# Urinary and Sexual Health after Treatment for Prostate Cancer:

## *Working together to optimize outcomes*


Ryan P. Terlecki, MD FACS

Associate Professor of Urology

Director, Men's Health Clinic

Director, GURS Fellowship in Reconstructive Urology, Prosthetic Urology, and Infertility

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# Disclosure of Financial Relationships

## Ryan P Terlecki, MD, FACS

Has disclosed relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

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# Objectives (in 20 minutes)

- Review data on incidence of urinary incontinence following surgery and radiation for prostate cancer
- Discuss outcomes of anti-incontinence surgery and impact of radiation therapy
- Define Penile Rehabilitation (PR)…If possible
- To discuss the current state of the art of PR after radical prostatectomy (RP) and the evidence for different strategies

# Audience Response Question 1

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# Audience Response Question 2

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# Post-prostatectomy incontinence

- Published studies on risk mostly involve retrospective data, with variable definitions and patients, typically without UDS data
- Reported rates vary from <10% to as high as 80%
- About 20% use pads after RP in long term

Hoyland et al. Rev Urol 2014
Holm et al. J Urol 2014
Haglind et al. Eur Urol 2015
Vicarra et al. Eur Urol 2012
Kao et al. J Urol 2000

# Post-prostatectomy incontinence

- No significant difference b/w open and robotic in prospective trial (meta-analysis of retrospective studies suggested benefit with RARP)

- Prostate Cancer Outcomes Study: 1291 men after RP; at 18 mos f/u, 8.4% ‘incontinent’, but only 31.9% with total urinary control

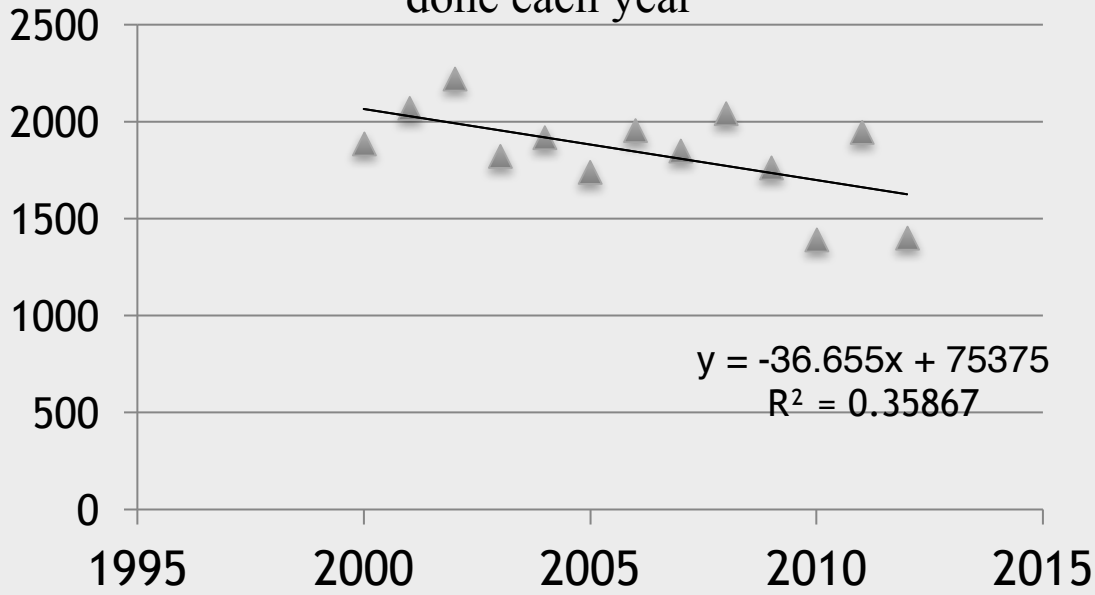
- Similarly, 65.6% self-reported UI per Kao et al.

Hoyland et al. Rev Urol 2014
Holm et al. J Urol 2014
Haglind et al. Eur Urol 2015
Vicarra et al. Eur Urol 2012
Kao et al. J Urol 2000

# Trends in repair

- 32,416 surgical procedures for male SUI were performed from 2000-2012; 20.790 AUS and 11,625 slings
- Over the study time period there was a significant decrease in the amount of total number of procedures done ($p$= 0.03).
- Rate of RP remained constant

**Figure 1:** Total number of incontinence procedures done each year

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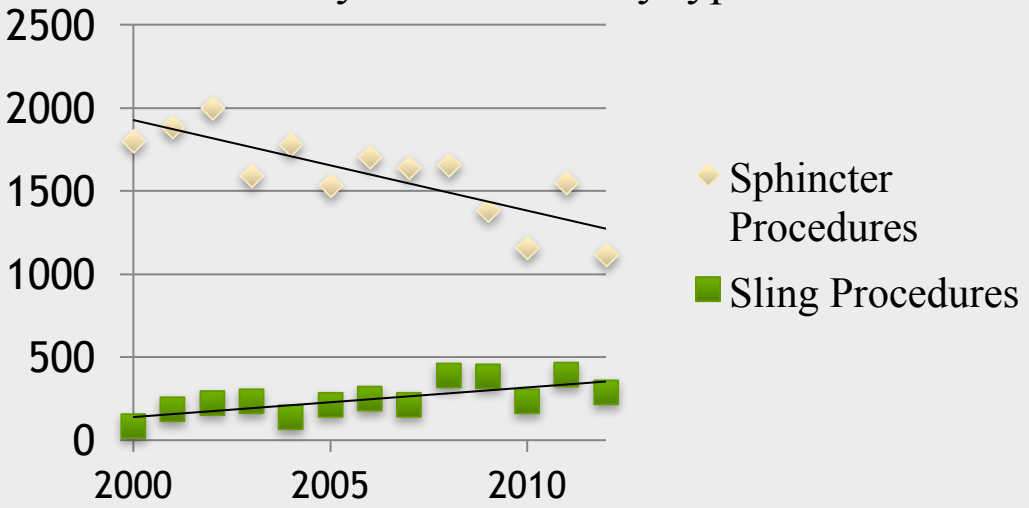
# Trends in repair

- When stratifying data by type of anti-incontinence surgery, only AUS placement saw a significant decrease ($p<0.01$).
- Sling procedures actually saw a significant increase ($p<0.01$).

**Figure 2:** Number of incontinence procedures done by year stratified by type



# What does this mean?

- Could be that continence outcomes are getting better (data to support)
- Could be that choice of sling is patient-driven (data to support)
- Could be that surgeons are more comfortable doing slings, using them to treat higher degrees of SUI, and/or more risk averse to doing AUS (data to support)

# Impact of Radiation

- 1/3 of patients will require adjuvant or salvage radiation at some point after RP
- Adjuvant IMRT shown to have late UI rate of 18% and USD rate of 6%
- Adjuvant RT has >2x worse UI than wait-and-see (SWOG 8794)

Thompson et al. JAMA 2006
Ost et al. Eur Urol 2009
Bolla et al. Lancet 2012
Petroski et al. Prostate Cancer Prostatic Dis 2004
Sowerby et al. Can Urol Assoc J. 2014

# Impact of Radiation

- Important to consider when long-term f/u of EORTC 22911 has shown that clinical PFS previously reported with adjuvant RT no longer significant; In patients >70y, adjuvant RT had detrimental effect on PFS and OS

- Continence may improve for 1-2 years after surgery (blurs data on overall impact of RT); Also issue of pathologic continence

- Timing (<6m vs >6m) does not seem to make a significant difference based on retrospective data

Thompson et al. JAMA 2006
Ost et al. Eur Urol 2009
Bolla et al. Lancet 2012
Petroski et al. Prostate Cancer Prostatic Dis 2004
Sowerby et al. Can Urol Assoc J. 2014

# Outcomes of repair after Rad Tx

- Meta-analysis of AUS complications in RP + RT patients (1886 pts, 15 studies, 1989-2014); No RCTs
  - Revision significantly higher in RT (37% vs 20%)
  - Persistent UI significantly higher in RT (29.5% vs 12.1%)

- Retrospective review 118 AUS pts w/hx of RP +/- RT
  - RR of erosion significantly higher for RT (4.05; 95% CI 1.1-15.3)

- Recent work shows AUS success drops from 89% to 56% (nonradiated vs irradiated)

Bates et al. BJUI 2015
Hird and Radomski. Can Urol Assoc J 2015
Van Bruwaene et al. BJUI 2015
Guillaumier et al. Urol Ann 2017. 9(3):253-56

# Outcomes of repair after Rad Tx

- Advance sling success 54% in RT pts vs overall rate of 75%

- Future data from MASTER trial
  - Male synthetic sling vs. Artificial urinary Sphincter Trial
  - Multicenter UK RCT for UI after prostate surgery (CA or benign)
  - Any age, any level of UI, no exclusion for prior RT
  - Aim to randomize 360 and follow another 360
  - Runs until 2019; only slated for 2y follow-up

Bates et al. BJUI 2015
Hird and Radomski. Can Urol Assoc J 2015
Van Bruwaene et al. BJUI 2015

# Postprostatectomy ED

- ED after RP is as high as 90% in some series (Mulhall and Morgentaler, 2007), but more recent data reports rates of 68%

- It is the most common long-term side effect after RP

Capogrosso et al. World J Mens Health 2016. 34(2):73-88

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# Regret

- “I wish I never had my prostate surgery”
- Men are willing to accept a 10% decrease in overall survival to preserve erectile function when considering treatment for prostate cancer.
- Dry and potent patients rarely have regret
- Preop counseling for VED and ICI demonstration reduced long-term postop regret by a factor of 10x (2 vs. 20%)

Kinsella et al. BJU Int 2012

# Impact

- The impact of sexual dysfunction is greater than that of incontinence (Arai et al. 1999)

- PP-ED has significant negative impact on quality of life (Litwin et al. 1999)

# “It’s OK”

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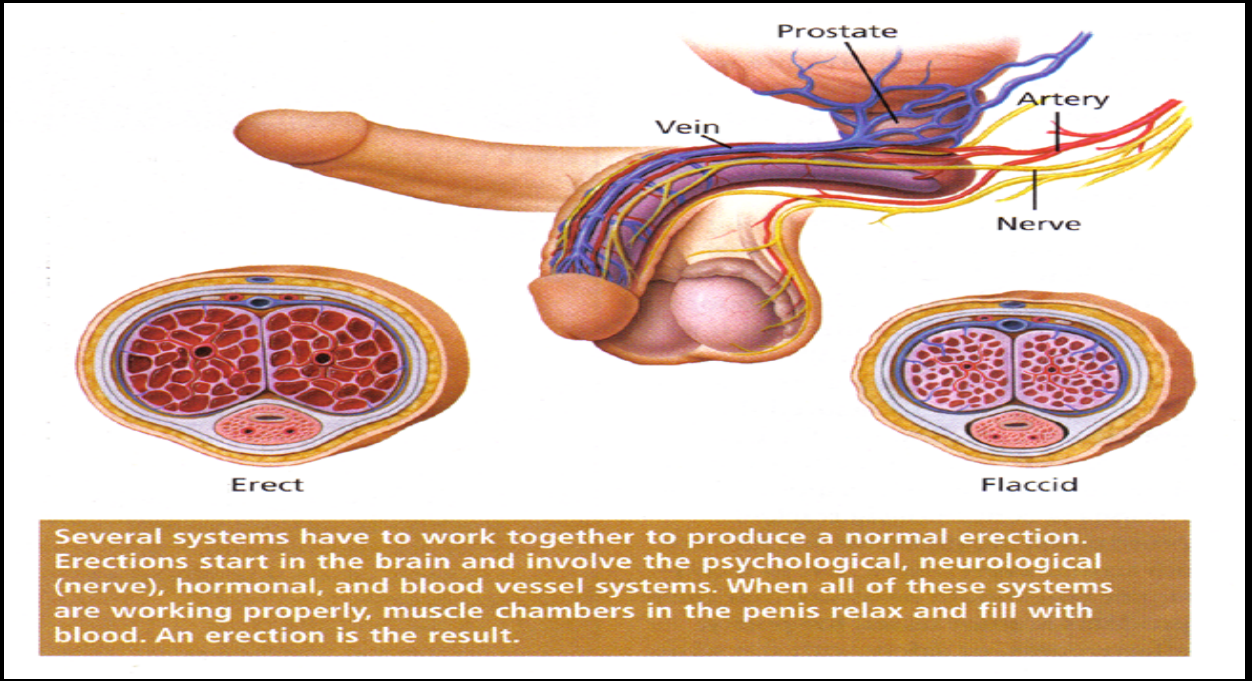
# Impact

- Intimacy is always important regardless of age
- She may hold his hand and say “it’s not important”…she doesn’t speak for him
- There is ALWAYS a psychological component to ED…consider inviting a counselor to join your team

# Plumbing and Electricity




Several systems have to work together to produce a normal erection. Erections start in the brain and involve the psychological, neurological (nerve), hormonal, and blood vessel systems. When all of these systems are working properly, muscle chambers in the penis relax and fill with blood. An erection is the result.

# Plumbing: Arterial Protection

- Accessory pudendal arteries
  - Above pelvic diaphragm
  - Prone to injury during RP
- Major inflow to penis in 70%, sole inflow in 10%
- Some suggestion of improved erectile function when preserved

Breza et al. 1989
Walz et al. 2010
Rogers et al. 2004

# Electricity: Cavernous nerves

- Poorly visualized plexus with variable configuration
- Injured by transection, traction, and thermal injury
- Neural injury leads to fibrosis via TGF-beta1 and pro-apoptotic factors
- Absence of nocturnal tumescence may contribute to hypoxic injury (“use it or lose it”)

Leungwattanakij et al. 2003

# Offering penile rehabilitation

- May seem like a no-brainer, but…
  - Cost
  - Convenience
  - Side effects

- Needs to address form AND function

# What is PR??

- A: Enabling sexual function after treatment for prostate cancer
- B: Restoring natural and spontaneous erections
- C: Getting the patient to preop status

# Penile Rehabilitation (PR)

- Probably a combination of B and C

- It is NOT the same as therapy for ED after RP

# Quality of Evidence for PR

- LOUSY!! (Too much ‘junk science’)

- Need major improvement in methodology
  - Small numbers
  - Nonrandomization
  - Nonblinding
  - Subjective endpoints
  - Lack of consensus

# Neurotrophic agents

- PDE5-inhibitors
- Brain derived growth factor
- VEGF
- Sonic hedgehog protein
- Immunophilin ligands (e.g. tacrolimus)
- EPO
- Stem cells?

Mulhall et al. 2008
Bella et al. 2007
Lee et al. 2002
Podlasek et al. 2007
Mulhall et al. 2008
Allaf et al. 2005

# PDE5-inhibitors

- Most promising of previous list
- Value of iNOS induction
  - Protects from apoptosis and fibrosis
  - Promotes endothelial protection/function
  - Recruits endothelial progenitor cells (chronic use)
- Shown to reduce cardiac necrosis in animal ischemia-reperfusion model (may make myocytes more resistant to hypoxia)

Ferrini et al. 2006
Musicki et al. 2005
Foresta et al. 2009
Salloum et al. 2007

# PDE5-inhibitors

- For the small percentage of those undergoing non-NS RP, benefits STILL noted

- Speculation of non-neuronal stimulation of NO production via endothelial NOS (eNOS)

Garcia-Cardoso et al. 2010

# “Shrinkage”!!!

# Shrinkage

- Munding et al found that 71% of RRP pts had 0.5-4.0 cm decrease in SPL by 3 months postop (50% of patients lost at least 1 cm)
- Savoie et al found 68% pts have shortening
- Fraiman et al found loss of length to average 9%
- Length preservation and recovery of erectile function seem to follow each other

Munding et al. Urology 2001
Savoie et al. J Urol 2003
Fraiman et al. Mol Urol 1999

# Shrinkage

- A randomized study of 94 pts after RALRP with 11 month f/u was reported in 2011
- Patients standardized on PR (Muse or 50 mg Viagra nightly)
- 1 month postop, avg loss of 0.64 cm, but seemed to be recovery of length back to baseline by 9 months in patients with recovery of erectile function

Engel et al. J Endourol 2011

# Length Preservation?

- 65 patients after BNSRRP randomized to no treatment or tadalafil 3d/wk and eval'd at 3, 6, and 12 months
- Preop length/circumference measured flaccid and at full erection with 30 mg papaverine and manual stimulation
- No sig diff b/w groups preop or in postop potency
- Tadalafil preserved penile length

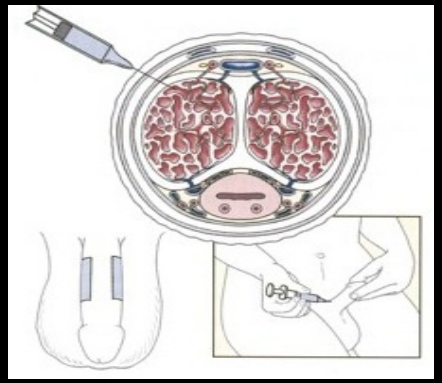
Aydogdu et al. Int Braz J Urol 2011

# Cialis

- After 5 days, steady state is reached on 5 mg that is half of peak concentration of on-demand 20 mg
- Data is mixed regarding daily or on-demand usage
- Patients with intermediate risk of ED shown to have better recovery with daily usage

Briganti et al. J Sex Med 2012

# Intracavernosal Injections (ICI)



- Subsequent study in 2006 showed early ICI with sildenafil to possibly promote earlier return of spontaneous erections in 22 men

- Addition of sildenafil allowed lower doses of ICI with less penile discomfort

Nandipati et al. 2006

# ICI

- Since 1983
- PGE1 (Alprostadil): generic, Edex, Caverject
- Bimix: Papaverine + Phentolamine
- Trimix: Bimix + PGE1
- Quadmix: Timix + Atropine (0.15 mg/mL)

# Trimix

- Stable for 6 months if frozen, 1 month if refrigerated, and 3 weeks at room temperature; Keep in fridge
- Less pain than PGE1 alone (Baniel et al 2000)
- PGE1 (10 mcg/mL): Vasodilator; Short half-life; Responsible for the ‘burning’ pain
- Papaverine (30 mg/mL): Vasodilator; causes fibrosis
- Phentolamine (1 mg/mL): alpha blocker

# Evidence

- Montorsi et al (1997)
  - Proposed PR
  - 12 wks of ICI (3x/w) s/p NSRP vs. nothing
    - 67% vs. 20% spontaneous erection rate
    - Only 12 ICI pts, no long-term f/u, no duplicate

- Mulhall et al (2005)
  - ICI and PDE5Is seemed to help
  - Retrospective, Nonrandomized

# Evidence

- Padma-Nathan et al (2008; Levine's group)
  - RCT, multicenter
  - 4w postop; 36 wks of nightly Viagra 50, 100, or placebo; 8 wk 'washout'
  - Subgroup with NPT at 12, 24, 36, 44 wks
  - Stopped early for presumed lack of efficacy??? (20% vs. 4%)
  - NPT showed objective benefit of PR and suggestion of window of opportunity

# REINVENT (multicenter RCT)

- 14 d postop randomized to three groups for 9 m
  - 10 mg QHS vardenafil and placebo OD
  - Flex dose (10 mg and could titrate 5-20mg) QHS vardenafil and placebo OD
  - QHS placebo with placebo OD
- 2 month ‘washout’, then 2 month for anyone to use vardenafil OD
- On demand appeared better than nightly
- All benefits gone after washout
  - Questions long-term benefit of PDE5Is
  - Perhaps 9 months not long-enough

Montorsi et al. 2008

# Obstacles

- Erectile function decreases with age
- Social and psychological components
- Importance of partner
- High drop-out rate (up to 73%)

Knoll et al. 2009
Salonia et al. 2008

# The Waiting Game

- Some data has suggested function may improve 2-4 years postop

- However, after 2 years many suggest that patients be considered for IPP

Glickman et al. 2009

# VED


- Antihypoxic, Antiapoptotic, Antifibrotic
- In animal model
  - Improves intracavernosal pressure
  - Reduces HIF-1 alpha expression and apoptotic indices
  - Decreases TGF-beta 1 expression
  - Increases smooth muscle/collagen ratio
  - Preserves eNOS expression

Yuan et al. 2010

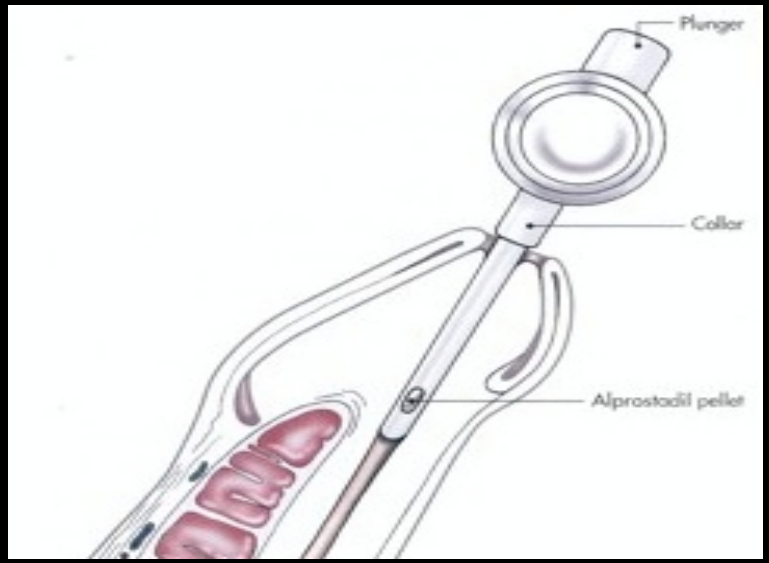
# VED

- Increases oxygen to penis when used WITHOUT constriction ring
- Kohler et al showed that early use prevented loss of length (1-2 cm)
- Key points
  - Well tolerated in absence of ring
  - No systemic side effects
  - Gets patient involved in PR

Bosshardt et al. 1995
Kohler et al. 2007

# MUSE

- Seems to work regardless of nerve-sparing status of operation
- Raina et al showed 9 months of 3x/wk increased rate of subsequent natural erections




Raina et al. 2005

# Gene Therapy

- Multiple candidate genes
  - NO-mediated genes
  - Ion channels
  - Growth Factors
  - Neurotrophic factors (BDNF, GDNF)

Kendirci et al. 2006
Yoshimura et al. 2010
Melman et al. 2005
Bakircioglu et al. 2001
Kato et al. 2009

# Tissue Engineering

- Wessels was able to place autologous ECs into corpora that remained viable (1999)
  - Thus the concept of using smooth muscle cells for gene therapy (probably more efficacious in delivery of iNOS)

- Atala was able to use matrices with human corporal cells and ECs (2002)
  - Can now grow patient specific corpora

# My ‘two-cents’

- Waiting to see if patients maintain potency without assistance could theoretically be detrimental

- Regardless if early postoperative erectaids ultimately improve subsequent spontaneous erections, early use may help avoid postop depression that could inhibit return of function

# Recommendations (9) ICSM 2015

- Discuss ED as risk preop
- Use validated instrument (e.g. IIEF)
- Insufficient evidence that one technique is superior
- Favorable predictors: young, preop EF, bilateral NS
- Inform patients of pathophysiology (seems odd)

Salonia et al. J Sex Med 2017; 14:285-296

# Recommendations (9) ICSM 2015

- Recovery can take several years
- Conflicting data on value of PR with PDE5i
- Inadequate data to support any PR regimen as optimal
- Men having RP also at risk for decreased libido, change in orgasm, anejaculation, Peyronie-like disease, and changes in penile size

Salonia et al. J Sex Med 2017; 14:297-315

# Hit em’ hard??

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# MSKCC

- Preop counseling and low dose PDE5i for 2w preop (quarter of max dose)
- PDE5i at catheter removal; low dose every other night and max dose once/week
- If responding at 6 wks, low dose 5x/wk and high dose 2x/wk
- If not responding, ICI 2x/wk and low dose PDE5i 5x/wk (rechallenge with meds at 1y)
- F/U q4m until 24 months

Mazzola and Mulhall; Urol Clin 2011

# My Program

- Assess SHIM-5 and SPL at each visit (q3m)
- Instruct to bring partner
- VED 10 min/d after Foley d/c; mark exterior
- Nightly dose of sildenafil or daily tadalafil
- Nightly penile massage even in absence of erections (involve partner)
- Concomitant active treatment of even mild SUI (pelvic floor PT)

Raina et al. 2006
Raina et al. 2005

# Audience Response Question 1

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# Audience Response Question 2

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# Conclusions

- Post-prostatectomy SUI threatens QOL
- Surgical trends appear to be changing and radiation has a detrimental impact on outcomes
- Despite robust animal/in-vitro data, probably still not enough human evidence to make penile rehabilitation ‘standard of care’
- PR not significantly harmful (can be costly), but more research is needed