Androgens After Prostate Cancer:
Are We Ready?

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Historical Basis for Concern

In 1941 – Huggins & Hodges reported:
1. Reducing T to castrate levels caused prostate cancer to regress
2. Administration of exogenous T caused prostate cancer to grow

(based on a single patient)
Number of articles showing testosterone therapy causes prostate cancer in PSA era

None!

Discussion
- Effect of TRT on Normal Prostate Tissue
- Prostate Saturation Theory
- Low Testosterone as a Risk Factor for Prostate Cancer
- TRT in Men with a History of Prostate Cancer
- TRT in Men with Untreated Prostate Cancer

Effect of TRT on Normal Prostate Tissue?
**Effects of TRT on Prostate Tissue of Aging Men with Low Serum T**

- R, DB, 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

Prostate Saturation Model

Saturation Model of Physiologic Testosterone Replacement

“Normal Physiologic Range”

Saturation Effect

Serum testosterone level (ng/dL)

Prostate Growth (PSA)

Unsaturated

Normal Physiologic Range

Virtually Castrate

Saturation Saturation Model of Physiologic Testosterone Replacement


Saturation:

T for PCa is like “water for a thirsty tumor”

Growth

Once the “thirst” has been quenched, additional T has no further effect

Serum Testosterone

PSA at Supraphysiologic Levels of Testosterone

• Testosterone 600 mg or placebo weekly for 10 weeks
• PSA did not change significantly from baseline despite supraphysiologic testosterone levels (>2500 ng/dL)

• 451 hypogonadal men started on TRT for 12 months
• Divided into 2 groups
  • Group A: Testosterone < 250ng/dl
  • Group B: Testosterone > 250ng/dl
• ONLY in group A (Testosterone < 250ng/dl):
  • PSA correlates with testosterone and free testosterone
  • Significant rise in PSA after 12 months of TRT

Khera et al. J Urol. Sept 2011;186; 1005-1011

Serum PSA and Testosterone Flare


If one assumes that higher testosterone levels increase the risk for prostate cancer, then are lower testosterone levels considered protective against the development of prostate cancer?
Lower Testosterone Levels Increase the Risk for Prostate Cancer

- Morgentaler and Rhoden¹
  - 345 consecutive hypogonadal men with a PSA level less than 4.0 ng/mL
  - Prostate biopsy before initiating TRT
  - Low testosterone level (<250 ng/dl): 21% of men had prostate cancer
  - High testosterone levels (>250 ng/dl): 12% of men had prostate cancer
- Hoffman et al.²
  - 117 men diagnosed with prostate cancer
  - Low testosterone (<300 ng/dl): 47% chance of having prostate cancer on TRUS biopsy
  - Normal testosterone (>300 ng/dl): 28% chance of having prostate cancer on TRUS biopsy

¹Morgentaler and Rhoden, Urol, 2006
²Hoffman et al., J Urol, 2007

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=0.0005)
  - 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

Low Testosterone Levels Associated With More Aggressive And Higher Grade Prostate Cancer

- Hoffman et al.¹
  - 117 men diagnosed with prostate cancer
  - Incidence Gleason 8 or greater on TRUS biopsy
    - Low testosterone (<300 ng/dl): 11%
    - Normal testosterone (>300 ng/dl): 0% (p = 0.025)
- Patients with low total testosterone more likely to have positive surgical margins in RRP specimens²
- Lower testosterone and younger age resulted in a more aggressive disease and a worse prognosis in advanced prostate cancer³

¹Hoffman et al., J Urol, 2000
²Teloken et al., J Urol, 2005
Does giving testosterone to men with a history of prostate cancer increase the risk of recurrent prostate cancer?
Hypogonadal Patients without History of Prostate Cancer

• To date, there is no conclusive evidence that TRT causes prostate cancer

• Peak testosterone levels are seen in late teens & early 20’s, while peak prostate cancer 60’s-70’s

• Prostate cancer rate in over 7 published TRT trials was similar to screening trials of general population¹

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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

• Conclusions: 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

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¹ Hsing AW Epidemiol Rev 2001

Testosterone Replacement Therapy After Brachytherapy

- 31 men started TRT for a median of 2 years after brachytherapy
- Patients received TRT for a median 4.5 years
- Follow-up ranged 1.5 to 9.0 years (median, 5 years)
- Testosterone rose from 188 ng/dl to 498 ng/dl
- No patient stopped TRT because of cancer recurrence or demonstrated cancer progression


Testosterone Replacement Therapy after External Beam Radiotherapy

- Five hypogonadal men treated with TRT after EBRT
  - Follow-up of 14.5 months
  - Testosterone levels significantly increased
  - One patient had a transient increase in PSA, but none had levels >1.5 ng/ml
- Thirteen hypogonadal men treated with TRT after EBRT or brachytherapy²
  - Follow-up 29.7 months
  - Significant increase in testosterone levels
  - No significant increases in PSA or CaP recurrences

¹Morales et al. JU 2008; 103: 62
Testosterone After Radical Prostatectomy

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* PSA recurrence

TRT in High Risk CaP Patients

- Retrospective review of 103 hypogonadal men treated with TRT after RP between 2003-2011, and 49 non-hypogonadal controls having undergone RP treated during this time
  - **High Risk CaP** - post-surgical pathology with one or more of the following: Gleason score ≥ 8, 2) positive surgical margins, or 3) positive lymph nodes
  - **TRT Group** - 77 men with low/intermediate risk, CaP (non-high TRT group) with high-risk CaP
  - **Control Group** – 35 men non-high risk and 15 men high-risk CaP
- **Results:**
  1. 12 biochemical recurrences ONLY in high risk patients after 36 months
  2. 4 biochemical recurrence in TRT group
  3. 8 biochemical recurrence in control (non-TRT group)
TRT after Prostate Cancer

A total of 8 studies (abstracts + manuscripts) thus far have provided information on TRT after treatment for prostate cancer (RP, brachytherapy, EBRT)
- Total of 386 patients treated with testosterone after prostate cancer
- Only 6 men, or 1.5% of men, were noted to have a biochemical recurrence
- Recurrence rate is less than published series in favorable groups²
- TRT protective?

¹Morgentaler J Urol 2009; 181:972
²van Oort et al. Urol Oncol 2008 Epub

TRT and Prostate Cancer Cell Suppression

- Hatzoglou et al- membrane androgen receptor activation induced apoptotic regression of human prostate cancer cells in vitro and in vivo¹
- Sonnenschein et al. - androgens were able to trigger an inhibition of prostate cancer cell proliferation at higher concentration²
- Chuu et al. - androgens caused growth suppression and then reversion of androgen independent tumors to an androgen dependent tumors³

¹ Hatzoglou et al J Clin Endocrinol Metab 2005, 90:893-903
³Chuu et al Cancer Res 2005; 65:2082-4

TRT and Prostate Cancer Cell Suppression

- Prostate cancer LNCaP and MDA PCa 2b cells were treated with various levels of testosterone (T) (0 to 32ng/ml) or dihydrotestosterone (DHT) (0 to 8ng/ml)
- The growth rate of prostate cancer cells was assessed

Baylor College of Medicine
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 value 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

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Risk of Occult Prostate Cancer?

- Retrospective study of 13 men who elected surveillance of prostate cancer and received testosterone therapy for minimum of 6 months
- 12 men had Gleason grade 6 at initial biopsy, and 1 had Gleason 7 (3+4)
- Mean duration of testosterone therapy after diagnosis of prostate cancer was 23.5 months (range, 9-43 mo)

Testosterone Therapy With Untreated Prostate Cancer: Results

- No significant change in PSA
  - Initial: 5.5±6.4 ng/mL (range, 0.6-24.1 ng/mL)
  - Most recent: 3.7±2.6 ng/mL (P=.29)
- No change in prostate volume
  - Initial: 45.6±14.5 mL
  - Most recent: 52.4±19.8 mL (P=.11)
- No cancer progression seen in any individual
- No cancer identified in 54% of follow-up biopsies

PSA, prostate-specific antigen.

Conclusion

- While TRT does significantly impact PSA levels at low levels of serum testosterone, TRT does not appear to affect prostate size, or intra-prostatic testosterone levels. These findings may be due to the early saturation of androgen receptors within the prostate
- There is currently no evidence that TRT promotes the initiation of PCa in hypogonadal men
- To date there are 283 men reported in the literature receiving some form of TRT after prostate cancer treatment with low recurrence rates of <1%
- Larger randomized placebo controlled trials are needed to assess the safety and efficacy of TRT following prostate cancer treatment

Final Thought.....

- After a radical prostatectomy, if you do not replace testosterone levels in hypogonadal men to make them eugonadal, then how can you justify not lowering testosterone levels in eugonadal men to make them hypogonadal?
Thank you for your attention