

Conservative Management of Localized Prostate Cancer



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University of Toronto

Brampton Us-Too Group
November 13, 2007

Objectives

1. To understand the philosophy of active surveillance versus watchful waiting
2. To review the outcomes of patients on active surveillance at Sunnybrook
3. To variety, pros and cons of different treatment options



The Future of Prostate Cancer



Lead Time Bias and Prostate Cancer

1950-1970's

NATURAL HISTORY PROSTATE CANCER: 10 y

Clinically
Detectable

Asymptomatic
Metastases

Symptomatic
Metastases
Androgen
Sensitive

Symptomatic
Metastases
Androgen
Resistant

Death

Watchful Waiting

Castrate Therapies

Lead Time Bias and Prostate Cancer

1980-1990's

NATURAL HISTORY PROSTATE CANCER: 13 y

PSA Abnormal	Clinically Detectable	Asymptomatic Metastases	Symptomatic Metastases Androgen Sensitive	Symptomatic Metastases Androgen Resistant	Death
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**Local
Therapies**

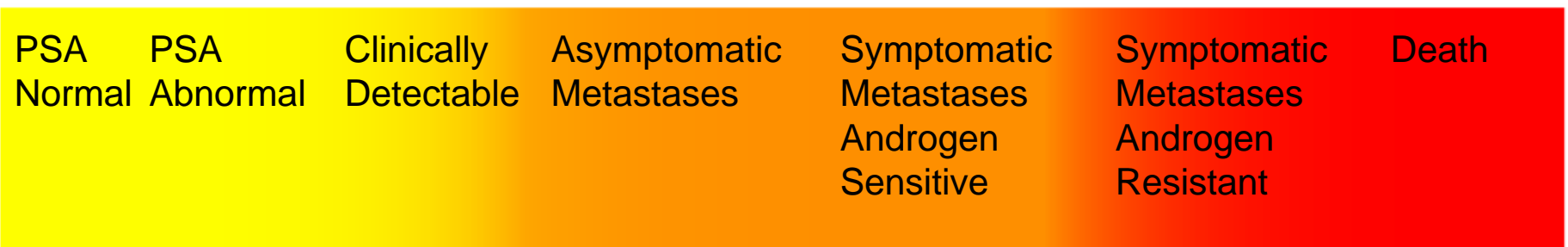
**PSA
Failure**

Castrate Therapies

Lead Time Bias and Prostate Cancer

2000-2010

NATURAL HISTORY PROSTATE CANCER: 16+ y



Local Therapies

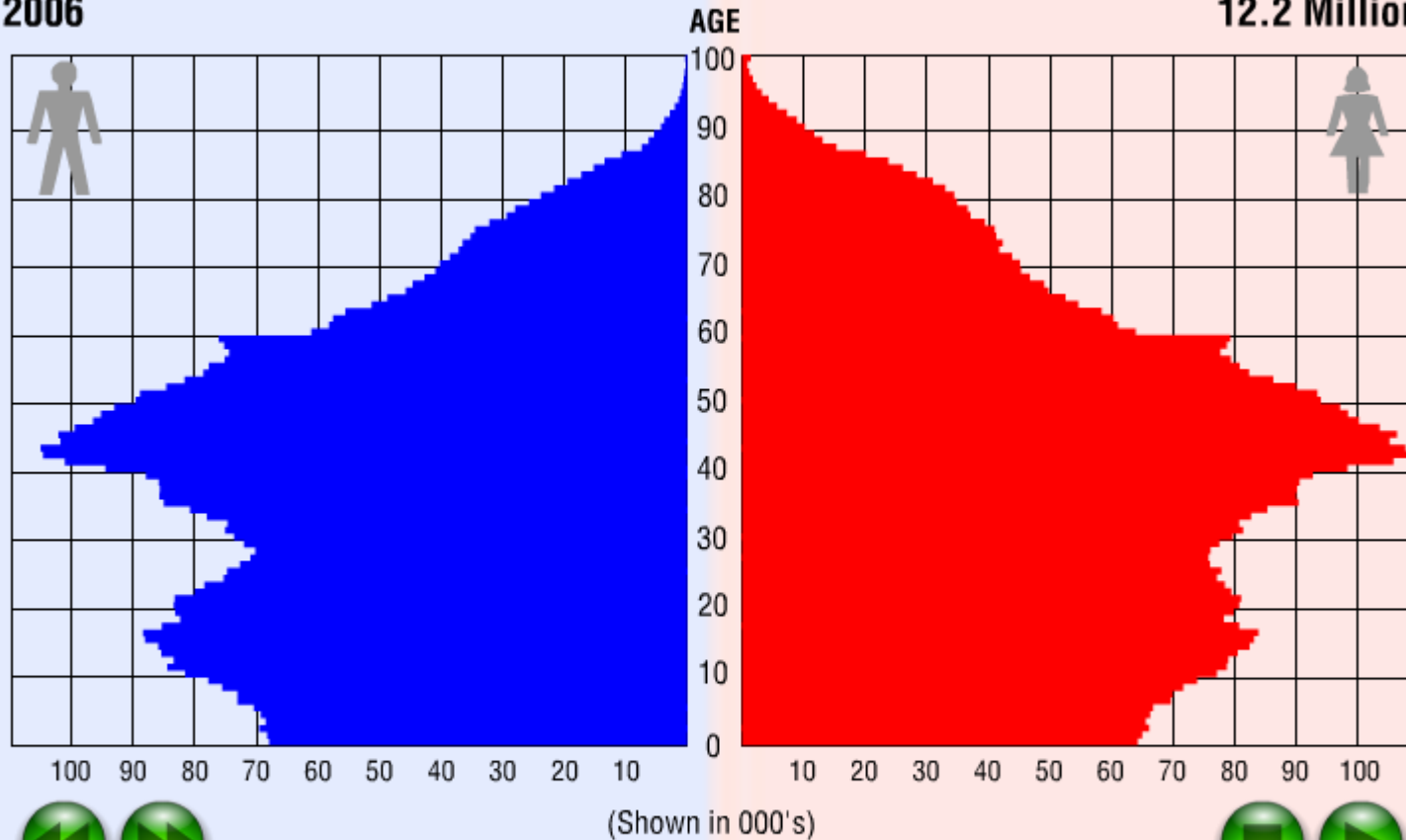
Castrate Therapies

PSA Failure

Age pyramid of the population of Ontario, 1956 to 2006

2006

12.2 Million



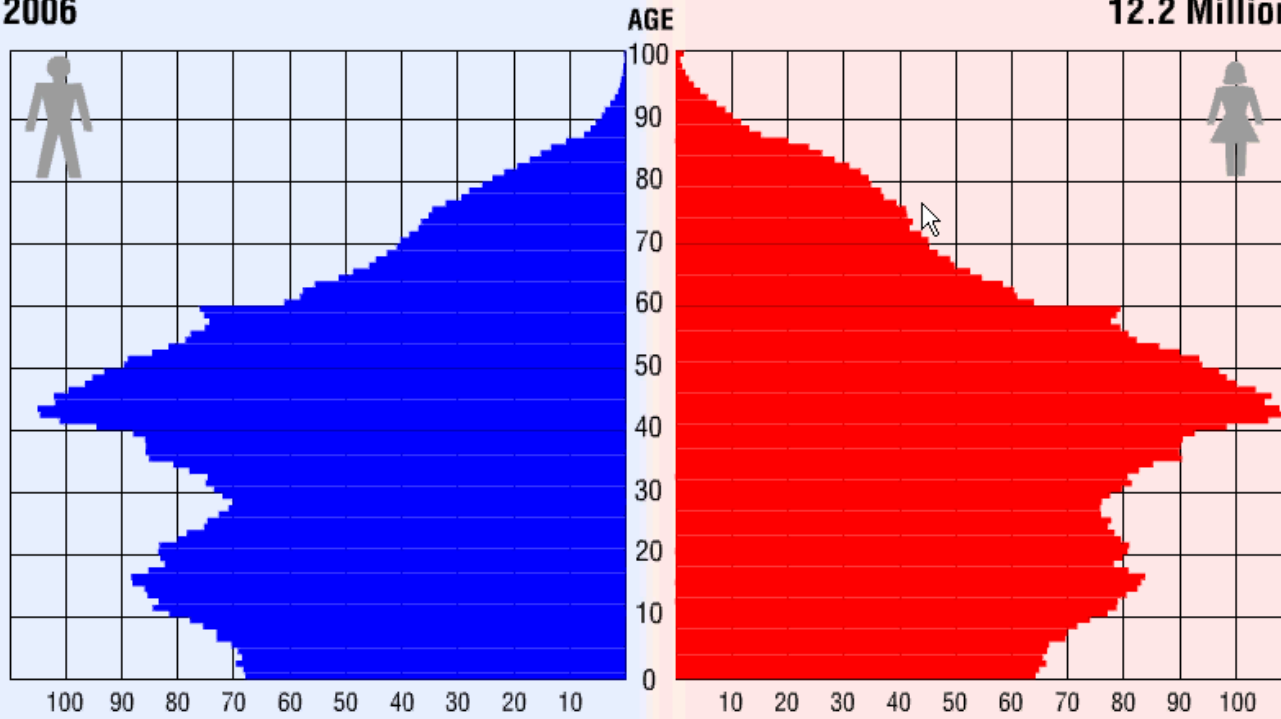
Statistics Canada
Statistique Canada

Canada

Age pyramid of the population of Ontario, 1956 to 2006

2006

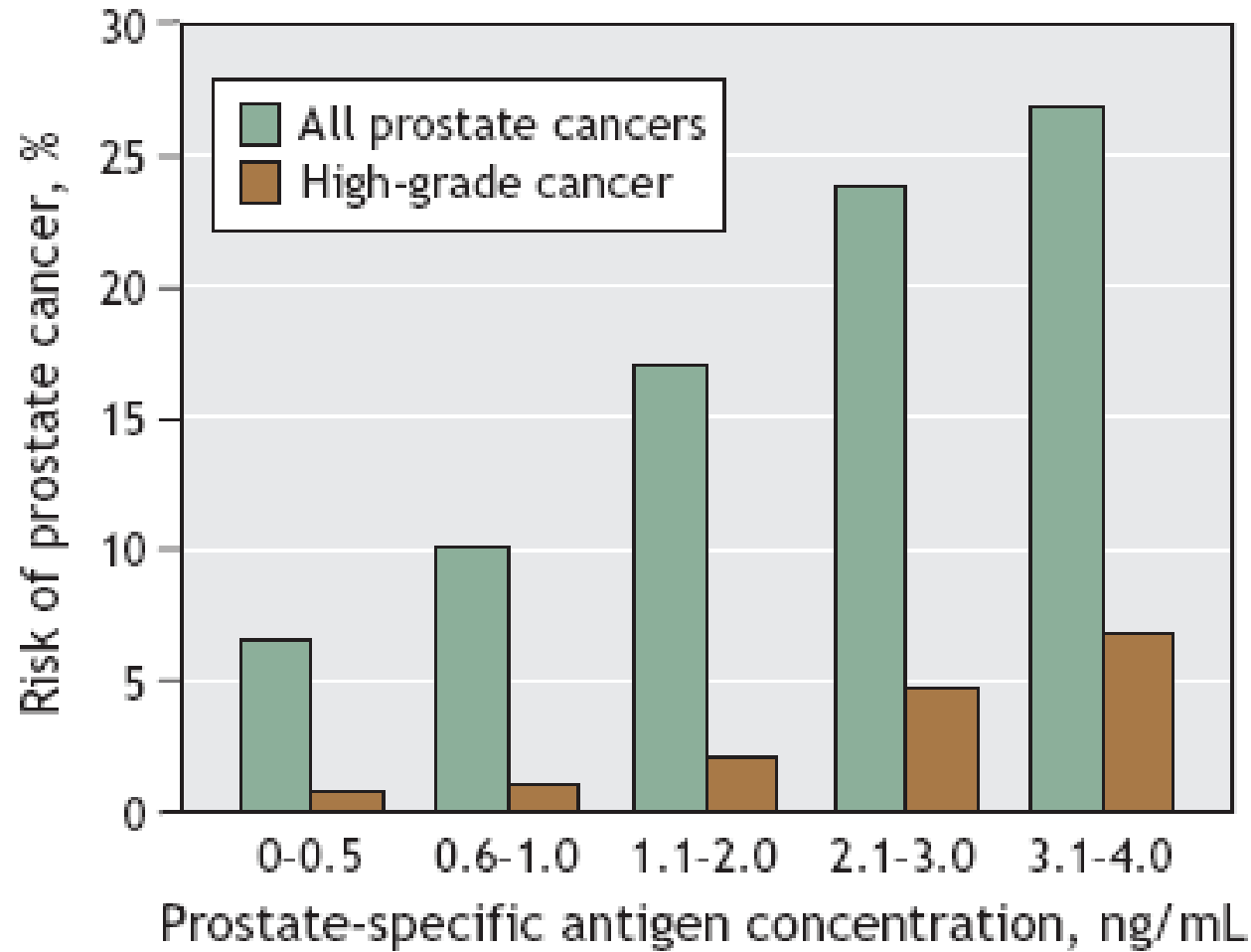
12.2 Million



Statistics Canada
Statistique Canada

Canada

No "Normal" PSAs



Background

- The number of men diagnosed with prostate cancer each year has increased over the last decade
 - In 1992, Canadian incidence 15,300
 - In 2005, Canadian incidence expected to be 20,500
 - Age-adjusted incidence has risen from 440 to 480 / 100,000 men from 1992-2001
- A greater proportion of men are being diagnosed

Background

- The chance of diagnosing “clinically insignificant prostate cancer” (CIPC), may be increased
- Studies report the proportion of men who are diagnosed with this entity to be 7-25%, depending on the definition used
- Autopsy series of men who died of other causes reveal the upper limit of the incidence of CIPC, since none of these men died of prostate cancer
- The incidence increases with age
 - 30% in 40's – 50's
 - 55% in 60's
 - 64% in 70's

The New England Journal of Medicine

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VOLUME 347

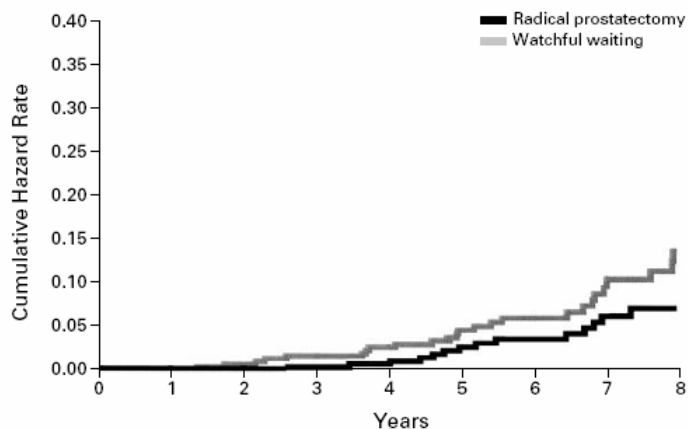
SEPTEMBER 12, 2002

NUMBER 11



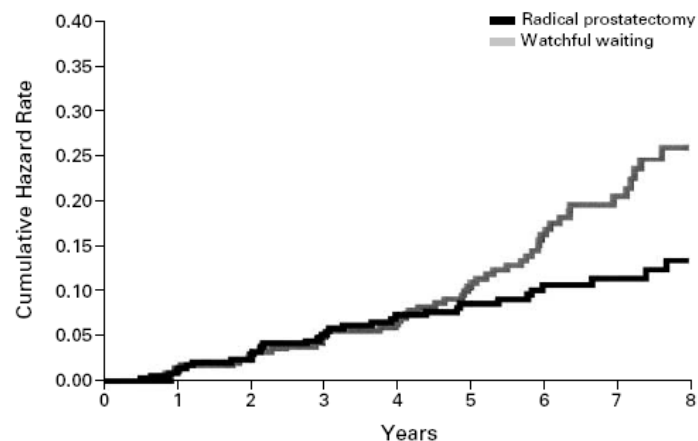
A RANDOMIZED TRIAL COMPARING RADICAL PROSTATECTOMY WITH WATCHFUL WAITING IN EARLY PROSTATE CANCER

LARS HOLMBERG, M.D., PH.D., ANNA BILL-AXELSON, M.D., FRED HELGESEN, M.D., JAAKKO O. SALO, M.D., PH.D.,
PER FOLMERZ, M.D., MICHAEL HÄGGMAN, M.D., PH.D., SWEN-OLOF ANDERSSON, M.D., PH.D., ANDERS SPÅNGBERG, M.D.,
CHRISTER BUSCH, M.D., PH.D., STEG NORDLING, M.D., PH.D., JUNI PALMGREN, PH.D., HANS-OLOV ADAMI, M.D., PH.D.,
JAN-ERIK JOHANSSON, M.D., PH.D., AND BO JOHAN NORLEN, M.D., PH.D.,
FOR THE SCANDINAVIAN PROSTATIC CANCER GROUP STUDY NUMBER 4*



No. AT RISK		0	1	2	3	4	5	6	7	8
Radical prostatectomy		347	343	339	308	281	233	185	134	89
Watchful waiting		348	346	337	302	275	231	185	121	82

Figure 2. Cumulative Hazard Rate of Death from Prostate Cancer.



No. AT RISK		0	1	2	3	4	5	6	7	8
Radical prostatectomy		347	340	331	294	263	220	172	126	82
Watchful waiting		348	341	329	291	262	216	167	106	69

Figure 3. Cumulative Hazard Rate of Development of Distant Metastasis.

Surveillance vs WW

PSA

100

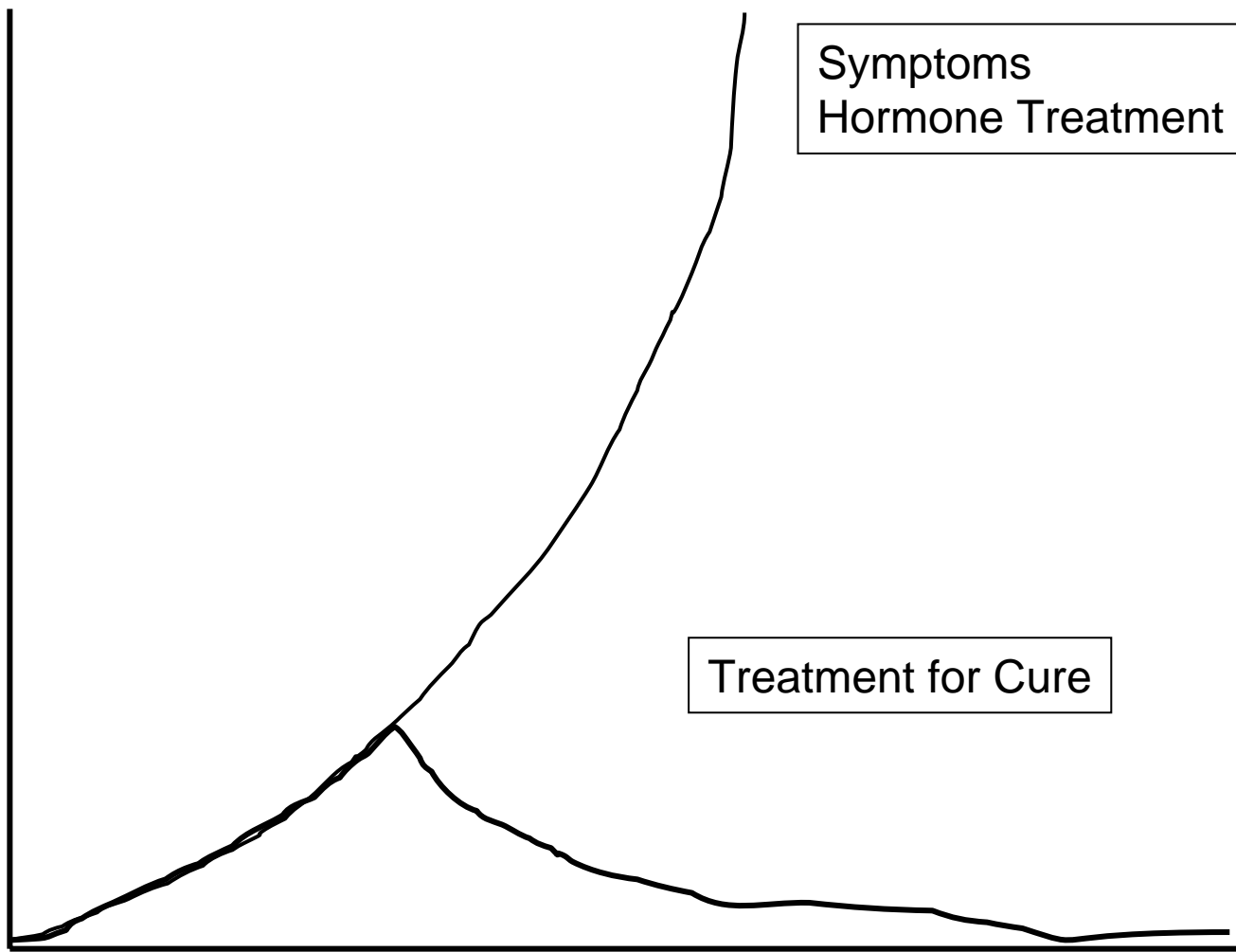
50

10

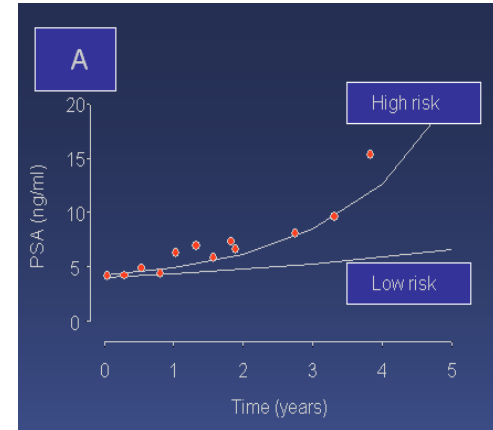
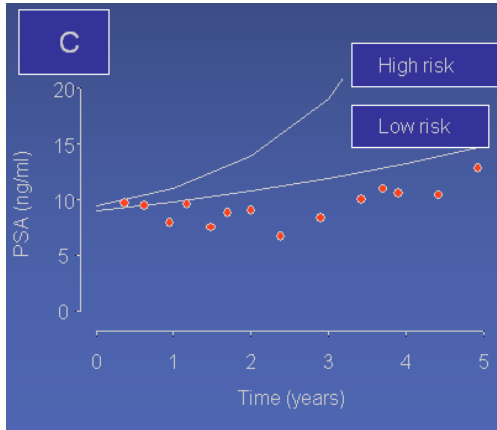
Symptoms
Hormone Treatment

Treatment for Cure

Time



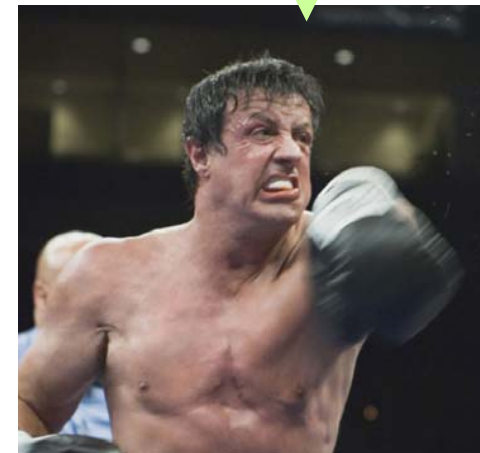
Prostate Growth Characteristics



Active Surveillance



Continue Surveillance



Radical Treatment

Sunnybrook Active Surveillance Program

Acknowledgements

To the 460 men who volunteered for the AS Study

Radiation Oncology

- D. Loblaw
- R. Choo
- C. Danjoux
- G. Morton

Radiation Therapy Research

- L. Holden

Urology

- L. Klotz
- R. Nam
- S. Sharir

Clinical Trials & Epidemiology

- L. Zhang
- A. Mamedov

Active Surveillance Cohort

1. Men (> 18 years old) with histopathologically confirmed adenocarcinoma of prostate within 12 months of study entry
2. No previous treatment
3. Clinical stage T1b-T2b N0 M0 (1997 TNM classification)
4. PSA < 15 ng/ml
5. Refused radical treatment

Baseline Investigations

1. History and Physical examination
2. Central pathology review
3. PSA, Creatinine, PAP
4. CXR
5. Bone scan and CT abdomen/pelvis at MD's discretion

Follow-up

- Physical including DRE q3 mo
- Bloodwork (PSA, Cr, PAP) q3 mo
- TRUS q6mo
- Bone Scan q1y x 2, then q2y
(q1y if PSA > 15)
- Prostate rebiopsy 12-18 mo post-accrual

Intervention

- Treatment individualized according to age, extent of disease, co-morbidities if any of:
 - PSA_{dt}* < 2 y (statistically significant) on ≥ 3 measures, ≥ 6 months, PSA ≥ 8
 - Gleason Grade $\geq 4+4$
 - Max dimension of clinical nodule \geq doubles
 - Patient request

*Doubling Time Calculation: Linear regression of $\ln(\text{PSA})$ on time

Results

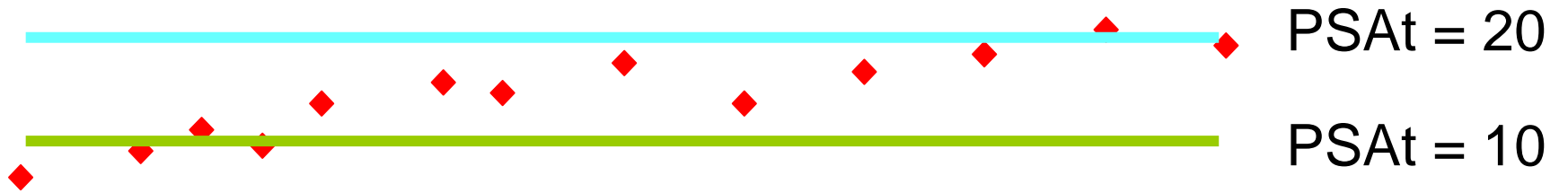
- $n = 231$
- Age at enrollment 71 y median, range 49 – 84 y
- Gleason ≤ 6 : 78%, Gleason 7: 22%
- iPSA < 10 : 84%, 10-15: 16%

Results

- 134/231 (58%) patients remained on surveillance
 - Patient choice 16%
 - Grade progression 4%
 - Clinical progression 9%
 - PSAdt criteria 10%
- As of Feb 2007, the median follow-up was 6.8 y (95% CI: 6.0 – 7.4y)
- Crude CSS analysis (January 2006): 98.8% (418 / 423)
 - Deaths occurred at 3.7, 5.1, 5.2, 5.3, 5.5 years after enrollment
- 24 (17.9%) have died of other causes; 6 (4.5%) have been lost to follow-up

PSA Thresholds

PSA



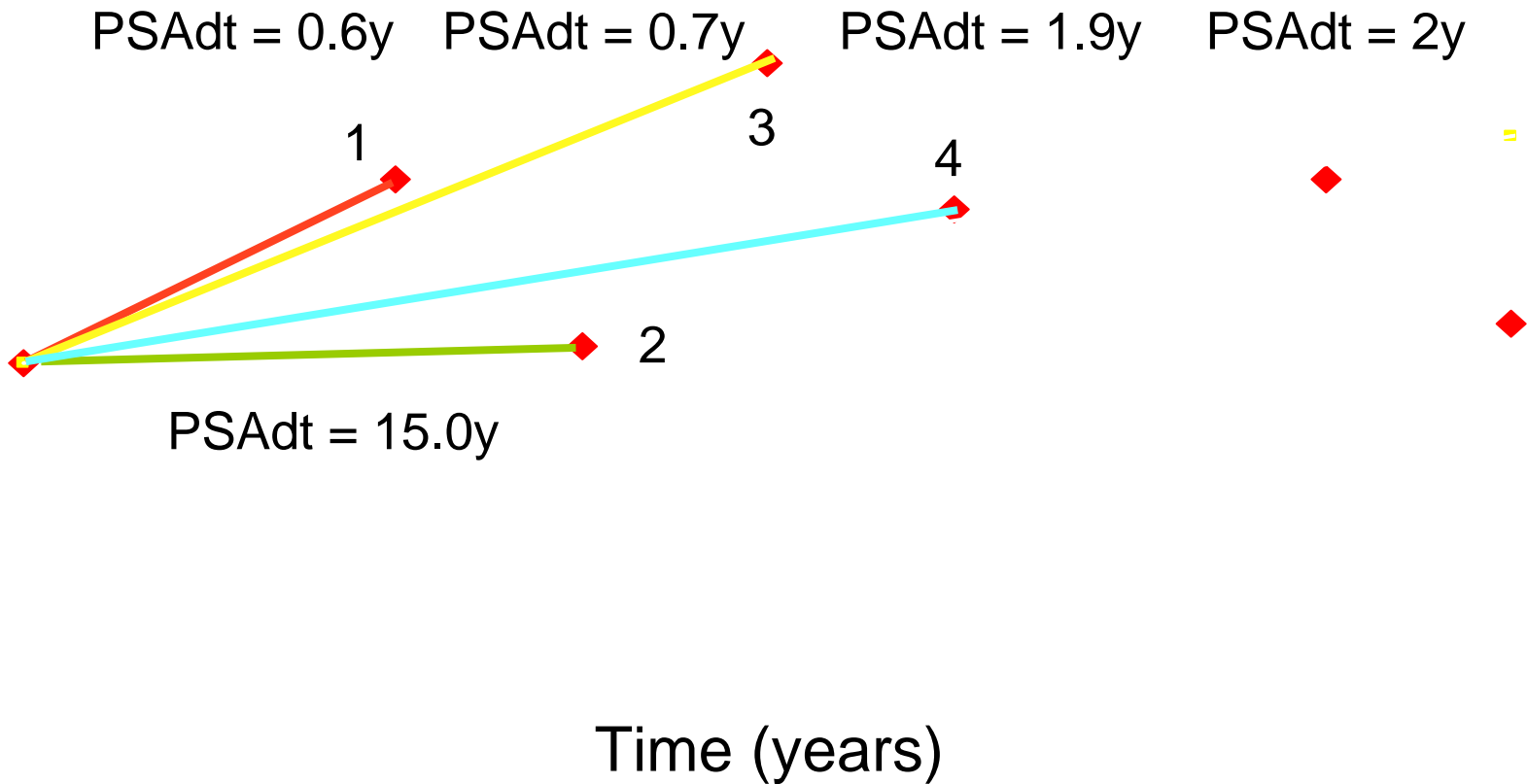
PSAt = 20

PSAt = 10

Time (years)

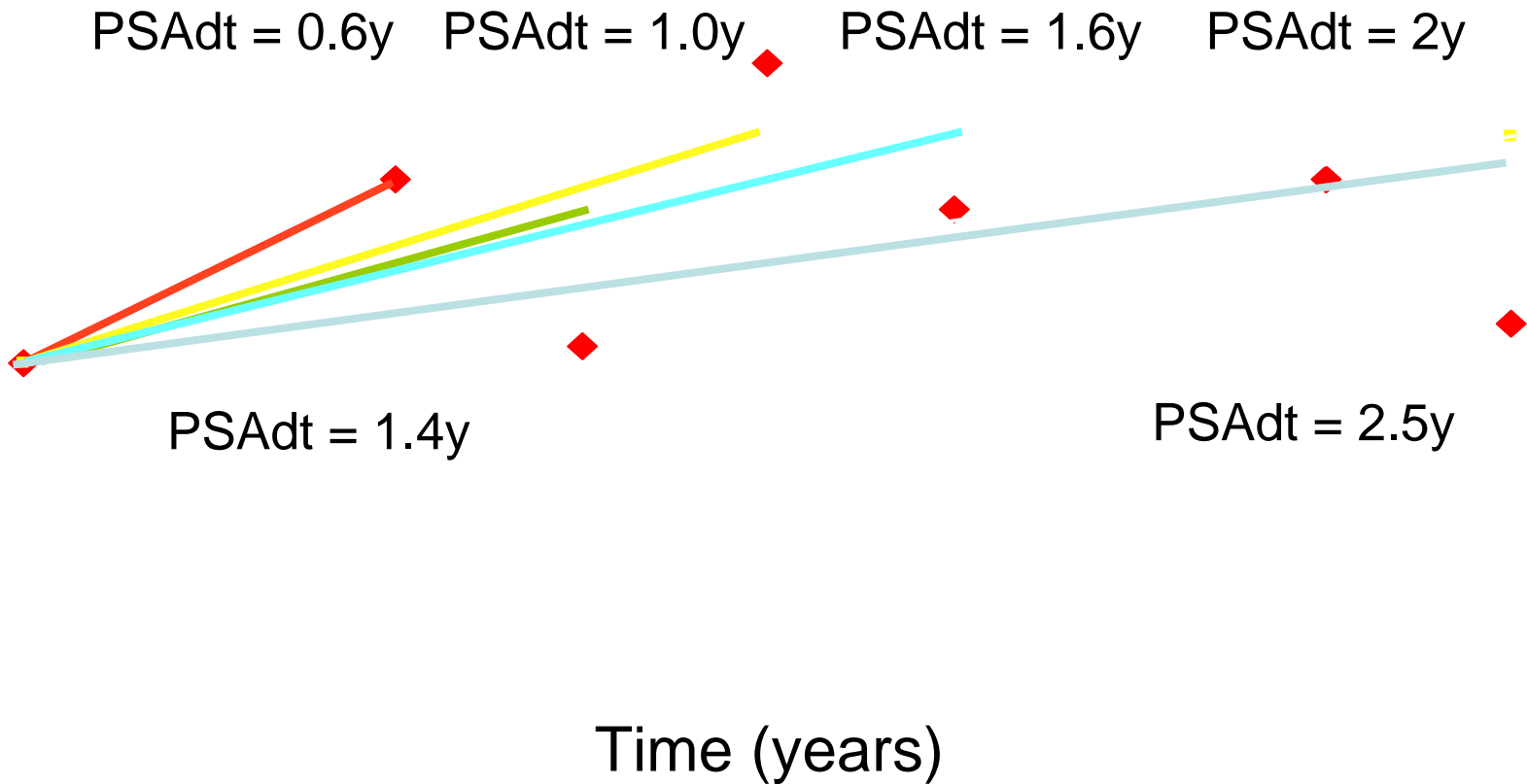
First-Last Doubling Time

PSA



Linear Regression Doubling Time

PSA



General Linear Mixed Modeling

- Allows for individual predictors of intercept and slope to be integrated into model
- For high risk line:
$$\ln(PSA) = 1.003 \times \ln(\textit{baseline PSA}) + 0.112 \times \textit{time} + 0.041 \times \textit{time}^2$$
- For low risk line:
$$\ln(PSA) = 1.03 \times \ln(\textit{baseline PSA}) - 0.0056 \times \textit{Age} + 0.046 \times \textit{Gleason} + 0.081 \times \textit{time} + 0.0038 \times \textit{time}^2$$

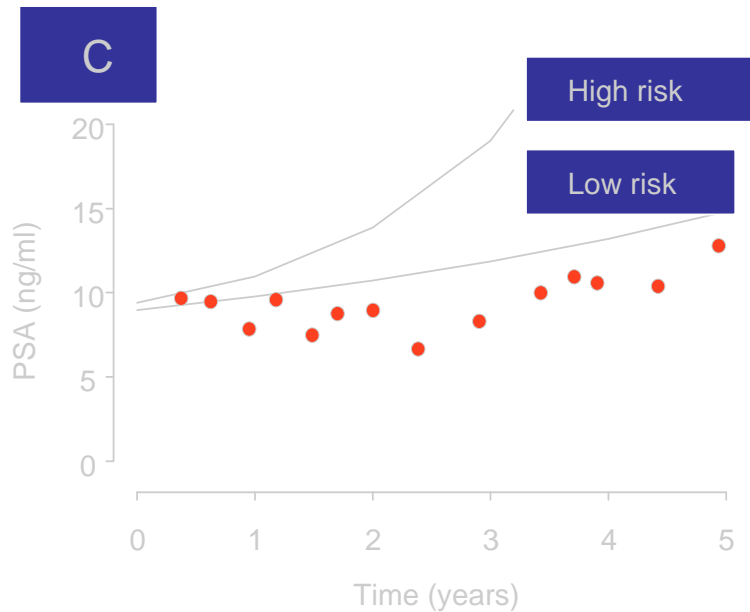
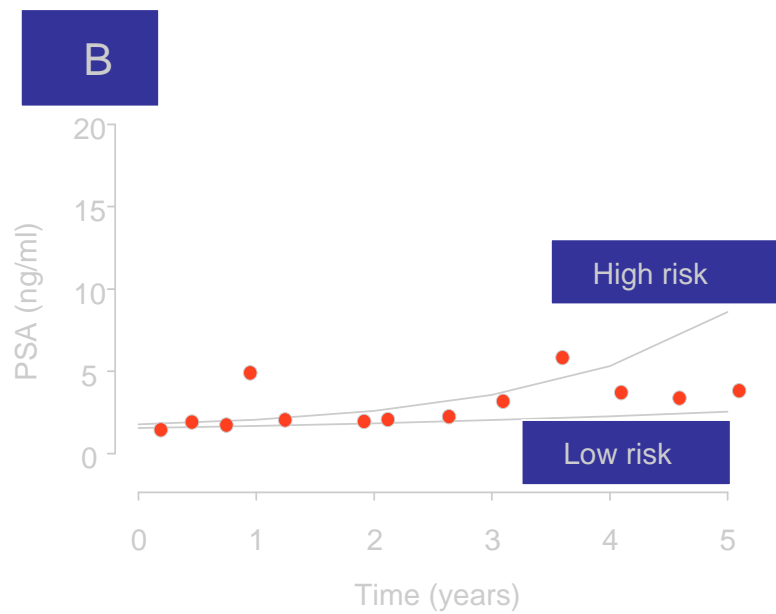
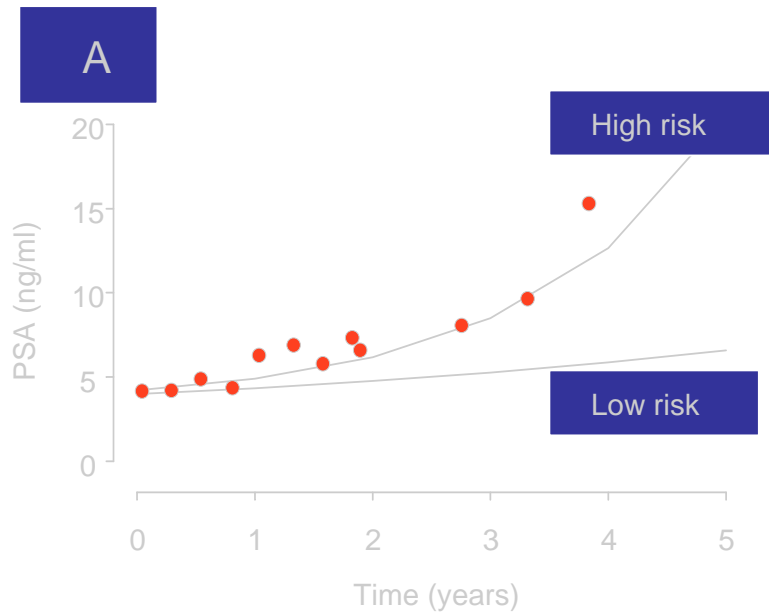


Figure 1: Risk Profiles (GLMM model)

Patient A: High risk for progression

– **intervene**

Patient B: Average risk for progression

– **continue follow-up q3mo**

Patient C: Low risk for progression

– **relax follow-up to q6mo**

Comparing PSA Triggers For Treatment For Men With Prostate Cancer On Active Surveillance

D. Loblaw¹, L. Zhang², L. Klotz³

¹Departments of Radiation Oncology, ²Clinical Trials and Epidemiology and ³Surgery, Sunnybrook Health Sciences Centre, University of Toronto



ASCO Prostate 2007

Objectives

- To compare commonly used PSA triggers for radical treatment for men with prostate cancer on active surveillance

Results

PSA Trigger	Patients Triggered (%)	Median / pt (range)
PSAt = 10	42/114 (37%)	4 (1-24)
PSAt = 20	14/134 (10%)	1.5 (1-9)
PSAdt first-last	52/134 (39%)	2 (1-11)
LR PSAdt	52/134 (39%)	2 (1-11)
Actual PSAv > 2y	66/134 (49%)	2 (1-10)
Calc PSAv > 2y	65/134 (49%)	2 (1-10)
GLMM PSAdt < 2y	0/134	

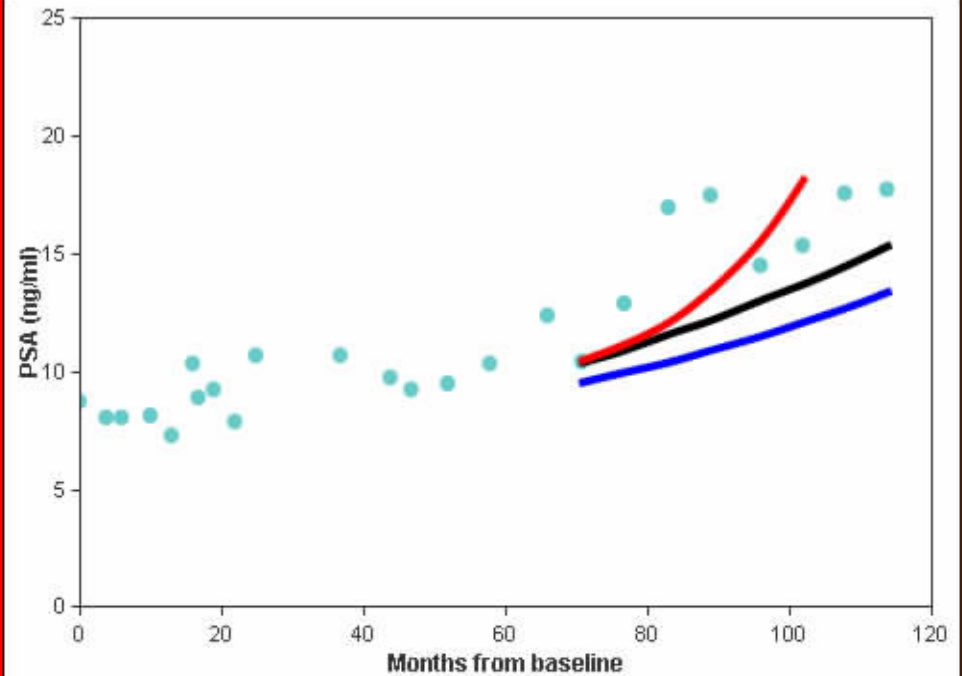
http://psakinetics.sunnybrook.ca

Baseline data for patient 3. Institution: TSRCC
Age: 79.0 years; Gleason: 6 (mean value used)

Start	End	YYYY-MM-DD	PSA
<input type="radio"/>	<input type="radio"/>	1995-10-20	8.70
<input type="radio"/>	<input type="radio"/>	1996-02-23	8.00
<input type="radio"/>	<input type="radio"/>	1996-05-16	8.00
<input type="radio"/>	<input type="radio"/>	1996-09-19	8.10
<input type="radio"/>	<input type="radio"/>	1996-11-28	7.30
<input type="radio"/>	<input type="radio"/>	1997-02-27	10.30
<input type="radio"/>	<input type="radio"/>	1997-03-27	8.90
<input type="radio"/>	<input type="radio"/>	1997-05-22	9.20
<input type="radio"/>	<input type="radio"/>	1997-09-04	7.90
<input type="radio"/>	<input type="radio"/>	1997-11-20	10.70

Set Start/End dates to process a subset of the data

More info



Select PSA metric:

Velocity (lin.model) Doubl.Time (exp.model)

Select patient:

3

then click:

Process

Summary: PSA doubling time = 6.4 years.

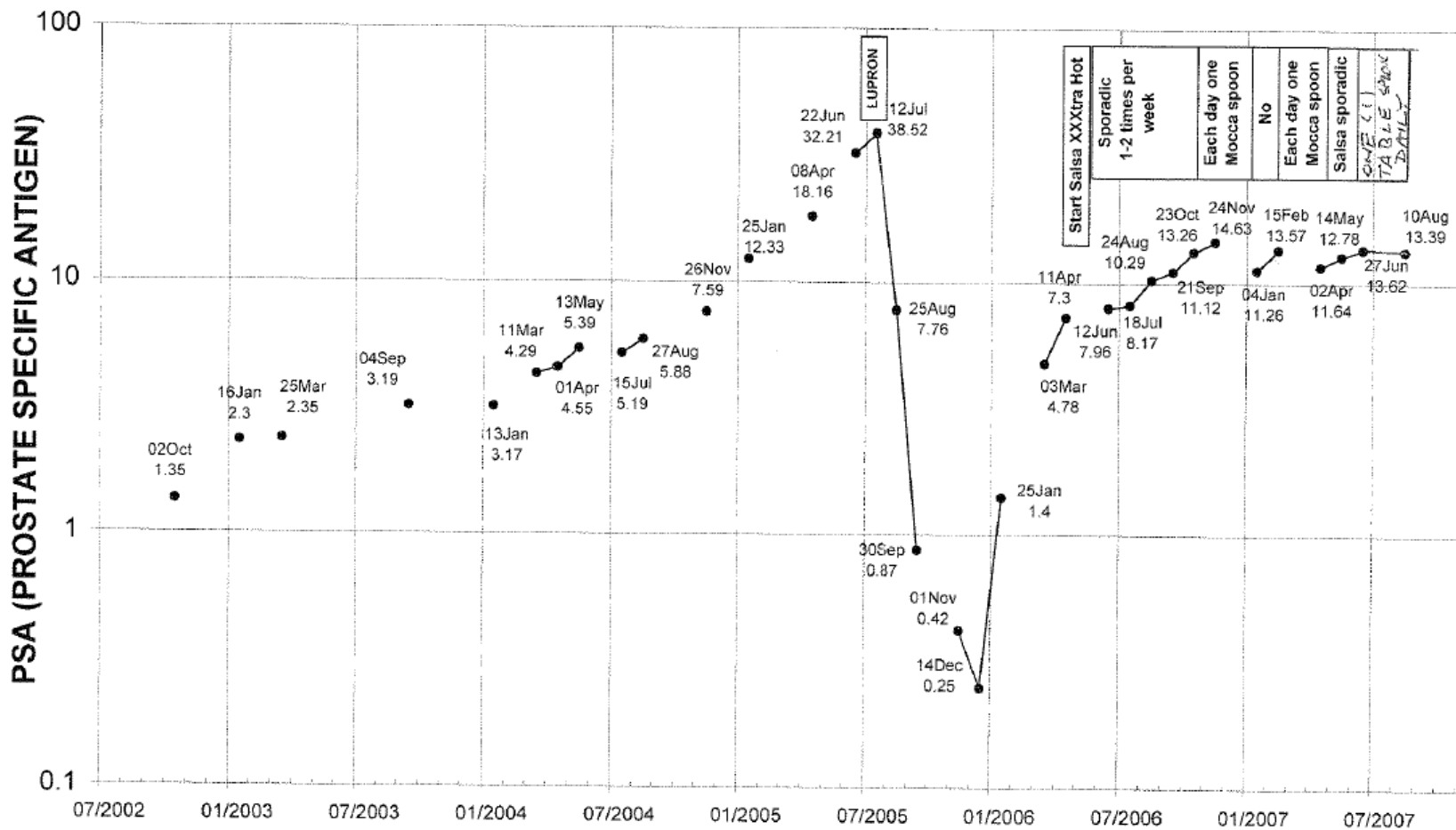
For the 3.5-year period PSA level was fluctuating between progression and non-progression lines therefore the patient should have ongoing close monitoring.

ASURE

- Active SURveillance REsearch program
- Platform of lifestyle, nutraceutical and pharmaceutical interventions to slow prostate growth



Capsaicin

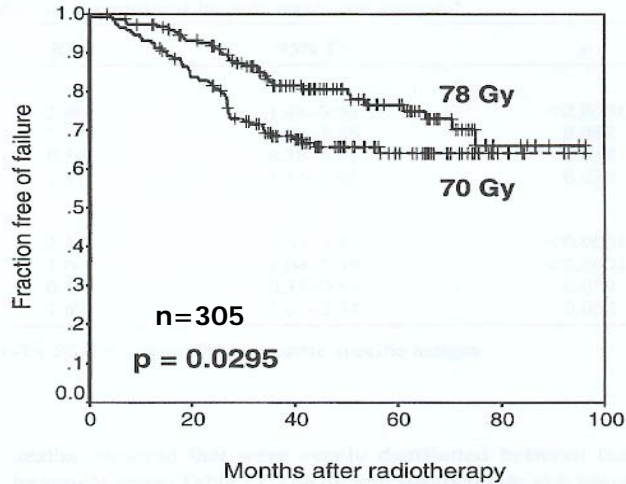




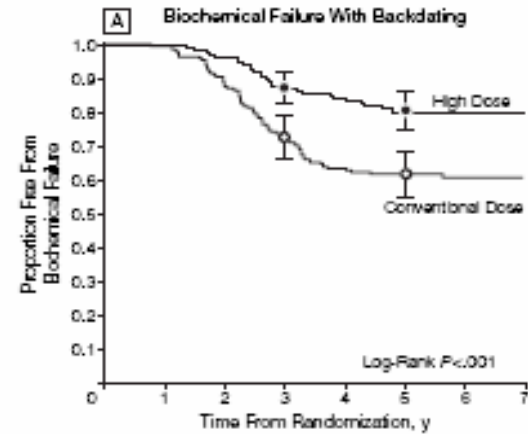
Prostate Hypofractionation

Dose Escalated Radiation Therapy

Pollack
IJROBP
2002



Zeitman
JAMA
2005



No. at Risk	106	194	191	184	163	111	53	20
High Dose								
Conventional Dose	107	197	192	170	156	90	33	11

Sathya
JCO
2005

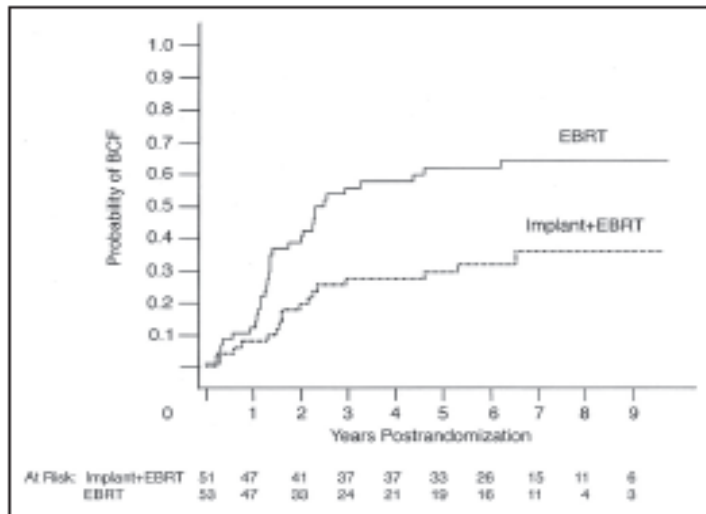
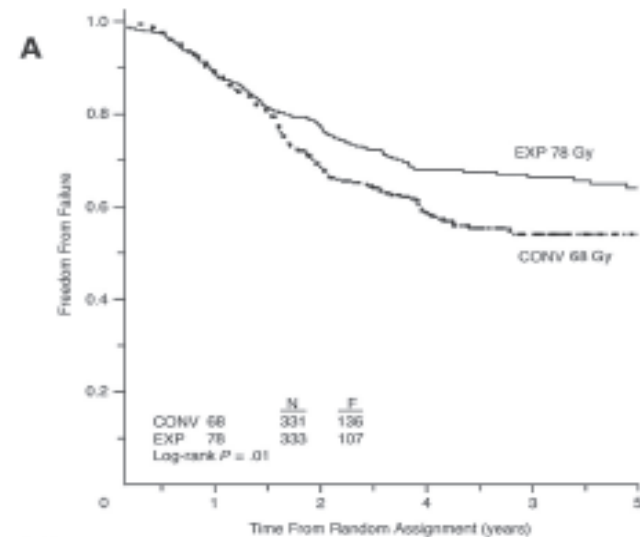


Fig 1. Probability of biochemical or clinical failure (BCF) by randomized treatment arm. EBRT, external-beam radiation therapy.



No. at risk:	CONV 68	331	290	208	134	80	49
CONV 68							
EXP 78	333	290	208	163	109	65	

Peeters
JCO
2006

What is the α/β of prostate cancer?

- Brenner and Hall, 1999 n=367
 - Ext beam vs I-125 implant
 - $\alpha/\beta = 1.5$ (95% C.I. 0.8-2.8)
- Fowler et al, 2001 n=735
 - Ext Beam vs I-125/Pd-103 vs HDR
 - $\alpha/\beta = 1.49$ (95% CI 1.25-1.76)
- Lukka et al, 2003 n=936
 - NCIC PR5 52.5 Gy/20 vs 66 Gy/33 RCT
 - $\alpha/\beta = 0.9$
- Yeoh et al, 2003 n=120
 - Australian 64 Gy/32 vs 55 Gy/20 RCT
 - $\alpha/\beta = 2.6$

Overall n = 2158
weighted $\alpha/\beta = 1.3$

Little Punches VS One Big KO!



Conventional



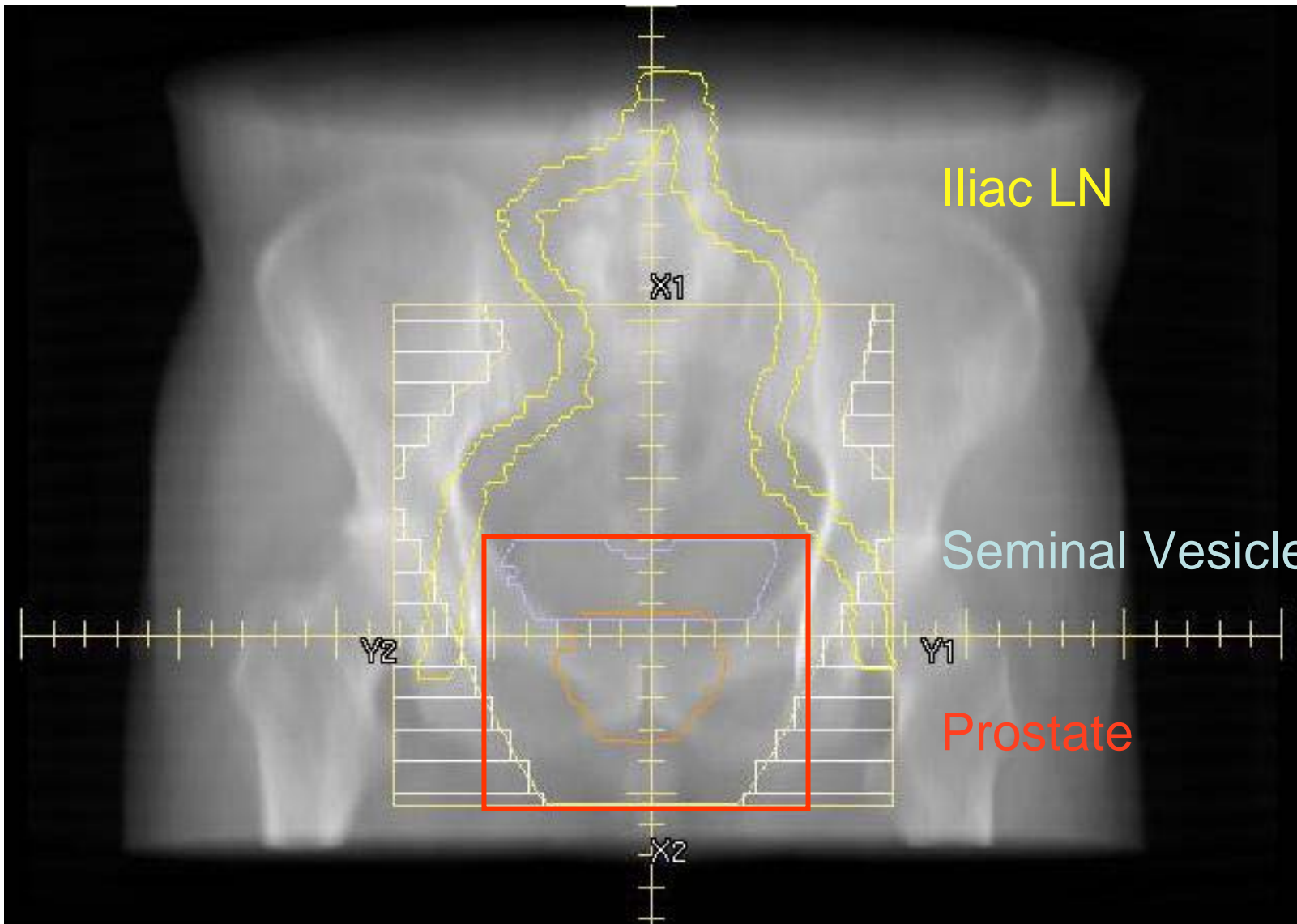
HART

Hypofractionated Radiotherapy Protocols Open

Risk Category	Trial	Phase	Duration
Low risk	pHART3	1/2	5 f / 5 wk
Intermediate risk	HDR single	2	16 f / 5 wk
	PROFIT	3	20 f / 4 wk
High Risk	pHART2	2	25 f / 5 wk



Advances in Technology



Iliac LN

Seminal Vesicles

Prostate

X1

X2

Y2

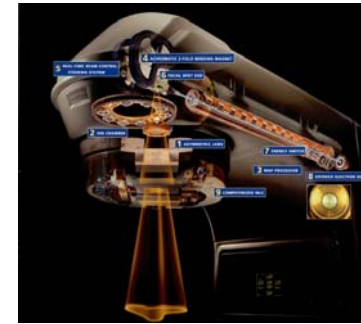
Y1

Radiotherapy Advances

CT
Plan



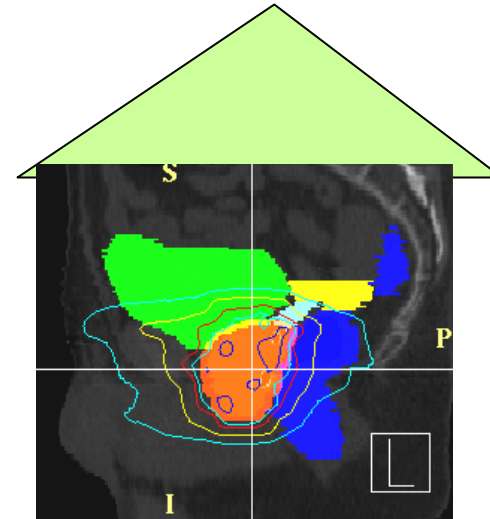
LINAC



Gold seed
insert



IMRT Plan



4 field
Absolute
7800.0 cGy
7410.0 cGy
5000.0 cGy
4000.0 cGy

10 mm margin

4 mm margin

Better Control

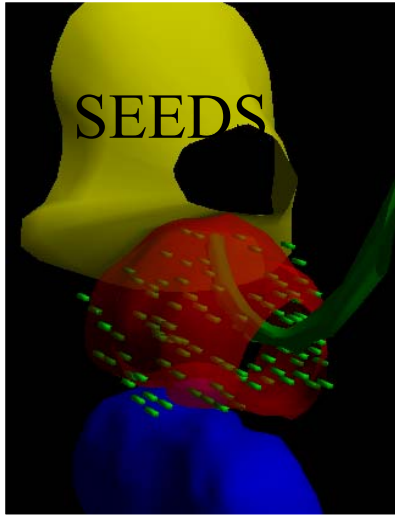
Fewer visits

- more convenient for patient
- Higher capacity for RT centre

Less side effects



Prostate Brachytherapy



Permanent

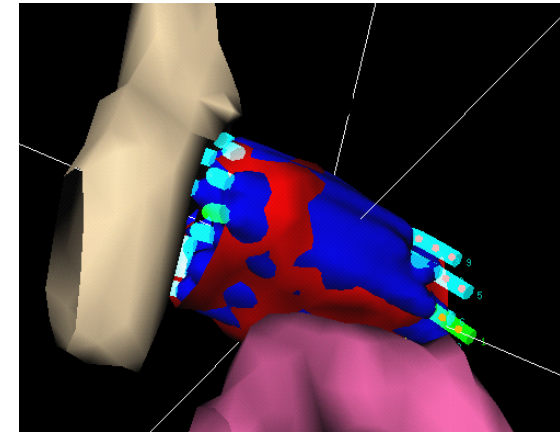
Temporary

Monotherapy

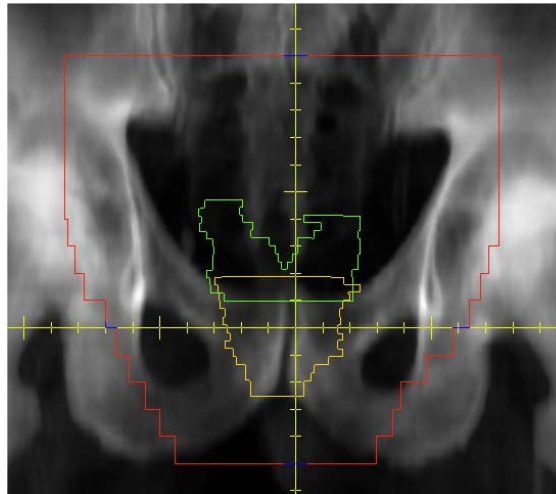
Low Risk Cancer

T1/T2, Gleason 6,
PSA <10

Combined with
External Beam



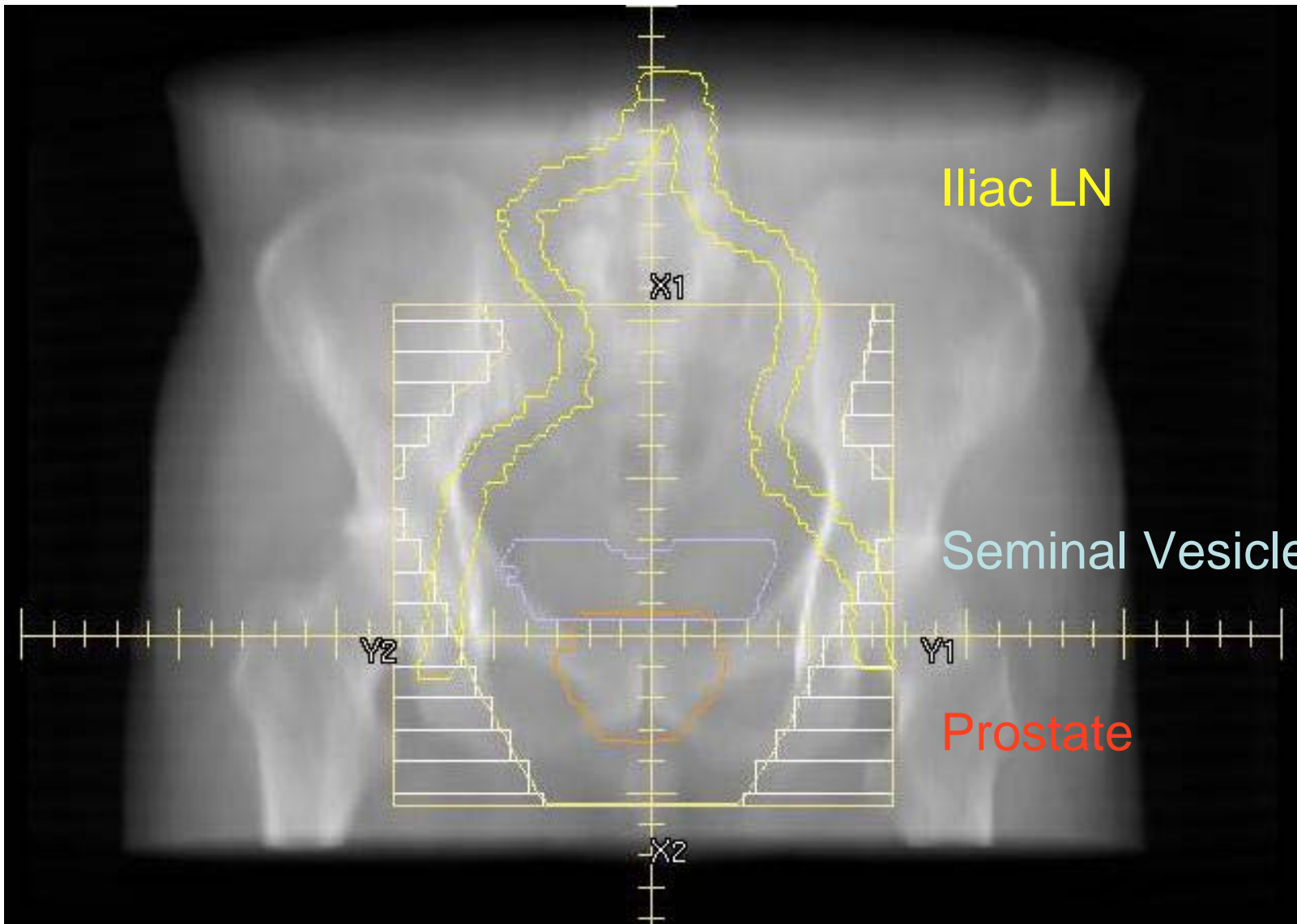
*Intermediate / high
risk*





Minimally Invasive Surgery





Iliac LN

Seminal Vesicles

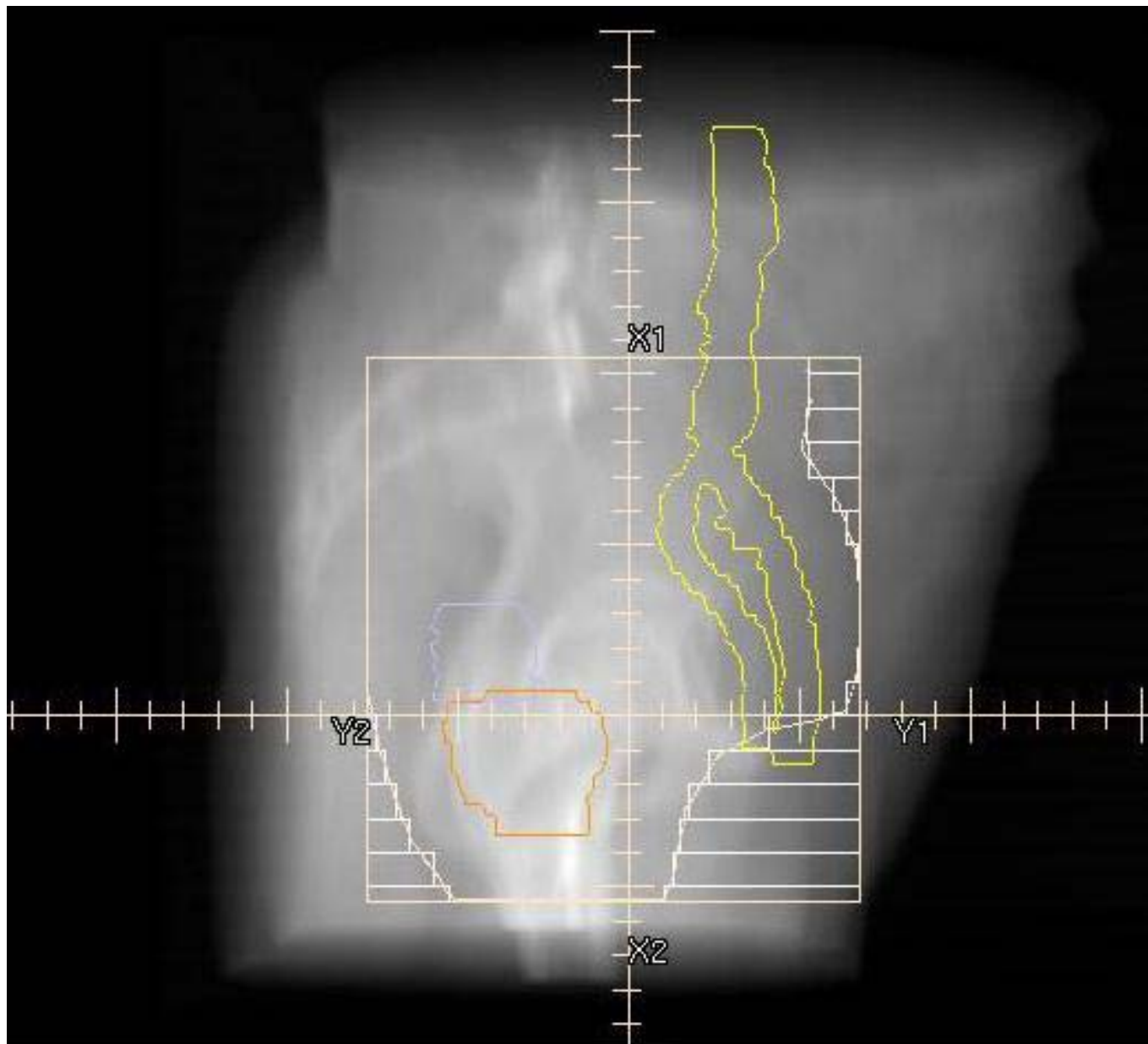
Prostate

X1

Y2

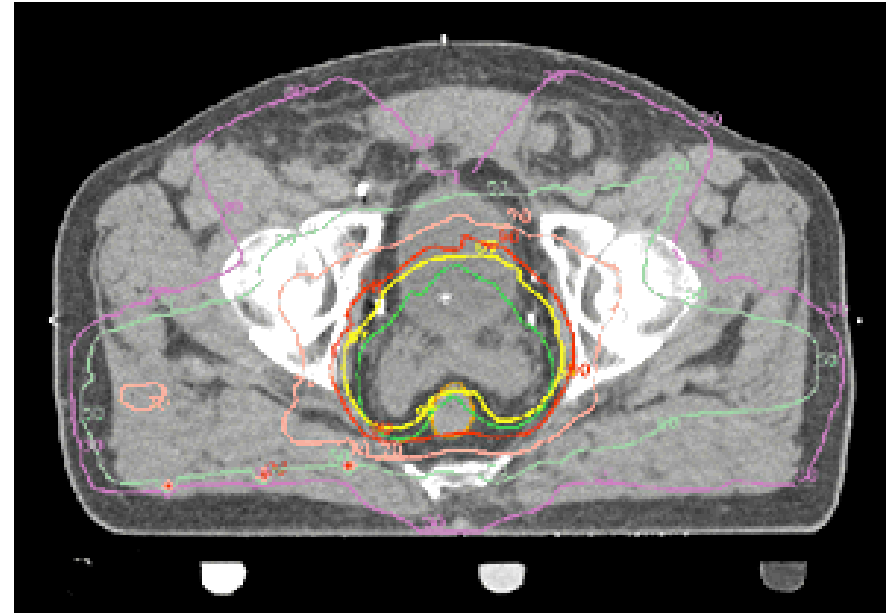
Y1

X2



Concomitant Boost to Prostate

- CTV = prostate only
- PTV = 4 mm (for intrafraction prostate motion)*
- Dose = 22.5 Gy in 25 fractions
- (total dose to prostate = 67.5 Gy in 25 fractions)
 - Equivalent to 82Gy / 41f
- Step & Shoot IMRT technique (7 – 9 fields)
- Daily on-line correction for prostate fiducial marker position prior to beam on time





Recurrent Prostate Cancer

After Radical Radiotherapy

Post-Radiotherapy Failure

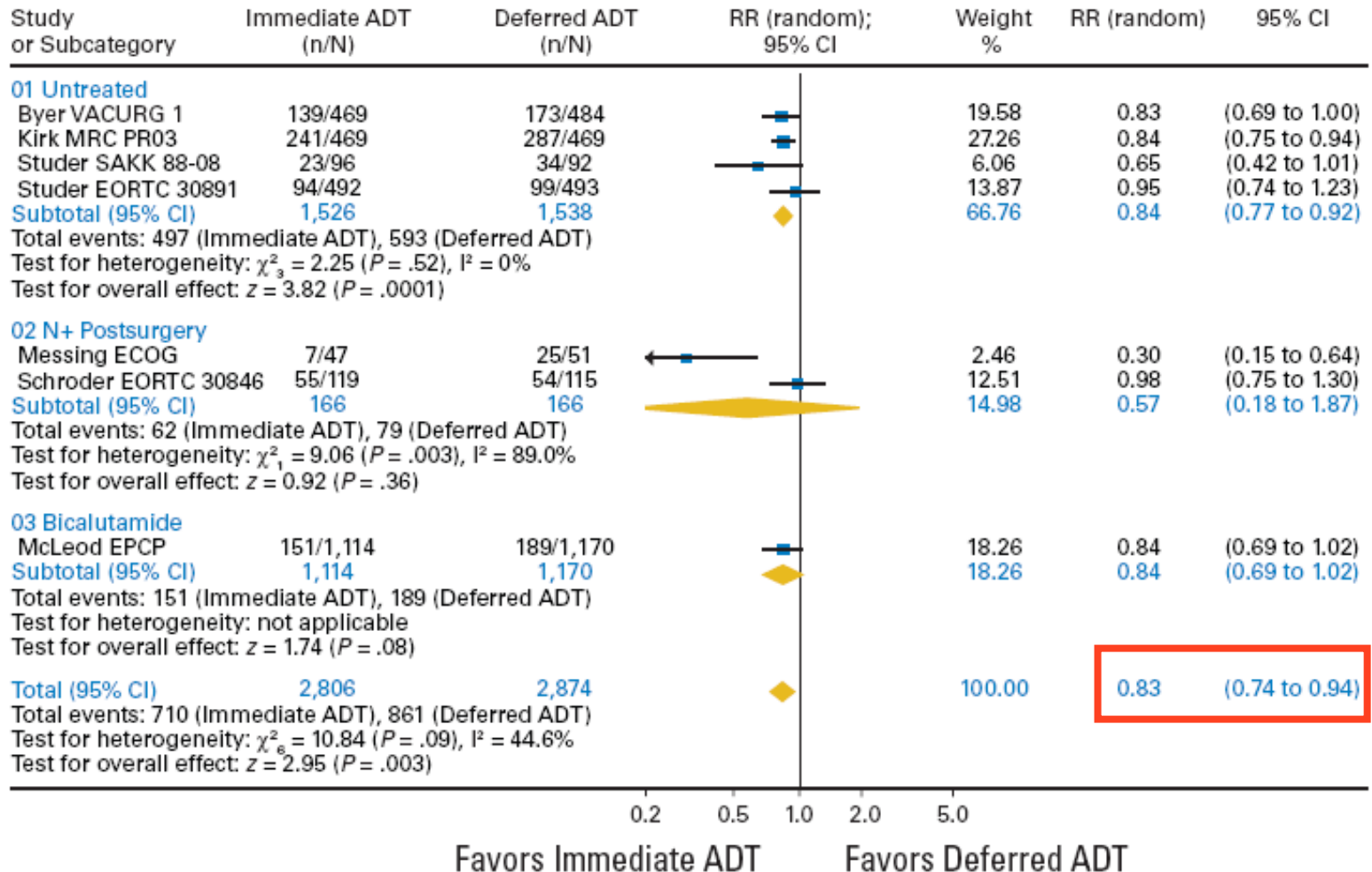
- Local therapies
 - Radical prostatectomy
 - Cryotherapy
 - HiFU
 - Seed brachytherapy*
- **ANDROGEN DEPRIVATION THERAPY**
 - ASCO Androgen Sensitive Guideline 2006
Update available April 2007

Patterns of Care Survey

Trigger PSA (ng/mL) for starting ADT	1994 Canada	2000 USA	2004 Canada
<10	20	28	53
10-20	18	50	36
20-50	32	20	11
>50	24	2	0

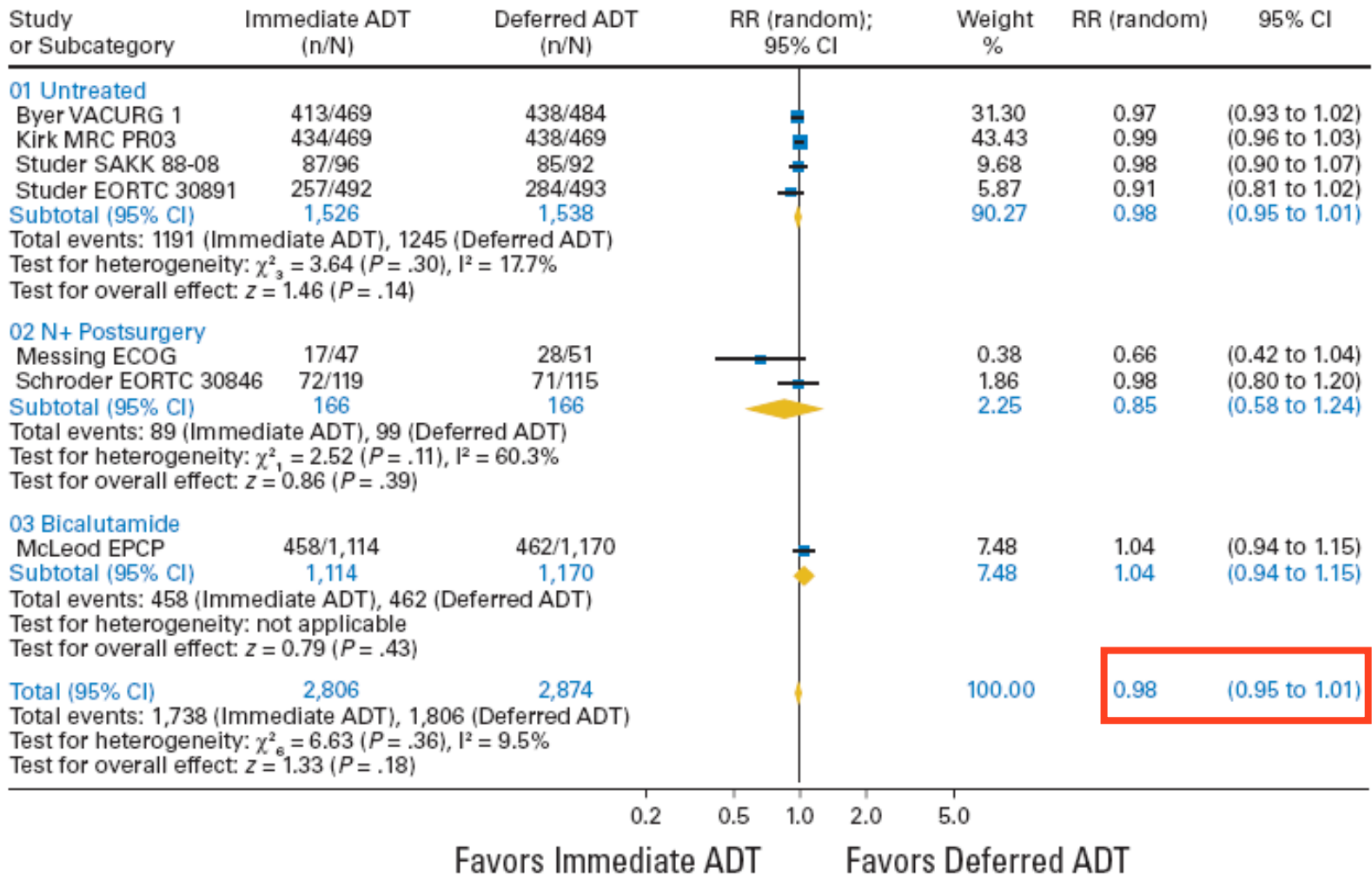
Prostate Cancer Mortality

Review: Timing of ADT in Prostate Cancer
 Comparison: 01 Timing of ADT
 Outcome: 02 Prostate Cancer Mortality



Overall Mortality

Review: Timing of ADT in Prostate Cancer
 Comparison: 01 Timing of ADT
 Outcome: 01 Overall Mortality



ORIGINAL ARTICLE

Risk of Fracture after Androgen Deprivation for Prostate Cancer

Vahakn B. Shahinian, M.D., Yong-Fang Kuo, Ph.D., Jean L. Freeman, Ph.D.,
and James S. Goodwin, M.D.

N Engl J Med 2005;352:154-64.

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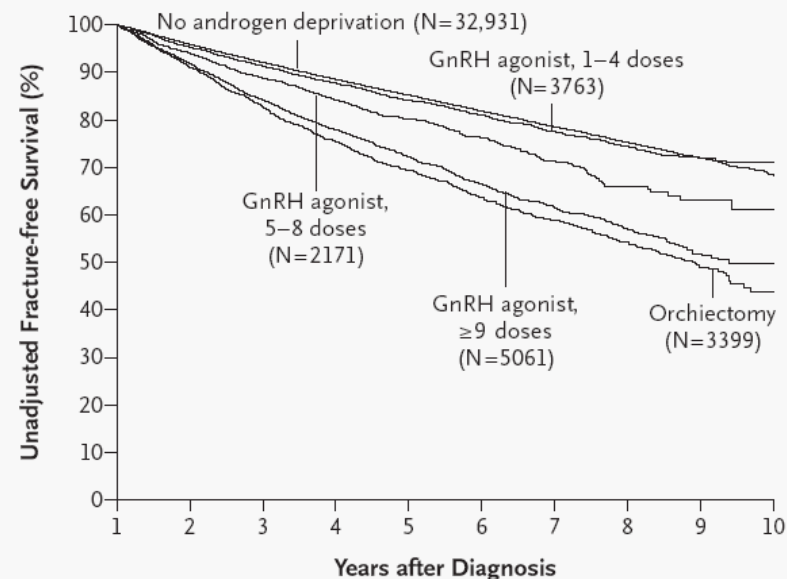


Figure 1. Unadjusted Fracture-free Survival among Patients with Prostate Cancer, According to Androgen-Deprivation Therapy.

The survival curves start at 12 months after diagnosis, and androgen deprivation was initiated within 6 months after diagnosis. GnRH denotes gonadotropin-releasing hormone. The number of doses is the number administered within 12 months after diagnosis.

Diabetes and Cardiovascular Disease During Androgen Deprivation Therapy for Prostate Cancer

Nancy L. Keating, A. James O'Malley, and Matthew R. Smith

Table 2. Rate of Incident Diabetes, Coronary Heart Disease, and Myocardial Infarction, and Sudden Death Associated With Androgen Deprivation Therapy, Unadjusted

Treatment	Incident Diabetes			Incident CHD			Myocardial Infarction			Sudden Cardiac Death		
	No.	95% CI	<i>P</i> *	No.	95% CI	<i>P</i> *	No.	95% CI	<i>P</i> *	No.	95% CI	<i>P</i> *
No treatment	20.9	20.3 to 21.5	ref*	61.3	60.2 to 62.4	ref*	10.9	10.5 to 11.3	ref*	9.0	8.6 to 11.1	ref*
GnRH agonist	29.0	27.3 to 30.7	< .001	72.3	69.4 to 75.2	< .001	13.5	12.5 to 14.5	< .001	12.9	11.9 to 13.9	< .001
Orchiectomy	24.5	22.1 to 26.9	.005	63.3	48.9 to 67.7	.39	13.2	11.6 to 14.8	.01	12.5	10.9 to 14.1	< .001

Abbreviations: CHD, coronary heart disease; ref, reference; GnRH, gonadotropin-releasing hormone.

**P* values based on two-sample hypotheses tests evaluating whether the rate for men during GnRH agonist treatment differed from the rate under no treatment and whether the rate for men treated with orchiectomy differed from the rate under no treatment. Patients with prevalent diabetes and coronary heart disease did not contribute data to the rates for incident diabetes and coronary heart disease, respectively.

ELAAT Study Schema

			<u>Outcomes</u>
Localized Prostate Cancer	R	Immediate LHRH	Time to Androgen Independent Disease
Asymptomatic biochemical failure post RT	A		
	N		
	D		• Cause specific survival
	O		• Overall survival
	M	Deferred LHRH	• Quality of Life
	I		• Complications of
	Z	(at symptom onset) (or PSA > 25ng/mL)	Advanced Malignancy
	E		• Bone Fractures