Management of Erectile Dysfunction Following Radical Prostatectomy

Craig D. Zippe, MD, Rupesh Raina, MD, Mamta Thukral, MD, Milton M. Lakin, MD, Eric A. Klein, MD, and Ashok Agarwal, PhD

Address
Andrology-Urology Research Laboratory, Urological Institute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, A100, Cleveland, OH 44195, USA.
E-mail: zippec@ccf.org

Current Urology Reports 2001, **2**:495–503
Current Science Inc. ISSN 1527–2737

Radical prostatectomy is the standard treatment for organ/specimen-confined prostate cancer, yet erectile dysfunction in selected series is still reported as high as 90% after this procedure. Thus, most men need adjuvant treatments to be sexually active following radical prostatectomy. These include vacuum constriction devices, intracorporeal injections of vasoactive drugs, and transurethral dilators, all of which have reported response rates of 50% to 70%. Unfortunately, long-term compliance is suboptimal, with a discontinuation rate of nearly 50% at one year. These non-oral options should be offered on an individual basis to patients who have failed oral therapy since efficacy and compliance vary. Also, these options should be considered in the early postoperative period to enhance sexual activity and penile oxygenation, which may prevent corporeal fibrosis. Early penile rehabilitation with intracavernosal injections or vacuum constriction devices should be encouraged to increase chances for recovery of rigid erections. In patients with some preservation of nerve tissue, oral sildenafil may be effective in promoting an earlier return of erectile function. The potential impact of sildenafil and other new oral therapies should encourage urologists to continue to perform and perfect the nerve-sparing approach.

Introduction

Radical prostatectomy has been the "gold standard" treatment for organ/specimen-confined prostate cancer for several decades. While data on cancer-specific survival and prostate-specific antigen (PSA) progression continues to improve with the detection of lower volume cancers, radical prostatectomy still is associated with significant morbidity [1]. While improved surgical knowledge has helped decrease the incidence of "total" incontinence to less than 5%, the incidence of erectile dysfunction has remained high and is reported as high as 90% [2]. While surgical technique and experience remain the dominant variables in outcome, other factors affecting postoperative erectile dysfunction include patient age, preoperative sexual function, psychological adjustment to cancer diagnosis, and coexisting medical diseases (*eg*, diabetes, hypertension). Other perioperative variables include stage of disease, preservation of neurovascular bundles, urinary incontinence, and adjuvant treatments (*eg,* radiation therapy, hormonal therapy) [3••].

A current dilemma surrounding erectile dysfunction following radical prostatectomy is the wide variation in potency rates reported in the literature. Following radical prostatectomy in the hands of experienced surgeons at centers of excellence, erectile function ranges between 40% and 85% [4,5]; however, for the procedure in general, the return of erectile function ranges from 9% to 40% [6–8]. This variance appears to be surgeon dependent, but it also may reflect the nonuniformity in data collection. The criteria of either a positive erectile response or sexual satisfaction are not applied universally. Variables include the qualitative difference between partial and full erection, percentage of rigid erections/attempts, and duration of vaginal intercourse.

Although erectile dysfunction is a common surgical complication that needs to be addressed, it is amenable to treatment if patients have the interest and desire. Safe, nonsurgical treatments with reasonable efficacy include intracorporeal injection of vasoactive drugs, transurethral vasodilators (MUSE; Vivus, Mountain View, CA), vacuum constriction devices (VCDs), and oral therapy (sildenafil citrate). Any of these treatments may have excellent compliance in an individual patient.

This article summarizes the standard treatments used to treat erectile dysfunction as well as the newer option, oral medications. We also discuss our institution's ongoing studies on "penile preservation" to enhance recovery of rigid erections during the period of neuropraxia that exists immediately following surgery.

Prevalence

Despite the high prevalence of erectile dysfunction following radical prostatectomy, most men are pleased with their decision to have surgery and can accept transient or permanent

dysfunction [9]. Younger, healthier men with good sexual function are the group most likely to experience distress at the prospect of losing erectile capacity as a result of treatment [10].

Recently, Valdivia *et al.* [11] reported that 91% of patients were satisfied with results of the surgery, but only 2.6% were potent enough to achieve vaginal intercourse after radical prostatectomy. Furthermore, only 29% of men with erectile dysfunction sought treatment for their condition. The loss of interest in seeking help for erectile dysfunction following radical prostatectomy is specific to each individual. Variables include spousal and patient reaction to the cancer, urinary incontinence, and delay in advising treatment.

A recent study at the Cleveland Clinic analyzed the erectile status and treatment options of patients at 1 year following nerve-sparing and non-nerve–sparing (NNS) radical prostatectomy. A sexually active population of 143 patients of mean age 63 years underwent nerve-sparing (63.6%) and NNS (36.3%) radical prostatectomy. Though 38% of patients (55 of 143) regained spontaneous erections (34% nerve-sparing; 4% NNS) with vaginal intercourse after surgery, 40% (22 of 55) were dissatisfied with the quality of erections and sought adjuvant treatment. The interesting aspect of the study is that 47 of the 88 men (53.4%) with erectile dysfunction did not seek any treatment, despite counseling [12]

This discrepancy in sexually active men between preoperative and postoperative interest is being addressed with more informed preoperative teaching and early postoperative activity with the use of erectaids. Currently, patients are enrolled in clinical studies investigating the early "prophylactic" use of vacuum erection devices and intracorporeal penile injections.

Vacuum Constriction Devices

Numerous published reports exist that describe VCDs as being very effective. These devices have been used successfully in a variety of patients with organic erectile dysfunction, including those patients treated for prostate cancer with either radical prostatectomy or radiation therapy [13]. Cookson and Nadig [14] reported follow-up results in patients treated with VCDs. They reported long-term efficacy and patient satisfaction rates of more than 80%, with statistically significant increase in the frequency of successful intercourse attempts in 79% of patients using the device for 1 year; these were maintained in 77% beyond the first year. However, despite this excellent satisfaction in this subset of patients, the overall dropout rate was 30% to 40%. Primary reasons for discontinuation were bruising and petechiae (5%), pivoting at the base of the penis (6%), coldness and numbness around the penis (5%), pain related to the VCD or constriction band (10%), and decreased ability to achieve orgasm with the device (10%).

Turner *et al.* [15] did a prospective comparison of intracorporeal injection of papaverine/phentolamine and external vacuum devices with regard to usage rates, effectiveness, side effects, dropout rates, and impact on patient sexual and psychological functioning. Both treatments were efficacious and safely used by patients, though dropout rates were higher for the group using intracorporeal injections (60% vs 20%). There were no differences in sexual or psychological impact between the two treatments.

While intracorporeal injections can produce a more natural and satisfactory erection, efficacy is not 100% and the continued use of needles lends itself to a 40% to 60% noncompliance rate after 1 year [16•] For these patients, VCD may be a reasonable alternative. Gould *et al.* [17] reported that 71% of patients who failed to achieve satisfactory erections by intracavernosal injection subsequently received adequate rigidity and satisfactory erection with VCD.

Although a published report describes efficacy rates of 60% to 80%, compliance after 1 year decreases to 50% to 70% [18] Noncompliant patients typically complain of tightness or pain from the constriction ring, diminished sensation of the phallus and glans, swiveling of the base of the penis with erection, and the laborious mechanics of using the vacuum device [19]. In addition, there is variability in the success of using the VCD each time, which leads to frustration.

One area of current interest is early intervention clinical protocols in the use of VCD to encourage early corporeal rehabilitation and prevention of post–radical prostatectomy veno-occlusive dysfunction by increasing the frequency of tissue oxygenation. Early sexual rehabilitation after radical prostatectomy may enhance earlier recovery of nocturnal erections, as treatments enhance oxygenation of the corpora cavernosa and prevent formation of collagen and fibrosis, a cofactor in smooth relaxation and erectile function [20].

In our experience, daily use of VCD after radical prostatectomy (with or without the constriction ring) to either maintain corporeal engorgement or achieve vaginal intercourse during the period of neuropraxia was associated with a high compliance rate (60 of 74 [80%]) and few complications. Of this series, 80% of the patients at 6 to 9 months reported having sexual activity (vaginal intercourse) with the VCD at a frequency of twice per week. This level of activity in the first 6 to 9 months helped maintain the sexual interest and comfort between the couples that existed preoperatively. At a mean interval of 9 months, the early (daily) use of VCD resulted in natural erectile function in 55% of patients (19 of 60), with 10 of these 19 patients (52%) having erections sufficient for vaginal penetration [21]. This potency rate (defined as vaginal penetration) of 52% at 9 months is significantly higher than potency with our contemporary series (without early VCD), which had a 24% natural potency rate at 12 months. Longer follow-up is needed to determine if early VCD use can increase the return of both nocturnal and rigid erections sufficient for vaginal intercourse. It does appear that early VCD encourages early sexual activity and interest in patients (and partners) who previously were inactive for a year or more, waiting for the period of neuropraxia to resolve.

Table 1. Response to abridged International Index of Erectile Function (IIEF) questionnaire of 60 postprostatectomy patients following early use of vacuum constriction devices (VCDs)

Question number	Item	Presurgery mean, %	Postsurgery mean, %	After VCD use mean, %
IIEF Q-2	Frequency of penetration	4.1	0.99	3.61
IIEF Q-7	Frequency of satisfactory intercourse	4.33	0.86	3.24
IIEF Q-10	Feeling of orgasm or climax	4.76	0.91	2.64
IIEF Q-12	Sexual desire	4.81	0.91	3.14
IIEF Q-13	Overall sex life	4.46	1.11	3.12
	Total IIEF Score	22.5	4.8	16

Data from Zippe *et al.* [21].

This improvement in sexual satisfaction within the first year with early VCD use is apparent by the increase in International Index of Erectile Function (IIEF) questionnaire scores seen at 9 months in our study (Table 1) [21].

Vacuum constriction devices are an important option in the armamentarium for clinicians who treat erectile dysfunction. The current models seem safe and are applicable to patients with mixed etiologies and risk factors. Rigidity is sufficient for vaginal penetration and intercourse in a very high percentage of cases. Satisfaction scores are high for both patients and partners in individual circumstances, and dropout rates and complications are less than those of intracorporeal injection.

Intraurethral Alprostadil (Prostaglandin E_1)

In November 1996, intraurethral alprostadil therapy (MUSE) received US Food and Drug Administration (FDA) approval for use in erectile dysfunction. This therapy currently represents an alternative method of delivering prostaglandin E_1 (PGE_1) to the erectile tissue by means of a pellet containing alprostadil (an analogue of PGE_1). The pellet is delivered into the male urethra and is absorbed by the cavernosal tissue through vascular communications from the corpus spongiosum. Intraurethral alprostadil, when introduced by Padma-Nathan *et al.* [22] in 1997, was reported to have an overall efficacy rate of 44%, but subsequent investigations could not confirm these initially favorable results and reported significant urethral pain and burning. Studies suggest that MUSE is much less successful in patients with erectile dysfunction caused by pelvic surgery or radical prostatectomy. Costabile *et al.* [23] examined the effect of transurethral alprostadil in 384 men with erectile dysfunction after radical prostatectomy and reported an overall success rate of 40%. However, Paolone *et al.* [24] at the Cleveland Clinic reported that MUSE was effective in only 15% in men who had pelvic surgery.

More recently, the efficacy and compliance of MUSE was studied in a contemporary radical prostatectomy series at the Cleveland Clinic using the IIEF questionnaire to validate responses. The results showed that MUSE was effective in 32% of patients. In this series, questions 3, 4, and 7 of the IIEF were added to get an efficiency score, and 31.6% of patients rated their response as good (Table 2). Moreover, 80% of the patients discontinued treatment, mainly because of an inadequate response or side effects. In this study, there were no statistically significant differences in the responses among different etiologic subgroups [25].

When intraurethral therapy is compared with intracavernosal injections, most patients who have tried both therapies favor injections and find that they produce a firmer erection. Porst [26] compared intraurethral and intracavernosal injections of PGE_1 and reported a significantly higher success rate and decreased side effects with injection at lower doses compared with intraurethral application. Since the introduction of oral therapy, the use of MUSE has decreased because comparative studies show that sildenafil has better efficacy and compliance. Recently, there have been clinical research efforts to use combination therapy with sildenafil and MUSE, to improve efficacy. A study conducted by Nehra *et al.* [27] (Rochester, MN), demonstrated that a combination of sildenafil (100 mg) and intraurethral PEG_1 (1000 μg) salvaged a refractory population of men with erectile dysfunction. The use of combination therapy will open a new area of interest in the treatment of erectile dysfunction. Further studies are required to confirm these interesting results.

The most common complication related to intraurethral therapy is discomfort in the penis, testes, legs, and perineal area, probably owing to the hyperalgesia related to the use of PGE_1. Additional complications include warmth or burning sensation in the urethra, minor urethral bleeding, and occasional leg vein swelling.

Intraurethal therapy (MUSE) is effective in selected patients and should remain in the armamentarium when considering options for erectile dysfunction. In many patients who do not respond to oral therapy following radical prostatectomy, this treatment option is preferred over intracavernosal injections and VCD.

Intracavernosal Injection Therapy

Intracavernosal injection became a standard treatment for erectile dysfunction in 1983 when it was introduced in the

Table 2. Responses to the International Index of Erectile Function (IIEF) questionnaire of 19 postprostatectomy patients before and after MUSE treatment.

Item*	Mean score† before surgery (± SD)	Mean score after surgery (± SD)	Mean score after MUSE (± SD)	*P* (before vs after intracavernosal therapy)§
Frequency of penetration	4.47 ± 1.07	1.36 ± 1.42	1.94 ± 1.47	<0.001
Frequency of maintained erection	4.63 ± 0.59	1.31 ± 1.29	2 ± 1	<0.001
Frequency of satisfactory intercourse	4.94 ± 0.22	1.78 ± 1.65	2.29 ± 1.57	<0.001
Efficacy score‡	14.05 ± 1.68	4.2 ± 3.45	5.94 ± 4.37	<0.001

*All items taken from the IIEF questionnaire.
†Answers were scored: 0 = no intercourse, 1 = never/almost never, 3 = sometimes, 5 = always/almost always.
‡Efficacy score: sum of responses to the three items.
§*P*-value by Wilcoxon rank-sum test.
Data from Thukral *et al.* [25].

United States at the 1983 Meeting of the American Urological Association [28,29]. With this therapy, patients could inject drugs such as PGE_1 (alprostadil) or alprostadil in combination with papaverine and phentolamine (as a triple mixture) directly into the cavernosal blood vessels to obtain an erection [29]. While phentolamine is a direct adrenoceptor blocker, alprostadil and papaverine act by modulating levels of cyclic 3′,5′-adenosine monophosphatase in the cells, eventually increasing the penile blood flow by relaxing the arterial and trabecular smooth muscles [30]. This combination of papaverine, phentolamine, and PGE_1, or trimix solution, permits a reduced dosage of each agent with increased safety and decreased morbidity [31].

The successful use of intracavernous injection therapy for erectile dysfunction after radical prostatectomy was reported in very early clinical series documenting the effectiveness of the technique. Dennis and McDougal [32] were the first to document the use of intracavernosal therapy in previously potent radical prostatectomy patients with success rates of 85%. A study by Rodriguez *et al.* [33] in 1997 revealed that intracavernous PGE_1 injection provided adequate rigidity in 95% of patients. Penile injections appear to be as effective in patients who had undergone NNS surgery as in patients who had undergone nerve-sparing procedures. The efficacy of injections also appears to be independent of the type of prostatectomy and the intracavernosal medication regimen used.

Despite their high degree of effectiveness, penile injections are not readily accepted by patients. Dropout rates in many series exceed 40%, despite therapeutic efficacy of more than 85% [34]. Factors that compromise success of therapy include pain associated with the injection (14%), difficulty in reproducing a successful injection (10% to 20%), penile fibrosis (2% to 15%) and availability of oral medications [35]. Despite multiple attempts to devise better delivery systems, many patients continue to have both physical and emotional difficulty using a needle for any length of time.

Using an institutional questionnaire, Mulhall *et al.* [36] found a good response in 75% of their patient group, which included patients with erectile dysfunction of all etiologies. They reported an attrition rate of 31% over a 38-month period, with cost, penile discomfort, and patient-partner problems being the major reasons for discontinuation. Lack of efficacy was the primary reason for discontinuation in only 14.1% of patients. In a similar study, Purvis *et al.* [37] also found that 87% of their patient sample (which included all etiologies) were fully or partially satisfied with intracavernosal injections. The discontinuation rate in their study was 58% over 2 years, with lack of spontaneity, penile discomfort, and cost of therapy being the main reasons for dissatisfaction. Inadequate rigidity, or lack of efficacy, was the primary reason for discontinuation in 18% of the patients.

Postprostatectomy patients treated with intracavernosal injections at The Cleveland Clinic were followed to analyze efficacy and satisfaction rates and to document the reasons for its discontinuation using the IIEF questionnaire. Though injections had considerable efficacy (mean efficacy score increased 2.7 times after use), with a rating of good to excellent in 68% of patients (Table 3), nearly 50% of patients discontinued therapy. The main reasons for discontinuation were insufficient erectile response, a preference for oral therapy, and the fact that the injections became an inconvenient, cumbersome procedure. Our results of reasonable efficacy but poor long-term compliance are consistent with other studies on penile injection [38].

Although penile injection therapy is often not routinely advised in the early postoperative period because of penile discomfort, patient anxiety, or lack of interest, there is some evidence that early rehabilitation of the penis is necessary to prevent lasting dysfunction. During the neuropraxia that follows nerve-sparing radical prostatectomy, early cavernous injection therapy may limit the development of hypoxia-induced tissue damage and produce an overall improvement in the recovery of spontaneous erections [39,40]. The neuropraxia, in our experience, may persist from 6 to 24 months. This concept is supported by a report by Montorsi *et al.* [41••], who

Table 3. Responses to the International Index of Erectile Function (IIEF) questionnaire of 98 postprostatectomy patients before and after intracavernosal injection treatment

Item*	Mean score† before surgery (± SD)	Mean score after surgery (± SD)	Mean score after intracavernosal injection therapy (± SD)	*P* (before vs after intracavernosal therapy)§
Frequency of penetration	4.78 ± 0.62	1.45 ± 1.53	3.91 ± 1.52	<0.001
Frequency of maintained erection	4.84 ± 0.63	1.30 ± 1.18	3.81 ± 1.67	<0.001
Frequency of satisfactory intercourse	4.79 ± 0.77	1.44 ± 1.38	3.61 ± 1.67	<0.001
Efficacy score‡	14.41 ± 1.85	4.2 ± 3.45	11.13 ± 1.67	<0.001

*All items taken from the IIEF questionnaire.
†Answers were scored: 0 = no intercourse, 1 = never/almost never, 3 = sometimes, 5 = always/almost always.
‡Efficacy score: sum of responses to the three items.
§*P*-value by Wilcoxon rank-sum test.
Data from Thukral *et al.* [38].

demonstrated that immediate postoperative biweekly intracavernous injections of alprostadil resulted in a normal erection recovery rate at 6 months that was significantly higher than the rate among nontreated controls (67% vs 20%, $P < 0.01$). These subjective results also were confirmed by hemodynamic and nocturnal testing. In a subsequent study, patients used intracavernosal injections of PGE_1 two to three times per week for 3 months and then switched over to daily sildenafil citrate therapy for 3 months. In this series, the spontaneous potency rates at 6 months were reported as high as 70%.

Further studies are required to confirm the results of these early intracavernosal injection studies and whether the 6- and 12-month potency rates are significantly better than age-matched controls with similar operations (stage of disease and type of nerve-sparing procedure). Similar to our results with early VCDs, early intracavernosal injections may promote more sexual activity and satisfaction, but not necessarily an earlier return to potency.

Problems with Standard Treatments

Although these three treatments (VCD, MUSE, and intracavernosal injections) have acceptable efficacy rates (33% to 68%), they also have high discontinuation rates (50% to 80%) [18,22,42]. The reasons for dissatisfaction include insufficient response to therapy, unacceptable side effects, and the feeling of anxiety and "unnaturalness" associated with using devices or injections. Not surprisingly, when oral therapy is introduced, many patients switch from the traditional treatments to sildenafil citrate.

Whether the introduction of newer, more efficacious agents or automated drug delivery systems can improve the long-term compliance of non-oral treatment options remains uncertain. In the meantime, it is important for surgeons to be aware of the long-term efficacy and compliance rates of the standard treatment options when counseling patients about erectile dysfunction following radical prostatectomy.

The Viagra Era—1998 and Beyond

The treatment algorithm for patients with erectile dysfunction improved dramatically with the availability of sildenafil citrate (Viagra; Pfizer, New York), the first effective oral medication. Following the landmark publication by Goldstein *et al.* [43] in 1998, sildenafil revolutionized the evaluation and treatment of erectile dysfunction so much so that sildenafil citrate is now the first treatment option for patients with erectile dysfunction of a variety of organic and psychogenic causes.

Sildenafil has provided a tremendous benefit to the patient after radical prostatectomy. In clinical trials, the response to sildenafil was 43% [44•]. Subsequent investigators reported satisfaction rates ranging from 15% to 80% [45–47]. Variables include preoperative sexual function and activity, reporting of successful intercourse/attempts, the nerve-sparing nature of the surgery, and length of time following surgery before sildenafil administration. Improved results are seen the longer the patient is out from surgery.

Researchers at The Cleveland Clinic were among the first to investigate the effects of this new oral medication in patients following radical prostatectomy and to study the impact of the presence or absence of the neurovascular bundles [48]. This study consisted of patients who were not able to have an erection or who had unsatisfactory erections following radical prostatectomy. All eligible men had a complete history and physical examination to exclude any contraindications to the drug. Also, those who used oral, sublingual, or transdermal nitrates were excluded. A total of 91 patients were enrolled. The patients' operative reports were reviewed, and the patients were stratified as to the type of nerve-sparing procedure they had undergone.

The mean age of the patients was 63.1 years, and the mean time interval from surgery to the start of sildenafil citrate was 18 months. Among the 91 patients, 53 (58.2%) had a bilateral nerve-sparing procedure, 12 (13.2%) had a unilateral nerve-sparing procedure, and 26 (28.6%) had an NNS procedure. Patients were started on 50 mg a day; the dose was titrated to 100 mg when needed.

Table 4. Characteristics of 91 postprostatectomy patients with erectile dysfunction before sildenafil citrate (Viagra) therapy

Patient characteristic	Overall (*n* = 91)	Bilateral nerve-sparing (*n* = 53)	Unilateral nerve-sparing (*n* = 12)	Non–nerve-sparing (*n* = 26)
Mean age, *y*	61.8	60.5	61.2	65.6
Median time from surgery to treatment, *mo*	18.4	22	14	14.5
Presurgery erectile status, %				
Full	0	0	0	0
Partial	15.1	18.2	14.3	11.5
None	84.9	81.8	85.7	88.8
Able to penetrate, %	0	0	0	0
Nocturnal erections present, %	21	24.2	28.6	15.4

Data from Zippe *et al.* [47].

Before surgery, 80 patients (87.9%) were able to achieve a full erection and 9 (9.8%) were able to achieve a partial erection (Table 4). After surgery, 22 of the patients (24.2%) were able to have a partial erection and 69 (75.8%) were not able to have an erection at all. After surgery, but before sildenafil use, none of the patients was able to achieve vaginal penetration. The mean time interval from radical prostatectomy to drug use was roughly greater than 12 to 14 months in all three subgroups.

Following treatment with sildenafil, 48 of the 91 patients responded to the drug: 38 of the 53 patients (71.7%) who had the bilateral nerve-sparing procedure, six of the 12 patients (50%) who had the unilateral nerve sparing procedure, and four of the 26 patients (15.4%) who had the NNS procedure (Table 5). It was unclear whether the 15% response rate in the NNS group was due to placebo effect, unrecognized residual nerve tissue, or a non-neurogenic mechanism.

We interviewed all of the patients' spouses or partners individually and found that the quality of erection was excellent in all 48 responders and that the mean duration of intercourse ranged from 4.5 to 12 minutes. The ability to achieve vaginal penetration and the quality of the erection correlated with a spousal satisfaction rate of 80%. Only 1% of the responding patients discontinued the medication, giving 99% compliance.

The impact of nerve preservation and the efficacy of sildenafil also was reported by Zagaja *et al.* [44•] from the University of Chicago, who showed an 80% response rate in men younger than 55 years when both nerve bundles were spared and a 40% response when one bundle was spared. However, in the 56- to 65-year-old group, the response rate dropped to 45% in the group with two nerves spared and to 0% in the group with one nerve preserved. In the older age group (>65 years), 33% of the patients responded when two bundles were spared, and none of the 10 patients responded when just one bundle was preserved. Also, in this series, sildenafil was ineffective during the first 9 months after prostatectomy.

Our study showed that the use of sildenafil citrate offers a chance to salvage roughly 70% of our impotent, motivated patients if a bilateral nerve-sparing procedure is done and 50% of patients if a unilateral nerve-sparing procedure is done. Our results suggest that urologists can initiate treatment with sildenafil at any time after surgery and should not be hesitant to increase the dosage to 100 mg. In our study, 70% of the successful patients were using the 100 mg dose. The potential impact of sildenafil (and its requirement for nerve tissue) should encourage urologists to continue to perform and perfect the nerve-sparing approach to give their patients the best chance of resuming sexual activity after radical prostatectomy [49,50].

Future Directions and Studies

New oral therapies

A myriad of new therapeutic agents is emerging for the treatment of sexual dysfunction. Oral pharmacotherapy currently is considered the first option for the majority of patients with erectile dysfunction. A number of experimental drugs have been evaluated in phase 1 and 2 clinical studies. The agent closest to clinical use is apomorphine SL, which has been approved for marketing in Europe. This drug has a central mechanism of action; it is administered sublingually 20 minutes prior to expected sexual activity. At the approved doses of 2 and 3 mg, apomorphine SL has been shown to induce a significantly higher percentage of erections than placebo. At the 2- to 3-mg dose, the principal side effect of nausea was acceptable at 4.7%.

There currently are new efforts to design phosphodiesterase-5 (PDE5) inhibitors with increased potency and selectivity. Rogers *et al.* [51] sequenced three distinct isoforms of PDE5 in human cavernosal tissue, heralding the advent of pharmacogenomics into the field of erectile dysfunction. Giuliano *et al.* [52] from Bicêtre, France and several other European centers showed that IC351 (Cialis; Lilly-ICOS, Indianapolis), a PDE5 inhibitor, significantly increased IIEF scores and was safe and well tolerated. The efficacy and safety of Cialis for the treatment of erectile dysfunction is currently being investigated in phase 3 clinical trials. The drug significantly improved erectile

Table 5. Comparison between patients with nerve-sparing and non–nerve-sparing (NNS) prostatectomies in response to sildenafil citrate (Viagra)

Variable	Bilateral nerve-sparing (*n* = 53)	Unilateral nerve-sparing (*n* = 12)	NNS (*n* = 26)	*P* value
Number of doses	8	8.5	6.5	NSF
Able to penetrate, % (*n*)	71.7 (38/53)	50 (6/12)	15.4 (4/26)	0.001
Mean duration of intercourse, *min*	10	4.5	12	NSF
Spouse satisfaction, % (*n*)	66 (35/53)	41.6 (5/12)	15.4 (4/26)	0.001
IIEF responders, *n*	38	6	4	
IIEF score				
Frequency of penetration	1.2–4.8	1.0–2.8	1.5–3.3	0.04*
Frequency of maintenance	1.2–4.8	1.0 –2.6	1.5–3.3	0.02*
Sexual satisfaction	1.3–4.2	1.2–2.5	1.3–3.0	0.02*

*Bilateral nerve-sparing vs unilateral nerve-sparing/NNS.
IIEF—International Index of Erectile Function; NSF—not significant.
Data from Zippe *et al.* [47].

function and was equally well tolerated by patients in the 10- and 20-mg dose groups.

Another PDE5 inhibitor, BAY 38-9456 (Vardenafil; Bayer Corp., West Haven, CT) is a new, potent, and selective PDE5 inhibitor that showed safety in phase 1 trials reported from two centers in Germany by Sachse *et al.* [53]. The results showed that Vardenafil is a selective and potent PDE5 inhibitor that potentiates nitric oxide–mediated relaxation and cGMP accumulation in human trabecular smooth muscle, supporting its use as a future therapeutic agent for the oral treatment of erectile dysfunction. Further clinical trials are required to assess the selectivity, pharmacokinetics, and period of responsiveness of these new drugs and their potential benefits in the treatment modality of erectile dysfunction after radical prostatectomy.

Intraoperative cavernous nerve stimulation

The intraoperative cavernous nerve stimulation system (CaverMap; Alliant Medical Technologies, Norwood, MA) is used to identify the location of the cavernous nerves during radical prostatectomy by monitoring tumescence response to intraoperative cavernous nerve stimulation. While most surgeons feel confident in identifying the neurovascular bundles, this may aid the surgeon in preserving the cavernous nerves in selected cases. It is still unclear if the use of the CaverMap translates into an improvement in erectile potency. The real problem appears to be the presence of neuropraxia following the surgery and not necessarily the identification of the neurovascular bundles. The main benefit of the CaverMap may be that it forces the surgeon to pay particular attention to the nerve-sparing component of the operation and to allocate the effort to perform it optimally [50].

Interposition of sural nerve grafts

Sural nerve grafts may act as templates for potential nerve regeneration after surgery [54]. Although nerve grafting is a time-consuming procedure that prolongs operation time, it may be a reasonable option in a young patient who has undergone a bilateral or unilateral NNS prostatectomy [55].

Kim *et al.* [55] recently reported on 12 potent men (mean age, 57 years) who underwent wide bilateral neurovascular bundle resection with sural nerve graft interpostion.

At 1-year follow-up, patient interviews were done and compared with a control group who had bilateral nerve resection without nerve grafting. Of the 12 grafted patients, four (33%) had spontaneous, unassisted erections sufficient for sexual intercourse with vaginal penetration. An additional five patients described partial erections of 40% to 60%, but with insufficient rigidity for penetration. The control group had significantly poorer sexual function in all components of the IIEF questionnaire, with only one patient achieving vaginal penetration. A follow-up period of 24 months may be necessary to evaluate the functional status of these nerve grafts and to assess whether they will respond to oral treatment with sildenafil citrate [56].

Early penile rehabilitation

An exciting, new approach to erectile dysfunction therapy is the potential for prophylactic pharmacotherapy to prevent erectile dysfunction or restore erectile function. We also are investigating whether "early rehabilitation" using cavernous injection therapy can maintain the vascular and cellular integrity of the penis during neuropraxia following nerve-sparing radical prostatectomy. Montorsi *et al.* [41••] studied whether postoperative intracavernosal injections of alprostadil (three times per week for 12 weeks) could enhance recovery of spontaneous erectile function in 12 men who had undergone nerve-sparing radical, retropubic prostatectomy. The results showed that eight of 12 patients (67%) experienced recovery of spontaneous erection. They concluded that early postoperative intracavernosal injection limited the development of hypoxia-induced tissue damage and produced an overall improvement in the recovery of spontaneous erections. However, in our hands, the early use of injections has had suboptimal

compliance, with nearly 50% of patients discontinuing treatment because of pain [20, 21].

Patients taking sildenafil citrate may benefit from early rehabilitation using vacuum constriction. Because the drug has limited efficacy during the early postoperative period, when the nerves are still recovering [47], we advise patients to temporarily use a VCD in hopes of preventing penile vascular insufficiency. We believe that early use of VCDs results in early return of nocturnal erections, which are sufficient for intercourse. However, further confirmatory studies are needed to support the concept of early penile rehabilitation.

Growth factors for cavernous nerve regeneration

Recent animal studies have provided promising results concerning the use of nerve and vascular growth factors in promoting the regrowth of damaged cavernous nerves and return of erectile function. Lee *et al.* [57] showed that intracorporeal administration of brain-derived neurotrophic factors after bilateral cavernous nerve cryoablation in rats prevents the degeneration of neural nitric oxide synthase containing neurons, with an enhancement of recovery of erectile function. In addition, the intracorporeal injection of vascular endothelial growth factor in rats with arteriogenic erectile dysfunction can provide a protective effect on erectile function.

It remains to be determined whether this concept is applicable to the human model, *ie*, whether nerve regrowth can be stimulated without theoretically increasing risk of prostate cancer recurrence or the stimulation of growth of microscopic residual cancer.

Conclusion

Despite the advent of nerve-sparing radical prostatectomy, erectile dysfunction still is a common surgical complication. Dysfunction rates vary from 10% to 100%, depending on the experience of the surgeon, the frequency with which he or she does the surgery, the nerve-sparing nature of the surgery, the state of the disease, the age and preoperative potency of the patient, and the reporting of successful response (defined as vaginal intercourse/attempts). The natural recovery of erection function may take as long as 24 months. Therefore, many men should be encouraged to receive adjuvant treatment. Although standard treatments (vacuum constriction, MUSE, and intracorporeal injections) are effective and still available, most patients prefer oral therapy because of its simplicity. Sildenafil citrate and the newer PDE5 inhibitors are only effective when functional nerve tissue is present. Patient enthusiasm for and compliance of oral therapies should encourage urologists to perform and perfect the nerve-sparing approach to give their patients the best chance of resuming sexual activity after radical prostatectomy for treatment of erectile dysfunction. Oral therapy does not appear to be very effective within the first 9 to 12 months when neuropraxia exists, and standard treatment options should be encouraged during this time to maintain good sexual health.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Schrader-Bogan CL, Kjellberg JL, McPherson CP, *et al.*: **Quality of life and treatment outcomes: prostate carcinoma patients' perspectives after prostatectomy or radiation therapy.** *Cancer* 1997, **79:**1977–1986.
2. Walsh PC, Marschke P, Ricker D, *et al.*: **Patient-reported urinary continence and sexual function after anatomic radical prostatectomy.** *Urology* 2000, **55:**58–61.
3. •• McCullough AR: **Management of erectile dysfunction following radical prostatectomy.** *Sex Dysfunction Med Pfizer* 2000, **2(1):**2–8.

This excellent review discusses available treatment options for erectile dysfunction following radical prostatectomy, as well as a framework for approaching patients with erectile dysfunction following radical prostatectomy.

4. Catalona WP, Basler JW: **Return of erections and urinary continence following nerve-sparing radical retropubic prostatectomy.** *J Urol* 1993, **150:**905–907.
5. Quinlan DM, Epstein JI, Carter BS, Walsh P: **Sexual function following radical prostatectomy: influence of preservation of neurovascular bundles.** *J Urol* 1991, **145:**998–1002.
6. Sexton WJ, Benedict JF, Jarow JP: **Comparison of long-term outcomes of penile prosthesis and intracavernosal injection therapy.** *J Urol* 1998, **159:**811–815.
7. Jarow JP, Nana-Sinkam P, Sabbagh M, *et al.*: **Outcome analysis of goal directed therapy for impotence.** *J Urol* 1996, **155:**1609–1612.
8. Jarow JP, Burnett AL, Geringer AM: **Clinical efficacy of sildenafil citrate based on etiology and response to prior treatment.** *J Urol* 1999, **162:**722–725.
9. Mazur DJ, Merz JF: **Older patients' willingness to trade off urologic adverse outcomes for a better chance at five–year survival in the clinical setting of prostate cancer.** *J Am Geriatr Soc* 1995, **43:**979–984.
10. Talcott JA, Rieker P, Propert KJ, *et al.*: **Patient reported impotence and incontinence after nerve–sparing radical prostatectomy.** *J Natl Cancer Inst* 1997, **89:**1117–1123.
11. Valdivia Navarro P, Gonzalvo A, Blas Marin M, *et al.*: **Quality of life after radical prostatectomy.** *Actas Urol Esp* 1997, **21:**903–908.
12. Zippe CD, Thukral M, Agarwal A, *et al.*: **Erectile dysfunction following radical prostatectomy in a pre-operative sexually active population.** *Poster presentation at the 95th Annual Meeting of the American Urological Association,* Atlanta, 2000.
13. Dutta TC, Eid JF: **Vacuum constriction devices for erectile dysfunction: a long-term, prospective study of patients with mild, moderate, and severe dysfunction.** *Urology* 1999, **54(5):**891–893.
14. Cookson MS, Nadig PW: **Long term results with vacuum constriction device.** *J Urol* 1993, **149:**290–294.
15. Turner LA, Althof SE, Levine SB, *et al.*: **Twelve-month comparison of two treatments for erectile dysfunction: self–injection versus external vacuum devices.** *Urology* 1992, **39(2):**139–144.
16. • Soderdahl DW, Thrasher JB, Hansberry KL: **Intracavernosal drug-induced erection therapy versus external vacuum devices in the treatment of erectile dysfunction.** *Br J Urol* 1997, **79:**952–957.

This interesting study compares two competing treatment options for erectile dysfunction.

17. Gould JE, Switters DM, Broberick GA, deVereWhite RW: **External vacuum devices: a clinical comparison with pharmacologic erections.** *World J Urol* 1992, **10:**68–70.
18. Blackard CE, Borken WD, Lima JS, *et al.*: **Use of vacuum tumescence device for impotence secondary to venous leakage.** *Urology* 1996, **41:**225–227.

19. Sidi AA, Becher EF, Zhang G, Lewis JH: **Patient acceptance of and satisfaction with an external negative pressure device for impotence.** *J Urol* 1990, **144:**1154–1156.
20. Fraiman MC, Lepor H, Telegrafi S, *et al.*: **Does early treatment of erectile dysfunction after nerve sparing radical prostatectomy lead to better long term return of natural function? [abstract].** In *Proceedings of the Society for the Study of Impotence Meeting, 2000.* Cleveland, OH: Society for the Study of Impotence; 2000.
21. Zippe CD, Raina R, Agarwal A, *et al.*: **Recovery of spontaneous erectile function after radical prostatectomy with or without early use of VCD.** *Paper presented at the North Central Section Meeting of the American Urological Association,* Cancun, Mexico, 2001.
22. Padma-Nathan H, Hellstrom WJ, Kaiser FE, *et al.*: **Treatment of men with erectile dysfunction with transurethral alprostadil.** *N Engl J Med* 1997, **336:**1–7.
23. Costabile RA, Govier FE, Ferrigni RG, *et al.*: **Safety of transurethral alprostadil in patients with erectile dysfunction following radical prostatectomy.** *J Urol* 1997, **157(4):**1424.
24. Paolone DR, Lankin MM, Ingleright BJ, *et al.*: **Intraurethral alprostadil therapy at The Cleveland Clinic Foundation.** *Abstract submitted to North Central Section American Urological Association Meeting,* Amelia Island, FL, 1998.
25. Thukral M, Lakin MM, Agarwal A, *et al.*: **Effectiveness of MUSE for erectile dysfunction after radical prostatectomy.** *Abstract submitted to the 74th North Central Section American Urological Association Meeting,* Scottsdale, AZ, 2000.
26. Porst H: **Transurethral alprostadil with MUSE versus intracavernous alprostadil: a comparative study in 103 patients with erectile dysfunction.** *Int J Impot Res* 1997, **9:**187–192.
27. Nehra A, Hakin LS, Barrett DM: **Combination of sildenafil and intraurethral prostaglandin E1 salvaged a selected population of men with ED.** *Abstract submitted to the 95th Annual Meeting of the American Urological Association,* Atlanta, 2000.
28. Brindley GS: **Pilot experiments on the action of drugs injected into the human corpus cavernosum penis.** *Br J Pharmacol* 1986, **87:**405–500.
29. Stakl W, Hasun R, Marberger N: **Prostaglandin E-1 in the treatment of erectile dysfunction.** *World J Urol* 1990, **8:**84–86.
30. Khan MA, Thompson CS, Sullivan ME, *et al.*: **The role of prostaglandins in the aetiology and treatment of erectile dysfunction.** *Prostaglandins Leukot Essent Fatty Acids* 1999, **60:**169–174.
31. McMahon R: **A pilot study for the role of intracavernosal injection of vasoactive intestinal polypeptide (VIP) and phentolamine mesylate in the treatment of erectile dysfunction.** *Int J Impot Res* 1996, **8:**233–236.
32. Dennis RL, McDougal WS: **Pharmacological treatment of erectile dysfunction after radical prostatectomy.** *J Urol* 1988, **139:**775–776.
33. Rodriguez Vela L, Gonzalvo Ibarra A, Bono Arino A, *et al.*: **Erectile dysfunction after radical prostatectomy. Etiopathology and treatment [in Spanish].** *Actas Urol Esp* 1997, **21:**909–921.
34. Lakin MM, Chen RN, Llorens SA, *et al.*: **Prostaglandin E1 injection therapy for post-prostatectomy impotence: an outcome analysis.** *J Urol* 1996, **155:**639.
35. Evans C: **Complications of intracavernosal therapy for impotence.** In *Textbook of Erectile Dysfunction.* Edited by Carson C, Kirby R, Goldstein I. Oxford, UK: Isis Medical Media; 1999:365–370.
36. Mulhall JP, Jahoda A, Cairney M, *et al.*: **The causes of patient dropout from penile self-injection therapy for impotence.** *J Urol* 1999, **162:**1291–1294.
37. Purvis K, Egdetveit I, Christiansen E: **Intracavernosal therapy for erectile failure—Impact of treatment and reasons for dropout and dissatisfaction.** *Int J Impot Res* 1999, **11:**287–299.
38. Thukral M, Lakin MM, Agarwal A, *et al.*: **Analysis of intracorporeal (IC) penile injection treatment based on the IIEF questionnaire in patients with erectile dysfunction following radical prostatectomy.** *Poster #4 presented at the 74th Annual North Central Section American Urological Association Meeting,* Scottsdale, AZ, 2000.
39. Moreland RB, Abdulmaged T, McMillin MA, *et al.*: **PGE1 suppresses the induction of collagen synthesis by transforming growth factor beta 1 in human corpus cavernosum smooth muscle.** *J Urol* 1998, **153:**811–815.
40. Fraiman MC, Lepor H, McCullough AR: **Changes in penile morphometrics in men with erectile dysfunction after nerve-sparing radical prostatectomy.** *Mol Urol* 1999, **3:**109–115.
41.•• Montorsi F, Guazzoni G, Strambi LF, *et al.*: **Recovery of spontaneous erectile function after nerve-sparing radical retropubic prostatectomy with and without early intracavernous injections of alprostadil: results of a prospective, randomized trial.** *J Urol* 1997, **158:**1408–1410.

This article introduced an exciting new approach to erectile dysfunction therapy for prophylactic pharmocotherapy to prevent erectile dysfunction or restoring early return of erectile function following radical prostatectomy.

42. Willke RJ, Glick HA, McCarron TJ, *et al.*: **Quality of life effects of alprostadil therapy for erectile dysfunction.** *J Urol* 1997, **157:**2124–2127.
43. Goldstein I, Lue TF, Padma-Nathan H, *et al.*: **Oral sildenafil in the treatment of erectile dysfunction.** *Sildenafil Study Group N Engl J Med* 1998, **338:**1397–1404.
44.• Zagaja GP, Mhoon DA, Aikens JE, Brendler CB: **Sildenafil in the treatment of erectile dysfunction after radical prostatectomy.** *Urology* 2000, **56(4):**631–634.

This study shows the result of sildenafil citrate in men with erectile dysfunction following radical prostatitis. An excellent discussion of the use, effectiveness, and side effects of the first approved PDE5 agent.

45. Feng MI, Huang S, Kaptein J, *et al.*: **Effect of sildenafil citrate on post-radical prostatectomy erectile dysfunction.** *J Urol* 2000, **164:**1935–1938.
46. Zippe CD, Thurkal M, Agarwal A, *et al.*: **The erectile dysfunction following radical prostatectomy.** *Indian J Urol* 2000.
47. Zippe CD, Kedia S, Kedia AW, Pasqualotto F: **Sildenafil citrate (Viagra) after radical retropubic prostatectomy: pro.** *Urology* 1999, **54:**583–586.
48. Zippe CD, Jhaveri FM, Klein EA, *et al.*: **Role of Viagra after radical prostatectomy.** *Urology* 2000, **55(2):**241–245.
49. Hong EK, Lepor H, McCullough AR: **Time dependent patient satisfaction with sildenafil for erectile dysfunction (ED) after nerve sparing radical retropubic prostatectomy.** *Int J Impot Res* 1999, **11:**15–22.
50. Klotz L, Herschorn S: **Early experience with intraoperative cavernous nerve stimulation with penile tumescence monitoring to improve nerve sparing during radical prostatectomy.** *Urology* 1998, **52(4):**537–542.
51. Rogers RS, Lin C-S, Lau A, *et al.*: **Expression of three isoform of cGMP binding cGMP specific phosphodiestrase (PDE 5) in penile cavernosum. Abstract No. 862.** *AUA 95th Annual Meeting,* Atlanta, 2000.
52. Giuliano F, Porst H, Padmanathan H, *et al.*: **Daily and on-demand IC351 treatment of erectile dysfunction. Abstract No. 894.** *AUA 95th Annual Meeting,* Atlanta, 2000.
53. Sachse R, Rohde G, Stark S, Klotz T: **Safety, tolerability and pharmacokinetics of bay 38-9456 in patients with erectile dysfunction. Abstract No.904.** *AUA 95th Annual Meeting,* Atlanta, 2000.
54. Sunderland S: **Nerve grafting and related methods of nerve repair.** In *Nerve Injuries and Their Repair: A Critical Appraisal.* Edinburgh: Churchill Livingstone; 1991:467–497.
55. Kim ED, Nath R, Kadmon D, *et al.*: **Bilateral nerve graft during radical retropubic prostatectomy: 1 year follow-up.** *J Urol* 2001, **165:**1950–1956.
56. Bakircioglu ME, Lin CS, Wefer J, *et al.*: **The effect of adenoassociated virus mediated brain derived neurotrophic factor in an animal model for neurogenic impotence.** *J Urol* 2000, **163:**198.
57. Lee MC, El-Sakka A, Bakircioglu E: **The effect of vascular endothelial growth factor on a rat model of arterial impotence.** *J Urol* 2000, **163:**198.