How does the PCa risk factors affect TRT?
Is TRT safe to prostate health?

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Ex President of SLAMS
Director of International Relations of
SBU – Brazilian Society of Urology
Which are the presumable risk factors for Prostate Cancer?
Their presence increase the risk for PCa?

- Intraprostatic DHT
- Having a normal prostate
- PIN
- PSA
- Testosterone level
- Patients With Treated PCa
- Patients With Untreated PCa
Effect of TRT on Intraprostatic Testosterone Levels
Effects of TRT on Prostate Tissue of Aging Men with Low Serum T

- RDB, PC trial of 44 men (44-78 years)
- Inclusion criteria:
  - T < 300 ng/dl
  - Symptoms of hypogonadism
- Randomly assigned to receive 150 mg TE or placebo q 2 weeks X 6 months
- 12-core TRUS prostate biopsies were performed at baseline and 6 months
- Primary outcomes: 6-month change in prostate T & DHT

Effects of TRT on Prostate Tissue of Aging Men with Low Serum T

* * p < .001
** ** p < .002
These data suggest that while 6 months of TRT normalizes serum androgen levels, it appears to have little effect on prostate tissue androgen levels and androgen dependent cellular functions.
DHT in Prostatic Tissue in Patients with Gleason Score $\geq 7$ to 10 was Significantly Lower than in those with Gleason Score of $\leq 6$

Having a Normal Prostate and TRT
Meta-Analysis of Placebo-Controlled Testosterone Trials in Middle-Aged and Older Men: Prostate Adverse Event Rates per 1,000 Patient-Years

Systematic Review: PCa risk in Men submitted to TRT

- 11 RPC studies
- 29 non PC studies in men without history of PCa
- 4 non PC studies in hypogonadal men with PCa

- None of them showed that TRT increased the risk of PCa or increased the Gleason score in PCa previously detected


- Texas Cancer Registry - 722 men – 8.7 years follow up
  - 397 men under TRT
  - 325 men without TRT
- Men under TRT
  - 22/397 (6.8%) of the men developed PCa
- Men without TRT
  - 32/325 (8.1%) of the men developed PCa
- After parity adjustment for age there were no difference in the risk of PCa (p=0.94)
- In a cohort of 580 men with a follow up of > 10 years again there were no difference in the risk of PCa
The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis

Cui Y, Zong H, Zhang Y. Prostate Cancer and Prostatic Disease; 2014(17):132-143

- 22 RCTs involving 2351 pts on TRT
- “... But as to the incidence of new prostate cancer, prostate biopsy, prostate nodule and abnormal PSA levels, there were no apparent difference between testosterone with placebo” ...
Prostate Cancer Incidence in 3 Cohorts on Long-Term TRT with Testosterone Undecanoate (TU, Nebido®) and in Screening Studies in the U.S. and Europe

<table>
<thead>
<tr>
<th>Study Cohort</th>
<th>Dr. Haider</th>
<th>Prof. Yassin</th>
<th>Prof. Zitzmann</th>
<th>PLCO [1]</th>
<th>ERSPC [2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>340</td>
<td>261</td>
<td>422</td>
<td>38,343</td>
<td>72,891</td>
</tr>
<tr>
<td>Age (range)</td>
<td>57.4</td>
<td>59.5</td>
<td>41</td>
<td>55–74</td>
<td>50–74</td>
</tr>
<tr>
<td>Follow-up</td>
<td>7 years</td>
<td>6 years</td>
<td>17 years</td>
<td>7 years</td>
<td>11 years</td>
</tr>
<tr>
<td>PCa cases</td>
<td>5</td>
<td>6</td>
<td>0</td>
<td>2,820</td>
<td>6,963</td>
</tr>
<tr>
<td>Proportion</td>
<td>1.5%</td>
<td>2.3%</td>
<td>0</td>
<td>7.35%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Incidence per 10,000 patient years</td>
<td>30.7</td>
<td>54.4</td>
<td>0</td>
<td>116</td>
<td>96.6</td>
</tr>
</tbody>
</table>


Haider A et al. J Urol, published online June 26, 2014
PIN and TRT
High Risk (HGPIN)

- HGPIN: 25-30% chance of prostate cancer on subsequent biopsies
- 75 hypogonadal men treated with TRT for 12 months
- All men underwent prostate biopsy prior to TRT
  - 55 men had benign biopsies (-PIN)
  - 20 men with PIN (+PIN)
- Results
  - No significant change in PSA in either group
  - One patient in +PIN group found to have prostate cancer on biopsy after abnormal DRE
- Conclusion: After 1 year of TRT, men with PIN did not have a greater increase in PSA or a significant increased risk of cancer than men without PIN

PSA and TRT
Testosterone and PSA

- **Rhoden and Morgentaler**¹
  - 48 hypogonadal men with TRT for 1 year
  - Overall mean increase in PSA was 0.31 ng/dl (p>0.5)
  - PSA increased in 57%, unchanged in 22%, and decreased in 21%

- **Grober et al.**²
  - TRT does not appear to significantly influence serum PSA expression
  - No significant correlation was identified between PSA and serum testosterone among eugonadal, untreated hypogonadal and hypogonadal men receiving TRT.

- **Bhasin et al.**³
  - 600mg of testosterone or placebo weekly for 10 weeks
  - PSA did not change significantly from baseline despite supraphysiological testosterone levels (>2800 ng/dl)

¹ Rhoden El, Morganter A Int J Impot Res 2006
² Grober et al. IJIR 2008; 20(6): 561
³ Bhasin et al. NEJM 1996; 335:1
Testosterone levels and Prostate Cancer

- Peak testosterone levels are seen in late teens & early 20’s, while peak prostate cancer 60’s-70’s
Low Testosterone Associated with Increased Risk of Prostate Cancer

  - Lower testosterone correlated with higher:
    • Pathological stage
    • Clinical stage
    • Biopsy Gleason grade

  - Lower testosterone correlated with:
    • Increased positive surgical margins
      - 39% in low TT vs 14.6% in normal TT

  - Lower testosterone correlated with:
    • Higher tumor density
    • Higher Gleason score
Lower Pre-operative Testosterone Levels Increase the Risk for Prostate Cancer Recurrence

- 272 patients with localized prostate cancer were treated with radical prostatectomy
- Preoperative testosterone measured in all patients
  - <300 ng/dl: 49 patients
  - >300 ng/dl: 223 patients
- Independent and significant predictors of PSA recurrence were:
  - Gleason score (p=0.006),
  - Surgical margin status (p=0.0001),
  - PSA (p=0.0001)
  - Preoperative testosterone level (p=0.021)
- Five-year PSA failure-free survival rates:
  - <300 ng/dl: 67.8%
  - >300 ng/dl: 84.9% (p=0.035)

Yamamoto, Eur Urol, 2007
TRT in Patients With Treated PCa
<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Follow-up (months)</th>
<th>PSA Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaufman 2004</td>
<td>7</td>
<td>24-132</td>
<td>-</td>
</tr>
<tr>
<td>Agarwal 2005</td>
<td>10</td>
<td>9-19</td>
<td>-</td>
</tr>
<tr>
<td>Mulhall 2008</td>
<td>22</td>
<td>8-40</td>
<td>1</td>
</tr>
<tr>
<td>Carrion 2008</td>
<td>14</td>
<td>12 (media)</td>
<td>-</td>
</tr>
<tr>
<td>Khera 2009</td>
<td>57</td>
<td>1-99</td>
<td>-</td>
</tr>
<tr>
<td>Sommer 2010</td>
<td>69</td>
<td>6-72</td>
<td>-</td>
</tr>
<tr>
<td>Sathyamoorthy 2010</td>
<td>133</td>
<td>12 (média)</td>
<td>-</td>
</tr>
<tr>
<td>Matsushita 2012</td>
<td>71</td>
<td>2-48</td>
<td>1</td>
</tr>
<tr>
<td>Patuszak 2013</td>
<td>103</td>
<td>1-49,5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>486</strong></td>
<td><strong>1-132</strong></td>
<td><strong>6 (1.23%)</strong></td>
</tr>
</tbody>
</table>
Mulhall et al. J Urol 2008;179(supp 4):426
Carrion et al. J Urol 2008;179(supp 4):428
Sommer et al. poster 1496 AUA 2010
Sathyamoorthy et al. J Urol 2010;183(suppl e 577)
## TRT post Brachytherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Follow-up (months)</th>
<th>PSA Pre TRT</th>
<th>PSA Post TRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarosdy 2006</td>
<td>31</td>
<td>18-108</td>
<td>NI *</td>
<td>100% &lt; 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>98% &lt; 0,5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74% &lt; 0,1</td>
</tr>
</tbody>
</table>

NI = Not informed

Cancer 2007;109(3)536-541
## TRT Post Radiotherapy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Follow-up (months)</th>
<th>PSA Pre TRT</th>
<th>PSA Post TRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Davilla 2008</td>
<td>6</td>
<td>9</td>
<td>0.15</td>
<td>0.1</td>
</tr>
<tr>
<td>Morales 2008</td>
<td>5</td>
<td>6-27</td>
<td>0.1-0.97 (0.3)</td>
<td>&lt; 0.1 – 1.08</td>
</tr>
<tr>
<td>Pastuszak 2013</td>
<td>13</td>
<td>0-23.7</td>
<td>0.1</td>
<td>&lt; 0.1</td>
</tr>
</tbody>
</table>

TRT post Orchiectomy

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Follow-up (months)</th>
<th>PSA Pre TRT</th>
<th>PSA Post TRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netto 2006 *</td>
<td>5</td>
<td>18 - 30</td>
<td>2,0 - 7,4</td>
<td>4,5 – 8,4</td>
</tr>
</tbody>
</table>

*PSA 7.4-12 in 1 patient: TRT interrupted and 20 months after with PSA stable, TRT was again instituted - (PSA < 10 – G 7 a 9 – No local recurrence or metastasis)

Netto et al. Prostate Cancer Prostatic Dis 2006;9:39-41
### TRT After Multiple Treatments

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Follow-up (months)</th>
<th>PSA Pre TRT</th>
<th>PSA Post RT</th>
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</thead>
<tbody>
<tr>
<td>Brawer 2004</td>
<td>1</td>
<td>14</td>
<td>Indetectable</td>
<td>Indetectable</td>
</tr>
</tbody>
</table>

RP (G 8) + Gosereline + Radiotherapy – TRT 16 months after Gosereline

TRT in Patients With Untreated PCa
TRT in patients with PCa under active surveillance

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Follow-up (months)</th>
<th>PSA Pre TRT</th>
<th>PSA PostTRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgentaler 2013</td>
<td>33</td>
<td>3 - 34</td>
<td>0.6 - 15.5</td>
<td>0.9 - 9.2</td>
</tr>
<tr>
<td>Mulhall 2014</td>
<td>15</td>
<td>6.2 - 11 y</td>
<td>3.7 +/- 1.2</td>
<td>5.6 +/- 1.1</td>
</tr>
</tbody>
</table>

Morgentaler A, et al. AUA 2013 Abstract 664; Mulhall ISSM meeting 2014 Abstract 035
<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>N of Patients</th>
<th>Follow up</th>
<th>PSA Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radical Prostatectomy</td>
<td>486</td>
<td>1– 132</td>
<td>6</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>31</td>
<td>18 - 38</td>
<td>-</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>24</td>
<td>0- 27</td>
<td>-</td>
</tr>
<tr>
<td>Orchietomy</td>
<td>5</td>
<td>18 - 30</td>
<td>-</td>
</tr>
<tr>
<td>Multiple Treatments</td>
<td>1</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>Active Surveillance</td>
<td>48</td>
<td>3 - 34</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>595</td>
<td>0 m – 11 y</td>
<td>6 (1,01%)</td>
</tr>
</tbody>
</table>
Are the presumable PCa risk factors affected by TRT?

- Intraprostatic DHT - NO
- Having a normal prostate - NO
- PIN - NO
- PSA - NO
- Testosterone level - NO
- Patients With Treated PCa - NO *
- Patients With Untreated PCa - NO *
Current Clinical Trial: NCT00848497

- FDA approved
- Randomized placebo controlled trial
- TRT in hypogonadal men starting 3 months after radical prostatectomy

**Inclusion Criteria:**
- Must have undergone a bilateral nerve sparing radical prostatectomy.
- Nadir PSA values should be less than 0.01 ng/ml on two consecutive occasions separated by 4 weeks at the start of treatment.

**Exclusion Criteria:**
- Testosterone level greater than 300 ng/dl
- Pre-operative SHIM score less than 17.
- Positive surgical margins or evidence of residual prostate cancer.
- Clinically suspected advanced disease or actual evidence of metastatic prostate cancer.
- Primary Gleason Grade greater than 3 or secondary Gleason Grade greater than 4 in the final pathologic specimen will be excluded.

http://clinicaltrials.gov/ct2/show/NCT00848497