Testosterone Replacement and Focal Therapy

Mohit Khera, M.D., M.B.A., M.P.H.
Associate Professor of Urology
Scott Department of Urology
Baylor College of Medicine
Houston, TX

Disclosures

- Consultant- Abbvie, Boston Scientific, Coloplast, Endo

Should hypogonadal patients following focal therapy be treated any differently than those patients being treated with other prostate cancer therapies?

A survey of Canadian urologists' opinions and prescribing patterns of testosterone replacement therapy in men on active surveillance for low-risk prostate cancer

Adam C. Millar, MD;[1] Dean S. Elterman, MD;[2*] Larry Goldenberg, MD;[3] Brandon Van Asseldonk, BASc;[4] Ashley Curtis, MA;[4] Keith Jarvi, MD[5]*

[1]Division of Endocrinology and Metabolism, Department of Medicine, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada; [2]Division of Urology, Department of Surgery, University Health Network, Toronto, ON, Canada; [3]Department of Urologic Sciences, University of British Columbia Vancouver, BC, Canada; [4]Division of Urology, Department of Surgery, University of Toronto, Toronto, ON, Canada; [5]Division of Urology, Mount Sinai Hospital, Toronto, ON, Canada

Table 1. Results of survey on physicians' beliefs regarding TRT in men with low-risk PCa and prescribing habits

Questionnaire item	Total "Yes" respondents (%)	Total "No" respondents (%)
1. Do you treat men with PCa?	53 (93%)	4 (7%)
2. Do you use active surveillance as one method to manage men with low-grade/low-stage PCa?	54 (95%)	3 (5%)
3. Do you prescribe TRT for patients with TDS without PCa?	49 (86%)	8 (14%)
4. Is it safe to prescribe TRT for patients on active surveillance?*	36 (63%)	20 (35%)
5. Does TRT increase risk of PCa progression in men on active surveillance?*	20 (35%)	36 (63%)
6. Would you offer TRT for TDS if on active suveillance for PCa?	37 (65%)	20 (35%)
7. Have you offered TRT for men with TDS on active surveillance?	20 (35%)	37 (65%)
8. Do you have men on active surveillance who are on TRT?	24 (42%)	33 (58%)
9. Is it safe to prescribe TRT for men who received curative treatment for PCa using the following:		
a) Radical prostatectomy	a) 55 (96%)	a) 2 (4%)
b) Radiation therapy**	b) 48 (84%)	b) 8 (14%)
c) Brachytherapy	c) 49 (86%)	c) 8 (14%)

Millar et al Can Urol Assoc J. 2016 May-Jun;10(5-6):181-184.

Incidence of Prostate Cancer in Men on TTh

- Prostate cancer rate in over 7 published TTh trials was similar to screening trials of general population[1]
- Meta-analysis of 19 placebo-controlled testosterone therapy studies in men with low or low-normal testosterone [2]
  - Comparison of men treated with testosterone vs placebo revealed no difference in:
    - PCa incidence
    - Change in PSA
    - Urinary symptom scores

[1] Hsing AW Epidemiol Rev 2001

[2] Calof OM, et al. *J Gerontol A Bio Sci Med Sci.* 2005;60(11):1451-1457

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

- The Registry of Hypogonadism in Men (RHYME) registry of treated and untreated hypogonadal men (*n* = 999)
- 750 (75%) initiated TRT
- Mean testosterone levels increased from 8.3 to 15.4 nmol/L in treated men, compared to 9.4 to 11.3 nmol/L in untreated men
- 55 prostate biopsies performed for suspected prostate cancer
- Proportion of positive biopsies was nearly 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

Debruyne et al BJU Int.2017 Feb;119(2):216-224

Testosterone Therapy in Men With Prostate Cancer

Alan L. Kaplan[a,], Jim C. Hu[b], Abraham Morgentaler[c], John P. Mulhall[d], Claude C. Schulman[e], Francesco Montorsi[f]*

[a] *Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA;* [b] *Department of Urology, Weill Cornell Medical College, New York, NY, USA;* [c] *Men's Health Boston, Harvard Medical School, Boston, MA, USA;* [d] *Sexual and Reproductive Medicine Program, Urology Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA;* [e] *Department of Urology, Erasme Hospital, Brussels, Belgium;* [f] *Department of Urology, Universita Vita-Salute San Raffaele, Milan, Italy*

Study	No. of patients	Intervention	Follow-up, mo	Gleason score (no. of patients)	Pretreatment PSA	Post-treatment PSA	Pretreatment T, ng/dl	Post-treatment T, ng/dl
Kaufman and Graydon [44]	7	RP	24	6 (6) 7 (1)	<0.1	<0.1	97	434
Agarwal and Oefelein [45]	10	RP	19	6 (2) 7 (7) 8 (1)	<0.1	<0.1	197	591
Khera et al [46]	57	RP	13	≤6(24) 7 (26) 8(4)	0.005	0.005	225	459
Pastuszak et al [47]	103	RP	27.5	<6 (1) 6,7 (72) ≥8 (9)	0.004	0.007	261	460
Sarosdy [48]	31	Brachytherapy	60	5 (3) 6 (19) 7 (6)	NA	<1	188	489
Balbontin et al [49]	20	Brachytherapy	31	≤6 (16) 7 (3) 8 (1)	0.7	0.1	343	587
Morales et al [50]	5	EBRT	14.5	6 (2) 7 (1) 8 (2)	0.1–0.97	<0.1–1.08	150	507
Pastuszak et al [51]	13	Brachytherapy and EBRT	29.7	6 (4) 7 (7) 8 (2)	0.30	0.66	178	368
Pastuszak et al [52]	98	Brachytherapy and EBRT	40.8	≤6 (47) 7 (28) 8 (7) 9 (4)	0.08	0.09	209	420
Kaplan et al [53,54]	1,181	RP EBRT Brachytherapy AS/WW	72	Well (9752) Mod (87 786) Poor (50 635)[b]	NA	NA	NA	NA
Morgentaler and Rhoden [55]	13	AS	30	6 (12) 7 (1)	5.5	3.6	238	664
Morales [57]	6	AS	N/A	6 (5) 8 (1)	5.66	NA	259	NA
Kacker et al [59]	28	AS	38.9	6 (22) 7 (6)	3.29	4.31	328	NA

AS = active surveillance; EBRT = external beam radiation therapy; Mod = moderate; PSA = prostate specific antigen; RP = radical prostatectomy; WW = watchful waiting.
[a] Adapted from Khera et al [8].
[b] SEER-Medicare data categorizes differentiation pattern (well, moderate, poor) rather than Gleason score.

Kaplan et al Eur Urol. 2016 May;69(5):894-903

Testosterone Replacement Therapy After Brachytherapy

- 31 men started TTh for a median of 2 years after brachytherapy
- Patients received TTh 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 TTh because of cancer recurrence or demonstrated cancer progression

Sarosdy A, *Cancer*, 2006.

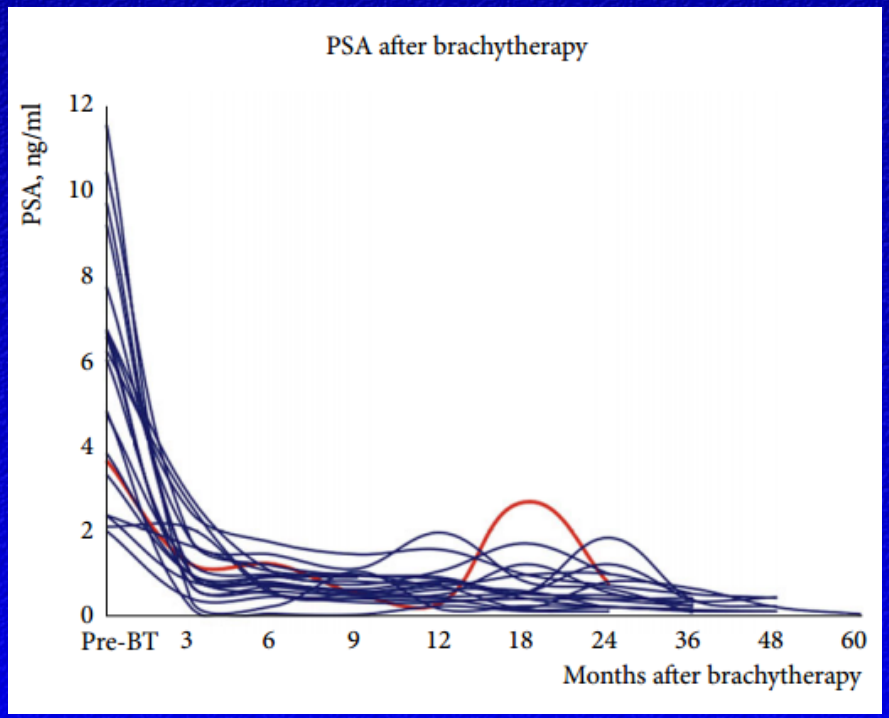
Testosterone Replacement Therapy after External Beam Radiotherapy

- Five hypogonadal men treated with TTh 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 TTh after EBRT or brachytherapy[2]
  - Follow-up 29.7 months
  - Significant increase in testosterone levels
  - No significant increases in PSA or CaP recurrences

[1]Morales et al. BJU 2008; 103: 62

[2] Pastuszak et al Int J Impot Res 2013 Jan;25(1):24-8.

T Therapy after Brachytherapy



- T therapy after brachy
- N=20
- Gleason ≤6: 16 men
- Gleason 3+4: 3 men
- Gleason 4+4: 1 man
- Median f/u 31 mo (12-41 mo)
- SHIM increased 16 to 22 (p=0.002)
- No PCa recurrences

Balbontin et al, BJUI 2014

Testosterone Therapy after Radiation Therapy for Low, Intermediate and High Risk Prostate Cancer

Alexander W. Pastuszak, Abhinav Khanna, Niraj Badhiwala, Abraham Morgentaler,* Mariam Hult,† William P. Conners,‡ Michael F. Sarosdy,§ Christopher Yang, Rafael Carrion, Larry I. Lipshultz‖ and Mohit Khera¶,**

- **98 hypogonadal men treated with TTh after XRT or brachytherapy**

Table 2. *Characteristics of patients with BCR*

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6
GI	7	Unknown	8	9	Unknown	7
ADT	No	No	Yes	Yes	Yes	No
RT type	Brachytherapy	EBRT	Brachytherapy	EBRT	Brachytherapy	Brachytherapy
RT end-TTh start (mos)	16	Not applicable	15	17	Not applicable	Not applicable
PSA (ng/ml):						
TTh start	2.8	1.9	Less than 0.003	0.2	0.76	Less than 0.01
BCR workup max	3.8	3.6	2.2	5.3	4.7	4.5
Followup end	0.91	3.6	1.2	40	4.7	Less than 1.0
TTh stopped	No	No	Yes	Yes	No	Yes
Prostate biopsy	No	No	Yes (neg)	No	No	Yes (neg)
Computerized tomography	No	No	Yes (neg)	No	No	No
Bone scan	No	No	Yes (neg)	No	No	No
TTh restarted	Not applicable	Not applicable	Yes	No	Not applicable	No
Outcome	Not applicable	Not applicable	Not applicable	Bicalutamide	Lost to followup	Bicalutamide

- **Among high risk patients, PSA increased from 0.10ng/dl to 0.36ng/dl**
- **Six (6.1%) men met criteria for biochemical recurrence**

Pastuszak et al. J Urol. 2015 Nov;194(5):1271-6

Testosterone After Radical Prostatectomy

Study	No. of Patients	Follow-up (months)	Pre TRT PSA	Post TRT PSA	Pre T	Post T
Agarwal et al	10	19	<0.1	<0.1	197	591
Kaufman et al	7	24	<0.1	<0.1	97	434
Khera et al	57	17	0.005	0.005	275	440
Pastuszak et al	103	27.5	0.004 (median)	0.007* (median)	261	460

* 4 PSA recurrences

Agarwal J Urol 2005.
Kaufman et al J Urol 2004.
Khera et al JSM 2009
Pastuskaz et al J Urol 2013

Testosterone Replacement Therapy in Patients with Prostate Cancer After Radical Prostatectomy

Alexander W. Pastuszak,* Amy M. Pearlman,* Win Shun Lai,* Guilherme Godoy,* Kumaran Sathyamoorthy,* Joceline S. Liu,* Brian J. Miles,* Larry I. Lipshultz† and Mohit Khera‡,§

- **Retrospective review of 103 hypogonadal men treated with TTh after RP between 2003-2011 and 49 eugonadal controls having undergone RP treated during this time**
  - **High Risk CaP - post-surgical pathology with one or more of the following: 1) Gleason score ≥8, 2) positive surgical margins, or 3) positive lymph nodes**
  - ***TTh Group* - 77 men with low/intermediate risk CaP (non-high risk) and 26 with high-risk CaP**
  - ***Control Group* – 34 men non-high risk and 15 men high-risk CaP**
- **Results:**
  - **12 biochemical recurrences ONLY in high risk patients after 36 months**
    - **4 biochemical recurrence in TTh group (15.3%)**
    - **8 biochemical recurrences in control (non-TTh group) (53.3%)**

Pastuszak et al J Urol. 2013 Aug;190(2):639-44

TTh after Prostate Cancer

- A total of 9 published studies thus far have provided information on TTh after treatment for prostate cancer (RP, brachytherapy, EBRT)
  - Total of 346 patients given TTh after treatment for their prostate cancer
- Only 10 men, or 2.8 % of men, were noted to have a biochemical recurrence
- Recurrence rate is <u>less</u> than published series in <u>favorable</u> groups[2]
- TTh protective?

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

TTh and Prostate Cancer Cell Suppression

- Hatzoglou et al- membrane androgen receptor activation induced apoptotic regression of human prostate cancer cells in vitro and in vivo[1]
- Sonnenschein et al. - androgens were able to trigger an inhibition of prostate cancer cell proliferation at higher concentration[2]
- Chuu et al. - androgens caused growth suppression and then reversion of androgen independent tumors to an androgen dependent tumors[3]

[1] Hatzoglou et al J Clin Endocrinol Metab 2005, 90:893-903
[2]Sonnenschein et al. Cancer Res 1989, 49:3474-81
[3]Chcuu et al Cancer Res 2005, 65:2082-4

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VOLUME 9 • WINTER 2013

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The Patrick C. Walsh Prostate Cancer Research Fund

A New Way to Treat Recurrent Prostate Cancer: More Testosterone?

Volume 9, Winter 2013

CANCER

Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: Results from a pilot clinical study

Michael T. Schweizer,*† Emmanuel S. Antonarakis, Hao Wang, A. Seun Ajiboye, Avery Spitz, Haiyi Cao, Jun Luo, Michael C. Haffner, Srinivasan Yegnasubramanian, Michael A. Carducci, Mario A. Eisenberger, John T. Isaacs, Samuel R. Denmeade†

- 14 patients with CRPC
- TE 400mg IM q month for 3 months
- Castrating therapy continued to suppress endogenous testosterone production, allowing for rapid cycling from supraphysiologic to near-castrate serum testosterone levels = bipolar androgen therapy (BAT)
- BAT was well tolerated and resulted in high rates of PSA (7 of 14 evaluable patients) and radiographic responses (5 of 10 evaluable patients)

Sci Transl Med.2015 Jan 7;7(269):

Bipolar Androgen Therapy for Men With Androgen Ablation Naïve Prostate Cancer: Results From the Phase II BATMAN Study

- 29 asymptomatic hormone sensitive (HS) prostate cancer patients
  - Low metastatic burden
  - Non-metastatic with biochemical recurrence
- 6 mo ADT followed by 400mg TC IM every 4 weeks for 3 months
- 59% of men had PSA < 4ng/dl after 18 mo (primary endpoint)
- Significant improvements noted in SF-36 and IIEF

Schweizer et al Prostate. 2016 Sep;76(13):1218-26

Asian Journal of Andrology (2014) 16, 1–5

www.asiaandro.com; www.ajandrology.com

Open Access

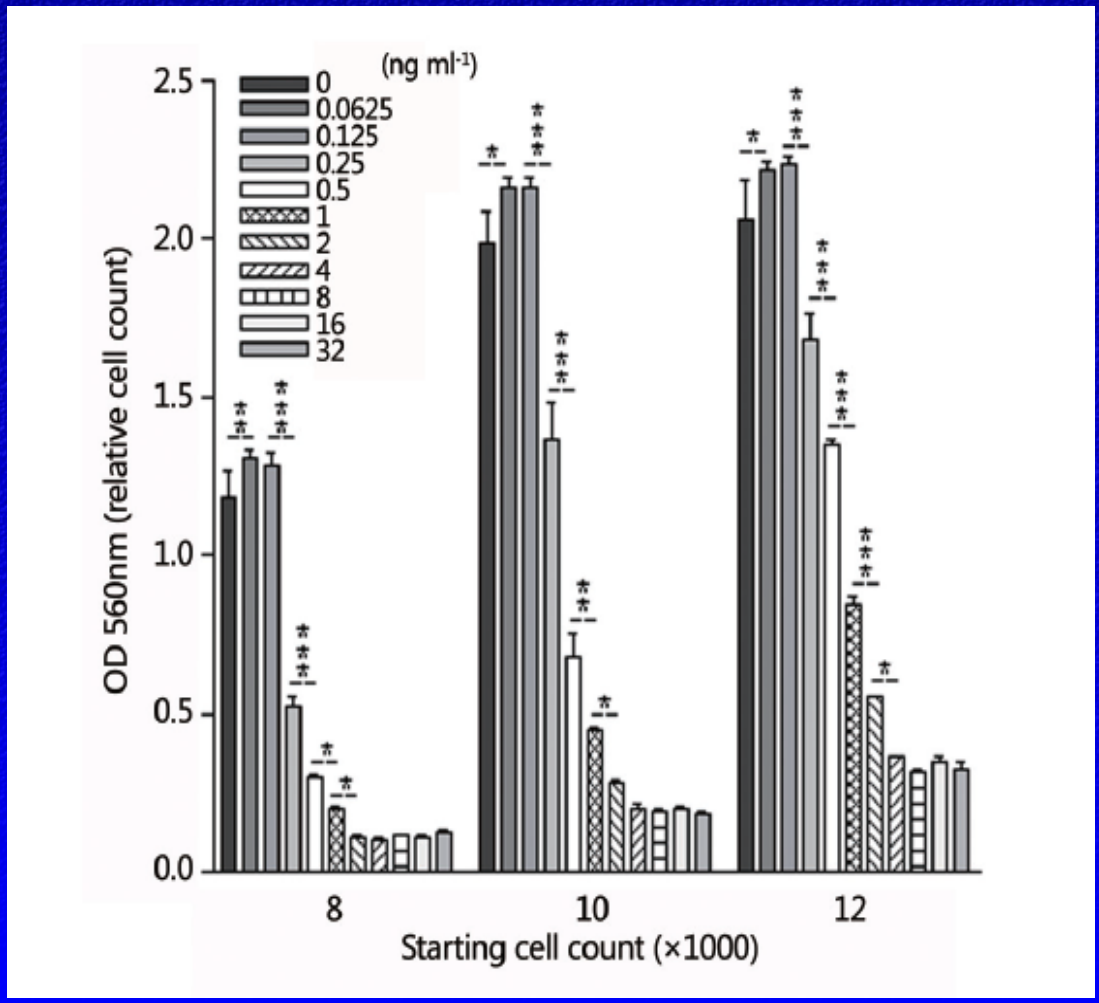
ORIGINAL ARTICLE

Prostate Cancer

Physiological normal levels of androgen inhibit proliferation of prostate cancer cells *in vitro*

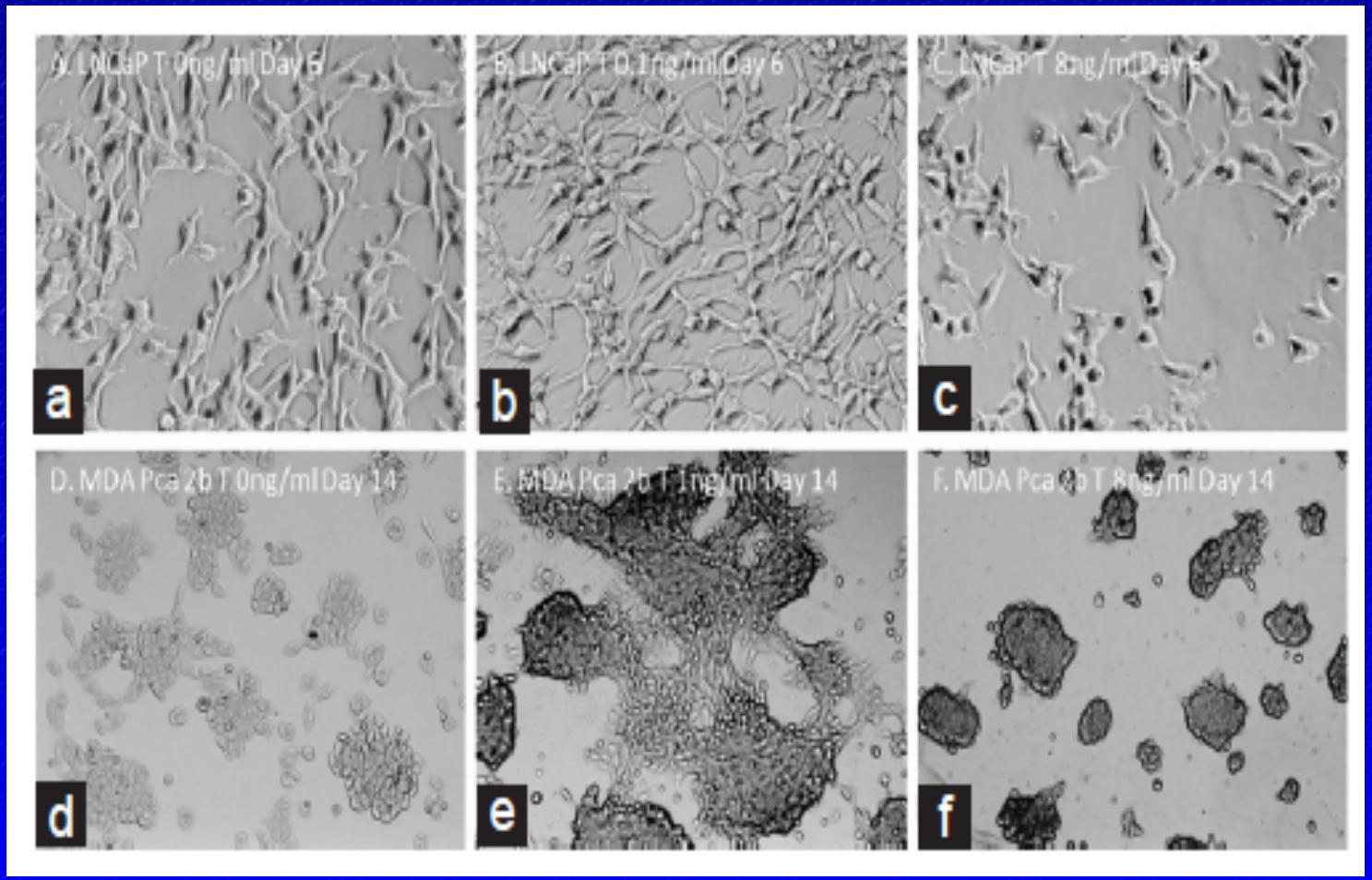
Weitao Song, Mohit Khera

- Prostate cancer LNCaP cells were treated with various levels of testosterone (T) (0 to 16ng/ml)
- 8-12K cells were seeded in triplets, T treatment for 10 days
- The growth rate of prostate cancer cells was assessed



Song W, Khera M: AJA 2014 Epub

LNCaP and MDA Pca 2b Cells Treated with Testosterone

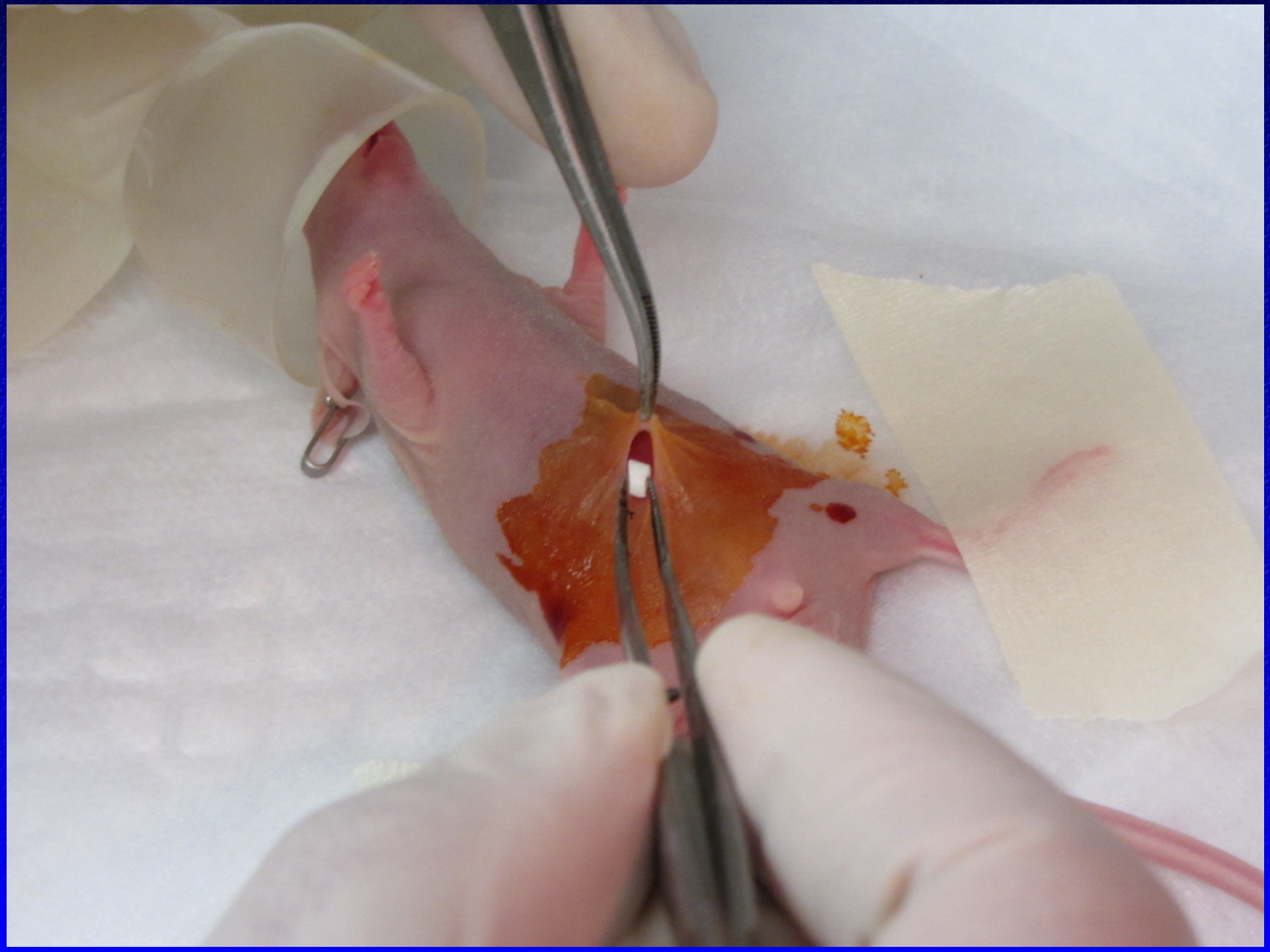


Song W, Khera M: AJA 2014 Epub

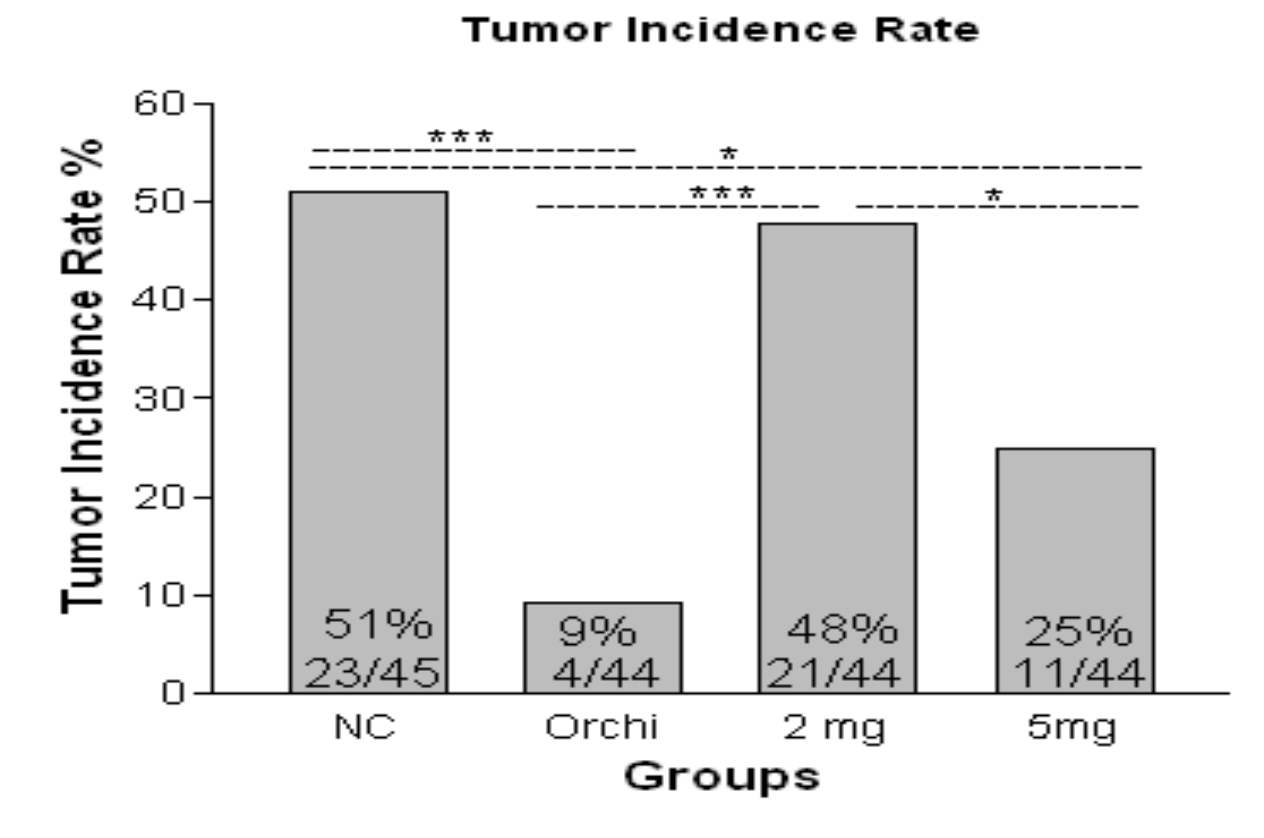
Testosterone and Prostate Cancer: In-vivo Experiments

- Male nude mice divided into 4 categories
  - Normal control (n=45)
  - Orchiectomy (n=44)
  - Orchiectomy + 2mg testosterone pellet (n=44)
  - Orchiectomy + 5mg testosterone pellet (n=44)
- 5 million LNCaP cells injected s.c. one week post surgery
- Mice followed for 84 days
- Serum testosterone and tumor size assessed

Song et al, BCM Cancer, accepted for publication August 2017



Tumor Development Rate



Baylor College of Medicine
Laboratory for Andrology Research
McNair Medical Institute

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

A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications

Mohit Khera [a,*], *David Crawford* [b], *Alvaro Morales* [c], *Andrea Salonia* [d], *Abraham Morgentaler* [e]

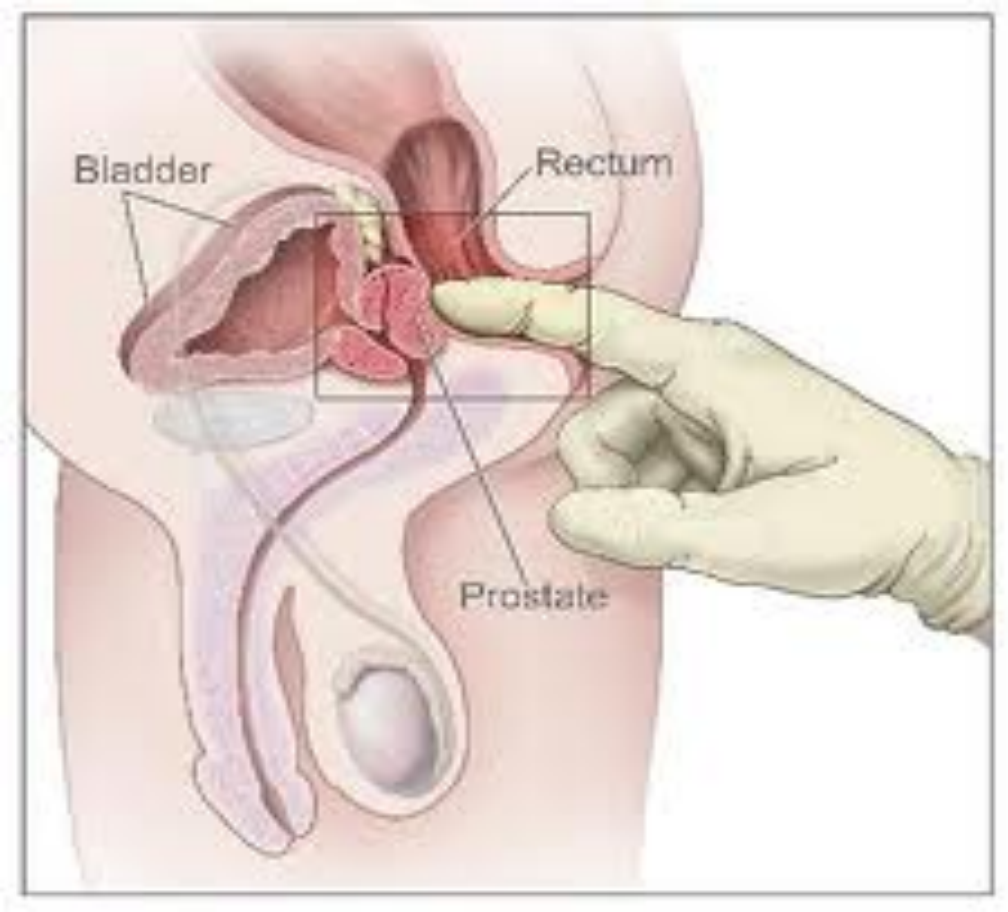
Table 2 – Criteria to consider before initiating testosterone therapy in men with history of treated prostate cancer

The clinical picture is consistent with a diagnosis of testosterone deficiency.
The patient must understand that safety data are limited and that there is an unknown degree of risk of PCa progression or recurrence.
The patient must be willing and able to provide informed consent.
No medical contraindications to testosterone therapy (eg, erythrocytosis) exist.
There is an undetectable or stable PSA level.
Clinicians must be prepared for the possibility of PCa recurrence or progression, which will occur in some men regardless of testosterone therapy but may be attributed to testosterone therapy by patients, family, or other clinicians.
Use testosterone therapy with extreme caution in men at high risk for PCa recurrence or progression.
Do not recommend testosterone therapy for men currently receiving any form of ADT.

PCa = prostate cancer; PSA = prostate-specific antigen; ADT = androgen-deprivation therapy.

Khera et al. Eur Urol. 2014 Jan;65(1):115-23

Risk of Occult Prostate Cancer?



Testosterone Therapy in Men With Untreated Prostate Cancer

Abraham Morgentaler,*, † Larry I. Lipshultz,‡ Richard Bennett,§ Michael Sweeney,§ Desiderio Avila, Jr.§ and Mohit Khera‖

From Men's Health Boston, Division of Urology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts (AM, MS), and the Department of Urology, Baylor Medical College, Houston, Texas (LIL, RB, DA, MK)

- **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)**

Morgentaler A et al. *J Urol.* 2011;185(4):1256-1260.

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 dentified in 54% of follow-up biopsies

PSA, prostate-specific antigen.

Morgentaler A et al. *J Urol.* 2011;185(4):1256-1260.

Can testosterone therapy be offered to men on active surveillance for prostate cancer? Preliminary results

Ravi Kacker[1], Mariam Hult[1], Ignacio F San Francisco[2], William P Conners[1], Pablo A Rojas[2], William C Dewolf[3], Abraham Morgentaler[1]

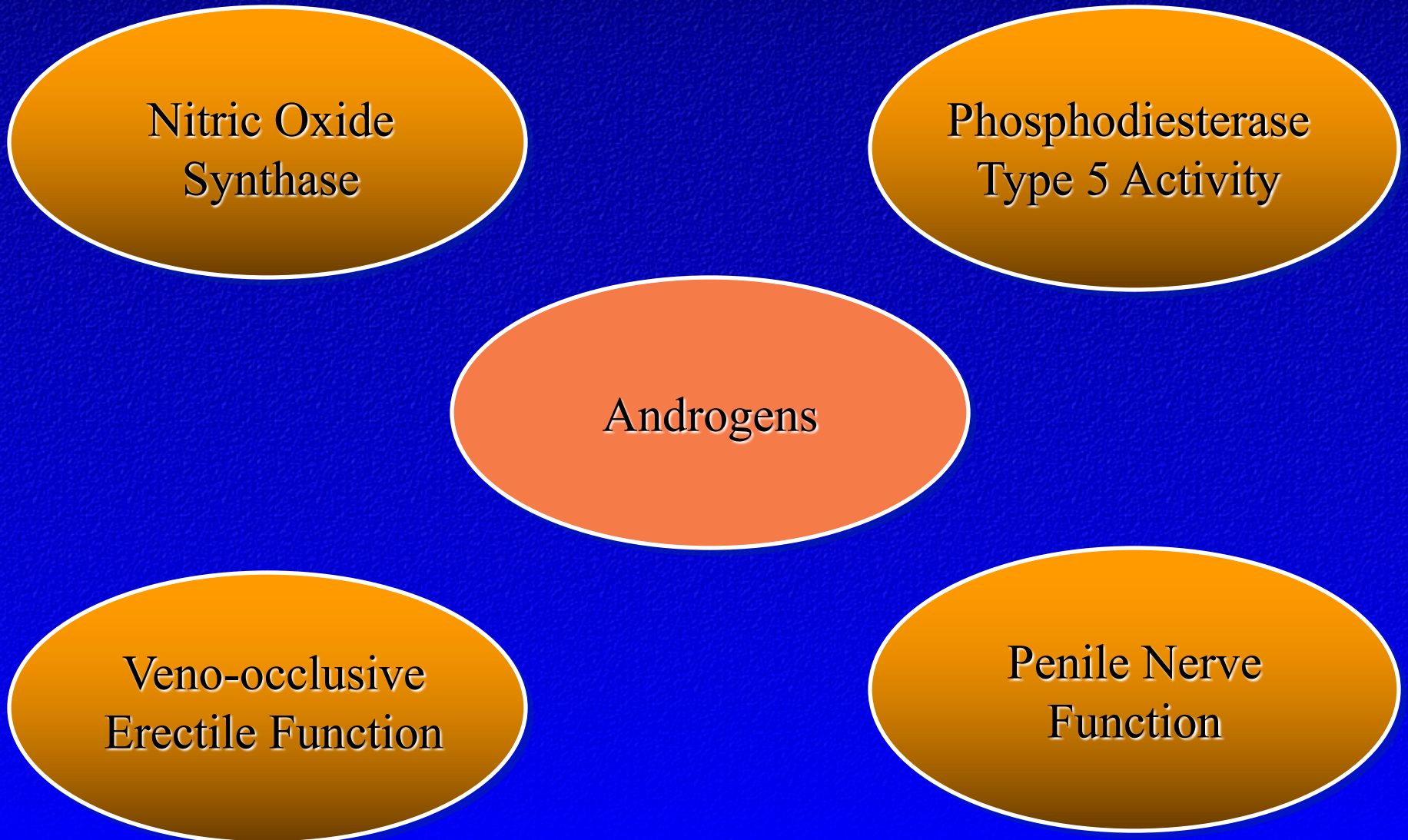
- 28 hypogonadal men on AS and TTh for at least 6 months
- Control: 96 hypogonadal men on AS and not receiving TTh
- Follow-up 38.9 and 42.4 months T and non-T group, respectively
- Non-T group (n=96): All men with GL 3+3
  - 43 (44.7%) developed biopsy progression, including 9 men (9.38%) with upgrading to Gleason 7 (3 + 4)
- T group (n=28): 22 men with GL 3+3 and 6 men with GL 3+4
  - GL 3+3: 7 (31.8%) men developed biopsy progression including 3 men (13.6%) who developed Gleason 3 + 4 PCa
  - GL 3+4: 2 (33.3%) men developed an increase in tumor volume, and none developed:upgrading beyond Gleason 3 + 4
- Conclusion: No difference in prostate cancer progression in men on AS receiving T and not receiving T

Kacker et al Asian J Androl. 2016 Jan-Feb;18(1):16-20.

TRT Following Radical Prostatectomy

Safety

Androgens and Erectile Function



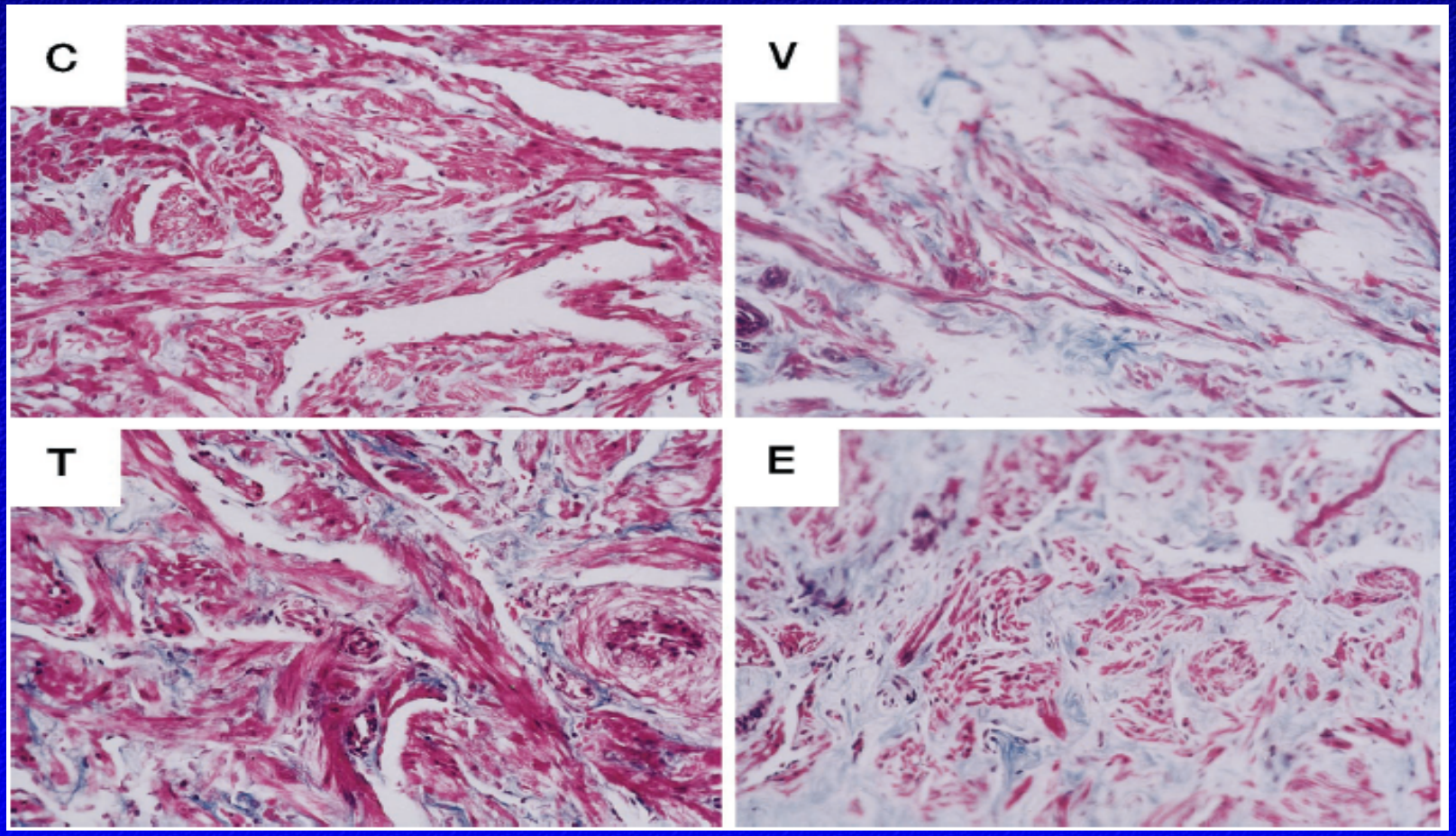
Traish et al Endocrinology1999; 140:1861

Androgens and Cavernosal Smooth Muscle

- Animals were treated for 7 days with vehicle alone, testosterone, or estradiol one week after bilateral orchiectomy
- Intact control animals received vehicle only
- Smooth muscle content was assessed by Masson's trichrome staining and computer-assisted histomorphometry

Traish et al Endocrinology 1999; 140:1861

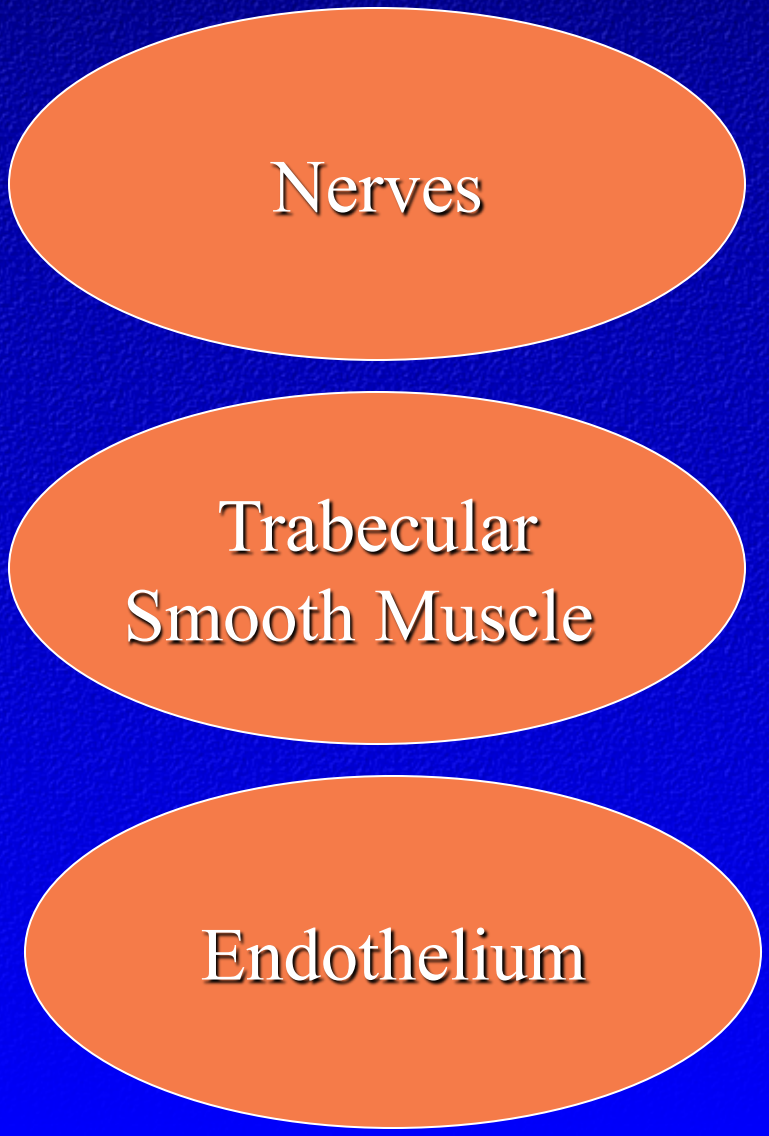
Results



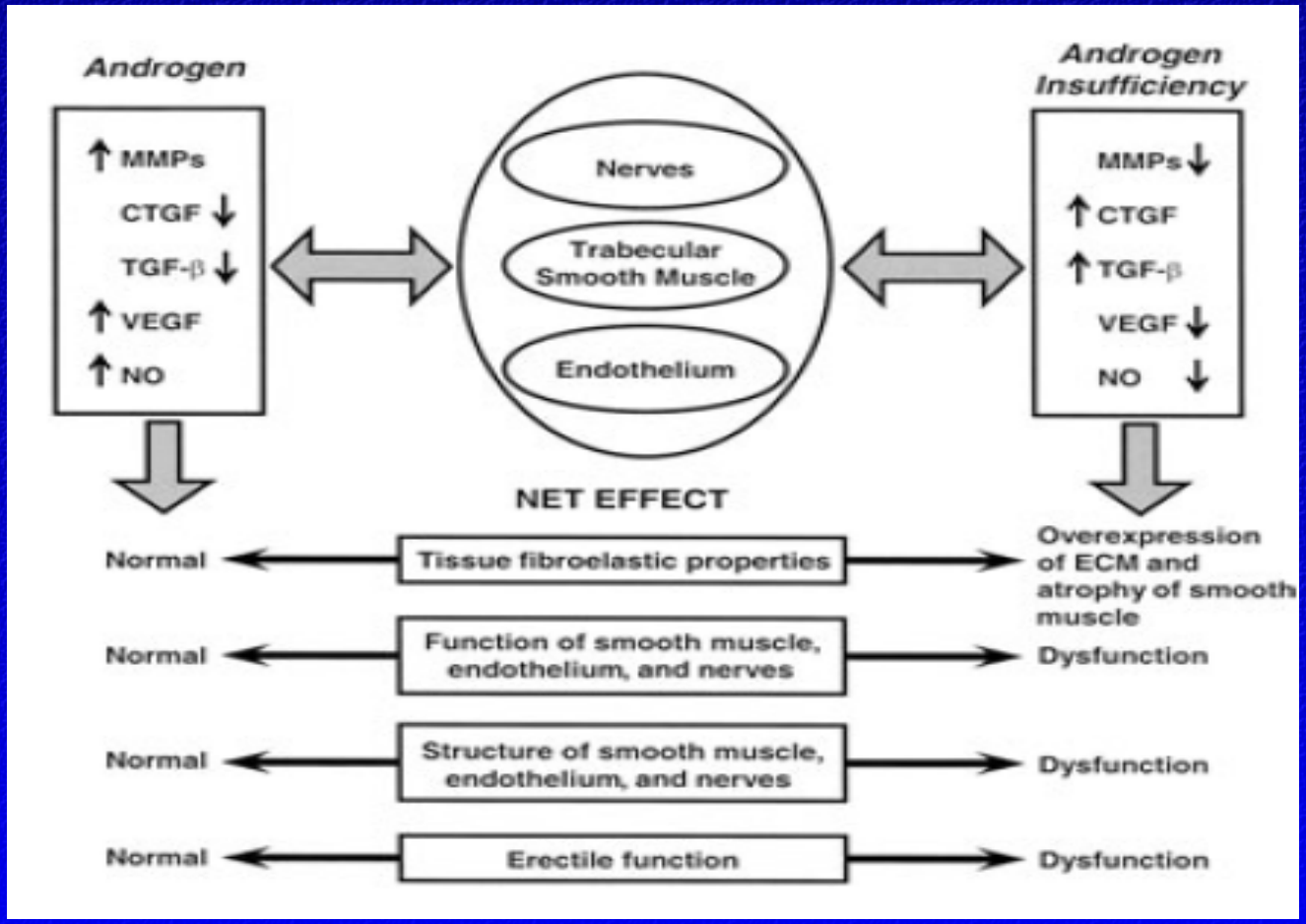
C= control, V= castrate, T= castrate+ testosterone, E= castrate +estradiol

Traish et al Endocrinology1999; 140:1861

The Focus of Erectile Preservation Following Radical Prostatectomy



The Focus of Erectile Preservation Following Radical Prostatectomy



Traish et al. J Androl. 2005: 26:242.

Conclusion

- There is currently no convincing evidence that TRT promotes the initiation of prostate cancer in hypogonadal men
- Hypogonadal men receiving TRT after history of prostate cancer appear to have low recurrence rates of prostate cancer and may be considered in men with a history of focal therapy
- A large randomized placebo controlled trial assessing the effects of TRT on prostate cancer is needed
- Androgens may play a key role in recovery of erectile function following radical prostatectomy