L' OTTIMIZZAZIONE DELLA TERAPIA DI DEPRIVAZIONE ANDROGENICA NEL PAZIENTE CON CARCINOMA DELLA PROSTATA

S. Arcangeli
S. Camillo-Forlanini

INTACT PROSTATE CANCER

Seminar article

Why does androgen deprivation enhance the results of radiation therapy?

Jennifer Y. Wo, M.D.[a,*], Anthony L. Zietman, M.D.[b]

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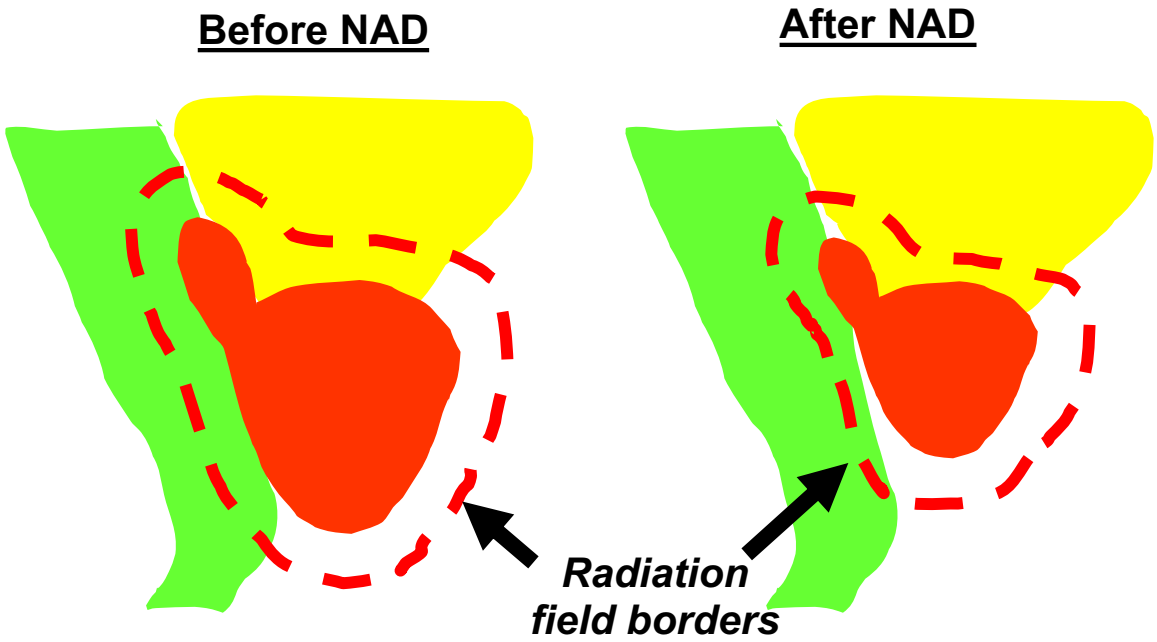
Technical advantages: Volume Reduction



Urologic Oncology: Seminars and Original Investigations 26 (2008) 522–529

Seminar article

Why does androgen deprivation enhance the results of radiation therapy?

Jennifer Y. Wo, M.D.[a,*], Anthony L. Zietman, M.D.[b]

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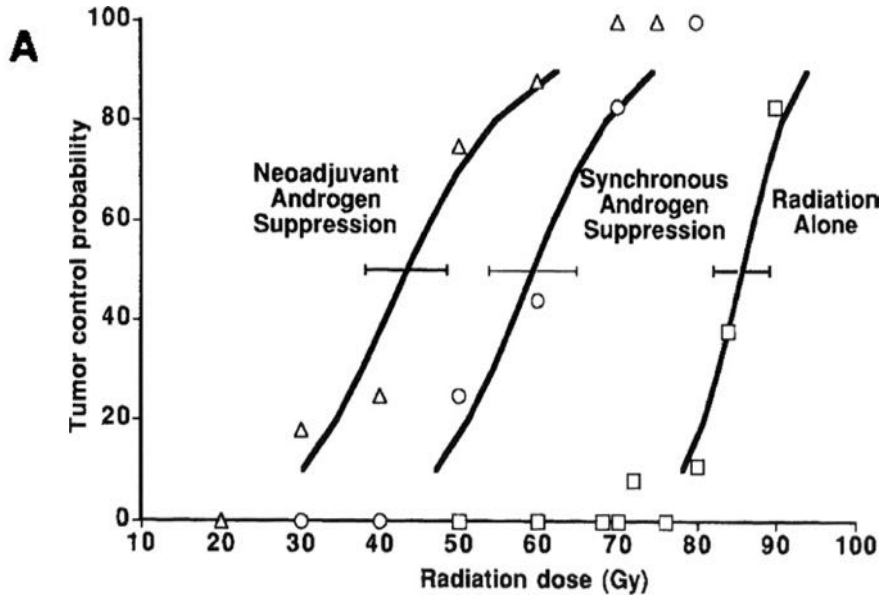
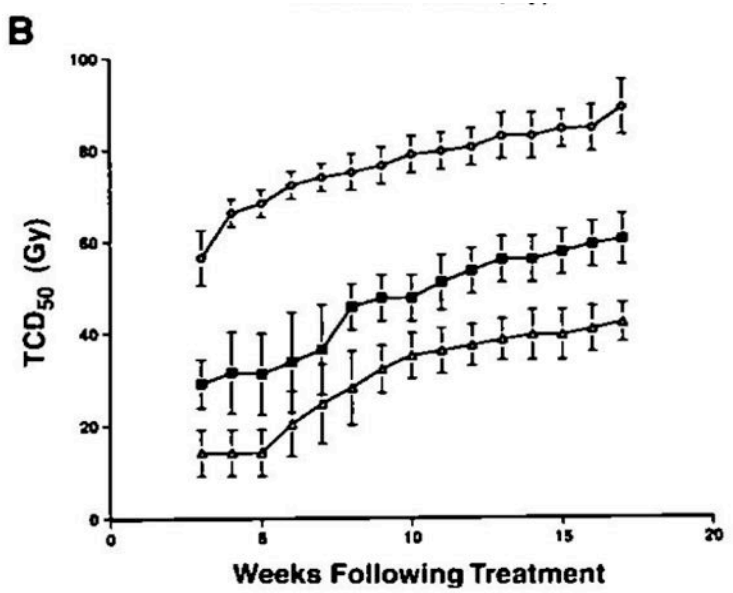
[b] *Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA 02114, USA*

Biological advantages: prior ADT increase the probability of eradicating tumor by irradiation





Urologic Oncology: Seminars and Original Investigations 26 (2008) 522–529

European Association of Urology

	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			**Locally advanced**

European Association of Urology 2015

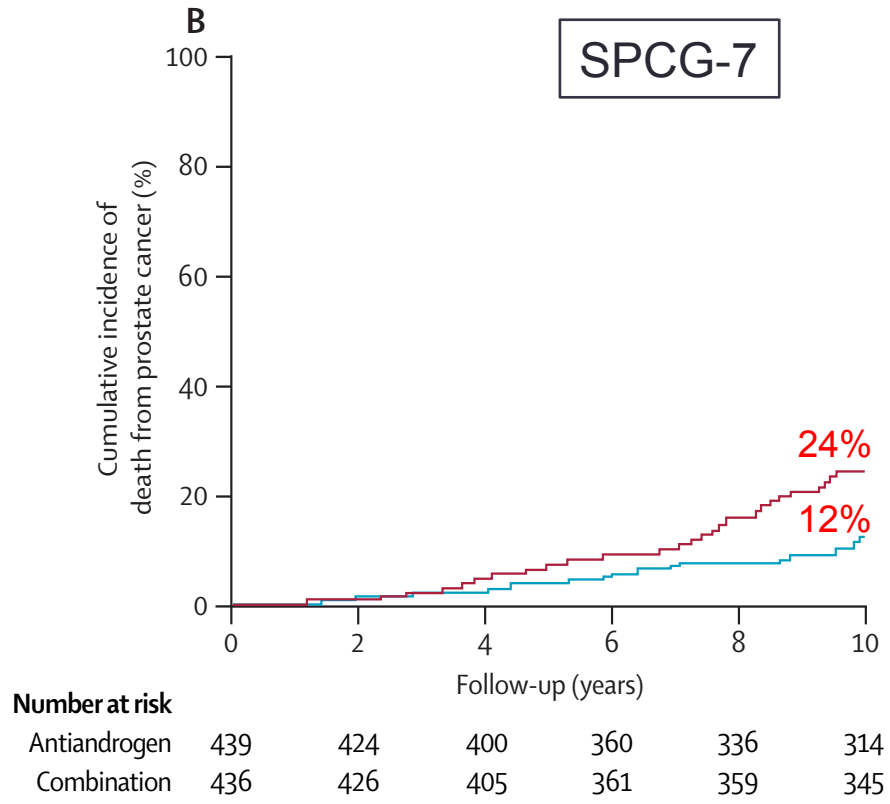
Intermediate risk PCa	**Radiotherapy**	In intermediate-risk PCa, the total dose should be 76-78 Gy, in combination with short-term ADT (4-6 mo).	A

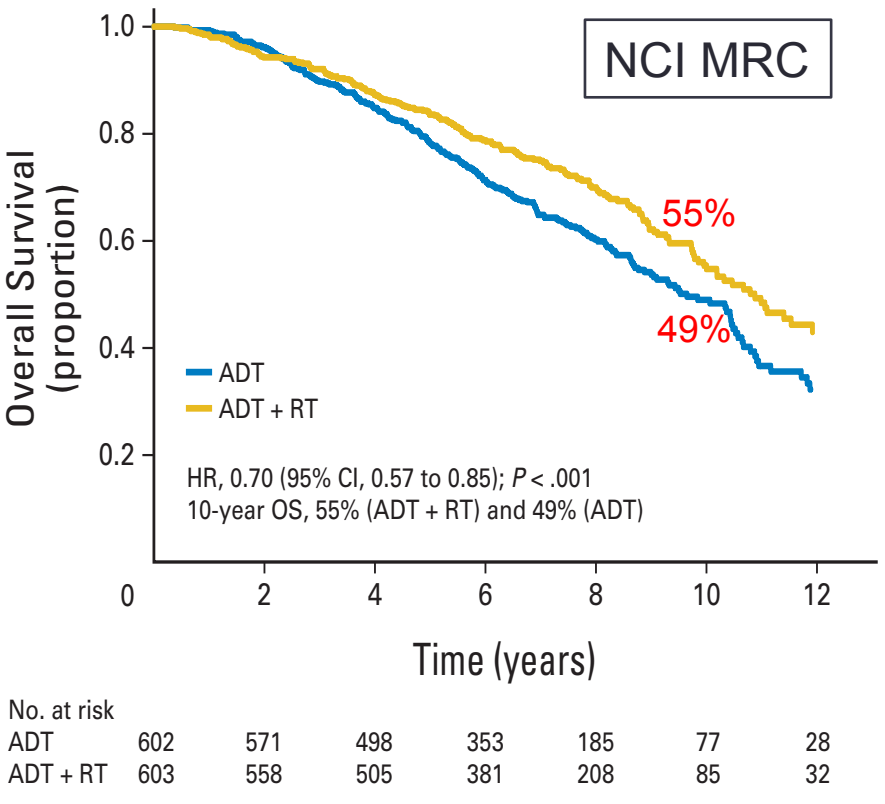
High risk PCa	**Radiotherapy**	In patients with high-risk localised PCa, the total dose is 76-78 Gy in combination with long-term ADT (2-3 yr is recommended).	A
		In patients with **locally advanced cN0** PCa, radiotherapy must be given in combination with long-term ADT (2-3 yr is recommended).	A

ADT ± RT

	SPCG-7 Widmark, *Lancet Oncol 2009*	NCI-MRC Mason, *JCO 2015*
Eligibility	T3 or T1b-2b/WHO G2-3; PSA <70; pN0 (if PSA >11)	T3-4 or T2 with PSA >40, or GS 8 with PSA >20; cN0/Nx
Patients	N=875 78% T3 Median PSA 16 19% WHO G3	N=1205 83% T3 Median PSA 28 18% GS 8-10
Treatment	70 Gy (no pelvic RT)	65-69 Gy (45 Gy pelvis)
Indefinite ADT	Anti-androgen	LHRH agonists
Median Follow up	7.6 yrs	8 yrs

ADT ± RT





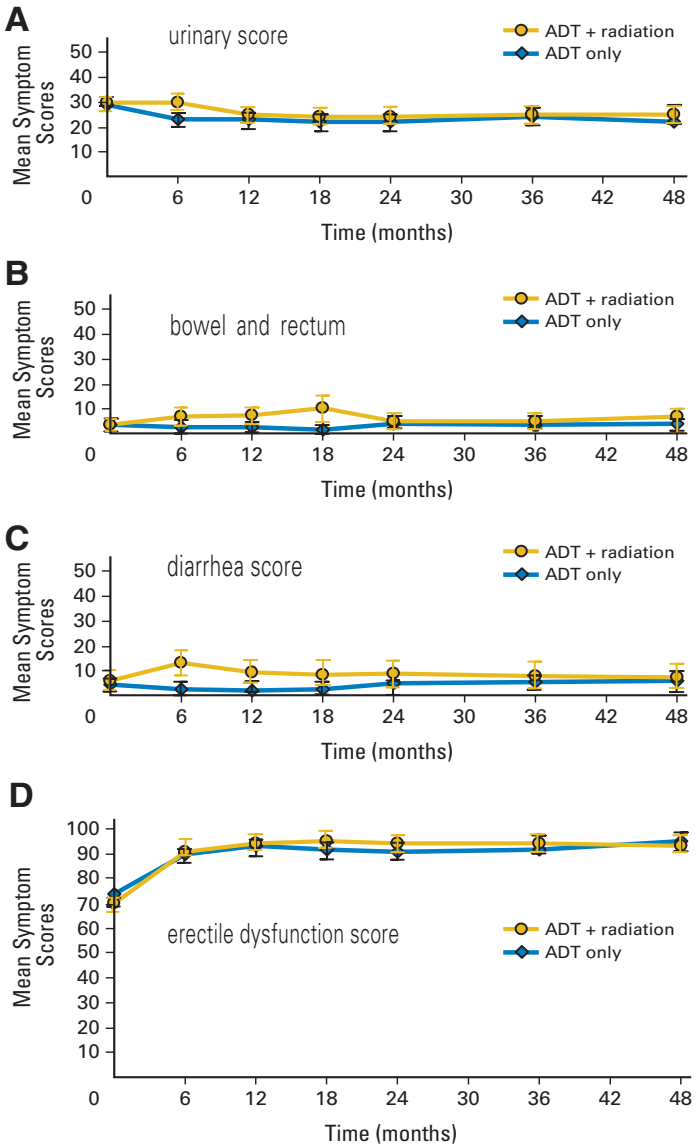
10 yrs	ADT+RT	ADT	*p*
bF	26%	75%	< 0.001
CSS	88%	76%	< 0.001
OS	70%	61%	0.004

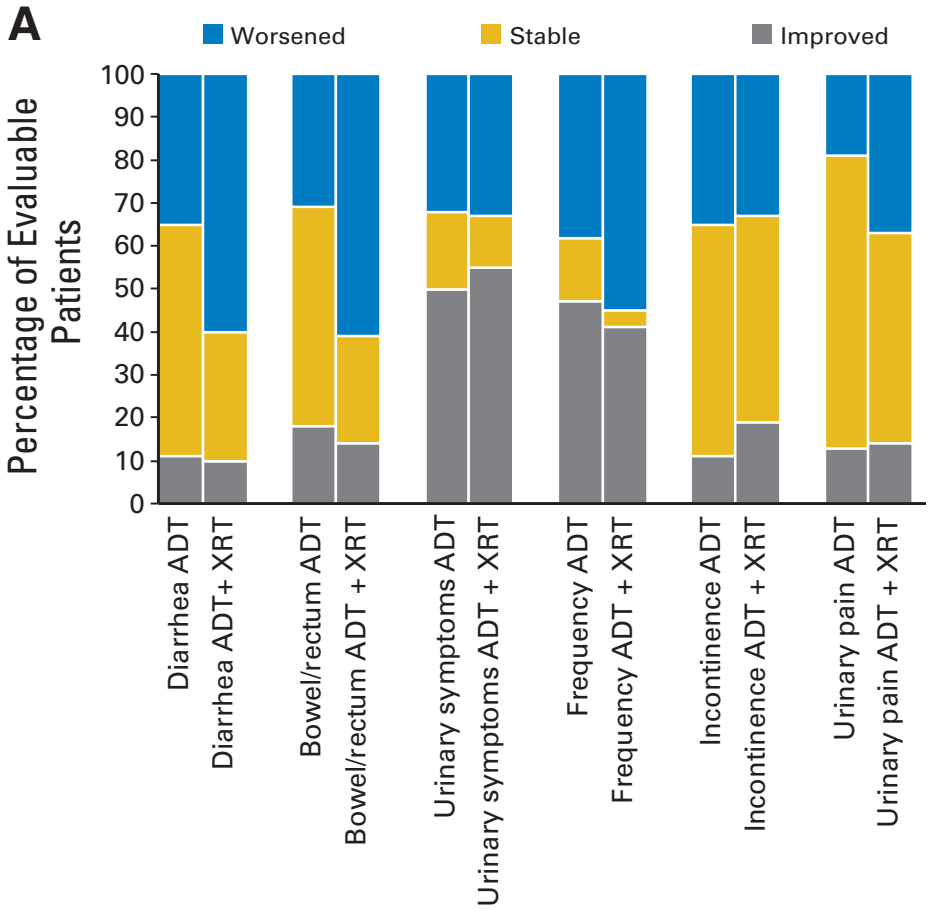
10 yrs	ADT+RT	ADT	*p*
TTP	63%	27%	< 0.001
CSS	68%	46%	< 0.001
OS	55%	49%	0.001

ADT ± RT

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Long-Term Quality-of-Life Outcomes From the NCIC CTG PR3/MRC PR07 Randomized Trial





RT+ADT & localized PCa

QUESTION	STUDY	DISEASE STAGE (%)	GLEASON SCORE (%)	NO.	MEDIAN FOLLOW-UP, y	TREATMENT ARMS	OVERALL SURVIVAL, %	PROSTATE CANCER-SPECIFIC MORTALITY, %
Localized disease: RT vs RT + ADT	TROG 96.01[119] HR PCa	T2b (26), T2c (34), T3,T4 (40), N0M0	≤6 (44), 7 (38), ≥8 (17)	818	10.6	RT 66 Gy	10 y, 57.5	10 y, 22
						RT + 3 mo ADT	10 y, 63.3[a]	10 y, 18.9[a]
						RT + 6 mo ADT	**13.3% OS benefit**	
	DFCI 95-096[115] IR PCa	T1b (2), T1c (46), T2a (23), T2b (30), N0M0	≤6 (28), 7 (58), ≥8 (15)	206	7.6	RT 67 Gy	8 y, 61	8 y, 12
						RT + 6 mo ADT	8 y, **13% OS benefit**	
	RTOG 94-08[105] IR PCa	T1 (49), T2 (51), N0M0	≤6 (62), 7 (28), ≥8 (9)	1979	9.1	RT 66.6 Gy	10 y, 57	10 y, 8
						RT + 4 mo ADT	10 y, **5% OS benefit**	

RT+ADT & locally advanced PCa

QUESTION	STUDY	DISEASE STAGE (%)	GLEASON SCORE (%)	NO.	MEDIAN FOLLOW-UP, y	TREATMENT ARMS	OVERALL SURVIVAL, %	PROSTATE CANCER-SPECIFIC MORTALITY, %
Locally advanced disease: RT vs RT + ADT	RTOG 86-10[illegible]	T2 (30), T3,T4 (70), N0 (92), N1 (8), M0	≤6 (30), ≥7 (70)	471	12.6	RT 65-70 Gy	10 y, 34	10 y, 36
						RT + 4 mo ADT	10	
	EORTC 22863[121]	T1 (1), T2 (10), T3 (80), T4 (9) N0 (89), M0	≤6 (62), 7 (28), ≥8 (9)	415	9.1	RT 70 Gy	10 y, 39.8	10 y, 30.4
						RT + 36 mo ADT		

IR PCa

Very HR PCa

8.8% OS benefit

20% PCSM benefit

RT & ADT duration

QUESTION	STUDY	DISEASE STAGE (%)	GLEASON SCORE (%)	NO.	MEDIAN FOLLOW-UP, y	TREATMENT ARMS	OVERALL SURVIVAL, %	PROSTATE CANCER-SPECIFIC MORTALITY, %
Duration of ADT	RTOG 92-02[123]	T2 (45), T3 (51), T4 (4), N0 (97), M0	≤6 (38), 7 (31), ≥8 (24)	1554	11.3	RT + 4 mo ADT	10 y, 51.6	10 y, 16.1
	EORTC 22[illegible]4	T2c (19), T3 (73), T4 (4), N1 (3), M0	≤6 (47), 7 (30), ≥8 (18)	970	6.4	RT + 6 mo ADT	5 y, 81	5 y, 4.7
						RT + 36 mo ADT	5	
	PCS IV[125]	T1c (24), T2a (20), T2b (31), T3 (24)	NA	630	6.5	RT + 18 mo ADT	5 y, 86	5 y, 4.7
						RT + 36 mo ADT	5 y, 91[a]	5 y, 3.4[a]
	RTOG 99-10[118]	T1b-T4, N0M0	≤7 (90)	1490	8.7	RT 70.2 Gy + 4 mo ADT	10 y, 66	10 y, 5
						RT + 8 mo ADT	10 y, 67[a]	10 y, 4[a]

HR PCa

Very HR PCa

Very HR PCa

HR PCa

13% OS benefit (in GS score 8-10)

3.8% OS benefit

no OS neither PSCM benefit

no OS benefit

RT & ADT duration

EORTC 22961 vs. PCS IV

Study	N. pts	Median f-up (years)	5-year Survival (%)		
Duration of ADT			6 months	18 months	36 months
EORTC[1]	970	6.4	80.6		85.3
PCS IV[2]	630	6.4		86.8	92.1

[1] Bolla M et al. N Engl J Med 2009

[2] Nabid A, et al. JCO 2013;31(S6):3 (abs)

Synthesis of Trials Data

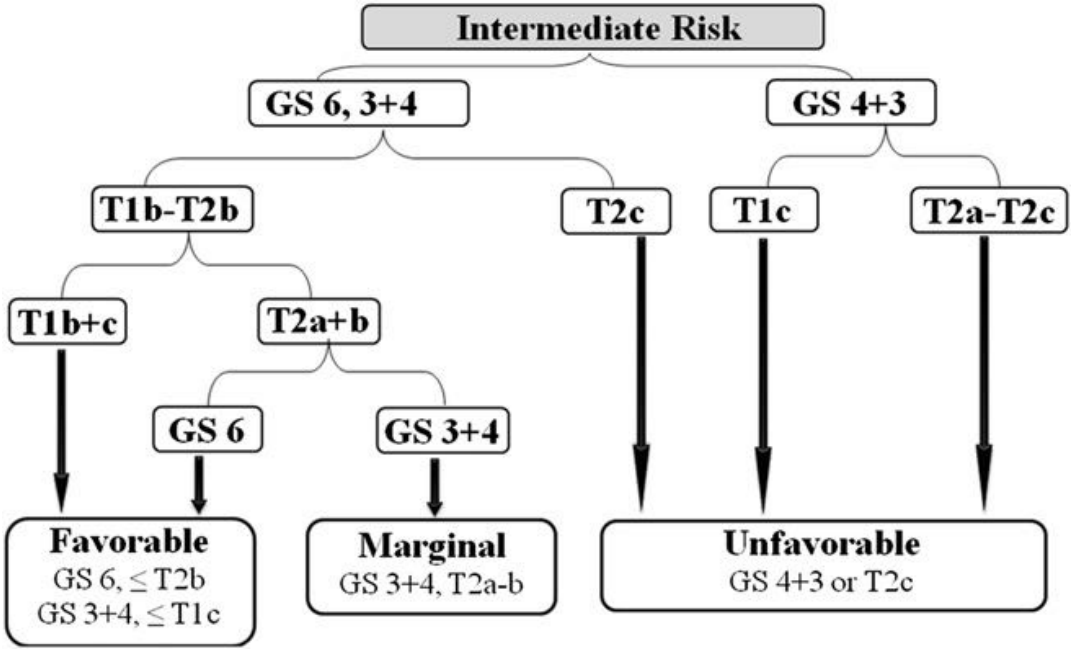
- **Overall Survival Benefit**
  - **EORTC 22863** – 3 yrs vs. 0 (18.3% at 10 yrs)
  - **TROG 9601** – 6 months vs. 0 (13.3% at 3 yrs)
  - **DFCI 95096** – 6 months vs. 0 (13% at 8 yrs)
  - **RTOG 8610** – 4 months vs. 0 (8.8% at 10 yrs)
  - **RTOG 9408** – 4 months vs. 0 (5% at 10 yrs)
  - **RTOG 9910** – 9 months vs. 4 months (1% at 10 yrs)
  - **EORTC 22961** – 3 yrs vs. 6 months (3.8% at 5 yrs)

Are these results transferable in daily clinical practice ?

- **Population**:

  inhomogeneity of

  intermediate risk group

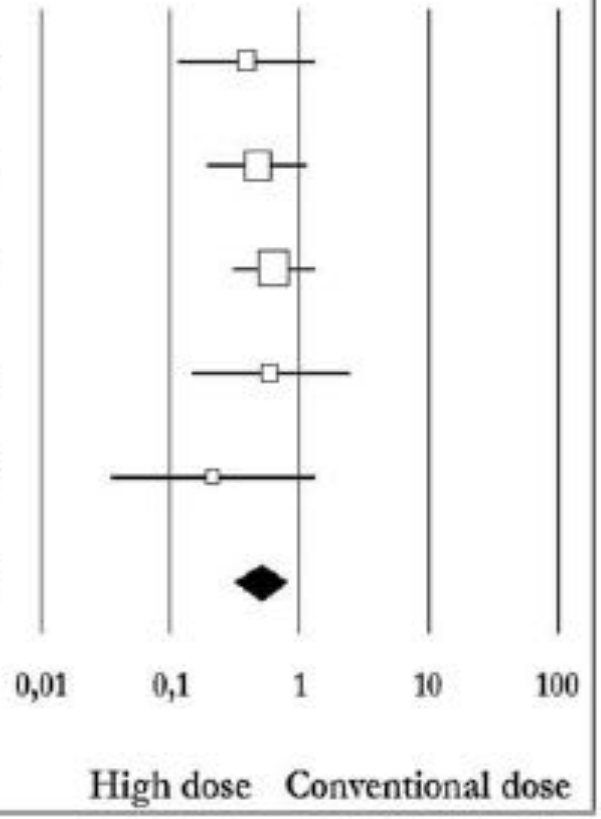


- **Intervention**: use of ineffective RT total dose

- **Outcomes**: improvement in OS and DFS likely overestimated

Dose Escalation RT Trials

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zietman et al	0,391	0,115	1,327	-1,980	0,048
Dutch	0,472	0,197	1,129	-2,217	0,027
MRC-RT01	0,632	0,303	1,321	-1,603	0,109
M.D.Anderson	0,590	0,144	2,415	-0,964	0,335
Sathya et al	0,214	0,035	1,321	-2,182	0,029
	0,502	0,315	0,799	-3,819	0,000



Dose Escalation is supported for all risk categories

CLINICAL INVESTIGATION Prostate

WHAT DOSE OF EXTERNAL-BEAM RADIATION IS HIGH ENOUGH FOR PROSTATE CANCER?

THOMAS N. EADE, F.R.A.N.Z.C.R.,* ALEXANDRA L. HANLON, PH.D.,† ERIC M. HORWITZ, M.D.,* MARK K. BUYYOUNOUSKI, M.D.,* GERALD E. HANKS, M.D.,* AND ALAN POLLACK, M.D., PH.D.*

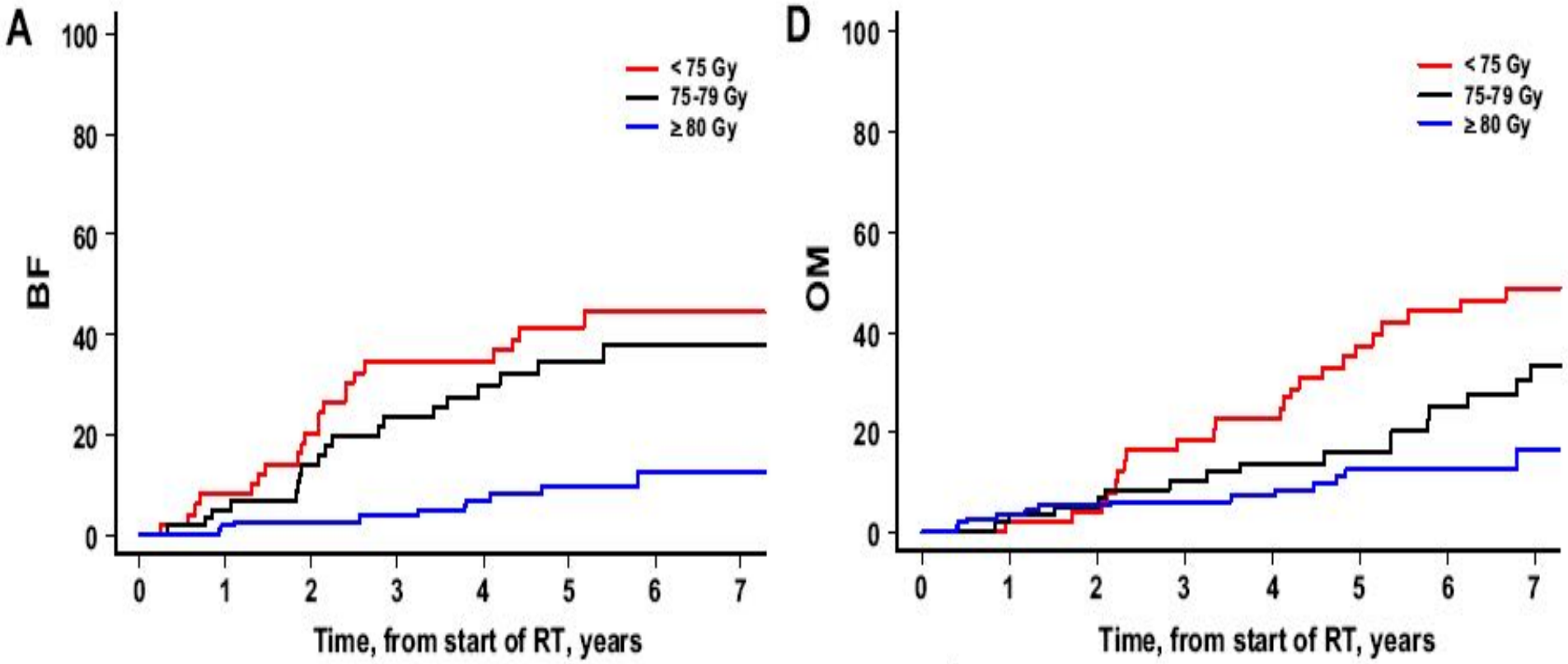
A decrease in BF secondary to dose escalation should translate into a reduction in distant spread (10). Our results more precisely define this relationship, showing that RT dose causes an 8% reduction in the risk of distant metastases for each 1 Gy delivered. We anticipate that as our median follow-up increases, the benefit of dose escalation will strengthen, because higher initial doses will proportionally increase local control and prevent the late wave of distant metastasis due to persistent local disease (34, 35). Follow-up >10 years is required

Int J Rad Oncol Biol Phys 2008

CLINICAL INVESTIGATION

RADIOTHERAPY DOSES OF 80 GY AND HIGHER ARE ASSOCIATED WITH LOWER MORTALITY IN MEN WITH GLEASON SCORE 8 TO 10 PROSTATE CANCER

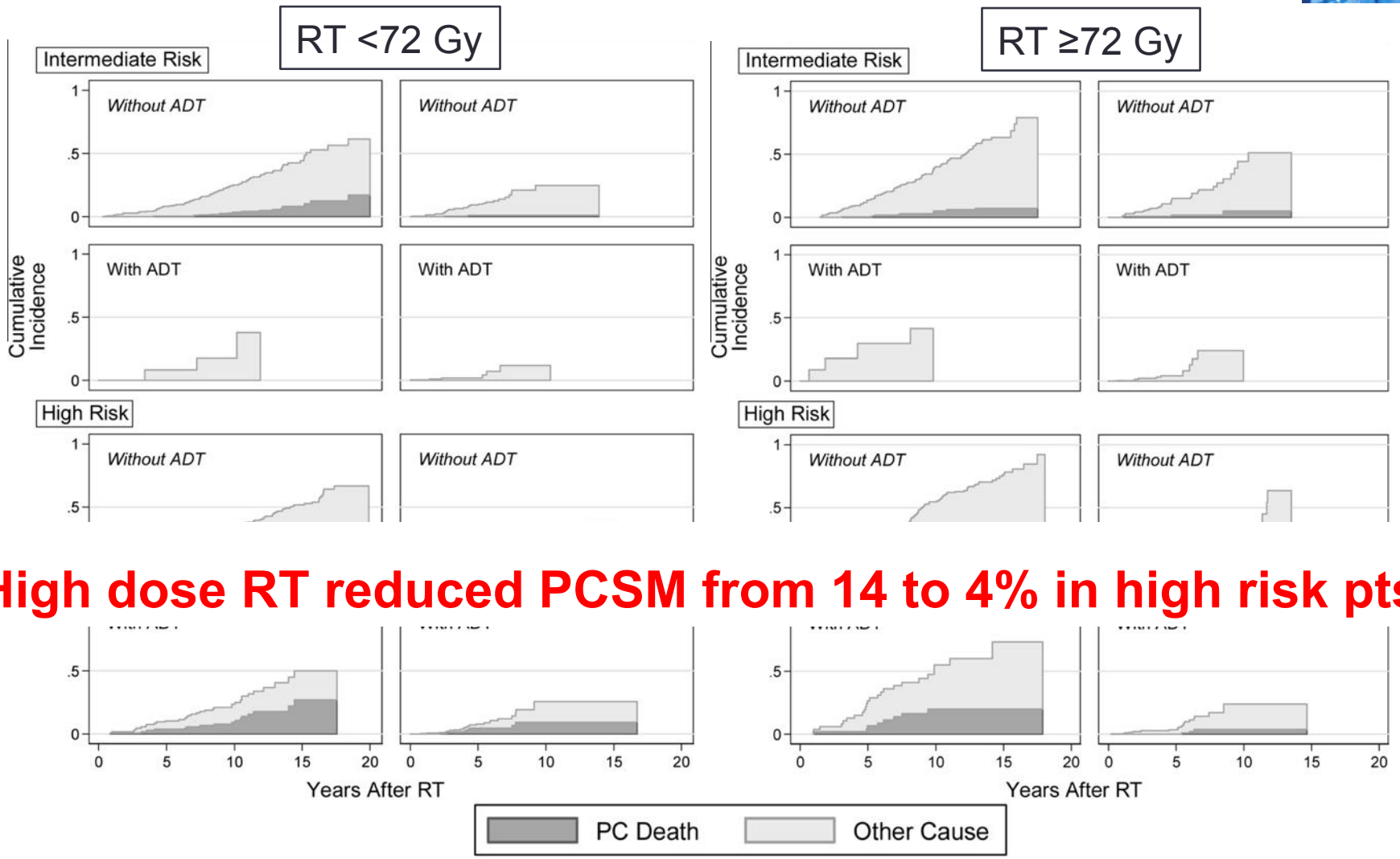
NIRAJ PAHLAJANI, M.D.,* KAREN J. RUTH, M.S.,† MARK K. BUYYOUNOUSKI, M.D.,‡



Int J Rad Oncol Biol Phys 2012

Prostate cancer-specific mortality after definitive radiation therapy: Who dies of disease?

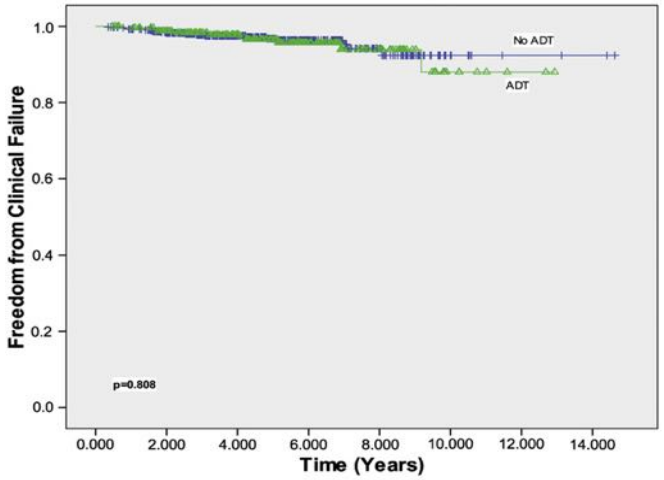
Outcomes of 2675 men with localised PC treated with RT ± ADT from 1987–2007

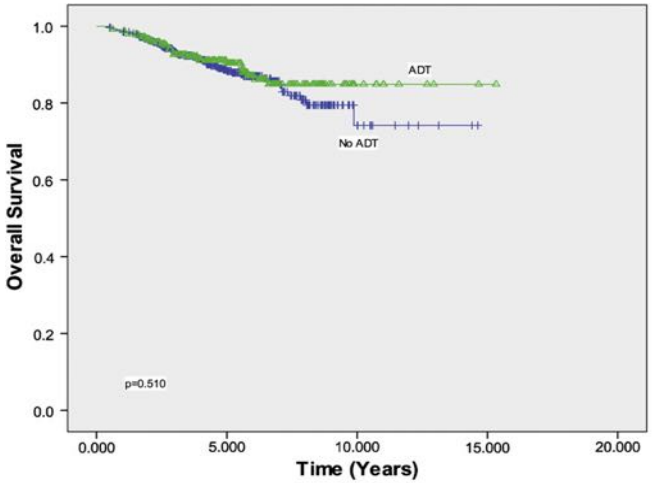


High dose RT reduced PCSM from 14 to 4% in high risk pts

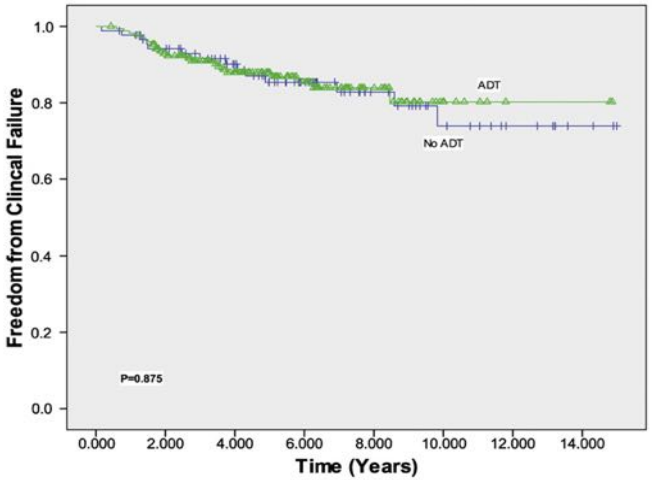
LACK OF BENEFIT FOR THE ADDITION OF ANDROGEN DEPRIVATION THERAPY TO DOSE-ESCALATED RADIOTHERAPY IN THE TREATMENT OF INTERMEDIATE- AND HIGH-RISK PROSTATE CANCER

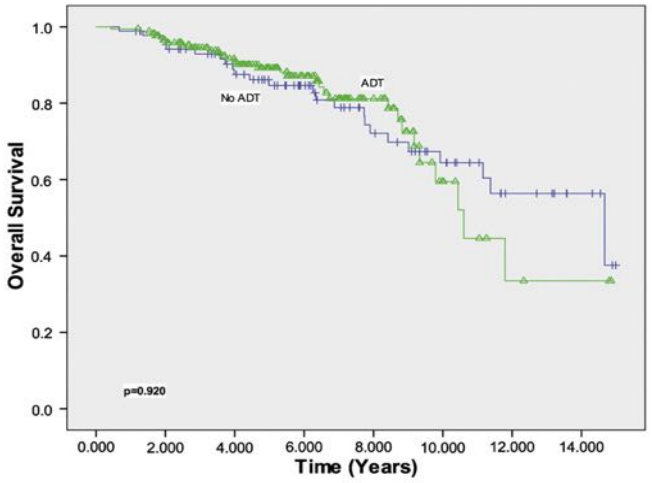
Intermediate Risk 75% **ADT 31.6%**





High Risk 25% **ADT 66%**





Dose escalated EBRT +/- ADT

Retrospective analysis of 234 men treated with 75-79.2 Gy and varying ADT

Covariate	Biochemical failure			Metastasis		
	P Value	HR	95% CI	*P* Value	HR	95% CI
PSA (log)	.003	2.7	1.4-5.2	.10	2.2	0.86-5.4
T stage						
T1-T2c	Reference			Reference		
T3-T4	.11	1.5	0.91-2.4	.10	1.8	0.89-3.7
Gleason Score						
2-6	Reference			Reference		
7	.36	1.4	0.67-3.0	.37	1.7	0.55-5.1
8	.14	1.8	0.82-4.1	.19	2.3	0.67-7.7
9-10	.009	3.3	1.3-8.1	<.0001	12.1	3.3-44
ADT group						
None	Reference			Reference		
STAD	.18	0.64	0.34-1.2	.002	0.27	0.11-0.63
LTAD	.03	0.46	0.23-0.93	<.0001	0.10	0.04-0.27
Age	.07	0.97	0.95-1.0	.90	1.0	0.97-1.0
CMI						
None	Reference			Reference		
1	.32	0.8	0.5-1.3	.11	0.5	0.2-1.2
2 or more	.12	0.6	0.3-1.2	.19	0.5	0.2-1.4

>≥1 year

Abbreviations: ADT = androgen deprivation therapy; CI = confidence interval; CMI = Charlson Comorbidity Index; HR = hazard ratio; LTAD = long-term ADT; PSA = prostate-specific antigen; STAD = short-term ADT.

Feng, IJROBP 2013

ASCO University
LIFELONG LEARNING

Does short-term androgen depletion add to high-dose radiotherapy (80 Gy) in localized intermediate-risk prostate cancer- Intermediary analysis of GETUG 14 randomized trial (EU-20503/NCT00104741).

Subcategory:
Prostate Cancer

Category:
Genitourinary Cancer

Meeting:
2011 ASCO Annual Meeting

Session Type and Session Title:
Poster Discussion Session, Genitour

Abstract Number:
4521

GETUG 14 – 80 Gy RT ± 4 months HT

- Median Follow up 3.1 yrs. Primary endpoint not reached
- Clinical or PSA control (86% vs. 92%; p=0.11)
- 377 pts with T1b-T3a

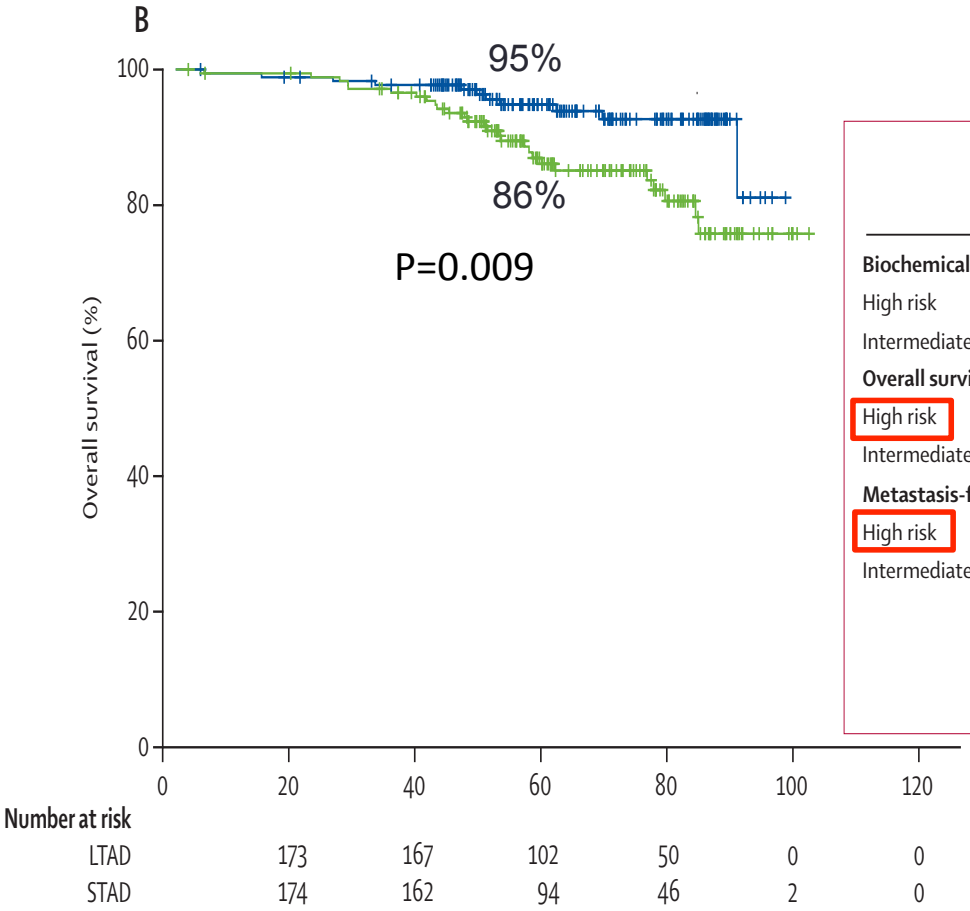
Citation:
J Clin Oncol 29: 2011 (suppl; abstr 4521)

Abstract:

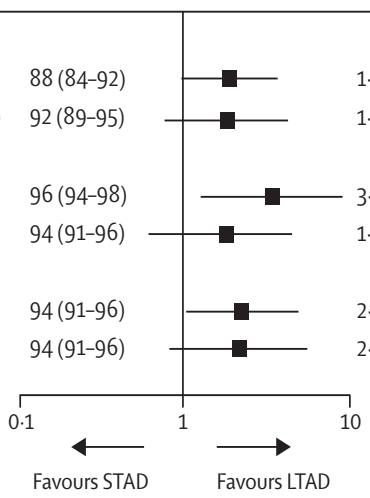
Background: randomized trial to evaluate the addition of 4-month androgen deprivation to high dose radiotherapy in localized intermediate risk prostate adenocarcinoma patients. **Methods:** eligible patients were randomly assigned to high dose radiotherapy (prostate 80 Gy; seminal vesicles 46 Gy) either alone (group RT) or in combination with 4-month androgen deprivation (flutamide + triptoreline starting 2 months before radiotherapy, group AD-RT). Lymphadenectomy was mandatory when the risk of node involvement was > 10% (Partin). The primary endpoint was biochemical (Phoenix definition) or clinical control. Secondary endpoints included survival, toxicity (CTCAE v3) and quality of life. The a-priori sample size was 450 patients (0.90 power to detect an increase from 75 to 85%, bilateral $\alpha = 0.05$). An intermediate analysis was planned 6 months after the last patient inclusion (bilateral $\alpha = 0.005$). **Results:** 377 patients were entered between October 2003 and July 2010. The trial was prematurely closed, due to slow accrual. Intention-to-treat analysis included 366 patients (188 RT, 178 AD-RT). Prognostic factors were well balanced between groups. The median follow-up duration was 37 months (range: 0 to 63). At 3 years, biochemical or clinical control probabilities were 86% [95% CI: 80%–92%] and 92% [87%–97%] in RT and AD-RT groups respectively ($p = 0.09$). Biochemical control probabilities were 91% [86%–96%] and 97% [94%–99.6%] in RT and AD-RT groups respectively ($p = 0.04$). The cumulative hazards of grade 3-4 toxicities were 6.4% and 2.8% (p=0.41) for digestive tract, 2.6% and 6.1% (p=0.14) for urinary tract, in RT and AD-RT groups respectively. **Conclusions:** The observed difference in favour of AD-RT did not reach statistical significance as defined for the present intermediary analysis. The final analysis is scheduled in 2013.

High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial

Lancet Oncol 2015; 16: 320–27



	Number of events			5-year rate (%, 95% CI)		Hazard ratio (95% CI)	p value
	N	STAD	LTAD	STAD	LTAD		
Biochemical disease-free survival							
High risk	189	23	13	76 (71–80)	88 (84–92)	1·91 (0·97–3·77)	0·054
Intermediate risk	166	14	8	88 (84–91)	92 (89–95)	1·82 (0·76–4·33)	0·174
Overall survival							
High risk	189	17	5	82 (77–86)	96 (94–98)	3·43 (1·26–9·32)	0·015
Intermediate risk	166	10	6	91 (88–95)	94 (91–96)	1·67 (0·61–4·60)	0·318
Metastasis-free survival							
High risk	189	20	9	79 (74–83)	94 (91–96)	2·27 (1·04–5·01)	0·041
Intermediate risk	166	13	6	89 (85–93)	94 (91–96)	2·14 (0·81–5·66)	0·124



Ongoing Trials High dose RT ± ADT

- **RTOG 0815** – 79.2 Gy RT ± 6 months HT in IR-HR PCa

  The only trial stratified by Adult Comorbidity Evaluation-27 comorbidity score

- **EORTC 22991** – 70 Gy/74 Gy/78 Gy RT ± 6 months HT in IR PCa

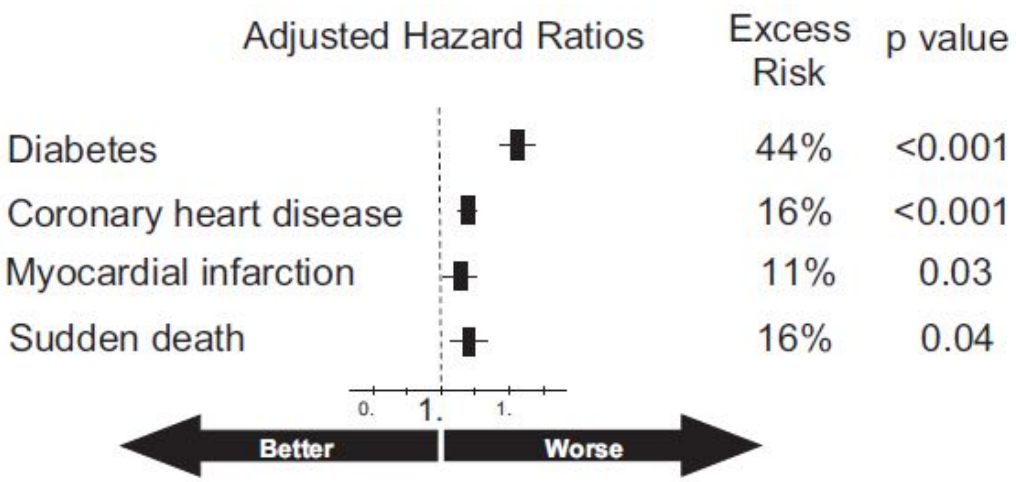
  - 819 pts from 14 European Countries

ADT for prostate cancer: true love or heartbreak?

"increased risk of diabetes (+44%) and certain cardiovascular diseases (+16%): heart attack, sudden cardiac death, stroke in men receiving these medications for the treatment of prostate cancer"

US Food and Drug Administration. October 20, 2010

SEER-Medicare



↓Insulin sensitivity
↑LDL, HDL and TG ↑Fat mass (↓lean mass)

Veterans Affairs

Table 3. Association between androgen deprivation therapy and diabetes, coronary heart disease, myocardial infarction, sudden death, and stroke*

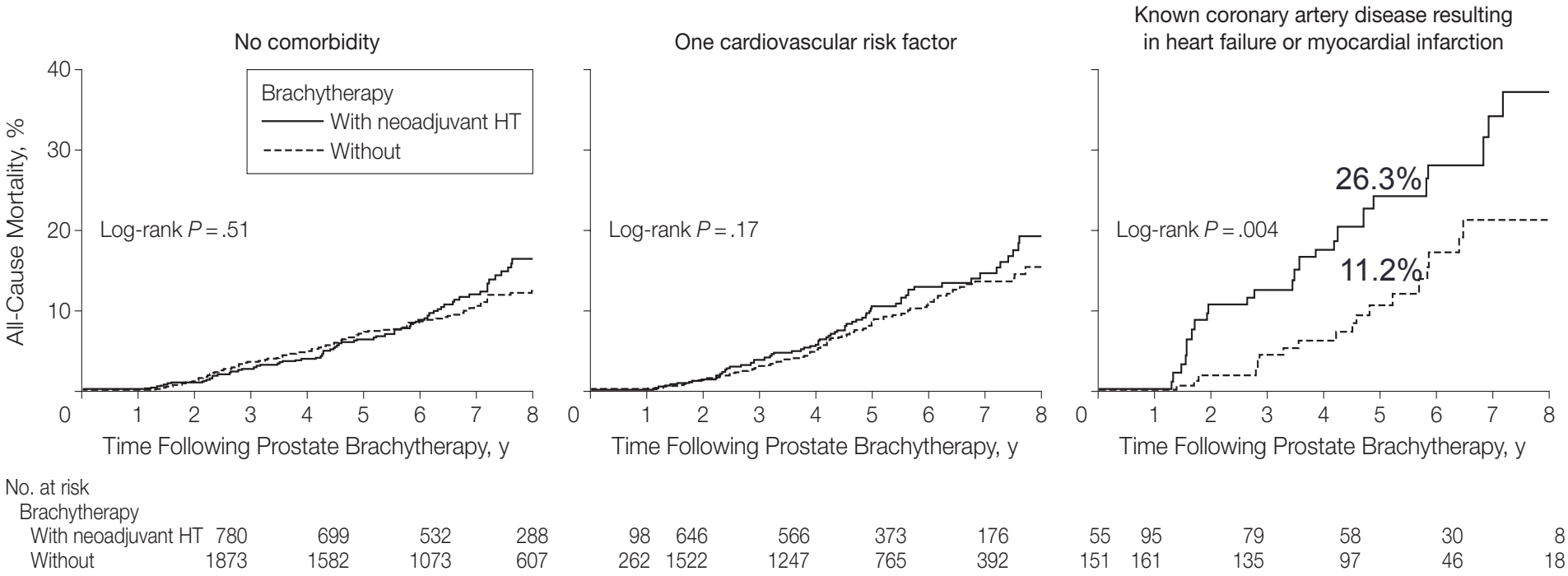
Treatment	Adjusted hazard ratio (95% CI)				
	Diabetes	Coronary heart disease	Myocardial infarction	Sudden cardiac death	Stroke
No androgen deprivation therapy	Reference	Reference	Reference	Reference	Reference
GnRH agonist	1.48 (1.31 to 1.67)	1.17 (1.06 to 1.39)	1.21 (1.01 to 1.44)	1.28 (1.05 to 1.57)	1.18 (1.02 to 1.36)
Orchiectomy	1.36 (0.79 to 2.31)	1.48 (1.00 to 2.20)	1.98 (1.15 to 3.41)	1.70 (0.86 to 3.34)	1.81 (1.15 to 2.84)
Combined androgen blockade	1.40 (1.01 to 1.93)	1.29 (1.00 to 1.66)	0.99 (0.59 to 1.64)	1.05 (0.60 to 1.87)	0.91 (0.60 to 1.39)
Oral antiandrogen	1.33 (0.75 to 2.36)	1.30 (0.85 to 1.20)	0.98 (0.43 to 2.19)	1.48 (0.69 to 3.14)	0.89 (0.46 to 1.73)

Absolute Excess Risk: ↑15 cases/1000 patient years

Keating, JCO 2006

Hormonal Therapy Use for Prostate Cancer and Mortality in Men With Coronary Artery Disease–Induced Congestive Heart Failure or Myocardial Infarction

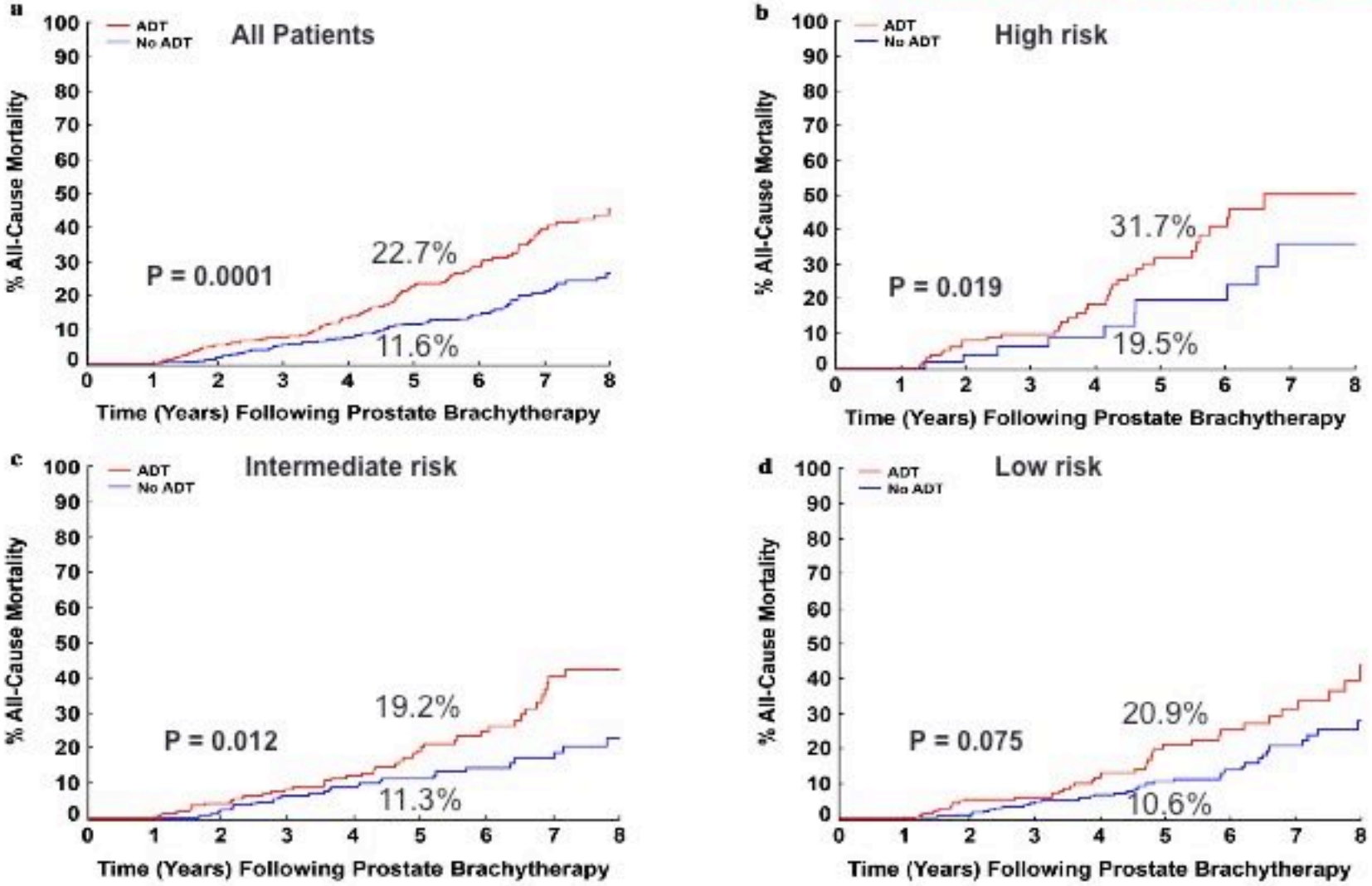
5077 PCa pts treated ± 4 months of neoadjuvant HT followed by RT



JAMA. 2009;302(8):866-873

INFLUENCE OF ANDROGEN DEPRIVATION THERAPY ON ALL-CAUSE MORTALITY IN MEN WITH HIGH-RISK PROSTATE CANCER AND A HISTORY OF CONGESTIVE HEART FAILURE OR MYOCARDIAL INFARCTION

14,594 cT1–T3a PCa pts treated with BRT + 4 months of neoadjuvant HT → **1,378 (9.4%) had a history of CHF or MI**



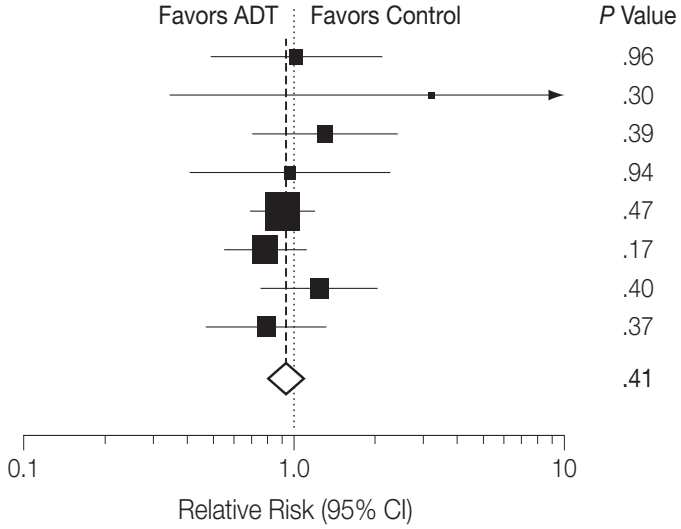
Androgen-deprivation Therapy and Cardiovascular Harm: Let's Not Throw Out the Baby with the Bathwater

Paul L. Nguyen *

Figure 2. Relative Risk of Cardiovascular Deaths Associated With ADT Among Patients With Prostate Cancer

Source	No./Total No. of Events: ADT	No./Total No. of Events: Control	Relative Risk (95% CI)	*P* Value
D'Amico et al,[3] 2008 (DFCI 95-096)	13/102	13/104	1.02 (0.50-2.09)	.96
Messing et al,[12] 2006 (ECOG/EST 3886)	3/47	1/51	3.26 (0.35-30.2)	.30
Bolla et al,[13] 2010 (EORTC 22863)	22/207	17/208	1.30 (0.71-2.38)	.39
Schröder et al,[14] 2009 (EORTC 30846)	10/119	10/115	0.97 (0.42-2.23)	.94
Studer et al,[15] 2006 (EORTC 30891)	88/492	97/493	0.91 (0.70-1.18)	.47
Efstathiou et al,[8] 2009 (RTOG 85-31)	52/477	65/468	0.78 (0.56-1.10)	.17
Roach et al,[9] 2008 (RTOG 86-10)	31/224	26/232	1.23 (0.76-2.01)	.40
Denham et al,[16] 2011 (TROG 96.01)	36/532	23/270	0.79 (0.48-1.31)	.37
Overall	255/2200	252/1941	0.93 (0.79-1.10)	.41

Test for heterogeneity: $Q = 5.12$; $P = .64$; $I^2 = 0\%$



In 8 RCTs, ADT did not ↑risk of CV mortality

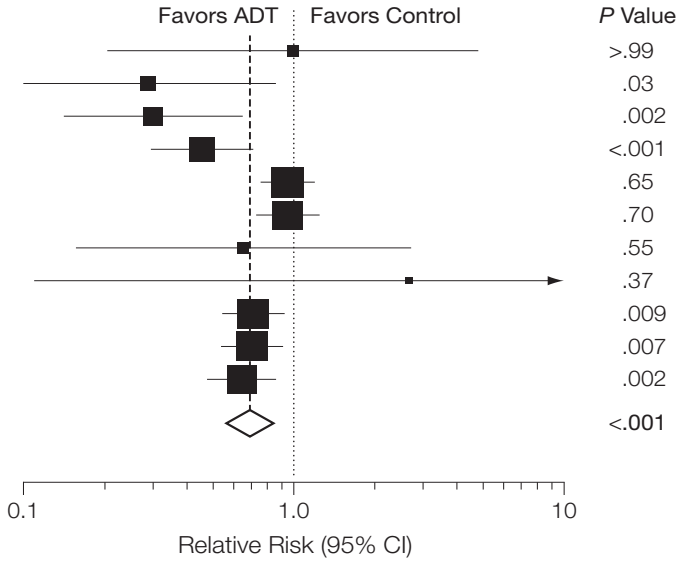
Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer

A Meta-analysis of Randomized Trials

Relative Risk of Prostate Cancer–Specific Mortality Associated With ADT Among Patients With Prostate Cancer

Source	No./Total No. of Events: ADT	No./Total No. of Events: Control	Relative Risk (95% CI)	*P* Value
Aus et al,[17] 2002 (Aus)	3/63	3/63	1.00 (0.21-4.77)	>.99
D'Amico et al,[3] 2008 (DFCI 95-096)	4/102	14/104	0.29 (0.10-0.86)	.03
Messing et al,[12] 2006 (ECOG/EST 3886)	7/47	25/51	0.30 (0.15-0.64)	.002
Bolla et al,[13] 2010 (EORTC 22863)	26/207	57/208	0.46 (0.30-0.70)	<.001
Schröder et al,[14] 2009 (EORTC 30846)	69/119	70/115	0.95 (0.77-1.18)	.65
Studer et al,[15] 2006 (EORTC 30891)	94/492	99/493	0.95 (0.74-1.23)	.70
Schulman et al,[18] 2000 (ESGNTPC)	3/192	5/210	0.66 (0.16-2.71)	.55
Yee et al,[19] 2010 (MSKCC)	1/72	0/64	2.67 (0.11-64.4)	.37
Efstathiou et al,[8] 2009 (RTOG 85-31)	82/477	113/468	0.71 (0.55-0.92)	.009
Roach et al,[9] 2008 (RTOG 86-10)	65/224	96/232	0.70 (0.54-0.91)	.007
Denham et al,[16] 2011 (TROG 96.01)	89/532	70/270	0.65 (0.49-0.85)	.002
Overall	443/2527	552/2278	0.69 (0.56-0.84)	<.001

Test for heterogeneity: Q = 24.57; $P = .006$; $I^2 = 59.3\%$



- 31% in PCa-specific Mortality

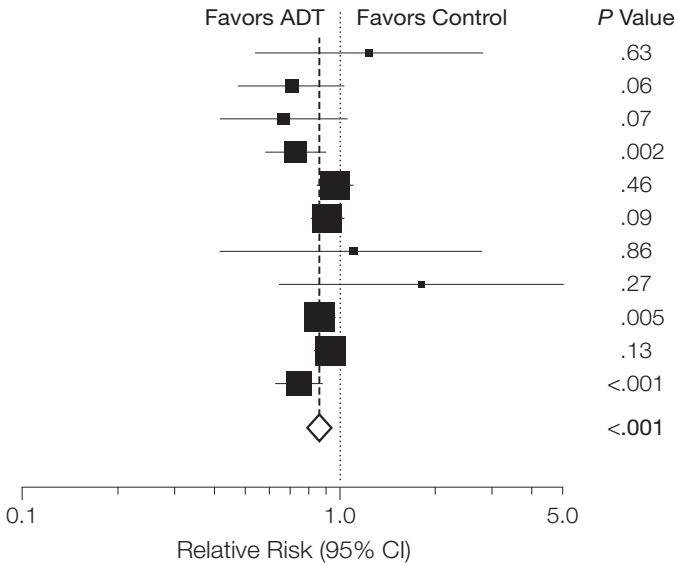
Association of Androgen Deprivation Therapy With Cardiovascular Death in Patients With Prostate Cancer

A Meta-analysis of Randomized Trials

Relative Risk of All-Cause Mortality Associated With ADT Among Patients With Prostate Cancer

Source	No./Total No. of Events: ADT	No./Total No. of Events: Control	Relative Risk (95% CI)	*P* Value
Aus et al,[17] 2002 (Aus)	11/63	9/63	1.22 (0.54-2.74)	.63
D'Amico et al,[3] 2008 (DFCI 95-096)	30/102	44/104	0.70 (0.48-1.01)	.06
Messing et al,[12] 2006 (ECOG/EST 3886)	17/47	28/51	0.66 (0.42-1.04)	.07
Bolla et al,[13] 2010 (EORTC 22863)	80/207	112/208	0.72 (0.58-0.89)	.002
Schröder et al,[14] 2009 (EORTC 30846)	96/119	97/115	0.96 (0.85-1.08)	.46
Studer et al,[15] 2006 (EORTC 30891)	257/492	284/493	0.91 (0.81-1.02)	.09
Schulman et al,[18] 2000 (ESGNTPC)	8/192	8/210	1.09 (0.42-2.86)	.86
Yee et al,[19] 2010 (MSKCC)	10/72	5/64	1.78 (0.64-4.93)	.27
Efstathiou et al,[8] 2009 (RTOG 85-31)	269/477	306/468	0.86 (0.78-0.96)	.005
Roach et al,[9] 2008 (RTOG 86-10)	164/224	184/232	0.92 (0.83-1.02)	.13
Denham et al,[16] 2011 (TROG 96.01)	198/532	136/270	0.74 (0.63-0.87)	<.001
Overall	1140/2527	1213/2278	0.86 (0.80-0.93)	<.001

Test for heterogeneity: $Q = 16.86$; $P = .08$; $I^2 = 40.7\%$

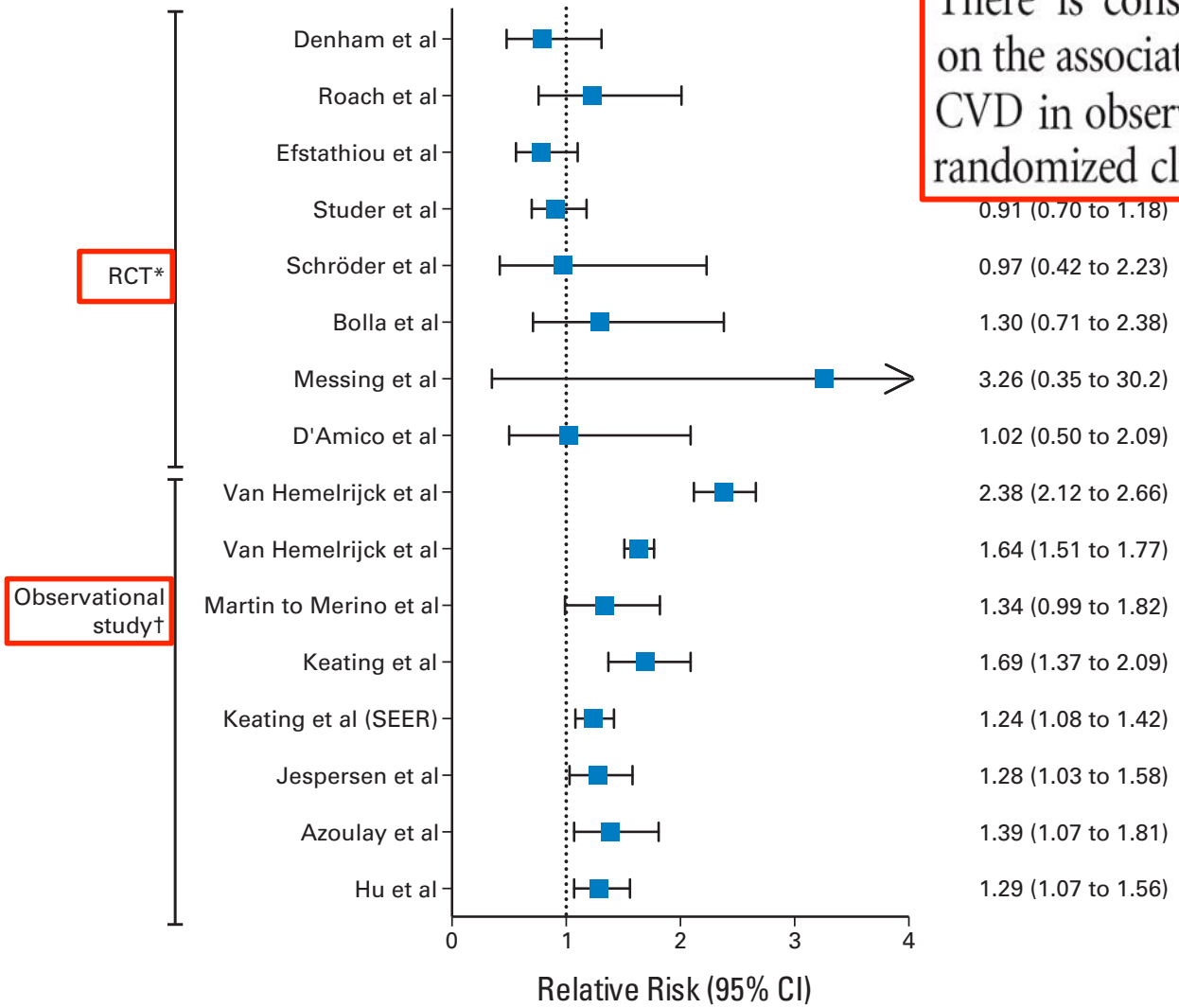


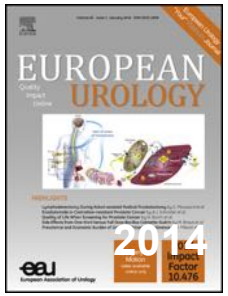
- 14% in Overall Mortality

Risk and Timing of Cardiovascular Disease After Androgen-Deprivation Therapy in Men With Prostate Cancer

Sean O'Farrell, Hans Garmo, Lars Holmberg, Jan Adolfsson, Pär Stattin, and Mieke Van Hemelrijck

There is considerable disagreement on the association between ADT and CVD in observational studies versus randomized clinical trials.





Toward Personalizing the Use of Androgen Deprivation Therapy to Maximize Benefit and Minimize Harm

Paul L. Nguyen *, *Anthony V. D'Amico*

EUROPEAN UROLOGY XXX (2014) XXX–XXX

Considering all of the data together, we suspect that while most healthy patients will not experience a higher risk of cardiac death as a result of ADT, there is likely to be a link between ADT and excess cardiac events, and these effects may be particularly pronounced in patients with a greater burden of comorbidities, in whom excess cardiac events may translate into a measurable increase in risk of cardiac death.

Such a hypothesis could only be tested properly in a randomized trial prospectively measuring nonfatal and fatal cardiac endpoints that stratify patients by comorbidity before randomization using a validated metric.

Picking the optimal duration of ADT in combination with RT

Class Risk	ADT duration*	Referring Trial
IR (unfavorable)	RT + 6 m.	DFCI 95096 TROG 9601
HR (i.e: GS 8-10; PSA>20)	RT + 18-28 m.	RTOG 9202 PCS IV
Very HR (T3-4 or >2 factors)	RT + 36 m.	EORTC 22863 EORTC 22961
Any T, N+	Long lasting ± RT	RTOG 8531 SPCG-7 NCI MRC

*** If >1 cardiovascular risk factors a risk-adapted strategy should guide clinical decisions**

POST-OPERATIVE PROSTATE CANCER

GETUG-AFU 16 trial

– 742 N0 pts with PSA-relapse randomised to RT alone vs RT + short-term ADT

- RT 66 Gy prostate bed ± 46 Gy pelvis
- Median follow-up 63 months

	RT (N=373)	RT + ADT (N=369)	HR	95% CI	*P*
5-yr PFS	62%	80%	0.50	0.38-0.66	<0.0001
5-yr OS	95%	96%	0.66	0.36-1.22	0.18

- QoL outcomes by QLQ-C30

	RT	RT + ADT
Worsened	26%	35%
Stable	56%	48%
Improved	19%	17%

Carrie C. J Clin Oncol 2015

Salvage RT & ADT

GETUG-AFU 16 trial

- Toxicities

Grade ≥3 toxicity	RT (N=373)	RT + ADT (N=369)
Acute genitourinary	1.1%	0.8%
Acute gastrointestinal	0.3%	0.3%
Late genitourinary	7.8%	7.2%
Late gastrointestinal	1.4%	1.7%
Late cardiac	0.3%	0.3%

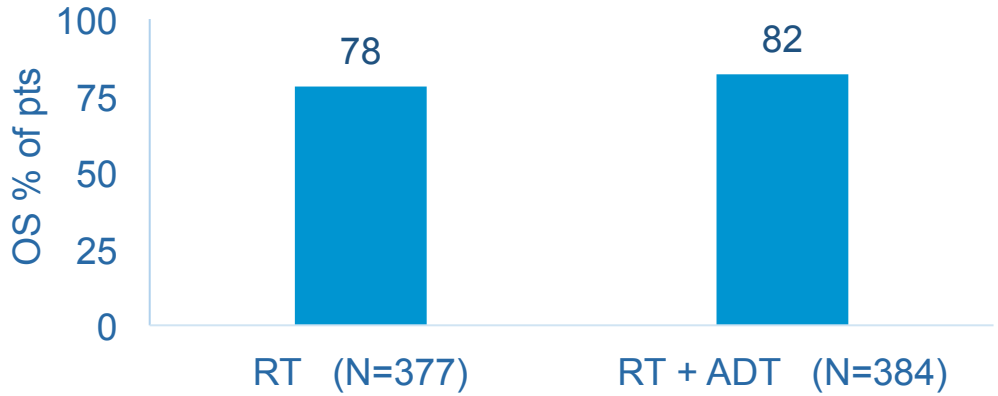
RT + short-term ADT vs RT alone as salvage tx for PSA relapse after RP significantly improved PFS without increasing G ≥3 toxicity

Carrie C. J Clin Oncol 2015

RTOG 9601 trial

– 761 N0 pts with elevated postop PSA (median PSA at study entry: 0.6 ng/ml) randomised to RT or RT + ADT (24 mo bicalutamide 150 mg)

- RT 64.8 Gy to prostate bed
- Median follow-up 12.6 yr



HR: 0.75; 95%CI: 0.58-0.98
P=0.036

	RT (N = 377)	RT + ADT (N = 384)	*P*
12-yr CSM	7.5%	2.3%	< 0.001
12-yr DM	23%	14%	<0.001
10-yr FFP	30%	42%	<0.001
Gynaecomastia	11%	70%	

NNT: 17

Shipley WU. IJROBP 2015

ADT OPTIMIZATION

Redefining Clinically Significant Castration Levels in Patients With Prostate Cancer Receiving Continuous Androgen Deprivation Therapy

Juan Morote, Anna Orsola,* Jacques Planas, Enrique Trilla, Carles X. Raventós, Lluís Cecchini and Roberto Catalán

From the Department of Urology, Vall d'Hebron Hospital and Autonoma University of Barcelona School of Medicine, Barcelona, Spain

Vol. 178, 1290-1295, October 2007
Printed in U.S.A.

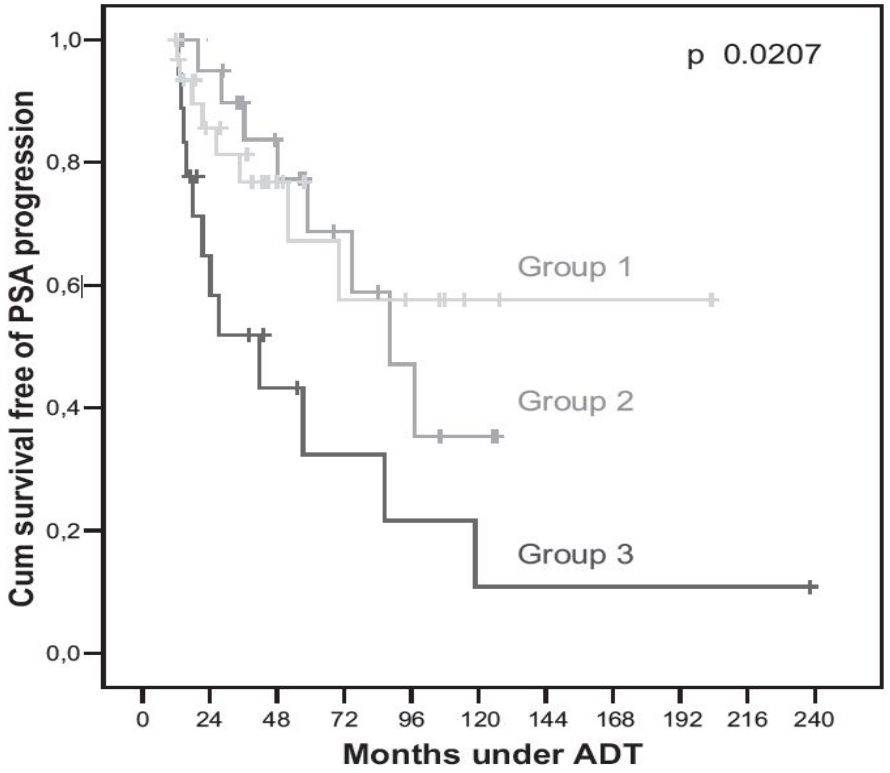


FIG. 1. Survival free of AIP according to serum testosterone behavior. Group 1, patients with all 3 serum testosterone determinations less than 20 ng/dl. Group 2, patients with breakthrough increases between 20 and 50 ng/dl. Group 3, patients with breakthrough increases greater than 50 ng/dl.

PFS according to Testosterone levels:

- Group 1 → T <20 ng/dL: **106 months**
- Group 2 → T 20-50 ng/dL: **90 months**
- Group 3 → T >50 ng/dL: **72 months**

European Association of Urology

The standard castrate level was < 50 ng/dL (1.7 nmol/L). It was defined more than 40 years ago, when testosterone level testing was limited. Current testing methods have found that the mean value of testosterone after surgical castration is 15 ng/dL [542]. This has led to a revisiting of the current definition of castration, with a more appropriate level defined as below 20 ng/dL (1 nmol/L). This new definition is important as better results are repeatedly observed with levels around or below 1 nmol/l compared to 1.7 nmol/L [543-

Int Urol Nephrol (2012) 44:1039–1044
DOI 10.1007/s11255-012-0134-z

UROLOGY – ORIGINAL PAPER

Goserelin versus leuprolide in the chemical castration of patients with prostate cancer

Élcio Dias Silva · Ubirajara Ferreira · Wagner Matheus · Eliney F. Faria · Gustavo D. Silva · Minori Saito · Auro A. S. de Souza · Azuil Laranjo Jr. · Otavio Clark · Luis Alberto Magna · Lísias Nogueira Castilho · Leonardo Oliveira Reis

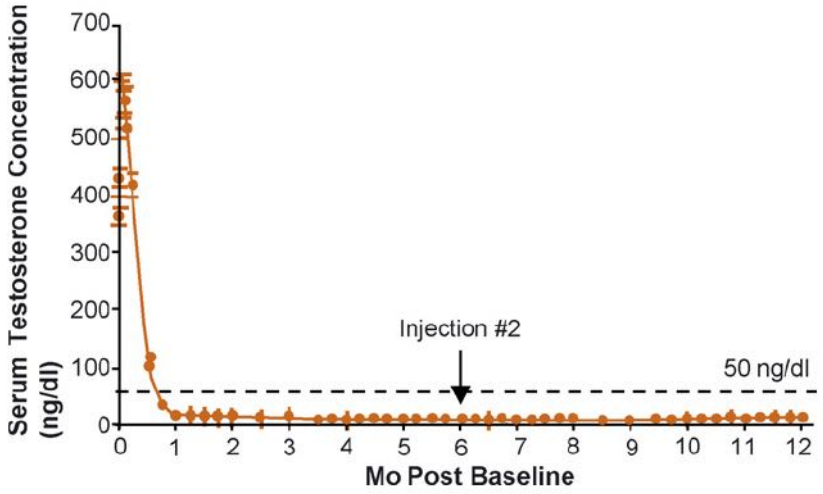
Table 3 Failure to obtain testosterone castration levels

Testosterone	Summary of the obtained results		
	Leuprolide 3.75	Leuprolide 7.5	Goserelin 3.6
Did not obtain ≤50 ng/dl (%)	26.3	25	35
Did not obtain ≤20 ng/dl (%)	68.4	30	45

A 12-Month Clinical Study of LA-2585 (45.0 MG): A New 6-Month Subcutaneous Delivery System for Leuprolide Acetate for the Treatment of Prostate Cancer

E. David Crawford,*,† Oliver Sartor,‡ Franklin Chu, Ramon Perez,‡ Gary Karlin§ and J. Steve Garrett‖

From the University of Colorado Health Sciences Center (EDC), Aurora and Atrix Laboratories, Inc. (SG), Fort Collins, Colorado, Louisiana State University (OS), New Orleans, Louisiana, San Bernardino Urological Associates (FC), San Bernardino, California, Urology Health Center (RP), New Port Richey, Florida and Lawrenceville Urology (GK), Lawrenceville, New Jersey



- **After 1 month from starting**

  T ≤ 50 ng/dL in **97%** patiens

  T ≤ 20 ng/dL in **83%** patients

  Median Time to T suppression: **21.3 days**

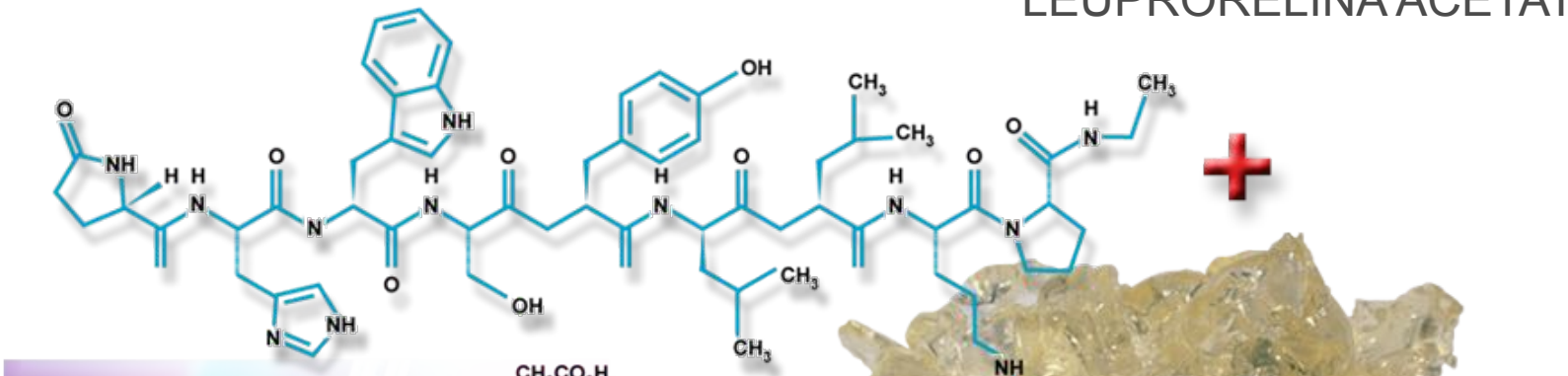
- **After 1 year from starting**

  T ≤ 50 ng/dL in **99%** patients

  T ≤ 20 ng/dL in **88%** patients

Eligard® 45 mg

LEUPRORELINA ACETATO



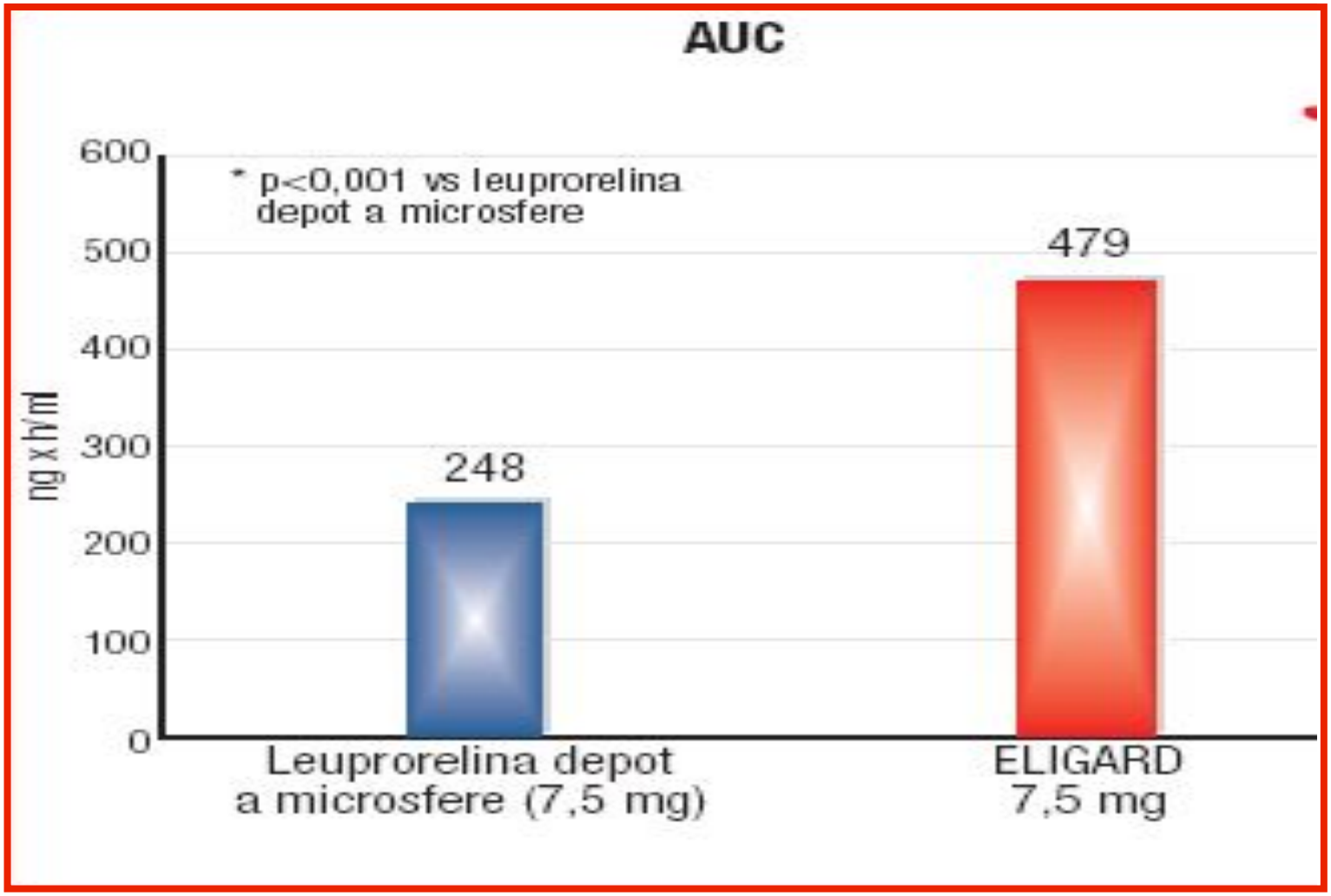
CARRIER LIQUIDO

ATRIGEL

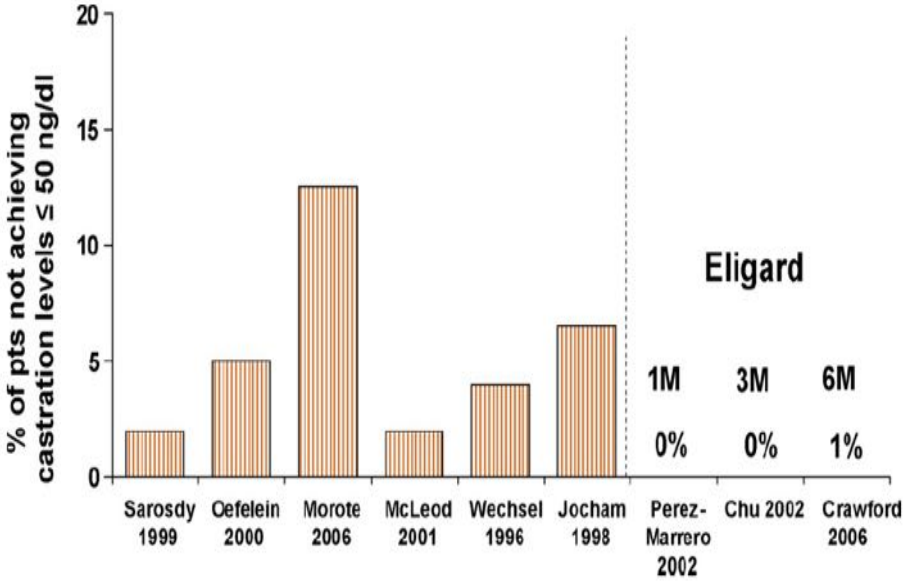
copolimero acidi DL-lattico e glicolico)
N-metilpirrolidone)

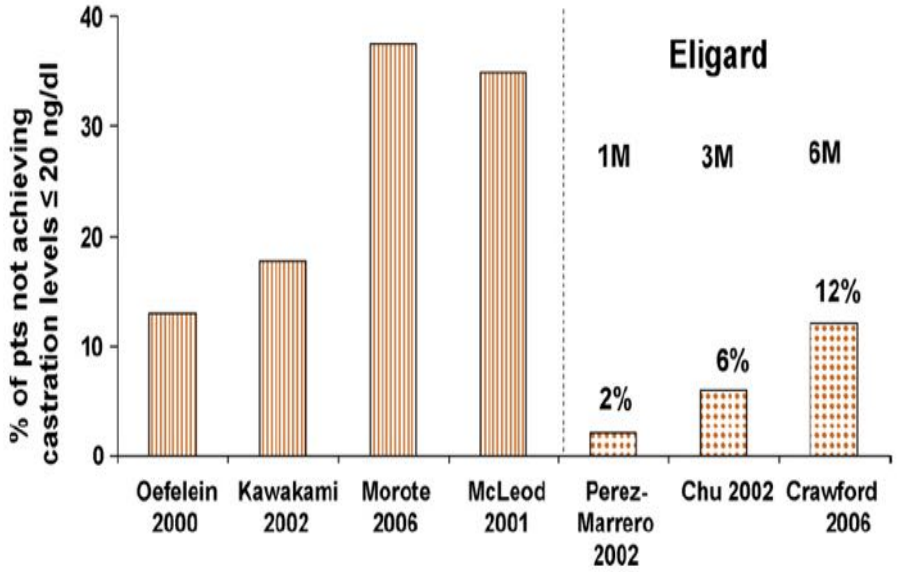
POLIMERO BIODEGRADABILE

Eligard® Pharmacokinetics



Eligard® 45 mg & Castration Levels

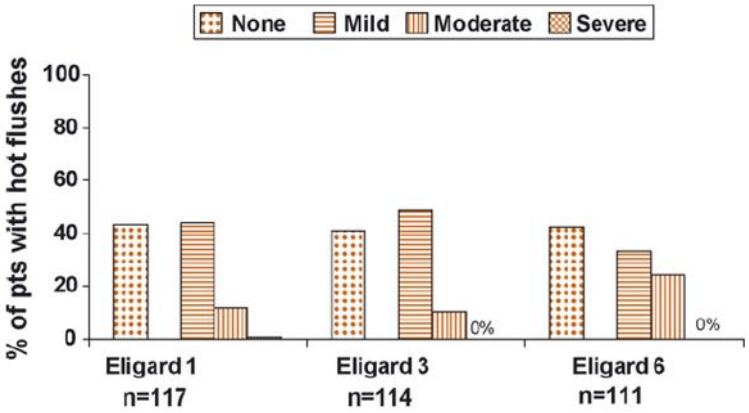




Tombal B & Berges R. Eur Urol Suppl 2007

Eligard® 45 mg: Safety Profile

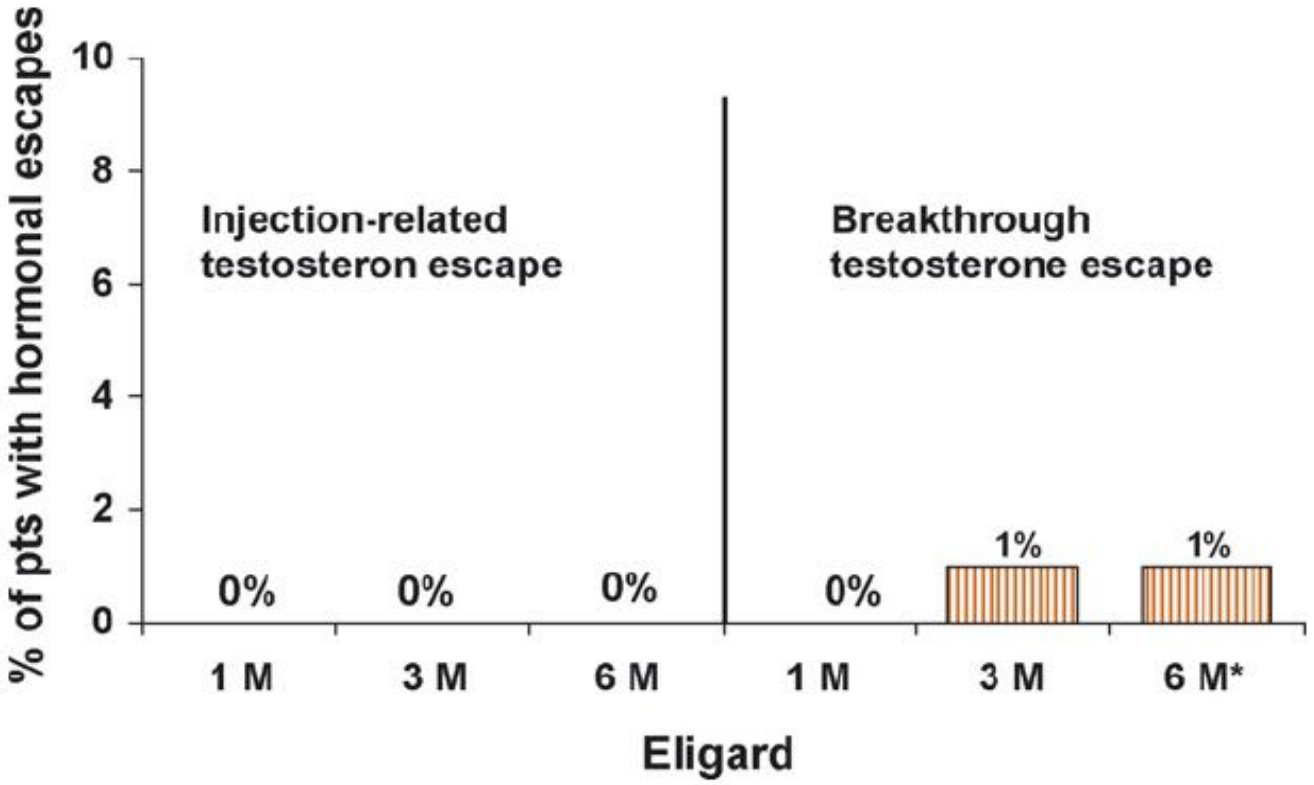
Adverse event (mild/moderate/severe)	Eligard, mg		
% of patients	45	22.5	7.5
Hot flushes	33/24/0	49/10/0	44/12/1
Fatigue	7/5/0	6/0/0	13/4/0
Testicular atrophy	5/2/0	2/0/0	4/1/0
Gynaecomastia	4/0/0	1/0/0	1/1/0
Injection site reactions	14/<1/0	89/14/0	29/4/<1



Schulman et al. BJU Int. 2007

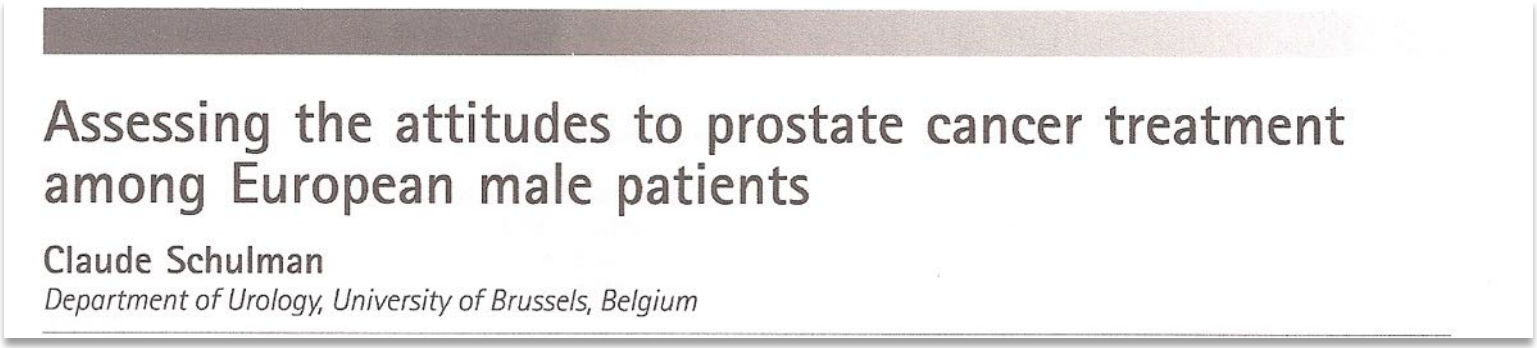
Tombal B & Berges R. Eur Urol Suppl 2007

Eligard® 45 mg & Testosterone Escapes



Tombal B & Berges R. Eur Urol Suppl 2007

Eligard® 45 mg: Quality of Life



Assessing the attitudes to prostate cancer treatment among European male patients

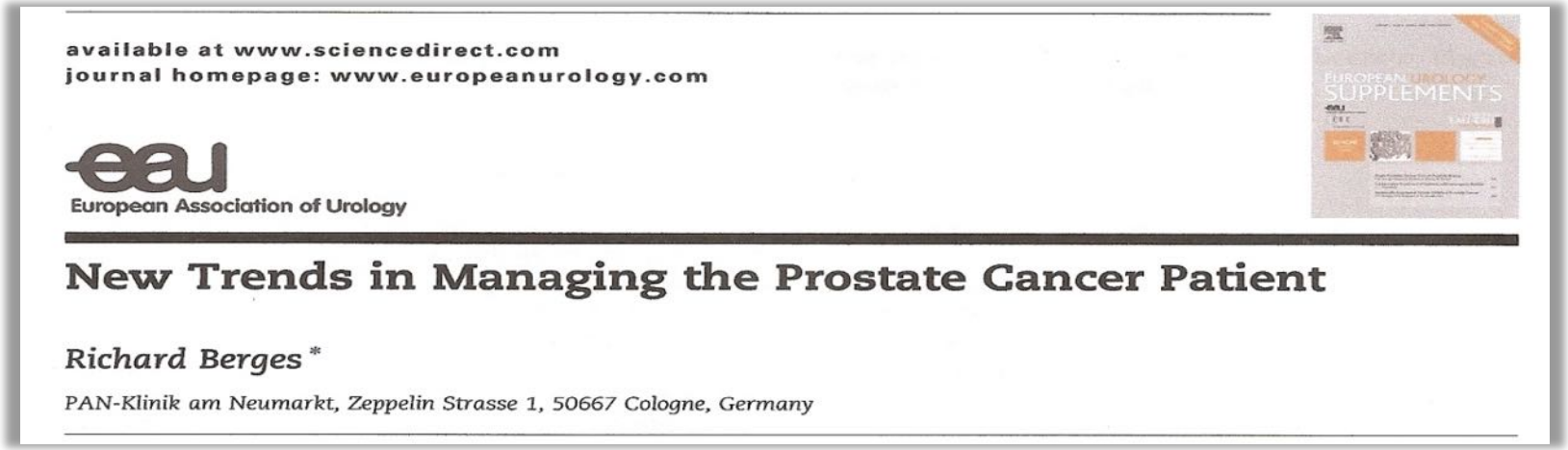
Claude Schulman
Department of Urology, University of Brussels, Belgium

68% of patients prefer the six-months ADT administration

"The idea of less discomfort and pain, improved quality of life, and fewer reminders of the disease were the main reasons given for the preference of fewer injections"

Schulman C. et al, BJU International 2007

Eligard® 45 mg: Quality of Life



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European Association of Urology

New Trends in Managing the Prostate Cancer Patient

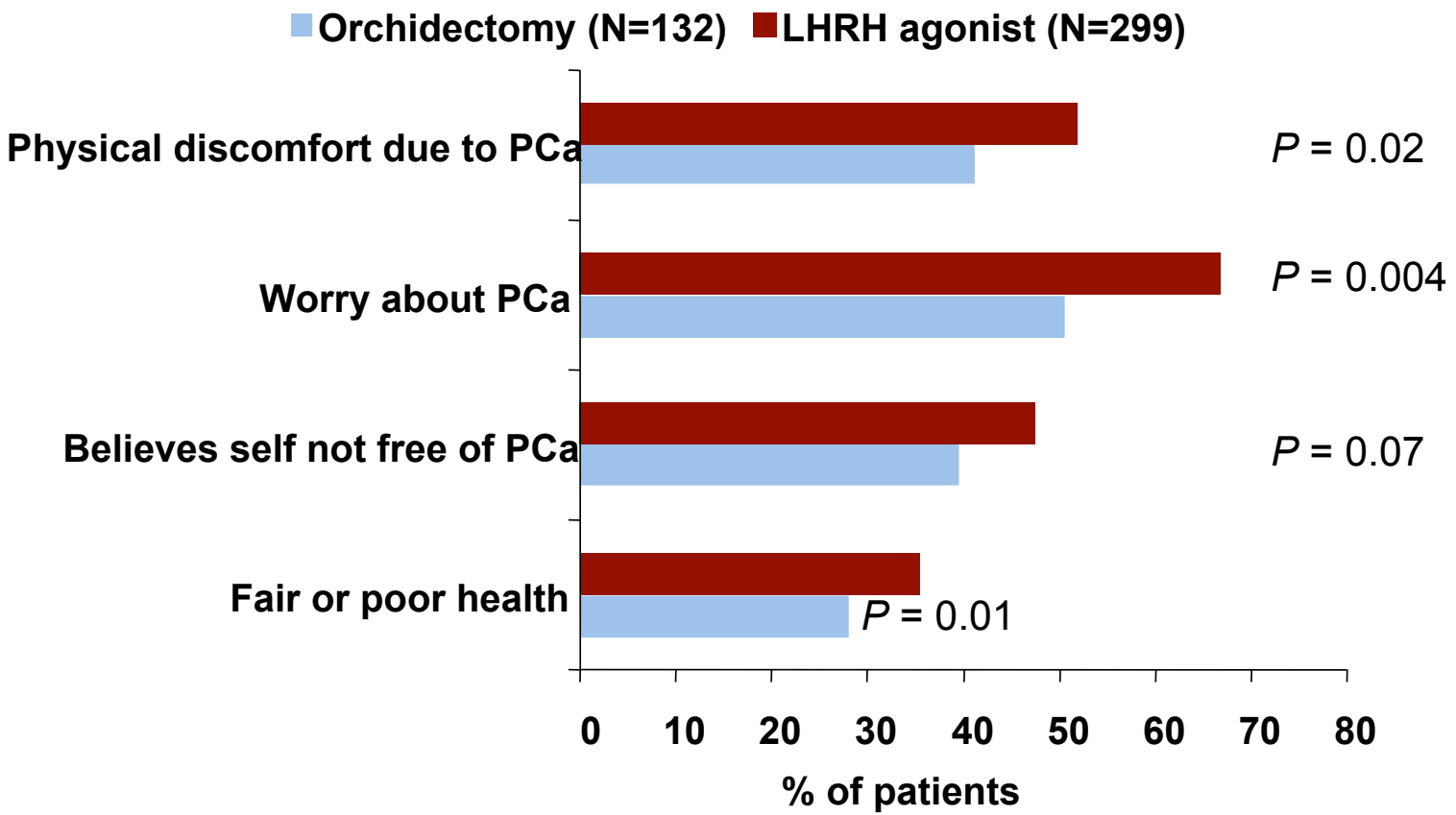
Richard Berges *

PAN-Klinik am Neumarkt, Zeppelin Strasse 1, 50667 Cologne, Germany

81% of patients < 70 yrs and 57% of patients > 70 yrs prefer the six-months ADT administration

Berges R. Eur Urol 2008

Eligard® 45 mg: Quality of Life



Potosky AL et al., J Clin Oncol 2001

Eligard® 45 mg: Italian Survey among Urologists

	%	
Elevata soppressione androginica \ soppressione ormonale costante	8	
Buona tollerabilità	4	
Comodità \ maggiore comodità per il paziente	18	Comodità della terapia **55%**
Migliora la qualità di vita/ meno disagi/ meno invasivo	16	
Maggiore compliance	10	
Minor rischio di ansia da trattamento	6	
Maggiore libertà del paziente rispetto al problema della malattia \ della terapia	5	
Minor ricorso al medico per la somministrazione	10	Ottimizzazione delle risorse **22%**
Decongestionamento degli ambulatori	5	
Costi minori	4	
Ottimizzazione delle risorse	3	
Nessuno in particolare	6	
Non so dare una risposta perchè non ho esperienza con questo dosaggio	11	

5 Rules for using ADT in combination with RT

1. Make sure all patients starting ADT are “medically optimized”
2. Avoid ADT in LR patients and in favorable IR (low-volume GS 3 + 4 = 7 with PSA <10), particularly if they have severe cardiac comorbidities
3. Do not withhold ADT in men with high-risk and locally advanced disease
4. Check that Testosterone < 20 ng/dl
5. Choose ADT administration that foster patients compliance

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Combination of androgen deprivation therapy and radiotherapy for localized prostate cancer in the contemporary era

Rolando M. D'Angelillo [a,*], Pierfrancesco Franco [b], Berardino De Bari [c], Alba Fiorentino [d], Stefano Arcangeli [e], Filippo Alongi [d]

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[b] *Department of Oncology, Radiation Oncology, University of Turin School of Medicine, Turin, Italy*
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