Management of low testosterone in prostate cancer survivors

Yu Seob Shin, MD, PhD

Department of Urology

Jeonbuk National University Medical School, Jeonju, Republic of Korea

AUA & ES Guidelines

Table 5. Differences in American Urological Association & Endocrine Society testosterone therapy recommendations

Recommendation topic	American Urological Association	Endocrine Society
Contraindications of testosterone therapy	- History of CV disease within past 6 months - Desire to have children - No significant clinical improvement despite adequate trial of TTh	- History of CV disease within past 6 months - Desire to have children - History of prostate cancer - History of uncontrolled heart failure - History of myocardial infarction - History of stroke - History of male breast cancer - Severe untreated obstructive sleep apnea - Hematocrit > 48%
History of cardiovascular disease	- Low T increases CV disease risk - TTh is not recommended if recent history of CV disease	- Insufficient evidence linking TTh to CV risk
History of prostate cancer	- Consider TTh on a case-by-case basis	- Should not use TTh if history of prostate cancer - Should not use TTh if PSA > 4 ng/mL or > 3 ng/mL in high-risk patients - Should not use TTh if palpable prostate nodule or induration

CV = cardiovascular; PSA = prostate-specific antigen; T = testosterone; TTh = testosterone therapy.

Sex Med Rev. 2021;9:149

2022 EAU guidelines

Recommendations	Strength rating
Fully counsel symptomatic hypogonadal men who have been surgically treated for localised prostate cancer (PCa) and who are currently without evidence of active disease considering testosterone therapy, emphasising the benefits and lack of sufficient safety data on long-term follow-up.	Weak
Restrict treatment to patients with a low risk for recurrent PCa (i.e., pre-operative PSA < 10 ng/mL; Gleason score < 7 [International Society for Urological Pathology grade 1]; cT1-2a)* and treatment should start after at least 1 year follow-up with PSA level < 0.01 ng/mL.	Weak
Safety data on the use of testosterone therapy in men treated for breast cancer are unknown.	Strong
Assess cardiovascular risk factors before commencing testosterone therapy.	Strong
Assess men with known cardiovascular disease (CVD) for cardiovascular symptoms before testosterone therapy and with close clinical assessment and evaluation during treatment.	Strong
Treat men with hypogonadism and pre-existing CVD, venous-thromboembolism or chronic cardiac failure, who require testosterone therapy with caution, by careful clinical monitoring and regular measurement of haematocrit (not exceeding 54%) and testosterone levels.	Weak
Exclude a family history of venous-thromboembolism before starting testosterone therapy.	Strong
Monitor testosterone, haematocrit at three, six and twelve months after testosterone therapy initiation, and thereafter annually. A haematocrit > 54% should require testosterone therapy withdrawal and phlebotomy. Re-introduce testosterone therapy at a lower dose once the haematocrit has normalised and consider switching to topical testosterone preparations.	Strong

EAU Guidelines on
Sexual and Reproductive Health

A. Salonia (Chair), C. Bettocchi, J. Carvalho, G. Corona, T.H. Jones, A. Kadioğlu, J.I. Martínez-Salamanca, S. Minhas (Vice-chair), E.C. Serefoğlu, P. Verze
Guidelines Associates: L. Boeri, P. Capogrosso, A. Cocci, K. Dimitropoulos, M. Gül, G. Hatzichristodoulou, A. Kalkanli, L.A. Morgado, V. Modgil, U. Milenkovic, G. Russo, T. Tharakan
Guidelines Office: J.A. Darraugh

European Association of Urology

Risk of Prostate cancer

Shifting the Paradigm of Testosterone and Prostate Cancer: The Saturation Model and the Limits of Androgen-Dependent Growth

Review – Prostate Cancer

Abraham Morgentaler [a,*], *Abdulmaged M. Traish* [b]

[a] *Division of Urology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, United States*
[b] *Department of Biochemistry and Division of Urology, Boston University School of Medicine, Boston, Massachusetts, United States*

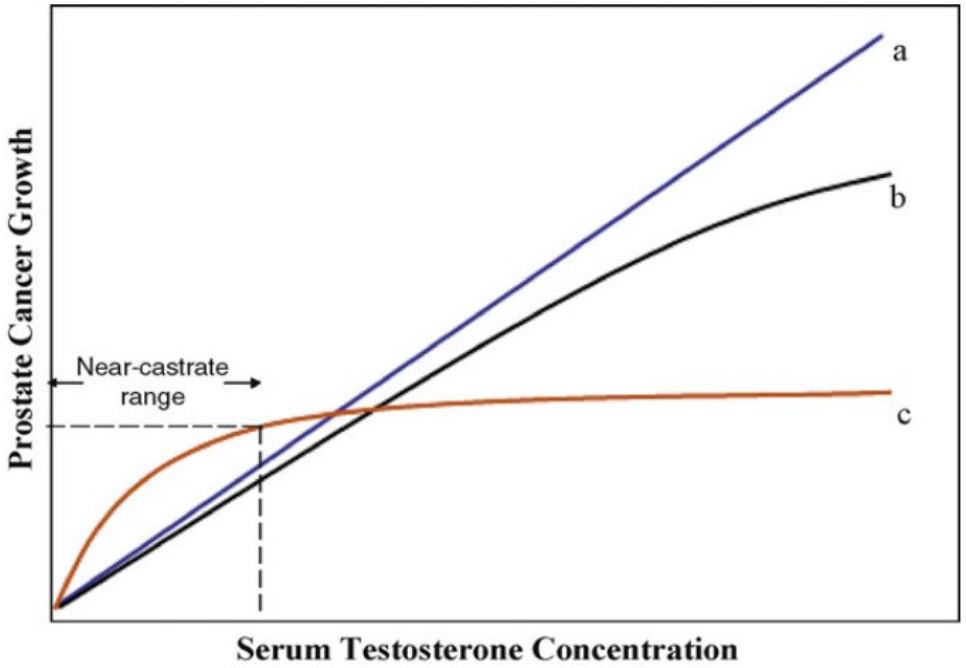


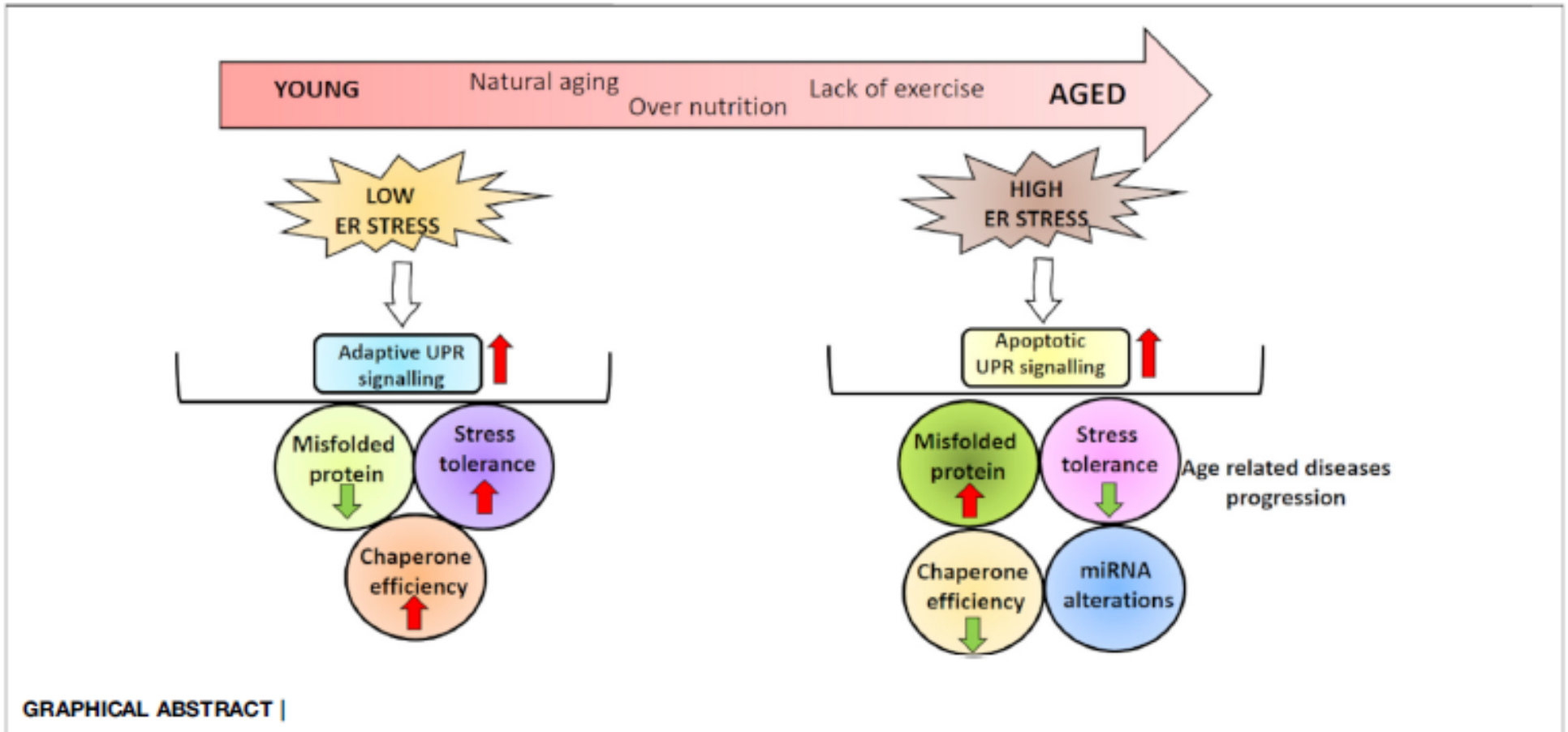
Fig. 5 – (a) The traditional model of testosterone (T)-dependent prostate cancer (PCa) growth suggested that greater serum T concentrations would lead to some degree of greater PCa growth (curves a, b). The Saturation Model (curve c) describes a steep T-dependent curve at T concentrations at or below the near-castrate range, with a plateau representing little or no further growth above this

Paradigm Shifting…

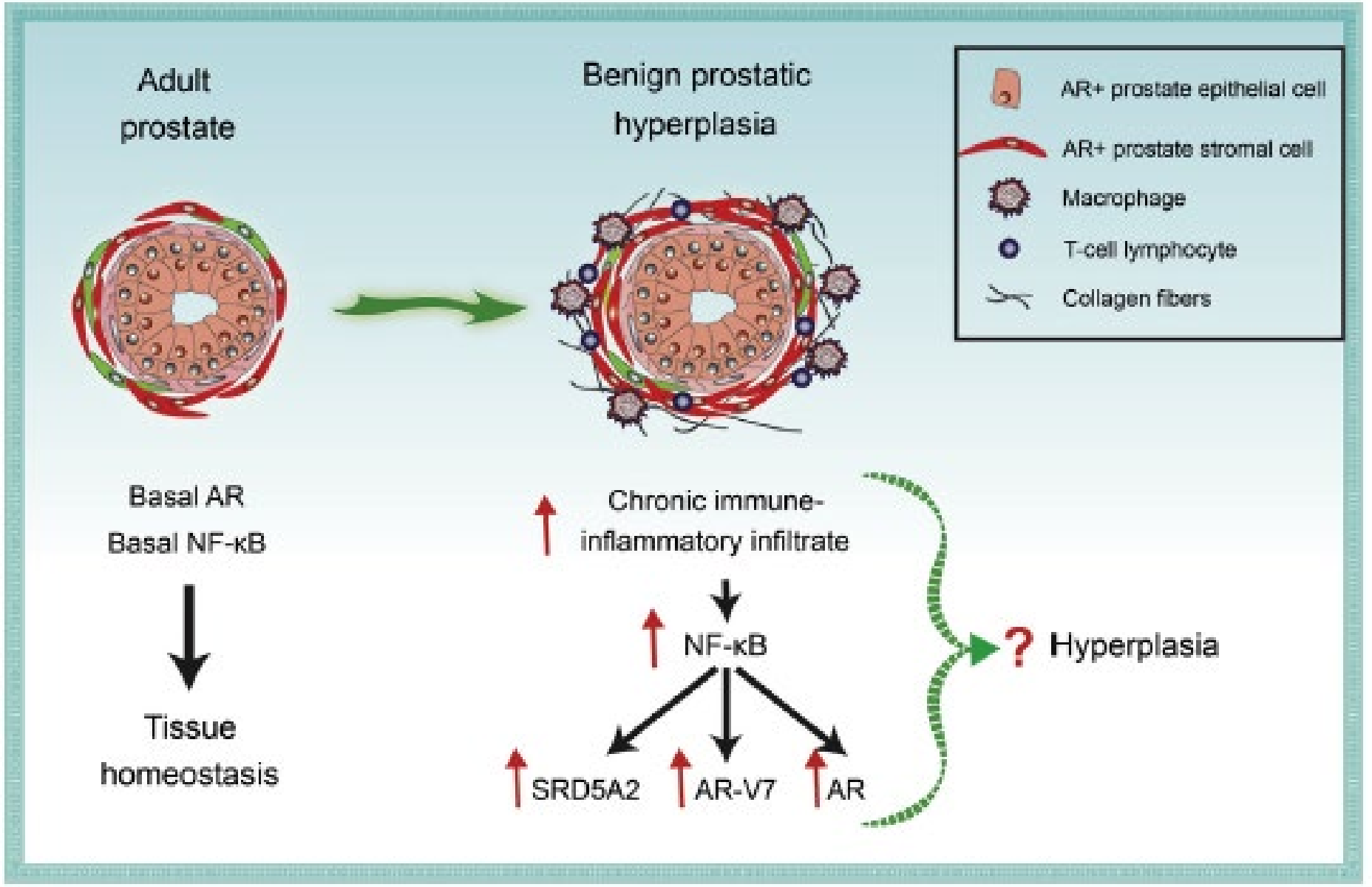
- Low T is associated high grade & stage Pca, recurrence rate, poor overall survival
- Androgen saturation model
- Supraphysiologic androgen therapy shows protective effect against Pca progression and a therapeutic agent for men with BCR

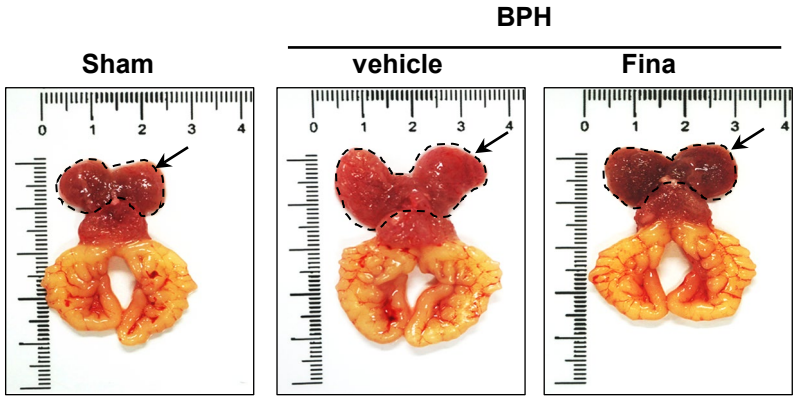
  → Bipolar androgen therapy

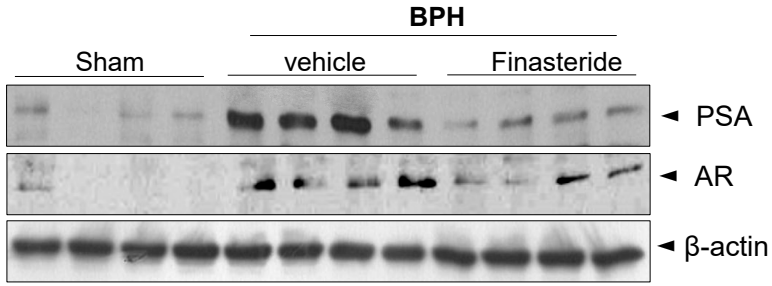
Eur Urol. 2009;55:310

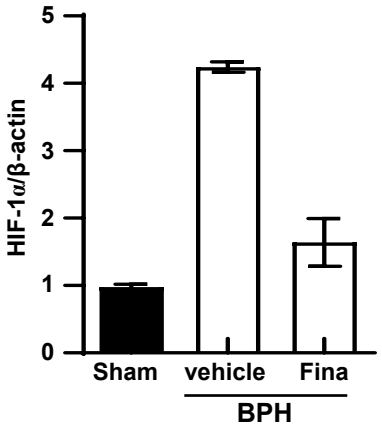


GRAPHICAL ABSTRACT |


Adult prostate
Benign prostatic hyperplasia
AR+ prostate epithelial cell
AR+ prostate stromal cell
Macrophage
T-cell lymphocyte
Collagen fibers
Basal AR
Basal NF-κB
Tissue homeostasis
Chronic immune-inflammatory infiltrate
NF-κB
SRD5A2
AR-V7
AR
? Hyperplasia


BPH
Sham
vehicle
Fina


BPH
Sham
vehicle
Finasteride
PSA
AR
β-actin


HIF-1α/β-actin
Sham
vehicle
Fina
BPH

Testosterone Treatment in Pca

- After definitive treatment of Pca (Radical Prostatectomy, RT)

- In men with Pca (Active surveillance, Advanced Pca)

Risk of Prostate cancer

Testosterone Replacement Therapy in Men with Untreated or Treated Prostate Cancer: Do We Have Enough Evidences?

Myong Kim[1], Seok-Soo Byun[2], Sung Kyu Hong[2]
[1]Department of Urology, Ewha Womans University Seoul Hospital, Seoul, [2]Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea

Table 2. Effect of TRT on oncologic outcomes in men with untreated and treated prostate cancer

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
Radical prostatectomy										
Kaufman [7]	2004	NA	16	7	0 (0.0%)	–	–	NA	Harmless	7
Agarwal [33]	2005	NA	19	10	0 (0.0%)	–	–	NA	Harmless	8
Davila [36][c]	2008	74 (mean)	12 (mean)	14	0 (0.0%)	–	–	NA	Harmless	10
Nabulsi [38][c]	2008	31	20	22	1 (4.5%)	–	–	NA	Harmless	11
Pushkar [39]	2008	NA	15 (mean)	16	0 (0.0%)	–	–	NA	Harmless	9
Khera [40]	2009	49 (mean)	13 (mean)	57	0 (0.0%)	–	–	NA	Harmless	11
Isbarn [45][c]	2010	43	19	69	0 (0.0%)	–	–	NA	Harmless	5
Sathyamoorthy [47][c]	2010	NA	8 (mean)	130	0 (0.0%)	–	–	NA	Harmless	9
Matsushita [50][c]	2012	37	19	71	1 (1.4%)	–	–	NA	Harmless	10
Pastuszak [52]	2013	27.5/16.5 (control)	15.2	103	4 (3.9%)	49	8 (16.3%)	0.24	Harmless	16
Nakano [55]	2014	69	33	1	0 (0.0%)	–	–	NA	Harmless	4
Wynia [56][c]	2014	NA	24	57	1 (1.8%)	54	8 (14.8%)	0.12	Harmless	11
Kühn [58]	2015	71	39.8	26	0 (0.0%)	–	–	NA	Harmless	10
Ory [61]	2016	NA	41	22	0 (0.0%)	–	–	NA	Harmless	10
Morgentaler [62][c]	2018	NA	52 (mean)	92	6 (6.5%)	–	–	NA	Harmless	9
Total population				697		103				

- All the included 15 studies implied that TRT might be harmless in patients with radical prostatectomy (progression rate: 0.0%–6.5%, 8–52 months of F/U)

World J Mens Health. 2021;39:705

Risk of Prostate cancer

Testosterone Replacement Therapy in Men with Untreated or Treated Prostate Cancer: Do We Have Enough Evidences?

Myong Kim[1], Seok-Soo Byun[2], Sung Kyu Hong[2]
[1]Department of Urology, Ewha Womans University Seoul Hospital, Seoul, [2]Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
Radiation therapy										
Sarosdy [35]	2007	NA	60	31	1 (3.2%)	–	–	NA	Harmless	13
Davila [36][c]	2008	57 (mean)	9 (mean)	6	0 (0.0%)	–	–	NA	Harmless	10
Morales [41]	2009	NA	15	5	1 (20.0%)	–	–	NA	Harmful	8
Pastuszak [51]	2013	NA	29.7	13	1 (7.7%)	–	–	NA	Harmless	9
Balbontin [53]	2014	NA	31	20	0 (0.0%)	–	–	NA	Harmless	9
Kühn [58]	2015	71	39.8	4	0 (0.0%)	–	–	NA	Harmless	10
Pastuszak [59]	2015	NA	40.8	96	6 (6.3%)	–	–	NA	Harmless	10
Ory [61]	2016	NA	41	50	3 (6.0%)	–	–	NA	Harmless	10
Morgentaler [62][c]	2018	NA	47 (mean)	50	1 (2.0%)	–	–	NA	Harmless	9
Total population				275		0				

- Of the nine studies, the results of one study implied that TRT might have harmful effects on the prognosis of patients with radiation therapy (progression rate: 20.0%, 15 months of F/U)

World J Mens Health. 2021;39:705

Risk of Prostate cancer

Testosterone Replacement Therapy in Men with Untreated or Treated Prostate Cancer: Do We Have Enough Evidences?

Myong Kim[1], Seok-Soo Byun[2], Sung Kyu Hong[2]
[1]Department of Urology, Ewha Womans University Seoul Hospital, Seoul, [2]Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea

Table 3. Effect of TRT on oncologic outcomes in men with local definitive treatment according to risk groups

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
Low-risk disease										
Kaufman [7]	2004	NA	17	6	0 (0.0%)	–	–	NA	Harmless	7
Agarwal [33]	2005	NA	19	2	0 (0.0%)	–	–	NA	Harmless	8
Sarosdy [35]	2007	NA	60	22	0 (0.0%)	–	–	NA	Harmless	13
Nabulsi [38][b]	2008	31	20	12	0 (0.0%)	–	–	NA	Harmless	11
Pushkar [39]	2008	NA	15 (mean)	13	0 (0.0%)	–	–	NA	Harmless	9
Khera [40]	2009	53.2 (mean)	17.2 (mean)	24	0 (0.0%)	–	–	NA	Harmless	11
Morales [41]	2009	NA	6	1	0 (0.0%)	–	–	NA	Harmless	8
Pastuszak [51]	2013	NA	29.7	4	0 (0.0%)	–	–	NA	Harmless	9
Pastuszak [52][c]	2013	27.5/16.5 (control)	15.2	77	0 (0.0%)	35	0 (0.0%)	1.0	Harmless	16
Balbontin [53]	2014	NA	31	16	0 (0.0%)	–	–	NA	Harmless	9
Nakano [55]	2014	69	33	1	0 (0.0%)	–	–	NA	Harmless	4
Wynia [56][bc]	2014	NA	24	57	1 (1.8%)	54	8 (14.8%)	0.12	Harmless	11
Kühn [58]	2015	71	39.8	20	0 (0.0%)	–	–	NA	Harmless	10
Pastuszak [59]	2015	NA	40.8	47	0 (0.0%)	–	–	NA	Harmless	10
Ory [61]	2016	NA	41	13	0 (0.0%)	–	–	NA	Harmless	10
Total population				315		89				

- All the included 15 studies implied that TRT might be harmless for low risk patients (progression rate: 0.0%–1.8% 6–60 months of F/U)

World J Mens Health. 2021;39:705

Risk of Prostate cancer

Testosterone Replacement Therapy in Men with Untreated or Treated Prostate Cancer: Do We Have Enough Evidences?

Myong Kim[1], Seok-Soo Byun[2], Sung Kyu Hong[2]
[1]Department of Urology, Ewha Womans University Seoul Hospital, Seoul, [2]Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea

Table 3. Effect of TRT on oncologic outcomes in men with local definitive treatment according to risk groups

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
Intermediate-risk disease										
Kaufman [7]	2004	NA	12	1	0 (0.0%)	–	–	NA	Harmless	7
Agarwal [33]	2005	NA	19	7	0 (0.0%)	–	–	NA	Harmless	8
Sarosdy [35]	2007	NA	60	6	0 (0.0%)	–	–	NA	Harmless	13
Nabulsi [38][b]	2008	31	20	7	0 (0.0%)	–	–	NA	Harmless	11
Pushkar [39]	2008	NA	15 (mean)	3	0 (0.0%)	–	–	NA	Harmless	9
Khera [40]	2009	44.8 (mean)	8.8 (mean)	26	0 (0.0%)	–	–	NA	Harmless	11
Morales [41]	2009	NA	7	1	0 (0.0%)	–	–	NA	Harmless	8
Pastuszak [51]	2013	NA	29.7	7	0 (0.0%)	–	–	NA	Harmless	9
Balbontin [53]	2014	NA	31	3	0 (0.0%)	–	–	NA	Harmless	9
Kühn [58]	2015	71	39.8	8	0 (0.0%)	–	–	NA	Harmless	10
Pastuszak [59]	2015	NA	40.8	28	2 (7.1%)	–	–	NA	Harmless	10
Ory [61]	2016	NA	41	29	1 (3.4%)	–	–	NA	Harmless	10
Total population				126		0				

- TRT might be harmless for intermediate-risk patients (progression rate: 0.0%–7.1%, 7–60 months of F/U)

World J Mens Health. 2021;39:705

Risk of Prostate cancer

Testosterone Replacement Therapy in Men with Untreated or Treated Prostate Cancer: Do We Have Enough Evidences?

Myong Kim[1], Seok-Soo Byun[2], Sung Kyu Hong[2]
[1]Department of Urology, Ewha Womans University Seoul Hospital, Seoul, [2]Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea

Table 3. Effect of TRT on oncologic outcomes in men with local definitive treatment according to risk groups

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
High-risk disease										
Agarwal [33]	2005	NA	19	1	0 (0.0%)	–	–	NA	Harmless	8
Sarosdy [35]	2007	NA	60	3	1 (33.3%)	–	–	NA	Harmful	13
Nabulsi [38][b]	2008	31	20	1	1 (50.0%)	–	–	NA	Harmful	11
Khera [40]	2009	43 (mean)	8 (mean)	4	0 (0.0%)	–	–	NA	Harmless	11
Morales [41]	2009	NA	18	3	1 (33.3%)	–	–	NA	Harmful	8
Pastuszak [51]	2013	NA	29.7	2	1 (50.0%)	–	–	NA	Harmful	9
Pastuszak [52]	2013	27.5/16.5 (control)	15.2	26	4 (15.4%)	15	8 (53.3%)	0.29	Harmless	16
Balbontin [53]	2014	NA	31	1	0 (0.0%)	–	–	NA	Harmless	9
Kühn [58]	2015	71	39.8	4	0 (0.0%)	–	–	NA	Harmless	10
Pastuszak [59]	2015	NA	40.8	11	2 (18.2%)	–	–	NA	Harmful	10
Ory [61]	2016	NA	41	29	2 (6.9%)	–	–	NA	Harmless	10
Total population				85		15				

- 5 studies (Of the 11 studies) implied that TRT might be harmful for patients with high-risk disease

  (progression rate: 18.2%–50.0%, 18–60 months of F/U)

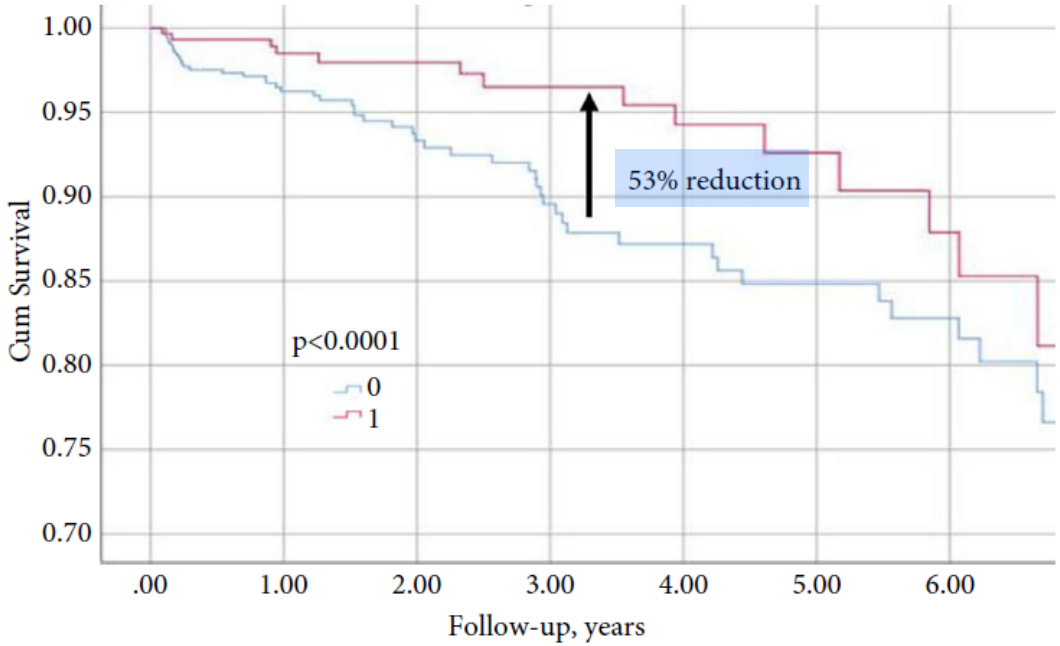
World J Mens Health. 2021;39:705

Risk of Prostate cancer

Testosterone replacement therapy reduces biochemical recurrence after radical prostatectomy

Thomas E. Ahlering*,†, Linda My Huynh*,†, Maxwell Towe*,†, Kaelyn See*,†, Joshua Tran*,†, Kathryn Osann*, Farouk M. el Khatib*,† and Faysal A. Yafi*,†

*Department of Urology, Irvine Medical Center Orange, and †Department of Medicine, University of California, Irvine, CA, USA



	B	SE	Wald	*P*	HR	95.0%	CI
Gleason Grade Group [1–4 (ref) vs. 5]	1.664	0.311	28.67	<0.001	5.28	2.872	9.708
Preoperative Free Testosterone (cont.)	-0.14	0.063	4.91	0.027	0.869	0.768	0.984
Pathological Stage [pT2 (ref) vs. pT3/pT4]	1.407	0.268	27.64	<0.001	4.084	2.417	6.901
TRT [TRT(ref) vs. cont.]	-0.616	0.313	3.88	0.049	0.54	0.292	0.997
Preoperative PSA (cont.)	0.058	0.012	23.65	<0.001	1.06	1.035	1.085

- Retrospective, 850 RP patients (18% TRT)
- Biochemical recurrence (53% reduction)

→ TRT vs non = 7.2% vs 12.6%

- TRT delayed time to BCR by 1.5 years.

Fig. 1 Proportionately matched Cox regression, adjusting for Gleason Grade Group, FT, pathological stage, and PSA level

BJU Int. 2020;126:91

Risk of Prostate cancer

Testosterone Replacement Therapy in Men with Untreated or Treated Prostate Cancer: Do We Have Enough Evidences?

Myong Kim[1], Seok-Soo Byun[2], Sung Kyu Hong[2]
[1]Department of Urology, Ewha Womans University Seoul Hospital, Seoul, [2]Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea

Table 2. Effect of TRT on oncologic outcomes in men with untreated and treated prostate cancer

Study	Year	Median FU from diagnosis (mo)	Median FU from TRT (mo)	TRT-treated arm		TRT-untreated arm		RR of TRT	TRT effect on prognosis	Study quality assessment (0–24)[a]
				No. of patient	Progression (%)	No. of patient	Progression (%)			
Active surveillance										
Morgentaler [42]	2009	NA	24	1	0 (0.0%)	–	–	NA	Harmless	5
Morales [48]	2011	NA	33	7	4 (57.1%)	–	–	NA	Harmful	8
Morgentaler [49]	2011	NA	30	13	2 (15.4%)	–	–	NA	Harmful	9
Berookhim [57]	2015	NA	26 (mean)	1	0 (0.0%)	–	–	NA	Harmless	9
Kacker [60]	2016	38.9/42.7 (control)	38.9	28	3 (10.7%)	96	9 (9.4%)	1.14	Harmless	15
Ory [61]	2016	NA	27	8	0 (0.0%)	–	–	NA	Harmless	10
Morgentaler [62][c]	2018	NA	51 (mean)	57	2 (3.5%)	–	–	NA	Harmless	9
Total population				115		96				

- 2 studies (of 7 studies) of implied that TRT might have harmful effects on the prognosis of patients with active surveillance (progression rate: 15.4%–57.1%, 30–33 months of F/U)
- 7 studies (of 9 studies) implied that TRT might have harmful effects in the prognosis of patients with advanced disease (progression rate: 38.5%–100.0%, 0.1–27.0 months of F/U)

World J Mens Health. 2021;39:705

Risk of Prostate cancer

Trends in Testosterone Therapy use in Prostate Cancer Survivors in the United States

Tony Chen, MD, Shufeng Li, MS, and Michael L. Eisenberg, MD Stanford University School of Medicine, Stanford, CA, USA

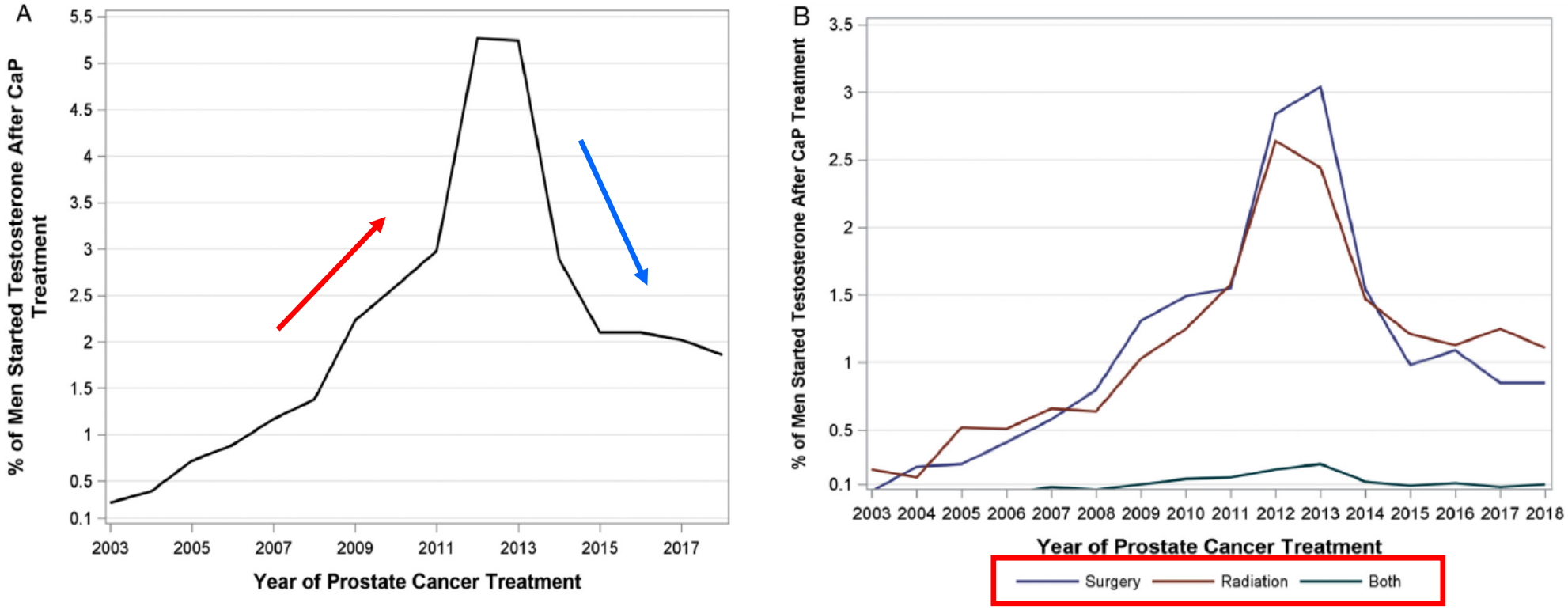


Figure 1. (A) Percentage of men started on Testosterone after prostate cancer treatment. (B) Percentage of men started on Testosterone after prostate cancer treatment, separated by treatment modality.

J Sex Med. 2021;18:1346

Patient should not be treated with testosterone replacement therapy if they have CaP with

High risk localized disease.

Positive surgical margins.

Positive lymph node.

Metastatic dsease.

Urol Oncol. 2020;38:661

Management of PSA elevations

- The average PSA increase after TRT is
  - 0.3 ng/ml in young hypogonadal men.
  - 0.44 ng/ml in older men.

J Androl. 2003;24:299

- Endocrine Society guideline suggests oncologic consultation if…
  - (a) PSA increases more than 1.4 ng/ml in the first 12 months
  - (b) PSA above 4 ng/ml is confirmed
  - (c) prostatic abnormality is detected on DRE

J Clin Endocrinol Metab. 2018;103:1715

- Because of the high test–retest variability in PSA levels, PSA elevations should be confirmed

→ repeating the test after 4 to 6 weeks

→ In the TTrials, half of the PSA elevations resolved spontaneously when the test was repeated

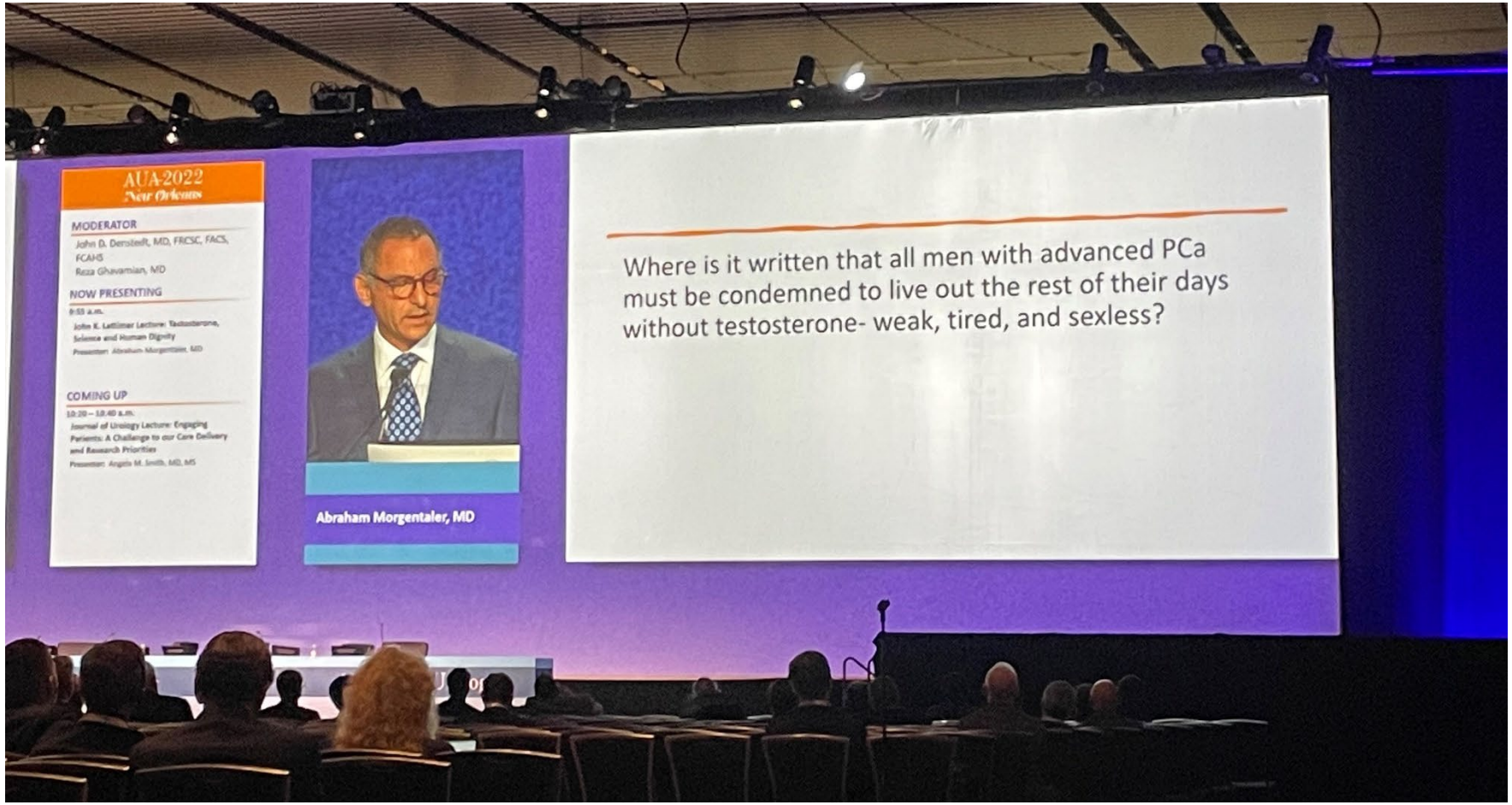
J Clin Endocrinol Metab. 2019;104:6238

2022 AUA (New Orleans) - Plenary Session

Abraham Morgentaler, MD, FACS

Men's Health Boston

Boston, Massachusetts



Conclusions

- TRT related risks…

→ Several guidelines suggest that testosterone therapy should be offered on an individualized basis after explicit discussion of the potential risks and benefits

- Identify the right patients for the right treatment strategy
- Correct risk stratification
- Patients' motivation and preference

Testosterone therapy should not be given with ADT unless in a clinical trial

감사합니다.