

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

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# Which are the presumable risk factors for Prostate Cancer ?

Their presence increase the risk for PCa ?

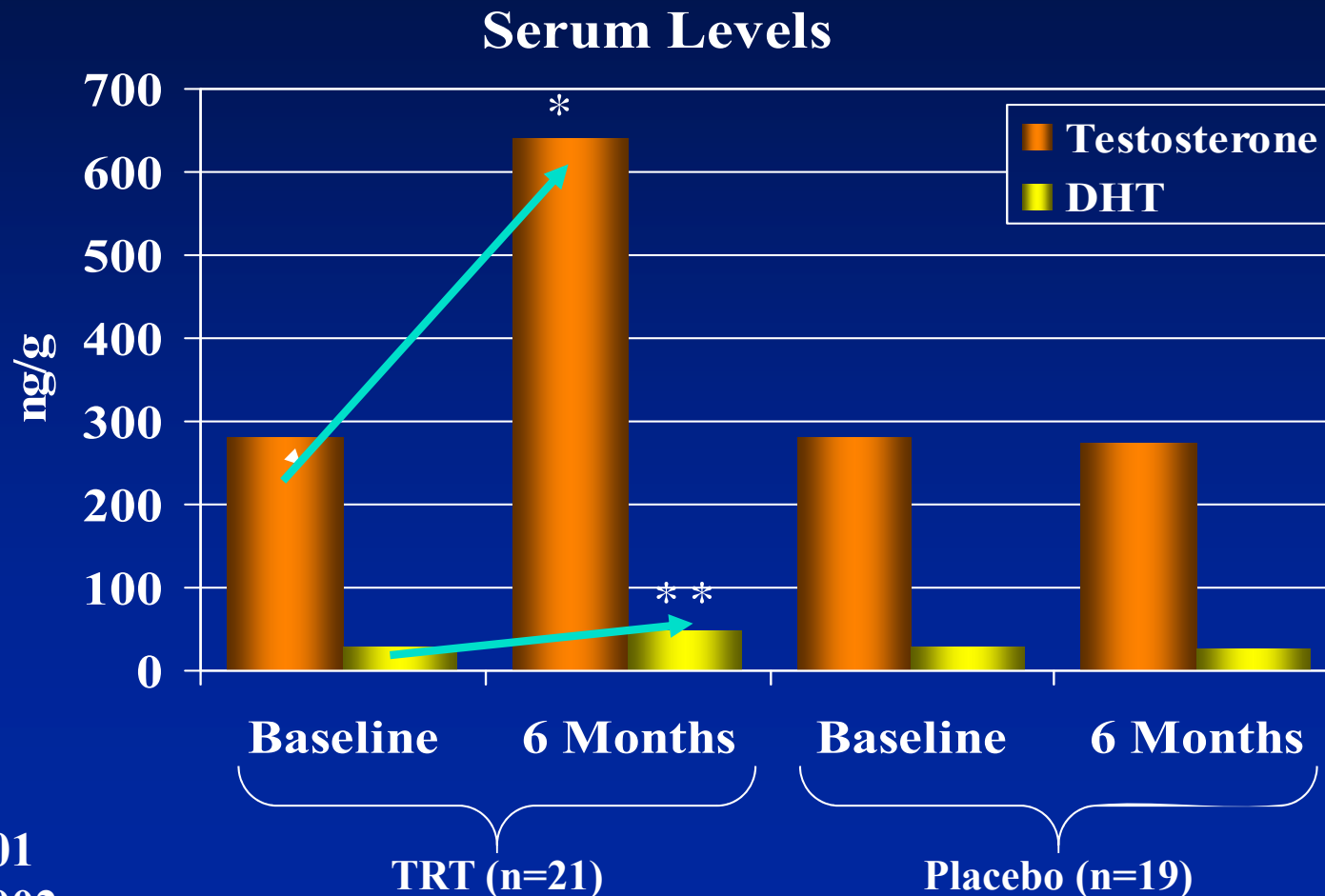
- Intraprostatic DHT
- Having a normal prostate
- PIN
- PSA
- Testosterone level
- Patients With Treated PCa
- Patients With Untreated PCa

# 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



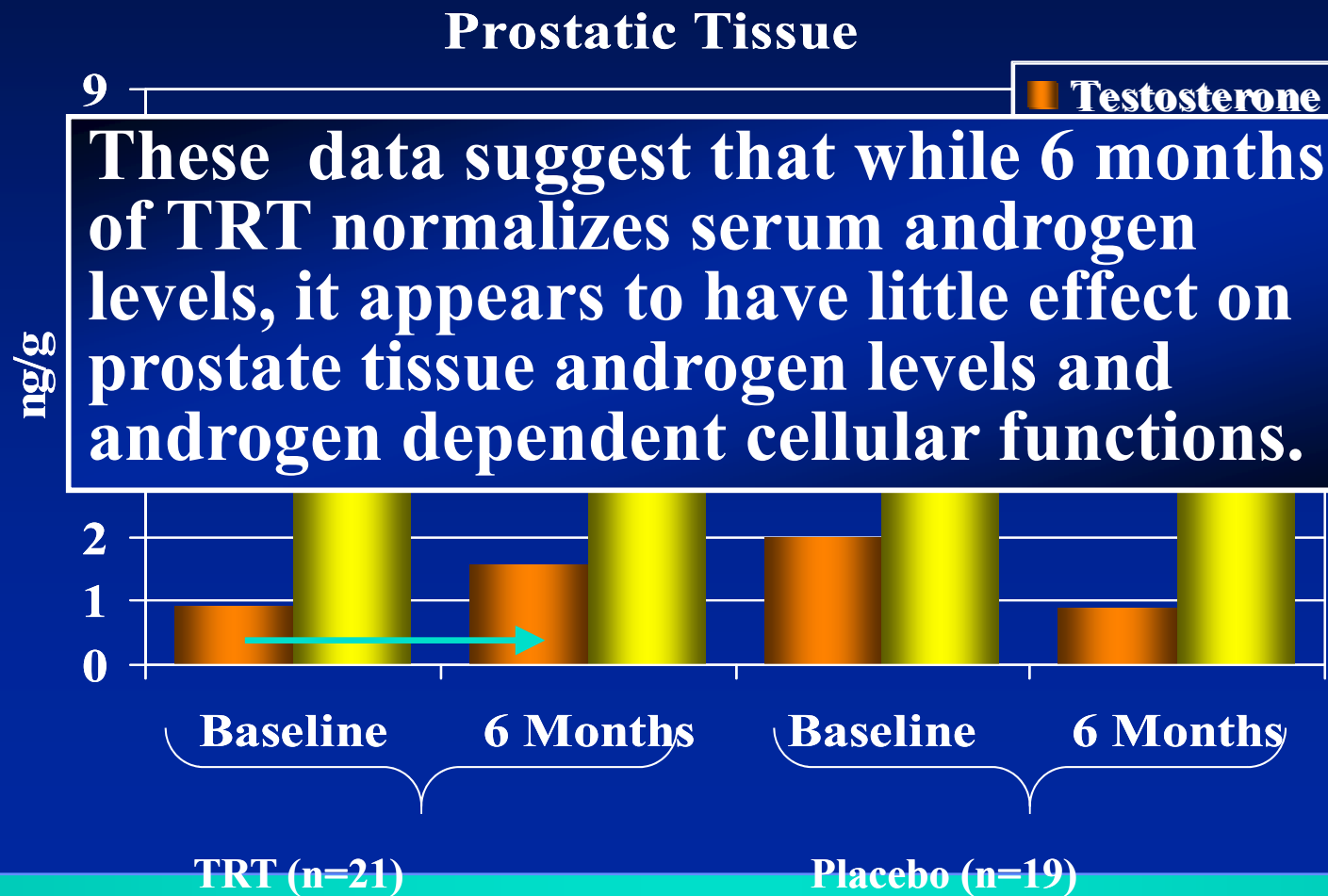
\*  $p < .001$

\*\*  $p < .002$

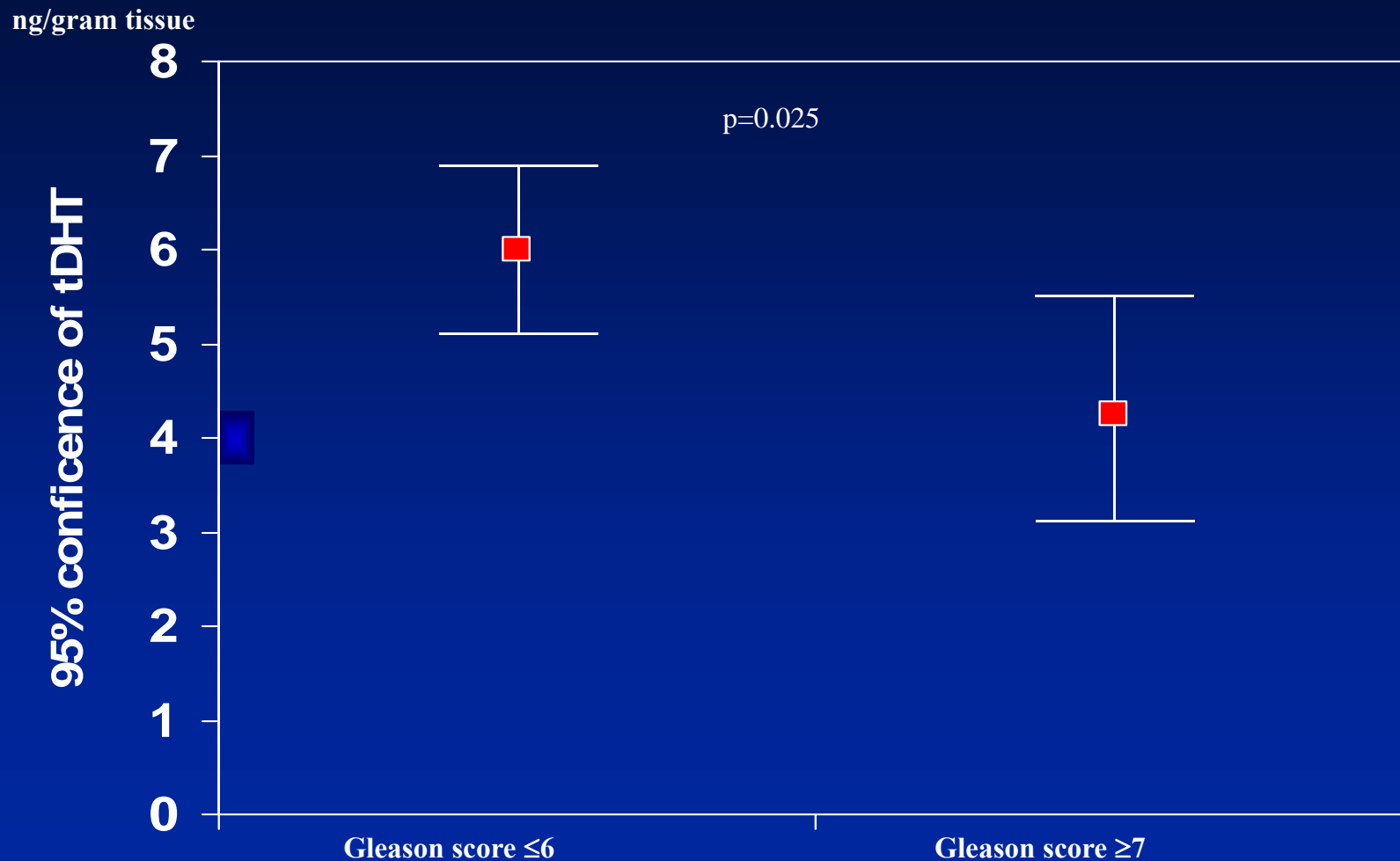
TRT (n=21)

Placebo (n=19)

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



# DHT in Prostatic Tissue in Patients with Gleason Score $\geq 7$ to 10 was Significantly Lower than in those with Gleason Score of $\leq 6$

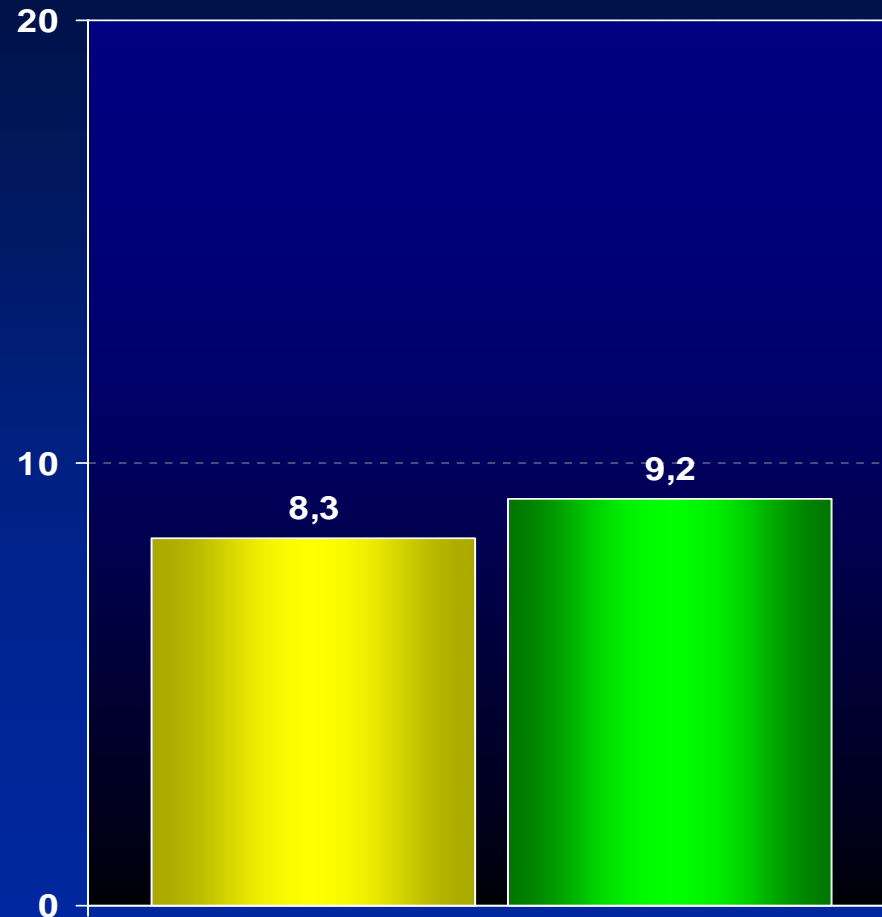


Nishiyama T et al. J Urol 176:1387-1391 (2006)

# 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



Diagnosed prostate cancer

Calof et al. J Gerontol 60A(11): 4051-4057 (2005)

# Systematic Review: PCa risk in Men submitted to TRT

- 11 RPC studies
- 29 non PC studies in men without hystory 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

# TRT

- Abstract 1506 - AUA 2013 – Eisenberg, et al.
  - 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

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

[1] Andriole G et al. New Engl J Med 360(13): 1310-1319 (2009); [2] Schröder F et al. New Engl J Med 366(11): 981-990 (2012)

Haider A et al. J Urol, published online June 26, 2014

# PIN and TRT

# High Risk (HG PIN)

- HG PIN: 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<sup>1</sup>
  - 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.<sup>2</sup>
  - 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.<sup>3</sup>
  - 600mg of testosterone or placebo weekly for 10 weeks
  - PSA did not change significantly from baseline despite supraphysiological testosterone levels (>2800 ng/dl)

<sup>1</sup> Rhoden EI, Morgentaler A Int J Impot Res 2006

<sup>2</sup> Grober et al. IJIR 2008; 20(6): 561

<sup>3</sup> 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

- Isom-Batz, et al. J Urol. 2005; 173: 1935-1937
  - Lower testosterone correlated with higher:
    - Pathological stage
    - Clinical stage
    - Biopsy Gleason grade
- Teloken, et al. J Urol. 2005; 174: 2178-2180
  - Lower testosterone correlated with:
    - Increased positive surgical margins
      - 39% in low TT vs 14.6% in normal TT
- Schatzl, et al. J Urol. 2003; 169: 1312-1315
  - 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)

# TRT in Patients With Treated PCa

# TRT post Radical Prostatec- tomy

Author	No. of Patients	Follow-up (months)	PSA Increase
Kaufman 2004	7	24-132	-
Agarwal 2005	10	9-19	-
Mulhall 2008	22	8-40	1
Carrion 2008	14	12 (media)	-
Khera 2009	57	1-99	-
Sommer 2010	69	6-72	-
Sathyamoorthy 2010	133	12 (média)	-
Matsushita 2012	71	2-48	1
Patuszak 2013	103	1-49,5	4
Total	486	1-132	6 (1,23%)

Kaufman et al. J Urol 2004,172:920-922

Agarwal et al. J Urol 2005;173:533-536

Mulhall et al. J Urol 2008;179(supp 4):426

Carrion et al. J Urol 2008;179(supp 4):428

Khera et al. J Sex Med 2009;6:1165-1170

Sommer et al poster 1496 AUA 2010

Sathyamoorthy et al. J Urol 2010;183(suppl e 577)

Matsuzhita et al. J Sex Med 2012;9(supp4):183:298

Patuszak et al. Int J Impot Res 2013 Jan;25(1):24-8

# TRT post Brachytherapy

Author	No. of Patients	Follow-up (months)	PSA Pre TRT	PSA Post TRT
Sarosdy 2006	31	18-108	NI *	100% < 1 98% < 0,5 74% < 0,1

NI = Not informed



# TRT Post Radiotherapy

Author	No. of Patients	Follow-up (months)	PSA Pre TRT	PSA Post TRT
Davilla 2008	6	9	0,15	0,1
Morales 2008	5	6-27	0,1-0,97 (0,3)	< 0,1 – 1,08
Patuszak 2013	13	0-23,7	0,1	< 0,1

Davilla et al. J Urol 2008;179(supp 4):428; Morales et al. BJU Int 2008;103:62-64

Patuszak et al Int J Impot Res 2013 Jan;25(1):24-8

# TRT post Orchiectomy

Author	No. of Patients	Follow-up (months)	PSA Pre TRT	PSA Post TRT
Netto 2006 *	5	18 - 30	2,0 - 7,4	4,5 – 8,4

•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)

# TRT After Multiple Treatments

Author	No. of Patients	Follow-up (months)	PSA Pre TRT	PSA Post RT
Brawer 2004	1	14	Indetectable	Indetectable

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

Brawer et al.Rev Urol 2004;6 (supp6):S35-S37

# TRT in Patients With Untreated PCa

# TRT in patients with PCa under active surveillance

Author	No. of Patients	Follow-up (months)	PSA Pre TRT	PSA PostTRT
Morgentaler 2013	33	3 - 34	0,6 – 15,5	0,9 – 9,2
Mulhall 2014	15	6.2 – 11 y	3.7 +/- 1.2	5.6 +/- 1.1

Tiype of Treatment	N of Patients	Follow up	PSA Increase
Radical Prostatectomy	486	1– 132	6
Brachytherapy	31	18 - 38	-
Radiotherapy	24	0- 27	-
Orchiectomy	5	18 - 30	-
Multiple Treatments	1	14	-
Active Surveillance	48	3 - 34	-
Total	595	0 m – 11 y	6 (1,01%)

# 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>