IPOGONADISMO,
PATOLOGIA PROSTATICA
E DISFUNZIONI SESSUALI:

Endocrinologo ed Urologo a confronto

28 SETTEMBRE 2018
MILANO
Starhotel Echo
Viale Andrea Doria 4

RUOLO DEL TESTOSTERONE NEL CARCINOMA DELLA PROSTATA: LUCI E OMBRE

Fiore Pelliccione

Diabetologia e Malattie Metaboliche

Ospedale "F. Renzetti" – Lanciano – CH

fiore.pelliccione@gmail.com

ANDROGENI & PROSTATA

STRETTO LEGAME

During fetal and adult life, prostate differentiation, development, growth and function are regulated both directly and indirectly Androgens (T, DHT)

DHT → masculinization, initiating formation of the prostate, penis and male reproductive tract

Masculinization programme window (genital tubercle sensitive to As) → between 8 weeks and 12 weeks gestation in humans

DHT → regulate more than 200 genes, including PSA

DHT-AR ligation in epithelial and stromal cells → synthesis of growth factors, which act on epithelial and stromal compartments in a paracrine and an autocrine manner

Isaacs JT. Testosterone and the prostate; Cambridge University Press. 2004

Matsushita S et al., Nat Rev Urol. 2018

UTILIZZO TESTOSTERONE (T) NEL TEMPO

SEXUAL MEDICINE REVIEWS

REVIEW

The History of Testosterone and the Evolution of its Therapeutic Potential

2018

Abraham Morgentaler, MD,[1] and Abdulmaged Traish, PhD[2]

1935-1940 "Honeymoon period"

1935 → isolation of T David KG et al., Physiol Chem 1935

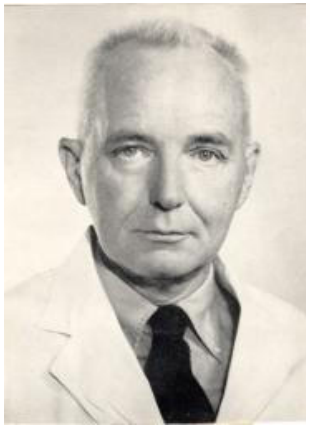
Early clinical experience with T in male hypogonadism Aub JC. NEJM, 1940

T treatment in peripheral vascular disease Baser et al., NEJM, 1942

T treatment in angina pectoris Walker TC. Med Rec Ann 1940; Walker TC. J Clin Endocrinol 1942; Hamm L. J Clin Endocrinol 1942; Lesser MA. NEJM 1942; Levine SA, Likoff WB. NEJM 1943; Waldman S. J Clin Endocrinol 1945

T & PCa

HOW THE T "DARK SIDE" BEGAN…



Canc Res 1941

Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

(From the Department of Surgery, the University of Chicago, Chicago, Illinois)

(Received for publication March 22, 1941)

8 men with metastatic PCa → castration/estrogen treatment → ↓ acid phosphatase, suggesting improvement in cancer status.

Daily injections of T in 3 men for 14 days → ↑ acid phosphatase.

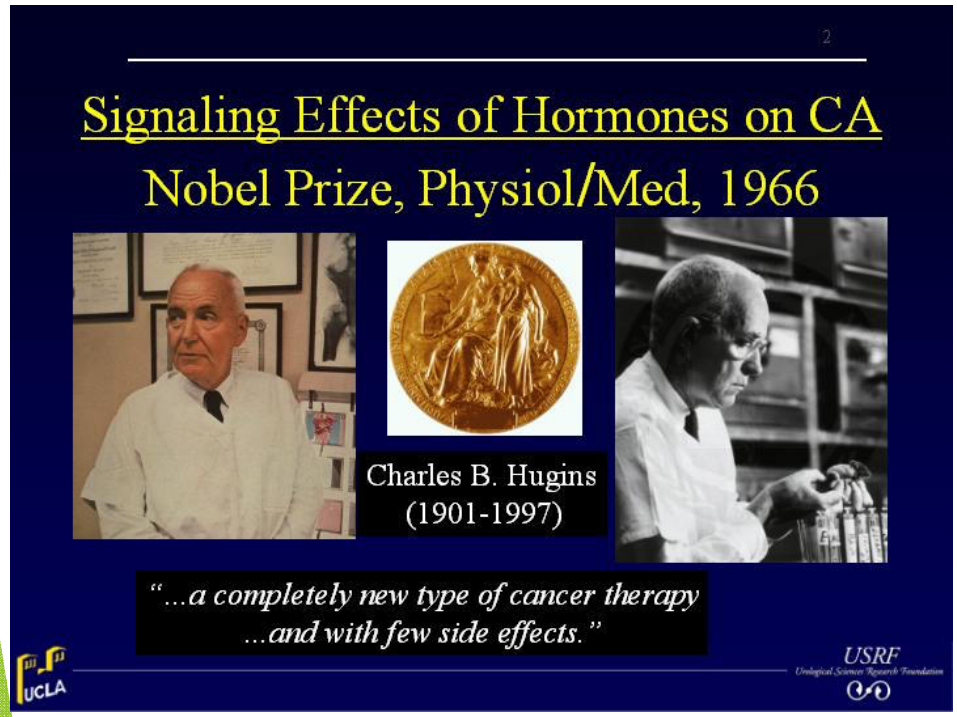
Conclusion: "PCa is activated by androgen injections."

Androgen deprivation therapy (ADT) became the mainstay of treatment for advanced PCa and remains so to this day

T & PCa

THE T "DARK SIDE" GOES ON…

Fowler and Whitmore: after T to 52 men with advanced and metastatic PCa 45 developed an "unfavorable response" within 30 days." Fowler JE, Whitmore WF Jr. J Urol 1981



THE «ANDROGEN HYPOTESIS»

- **PCa is androgen-dependent**
- **high T → contribute development PCa**
- **high T → PCa rapid growth**
- **low T → protective against PCa**
- **low T → causes PCa to regress. testosterone and prostate cancer was classified**

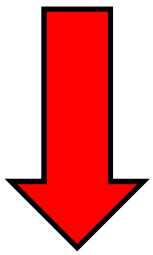
T in PCa is like "fuel for a fire" or "food for a hungry tumor"

T & PCa

THE T "DARK SIDE"

In the early 1990s, the use of T was rare, and limited to younger men with severe hypogonadism (due to pituitary tumors, anorchia, or genetic abnormalities such as Klinefelter syndrome)

Over the past 20 years → remarkable growth in the use of T therapy as a result of increased awareness of T deficiency and the benefits of treatment (improved sexual desire, performance, energy, increased muscle and bone density, metabolic status)



REEXAMINATION OF TRADITIONAL ASSUMPTIONS CONCERNING PCa AND T

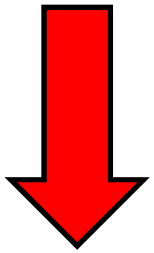
T & PCa

BREAKDOWN THE ANDROGEN HYPOTESIS

<u>Old data had been misinterpreted</u>.

1) Original report by Huggins and Hodges: a) daily injections of T and assessment of acidic phosphatase in 3 pts; b) results present for 2 pts; c) ↑ acidic phosphatase in 1 pt castrated (not in non-castrated one)

2) In the report by Fowler and Whitmore 3 hormonally intact men received daily T injections for up to 355 days without an unfavorable response.



Men on ADT respond differently to T administration compared with moderately hypogonadal men

T & PCa

BREAKDOWN THE ANDROGEN HYPOTESIS

Morgentaler A et al., JAMA 1996

77 TD men with normal PSA (<4.0 ng/mL) and a normal DRE

Prostate biopsy before initiating T testosterone therapy

11/77 (14%) PCa, the same rate expected in a random population.

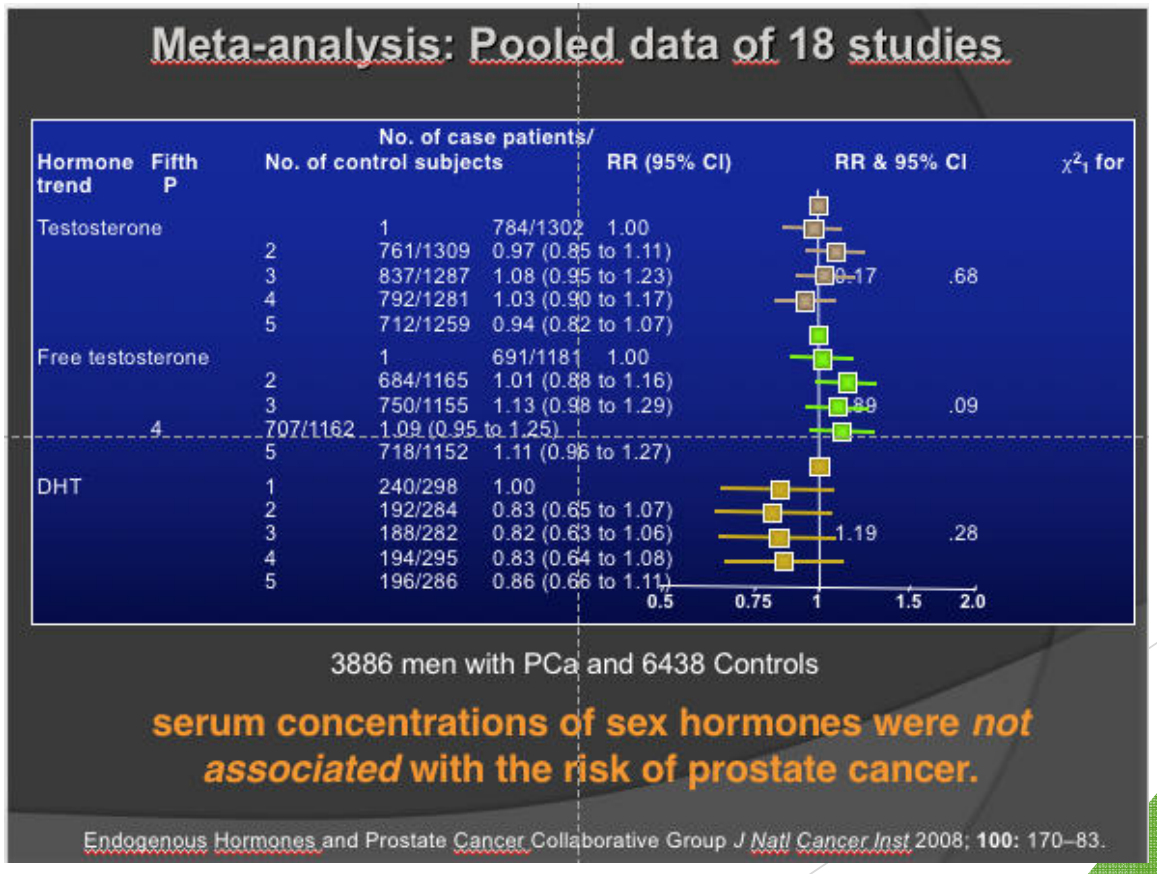
A subsequent study of prostate biopsies in a larger group of 345 men with TD deficiency confirmed the original results, with an overall cancer rate of 15%

Morgentaer A, Urology 2006

T & PCa

BREAKDOWN THE ANDROGEN HYPOTESIS

Subsequent longitudinal studies → no relationship between PCa and serum T or As.



HOWEVER…

ADT → rapid ↓ PSA; Stop ADT → rapid ↑ PSA

T administration to hormonally intact PCa men → no evidence of PCa progression

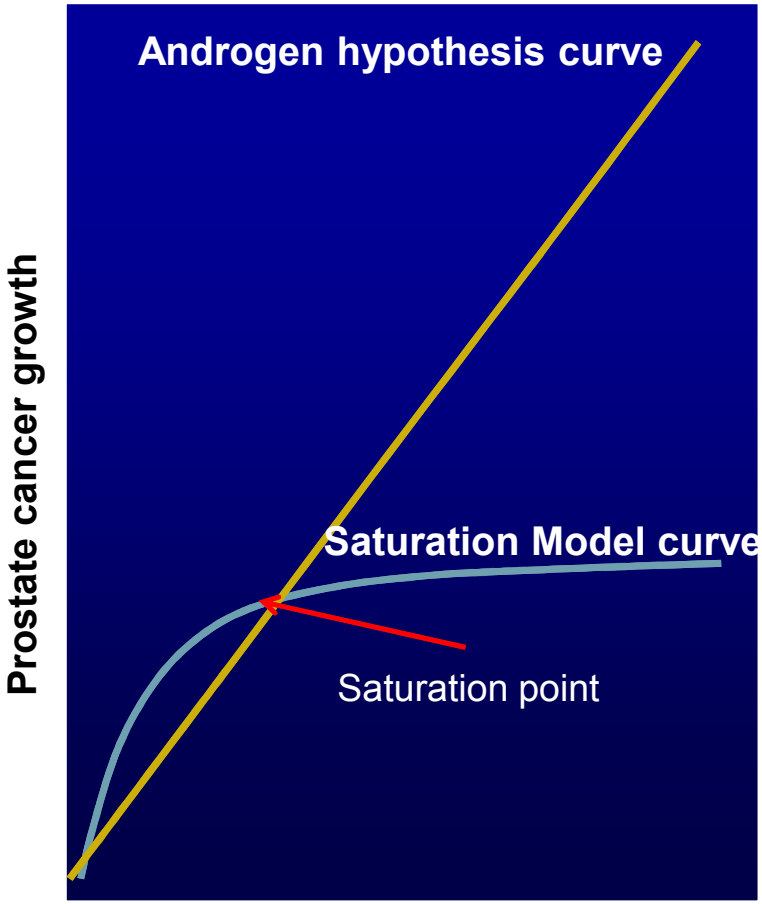
Highly sensitive to ADT (low T)

Indifferent to T variations at normal/high concentrations

T & PCa

THE SATURATION MODEL

Morgentaer and Traish, Eur Urology 2009

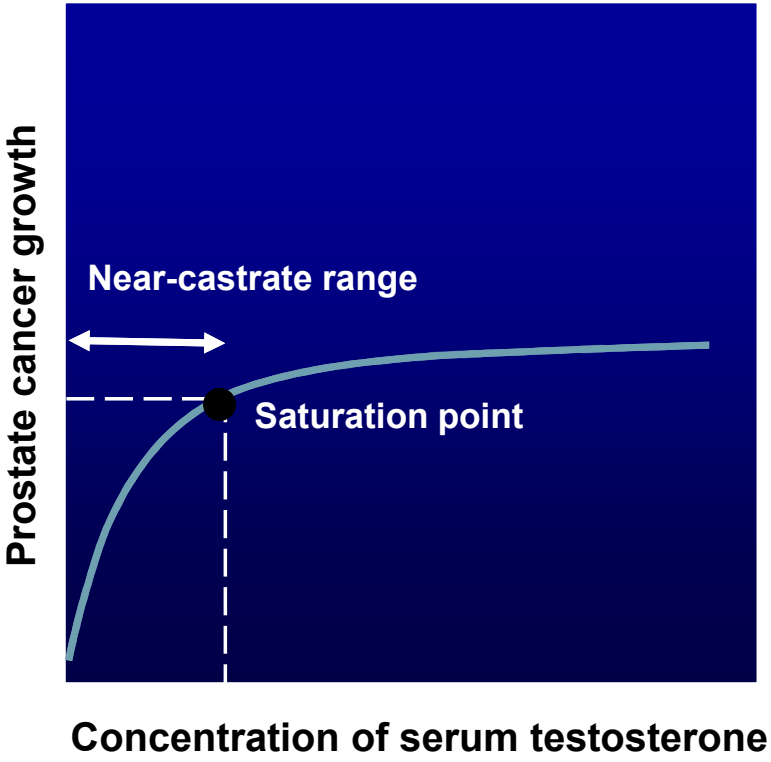


Binding DHT to AR:

- **high stereospecificity**
- **high affinity**
- **limited capacity: finite number of binding sites per cell.**
- **steep increase in binding seen with increasing As up to a plateau (filling of all binding sites).**

Once AR is saturated the presence of higher As concentrations should not elicit any further biochemical response.

T & PCa
THE SATURATION MODEL



Maximal DHT–AR binding (saturation):

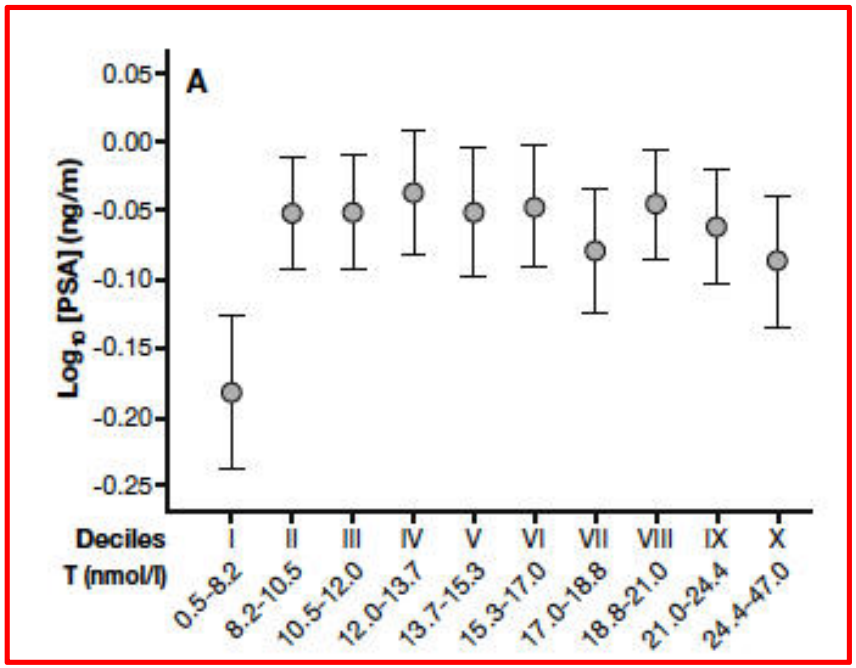
- **in vitro → 4 nmol/l (125 ng/dl)**
- **In vivo → 8 nmol/l (250 ng/dl) near-castrate/hypogonadism range**

Below saturation point → high prostate sensitivity to As (T-dependent phase)
Above saturation point → little/no As effects on prostate (T-independent phase)

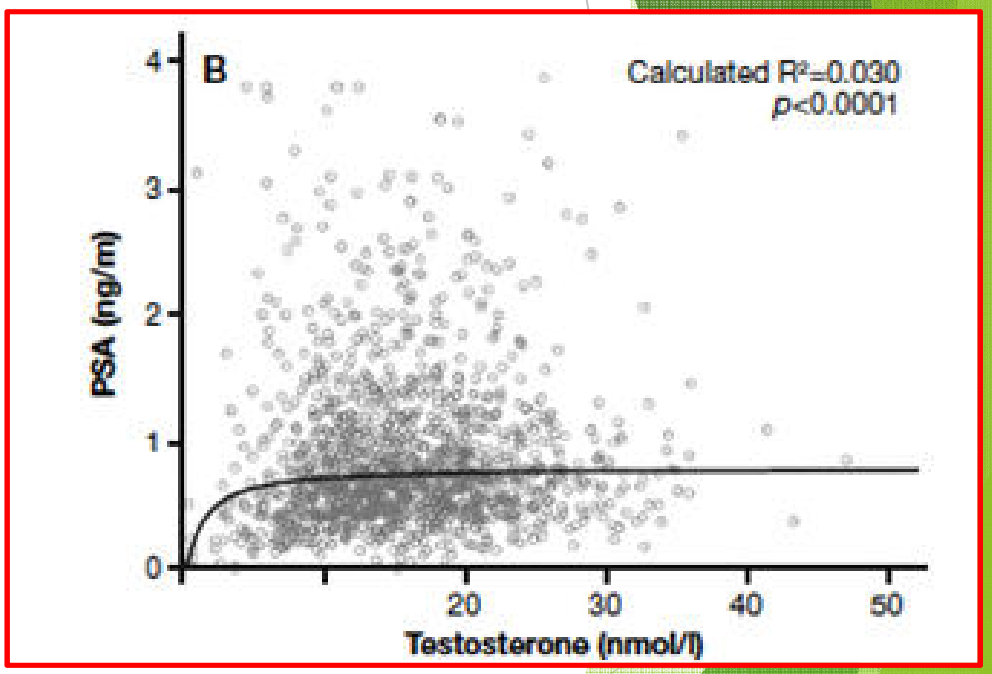
Eugonadal range (>12nmol/l-350ng/dl) → T and DHT in excess at physiologic concentrations

Morgentaler A & Traish AM. *Eur Urol* 2009; **55:** 310–21.

THE SATURATION MODEL IN HUMAN



PSA levels as a function of total T deciles in 2757 men



Relationship between T and PSA levels with a best-fitting regression curve

Corona G et al., J Sex Med 2010

THE SATURATION MODEL IN HUMAN

T administration to eugonadal men

31 healthy men (28 yr) randomozed to weekly T injections of 100mg, 250mg, or 500mg over the **40-wks**. Supraphysiologic T concentrations (1138 ng/dl and 1994 ng/dl) in 250mg and 500mg groups.
No significant changes in PSA or prostate volume. Cooper CS at al., J Urol 1998

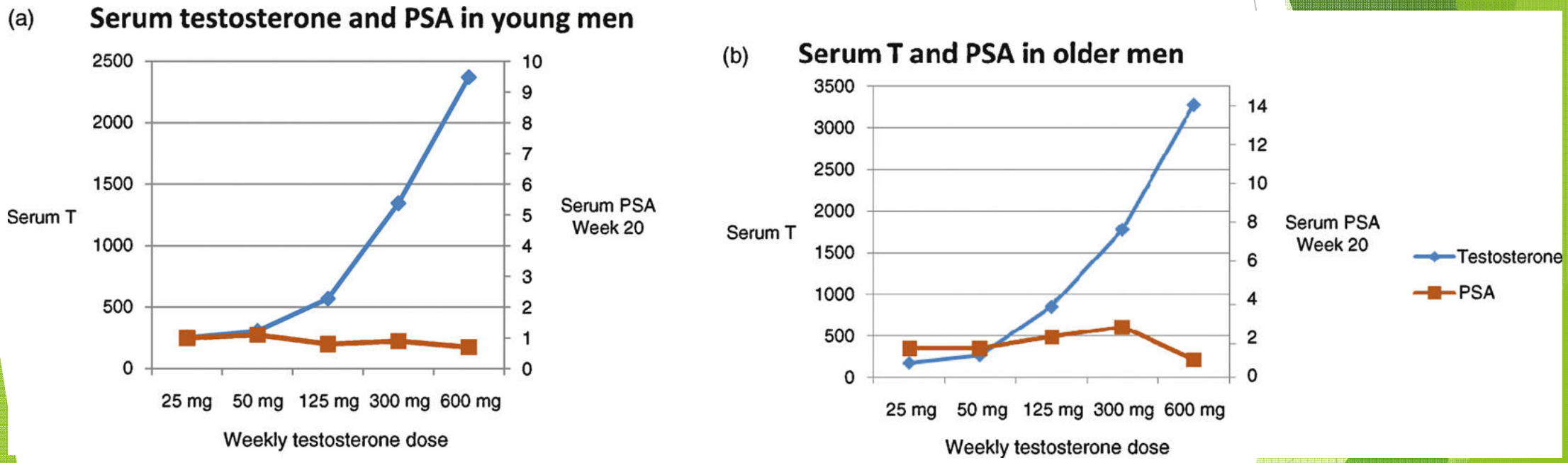
Men (19-40 yr) randomized to 600 mg T or placebo weekly for **10 wks**. Treated men → supraphysiologic T concentrations greater than 2800 ng/dl.
PSA levels did not change from baseline. Bhasin S et al., NEJM 1996

27 men treated with a T patch; and 31 men received placebo for **24 mo**.
No difference in PSA values were noted between the groups Nair KS et al., NEJM 2006

207 older eugonadal men randomized to oral T undecanoate or placebo for **6 mo**.
Changes in PSA levels were not different between groups Emmelot-Vonk MH et al., JAMA 2008

THE SATURATION MODEL IN HUMAN

T administration to eugonadal men

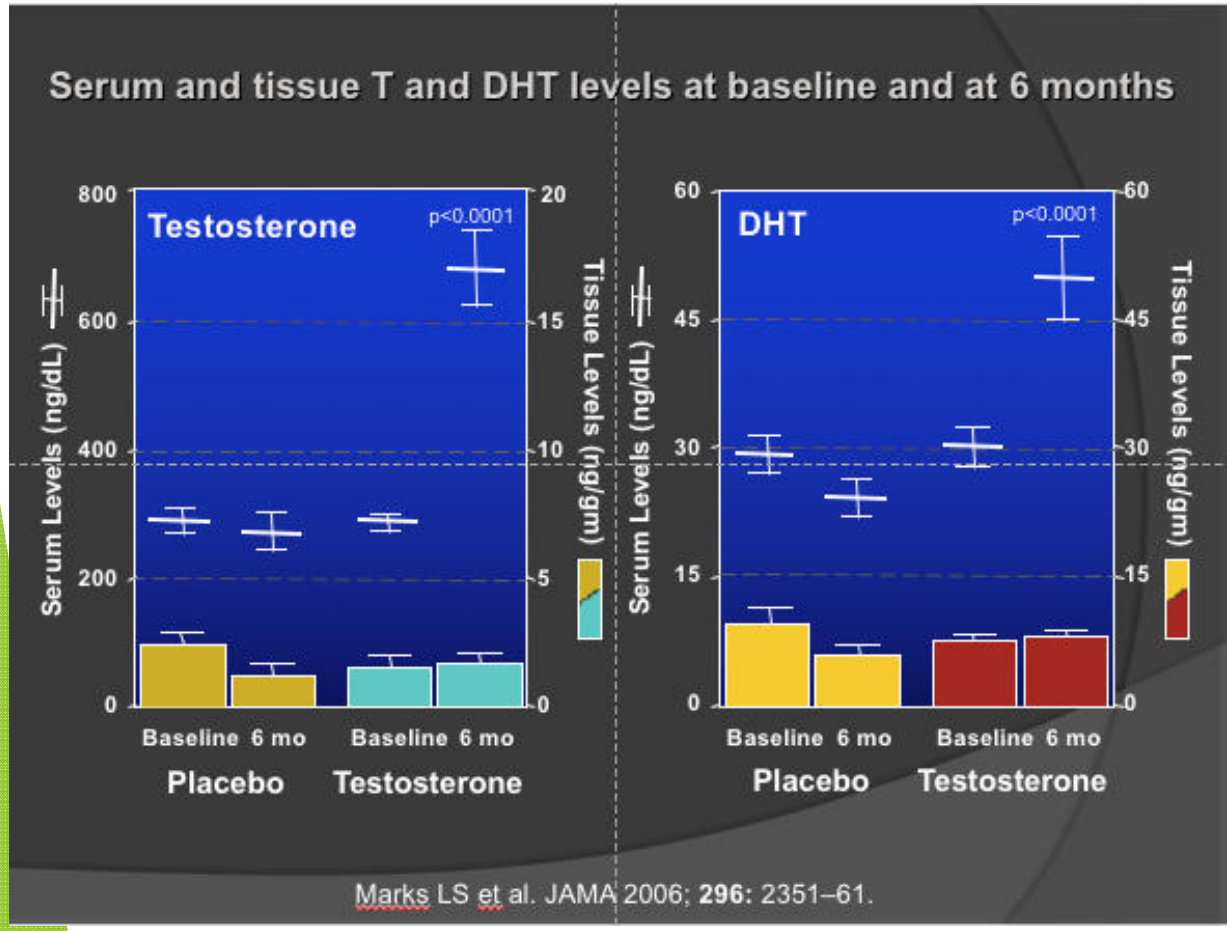


Bhasin S et al., Am J Physiol End Metab 2001

VARIATION OF T CONCENTRATIONS IN THE NEAR-PHYSIOLOGIC TO SUPRAPHYSIOLOGIC RANGE → NO EFFECT ON THE PROSTATE

THE SATURATION MODEL IN HUMAN

T administration and intraprostatic As



44 TD (TT <300 ng/dl) randomized to TE 150 mg every 2 wks or Pbo for 6 mo

Assessment of TT and DHT in serum and prostatic tissue

Intraprostatic TT and DHT unchanged despite large increases As in serum

T SAFETY: TRT IN HYPOGONADAL MEN

Data from longitudinal prospective studies

Testosterone treatment is not associated with increased risk of prostate cancer or worsening of lower urinary tract symptoms: prostate health outcomes in the Registry of Hypogonadism in Men

Frans M.J. Debruyne*, Hermann M. Behre†, Claus G. Roehrborn‡, Mario Maggi§, Frederick C.W. Wu¶, Fritz H. Schröder**, Thomas Hugh Jones††, Hartmut Porst‡‡, Geoffrey Hackett§§, Olivia A. Wheaton¶¶, Antonio Martin-Morales***, Eric J. Meuleman†††, Glenn R. Cunningham‡‡‡, Hozefa A. Divan¶¶ and Raymond C. Rosen¶¶ for the RHYME Investigators

BJUI
BJU International
2017

Large multi-national prospective registry of HG men designed and powered to assess PCA outcomes in men with HG receiving TRT compared with untreated

750 men received a form of TRT and 249 did not. Assessments were performed at 3– 6, 12, 24, and 36 months

Proportion of positive biopsies was identical in men on TRT (37.5%) compared to those not on TRT (37.0%)
There were no differences in PSA levels, total IPSS, or the IPSS obstructive sub-scale score by TRT status.

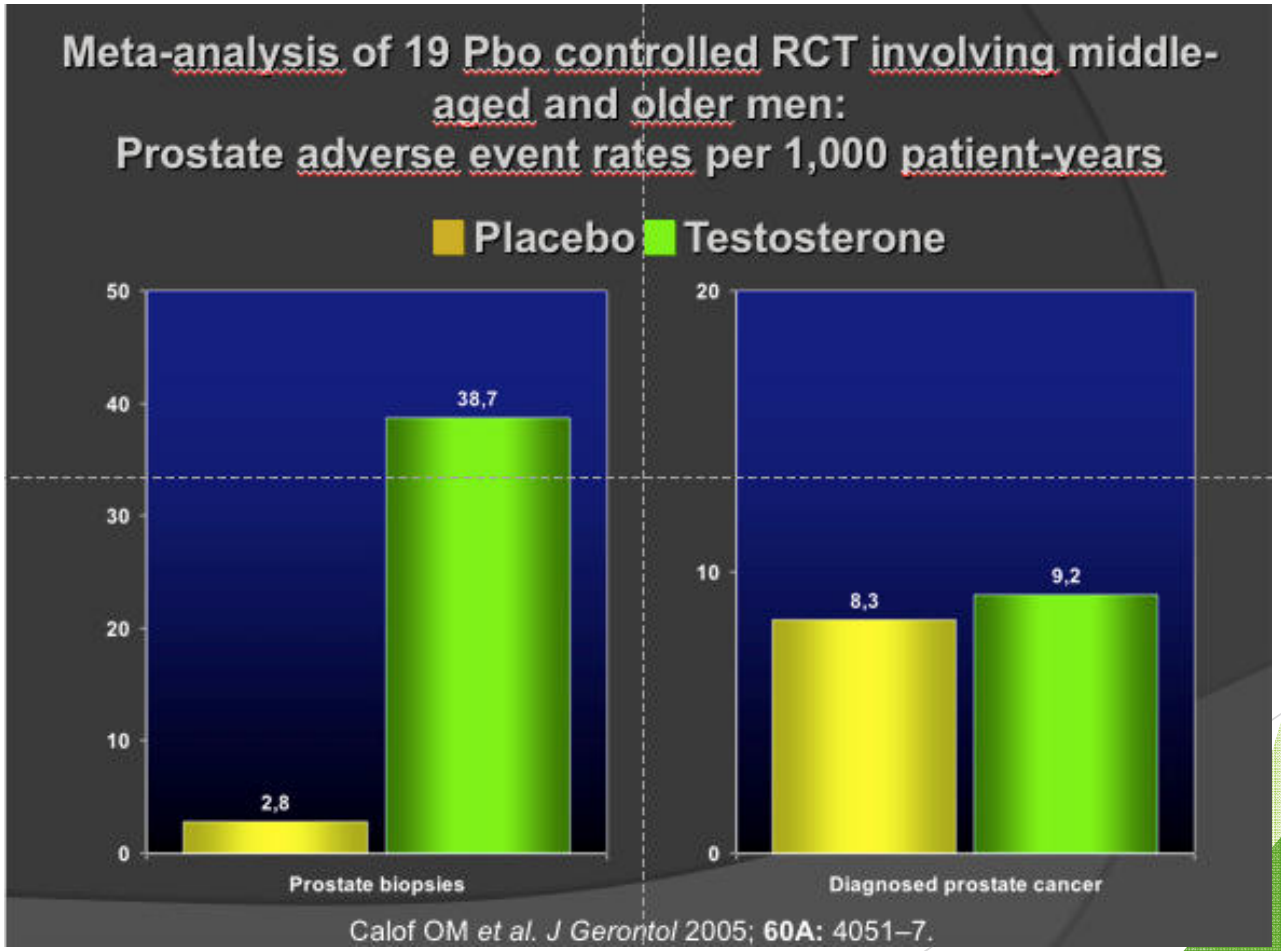
RESULTS SUPPORT PROSTATE SAFETY OF TRT IN NEWLY DIAGNOSED MEN WITH HG.

OTHER LONGITUDINAL REGISTRY STUDIES HAVE OBSERVED SIMILAR FINDINGS FOR LONG-TERM TRT EFFECTS ON PROSTATE OUTCOMES

Yassin DJ et al., World J Urol 2014; Francomano D et al., Urology 2014; Zitzmann M et al., J Sex Med 2013

T SAFETY: TRT IN HYPOGONADAL MEN

Data from meta-analyses of RCT



T SAFETY: TRT IN HYPOGONADAL MEN

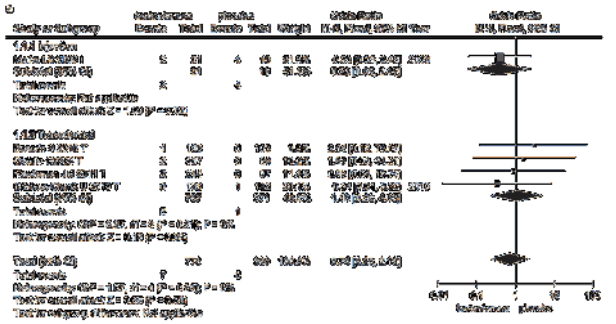
Data from meta-analyses of RCT

ORIGINAL ARTICLE

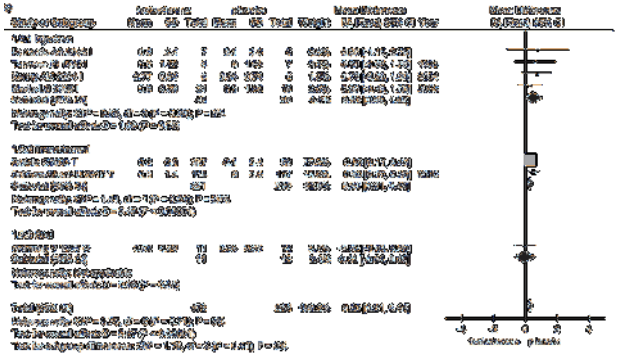
The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis

Y Cui, H Zong, H Yan and Y Zhang Prostate Cancer and Prostatic Disease (2014)

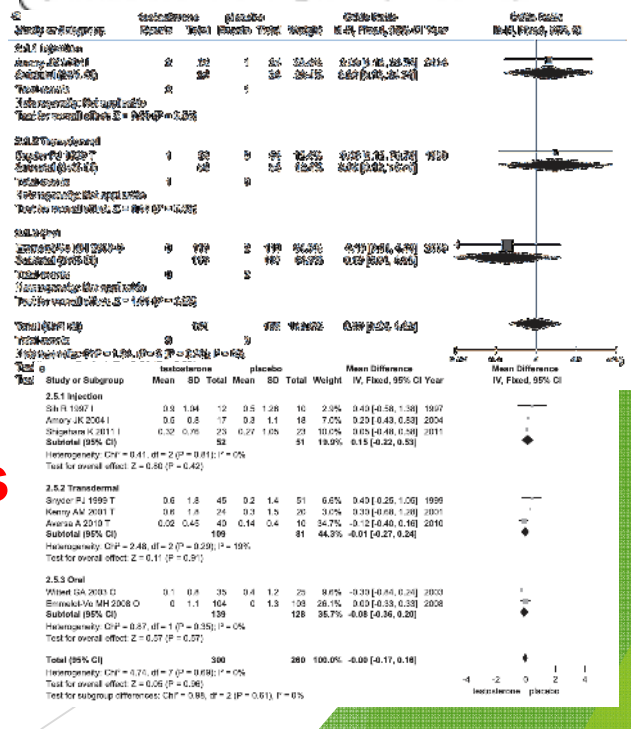
22 articles with 22 RCTs were included in the analysis: 11 RCTs compared testosterone with a placebo over the short term (<12 mo) and 11 RCTs compared testosterone with a placebo over the long term (12–36 mo).



PCa



PSA changes



T SAFETY: TRT IN HYPOGONADAL MEN

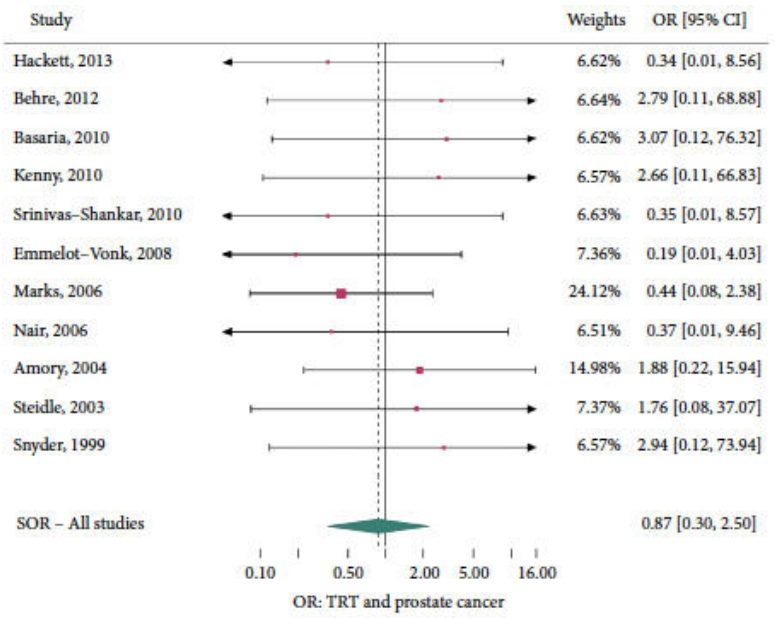
Data from meta-analyses of RCT

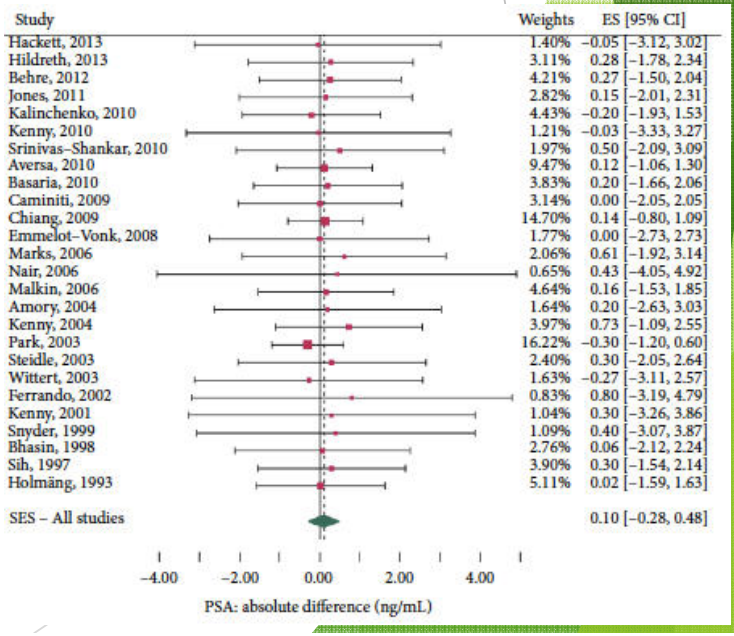
BJUI
BJU International

2016

Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis

Peter Boyle*,†, Alice Koechlin*,†, Maria Bota*,†, Alberto d'Onofrio†, David G. Zaridze‡, Paul Perrin§, John Fitzpatrick¶, Arthur L. Burnett** and Mathieu Boniol*,†



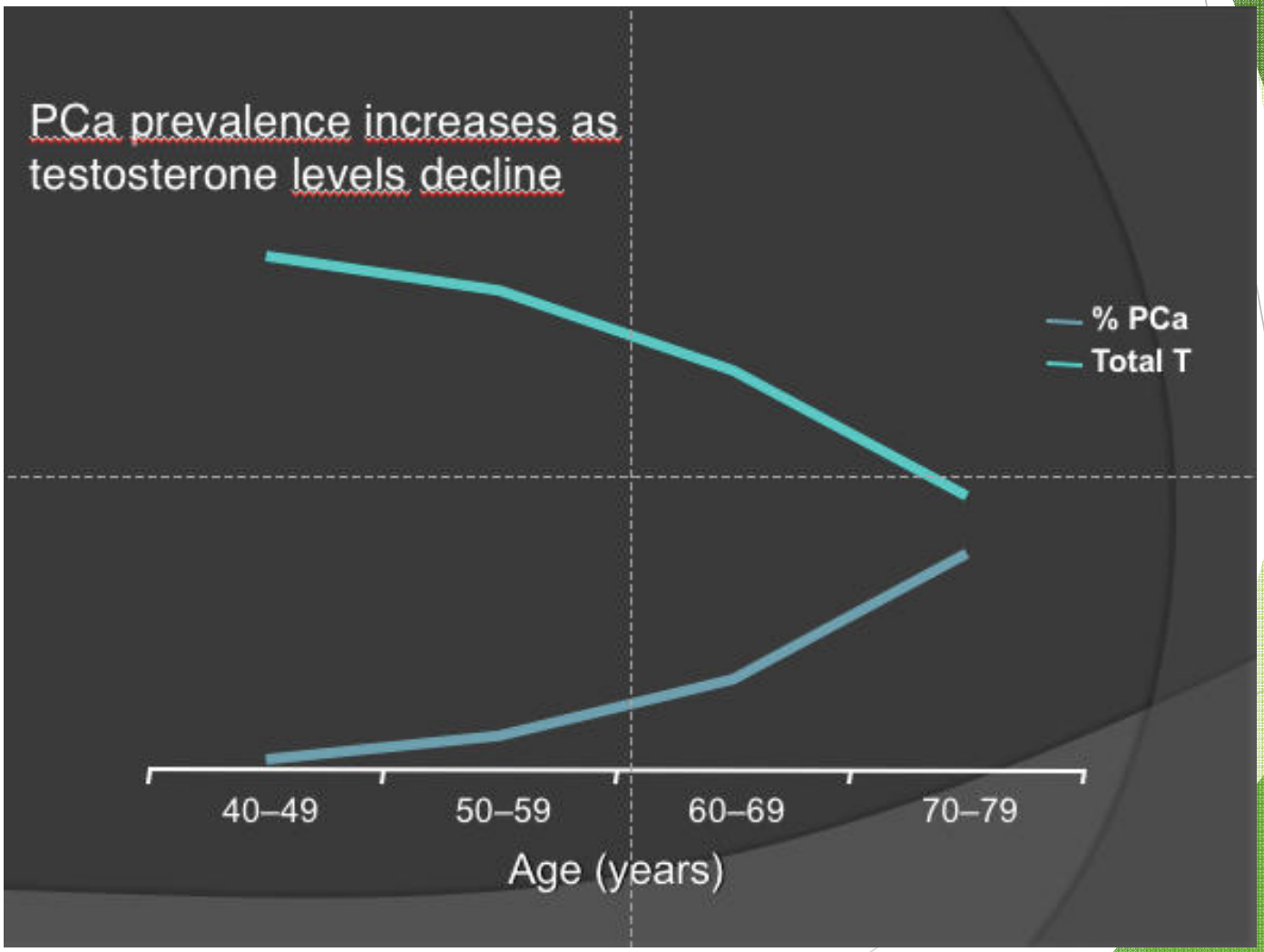


T SAFETY: TRT IN HYPOGONADAL MEN

Data from meta-analyses of RCT

TRT THERAPY HAS A LIMITED, IF ANY, CLINICALLY RELEVANT EFFECT ON PROSTATE-CANCER RISK IN INDIVIDUALS WITH LOW–NORMAL BASELINE TESTOSTERONE LEVELS.

LOW T AND PCa


PCa prevalence increases as testosterone levels decline
% PCa
Total T
40–49
50–59
60–69
70–79
Age (years)

LOW T AND PCa

- Incidence of biopsy-tissue-detected PCa in hypogonadal men → 14-15% (the same expected in random population) Morgentaler A et al., JAMA 1996; Urology 2006
- High-grade PCA (Gleason ≥ 8 or) was more likely to be found in men with TT < 300ng/dl Hoffman MA et al., J Urol 2000
- Lower TT levels → indipendent predictor of extracapsular extension Massengill JC et al., J Urol 2003
- Risk of seminal vesicle invasion increased significantly in men with low TT levels measured the day before RP Salonia A et al., Cancer 2011
- Increased rates of biochemical recurrence after RP in patients with low TT Yamamoto S et al., Eur Urol 2007
- Preoperative TT <300 ng/dl → poorer prognosis among men with metastatic PCA → survival duration reduced by 6 mo compared with men with TT > 300 ng/dl Ribeiro M et al., Am J Clin Oncol 1997

LOW T ASSOCIATED WITH INCREASED RISK OF PCA, GREATER AGGRESSIVENESS OF DISEASE AND POORER PROGNOSIS

TAKE HOME MESSAGES

- **STRETTA ASSOCIAZIONE TRA TESSUTO PROSTATICO ED ANDROGENI**
- **RAPPORTO PCA E T RIVALUTATO ALLA LUCE DEL MODELLO DI SATURAZIONE VS IPOTESI ANDROGENICA**
- **MODELLO DI SATURAZIONE: NESSUN RAPPORTO TRA As ENDOGENI E PCA**
- **MODELLO DI SATURAZIONE: SICUREZZA TRT IN SOGGETTI IPOGONADICI (STUDI OSSERVAZIONALI PROSPETTICI E METANALISI DI RCT**
- **MODELLO DI SATURAZIONE: ASSOCIAZIONE TRA BASSO T E PCA**
- **MODELLO DI SATURAZIONE: SICUREZZA TRT IN IPOGONADICI CON PREGRESSO PCA??**


Grazie