Optimizing Sexual Function Outcomes in the Man With Prostate Cancer

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It takes 50 years to get a wrong idea out of medicine, and 100 years a right one into medicine.

John Hughlings Jackson
Neurologist

Optimal Outcomes

Optimal sexual function outcomes after prostate cancer therapy requires full informed consent prior to therapy which mandates that the clinician give the patient realistic expectations
Barriers to Optimal Outcomes

- Clinician
- Patient
- Health care environment
- Knowledge
- Technical expertise
- Sub-standard technology
- Insufficient support
- Bias
- Financial

What Treatment Should I Have for My Prostate Cancer?

<table>
<thead>
<tr>
<th></th>
<th>Radical Prostatectomy</th>
<th>Radiation Therapy</th>
<th>Hormone Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile dysfunction</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Painful ejaculation</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Blood in semen</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Urine leakage at orgasm</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Penile shortening</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Blood in urine</td>
<td>+</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Loss of muscle</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Weight gain</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
</tbody>
</table>

+++ expected
+++ common
++ occasional
+ rare
- = some
Optimal Outcomes

Bottomline

- There are numerous ways in which patients fail to receive good information and realistic expectations
- Clinicians often avoid discussing sex because of discomfort with the topic
- Clinicians often practice ageism
- Patients must be proactive in getting the information they want and need

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Prostate Cancer

Sexual Dysfunctions

- Erectile dysfunction
- Low libido
- Failure to ejaculate
- Premature ejaculation
- Retarded ejaculation
- Absence of orgasm
- Painful orgasm
- Orgasm associated urine leak
- Penile length alterations
- Penile curvature
Non-ED Sexual Dysfunction
Bottomline

- There are a variety of sexual dysfunctions associated with RP, RT and hormone therapy
- It is important that the patient familiarize himself with these problems
- It is unlikely that most clinicians will address all these problems pre and post-treatment

Open vs Robotic?
An analysis of sexual health information on radical prostatectomy websites

Table 3: Factors Explored On Radical Prostatectomy Websites

<table>
<thead>
<tr>
<th>University vs community practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the center have a specific robotic prostatectomy site?</td>
</tr>
<tr>
<td>Is there a link from the institution’s main website to the prostatectomy site?</td>
</tr>
<tr>
<td>Has information between cut and pasted directly from the intuitive website?</td>
</tr>
<tr>
<td>Is there a link to the intuitive surgical website?</td>
</tr>
<tr>
<td>Is ED mentioned as a complication of radical prostatectomy?</td>
</tr>
<tr>
<td>Is this information accurate?</td>
</tr>
<tr>
<td>Is this information comprehensive?</td>
</tr>
<tr>
<td>Is the site specific to a single surgeon?</td>
</tr>
<tr>
<td>Is open radical prostatectomy mentioned on the robotic prostatectomy site?</td>
</tr>
<tr>
<td>Is robotic prostatectomy mentioned on the open site?</td>
</tr>
<tr>
<td>Is it suggested that the prostatectomy approach is better than the other technique?</td>
</tr>
<tr>
<td>Have ED figures been explicitly mentioned?</td>
</tr>
<tr>
<td>Are there references to support the figures mentioned?</td>
</tr>
</tbody>
</table>

Table 1 Grading of information on erectile function

<table>
<thead>
<tr>
<th>Grade</th>
<th>Total</th>
<th>University</th>
<th>Private</th>
<th>ORP</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>70</td>
<td>36</td>
<td>34</td>
<td>20</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>13</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>C</td>
<td>38</td>
<td>44</td>
<td>32</td>
<td>46</td>
</tr>
<tr>
<td>U</td>
<td>43</td>
<td>36</td>
<td>50</td>
<td>25</td>
</tr>
</tbody>
</table>

P < 0.05, *Private vs Academic RARP, **ORP vs RALP.

Technique vs Surgeon?

<table>
<thead>
<tr>
<th>Variable</th>
<th>X²</th>
<th>HR (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum PSA level</td>
<td>0.44</td>
<td>0.99 (0.97, 1.01)</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical Stage</td>
<td>0.04</td>
<td>0.99 (0.79, 1.76)</td>
<td>0.9</td>
</tr>
<tr>
<td>Biopsy Gleason Score</td>
<td>0.09</td>
<td>0.96 (0.77, 1.22)</td>
<td>0.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.02</td>
<td>0.98 (0.75, 1.36)</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2.92</td>
<td>0.73 (0.52, 1.04)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.13</td>
<td>0.85 (0.58, 1.09)</td>
<td>0.8</td>
</tr>
<tr>
<td>Age</td>
<td>48.82</td>
<td>0.95 (0.93, 0.96)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Surgeon Volume</td>
<td>4.82</td>
<td>0.99 (0.98, 0.99)</td>
<td>0.02</td>
</tr>
<tr>
<td>Surgeon</td>
<td>39.5</td>
<td>NA</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

Bianco F et al. AUA 2008
Table 2: Expectations Regarding Erectile Dysfunction And Treatment

<table>
<thead>
<tr>
<th></th>
<th>Open n</th>
<th>Robotic</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to recovery of functional erections (months)</td>
<td>12</td>
<td>6</td>
<td>0.02</td>
</tr>
<tr>
<td>Proportion of patients having recovery of EF to baseline level (%)</td>
<td>50</td>
<td>75</td>
<td>0.01</td>
</tr>
<tr>
<td>Potential for need to use intracavernosal injections (%)</td>
<td>20</td>
<td>4</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* comparing open and robotic prostatectomy patients

Table 3: Expectations Regarding Ejaculation & Orgasm

<table>
<thead>
<tr>
<th></th>
<th>Open n</th>
<th>Robotic</th>
<th>p Value1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anejaculatory status (%)</td>
<td>70</td>
<td>60</td>
<td>NS</td>
</tr>
<tr>
<td>Potential for change in nature of orgasm (%)</td>
<td>10</td>
<td>12</td>
<td>NS</td>
</tr>
<tr>
<td>Potential for orgasmic pain (%)</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Potential for clitoral pain (%)</td>
<td>2</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Knowledge of ACTIS loop (%)</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>

* comparing open and robotic prostatectomy patients

![Graph showing 5-year probability of freedom from BCR (%) vs Surgeon experience (number of prior surgeries)]
External Beam vs Seeds?

Chronology

After Berson & Emery, Economic Implications of Advancements in Radiation Technology
Multiple Techniques for RT Delivery

- EBRT
- 3 DCRT
- IMRT
- VMAT
- IGRT
- ART
- Tomotherapy
- Low dose rate (LDR)
- High dose rate (HDR)
- Stereotactic radiotherapy
- Tomotherapy
- LINAC based
- Cyberknife

Mechanisms of ED

- Cavernous nerve injury
- Accessory pudendal artery injury
- Erection tissue damage
- Confidence erosion


What Does Nerve Sparing Mean?
IMRT

Erection Tissue: Dose reduction with IMRT vs 3D-CRT

<table>
<thead>
<tr>
<th>Dose</th>
<th>Tech.</th>
<th>Dmean</th>
<th>% diff.</th>
</tr>
</thead>
<tbody>
<tr>
<td>73.8Gy</td>
<td>3D IMRT</td>
<td>29.7</td>
<td>16.9</td>
</tr>
<tr>
<td>81Gy</td>
<td>3D IMRT</td>
<td>31.8</td>
<td>17.1</td>
</tr>
<tr>
<td>90Gy</td>
<td>3D IMRT</td>
<td>34.4</td>
<td>17.5</td>
</tr>
</tbody>
</table>

Androgen Deprivation Therapy
Mechanisms of Sexual Dysfunction

- Testosterone is required for libido and erection tissue health
- Animal castration is how we study venous leak
- It appears 4-6 months of ADT is enough to cause irreversible erection tissue damage
- ADT reduces ability to have preservation of EF after RT including response to ED medications
Why Are ED Rates So Variable?

- The way data is collected
- The way ED is defined
- Variation in the patients studied

Defining and Reporting Erectile Function Outcomes After Radical Prostatectomy: Challenges and Misconceptions

John P. Mulhall*,†

From the Sexual and Reproductive Medicine Programs, Urology Service, Memorial Sloan Kettering Cancer Center, New York, New York.

Mulhall, JP. J Urol Feb 2009

Recovery of Erections Nomogram

![Nomogram Image]
EF Recovery
Bottomline

- Approximately 50% of men after RP have recovery of erections good enough for intercourse without medications
- Only 15-20% of men at MSKCC return to baseline EF
- EF rates of >90% are unrealistic
- ED rates after RT are difficult to define
- ED rates appear to be similar between RP and RT three years after treatment

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
Animal Data

- Muller A et al. The functional and structural consequences of cavernous nerve injury are ameliorated by sildenafil citrate. J Sex Med, 2008; Epub ahead of print
- Kovanecz I et al. Long-term continuous sildenafil treatment ameliorates CVOD induced by cavernosal nerve resection in the rats. IJIR, 2008; 20:202
- Ferrini M et al. Vardenafil prevents fibrosis and loss of smooth muscle after bilateral cavernosal nerve resection in the rat. Urology, 2006; 68:429
- Vignozzi L et al. Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. J Sex Med; 2006; 3:419
- Kovanecz I et al. Chronic daily tadalafil prevents the corporal fibrosis and vasoocclusive dysfunction that occurs after cavernosal nerve resection. BJUI; 2008; 101:203
- Lyslak JJ et al. Tadalafil increases AKT and extracellular signal-related kinase 1/2 activation and prevents apoptotic cell death in the penis following denervation. J Urol, 2008; 179:779

Human Study Data

  - Randomized 30 men: ICI vs no treatment for 12w
  - 67% vs 20% recovery of natural EF at 6m after RP
  - Non-randomized, 132 patients : 3 erections/week
  - Improvement in natural, sildenafil and ICI response
- Padma-Nathan et al. IJIR 2008
  - RCT, 76 patients, V50, V100, Pbo
  - Nightly intervention 4-40w after RP
  - Spontaneous erectile function assessed
  - 27% vs 4% responders
  - Greater chance of preserving preoperative EF
Human Study Data

  - 21 RP patients, randomized to V50 or V100 QOD
  - Corporal biopsy re-RP and at 6m postoperatively
  - Preservation of SM content with sildenafil use

  - Non-randomized, 41 patients: V25 QHS vs control
  - SHIM scores: decrease of 0.2 vs 6.3 pre vs post-RP

  - 423 patients in 87 centers
  - No difference between Levitra nightly/on-demand

PDE5 Inhibitors & Rehabilitation

- Increase oxygen during nocturnal erections?
- Erection muscle protection?
- Endothelium protection?
- Neuroregeneration?
Principal Arguments

- Against:
  - Unproven strategy - Lack of level I EBM
  - Translating animal data to human model
  - REINVENT study
  - High cost

- For:
  - ED associated with depression and reduced QOL
  - Erection tissue damage is time-dependent
  - Signal that studies are positive
  - Recommended by ICSM 2009

Erectile Tissue Preservation for Radiation and ADT Patients?
ED Treatments
Comparing PDE5 Inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sildenafil (Viagra)</th>
<th>Vardenafil (Levitra)</th>
<th>Tadalafil (Cialis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of action</td>
<td>12h</td>
<td>12h</td>
<td>36h</td>
</tr>
<tr>
<td>Speed of onset</td>
<td>30-60 min</td>
<td>30-60 min</td>
<td>2-4h</td>
</tr>
<tr>
<td>Food impact</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Side effects</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Oral Therapy Dosing

- Maximum dose is a reasonable starting dose
- Down Titrate for side effects or excellent response
- Adequate patient instructions
  - Empty stomach (Viagra, Levitra)
  - Sexual stimulation required
  - Wait one hour prior to commencement (V, L)
  - Wait 4h prior to initiation with Cialis
- Duration of action
- Follow-up with patient
Penile Injection Therapy

Transurethral Therapy

MUSE® (alprostadil)
Best Outcomes with Treatment

- Best technology
- Best physician experience
- Best physician judgement
- Best institutional support systems
- Most informed patient

Key Issues

- Patients think that the treating physician will tell them all they need to hear, when in fact the physician will tell the patient what he/she thinks they need to hear
- Don’t be afraid to ask “why?”
- Don’t be afraid to ask why “active surveillance” is not an option for you
- Don’t be afraid to ask about the treating physician’s experience and current treatment volume
- Think seriously in terms of “survival benefit”
- Think before deciding on a treatment how important quality of life is to you
- Don’t be afraid to take your time in deciding on a treatment