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REVIEW
Sexual dysfunction after pelvic surgery

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Pelvic surgeries are among the most common causes of organic sexual dysfunction in men and women. The impact of nerve-sparing surgery on potency has been well documented in radical prostatectomy. However, its impact on potency needs to be evaluated in other pelvic surgeries. Sexual dysfunction is highly prevalent even after multiple technical advances in the field of oncological surgeries. The prevalence varies from 8 to 82%, depending on the type of pelvic surgery. In females, sexual dysfunction has not been evaluated adequately using validated questionnaires. However, in subspecialized circles, treatment for female sexual dysfunction is becoming routine. Currently, physicians have several options for the treatment of erectile dysfunction (ED) in men. Since the introduction of oral PDE-5 inhibitors, oral therapy has become the first-line treatment option for ED, irrespective of etiology. Currently available treatment options for the female sexual dysfunction include estrogens, androgens, phosphodiesterase inhibitors, and dopamine receptor antagonists. Initial reports regarding the role of early rehabilitation are encouraging and may become the part of routine practice in the management of ED after pelvic surgery. In this article, we summarize the sexual dysfunction following pelvic surgeries and their management.
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Introduction

Erectile dysfunction (ED) is defined as the inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse.[1] Several factors have been implicated in the etiology of ED. Vascular and neurogenic causes are the most common among them. Diabetes, smoking and hypertension are the most important risk factors for vasculogenic sexual dysfunction. Neurological dysfunction is mainly associated with certain neurological syndromes like autonomic neuropathy. Sexual dysfunction after pelvic surgery has been an important and under-reported cause of ED. The pathophysiology of sexual dysfunction after pelvic surgery is unique because it can be either vascular or neurogenic factors alone, or a combination of both. The pelvic surgeries in males that are associated with considerable ED include radical prostatectomy (RP), radical cystoprostatectomy (cystectomy) and low anterior or abdominoperineal resections (APRs) for rectal cancer. The pelvic surgeries in females associated with sexual dysfunction include radical cystectomy (RC) for bladder cancer, radical hysterectomy for cancers of the cervix and endometrium and, potentially, simple hysterectomy for benign tumors.

In this article, we summarize male and female sexual dysfunction following pelvic surgeries for prostate, bladder and rectal cancer. We also discuss our experience in the treatment of sexual dysfunction following RP and RC.

ED after RP

Radical retropubic prostatectomy (RRP)
Prostate cancer has been the most commonly diagnosed noncutaneous malignancy in men older than 60 years.[2] RP has been the 'gold standard' treatment for organ/specimen-confined prostate cancer for several decades.[3,4] However, significant postoperative complications such as urinary incontinence and ED have encouraged to choose alternative treatments such as prostate brachytherapy or external beam radiotherapy.[3] While improved surgical techniques have decreased the complication rate of 'total' and stress-induced incontinence to less

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than 10%, urologists still report that the majority of patients experience ED following RRP.[3–5]

Until recently, ED following RP was not an overwhelming concern, as most prostate cancers were detected in older men.[6] However, since the advent of PSA screening in the late 1980s, more patients are being detected at a younger age and at an earlier stage. Quality of life has become a major issue in these young patients. Since most of these surgical patients ultimately regain continence, ED has emerged as an important quality of life issue following RP. Historically, quantifying ED after RP has been vague without sufficient validation.

While the surgical technique and experience remain the dominant variables in outcome, other factors that can affect postoperative ED include the patient's age, preoperative sexual function, psychological adjustment to a cancer diagnosis and coexisting medical diseases (i.e. diabetes, hypertension). Other preoperative variables include the stage of disease, preservation of the neurovascular bundles, urinary incontinence and adjuvant treatments (radiation therapy and hormonal therapy).[3]

The incidence of erectile function following RP in the hands of experienced surgeons at centers of excellence ranges between 40 and 85%.[4,5,7,8] Walsh and Donker[9] first introduced nerve-sparing surgery in 1982. Since the last two decades, many urologists have pioneered this modification. Walsh *et al.*[5] reported potency rates of 86% in patients after bilateral nerve-sparing RP. Similarly, Kundu *et al.*[10] reviewing in large series of Catalona reported the return of natural erections sufficient for intercourse in 76% (1346/1770) of patients following bilateral nerve-sparing RP. However, many surgeons with limited experience have not mastered the technique of nerve-sparing surgery, which has led to the variability in reporting. Owing to the variations in technique, potency rates reported in the literature are not comparable. The variables that explain the variations include: number of nerve-sparing procedures, single vs multisurgeon series, volume of procedures, method and definition of the potency. Generally, all the reports in the literature confirmed the fact that nerve-sparing surgery significantly increases the return of natural erections after RP (Table 1). The reported potency rates after bilateral nerve-sparing RP in most series varies from 53 to 86%.[4,5,7,8]

The current dilemma acknowledging ED following RP is due to wide variation in the potency rates reported in the literature. This variation appears to be dependent not only on the above variables, but also may be due to nonuniformity in data collection. Variables include the qualitative difference between partial and a full erection, the percentage of rigid erections/attempts and the duration of vaginal intercourse.

The importance of the surgeon's experience, which translates into volume of procedures, cannot be overstated. Experienced surgeons still report improvement in potency rates even after 1000 surgeries. Catalona reported that potency rates increase with the experience of surgeon. In their first 1000 patients, recovery of potency was observed in 68% of cases, which increased up to 78% in their next 2000 surgeries.[10] The potency rates also varied according to the institution.[11,12] However, not all large volume series show excellent potency results, with many series report potency rates ranging from 11 to 20%. The reasons for low potency rates are often due to inclusion of multisurgeon results and also due to high percentage of non-nerve-sparing surgeries.[13–15]

Age is also shown to have a significant influence on the recovery of erectile function, since there is a significant decline in the potency with increasing age. Most series reported 59–82% potency in patients less than 60 years compared to 36–57% in patients with more than 60 years of age.[7,12,15,16] Kundu *et al.*[10] reported that patients with 40–50 years of age, who underwent bilateral nerve-sparing surgery, have almost twice the chance of regaining potency than the patients in 70s. Age also correlates

Table 1 Relation between nerve-sparing status and potency after radical prostatectomy

Authors/year	*Follow-up (months)*	*Type of RP*						*Total*	
		NNS		*UNS*		*BNS*			
		n	*Pot (%)*	n	*Pot (%)*	n	*Pot (%)*	n	*Pot (%)*
Quinlan *et al.*/1991[7]	46	7	0	109	56	387	76	503	68
Catalona *et al.*/1993[15]	18			59	41	236	63	295	59
Geary *et al.*/1995[113]	18	187	1	203	13	69	31	459	20
Talcott *et al.*/1997	12	12	0	18	0	19	21	49	15
Walsh *et al.*/2000[5]	18					57	86	64	86
Salomon *et al.*/2002[114]	12	13	38.4	13	53.8	17	58.8	100	49.3
Varkarkis *et al.*/2004[115]	12					13	81	26	50
Kundu *et al.*, Catalona/2004[10]	18			64	53	1770	76	1834	75

NNS = non-nerve sparing; UNS = unilateral nerve sparing; BNS = bilateral nerve sparing; *n* = total no. of patients who underwent surgery.

with the preoperative potency status. Preoperative potency status has been reported to influence the recovery of erectile function. Geary *et al.*[16] and Rabbani *et al.*[14] reported that preoperative erectile status has a significant impact on the recovery of spontaneous erections.

The long-term potency status (>5 years) following RP has not been previously reported. Most published series reporting potency have a mean follow-up of only 12–24 months.[11–14] The paucity of literature on long-term potency status following RP prompted us to study this question.[17] We obtained 1 and 5 years potency data on 141 preoperative sexually active patients, who underwent RP between 1996 and 1999. Variables analyzed after the mean follow-up period of 6.4 ± 1.8 years included: sexually active or not with or without erectaids, presence of natural erections, nerve-sparing status (NS) and reasons for sexual inactivity (loss of interest, cardiovascular factors, urinary incontinence, loss of spouse, hormonal treatment). At 1 year, 113/141 (80%) patients were sexually active, achieving vaginal intercourse (including drug therapy and erectaids), and 28 (20%) were sexually inactive. The reasons for sexual inactivity were incontinence (15/28, 53%), loss of interest in sex (10/28, 36%) and loss of libido (3/28, 11%; hormonal therapy). Of the 113 sexually active patients achieving vaginal intercourse, four (3.5%) had natural erections sufficient for vaginal intercourse, 55 (48.7%) were using sildenafil alone, 26 (23%) intracavernosal (IC) injections, 19 (16.8%) vacuum constriction device (VCD) and nine intraurethral alprostadil (MUSE). At 5 years, 70/113 (62%) remained sexually active, achieving vaginal intercourse. Of the 70 patients, 16 (22.9%) had natural erections sufficient for intercourse (15/16 NS), 21/70 (30%) were still using sildenafil alone, 10 (14.3%) IC injections, five (7%) VCD, 11 (15.7%) were using combination therapy, sildenafil with VCD, ICI or MUSE. An additional seven (10%) patients switched to tadalafil alone. At 5 years, 43/113 (38%) were sexually inactive. The reasons for sexual inactivity include: loss of interest – 17 (39.5%), cardiovascular/neurological diseases – 18 (42%), hormonal treatment – three (7%), loss of partner – three (7%), and two were due to other surgeries.

Overall, of the 141 sexually active patients at 5 years, only 70 (50%) are sexually active. In this sexually active group at 5 years, only 23% (16/70) had natural erections sufficient for vaginal intercourse, while the other 77% were drug or erectaid dependant. This long-term analysis revealed that sexual activity in preoperative sexually active patients decreases by 50% at 5 years – with the loss of interest and medical co-morbidities being the primary reasons for discontinuation. In conclusion, the vast majority of the RP populations are dependent on the oral (or) erectaids.

Radical perineal prostatectomy (RPP)
Dr Hugh Young from the John Hopkins Hospital first performed and reported the technique of RPP 100 y ago. Since then, RPP has gone through various phases of popularity. The introduction of nerve-sparing RPP by Walsh in 1984 further reduced its popularity. However, as more patients are detected in earlier stages, eliminating the need for pelvic lymph node dissection, the enthusiasm for perineal approach has increased.[18] However, there is a paucity of reports on potency following RPP. Harris *et al.*[19] reported that 60% of patients are potent after RPP. In a prospective study, Frazier *et al.*[20] reported 77% potency after a bilateral nerve-sparing RPP. Weldon *et al.*[21] also reported that 68% of unilateral nerve-sparing and 73% of bilateral nerve-sparing prostatectomy patients had return of natural erections. However, in Weldon's report, 170 of the 220 cases have been excluded due to suboptimal preoperative erectile function. The major limitations of RPP are lack of sufficient volume and lack of number of surgeons performing the surgery.

Currently, there are no reported randomized prospective data comparing the return of erectile function following radical perineal and RRP.

Laparoscopic RP
Schuessler first reported laparoscopic RP in 1992. However, this procedure did not gain momentum until after 1997. Currently, it is accepted among the urologists as a promising and alternative surgical technique for prostate cancer treatment. The development of advanced laparoscopic techniques and robot-assisted technology has resulted in several new surgical approaches for treating organ-confined prostate cancer. Unfortunately, after a large learning curve of their 550 patients, Guillonneau *et al.*[22] reported that 31/47 consecutive (66%) preoperatively potent patients, who underwent bilateral nerve-sparing surgery, were able to have intercourse with or without sildenafil (Table 2). Rassweiller *et al.*[23] reported in their first 180 laparoscopic RP series that 4/10 (40%) patients with nerve sparing had erections sufficient for vaginal intercourse with sildenafil. Katz *et al.*[24] reported that, of 143 preoperatively potent patients, only 23% were able to have sexual intercourse at 12 months.

While a few experienced laparoscopic surgeons report potency rates comparable to open retropubic RP, the delay in reporting potency status from the established centers of experience would indicate that ED is a significant problem following laparoscopic RP. The instrument of reporting postoperative potency following open RRP with baseline and chronological fashion needs to be integrated into laparoscopic and robotic prostatectomy.

Table 2 Erectile function following laparoscopic radical prostatectomy

Author/year	Follow-up (months)	No. of patients	Type of RP	Potent	Percentage
Turk I/2001[116]	—	44	BNS (5), UNS (39)	26/44	59%[a]
Hoznek et al./2001[117]		47	UNS	7/26	28%
			BNS	10/21	46%
Eden et al./2002[118]	10	100	BNS (58%)	—	62%
			BNS		
Guillonneau et al./2002[22]		47	BNS	40	85%[b]
				31	66%[a]
Rassweiler et al./2004[119]	36				34–67%

[a]Spontaneous erections sufficient for intercourse; BNS = bilateral nerve sparing; UNS = unilateral nerve sparing; RP = radical prostatectomy.
[b]Spontaneous erections.

Sexual dysfunction after RC

RC has been the standard treatment for aggressive superficial bladder cancer and invasive carcinoma,[25] which consists of removal of the bladder, prostate, seminal vesicles and vas in males, bladder, urethra, anterior vaginal wall, uterus and ovaries in females. The treatments used to manage genitourinary cancers have been commonly associated with sexual dysfunction. The end points of RC are primarily focused on continence and the recurrence. Sexual dysfunction after RC may be due to direct trauma or from physical and emotional disturbances. Other factors that may have an impact on sexual life and quality of life after cystectomies are type of urinary diversion or orthotopic bladder substitution, nerve-sparing modification, urethral resection and vaginal sparing in females.

ED in males

ED is a common complication after RC. Walsh and Donker[9] first demonstrated that impotence after RP occurs mostly due to injury to neurovascular pedicle. They also demonstrated the relationship between the cavernous nerves and seminal vesicles.[26] These anatomical studies on the neurovascular bundles were instrumental in helping researchers modify their technique in radical cystoprostatectomy. Walsh in 1984 was the first to show that a modified surgical technique (nerve sparing) resulted in the increased postoperative potency of individuals who had undergone radical cystoprostatectomy.[27] Of the 11 patients who had undergone nerve-sparing procedures in this study, nine (82%) had regained sexual potency after 1 year.[26] Brendler et al.[28] in 1990 used the same technique to preserve potency and showed that nerve-sparing modification did not compromise cancer control rates after cystoprostatectomy. They reported that 64% of patients who underwent radical cystoprostatectomy were potent after surgery. Schoenberg et al.[29] in 1996 reported the 10-year experience with nerve-sparing radical cystoprostatectomy at the John Hopkins Hospital. In this 10-year report, 42% (33/78) nerve-sparing cystectomy patients were able to achieve erections sufficient for sexual intercourse. They also found that age at the time of surgery also had a significant impact on the recovery of sexual function following nerve-sparing cystectomy: 62% in men 40–49-year, 47% in men 50–59-year, 43% in men 60–69-year and 20% in men 70–79-year old have regained potency. These early reports were institution specific and have not been reproduced by other centers. However, these early reports from John Hopkins have recently opened a new era of technical interest in performing nerve-sparing RC in males and females.

Recently, results from the other nerve-sparing studies demonstrated that return of spontaneous erection rates varying from 36 to 82% depends upon the definition of potency and modification of the technique (Table 3).[29–33] Urethral-sparing RC in females, prostate and seminal vesicle-sparing RC in males have been shown to improve the sexual function. Preservation of these structures reduces the chances of injury to the cavernosal nerves, without any apparent oncological compromise. The oncological safety of these conserving operations is still been evaluated.

In Europe, there has been considerable interest in 'sexuality-preserving cystectomy', first introduced by Horenblass. Horenblass's sexuality-preserving cystectomy consists of pelvic lymph node dissection followed by cystectomy and neobladder alone, with preservation of the vas, prostate and seminal vesicles in males. In females, he proposed total preservation of the internal genitalia and urethra, with neobladder reconstruction. An ileal neobladder is anastomosed to the margins of the prostate in males and urethra in females. In a series of 13 patients (10 males, 3 females), Horenblass reported that 7/10 men who underwent surgery with this modification had return of normal erections on Rigiscan measurement and all women (3/3) reported normal vaginal lubrication.[34] In a later update, this group reported that 20/24 males were sexually active with or without erectaids and concluded that

Table 3 Sexual function after radical cystectomy

Author/year	*Type of surgery*	*Follow-up (months)*	*Total (no.)*	*Potent n (%)*	*Potency definition*
Walsh *et al.* (1984)[27]	NSRC	12	11	9 (82%)	Erection sufficient for vaginal penetration
Brendler (1990)[28]	NSRC (without urethrectomy)	12	42	27 (64%)	Able to have sexual intercourse
	NSRC + urethrectomy		12	2 (17%)	
Fray Marshal (1991)[31]	NSRC + ileal conduit	6–12	21	15 (71%)	Sexual intercourse possible or not
Nordstrom (1992)[38]	Non-NSRC/ileal conduit		M-29	3 (10%)	Erections sufficient for intercourse
			F-6	1	
Koraitim (1992)[30]	NSRC	3–36	18	9 (50%)	Not defined
Schoenberg (1996)[29]	NSRC	—	78	33 (42%)	Erections adequate for sexual intercourse
Tomic (1992)[120]	NSRC + urethrectomy	—	9	2 (22%)	
	NSRC without urethrectomy		12	8 (66.7%)	
Bjerre (1997)[42]	NSRC + ileal conduit	54	F	18%	Sexually active (maintained coital frequency)
	NSRC + neobladder	8		44%	
Horenblass (2001)[34]	NSRC	42	M-10	7 (70%)	Normal erections (rigiscan)
			F-3	3	Normal vaginal lubrication
Vallancien *et al.* (2002)[36]	NSRC (prostate sparing)	38	61	50 (82%)	Erections sufficient for intercourse
Zippe (2004)[37]	RC	47.6 + 22.7(M)	49	9 (14%)	Erections sufficient for intercourse
	NSRC + neobladder		16	8 (50%)	

NSRC = nerve-sparing radical cystectomy; M = male; F = female.

preservation of the prostate and neurovascular pedicle led to improved sexual function.[35] The oncologic concern with this procedure is that prostatic urethra and seminal vesicles can be a potential site for recurrence. In addition, there are urodynamic concerns leaving the prostate since the obstruction may occur secondary to weak detrussor of small bowel. Longer follow-up with more patients is required to rule out these concerns.

In 2002, Vallancien *et al.*[36] proposed an alternative nerve-sparing cystectomy approach, which includes a TURP before cystectomy. The principles include a TURP leaving the prostatic capsule with nerve-sparing cystectomy, with preservation of seminal vesicles and vas deferens. In 61 sexually active preoperative patients, they reported 50 (82%) had maintained their potency after a mean follow-up of 3.8 years. While the oncological concerns (leaving prostatic urethra) with Vallancien's modification is less worrisome, the task of performing a TURP before a lengthy cystectomy and neobladder is not popular. Also, a deep TURP leaving the prostatic capsule intact does not guarantee that the nerves are not damaged. Despite these concerns, Vallancien and his colleagues offered a new dimension to a difficult problem and should be congratulated for their insight.

The potency rates reported after RC in the literature vary considerably. Several reports published comprised of small number of patients and with limited postoperative follow-up.[35–37] Earlier reports defined potency as only 'return of natural erections'; however, more recent reports have defined potency as 'erections sufficient for satisfactory intercourse', a structured definition that explains the low potency rates. The results from the John Hopkins series have not been uniformly confirmed by the other centers of excellence. This may be due to poor definition of potency in different articles (erections or erections sufficient for vaginal penetration or erections sufficient for sexual intercourse) (Table 3). However, surgeons at the John Hopkins Hospital pioneered the nerve-sparing surgical technique of RP, which was extended to the RC procedure. Undoubtedly, nerve-sparing surgeries have been performed from a longer period of time, at a higher frequency and in much higher technical levels, which may explain their results.

We conducted a retrospective study regarding the potency after the RC at the Cleveland Clinic Foundation. In a 5-year interval, we identified 49 preoperative sexually active patients, who underwent RC.[37] These patients completed the International Index of Erectile Function (IIEF-15) before and after surgery (minimum follow-up of 1 year), and after the use of sildenafil citrate or any additional erectaid. At a mean follow-up of 47.6 ± 22.7 months, 42 (86%) of the 49 patients were unable to achieve vaginal penetration after surgery. The mean total sexual health inventory for men (SHIM) (IIEF-5) score of the 49 patients at baseline was 22.1 ± 4.0. After surgery, the mean total SHIM score for the entire group was 4.33 ± 5.72. Of these 49 patients, seven had erections sufficient for intercourse with a mean SHIM score of 21.1 ± 4.1 and four had erections insufficient for vaginal intercourse requiring erectaids. Six out of these seven patients underwent nerve-sparing RC. We also evaluated the role of sildenafil in these patients. Out

of 42 patients, 22 attempted sildenafil therapy; however, only two patients had erections sufficient for vaginal penetration. We stratified the degree of ED (using SHIM scores) by the type of urinary diversion. The difference in the mean total SHIM score of 5.24 ± 6.21 after orthotopic substitution was statistically significant ($P < 0.05$) compared with that after ileal conduit (mean total SHIM score 1.13 ± 0.33) and cutaneous continent (mean total SHIM score 1.33 ± 0.58) diversions. However, this difference was not as clinically significant, because the difference between 'almost never or never' does not differ in the SHIM questionnaire from 'did not attempt.'

When nerve-sparing surgery performed, our data reflect the potency rates similar to John Hopkins following nerve-sparing RC. Unfortunately, nerve sparing was performed on only 30% of sexually active patients, illustrating either our concern about oncological issues or lack of sensitivity to quality of life issues.

Although the main objective of RC is the cure, erectile function in selected patients has become an important quality of life issue. Better screening programs with early urine tests may detect the malignancy in early stages, leading to stage migration, and the detection of more patients at an earlier age. Earlier detection will allow perform more nerve-sparing surgeries, which should improve erectile function and quality of life for our cystectomy patients.

Sexual dysfunction in females

Sexual dysfunction is a major concern of many young female patients undergoing pelvic surgery.[38,39] During RC, the neurovascular bundles (located on the lateral walls of the vagina) are usually removed or damaged along with the removal of the bladder, urethra and anterior vaginal wall.[38–40] In addition, significant devasularization of the clitoris often occurs with removal of the distal urethra, affecting subsequent sexual arousal and desire.[38–41] The type of urinary diversion also has been implicated hypothetically to influence the sexual dysfunction after RC. In the initial reported series by Nordstrom and Nyman,[38] five out of six patients reported sexual dysfunction after RC with ileal conduit. Most important reasons for their dysfunction were loss of sexual desire, vaginal dryness and dyspareunia. However, later studies by Bjerre *et al.*[42] and Zippe *et al.*[43] failed to reveal any significant difference between the type of urinary diversion and sexual dysfunction. Bjerre *et al.* evaluated sexual profile after different types of urinary diversion in women with RC. A total of 37 patients completed the questionnaire, 17 patients underwent RC with continent urinary diversion; 20 patients underwent RC with ileal conduit. Data were analyzed in 33 patients; no significant difference between the two types of diversion was obtained. The lack of validated questionnaire, combined with a small number of patients in each group, may be an important reason for failure to obtain significant difference between the types of diversion.

We conducted a study to evaluate the sexual dysfunction after RC with different types of urinary diversions. The baseline and follow-up data were obtained from 34 women who underwent RC between 1997 and 2002, who were interested to participate in the study. Of 34 patients, 27 were sexually active before surgery. Out of 27 patients, 10 (37%) underwent orthotopic urinary diversion (Studer), seven (26%) underwent continent cutaneous diversion (Indiana) and 10 (37%) underwent ileal conduit diversion. A 10-item version of the self-administered Index of Female Sexual Function (IFSF) questionnaire was used to assess sexual dysfunction. The specific domains analyzed in the IFSF include the degree of vaginal lubrication, ability to achieve orgasm, degree of pain during intercourse, overall sexual desire and interest, and overall sexual satisfaction, with responses graded on a scale of 1 (almost never, never) to 5 (almost always, always). The total mean baseline IFSF score decreased from 17.4 ± 7.23 to 10.6 ± 6.62 after RC ($P < 0.05$). The most common symptoms reported by the patients included diminished ability or inability to achieve orgasm in 12 (45%), decreased lubrication in 11 (41%), decreased sexual desire in 10 (37%) and dyspareunia in six patients (22%). Only 13 (48%) of the 27 patients were able to have successful vaginal intercourse, with 14 (52%) reporting decreased satisfaction in overall sexual life after RC. When IFSF scores are stratified according to the type of urinary diversion, there was no difference between the pre- and postoperative IFSF scores. Smaller number of cases in each group may be the reason for lack of significance.

Our study revealed that sexual dysfunction is a prevalent problem after RC. Sexual function is affected in all the domains, including decreased orgasm, decreased lubrication, lack of sexual desire and dyspareunia. Our results also revealed that the type of urinary diversion has not affected sexual dysfunction.

Our recent report on the magnitude of sexual dysfunction after cystectomy, as well as recent reports on surgical modification, has stimulated us to consider the surgical modifications in the standard cystectomy procedure. We provide much better quality of life for our female cystectomy patients with this modification.

Female cystectomy (quality of life cystectomy) – surgical modification

Walsh *et al.*[44] popularized the role of nerve-sparing surgery in men with prostate cancer, which later

incorporated into male RC. In limited literature reports, RC has been shown to affect the sexual activity in females. Similar to males, more recently the technique of RC has been modified. Stenzl *et al.*[41] first reported in 1995 that removal of distal urethra has been associated with significant devascularization of clitoris and reduced sexual arousal. They also reported that preservation of urethra was not associated with increased risk of local recurrence. Burkhard and Studer,[45] in reviewing Dr Studer's series, reported that complete resection of the cranial two-thirds of the vagina with the caudal border of resection just below the bladder neck results in dissection of most of the autonomic nerves to the urethra and vagina in women. However, if the lateral vaginal walls were left intact, the majority of plexus fibers to the urethra may be preserved with careful dissection of the bladder neck and cranial urethra. They further reported recently that preservation of the neurovascular pedicle was associated with significant improvement in recovery of erectile function.[46] This pioneering work by Studer and colleagues has made the urologists realize the importance of nerve-sparing surgery in female RC.

Our surgical modifications include:

(1) infraumbilical incision (minimizes pain, allows earlier mobilization);
(2) preservation of neurovascular bundle (careful identification and preservation of bundles on the lateral vaginal wall enhances clitoral sensation);
(3) preservation of anterior vaginal wall (enhances vaginal lubrication);
(4) avoidance of routine hysterectomy (eliminates the risk for vesicovaginal fistula);
(5) elimination of routine suprapubic tube (to reduce postoperative morbidity/cosmetic scarring);
(6) anterior vaginal tubularization preferred vs posterior vaginal flap in sexually active females (preserves the depth of vagina);
(7) subcuticular skin closure (to increase the body image).

In our center, we retrospectively evaluated the sexual function outcome in six women who underwent nerve-sparing RC with orthotopic bladder substitution (quality of life cystectomy) with contemporary non-nerve-sparing orthotopic urinary diversion ($n=7$).[47] No patients in the study group received postoperative radiotherapy. All patients were evaluated with Female Sexual Function Index (FSFI) score at 6-monthly intervals.[48,49] The specific domains analyzed in our questionnaire included pain-free intercourse, degree of vaginal lubrication, overall sexual desire and interest, arousal, ability to achieve orgasm and overall sexual satisfaction. In the nerve-sparing group, the baseline (pre-operative) FSFI score vs 12-month postoperative FSFI scores (29.8 vs 27.6) showed no decline compared to the non-nerve-sparing group, which showed a marked decline after surgery (29.6 vs 11). Significant vaginal dryness, lack of arousal and dyspareunia has led to discontinuation of sexual intercourse in the non-nerve-sparing group.

Neurovascular preservation improves sexual function after surgery compared to the non-nerve-sparing group, and may also improve the urinary continence following orthotopic neobladder substitution.

Sexual dysfunction after other pelvic surgeries

Sexual dysfunction following radical and simple hysterectomy

Hysterectomy is the most common pelvic surgery performed in women of all ages. More than half a million women undergo hysterectomy for different reasons each year in the US.[50] The majority of women were not evaluated for sexual life after hysterectomy; of the women who were willing to report about the sexual function, 15–37% were shown to have a considerable decrease in the sexual life after the surgery.[51,52] The pathophysiology, implicated in sexual dysfunction after hysterectomy, includes lack of vaginal lubrication and loss of libido. Both of these complications are further aggravated by bilateral oophorectomy, especially following radical hysterectomy. Two most important causes of postoperative dyspareunia are vaginal dryness and short vaginal vault.

Quality of life issues are becoming significant end points in gynecological surgical patients. These issues have not been reported adequately in the literature. The introduction of cervical screening programs (annual pap smear) has resulted in early detection of cervical cancer at a younger age. This age migration can potentially make sexual function a major postoperative issue in the gynecological surgery. Although the reports of sexual function after gynecological surgeries dates back to 1980s, lack of standard questionnaire and definitions has produced wide variations in the literature reports.

In a population-based epidemiological study in Sweden, Bergmark *et al.*[53] reported that reduced sexual satisfaction and dyspareunia were the primary sources of symptom-induced distress following treatment of cervical cancer. Recent studies by Jensen *et al.*[54] demonstrated that patients treated with radical hysterectomy and radiotherapy suffered short-term sexual difficulties, such as dyspareunia and vaginal dryness, leading to decreased sexual satisfaction. However, some of these postoperative problems subsided 6 months after surgery. Studies involving the surgeries of ovarian malignancies report similar rates of sexual dysfunction.[55] The data on sexual dysfunction following treatment of

endometrial and vulval cancer are limited in the literature. There is definitive increase in the awareness about the impact of surgeries for gynecological cancer and its effect on female sexual function. The assessment and treatment of sexual function should become an important part of the standard care of women diagnosed and treated for gynecological cancers.

Although simple hysterectomy is the most common gynecological surgery, sexual dysfunction after this surgery has not been widely reported. The paucity of literature is a major limitation. Sexual dysfunction after hysterectomy is associated with the etiology for the hysterectomy and various preoperative conditions such as dyspareunia and dysmenorrhea. Several studies report that sexual function improves after simple hysterectomy in 30–50% of patients.[56–58] The potential explanation for improvement includes the relief from preoperative dyspareunia and dysmenorrhea.[56] The Maryland women's health study revealed that women after simple hysterectomy had improvement in overall sexual functioning without change in the frequency of orgasm.[59] Dragisic *et al*.[60] reported no change in sexual desire, orgasm frequency or orgasm after simple hysterectomy. Questions have been raised regarding the impact of the type of hysterectomy (vaginal vs abdominal) on sexual function. However, El-Toukhy *et al*.[61] in 2004 reported no significant difference in the sexual function after abdominal or vaginal simple hysterectomy. It would appear from the reported literature that simple hysterectomy does not have adverse effects on sexual function. These reports need to be confirmed from validated questionnaire that can stratify the different domains of sexual function, which include orgasm, desire and arousal, pain during the intercourse, lubrication and satisfaction.

Recently, there is a growing interest about sexual dysfunction following pelvic surgery among the gynecologists. This increased awareness will lead to development of better surgical techniques and better information on postoperative sexual dysfunction. The risk and benefits of any pelvic surgery should include in an accurate informed consent on sexual dysfunction. In the future, sexual function will soon become a routine discussion in the informed consent of gynecological surgery.

Sexual dysfunction following rectal surgeries

Sexual dysfunction after nonrectal cancer surgeries
Simple proctocolectomy is still commonly performed for many benign conditions including inflammatory bowel disease. Stahlgren and Ferguson reported in 1959 that 25% (5/25) of men who underwent proctectomy for benign disease complained of varying degrees of impotence. In a contemporary proctocolectomy series from Oxford reported, most of the patients having ED after surgery were above the age of 50. Although the reported ED in their series was 3.8%, 13.5% had minor complaints in erectile function.[62] Interestingly, Watts *et al*.[63] observed an increase in the sexual activity in most of the women after simple proctocolectomy for inflammatory bowel disease as a result of increased physical well being. Based on the literature, it would appear that simple proctocolectomy does not have significant impact on the sexual function unless it is for inflammatory bowel disease, and, in that situation, sexual activity appeared to be increased.

Sexual dysfunction after rectal cancer surgeries
Sexual dysfunction has been a major complication after radical rectal surgeries because of injury to the pelvic plexus.[64] Low anterior resection and APRs are still the most commonly performed curative surgeries for rectal cancer. Sexual dysfunction rates after these oncological surgeries vary from 10 to 60%.[65] When multimodality treatments are used, which include neoadjuvant and adjuvant radiation, sexual dysfunction also increases.[66]

APR carries a higher risk of postoperative sexual dysfunction than sphincter-saving procedures.[67] The reported impotence rates after APR in the literature varied from 15 to 92%.[64] The permanent colostomy made after APR has also shown to alter the body image and increases the rate of postoperative sexual dysfunction. Most of these studies were retrospective in nature and included various age groups with different base line function. Danzi *et al*.[68] reported an impotence rate of 48% in their prospective study following APR. Although sphincter-saving surgery is reported to have better potency rates, ED still varies from 14 to 73%.[68,69] Similar to reports following RP, the patient's age has been shown to significantly influence postoperative sexual dysfunction. Patients older than 60 have a higher risk of sexual dysfunction than younger patients.[69] Fazio *et al*.[70] reported that patients younger than 50 years had a minimal risk of sexual dysfunction. Other factors that have been shown to affect the impotence after surgery include tumor stage, surgical technique and experience of the surgeon. The surgical technique of an experienced surgeon in dissecting the correct planes can potentially influence postoperative return of potency.

Most experienced surgeons are currently performing total mesorectal excision (TME) with preservation of the neurovascular bundles. The TME procedure reduces the sexual dysfunction rates.[71] Enker *et al*. in 1997 reported that APR, when performed in accordance with the principles of TME and autonomic nerve preservation, ensures the greatest likelihood of resecting all regional disease while preserving both sexual and urinary functions. They showed that 57% of patients undergoing APR

and 85% of patients undergoing sphincter preservation surgeries were able to maintain their urinary and sexual functions.[72] Pocard *et al*.[73] reported with TME and autonomic nerve preservation that 4/7 seven women were able to achieve orgasm similar to their preoperative status. With the increasing popularity of laparoscopy, certain surgeons now perform laparoscopic assisted TME. Quah *et al*.[74] reported that sexual dysfunction rates were higher after laparoscopic surgery than open surgery in men, but there was no difference in women. Owing to paucity of reports in the literature, it may be too early to reach any conclusion regarding the sexual function following laparoscopic TME. However, whether the approach is open or laparoscopic, preoperative counseling regarding the potential postoperative sexual dysfunction is essential. ED following rectal cancer surgery is further compounded by the frequent use of neoadjuvant and adjuvant radiotherapy.[74] A recent study by Mannaerts *et al*.[66] showed that the preoperative ability to have an orgasm disappeared in 50% of males and 50% of females following multimodality rectal cancer treatment.

Sexual dysfunction rates following treatment for rectal cancer are significant and should be an essential part of preoperative counseling. With the technical modification such as TME and autonomic nerve sparing, sexual function rates will continue to improve. Unfortunately, many rectal cancers are locally advanced and require multimodality treatment, which increase the risk of sexual dysfunction.

Management of male sexual dysfunction

Treatment of male ED is rapidly evolving. Researchers have made great strides in understanding the complex neural and vascular pathways that are essential for normal erectile function. Recent advances in the understanding of the pathophysiology of erection and its interaction with the central and peripheral neurotransmitters have led to the development of new medications. Discovery of nitric oxide as a neurotransmitter in cavernosal tissue has given ways for the development of specific pharmacological agents to restore the potency. In the current-day practice, physicians have several treatment options available for the treatment of ED.

Prior to the introduction of oral therapy, standard treatments available included IC injections, intraurethral injection of prostaglandin E1 (MUSE) and application of a VCD. All three options are safe but produce variable satisfaction rates. In an individual patient, either of these erectaid treatments can have satisfactory efficacy and excellent compliance. The introduction of the first effective oral agent for ED, sildenafil citrate, revolutionized the management of ED and significantly increased the number of men coming forward for evaluation and treatment. Sildenafil is effective in most men in the general population with ED, including men with spinal cord injury, diabetes mellitus and patients who have had nerve-sparing RP. Recently, the introduction of two additional oral therapies vardenafil and tadalafil has increased the public awareness for treatment of ED.

In the following sections, we discuss the standard and oral treatment options available for the treatment of ED following RP.

Standard treatment options

Vacuum constriction device (VCD)

VCD is one of the oldest treatments available for ED. It was introduced in 1980s into clinical practice. The efficacy rates reported in the literature vary from 60 to 80%.[75] The compliance decreases to 50–70% after 1 year of activity.[76] Blackard *et al*.[77] reported that VCD was effective in patients with venous leak syndrome. Twenty of 29 patients with venous leak reported satisfactory results with the VCD. The major reasons for discontinuation are tightness of constriction ring at the base, swelling of glans, petechiae at the base of penis and laborious mechanism of use.[75]

VCDs are an important option in the armamentarium for clinicians, who treat ED. Current models are safe and can be used in patients with mixed etiologies and risk factors. The rigidity is sufficient for vaginal penetration and intercourse in a very high percentage of cases.

IC injections

IC injections were first introduced in early 1980s and these vasoactive agents revolutionized the treatment of ED. The major advantage of IC injections is that they bypass the effective neural transmission from the cavernosal endothelial cells and are effective even in patients with organic vasculogenic ED. Papavarine was the first substance studied extensively in 1980s. It is a nonspecific phosphodiesterase (PDE) inhibitor that increases cyclic AMP and cyclic GMP.[78] Phentolamine, another vasoactive agent, is a direct α-adrenoceptor blocker. However, phentolamine alone cannot produce rigid erections, so it is commonly used in combination with other agents.[79] Alprostadil, a third vasoactive agent, is a synthetic analogue of prostaglandin E1 and gained wider acceptance because it is effective and has a lower incidence of side effects.[80] However, in patients with significant vasogenic impotence, a mixture of all the three drugs (prostaglandin E1, Papavarine and phentolamine) is commonly used. This three-drug mixture is referred to as Trimix. These drugs act through different mechanism synergistically to produce maximal erectogenic effect and to minimize the individual side effects.

Long-term compliance with IC injections appears to be a significant issue. When reviewing our 10-year database at the Cleveland Clnic Foundation, we identified only 102 patients who were using IC injections on a long-term basis (at least 2 years). Of these 102 patients, 71 (70.6%) were compliant for a mean period of 3.7 years with the IC injections. In our database, the majority of IC patients switched to oral therapy or discontinued injections because they were cumbersome and inconvenient.[81]

Despite having a high degree of therapeutic efficacy (more than 85%), patients do not readily accept penile injections, and dropout rates in many series have exceeded 40%.[82] In evaluating the reasons for discontinuation, 10–20% stopped injections because of an unsatisfactory erection, 14% because of pain, 2–5% because of penile fibrosis and corporal plaque.[83]

Intraurethral alprostadil (MUSE)

MUSE represents an alternative method of delivering the PGE1 into erectile tissue. Through the medicated urethral system for erection, a pellet containing alprostadil is delivered into the male urethra, which is absorbed by the cavernosal tissue through vascular communications from the corpus spongiosum. Padma-Nathan *et al.*,[84] in 1997, reported that MUSE has an overall efficacy of 44%; however, this results were not consistent in subsequent series. Costabile *et al.*[85] later reported that the overall success rate with the MUSE was 40%. Major drawbacks with the intraurethral MUSE were urethral discomfort, low response rate and inconsistent efficacy.[86]

In reviewing our experience with MUSE in the post-prostatectomy patients, 55% (30/54) of the patients achieved and maintained erections sufficient for sexual intercourse while on MUSE and 48% (26/54) continued therapy on long term. A total of 28 patients (52%) discontinued treatment after a mean use of 8 ± 1.4 months. The reasons for discontinuation were insufficient erections ($n=16$), switching to other ED therapies ($n=4$), natural return of erections ($n=4$) and urethral pain and burning ($n=4$). Excluding the patients ($n=8$) who preferred other therapies and return of natural erections, the compliance to MUSE was 63%.[87]

MUSE provides an important alternative treatment option for the physicians, especially in patients after surgery not responding to oral therapy, not willing to opt for either injections, VCD, or not preferring implantation of penile prosthesis.

Oral medications

Introduction of sildenafil citrate and the other subsequent PDE-5 has revolutionized the treatment of ED after RP and have become the first treatment options after RP. PDE-5 inhibitors increase the cGMP concentration in the cavernosal muscle and produce smooth muscle relaxation. Due to the early release of sildenafil in 1998, this drug has been extensively investigated in our prostatectomy population.

Researchers at Cleveland Clinic have been among the front-runners to investigate the role of sildenafil in RP population. In our earlier experience, we found that 52% (48/91) of post-RP patients responded to sildenafil. Patients who underwent bilateral nerve-sparing surgery have a better response than patients who underwent unilateral or non-nerve-sparing surgery.[88] In a 3-year follow-up study, we re-evaluated the 43/48 patients who returned the questionnaire. Of 43 patients, 31 (72%) are still continuing to use sildenafil. This study indicated that most patients who initially responded to sildenafil continued to use the drug on a long-term basis.[89]

We also evaluated the factors affecting the efficacy of sildenafil citrate, which are predictors of satisfactory outcome of sildenafil citrate treatment for ED following RP. Four factors were identified to have significant association with successful outcome: the presence of at least one neurovascular bundle, preoperative SHIM (IIEF-5) score $\geqslant 15$, age $\leqslant 65$ years, and interval from RP to drug use >6 months ($P<0.001$).[90] Currently, the only contraindication to the use of sildenafil is the use of nitroglycerine or nitrate-containing compounds, which may cause hypotension. The most common side effects of the drug were transient headaches (24%), flushing (14.5%), dizziness (8.6%), dyspepsia (5.6%) and nasal congestion (3%). However, only 5% discontinued because of these side effects.

Recently, two new PDE-5 inhibitors have been approved for the treatment of ED. Tadalafil and vardenafil are two newly approved PDE-5 inhibitors that have shown to be effective for the treatment of ED. Tadalafil (Cialis) is shown to be safe and well tolerated. The drug significantly improved erectile function and was well tolerated at the 10- and 20-mg dose. Padma-Nathan *et al.*[91] reported that on-demand Cialis has significantly improved the erectile function compared to the placebo in general population. Recently, Montorsi *et al.*,[92] in 2004, conducted a randomized, double-blind, placebo-controlled multi-center study that included 303 men (mean age 60 years) with normal preoperative erectile function who had undergone a bilateral NS RP. The interval between the surgery and initiation of tadalafil varied from 12 to 48 months. The patients were randomized (2:1) to tadalafil ($n=201$) or placebo ($n=102$). Patients receiving tadalafil reported greater improvement in all primary and secondary end points ($P<0.001$) compared to the placebo group. Patients randomized to tadalafil group also reported a significant improvement in the mean IIEF erectile function domain score ($P<0.001$) vs placebo. For all randomized

patients who received tadalafil, the mean percentage of successful penetration attempts was 54% and the mean percentage of successful intercourse to completion was 41%. In a subgroup of patients who showed some postoperative tumescence, these values increased to 69 and 52%, respectively. The most commonly reported side effects included headaches (21%), dyspepsia (13%) and myalgia (7%). This large randomized controlled trial demonstrated that tadalafil is efficacious and well tolerated in post-RP patients.

The other new PDE-5 inhibitor, vardenafil (Levitra), has been tested as well in patients with ED following RP. Brock *et al.*[93] reported the results of a multicenter, placebo-controlled, randomized study. In this study, the average intercourse success rate per patient receiving 20 mg vardenafil was 74% in men with mild to moderate ED and 28% in men with severe ED, compared to 49 and 4% for placebo, respectively. Adverse effects reported were mild to moderate headache, flushing and rhinitis. This study similarly demonstrated that vardenafil was efficacious and well tolerated in the RP population and it reported to improve all the key indices of erectile function.

Our center was the first to conduct a prospective study comparing the efficacy and side effects of all the three oral PDE-5 inhibitors (sildenafil, vardenafil and tadalafil).[94] In this prospective study, 23 men with ED after nerve-sparing RP who had responded to 100 mg of sildenafil were given 20 mg tadalafil for 5 weeks, then 20 mg vardenafil for 5 weeks. After 5 weeks of each PDE-5 inhibitor treatment, patients had 1-week PDE-5 inhibitor free period. In all, 20 patients completed 20 mg of tadalafil for 5 weeks and 13 patients completed 20 mg of vardenafil for 5 weeks. An additional 10 patients completed both 20 mg of tadalafil for 5 weeks and 20 mg of vardenafil for 5 weeks. After 5 weeks of each PDE-5 inhibitor, patients were asked to complete the SHIM questionnaire, rigidity score, side effect profile, specifying frequency, duration and severity. Of the 23 patients, 20/23 (87%) patients completed 20 mg of tadalafil for 5 weeks, but 3/23 (13%) patients discontinued use of tadalafil due to side effects. Overall, the mean SHIM score for the tadalafil group ($n = 20$) was 18.7. This score compared favorably with the sildenafil group ($n = 20$), which has an SHIM score of 19.85. In comparing individual SHIM scores between the two drugs, 12/20 had similar scores, 6/20 had higher SHIM scores with sildenafil and 2/20 had higher SHIM scores with tadalafil. When the rigidity score results were added to the SHIM, 8/12 patients who previously had equal SHIM scores now have scores that reflected one drug more efficacious (six – sildenafil, two – tadalafil), and only four patients had equal scores.

Of the 23 patients, 13/23 (57%) patients completed 20 mg of vardenafil for 5 weeks without any discontinuation because of side effects, with a mean SHIM score for vardenafil of 19.53. This score compared favorably with sildenafil ($n = 13$) 19.85. In comparing individual SHIM scores, 9/13 had equal SHIM scores, 2/13 had greater sildenafil SHIM scores and 2/13 had greater vardenafil scores. After adding the rigidity score results to the SHIM score, four of the nine patients showed one drug more efficacious than the other (two – sildenafil, two – vardenafil), which was consistent with the patients' choice of most potent medication.

In all, 10 patients completed both 20 mg of tadalafil for 5 weeks and 20 mg of vardenafil for 5 weeks. The SHIM scores for these 10 patients compared favorably with that of sildenafil 20.3 (mean SHIM scores for tadalafil 18.2; and vardenafil19.9)

Based on SHIM scores, sildenafil, tadalafil and vardenafil are equally efficacious treatments in patients with ED following nerve-sparing RP. The mean SHIM scores for all the three drugs did not significantly differ among the users. We found that the side effects determined the choice of PDE-5 inhibitors in 60% of patients, and efficacy determined the choice in the remaining 40% of patients. The inclusion of rigidity question has shown that sildenafil produces more rigid erections compared to the other two oral PDE-5 inhibitors. Future randomized double-blind trials alternating the usage of the drugs would be required to answer this question. However, it appears that the individual selection of the best drug will vary with each individual, based on its efficacy and side effects.

Early penile rehabilitation

Introduction

The introduction of prostate screening programs, which include annual digital rectal examinations and PSAs, has led to earlier detection of most prostate malignancies. Earlier detection has significantly improved cancer cure, allowing us to redirect our focus towards quality of life issues. It has become apparent that erectile function is a significant problem following RP. Currently, potency rates range between 30 and 60% in the reported literature. Potency rates from the experienced surgeons would indicate that, even after a considerable volume of experience, ED following nerve injury is a major problem.

Urologists have been the pioneers in recognizing the impact of radical pelvic surgery on sexual dysfunction. Multiple authors have reported their techniques on nerve-sparing RP from the retropubic, perineal or laparoscopic approach. These reports have provided the stimulus for the other surgical fields to perform the nerve-sparing technique. In the world of colorectal surgeries, exciting new techniques for the treatment of rectal cancer has evolved like autonomic nerve preservation with TME. The

concept of sexual dysfunction is evolving in the field of radical and as well as simple hysterectomies also. More urologists performing transvaginal sling procedures are recognizing female sexual dysfunction as an important issue. The concept of nerve-sparing surgery will soon be followed in radical and simple hysterectomy as well. These other disciplines will soon discover what urologists have learned, that despite anatomical nerve sparing there is still dysfunction due to the period of neuropraxia.

When analyzing potency rates following RP, it would appear that our focus should be into the rehabilitation and nerve recovery rather than looking for the further advances in the surgical technique. Urologists have led the way into early rehabilitation programs to promote the nerve recovery and nerve regeneration. These programs will soon evolve into other disciplines that are performing pelvic surgeries. Performing anatomical nerve-sparing procedures rarely guarantees immediate postoperative recovery of potency. So the other disciplines will soon develop early rehabilitation programs. We will discuss our experience with various early programs intended to shorten the period of neuropraxia after RP.

Role of oral medications in early penile rehabilitation

There is a growing interest among urologists regarding the early use of daily oral sildenafil. This was first reported by Padma-Nathan *et al.*,[95] who conducted a randomized controlled study in 76 men (oral sildenafil daily (50 mg, $n=23$; 100 mg, $n=28$), placebo = 25) who underwent nerve-sparing RP with normal preoperative erectile function. Sildenafil was given for 36 weeks in the study group. After 48 weeks (~11 months) follow-up, 14 of 51 (27%) patients receiving sildenafil demonstrated return of spontaneous erections compared to one of 25 (4%) in the placebo group. This study revealed that oral daily sildenafil increased the return of erections to seven-folds compared with placebo group and was well tolerated. However, this study has been criticized because the return of spontaneous erections in the placebo group was only 4%, which is very low compared to the other reported series in the literature. Further multicenter randomized studies are ongoing to investigate the potential benefit of daily sildenafil following radical RP.

Early MUSE

We recently completed a prospective nonrandomized study on the use of early MUSE after RP at the Cleveland Clinic Foundation. To our knowledge, this is the only report in literature. We included a total of 91 patients. Of the 91 patients, 56 received early MUSE and 35 (Control group) did not receive any early treatment. Patients in the early MUSE group received 125 μg 3 times/week for the first 6 weeks. At 6 weeks, the MUSE dose was titrated to 250 μg, 3 times/week for 4 months. Patients who could not tolerate the 250 μg doses remained at 125 μg for 4 months. Treatment efficacy was analyzed by the patient's response to the Sexual Health Inventory of Men (SHIM) questionnaire. In the MUSE Group, 38/56 (68%) continued MUSE treatment. At 6 months, 28/38 (74%) of the patients resumed sexual activity, 15/28 (53%) had natural erections sufficient for vaginal penetration without MUSE and 13/28 (47%) continue to use MUSE as an adjuvant treatment for successful intercourse. Overall, including those who discontinued MUSE, at 6 months 27% (15/56) achieved natural erections sufficient for sexual intercourse. The MUSE discontinuation rate was 32% (18/56). Nine of the 18 (50%) discontinued because of inadequate erections, five (28%) due to loss of sexual interest and four (22%) due to local pain/burning. In the Control Group, 13/35 (37%) resumed sexual activity, 4/13 (30.7%) had natural erections sufficient for vaginal penetration, 9/13 (69.3%) were dissatisfied with the erections and used oral therapy/erectaids as adjuvant treatments. Overall, in the control group 11% (4/35) at 6 months achieved natural erections sufficient for satisfactory sexual intercourse.

In our experience, early MUSE therapy following RP increased the frequency of sexual activity, increased the incidence of spontaneous erections sufficient for intercourse and appeared to shorten the neuropraxia period.

Early VCD

We recently completed a prospective nonrandomized study on the use of early VCD after RP at the Cleveland Clinic, which included 109 patients who underwent RP between August 1999 and October 2001.[96] Of the 109 patients, 74 (Group 1) patients used early VCD daily for 9 months and 35 observed without any erectogenic treatment (Group 2). Treatment efficacy was analyzed by responses to the SHIM. Patient outcome regarding the compliance changes in the penile length and circumference, return of natural erection and ability for vaginal intercourse was also assessed. After a minimum follow-up of 9 months, 80% (60/74) in Group 1 successfully used their VCD with a constriction ring for vaginal intercourse at a frequency of twice per week, with an overall spousal satisfaction rate of 55% (33/60). Of these 60 patients, 19 (32%) reported return of natural erections at 9 months, with 10/19 (52%) having erections sufficient for sexual intercourse. The abridged IIEF-5 score significantly increased after VCD use in both the NS and NNS groups. After a mean use of 3 months, 14/74 (18%) discontinued treatment. Overall, in the early VCD group, 14% (10/74) had natural erections sufficient for sexual intercourse.

In Group 2, 37% (13/35) of patients regained spontaneous erections at a minimum follow-up of 9 months after surgery. However, only four of these patients (29%) had erections sufficient for successful vaginal intercourse and the rest of the patients (71%) sought adjuvant treatment. Overall, in the control group at 9 months, 11% (4/35) achieved natural erections sufficient for satisfactory sexual intercourse. Note that 11% vaginal intercourse rates were identical in both the Group 1 and 2.

Interestingly, when assessing the penile length and girth after surgery, of the 60 compliant patients, only 14 (23%) reported a decrease in penile length and girth at 9 months (range, 4–11 months), with 12/14 (85%) noncompliant patients complaining of decrease in penile length and girth. In the control group, 22/35 (63%) reported decrease in penile length and circumference, demonstrating that routine early use of the VCD helps in preventing the decrease in penile length and circumference.

We concluded that early use of VCD following RP facilitates early sexual intercourse, early patient/spousal sexual satisfaction, potentially an earlier return of natural erections sufficient for vaginal penetration and preservation of penile length and girth.

Early injections

Montorsi *et al.*[97] from Milan, Italy, first reported their experience using intracavernous injections in 1997. Of the total 30 patients who underwent nerve-sparing RP, 15 were randomized into Group 1 (alprostadil injections 3 times/week for 12 weeks) and another 15 patients were randomized into Group 2 (observation without erectaids). The dose of PGE1 varies from 4 to 14 μg, with a mean dose of 8 μg. At 6 months, 67% of the patients in the injection group reported to have return of spontaneous erections sufficient for satisfactory intercourse compared to 20% in the observation group. We initiated a similar study in 2001 with a dose of 10 μg PGE1 at the Cleveland Clinic Foundation. Of the eight patients, six discontinued because of pain, which prompted us to discontinue our early PGE1 program 3 years ago.

Recently, we wanted to re-examine the role of early intracorporeal injections, with lower dose of PGE1 (4 μg/2–3 times/week) starting at 2 weeks after RP, combined with oral sildenafil (50 mg/day). We reduced the injection dose to 4 μg, to get partial erections with minimal, if any, pain. Our goal was to have a compliance of more than 90%. Further modifications have been made according to the tolerance of patient and response; the dose of PGE1 was reduced to 2 μg in some patients with the same response to minimize the adverse effects and maximize the compliance. We included a total of 18 patients in this study. Of the total 18 patients, 16 were using injections with Viagra and two were using daily sildenafil alone. Of the total 16 patients, two increased the dose up to 8 μg without any pain (one having mild discomfort), six patients continuing the same dose of 4 μg and the rest of the patients decreased the dose. Of the eight patients who decreased the dose, six are using 2 μg dose and two patients further reduced the dose to 1 μg. Patients who were not willing for the injections given daily 50 mg oral sildenafil alone. Two patients were started only on Viagra. We are currently investigating the role of injections and oral sildenafil in patients who underwent nerve-sparing RC also. We included two patients in the study. Until now, the compliance with this program is 100%. After a mean follow-up of 10 weeks (4–18 weeks), 15/16 patients were sexually active. One patient sexually inactive due to incontinence. Our early data revealed that lower doses of IC PGE1 (4, 2 and 1 μg) with sildenafil was as effective as high doses of PGE1 alone (8 μg), without any penile discomfort (Table 4). The reasons for these high compliance rates are good counseling and follow-up by the physician and proper dose modification according to the patient's desire and side effects. Early injection facilitated early sexual intercourse, patient and spousal satisfaction.

Table 4 Preliminary data of early injection study

Drug injections	*Dose*	*No. of patients*	*Rigidity*	*Adverse effects*	*Natural erections*	*Sexually active* (n = 15)		
	PGE1 (μg)			*Discomfort* (n)	*Partial*	*Injections alone* (n)	*Injections + sildenafil* (n)	*Viagra alone* (n)
PGE1 (μg) + sildenafil	8	2	>80	1	1	1	0	0
	4	6	70–90	1	1	4	2	0
	2	6	70	0	1	0	6	0
	1	2	70	0	0	0	2	0
Sildenafil alone (50 mg/day)		2		0	0	0	0	0
Total		18		2	3	5	10	0

Rigidity was assessed on a visual analogue scale of 1–100, PGE1 = prostaglandin E1. Natural erections were defined as any spontaneous erections or nocturnal erections.

Future directions

Cavernous nerve reconstruction

Cavernosal nerve reconstruction using genitofemoral or sural nerve has generated a considerable interest in an attempt to preserve the erectile function. The indications for reconstruction in the current-day practice are relatively few and are used mostly in young patients undergoing non-nerve-sparing surgery for advanced disease. Quinlan *et al.*,[98] in 1991, first performed cavernous nerve reconstruction using genitofemoral nerve in a rat model.

This genitofemoral nerve reconstruction was subsequently used in humans by Walsh.[99] Recently, Kim *et al.*,[100] in 2001, using sural nerve grafts, reported that 26% (6/28) of men who underwent bilateral sural nerve grafting had regained spontaneous erections sufficient for intercourse, with a total SHIM score of 20. These results were supported by Anastasiadis *et al.*,[101] who reported that 33% (4/12) regained spontaneous erections sufficient for intercourse, with a total SHIM score of 20. Currently, the largest group advocating sural nerve grafting is from the Memorial of Sloan Kettering Cancer Centre, who continues to refine the technique of sural nerve grafting as well as intra-operative nerve testing with Cavermap system. Sural nerve grafting has not been widely adopted among the centers of excellence may be due to technical difficulties in harvesting the nerve graft and coordination required between plastic surgeons to perform the sural nerve grafts.

Whether the technique of cavernous reconstruction is necessary in every surgeon's arnamentarium remains to be seen. In our experience, most aggressive high-volume tumors can be excised using either the unilateral or the bilateral technique of partial neurectomy, without complete excision of neurovascular bundle.

Neuroprotective agents

Recently, there has been considerable interest generated in neuroprotective and neurotrophic interventions to restore cavernous nerve function in the face of nerve injury. Early consideration has been given to using the neurotrophic growth factors (nerve growth factor and fibroblast growth factor) with combination of nerve grafts. As the field of therapeutic neurogenesis continues to evolve, the focus has shifted towards the immunophilin, a receptor protein, which has been shown to exert diverse neural functions, including the regulation of nitric oxide. Immunophilin is a receptor protein for immunosuppressants like FK 506 and cyclosporin; so the main prospective is now shifted to the stimulation of immunophilin by administering the FK 506. Lee *et al.*,[102] in 2000, reported that FK 506 promotes both the nerve regeneration and functional recovery on rats with tibial nerve damage. Sezen *et al.*[103] from John Hopkins Hospital, in 2002, studied the effect of systemically administered FK 506 on rats with cavernous nerve injury. They reported that receptor protein for FK 506 was upregulated immediately after the injury. They failed to demonstrate any further advantage of FK 506 in animal models. However, these initial studies from Dr Arthur Burnett's laboratory have generated a new area of interest in the field of nerve recovery and nerve regeneration.

Recently, the role of vascular growth factors in promoting the regrowth of damaged cavernous nerves and return of erectile function has been investigated in animal models at the University of California by Lue and colleagues.[104,105] Lin *et al.*[104] from the same laboratory demonstrated that intracavernous administration of vascular endothelial growth factors (VEGF) facilitates the recovery of nitric oxide synthase genes, which may promote the earlier recovery of sexual function. Lee *et al.*[105] from the same group later reported that IC injection of VEGF increases the recovery of erectile function in the rat models. Lue and associates[104,105] are currently formulating a prospective human trial to investigate the role of IC injection of VEGF administered at the time of RP in facilitating an early return of erectile function.

Nitric oxide synthase donors

In 2000, Burnett *et al.*[106] illustrated that viral vectors can be injected into cavernosal bodies to rejuvenate the stem cells in an attempt to increase the endothelial nitric oxide synthase activity. This laboratory research is exciting because it can be used to regenerate any form of endothelial damage. Whether the stem cells can be rejuvenated with this technology remains to be seen; however, this offers an exciting model for the future research.

Recently, the area of interest is shifted to nitric oxide donors, drugs that increase the nitric oxide synthesis in the cavernosal bodies. Fillippi *et al.*,[107] in 2003, investigated the effects of NCX 4050 (a drug belonging to a new class of NO donors) on isolated preparations of human and rabbit corpus cavernosum. They reported that NCX 4050 increase the guanyl cyclase activity and produce the smooth muscle relaxation in both human and rabbit cavernosal model. Recently, Kalsi *et al.*[108] reported that NCX 911, a nitric-oxide-releasing PDE-5 inhibitor, produces the relaxation of cavernosal smooth muscle by increasing the endogenous NO. These two agents may be promising future options for patients with impaired NO release from the endothelium. However, the efficacy of these agents needs to be confirmed in human-based studies.

Female sexual dysfunction

Recognition and appreciation of female sexual dysfunction is currently evolving, thus treatments

have not been universally sought. However, in subspecialized circles, treatment for FSD is becoming routine. Numerous medications are available for the treatment of FSD, including hormones and vasoactive drugs. However, no single treatment has been proven to be effective.

Currently available treatment options include estrogens, androgens, PDE inhibitors and dopamine receptor antagonists. Women suffering from a lack of sexual desire are probably more responsive to androgens, estrogens and dopamine receptor antagonists, whereas those with sexual arousal disorder may be more responsive to PDE inhibitors and prostaglandins.[109] Estrogens have been the mainstay treatment for FSD; they have been shown to improve the clitoral and vaginal sensitivity, vaginal lubrication and also sexual desire.[110] Androgens have been used in the treatment of FSD because of the assumption that FSD is an androgen-deficiency disease. Testosterone has been shown to increase the clitoral sensitivity and sexual arousal.[111]

The role of PDE-5 inhibitors in female sexual dysfunction is still unclear. Earlier industrial supported research failed to demonstrate a benefit in female sexual dysfunction following the use of PDE-5 inhibitors. Unfortunately, these studies included patients from all various etiologies and not evaluated fair physiologic outcome response. Our early data in treating post-cystectomy patients with severe organic dysfunction would suggest that these agents add to improve clitoral sensation and vaginal lubrication. Our data are consistent with the literature, which show increase in sensation.[112] Obviously, further trials are essential to assess the effectiveness of PDE-5 inhibitors in specific stratified subgroups of FSD.

On the horizon, we will continue to see the progressive investigations to use multimodality treatment to treat FSD. These treatments include systemic estrogens and androgens to increase libido and vaginal estrogens and PDE-5 inhibitors to increase the local vaginal lubrication and arousal. Despite the multiple treatment variables, we still need to quantitate the success of these multimodality treatments with validated questionnaire.

Summary

Sexual dysfunction is a prevalent problem following major pelvic surgeries. In sexually active patients, this frequent complication and the treatment must be thoroughly addressed prior to surgery. Currently, we have several options available for the treatment of ED. Oral therapy using PDE-5 inhibitors (sildenafil, vardenafil and tadalafil) has been shown to have good compliance; however, lack of efficacy resulted in considerable attrition. Unless there is a functioning nerve tissue to stimulate nitric oxide release, none of the PDE-5 inhibitors will be effective. Our early treatment options include intraurethral alprostadil (MUSE), VCD and IC injections. Our data support the concept that all three of these early nonoral options promote frequent sexual activity in the first year, in which neuropraxia exists. Only early pharmacological stimulation appears to improve the return of natural erections and shorten the period of neuropraxia. The early penile rehabilitation following RP facilitates early sexual intercourse, early patient/spousal sexual satisfaction, potentially an earlier return of natural erections sufficient for vaginal penetration.

In the future, as screening programs continue to detect malignancies at an earlier stage, the enthusiasm for quality of life, such as erectile function, will continue. This will help lead us into the next decade of treatments. Soon, there will be a greater knowledge on the use of neuroprotective agents for the corpora cavernosum and the use of intracorporeal vectors that can replace damaged endothelial cells and promote the nitric oxide synthesis. The understanding of nerve injury and nerve regeneration and its treatments will be an exciting research area in the next decade, since these early penile rehabilitation programs may supercede any further technical advancements.

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