

Strategies for preventing erectile dysfunction induced by radical prostatectomy

By Edward D. Kim, MD

Despite refinements in technique, erectile dysfunction remains a troublesome source of morbidity following nerve-sparing RRP. A variety of operative and postoperative measures, however, have the potential to help restore sexual function in these men.

Advances in surgical technique have significantly decreased the risk of morbidity following radical retropubic prostatectomy (RRP). Although use of the nerve-sparing technique has become common, the risk of erectile dysfunction remains a significant concern, with overall potency rates of 30% to 60%. This article reviews several preventive operative and postoperative measures that have the potential to help preserve erectile function.

OPERATIVE STRATEGIES

Modifications to the nerve-sparing technique, intraoperative cavernous nerve stimulation, interposition sural nerve grafting (SNG), and simultaneous inflatable penile prosthesis placement may all improve the possibility of retaining potency after RRP.

Modifications to the nerve-sparing technique

In the 1980s, detailed cadaveric anatomic studies precisely identified the autonomic nerves from the pelvic plexus to the corpora cavernosa, prompting Walsh to introduce the technique of sparing the neurovascular bundles (NVB) for preservation of potency.^{1,2}

The principle variables influencing the return of sexual function after RRP are patient age and the extent of NVB preservation. When both NVBs are preserved, potency rates generally range from 30% to 60%, but may reach as high as 71%.^{2,3} Approximately 20% to 60% of men retain potency after a unilateral nerve-sparing procedure. When both NVBs are intentionally resected, return of function is the exception.

Walsh and colleagues recommend that surgeons videotape and review their own RRP technique to improve patient recovery of sexual function.⁴ Using this analysis, the overall potency rate with the nerve-sparing technique improved to 86% at 18 months postoperatively.⁴ The following technical steps were identified as being important for the preservation of potency:

- Back-bleeders from the proximal dorsal vein on the anterior surface of the prostate should be oversewn in a V-shaped fashion rather than vertically in the midline. This minimizes anterior displacement of the NVBs.
- Because the NVB may deviate medially at the prostatic apex, it is important to avoid dividing the striated sphincter at the prostatic apex too far posteriorly to the smooth muscle of the urethra when placing urethral suture. This prevents damage to the NVB.
- Since division of the posterior urethra too close to the prostate increases the risk of NVB damage, the urethra should be divided at its midpoint between the apex and the urethral stump.
- Excellent hemostasis minimizes the risk of postoperative inflammation of the NVBs. Cautery should be avoided and small hemoclips can be used to provide control of small bleeders.

Intraoperative cavernous nerve stimulation

At times, anatomic variability may make it difficult to precisely identify the cavernous nerves prior to prostate removal. Some clinicians believe that use of the CaverMap nerve stimulator (Alliant Medical Technologies, Norwood, Mass) may allow for precise localization of the NVBs during RRP. The probe is placed on the NVB, resulting in penile tumescence or detumescence as measured by a penile strain gauge. The role of cavernous nerve stimulation in improving potency outcomes with nerve-sparing RRP is still being defined. While numerous studies demonstrate that electrical stimulation of the cavernous nerves results in penile tumescence,^{5,6} it is unclear whether potency outcomes are actually improved.

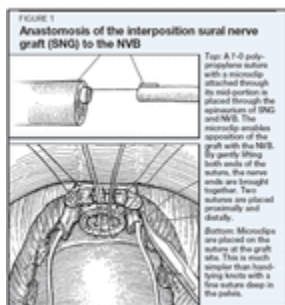
In 1998, Klotz reported that CaverMap stimulation identified the course of the NVBs and resulted in superior potency rates compared with those in patients for whom the device was not used.⁷ In a follow-up multicenter study (6 centers, 61 patients), CaverMap-assisted prostatectomy led to improved erectile function as assessed by RigiScan testing (Dacomed Corp, Minneapolis, Minn) and questionnaires.⁸ A minimum change in tumescence of 0.5% was considered a positive response. From their series of 63 patients, Chang and colleagues concluded that men who experience intraoperative tumescence are more likely to regain successful postoperative sexual function than those who have no response.⁹ Of 30 men with an intraoperative stimulated tumescence response, 24 (80%) were potent postoperatively compared with only 1 of 5 (20%) with no stimulated nerve response.

Other studies have failed to confirm Klotz's findings. Even with a 77% positive response to cavernosal stimulation, Kim and associates observed that most patients remained impotent at 12 months postoperatively.¹⁰ Holzbeierlein and co-workers caution that a positive response does not necessarily correlate with the precise anatomic location of the cavernous nerves.¹¹ They caution that considerable background variability related to anesthesia, surgical manipulation, and other undefined factors may cause minor but measurable changes in penile circumference.

A multicenter prospective study was recently undertaken to determine whether CaverMap stimulation improves the ability to identify the cavernous nerves intraoperatively and to predict the recovery of sexual function.¹² The device demonstrated an 87.8% sensitivity and 54% specificity in locating NVB previously identified by experienced surgeons. The study concluded that the lack of specificity limits the use of cavernosal stimulation for deciding which structures can be safely preserved or excised. In addition, since nearly all patients had a positive response after prostate removal, the value of stimulation for predicting recovery of sexual function remains unclear.¹²

Interposition sural nerve grafting

The technique of interposition SNG was designed to offer patients the possibility of maintaining spontaneous erections—which are quantitatively related to preservation of autonomic innervation—when the cavernous nerves have been resected during RRP.¹³ Preliminary animal studies in a rat model demonstrated that the SNG effectively acts as a template for nerve regeneration.¹⁴ Figure 1 illustrates our method for securing the anastomotic sutures.¹⁵



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Researchers at the Baylor College of Medicine recently described a series of 23 men undergoing bilateral SNG, reporting a 42% sildenafil citrate (Viagra, Pfizer) potency rate at a mean follow-up of 23 months (Table 1).¹³ Overall, 52% of patients had return of partial or full erections. The best return of function was observed at 18 to 24 months, and no men had return to intercourse for at least 1 year after surgery. Validated erectile

function and partner questionnaires were supportive. Morbidity, consisting mostly of numbness on the side of the foot, was minimal.

TABLE 1						
Results of bilateral interposition SNG						
					No intercourse	
Series	No. patients	No. potent with sildenafil (%)	Unassisted intercourse	Intercourse with sildenafil only		
					40% to 60% rigidity	<20% rigidity
Kim et al ¹⁵	23	10 (43)	6 (26)	4 (17)	2 (9)	11 (48)
Wood et al ¹⁶	30	13 (43)	7 (23)	6 (20)	5 (17)	12 (40)
Total	53	23 (43)	13 (25)	10 (19)	7 (13)	23 (43)

Researchers from the M. D. Anderson Cancer Center recently reported similar results in 30 patients following bilateral nerve resection and bilateral SNG.¹⁶ At a median follow-up of 22 months, 7 (23%) patients were able to achieve medically unassisted intercourse and 13 (43%) were potent with sildenafil. The remaining 20 (60%) regained at least 40% rigidity. Similar confirmation by other institutions is needed to further clarify the role of SNG. Studies are also needed to establish the potential advantages of:

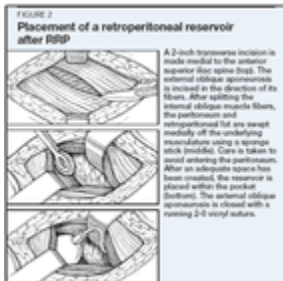
- unilateral SNG in men undergoing unilateral nerve-sparing RRP,
- assistance of cavernosal stimulation,¹⁷
- the laparoscopic approach (currently being performed in Europe),
- advances in technical performance, and
- use of nerve growth factors.

Critics of SNG have focused on the infrequent need to resect the NVB and the excellent potency rates following nerve-sparing RRP.¹⁸ Other concerns include the complexity of performing an anastomosis to a nerve plexus, the ability of autonomic nerves to regenerate, and the extent of NVB resection.

Simultaneous inflatable penile prosthesis placement

Khoudary and colleagues report that simultaneous inflatable penile prosthesis placement at the time of RRP is safe and feasible for men who have pre-existing erectile dysfunction or who are undergoing a non-nerve-sparing procedure.¹⁹ This avoids a separate operative procedure and does not lead to an increased rate of prosthesis infection, despite prolonged bladder catheterization and extensive surgery.

Alternately, placement of an inflatable prosthesis at a separate setting after RRP is not difficult. Urologists experienced with prosthesis placement are familiar with retroperitoneal placement of the reservoir, which uses an approach similar to the Palomo high retroperitoneal varicocelectomy technique (Figure 2). This avoids potential injury to the bladder and difficult dissection secondary to perivesical scarring that may be encountered when attempting to place the reservoir in the space of Retzius.

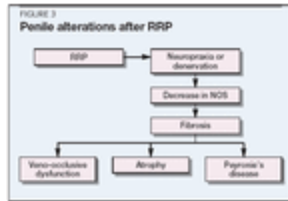


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POSTOPERATIVE STRATEGIES

Although the pathophysiology of erectile dysfunction after RRP is traditionally considered neurogenic, arterial and corporal smooth muscle alterations also may play a prominent role, contributing to the failure of many patients to recover erectile function even after meticulous bilateral nerve-sparing procedures or SNG.²⁰⁻²²

Following RRP, the cavernous nerves suffer from varying degrees of neuropraxia or denervation. While these injuries may be temporary, they result in a decrease in nitric oxide synthase expression within the corporal smooth muscle²³ and an increase in the expression of transforming growth factor- β . Eventually, these changes may result in fibrosis of the cavernous smooth muscle. In a rat model, denervation was shown to lead to increased apoptosis within the cavernous smooth muscle.²⁴ These processes lead to the clinical manifestations of penile atrophy and shrinkage, Peyronie's-like fibrotic changes, and the development of corporal veno-occlusive dysfunction (Figure 3).



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Penile atrophy

According to several series, the majority of men appear to experience a decrease in penile size following RRP. In their series of 100 men undergoing nerve-sparing RRP, McCullough and colleagues obtained penile measurements pre- and postoperatively in the flaccid and erect states (erections were induced with intracavernous injection).²⁵ Postoperatively, flaccid and erect measurements of length and circumference decreased 8% and 9%, respectively ($P > 0.05$). The most substantial change was seen 4 to 8 months postoperatively, when penile volume decreased 19% (flaccid) and 22% (erect).

Wessells and associates reported that 3 months after RRP, stretched penile length had decreased in 22 (71%) of 31 men (range, 0.5–4.0 cm).²⁶ Overall, 15 (48%) experienced considerable shortening (>1.0 cm), 5 (16%) had no change, and 4 (13%) had an increase in penile length (range, 0.5–1.0 cm).

Fibrotic changes

In 409 men undergoing RRP, Ciancio and Kim reported that 45 (11%) experienced fibrotic changes within the corporal bodies suggestive of Peyronie's disease.²⁷ Of 110 men evaluated and treated for post-RRP erectile dysfunction, 45 (41%) had these fibrotic changes. Approximately 10 months after RRP, 42 (93%) of the 45 with fibrotic changes had developed curvature, 11 (24%) exhibited waist-band narrowing, and 31 (69%) had palpable plaques. At a mean follow-up of 24 months after diagnosis, following pharmacotherapy and use of vacuum constriction devices, 40% of patients reported that their condition had improved, 50% remained unchanged, and 10% progressed. Patients commonly described frustration due to accompanying penile shrinkage and corporal veno-occlusive dysfunction (CVOD) resistant to intracavernous injection therapy and sildenafil.²⁷

CVOD and arterial insufficiency

The development of CVOD implies damage to the smooth muscle mechanism of the corporal bodies. These men commonly present with difficulty maintaining a rigid erection or can only achieve a partial erection. In these men, high-dose intracavernous injection therapies are often unable to produce a durable, rigid erection. These men may

also present initially with good postoperative erections, but then experience increasing difficulty as time progresses.

Mulhall and co-workers studied the hemodynamic effects of bilateral nerve-sparing prostatectomy in a group of 96 men (mean age, 54 years).²⁸ Hemodynamic diagnoses included normal vascular status in 34 (35%), arterial insufficiency in 57 (59%), and CVOD in 25 (26%). There was a statistically significant correlation between the postoperative duration of erectile dysfunction and the incidence of venous leakage (14% at <4 months vs. 35% at 9–12 months), suggesting that the incidence of venous leakage increases with increasing duration of erectile dysfunction. In this study, 47% of the men with normal arterial status, 31% of those with arteriogenic erectile dysfunction, and 8% of the CVOD group regained functional erection, suggesting that the prognosis for the return of functional erection is worst when venous leakage is present.

In some men, the accessory internal pudendal artery may provide the principal blood supply to the penis. Cadaver studies have identified these arteries traveling over the anterolateral surface of the prostate, supplying a significant portion of penile blood flow in 70%.²⁹ These arteries, however, were identified by gross inspection in only 33 (4%) of 835 men undergoing RRP.²⁹ Pharmaco-angiographic investigations demonstrate that 28 (35%) of 79 men with erectile dysfunction after radiation therapy for prostate cancer had an accessory artery.³⁰ It is unclear whether damage to this artery contributes to post-RRP erectile dysfunction. Preservation of the accessory internal pudendal artery, which can be technically difficult, may not result in improved potency rates compared with control patients.²⁹

Rehabilitation therapy

In an effort to minimize the changes that may occur in the penis after RRP, the concept of rehabilitation therapy of the penis has emerged (Table 2). While these suggestions are based on treatment experience and initial studies, they lack scientific validation in terms of large-scale, controlled trials. My approach is to begin such treatment shortly after surgery, starting with a pharmacologic agent and a vacuum constriction device. Most men are eager to try sildenafil, but become frustrated when initial treatment fails. Although intracavernous injection therapies and vacuum devices are successful, many men become indifferent to continuous, long-term rehabilitative therapies and require physician encouragement to remain compliant.

TABLE 2 Treatment options for the post-RRP patient		
Treatment	Start time	Caveats and suggestions
Sildenafil citrate	6–8 weeks after surgery or when continent	• May be ineffective initially
		• Best results 18–24 months postoperatively
		• Most patients require a dose of 100 mg
		• May improve endothelial function
Intracavernosal injection therapy	6–8 weeks after surgery or when continent	• Use several times weekly
		• Intraurethral alprostadil (MUSE, Vivus) may be an effective alternative in a minority of men
		• May improve endothelial function
Vacuum constriction devices	6–8 weeks after surgery	• Use daily (multiple short repetitions) without constriction ring
		• Constriction ring minimizes urine leakage when used for intercourse
		• Low-flow ischemic erection is not physiologic
		• May prevent atrophy and fibrosis

Montorsi and colleagues demonstrated that early postoperative initiation of alprostadil injection therapy significantly increased the recovery rate of spontaneous erections after nerve-sparing RRP.³¹ Men were randomized to injections 3 times a week for 12 weeks (n = 15) or to observation without any erectogenic treatment (n = 15). Return of spontaneous erections was reported in 10 (67%) treated men versus only 3 (20%) of the men receiving no therapy. The authors suggest that vasoactive injections improve cavernous oxygenation, thereby limiting the development of hypoxia-induced tissue damage.³¹

Another unanswered question is whether sildenafil can improve long-term endothelial function after nerve-sparing RRP in a similar manner to injection therapy. Montorsi and associates demonstrated that sildenafil, taken at bedtime, significantly improved nocturnal erectile activity compared with placebo in men with erectile dysfunction.³² While nocturnal erections likely contribute to maintenance of the morphodynamic integrity of smooth muscle cells within the corpora cavernosa, it is unknown whether long-term erectile function is improved after RRP. Men using sildenafil after RRP should be counseled that initial lack of response is not uncommon and that best results are seen 18 to 24 months postoperatively.³³

In the future, nerve and vascular growth factors may play a role in minimizing penile changes after RRP. Using a rat model, Lue and colleagues demonstrated that intracavernous injection of adeno-associated virus–brain-derived neurotrophic factor may prevent the degeneration of neuronal NOS-containing neurons in the major pelvic ganglia and facilitate the regeneration of neuronal NOS-containing nerve fibers in penile tissue, thereby enhancing the recovery of erectile function after bilateral cavernous nerve injury.³⁴ The same laboratory reported that intracavernous injection of vascular endothelial growth factor can restore erectile function in a rat model of traumatic arteriogenic erectile dysfunction.³⁵ A preliminary report from Burnett and associates indicates that immunophilin ligand FK506 may be neuroprotective for penile innervation.³⁶

Conclusions

Despite refinements in technique, erectile dysfunction remains a troublesome source of morbidity after nerve-sparing RRP. With overall potency rates of 30% to 60%, further improvements are warranted. Intraoperative modifications in nerve-sparing technique with videotape review and the use of cavernosal stimulation have recently been described. Interposition SNG appears promising, but requires further confirmation. During the last several years, increasing attention has focused on maintaining end-organ integrity by minimizing penile smooth muscle changes secondary to neuropraxia, including atrophy, fibrosis, and CVOD. While initial strategies for penile rehabilitation therapy have focused on use of intracavernous injection therapies and sildenafil, future treatments may involve use of nerve and vascular growth factors.

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