When we should start TRT after a radical prostatectomy

The Right Timing & The Right Patient

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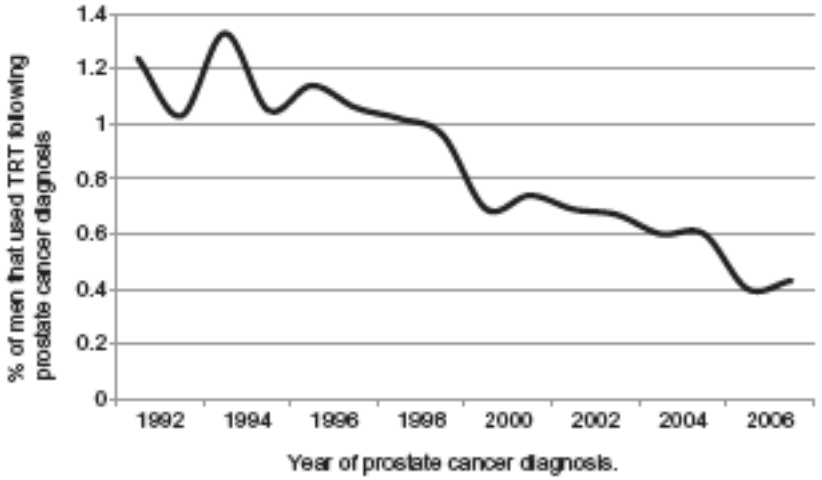
TRT after RP – Current TRT use across US



SEER data

Figure 1 Use of testosterone replacement therapy in men diagnosed with prostate cancer in a given year

		Before propensity weighting			After propensity weighting		
Variable	Categories	No TRT N (%)	TRT N (%)	*P* value	No TRT N (%)	TRT N (%)	*P* value
Grade	Well	9,752 (6.5)	130 (11.0)	<0.0001	9,807 (6.6)	92 (8.0)	0.2473
	Moderately	87,786 (59.3)	742 (62.8)		87,851 (59.3)	673 (59.0)	
	Poorly	50,635 (34.2)	309 (26.2)		50,555 (34.1)	377 (33.0)	
Clinical Stage	T1	59,279 (40.0)	460 (39.0)	0.071	59,283 (40.0)	482 (42.3)	0.6018
	T2	74,733 (50.4)	629 (53.2)		74,786 (50.5)	560 (49.1)	
	T3	4,618 (3.1)	35 (3.0)		4,617 (3.1)	33 (2.9)	
	T4	9,543 (6.5)	57 (4.8)		9,527 (6.4)	66 (5.7)	
Initial Treatment	ADT	25,044 (16.9)	155 (13.1)	<0.0001	25,006 (16.9)	191 (16.7)	0.9012
	RP	27,143 (18.3)	292 (24.7)		27,225 (18.4)	212 (18.5)	
	RT	74,974 (50.6)	598 (50.7)		74,994 (50.6)	588 (51.5)	
	WWAS	21,012 (14.2)	136 (11.5)		20,986 (14.1)	151 (13.3)	

Kaplan AL et al. J Sex Med 2014

TRT after RP – The right Timing - Late?

Should Hypogonadal Men With Prostate Cancer Receive Testosterone?

The timing of T therapy initiation remains undefined but it has been vaguely described as "after a prudent interval," which, of course, is of little help to the clinician. I believe (without much evidence to support it) that for men who underwent radical prostatectomy the "prudent interval" is achieved once the PSA is no longer detectable. This nadir can be reached fairly early, depending on the preoperative levels. The situation is less simple for

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Morgentaler A & Morales A. J Urol 2010

EAU - GUIDELINES

Definition: male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life (1).

Hypogonadism is diagnosed on the basis of persistent signs and symptoms related to androgen deficiency and assessment of consistently low testosterone levels (at least on two occasions) with a reliable method (1-5).

In patients operated on for localised prostate cancer, testosterone therapy should not start before 1 year of follow-up without PSA recurrence has been completed.	4	B

http://www.uroweb.org/gls/pdf/18%20Male%20Hypogonadism_LR.pdf
http://www.uroweb.org/gls/pdf/1607%20Prostate%20Cancer_LRV3.pdf

EAU guidelines 2014

0022-5347/04/1723-0920/0
THE JOURNAL OF UROLOGY®

Vol. 172, 920–922, September 2004
Printed in U.S.A.
DOI: 10.1097/01.ju.0000136269.10161.32

ANDROGEN REPLACEMENT AFTER CURATIVE RADICAL PROSTATECTOMY FOR PROSTATE CANCER IN HYPOGONADAL MEN

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From Aurora Urology, Urology Research Options, Aurora, Colorado (JMK), and Hartford Hospital, Hartford, Connecticut (RJG)

tive surgery for prostate cancer is lacking. The authors have treated 7 such patients, and this report discusses the cases and the general issue of T replacement in hypogonadal men who have undergone curative radical prostatectomy.

In our series of 7 men assembled from a retrospective review of the records of 2 busy private urology practices, T replacement for the management of hypogonadal symptoms has been beneficial and safe, with no evidence of local recurrence or distant spread of prostate cancer after followup ranging from 1 to 12 years.

Hypogonadal men treated with testosterone after radical prostatectomy

Pt No.	Prostatectomy Yr	Age at Prostatectomy	Gleason Score/Surgical Margin	Pre-Prostatectomy PSA	Pretreatment Serum T	T Start	T Preparation	Serum T After T Treatment
1	1993	70	6/Neg	6.6	269	2002	Patch	214–260
2	1991	50	6/Pos	5.2	Not available	1991	Depot	Not available
3	2001	66	7/Neg	4.4	51	2002	Gel	214
4	2002	64	6/Neg	5.3	50	2002	Gel	307
5	1995	67	6/Neg	Not available	Not available	2000	Depot	740
6	2002	55	6/Neg	4.7	Not available	2002	Patch	563
7	1994	64	6/Neg	Not available	19	1998	Patch	545

PSA less than 0.1 ng/ml in all 7 patients.

Kaufman JM, et al. J Urol 2004

Testosterone Replacement Therapy Following Radical Prostatectomy

J Sex Med 2009;6:1165–1170

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#57 patients treated with TRT after RP

Table 1 Pre- and post-testosterone replacement therapy (TRT) prostate-specific antigen (PSA) and testosterone values

Gleason	Age	Pre-TRT PSA (ng/dL)	Pre-TRT testosterone (ng/dL)	Post-TRT PSA (ng/dL)	Post-TRT testosterone (ng/dL)	Months follow-up after initiating TRT
≤6 (N = 24)	62	<0.1	276	<0.1	639	17.2
7 (N = 26)	59	<0.1	262	<0.1	350	8.8
≥8 (N = 4)	70	<0.1	139	<0.1	538	7.0

TRT was effective in significantly increasing serum T values **without significantly increasing PSA levels**

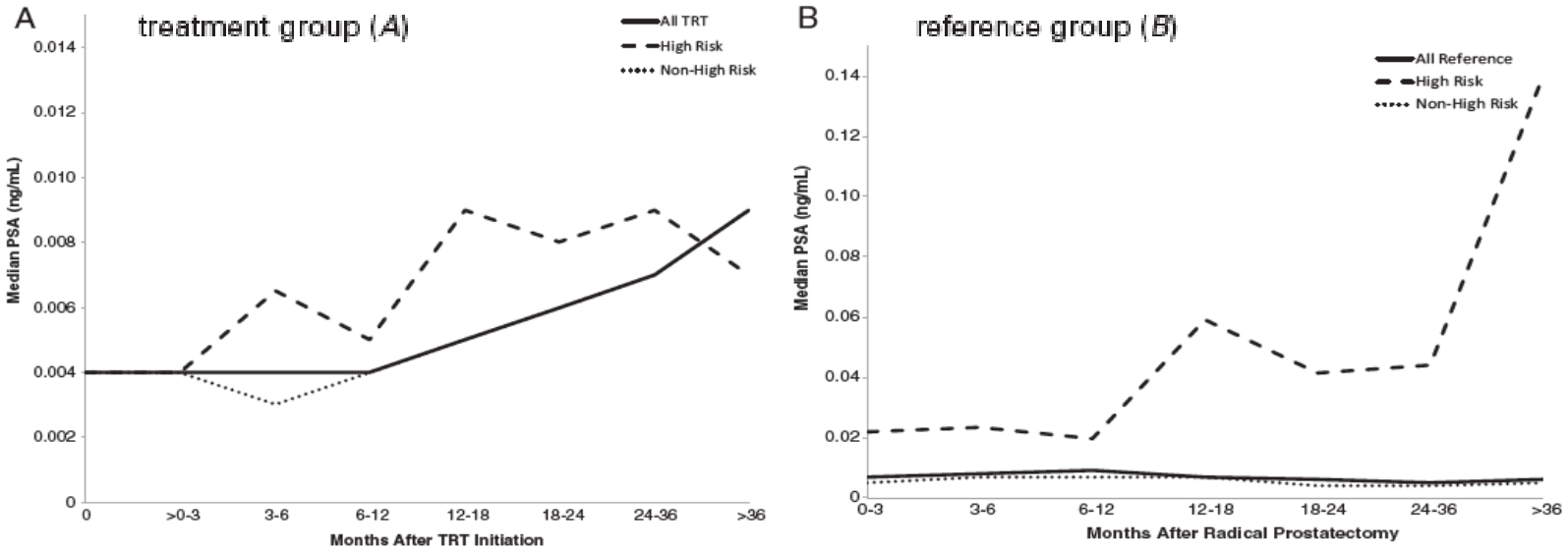
Evidence **does not support the hypothesis that existing subclinical PCa will be stimulated by TRT** in hypogonadal men

Khera M, et al. J Urol 2009

Testosterone Replacement Therapy in Patients with Prostate Cancer After Radical Prostatectomy

103 hypogonadal men treated with TRT after RP (treatment group)

49 nonhypogonadal men after RP (reference group)



- **Small significant increase in PSA** in the treatment group but not in the reference group
- The mean time to TRT initiation in the treatment group was **12.3 months**

Pastuszak AW, et al. J Urol 2013

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

TRT after RP – Retrospective published series

Table 1 – Results of testosterone therapy in men with prostate cancer

Study	No. of patients	Intervention	Follow-up, mo	Gleason score (no. of patients)	Pretreatment PSA	Post-treatment PSA	Pretreatment testosterone, ng/dl	Post-treatment testosterone, ng/dl	Comments
Agarwal et al. [39]	10	RP	19	6 (2) 7 (7) 8 (1)	<0.1	<0.1	197	591	No PSA recurrences
Kaufman et al. [38]	7	RP	24	6 (6) 7 (1)	<0.1	<0.1	97	434	No PSA recurrences; longest follow-up = 12 yr
Khera et al. [40]	57	RP	13	≤6 (24) 7 (26) 8 (4)	0.005	0.005	255	459	No PSA recurrences
Pastuszak et al. [41]	103	RP	27.5	<6 (1) 6,7 (72) ≥8 (9)	0.004	0.007	261	460	Included 26 men with high-risk PCa and positive margins or nodes or Gleason score >8; comparison group of 49 men with RP without testosterone therapy; four PSA recurrences in the testosterone therapy group (4%), eight recurrences in the comparison group (16%)

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 M, et al. Eur Urol 2014

TRT after RP – High Risk Patients

	All Pts		High Risk Pts		Nonhigh risk Pts		TRT vs Reference p Value	TRT vs Reference p Value*
Treatment group:								
No. pts	103		26		77			
Median ng/ml/yr PSAV (IQR), No.	0.002	(0.001–0.003), 89	0.002	(0.001–0.011), 22	0.001	(0.001–0.002), 67	1.000	
No. suspected BCR (%)†	4	(4)	4	(15)	0	(0)	0.015	0.03
No. BCR defined as a single PSA greater than 0.2 ng/ml (%)	2	(2)	2	(8)	0	(0)		
No. discontinued TRT for reason other than suspected BCR (%)‡	15	(15)	2	(8)	13	(17)		
Reference group:								
No. pts	50		15		35			
Median ng/ml/yr PSAV (95% CI), No.	0.0002	(−0.001–0.010), 27	0.018	(−0.012–0.106), 10	−0.0003	(−0.001–0.004), 17		
No. suspected BCR (%)†	8	(16)	8	(53)	0	(0)		
No. BCR defined as a single PSA greater than 0.2 ng/ml (%)	5	(10)	5	(33)	0	(0)		

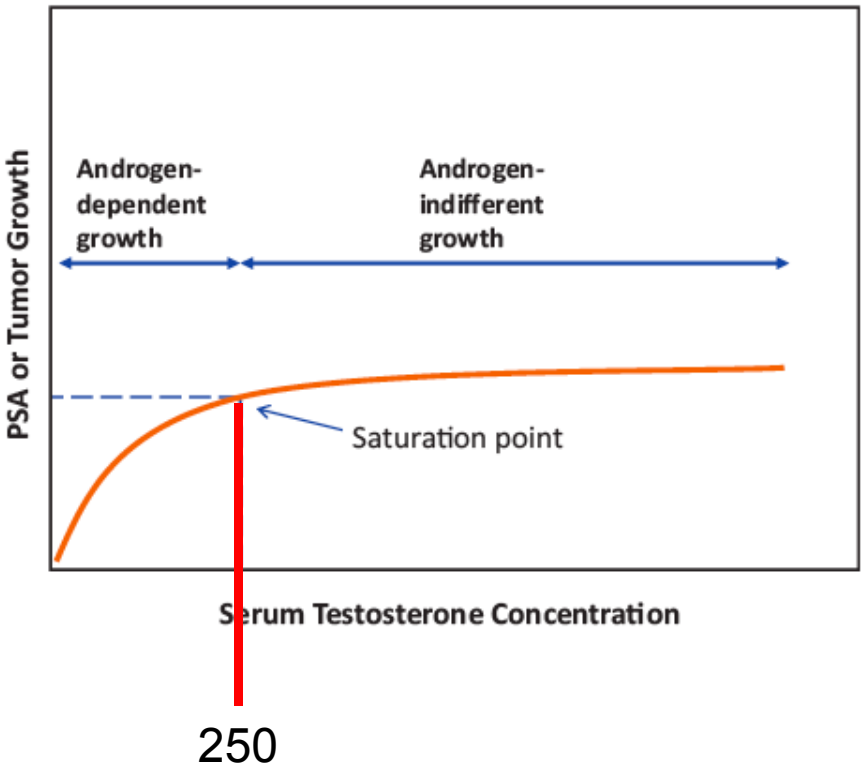
Men were grouped into **high risk** and **nonhigh risk** groups
High risk patients were identified as having at least 1 of
1) GS ≥ 8
2) SM+
3) pN+

After a median 27.5-mo FU, there were 4 BCRs (4%) in the TRT high risk group versus 8 BCRs (16%) in the reference high risk group

Pastuszak AW, et al. J Urol 2013

TRT after RP – High Risk Patients: the saturation model

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



- Increasing androgen concentrations produce increasing prostate tissue growth, as reflected by PSA concentrations, **until a limit is reached** (the saturation point) beyond which there is no further increasing
- **PCa is sensitive to changes in androgen at low concentrations** (androgen dependent) but does not respond to changes in androgen concentrations above the saturation point (androgen indifferent)

In clinical practice the saturation point appears to be approximately **8 nmol/l or 250 ng/dl** subject to interindividual variation

Concern about TRT exists for the man with severely depressed serum T (less than 150 ng/dl)

Khera M et al. Eur Urol 2014

Figure 1a testosterone

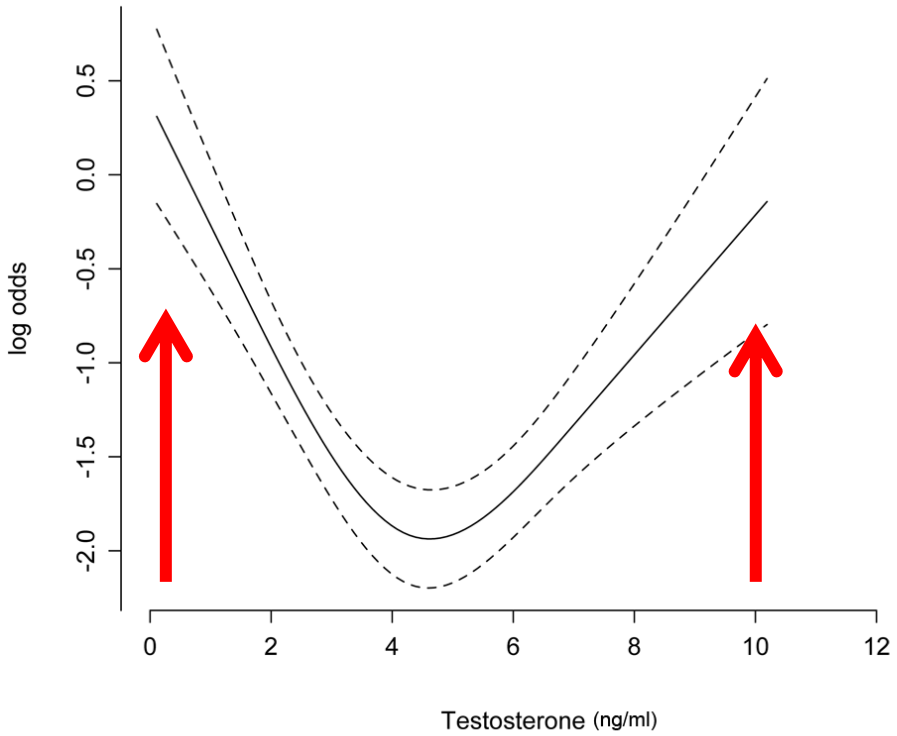


Figure 1b estradiol

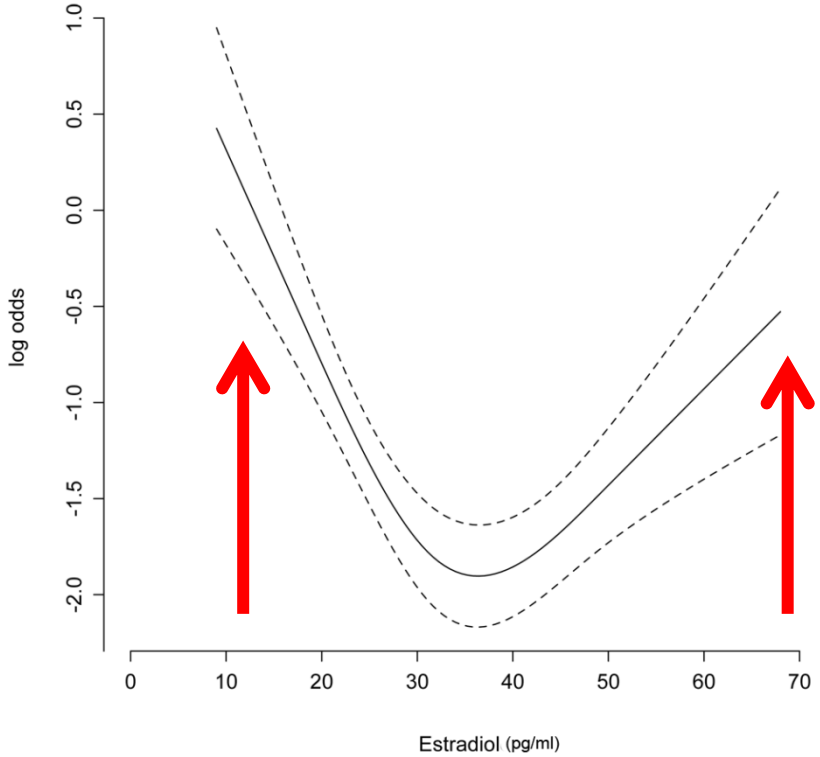
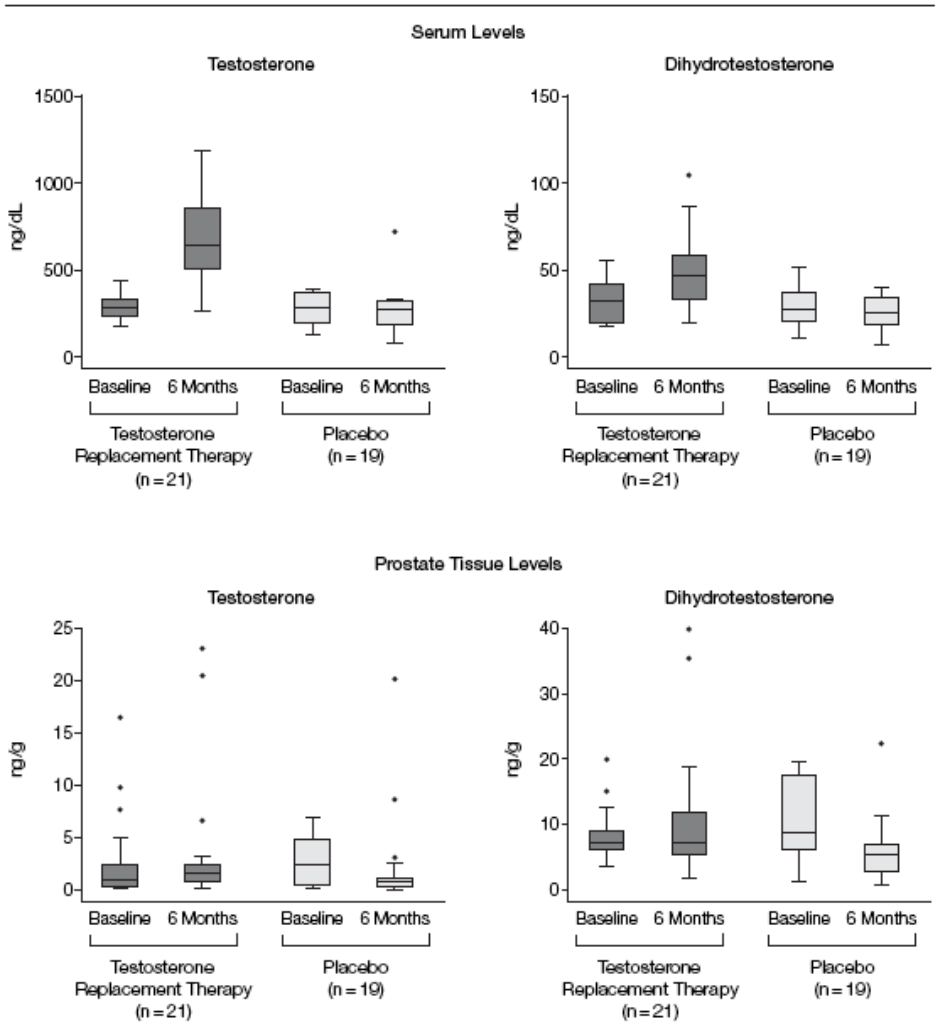


Figure 1a-1B depict the relationship between serum tT levels (ng/ml) and E_2 levels (pg/ml) and high-risk PCa at RP, respectively
[Y axis represents the risk (logarithmic scale) of high risk PCa at RP]

High-risk PCa was significantly more frequent both for the lowest and the highest circulating levels of serum tT and E_2 (all $p \leq 0.03$), depicting a nonlinear U-shaped risk behavior

Salonia A, et al. Clin Cancer Res 2012;18:3648-57

TRT after RP – High Risk Patients: a protected hormonal milieu



In a 6-mo study of TRT in hypogonadal men, **no increase in intraprostatic T or DHT concentrations were noted despite substantial increases in serum T level**

Marks LS, et al. JAMA 2006

TRT after RP – Is there a right Timing?

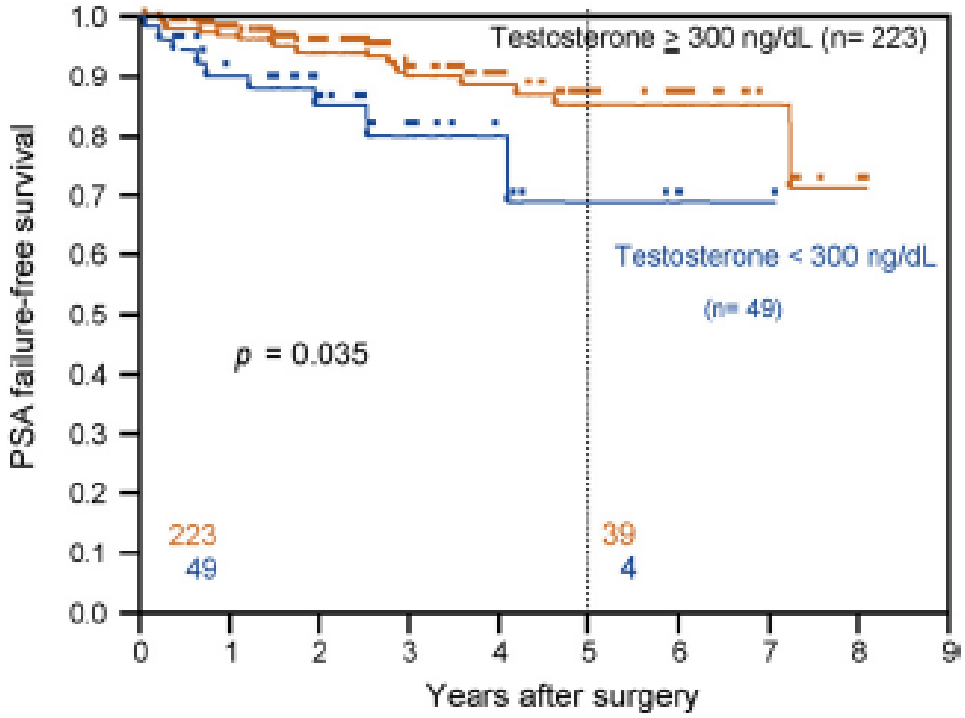
Early

Later

The optimal timing of initiating TRT after local therapy cannot be determined using currently available data

TRT after RP – The right Timing – Early?

- 304 patients diagnosed with clinically localized PCa who had been treated with RP alone
  - **Preoperative T was an independent and significant predictor of PSA failure** along with RP GS
  - 5-year PSA failure–free survival rate of the patients with preoperative low T (67.8%) was significantly worse than that with normal T (84.9%)

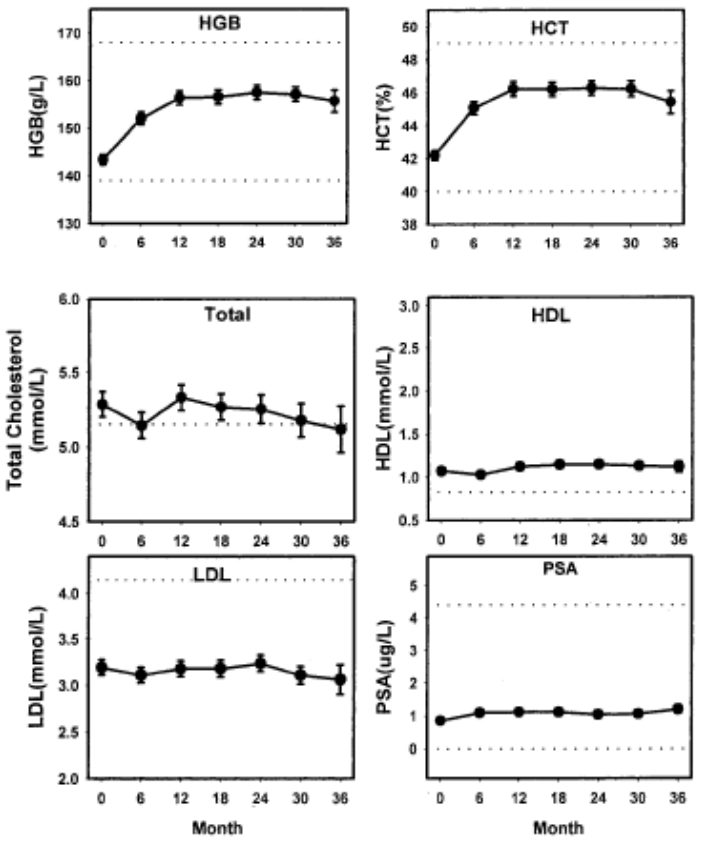


Yamamoto S, et al. Eur Urol 2007

TRT after RP – The right Timing - Early?

- Emerging evidence suggests there may be benefits of having a normal serum T for **general health issues**, as it is associated with reduced risk of:
  - diabetes
  - atherosclerosis
  - MetS
  - osteoporosis and fractures

- Several studies have even indicated **improved longevity** for men with normal vs low T



Wang C et al. J Clin Endocrinol Metab 2004

Standard Operating Procedure for the Preservation of Erectile Function Outcomes after Radical Prostatectomy

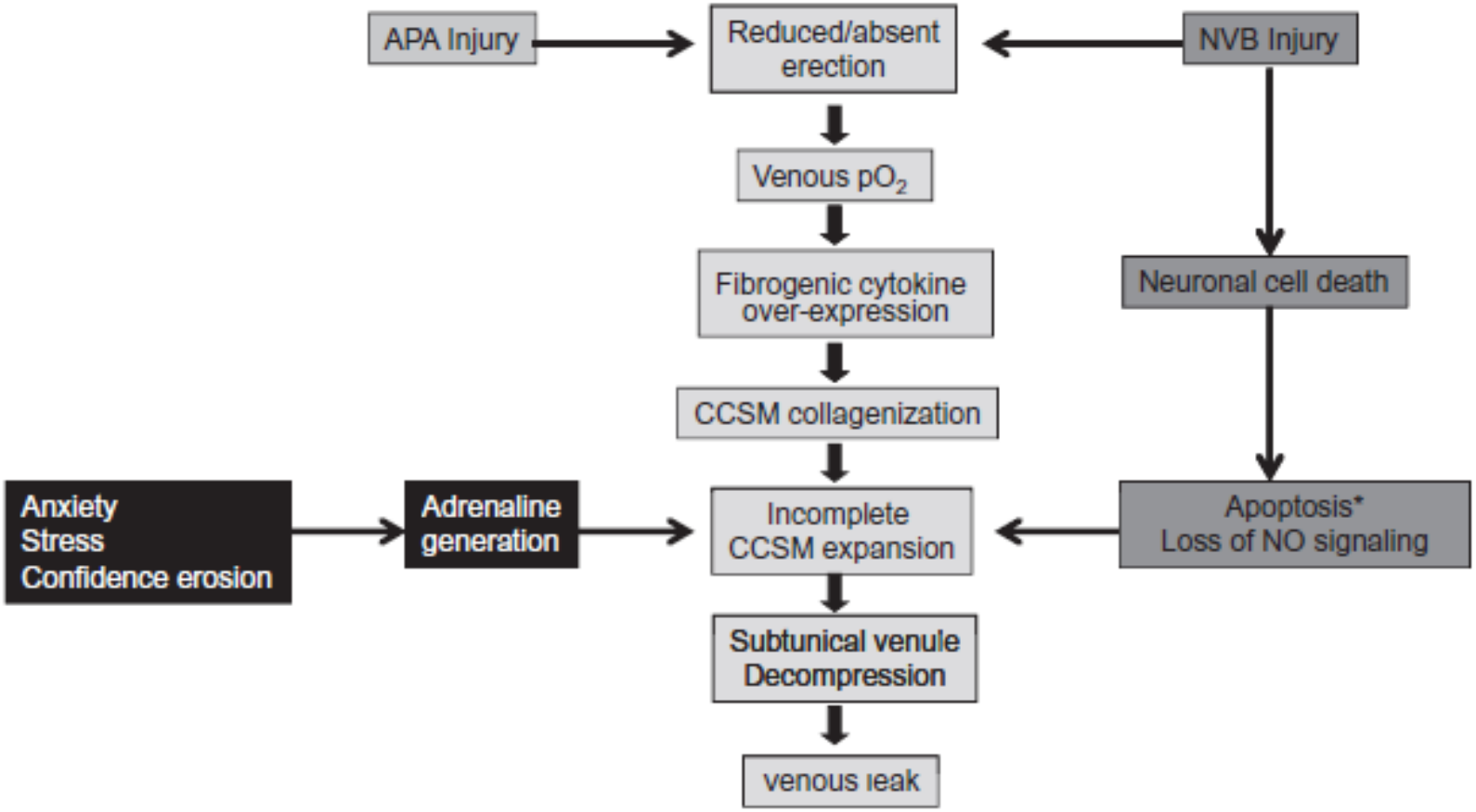
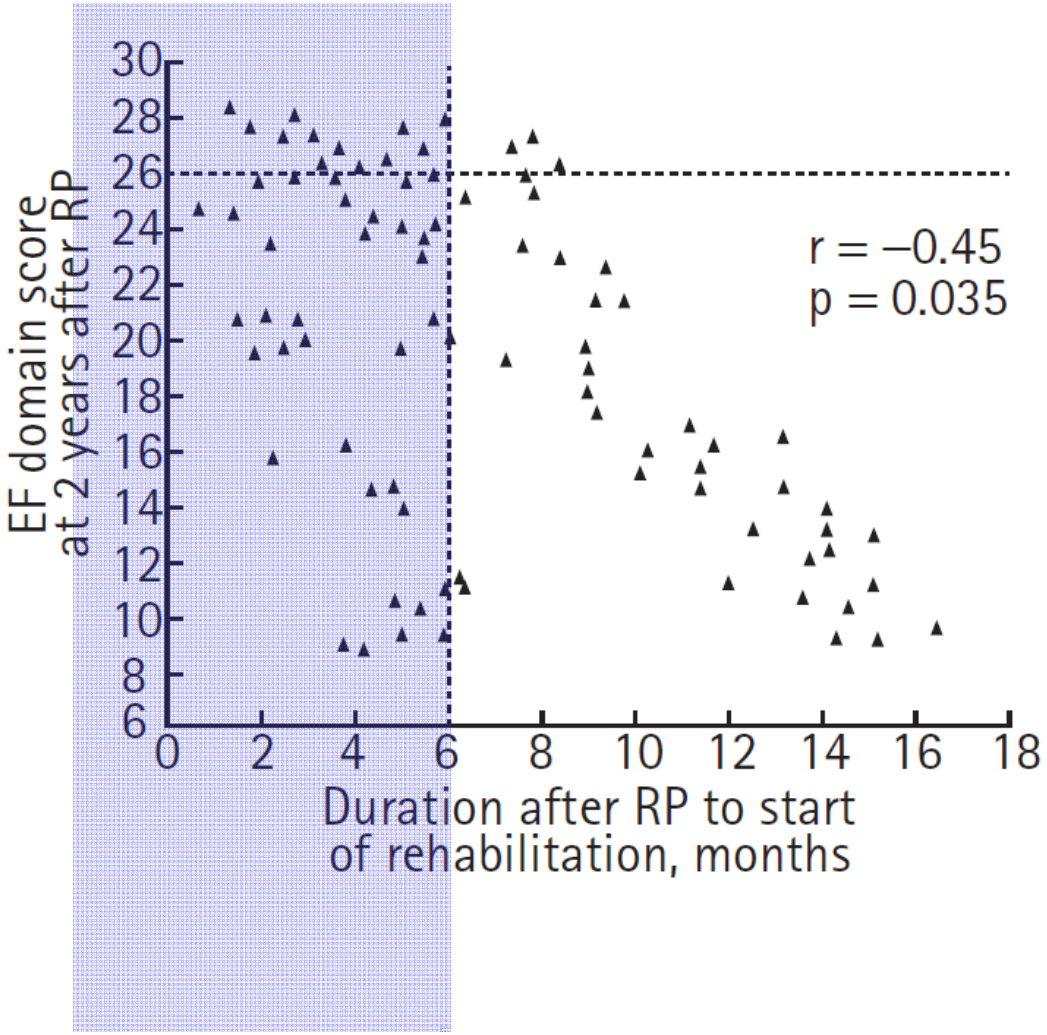


Figure 1 Schematic representing the pathophysiology of erectile dysfunction after radical prostatectomy. *Apoptosis occurs in nerves, smooth muscle, and endothelium as a result of neural trauma. APA = accessory pudendal artery; CCSM = corpora cavernosa smooth muscle; NVB = neurovascular bundle; pO_2 = partial pressure of oxygen

Mulhall JP, et al. J Sex Med, 10:195-203, 2013

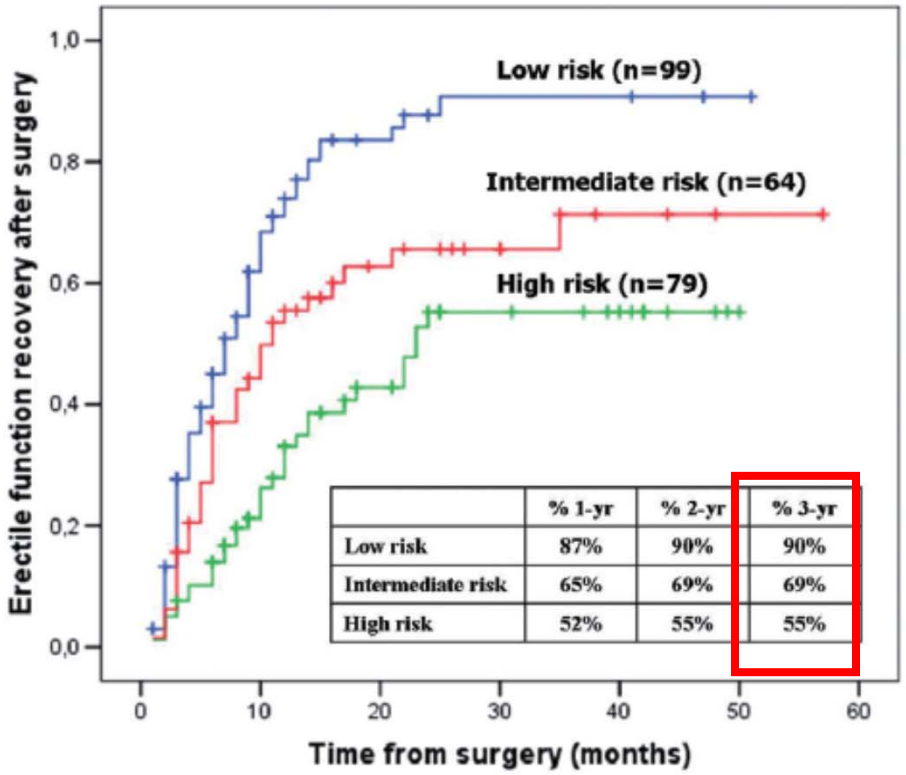
The timing of penile rehabilitation after bilateral nerve-sparing radical prostatectomy affects the recovery of erectile function



Mulhall J, et al. BJU Int, 105:37-41, 2009

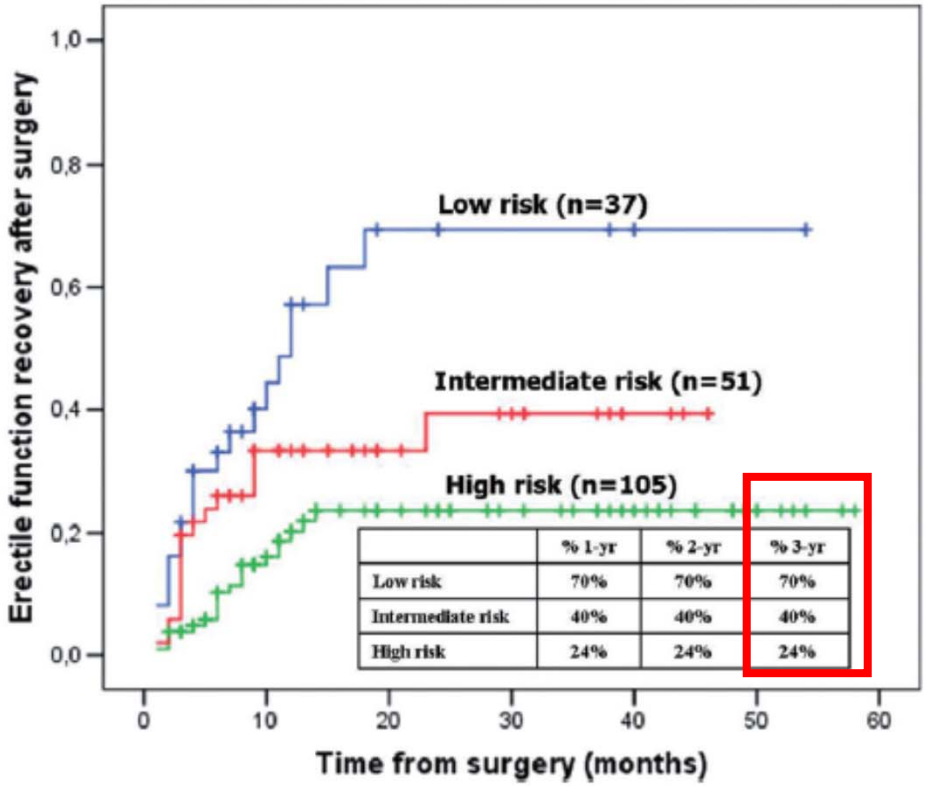
Overall EF recovery rate according to postop ED risk stratification

Pts taking PDE5i



	% 1-yr	% 2-yr	% 3-yr
Low risk	87%	90%	90%
Intermediate risk	65%	69%	69%
High risk	52%	55%	55%

Pts not taking PDE5i



	% 1-yr	% 2-yr	% 3-yr
Low risk	70%	70%	70%
Intermediate risk	40%	40%	40%
High risk	24%	24%	24%

P<0.001

Briganti A, et al. J Sex Med, 7:2521-2531, 2010

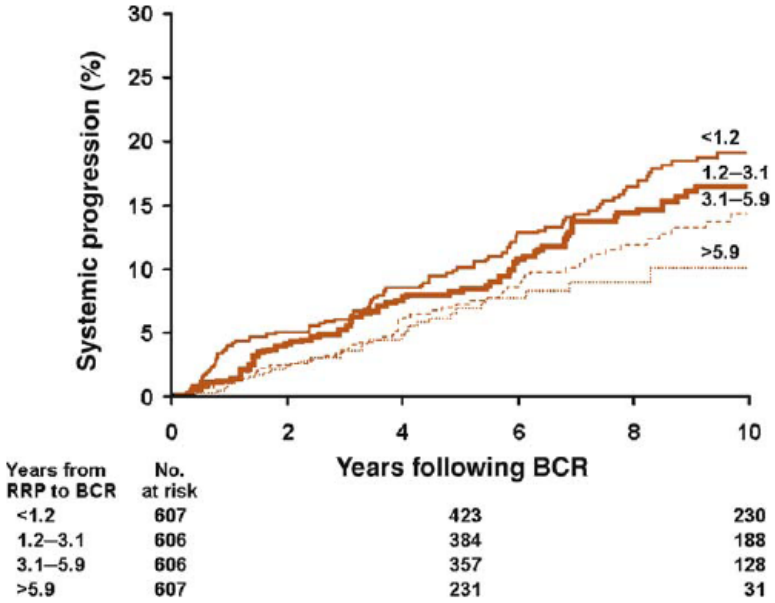
TRT after RP – The right Timing - Early?

- Testosterone does play a role in **EF**
- Testosterone has been shown to have an effect on **NOS release, PDE5 expression and activity** and in **cavernosal nerve function** and to contribute to penile **veno-occlusive disease**
    - Testosterone supplementation may **slow the progression of venous leak** following RP in hypogonadal men
    - Neuropraxia can lead to early ED and subsequent corporal smooth muscle damage. However, **androgens have been shown to improve cavernosal nerve function**

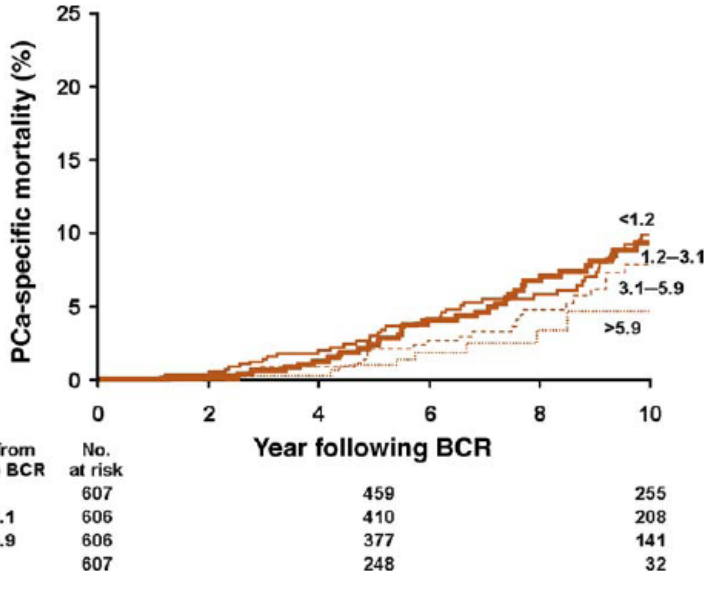
This data would suggest that **hypogonadal men after RP may have a disadvantage in EF recovering** when compared with eugonadal men

Khera M, et al. J Sex Med 2009

TRT after RP – The right Timing - Late?



Years from RRP to BCR	No. at risk		
<1.2	607	423	230
1.2–3.1	606	384	188
3.1–5.9	606	357	128
>5.9	607	231	31



Years from RRP to BCR	No. at risk		
<1.2	607	459	255
1.2–3.1	606	410	208
3.1–5.9	606	377	141
>5.9	607	248	32

Patients with **early PSA events show worst outcomes**

Boorjan SA et al. Eur Urol 2011

TRT after RP – The right Timing - Late?

	Time to TRT from RP
Kaufman et al	≥ 8 mo
Khera et al	Mean of 36 mo
Pastuszak et al	Mean of 12.3 mo

Kaufman JM, et al. J Urol 2004

Khera M, et al. J Urol 2009

Pastuszak AW, et al. J Urol 2013

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

TRT after RP

- The **small size and limited duration of published case series** make it **difficult to assess the overall safety** of TRT after definitive treatment for Pca

- **Large, randomized prospective studies will be needed** to provide reliable safety information

- We are aware of a **single controlled prospective study to date following RP** (Baylor College of Medicine, Clinical- Trials.gov identifier NCT00848497)

Khera M, et al. Eur Urol 2014

TRT after RP

In the end clinicians must make their own determination regarding the relative merits of T therapy for men with a history of PCa, considering individual circumstances, patient desires and the rapidly changing assessment of risk in this situation. Whereas most clinicians are familiar with the ethical concept "Primum non nocere," or "First, do no harm," all medical treatments entail some degree of risk, as does withholding treatment. A lesser known, but arguably more appropriate dictum for medical care is "Salus aegroti suprema lex," or "Do what is best for the patient," a concept that incorporates clinical judgment amid uncertainty, and honors the wishes and goals of the patient.

Morgentaler A. J Urol 2013