can be advanced at a clinical therapeutic level for radical prostatectomy.

Immunophilin Ligands

The immunosuppressive drug tacrolimus (FK506) has been demonstrated to have neuroprotective and neuroregenerative properties in physiologic animal models of neurodegenerative disorders and peripheral nerve injuries.[34,35] This drug is a prototype of a neuroimmunophilin ligand having affinity for receptor proteins (immunophilins) highly localized in neuronal tissues. Both the prototypical drug and the nonimmunosuppressive derivative GPI1046 have been evaluated in cavernous nerve-injured rat models and have been shown to have pharmacotherapeutic benefits in preserving cavernous nerve morphology and to facilitate the recovery of cavernous nerve neurostimulated erections.[36,37] The mechanism of action of these agents is still unclear, but it is thought that their actions target injured nerves and might involve specific FK506 binding proteins (specialized immunophilins).[38] Alternative hypotheses have included roles of immunophilin ligands serving as antioxidant agents involved in glutathione upregulation[39] and as antiapoptotic factors.[40] Studies have shown that immunophilin ligands do not exert growth proliferative effects on prostate cancer cells in vitro, suggesting their particular advantage amid postoperative risks of persistent or recurrent prostate cancer.[41]

Evidence that immunophilin ligands have potent neuroprotective and neurotrophic properties has fostered interest in their use clinically after radical prostatectomy. A phase II multicenter, randomized, double-blind, placebo-controlled trial of the nonimmunosuppressive immunophilin ligand GPI1485 is nearing completion, having enrolled approximately 200 preoperatively potent men undergoing anatomic bilateral nerve-sparing radical prostatectomy (MGI Pharma, Bloomington, MN). The primary endpoint of the study is erectile function after 6 months of treatment, as determined according to the erectile function domain of the International Index of Erectile Function questionnaire. The patients are serially evaluated at 3-month intervals up to 12 months after the surgery. Efficacy and clinical safety data are currently being accrued. This study offers an original demonstration of the feasibility of the clinical use of neuromodulation as a therapeutic adjunct for promoting erectile function recovery after nerve-sparing radical prostatectomy.

Other Therapies

At the clinical level, several additional treatments have been investigated as possible neuromodulatory interventions for radical prostatectomy. One such option is the use of corticosteroids; 2 reports in the literature describe their evaluation in the setting of anatomic nerve-sparing radical prostatectomy. In one study,[42] the corticosteroid methylprednisolone administered for 6 consecutive days immediately after the surgery showed no greater improvement in erection recovery than that resulting from placebo treatment up to 12 months after surgery. Similarly, in a separate study,[43] the local application of betamethasone cream 0.1% to the cavernous nerves at the time of radical prostatectomy yielded no discernible improvement in erection recovery compared with that of no treatment up to 12 months postoperatively. No complications were associated with either of these studies. Although early results would suggest unlikely benefit associated with the use of corticosteroids, it remains possible that these trials did not achieve a sufficient duration of treatment to counteract an inflammatory basis for the tissue injury. It remains entirely possible that a more intensive treatment regimen or a regimen that includes preoperative dosing for prophylaxis might still offer therapeutic benefit.

Electrical stimulation of the cavernous nerves might also be considered a prospective neuromodulatory intervention in this clinical setting. Although this intervention has been demonstrated to produce measurable tumescence intraoperatively,[44] it is entirely plausible that such treatment could exert neurotrophic effects and

thereby promote spontaneous erectile function recovery after the surgery. A small clinical trial was reported, showing that electromyostimulation of the corpus cavernosum led to improved spontaneous erectile function and responsiveness to vasoactive drugs in men with erectile dysfunction.[45] Excitement associated with this approach has led to the initiation of a clinical trial to evaluate the feasibility of an implantable electrical stimulator for patients undergoing nerve-sparing radical prostatectomy (Advanced Bionics, Sylmar, CA).

Conclusions

The new frontier of radical prostatectomy for clinically localized prostate cancer, beyond the use of anatomic nerve-sparing techniques, involves the application of adjunctive strategies to improve functional outcomes postoperatively. This matter is particularly relevant in the realm of sexual function after the surgery. Current demands for improved functional outcomes after this surgery indicate that it will no longer be acceptable for men to endure incomplete or delayed functional recovery of erectile function or require erectile aids to perform sexually. In response to this demand, several strategies are currently being advanced for potential use in this clinical setting. Prominent among these are pharmacologic rehabilitation therapy and neuromodulatory therapy as therapeutic adjuncts for the surgery. After their proper, rigorous evaluations, such advances can be brought to patients with the correct expectation that patients will experience improved postoperative erectile function outcomes. ■

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Main Points

- Currently, men undergoing anatomic nerve-sparing radical prostatectomy often experience incomplete or delayed recovery of erectile function.
- Because erections are eventually recovered in many men who undergo anatomic nerve-sparing radical prostatectomy, a predominantly neurogenic pathogenesis for the disorder is likely.
- Two studies have generated enthusiasm for the application of pharmacologic therapies (with alprostadil and sildenafil) for erection rehabilitation or even prophylaxis in men undergoing cavernous nerve-sparing radical prostatectomy, but additional controlled trials are needed to fully establish a therapeutic benefit.
- Neuromodulation therapy consists of neuroprotective and neurotrophic interventions and conceivably would apply to a host of pelvic surgical procedures, including radical prostatectomy; potential neuromodulatory therapeutic interventions include neurotrophins and immunophilin ligands.
- Further investigation is needed before the adjunctive use of neurotrophins can be advanced at a clinical therapeutic level for radical prostatectomy.
- A phase II multicenter, randomized, double-blind, placebo-controlled trial of the nonimmunosuppressive immunophilin ligand GPI1485 in preoperatively potent men undergoing anatomic radical prostatectomy is nearing completion.
- Electrical stimulation of the cavernous nerves might also be considered a prospective neuromodulatory intervention; a clinical trial has been initiated to evaluate the feasibility of an implantable electrical stimulator for patients undergoing nerve-sparing radical prostatectomy.

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