Objectives

• Review the anatomy/physiology of normal erectile and continence mechanisms.

• Discuss factors that influence outcomes post-operatively.

• Discuss post-operative protocols for more rapid restoration of urinary continence.

• Discuss pre- and post- operative protocols for penile rehabilitation/erectile preservation.
Incidence of Prostate Cancer is on the Rise

2020 Estimates
Surgical Treatment of Prostate Cancer

Prostatectomies in the United States, 2000-2008

Post-radical prostatectomy expectations about sexual function unrealistic
Patient education about post-surgical outcomes is necessary

By: Mac Overmyer

Chicag—A significant number of patients undergoing open or robotic radical prostatectomy have unrealistic expectations regarding postoperative sexual function, according to a study from Weill Cornell Medical College, New York.

The study, presented here at the AUA annual meeting, found that many patients were unaware that the prostatectomy would lead to an inability to ejaculate, and “almost none understood that there are documented orgasm changes or that radical prostatectomy may be associated with Peyronie’s disease,” the authors wrote.

“I think there are many patients who just have false expectations going into their prostate surgery,” senior author John Mulhall, MD, who was an associate professor of urology at Weill Cornell at the time of the study, told Urology Times. “They think they are going to get back to the way they were before the operation. For a significant number of men, that is just not true. They are not going to ejaculate. There are patients who are going to have orgasmic dysfunction. There are penile length loss issues, and many appear to just not know that.”

The researchers posed 11 questions to 336 patients, 216 of whom had undergone open radical prostatectomy and 120 who had undergone the robotic procedure. The procedures were performed by nine different referring urologists.

Only 10% of the open procedure patients and 12% of the robot-assisted laparoscopic prostatectomy (RALP) patients said they knew that their orgasms would be different after their respective procedures. While 70% of the open surgery patients and 60% of the RALP patients understood that they would not ejaculate (produce semen) following the operation, only 2% of the RALP patients seemed to know that the procedure carried the risk that pain might accompany orgasm or that orgasm might be accompanied by urine leakage. None of the RALP patients seemed to be aware of these possible sequelae, and neither group knew that Peyronie’s disease was also a potential risk of the procedure.
Prostate Surgery and Urinary Incontinence
Post Prostatectomy Urinary Incontinence

- Common and costly- direct economic burden for UI from any cause in men ~ US$ 3.8 billion/year.

- Prevalence ranges from 8-56% at ≥ 1 year.

- Significant burden to patients- cost of pads, catheters, clamps, as well as lost productivity.

- Negative impact on sexual function.

MacDonald et. al. BJU 2007; 100: 76-81
Urinary Continence Mechanisms

Proximal Sphincter Unit: “The Complex of Santorini” - bladder neck, prostate, and prostatic urethra to the verumontanum.

Distal Sphincter Unit: rhabdosphincter, para-urethral skeletal musculature, and supporting fascial investments.
Musculo-Facial Support Mechanisms of the Urethral

**Puboprostatic Ligaments**
Support the external striated urethral sphincter and preserve the urethra in its normal place in the pelvic floor.

**External Urethral Sphincter**
Horseshoe or “omega” shaped with bulk of fibers anteriorly and connective tissue/elastic fibers dorsally. Contains outer striated and inner smooth muscle components. Slow and fast twitch fibers present.

**Prostatic Neurovascular Bundle**
Situated posterolaterally and symmetrically to the prostate. Enclosed within the layers of the periprostatic fascia.
Musculature of the Bladder Neck and Urethra

VS = vesical sphincter (B); la = levator ani; sp = Santorini plexus;
External Sphincter (C); X = smooth muscle of external sphincter;
* = striated part of external sphincter; • = urethral lumen
Anatomy of the Neurovascular Bundle

Factors That Influence Post-Operative Urinary Continence

- Age of patient - reduced elasticity of pelvic floor muscles, limited ability for nerve recruitment
- Functional Status/Medical Comorbidities
- Surgeon experience/surgical technique
- Implementation of a Pelvic Floor Muscle Training program post-operatively
Goals of Pelvic Floor Muscle Training

- Strengthening the pubococcygeus muscles of the pelvic floor (levator ani). May also strengthen ischiocavernosus and bulbospongiousus muscles
- Improve bulkiness of the muscles by provoking hypertrophy
- May decrease uninhibited bladder contractions
Types of PFMT Programs

- **Exercises** to strengthen pelvic floor muscles (*Kegel’s*)
- Physiotherapy with **biofeedback**
- Physiotherapy with rectal **electrical stimulation**
- “Other” advertised programs/devices
Four Phases in the Performance of PFM Exercises

- **Awareness** of function and coordination of the PFM’s.
- **Gains** in muscle identification, **control**, and **strength**.
- **Thickening**, broadening, and **bulking** of the muscles to increase **endurance**.
- **Realization of improvements** in symptoms indicating that the muscles are responding to therapy.
Examples of PFMT Routines

15 Minute Routine → focuses on 3 types of exercises:

1. **Quick Contractions**: to improve muscle recruitment and reflex
2. **Slow Intense Contractions**: to improve muscle strength/gain mass
3. **Slow Sustained Contractions**: to improve muscle endurance

- Instruct patient to exercise two-three times per day
- There should be 5-10 seconds of rest after each slow contraction
- Exercises can be performed in different positions- lying, standing, and sitting
- When performed along with other activities such as walking, may improve muscle endurance
- Contractions performed at terminal portion of voiding may help evacuate urine from bulb of the urethra
Benefits of Pelvic Floor Training

- Difficult to interpret data from published clinical trials due to significant differences in definitions of PPI, patient populations, surgical technique, post-surgical interventions, evaluation methods, and outcome measures.
  

- The general trend is reduction in continence recovery time with little difference in overall continence rates at 12 months post-operatively.
  

- No convincing data showing added benefit of combined PFMT and biofeedback/electrical stimulation.
  
  MacDonald et al. BJU Int 2007 Jan;100: 76-81

- A SB RCT published in the British Medical Journal simple exercises proved to be more effective than electro-stimulation in treatment of SUI.
  
  Bo et al. BJM 318; 20: 487-93
Estimated rate of climacturia in the literature varies between 45% and 93%.

Lee et al. - 45% of men post RRP had climacturia with a mean follow-up of 23.6 months. Of those 68% reported only rare or occasional leakage at orgasm while 21% reported that it occurred always or most of the time.

In approximately 50% of those who report climacturia - significant bother is present.

Mitchell et al J Urol 2011; 186: 982. - more than 10% of those with no SUI reported major bother from incontinence during sexual activity.

Of men with who undergo surgery for PPI (male sling or AUS), the overwhelming majority with marked bother due to incontinence during arousal and climax achieve significant improvement in sexual quality of life after the surgical procedure.
Post Prostatectomy Incontinence: Foreplay Incontinence

- *Guay and Seftel* identified urinary leakage in **38%** of men post-RRP occurring during kissing, hugging, or genital foreplay.

- All of the men reported bother associated with this problem.

- **25%** avoided sexual contact because of the incontinence.

- Use of a venous constriction band was found to be helpful in preventing incontinence episodes and subjectively led to greater sexual satisfaction.

*Guay and Seftel* IJIR 2008; 20: 199
So.....What is the “Best Practice Policy” for Treatment of PPI ??

- Difficult to set a standard as most studies show similar outcomes at 12-18 months post-operatively.

- Better surgical technique (BNS-RRP, anatomical restoration of rhabdosphincter) has resulted in shorter time interval to continence recovery.

- Patient expectation, motivation, participation, and compliance often determines what is best.
Post-Prostatectomy Erectile Dysfunction and Penile Rehabilitation

"I'm sure it's his heart ... none of his arteries get hard."
Anatomy of Penile Erection

Flaccid Penis

Erect Penis

Physiology of Penile Erection

Stimulus

- Nitric oxide (NO) released
- cGMP formation
- Vascular smooth muscle relaxation
- Influx of blood into sinusoids
Biochemistry of Penile Erection: cGMP

Penile/sexual stimulation

PNS (NANC nerve)

nNOS

NO

Penile vascular and cavernosal smooth muscle cell

Guanylate cyclase

↑cGMP

↓Ca²⁺

Smooth muscle relaxation in corpora cavernosa/dilation of blood vessels

Penile erection

cGMP = cyclic guanosine monophosphate.
NANC = nonadrenergic/noncholinergic.
NO = nitric oxide.
nNOS = nitric oxide synthase.
PNS = parasympathetic nervous system.

Biochemistry of Penile Erection: cAMP

Sexual stimulation

(PG synthesized by cavernosal smooth muscle cell)

PG

PK

↓Ca²⁺

↑cAMP

Smooth muscle relaxation in corpora cavernosa/dilation of blood vessels

Penile vascular and cavernosal smooth muscle cell

Penile erection

cAMP=cyclic adenosine monophosphate.
PG=prostaglandin.
PK=protein kinase.

Post-Prostatectomy ED: Introduction

• CaP is a leading form of cancer diagnosed in men over 50 years of age with more than 200,000 new detections annually in the USA. Approximately 25% of these patients will elect to undergo surgical treatment.

• Penson and Litwin in 2003 reported that sexual dysfunction was the most important quality of life issue 24 months from the time of primary CaP treatment.

• In a prospective cohort of 580 patients treated with RRP, EBRT, or brachytherapy for localized CaP, sexual bother was much more common than urinary or bowel bother at all time points, regardless of the primary therapy.

• Walsh and Donker(1982)-revolutionized RRP by delineating the periprostatic anatomy and by performing the nerve-sparing technique.

• Reported potency rates post-RRP in centers of excellence= 70-86%. In community Urologists= 21-50%, even after bilateral NSS.

Post-Prostatectomy ED Causes: Impairment in Cavernosal Oxygenation

- Goldstein et al. in 1982 first reported the role of cavernosal smooth muscle in normal erections.

- *Azadzoi et al. J Urol 1995; 153:2* - utilizing a canine model, showed that sub-tunical oxygen tension in the flaccid penis was close to 100 mmHg, consistent with predominantly arterial circulation, whereas deep cavernosal oxygen tension measurements showed values consistent with venous blood flow.

- Normal smooth muscle content and function are essential in initiation and maintenance of erection. + correlation between SM content and intra-cavernous pO2 levels. *(Sattar et al. J Urol 1995; 154:1736)*

- Integrity and function of smooth muscle is dependant on tissue oxygenation. Venous pO2- favors secretion of inflammatory cytokines (TNF-β). Oxygenation favors production of endogenous prostanoids (PGE-1) which, in turn, shuts off fibrogenic cytokine production. *(Moreland et al. IJIR 1995; 10:113)*

- Loss of spontaneous erections/NPT  
  Persistent flaccid state  
  Persistent hypoxia  
  Changes in structure/function of corpora cavernosa
Post-Prostatectomy ED Causes: Changes in Cavernous Nerve Input

- In rat model- bilateral CNI led to decreased NO-synthase staining as early as 3 weeks after injury. (Carrier et al. J Urol 1995; 153:1722)

- Increased apoptosis in corporal SM after cavernous nerve injury. (Klein et al. J Urol 1997; 158:626)

- Decreased penile wet weight and DNA content in models of both unilateral and bilateral CNI- the later group had greater changes. (User et al. J Urol 2003; 169:1175)

- Cavernous neurotomy leads to up-regulation of fibrogenic cytokines and collagenization of corporal SM. (Leungwattanaki et al. J Androl 2003; 24:239)

- "Competitive Sprouting" (sympathetic hyper-innervation) – concept that when autonomic nerves are injured, sympathetic fibers are biologically primed to recuperate from injury and regenerate more quickly, resulting in unantagonized sympathetic tone in the end organ. (Zhou et al. Circ Res 2004; 95:76)
Post-Prostatectomy ED Causes: Changes in Corpora Cavernosa

- In both animal and human models damage to cavernous nerves results in apoptosis of smooth muscle cells.

- Penile hypoxia → induction of TGF-β1 → increased collagen synthesis → increased synthesis of endothelin-1.

- Hypoxia → increased deposition of connective tissue (fibrosis) → decreased penile distensibility → veno-occlusive dysfunction → ED.

- *Mulhall et al. J Urol 2002* showed that the incidence of venous leak increased with the post-op time interval. (14% at 4 months, increased to 35% between 9 and 12 months.)
Post-Prostatectomy ED: Negative Outcomes

- Decreased quality/quantity of spontaneous and nocturnal erections decreased spontaneous sexual activity relationship stress.
- Decreased tissue responsiveness to PDE5’s.
- Changes in length/volume of the penis.
Do Men Really Lose Length/Girth Post RRP ??

• **McCullough et al. Mol Urol 1999** – studied 100 men post-RRP. Preoperative and post-operative flaccid and erect measurements taken. Demonstrated an overall mean reduction of 9% in erect penile length and reduction of 22% in volume.

• **Munding et al. Urol 2001** - studied 31 men pre- and post-RRP. Showed that 71% of patients had a decrease in penile length compared to baseline with 48% of men demonstrating a > 1 cm loss with a range of loss between 0.5 cm and 4cm.

• **Gontero et al. J Urol 2007** - Penile length/girth continues to decrease for at least 1 year post-RRP with a maximum degree of shortening occurring at the time of catheter removal.
Factors Influencing Penile Length, Girth, and Volume

- Cavernous nerve injury-associated structural alterations → SM apoptosis.
- Cavernous hypoxia-induced structural changes → Corporal fibrosis.
- “Competitive spouting” → Sympathetic hyper-innervation.

Nerve-sparing surgery and earlier recovery of erectile function have been shown to have an independent protective effect on loss of penile length.

Post RRP Peyronie’s Disease

- Medical News Today (June 2008), reported on a retrospective review of 589 men who had their prostate cancer treated by a RP. Of these men, 102/589 developed PD for an incidence rate of 17%. Mean curvature was 32 degrees. No mention was made if they were measured for loss of penile dimensions.

- Tal et al. JSM 2010; 7: 1254- retrospective review of 1011 subjects who underwent RRP. PD incidence = 15.9%.
  - Mean time to develop PD after RRP was 13.9 ± 0.7 months.
  - Mean curvature magnitude was 31 ± 17 degrees
  - 77 men developed PD within 1 year post-RRP, 139 within 2 years, and 161 within 3 years.

- Weill Cornell Medical College Study Presented at 2009 AUA- looked at patient expectations post-RRP. No patients were aware that PD is a potential risk of the procedure.
MEGAN FOX
God's cure for Erectile Dysfunction
Penile Rehabilitation: *What is it??*

Development of a structured program to improve penile healing and preserve erectile tissue health.

**GOALS**

- Promote early return of *erection*- either natural “spontaneous” or in response to oral medications.
- Improve cavernous *oxygenation* which may help reduce fibrosis and apoptosis.
- Prevention of penile *size* reduction.

*Therapy must be individualized to optimize cost and compliance.*
Oral Medications and Penile Rehab


- Cavernosal biopsy showed significant *smooth muscle preservation* (decreased apoptosis) 6 months post-RRP in men taking Sildenafil 50mg every other night and *improved SM content* in men taking Sildenafil 100mg every other night. (Schwartz et al. J Urol 2004; 171:771)

- Animal models suggest *enhanced endothelium dependant relaxation* of cavernous SM after chronic treatment with PDE5’s. Also, *erectile response enhanced* with acute sildenafil when chronically treated with sildenafil. (Behr-Roussel et al. Eur Urol 2005; 47:87)

- In a randomized prospective study of 76 men with normal preoperative sexual function who underwent NS-RRP, sildenafil 50 or 100mg (or placebo) was given for 36 weeks. At the time of follow-up (≈ 11 months) 27% of the patients receiving sildenafil had natural erections sufficient for intercourse compared to 4% in the placebo group. (Padma-Nathan et al. J Urol 2003; 169:375)
Intra-Urethral Alprostadil [Muse®] and Penile Rehab

- IUA shown to be effective in men post-RRP regardless of nerve status. *(Costabile et al. J Urol 1998; 160:1324)*

- IUA shown to arterialize blood in the penis even at small doses (125 mcg/m) despite creating a sub-erectile state. At 250mcg IUA arterialized the penis at a level comparable to ICI. *(Lepor et al. Unpublished data)*

- IUA more efficacious than sildenafil in increasing flaccid corporal oximetry post NS-RRP (250 mcg/m vs. 50 mg). *(McCollough et al. J Urol 2009; 181:525)*

- IUA in combination with sildenafil has been shown to be effective in salvage of PDE5 non-responders following NS-RRP. *(Raina et al. J Androl 2005; 26:757)*
Montorsi et al. (1997)- postulated that early use of alprostadil post-RRP would lead to increased corporal oxygenation. 30 patients randomized to ICI vs. no therapy for 12 weeks. At 6 months 67% of patients in the ICI group and 20% in the observational group reported return of spontaneous erections sufficient for intercourse.

In a study of post-RRP patients (N=132), penile rehab with ICI vs. no rehab was shown to improve recovery of spontaneous functional erections (52% vs. 19%), sildenafil response (64% vs. 24%), and ICI response (95% vs. 76%). (Mulhall et al. J Sex Med 2005; 2:532)

Earlier return to spontaneous sexual activity may have physiological and psychological benefits.
Vacuum Erection Device

We just want to pump you up !!
The first known description of vacuum therapy was published in 1871 in the American Family Physician Domestic Guide To Health -written by John King, MD.

Dr. King wrote, "When there is impotency, with a diminution in the size of the male organ, the organ should be shampooed every day, and a liniment applied to it and the neighboring parts..." "In addition to this the glass exhauster should be carefully applied to the part, once every day. The glass exhauster is a cylindrical glass tube, about nine inches in length, and two inches in diameter; one end is open, the other is fitted with a nipple for a small exhausting pump to be placed upon, the same as in a cupping glass. The male organ being placed in this glass, the air is exhausted, the blood fills the vessels of the part, and thus excites a new action.

Great care must be taken not to exhaust the air too rapidly or to too great a degree, as injury to the parts would follow."
Vacuum Therapy and Penile Rehab

- In the rat model VED therapy post BCNC was shown to significantly increase ICP/MAP ratios, reduce penile shortening, reduce changes in penile girth, reduce TGF-β1/collagen/apoptosis, and increase SM actin and eNOS. (Yuan and Wang J Urol 183; s4:344)

- Early VED use may encourage early return to sexual activity and sexual interest in patients post RRP. (Zippe et al. Abstract presented at North Central AUA 2001)

- In one study 28 men where followed for 6 months post-RRP: those randomized to daily VED use had higher SHIM scores at 6 months and no significant change in stretched flaccid length. Controls (no VED) had mean loss of length of 2cm. (Kohler et al. BJU Int 2007; 100:858)
"Neutraceuticals" and Penile Rehab

- L-Arginine is the substrate for NO production. Supplementation may increase NO bioavailability ?? May improve endothelium-dependant NO-mediated vasodilation.

- May improve effectiveness of oral PDE5’s when used in combination.

- May inhibit Rho-kinase ??

- In Rat model- shown to reverse age-related decline in erectile response (Moody et al. J Urol 1997; 158)
L-arginine and phosphodiesterase (PDE) inhibitors counteract fibrosis in the Peyronie's fibrotic plaque and related fibroblast cultures.

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Abstract

Inducible nitric oxide synthase (iNOS) is expressed in both the fibrotic plaque of Peyronie's disease (PD) in the human, and in the PD-like plaque elicited by injection of TGFbeta1 into the penile tunica albuginea (TA) of the rat. Long-term inhibition of iNOS activity, presumably by blocking nitric oxide (NO)- and cGMP-mediated effects triggered by iNOS expression, exacerbates tissue fibrosis through an increase in: (a) collagen synthesis, (b) levels of reactive oxygen species (ROS), and (c) the differentiation of fibroblasts into myofibroblasts. We have now investigated whether: (a) phosphodiesterase (PDE) isoforms, that regulate the interplay of cGMP and cAMP pathways, are expressed in both the human and rat TA; and (b) L-arginine, that stimulates NOS activity and hence NO synthesis, and PDE inhibitors, that increase the levels of cGMP and/or cAMP, can inhibit collagen synthesis and induce fibroblast/myofibroblast apoptosis, thus acting as antifibrotic agents.

We have found by immunohistochemistry, RT/PCR, and Western blot that PDE5A-3 and PDE4A, B, and D variants are indeed expressed in human and rat normal TA and PD plaque tissue, as well as in their respective fibroblast cultures. As expected, in the PD fibroblast cultures, pentoxifylline (non-specific cAMP-PDE inhibitor) increased cAMP levels without affecting cGMP levels, whereas sildenafil (PDE5A inhibitor) raised cGMP levels. Both agents and L-arginine reduced the expression of collagen I (but not collagen III) and the myofibroblast marker, alpha-smooth muscle actin, as determined by immunocytochemistry and quantitative image analysis. These effects were mimicked by incubation with 8-Br-cGMP, which in addition increased apoptosis, as measured by TUNEL. When L-arginine (2.25 g/kg/day), pentoxifylline (10 mg/kg/day), or sildenafil (10 mg/kg/day) was given individually in the drinking water for 45 days to rats with a PD-like plaque induced by TGF beta1, each treatment resulted in a 80-95% reduction in both plaque size and in the collagen/fibroblast ratio, as determined by Masson trichrome staining. Both sildenafil and pentoxifylline stimulated fibroblast apoptosis within the TA.

Our results support the hypothesis that the increase in NO and/or cGMP/cAMP levels by long-term administration of nitricergic agents or inhibitors of PDE, may be effective in reversing the fibrosis of PD, and more speculatively, other fibrotic conditions.
Protocols for Post-Prostatectomy
Penile Rehab

■ 2-4 WEEKS PRIOR TO SURGERY (if possible)
  - Assessment questionnaires (IIEF, AMS, SEP, EPIC, IPSS).
  - ED Risk Assessment.
  - Patient/Partner Counseling (discuss basics of rehab, medications, VED).
  - Begin prophylactic therapy with PDE5’s.

■ 10-14 DAYS AFTER SURGERY
  - Foley catheter is removed.
  - Medical Therapy is typically started (2g/day L-Arginine, nightly PDE5, IUA (125-250 mcg/3x weekly, Vacuum therapy 20 minutes/day).

■ ONE MONTH AFTER SURGERY
  - Continue medical therapy as previously directed.
  - Start utilizing PDE5’s prior to intercourse (PDE5 challenge).
  - IUA titration/challenge.
  - Combo therapy prior to intercourse (PDE + IUA, PDE + VED)

■ THREE MONTHS AFTER SURGERY
  - Consider penile injection therapy 2-3x/week if previously used medications not effective.
  - Re-challenge with PDE5 q 2 months.
When To Consider an IPP

- In patients who do not appropriately respond to medications.
- In patients who cannot use medications/VED due to medical co-morbidities and/or functional limitations.
- In patients who are not interested in more conventional treatments.

Benefits

High rates of satisfaction among patients/partners.
Infection/mechanical failure rates have continued to decline.
The only true “cure” with no risk of decline in efficacy over time.
Summary: Take Home Points

• PPI incontinence exists in different forms.

• PPI negatively affects many aspects of QOL.

• Interventions can reduce degree/duration of PPI.

• PP-ED is inevitable. Penile rehabilitation/erectile restoration programs can improve outcomes.