Penile rehabilitation is beneficial after pelvic oncology surgery: PRO

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Disclosures

• Grants: NIH K08, NIH R03, AUA Rising Star Award, Prostate Cancer Spore Grant, Johns Hopkins Greenberg Bladder Cancer Institute.

• Clinical trials: Heat Biologics, Taris Biomedical, Photocure, FKD, NCI.

• Consultant: Photocure

• Speaker: Pfizer
Realities of post-pelvic oncology surgery ED

• Current treatments are “on-demand” and temporary
• Current treatments are less than satisfying
• We still have not identified a corrective intervention and/or preventive strategy that has a true disease-specific molecular approach to preservation of penile erection.
• Discussion with patient and partner about:
  – Predictability of erection loss
  – Time-course of erection recovery.
  – Psychological stress on couple
Sexual Dysfunction after Radical Prostatectomy

- May take up to 4 years to recover
- May have compromised full erections (diminished erection quality)
- Requires erection aids in the interim (PDE5 inhibitors, intracavernous injections, MUSE, VED)
- Other sexual dysfunctions also associated with RP – climacturia, penile shortening, peyronie’s disease, changes in orgasm.

Walsh PC, et al. Urology 2000
Mulhall JP, Bivalacqua TJ, Becher E J Sex Med 2013
Histological Alterations In Cavernous Tissue After Radical Prostatectomy

A, C – Before RRP;  B, D – 2 mths after RRP

Marked Increase in Collagen Fibers, Decrease in Elastic and Smooth Muscle Cell Fibers

Erectile tissue microstructure in patients after RRP becomes progressively disorganized

Iacono F et al., J Urol 2005
Penile Rehabilitation

• **Definition:** Penile rehabilitation (erectile tissue preservation) is defined as the use of any drug or device at or after radical prostatectomy to maximize erectile function recovery

• **Purpose:** The prevention of corpus cavernosal smooth muscle structural alterations to maximize chances of a man returning to his preoperative erectile function level
Current Medical Management for Erection Preservation following Radical Prostatectomy

- PDE5 inhibitor therapy.
- Intracavernous injection therapy (ICI)
- Vacuum Erection Device (VED)
- MUSE (intraurethral alprostadil)
- Experimental approaches – EPO, FK506, ARBs, Statins, stem cells
So does it work?

• My esteemed colleague will present you data to suggest its ineffective…..
• It's not cost-effective….
• RCT don’t support its use….
• Ok so now lets really talk about evidence and why we as a society should support “penile rehabilitation” !!
Erectile Function Rehabilitation after RP: Practice Patterns among AUA Members

**Aim:** To explore EF rehabilitation practice patterns of AUA urologists.

**Results:** 43% rehabilitate all patients, 57% only selected patients; 89% of RP surgeons performed rehabilitation vs. only 66% who do not perform RP (P < 0.0001).

The timing of penile rehabilitation after NS-RP affects the recovery of erectile function

* Retrospective analysis

Mulhall JP et al. BJU Int. 2010
REINVENT Trial

* BILATERAL NERVE SPARING RADICAL PROSTATECTOMY

REINVENT Trial: Vardenafil.

* p < 0.0001 for comparison of vardenafil on demand versus placebo

Percentage of Men with IIEF-6 > 21 for PRN vs. Nightly Viagra patients at 1 - 13 months post-surgery

Pavlovich CP et al. BJU Int. 2013
REACTT Trial: Tadalafil

* BILATERAL NERVE SPARING RADICAL PROSTATECTOMY

Effect of PDE5 inhibitor therapy on penile length

PDE5 inhibitors are myogenic

I Kovanecz et al. IJIR 2008

Sun XZ et al. Clin Exp Pharm Physiol. 2010
PDE5 localization within ECs

BAEC - Immuno-EM for PDE5

Limitations to current RCT

• Performed in bilateral NS RP patients
• One dose of PDE5 inhibitors.
• Duration of use may be sub-optimal
• Evaluated one time point (12-13mths) post treatment
• More importantly, EF was only assessed not the impact of treatment on patient and partner...
The impact of post-RP sexual dysfunction on couples.

• Partners are distressed about the loss of sexual relationships (Tanner, J Midwifery & Women’s Health, 2013, Harden, Onc Nsg Forum, 2013, Ramsey, J Sex Med, 2013)


Courtesy Daniels Wittmann PhD LMSW – U. Mich
Men's experience with penile rehabilitation following radical prostatectomy

Six primary themes emerged:
(1) frustration with the lack of information about post surgery ED;
(2) negative emotional impact of ED and avoidance of sexual situations;
(3) negative emotional experience with penile injections and barriers leading to avoidance;
(4) the benefit of focusing on the long-term advantage of ER versus short-term anxiety;
(5) using humor to help cope; and
(6) the benefit of support from partners and peers.

Nelson CJ et al. Psychooncology 2015
What helps sexual recovery for couples after radical prostatectomy?

- Fostering realistic expectations prior to treatment
- Engagement in penile rehabilitation as an aspect of sexual self-care.
- Early use of erectile function treatments in regular, ongoing sexual activity.

Wittmann, J Sex Med, 2014
Management of prostate cancer in the USA and internationally
Surveillance for *favorable risk* prostate cancer has been adopted around the world.

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Proportion of men on active surveillance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UNITED STATES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPSURE (Cooperberg 2015)</td>
<td>2010-2013</td>
<td>40</td>
</tr>
<tr>
<td>MUSIC (Womble 2014)</td>
<td>2012-2013</td>
<td>49</td>
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<tr>
<td><strong>SWEDEN</strong></td>
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<tr>
<td>National registry (Loeb 2013)</td>
<td>2007-2011</td>
<td>46</td>
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<tr>
<td><strong>AUSTRALIA</strong></td>
<td></td>
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<tr>
<td>Registry (Weerakoon 2015)</td>
<td>2010-2012</td>
<td>40</td>
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Johns Hopkins Radical Prostatectomy Experience

- We examined the risk classification of men who underwent radical prostatectomy (RP) at our institution since January 2001, with particular focus on the contemporary era (2011-2015).

- The proportion of the RP population composed of high-risk (HR) and very high-risk (VHR) cancers increased from 5.1% in 2001-2005 to 7.6% in 2006-2010 and 13.5% from 2011 to present (p<0.001).

**High-Risk Men in RP Population**

<table>
<thead>
<tr>
<th>Year</th>
<th>Proportion (%)</th>
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<tbody>
<tr>
<td>2011</td>
<td>6.9</td>
</tr>
<tr>
<td>2012</td>
<td>11.5</td>
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<tr>
<td>2013</td>
<td>15.6</td>
</tr>
<tr>
<td>2014</td>
<td>18.2</td>
</tr>
<tr>
<td>2015</td>
<td>20.2</td>
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Jeffrey J. Tosoian, MD, MPH, Ashley E. Ross, MD, PhD – AUA 2016
How should we be addressing post-RP ED?

• Medical Therapy
  – PDE5 inhibitors, ICI may allow for preservation in current RP population.

• Patient Selection
  – Penile rehab may be helpful in men who undergo non-NS/partial NS.

• Bottom line, we can do better with trials addressing different patient populations, different agents, and good translational science to address the problem....
What does the future hold for enhanced recovery and preservation of erectile function following pelvic oncologic surgery?
Pathophysiology of Post-RP ED

Injury to Cavernous Nerves

**NVB** Apoptosis & Neuronal Cell Death

Decrease in Smooth Muscle and Endothelial Cell Content

**PENIS** FIBROSIS

Erectile Dysfunction
(Veno-Occlusive and/or Arterial)
Local applications: penile and MPG

Delivery methods:
• Intravenous
• Intracavernosal
• Local application on neurovascular bundle

BUT THE MOST IMPORTANT ASPECT IS TIMING AND TREATING THE UNDERLYING DISEASE PROCESS!!!

Bivalacqua TJ, Strong T. J Sex Med. 2008 5:268-75
Kim IG et al. Tissue Eng Part A. 2013;19:14-23
Next generation therapies

• Protein and gene therapies to augment natures own repair pathways
• Stromal Derived Factor-1 is a small, highly conserved, chemokine, which binds to CXCR4 and CXCR7
• Upregulated in multiple tissues (neuronal, heart, muscle) following injury
• Potent stem cell chemo-attractant
• Endogenous anti-apoptotic, angiogenic, and neurogenic properties
SDF-1 Treatment

Ex-Vivo Organoid

Control

SDF1 500 ng/mL

24 Hr

48 Hr

72 Hr

In-Vivo

BCNI + Penile Saline Injection

BCNI + Penile SDF-1 Injection

Intracavernosal Pressure (mmHg)

Systemic Pressure (mmHg)

Sopko N et al. AUA Moderated poster 2016
Novel Delivery Methods – Hydrogel Conjugation

Conclusion

• The utilization of medical therapy to enhance erection recovery post-RP goes beyond just simply erections but assists in improvement in sexual health, engagement in cancer treatment, and relationship with partner.

• We clearly need to develop disease-specific therapies focusing on preservation of autonomic innervations of penis as well as corporal vasculature.