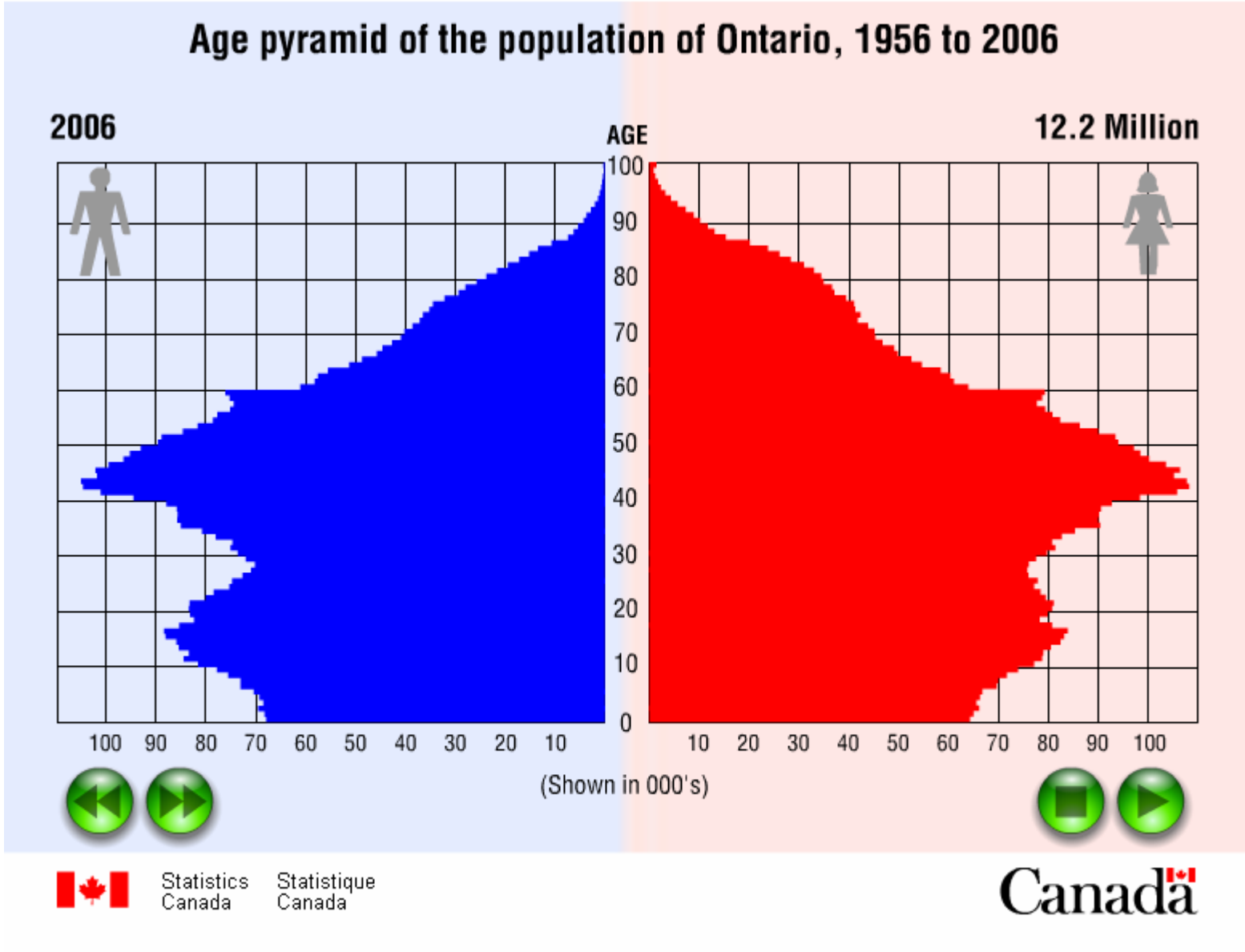
Embracing Technology & Timing of Salvage Hormones

Andrew Loblaw BSc, MD, MSc, FRCPC, CIP
Department of Radiation Oncology
Sunnybrook Health Sciences Centre
University of Toronto

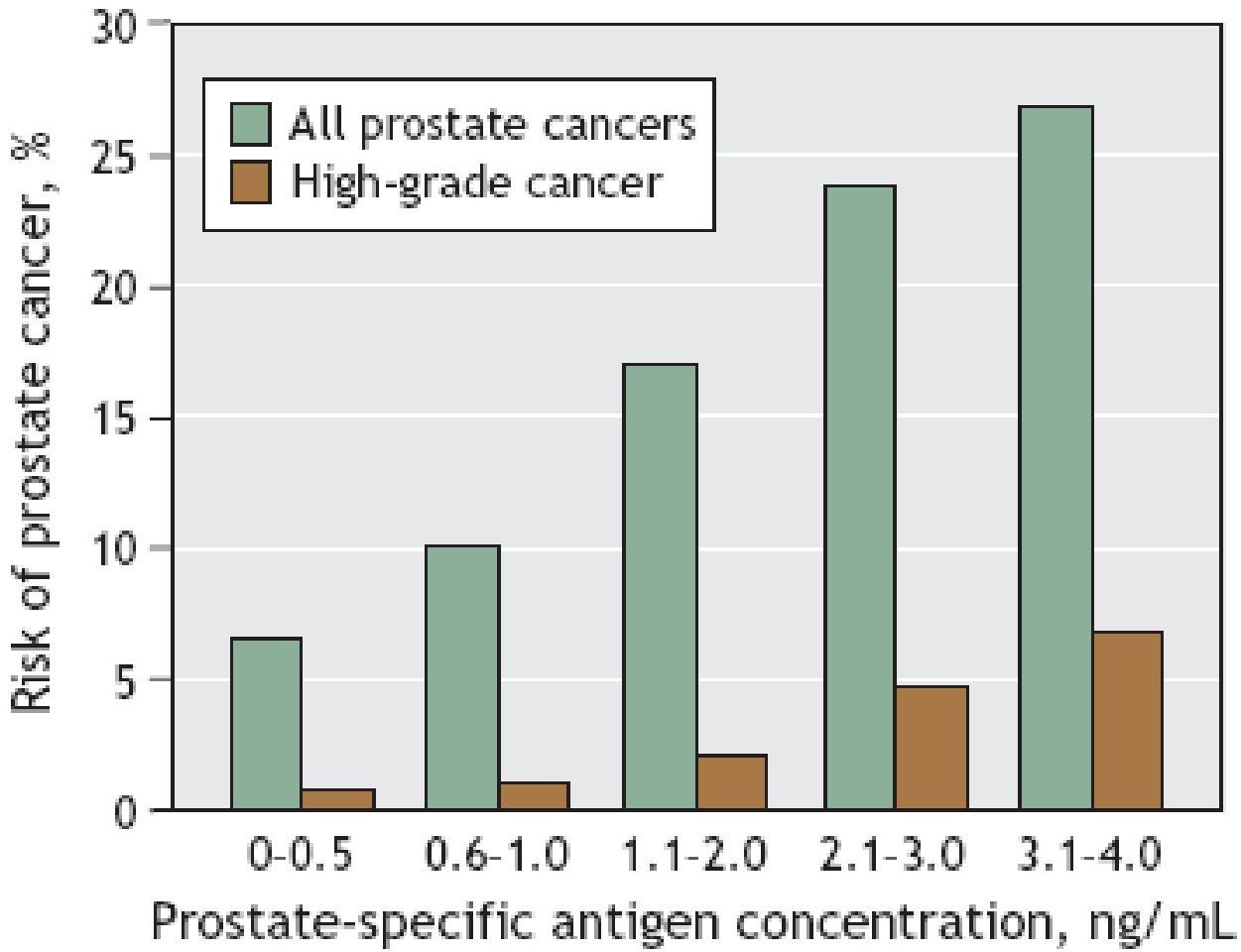
Us Too, Brampton
October 13, 2009

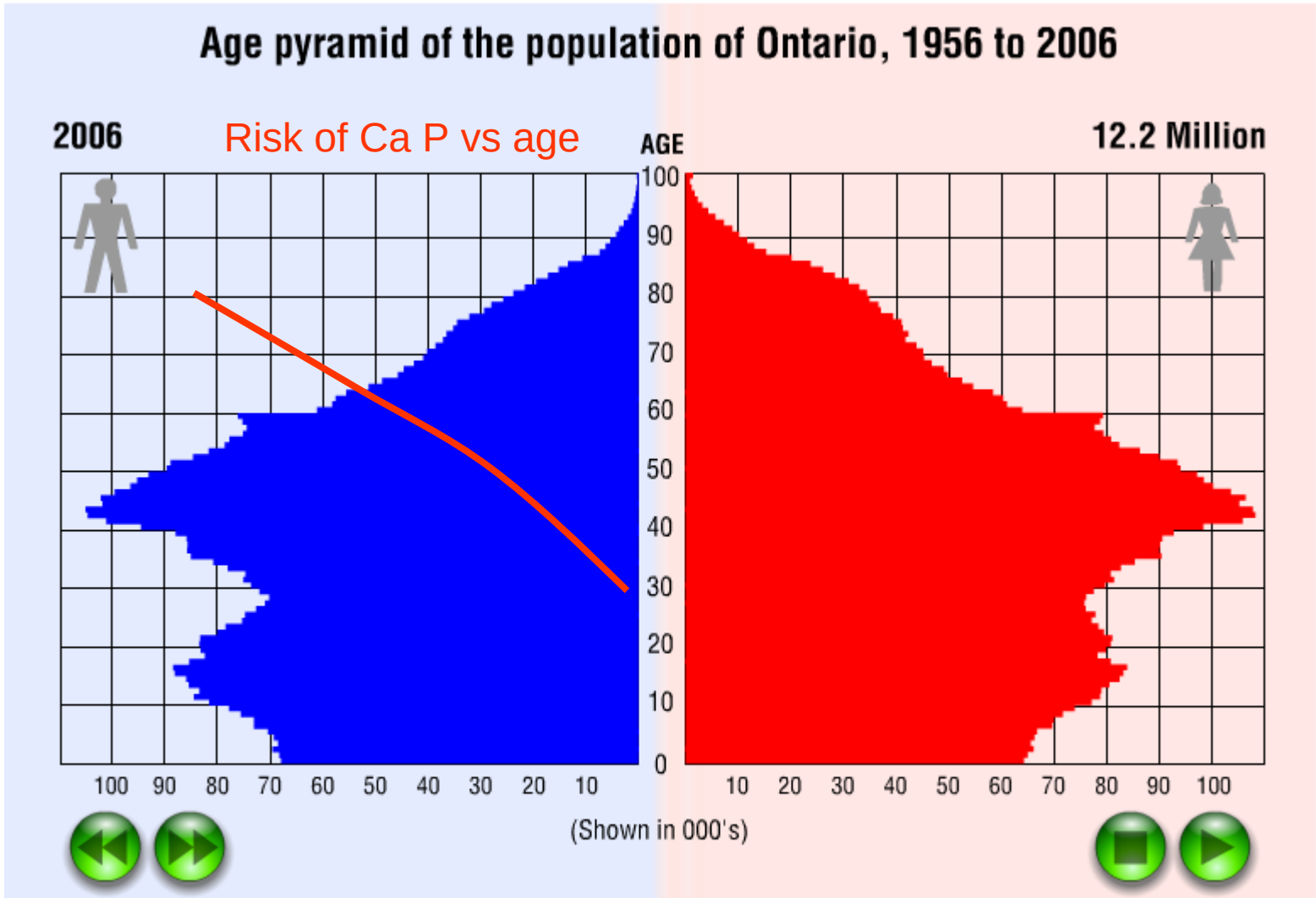
The Future of Prostate Cancer



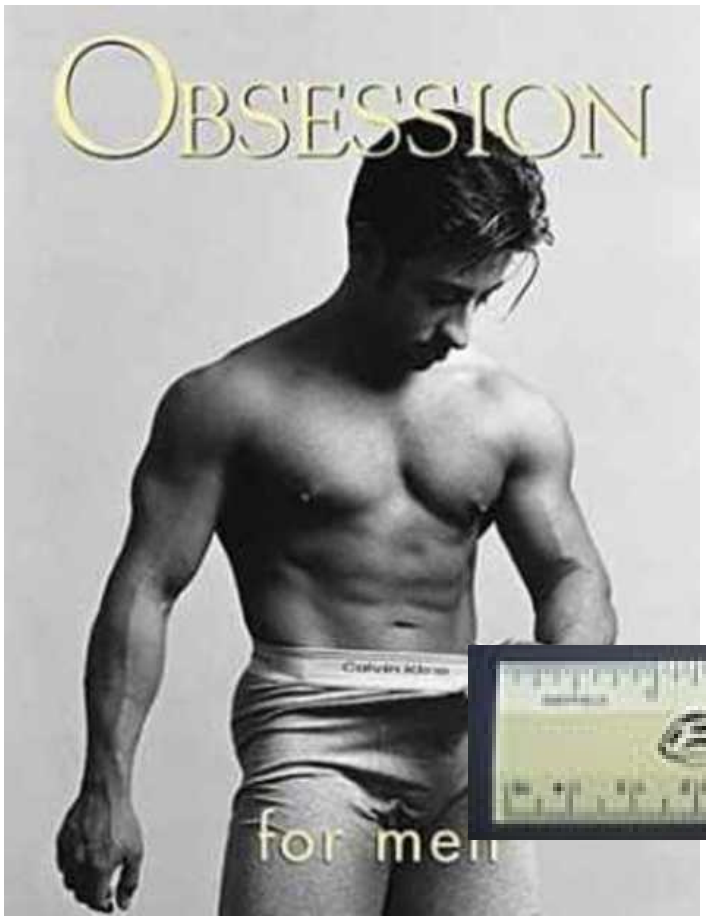
http://www12.statcan.ca/english/census06/analysis/agesex/vignettes/on06pymd.html

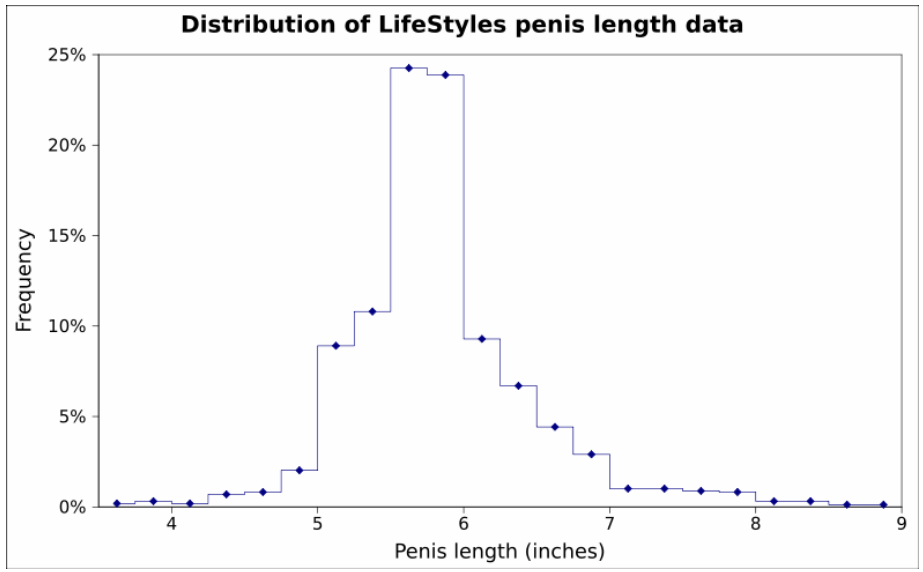
No "Normal" PSAs



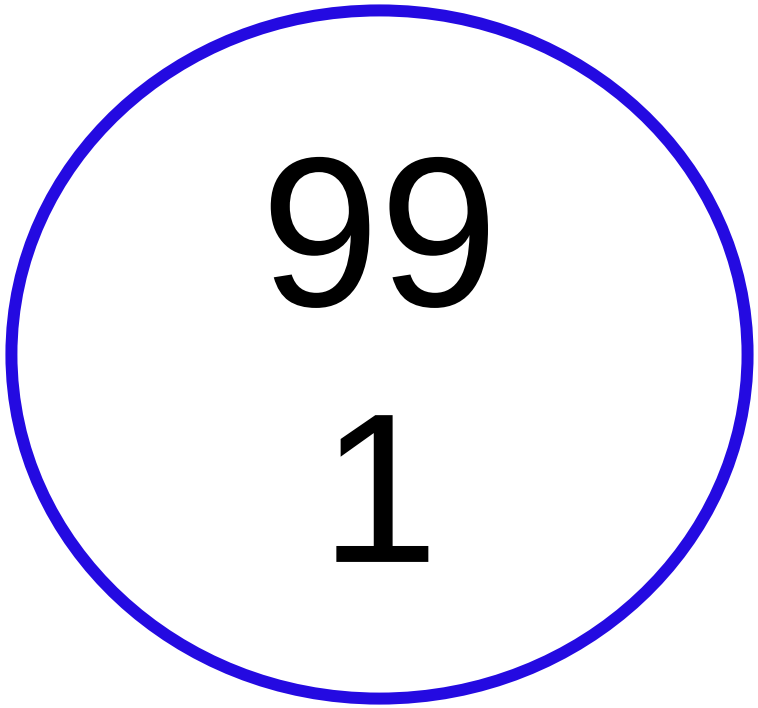

Age pyramid of the population of Ontario, 1956 to 2006
2006
Risk of Ca P vs age
AGE
12.2 Million
100
90
80
70
60
50
40
30
20
10
0
100 90 80 70 60 50 40 30 20 10
10 20 30 40 50 60 70 80 90 100
(Shown in 000's)
Statistics Canada
Statistique Canada
Canada

What's our Yardstick in Prostate Ca?



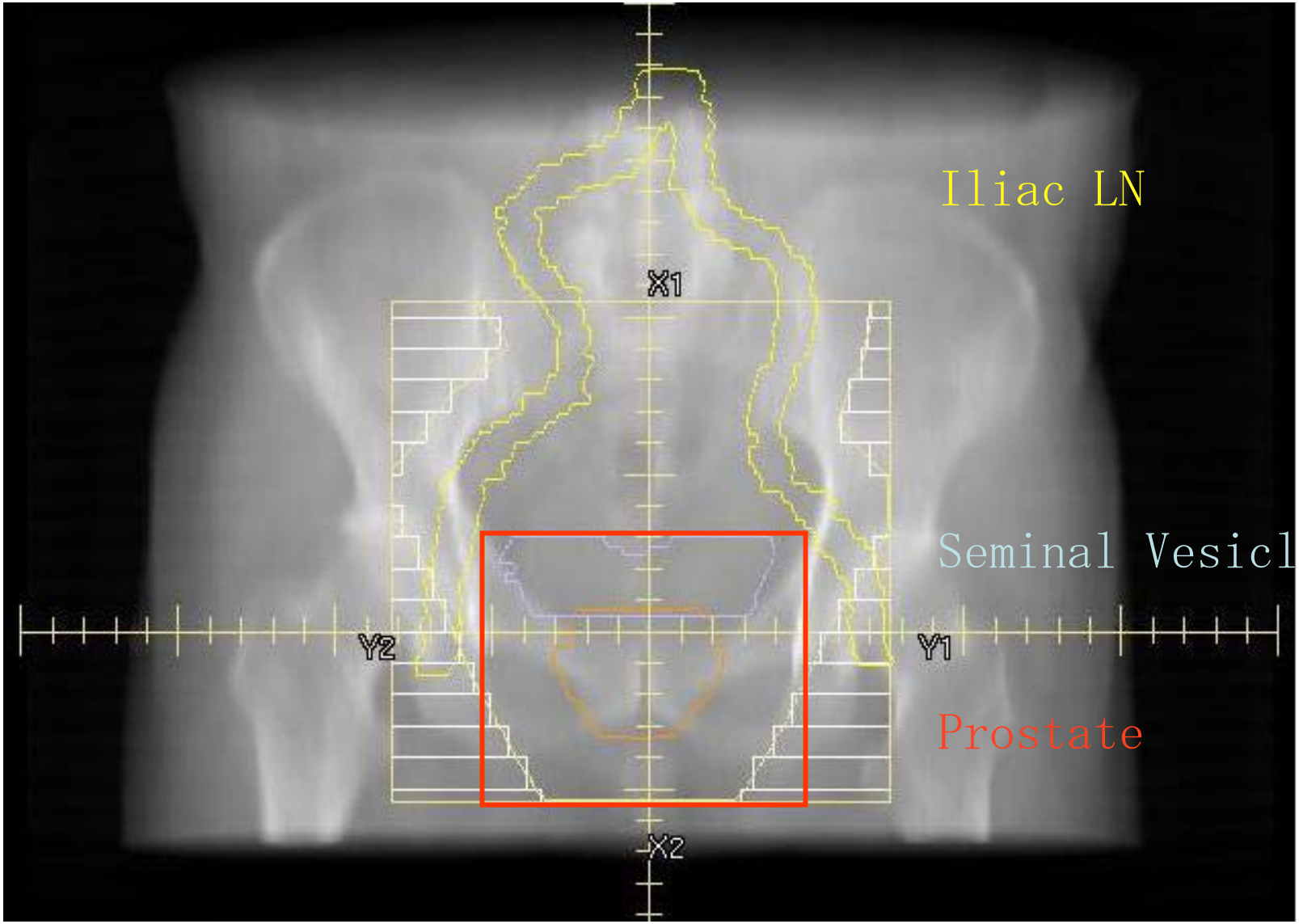


CURE WITHOUT

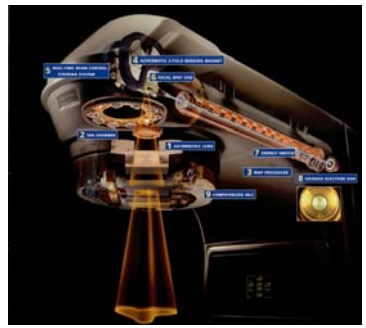


COMPROMISE

Advances in Technology


Iliac LN
X1
Seminal Vesicles
Y2
Y1
Prostate
X2

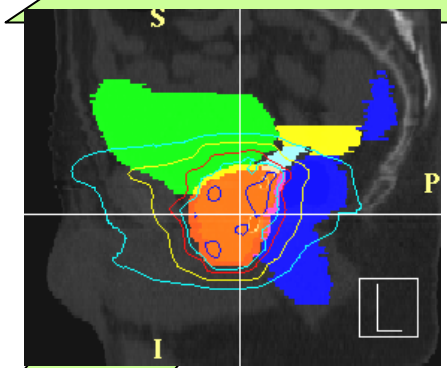
Radiotherapy Advances



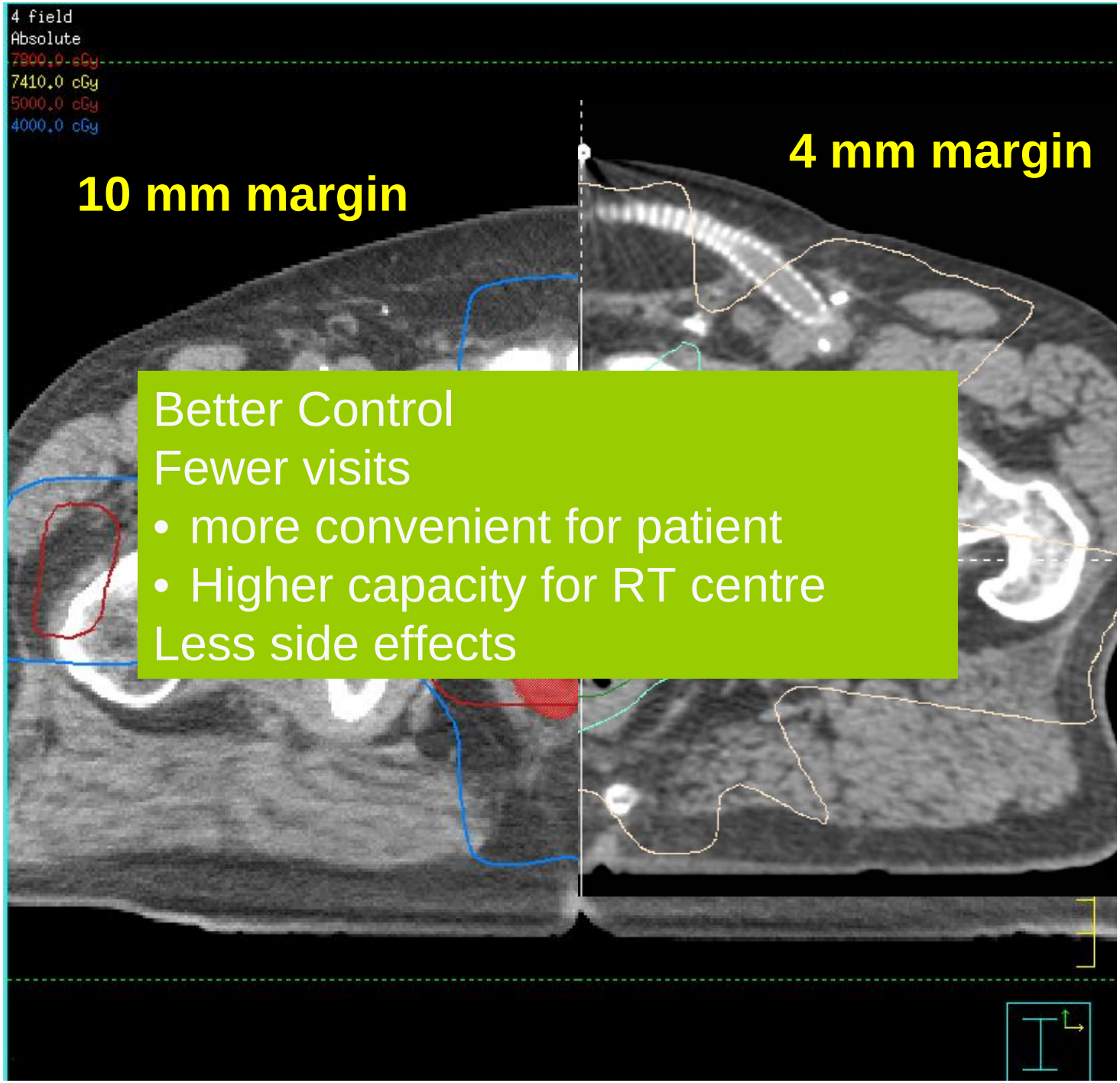
LINAC

IGRT

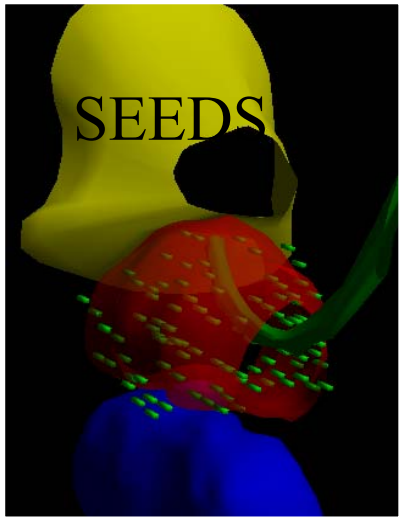
Gold seed insert



IMRT Plan

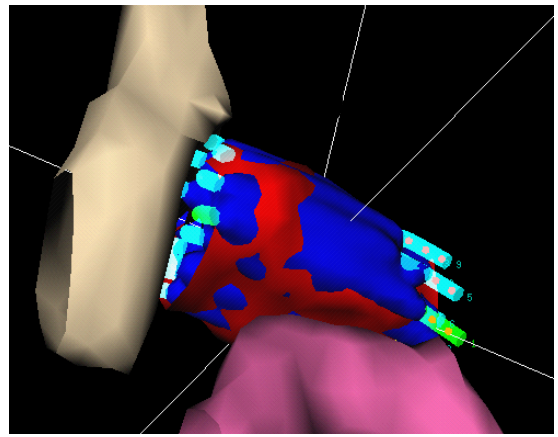

4 field
Absolute
7800.0 cGy
7410.0 cGy
5000.0 cGy
4000.0 cGy
10 mm margin
4 mm margin
Better Control
Fewer visits
• more convenient for patient
• Higher capacity for RT centre
Less side effects

Prostate Brachytherapy



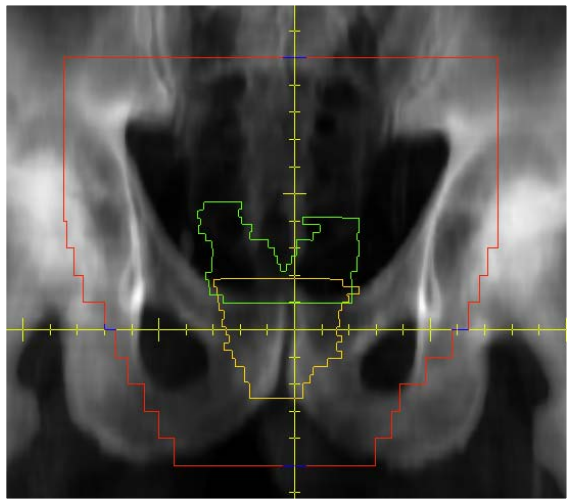
Permanent

Temporary



Monotherapy

Combined with External Beam



Low Risk Cancer

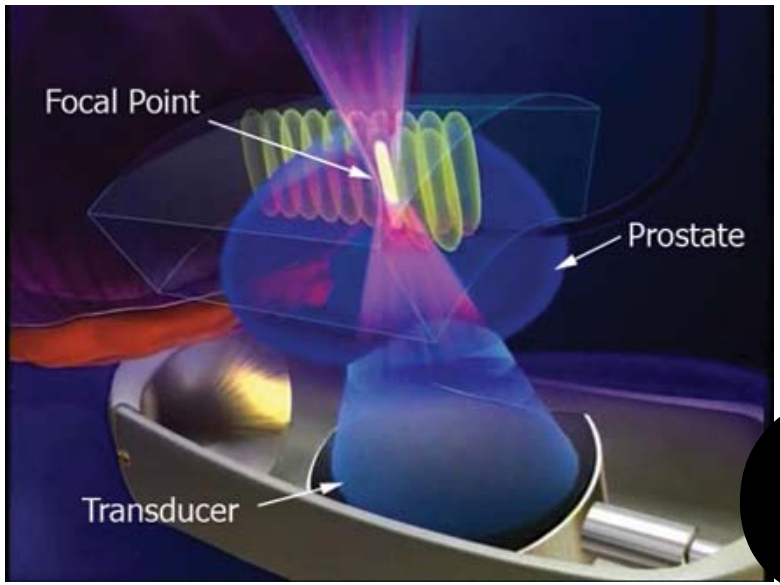
IPSS < 15, Vol < 50 cc

Intermediate / high risk

IPSS < 15, Vol < 50

Minimally
Invasive Surgery

HIFU



$

Agency Links: Home | Contact Us | Help | Site Map

BC Cancer Agency
CARE & RESEARCH

Search Go

Patient/Public Info | Regional Services | Health Professionals Info | About BCCA

BC Cancer Agency >> Health Professionals Info >> Cancer Management Guidelines >>

Genitourinary
Prostate
- 1. Predisposing Factors & Prevention
- 2. Screening & Early Detection
- 3. Diagnosis
- 4. Staging
- 5. Management
- Brachytherapy Guidelines
- HIFU
- Osteoporosis Screening Guidelines
- PSA Screening

HIFU

Print this Page

Updated 12 May 2009

Efficacy data does not allow meaningful assessment as to the benefit-risk ratio of high intensity focus ultrasound (HIFU) as a primary treatment for localized prostate cancer, and hence cannot currently be recommended as standard therapy given current alternatives.

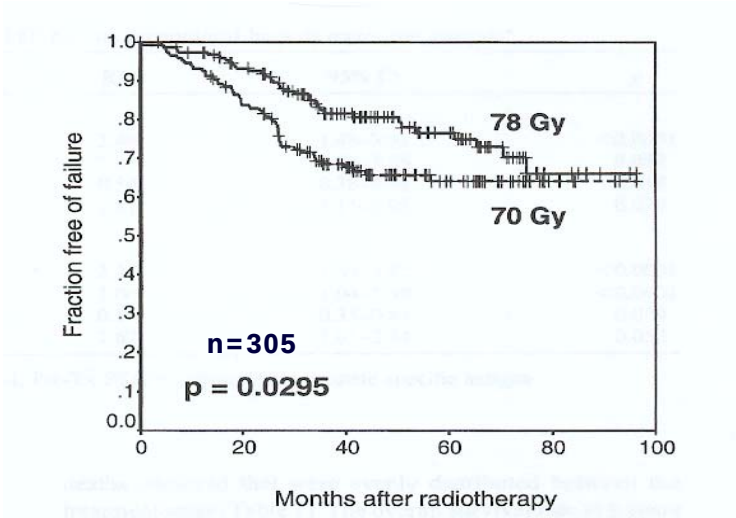
HIFU must be developed in a controlled manner within the context of a clinical trial, which **should be approved by an Ethical Review Board (ERB)**, who should also monitor patient selection, informed consent, accrual, complication rates and other outcomes information. The BC Cancer Agency Genitourinary Tumour Group should also receive patient treatment data so that it may be added to data on other comparative modalities including active surveillance, prostatectomy, and radiotherapy.

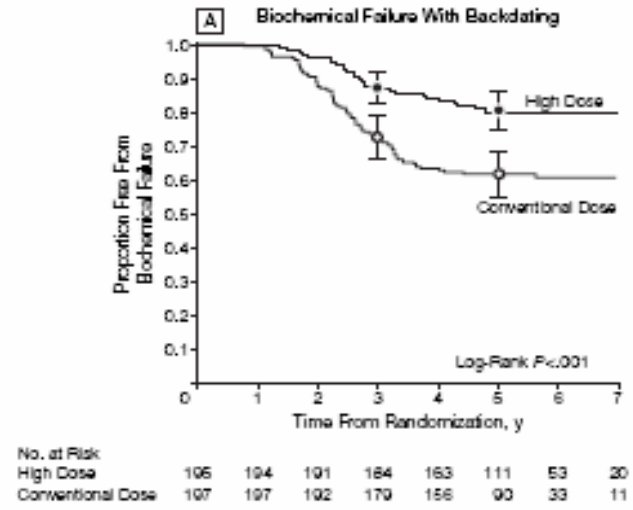
In cases of radiorecurrent localized prostate cancer, where treatment options are more limited and associated with significant morbidity, HIFU could be considered a salvage treatment option associated with discussion of alternatives including salvage prostatectomy, cryotherapy, brachytherapy, or androgen deprivation therapy. Although again this should be in the context of an ethics approved protocol with the intention of collecting data prospectively for the purpose of publication in a peer reviewed journal.

You can download the full BCCA-GUTG assessment HIFU for prostate cancer report.

Prostate Hypofractionation

Dose Escalated Radiation Therapy





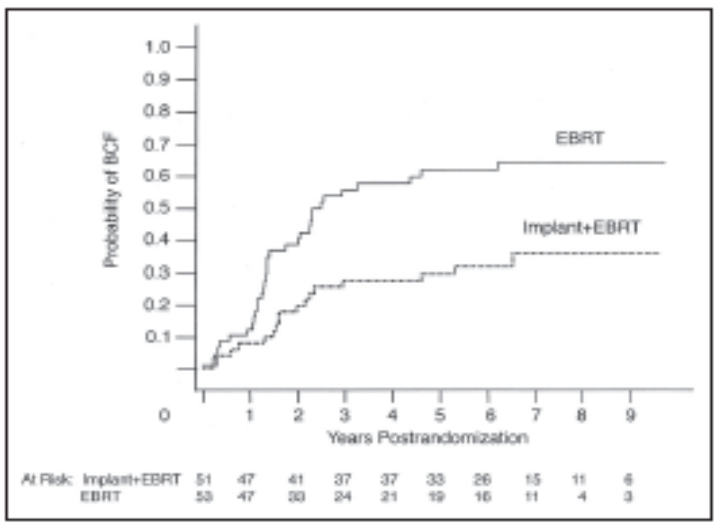
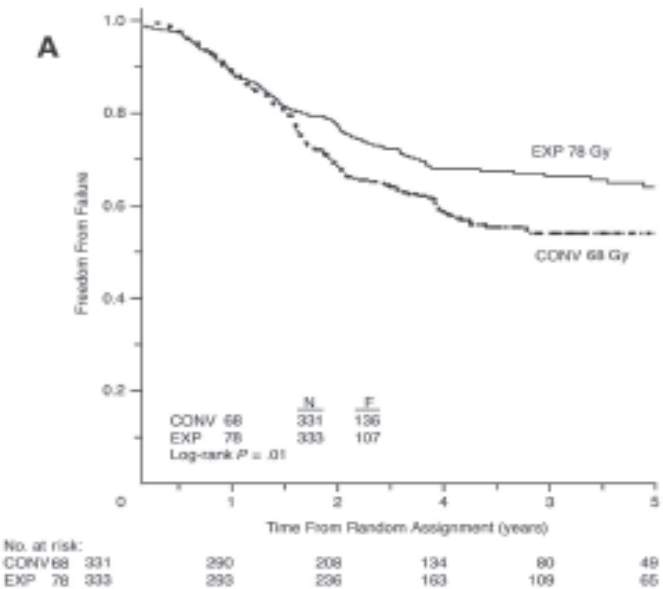
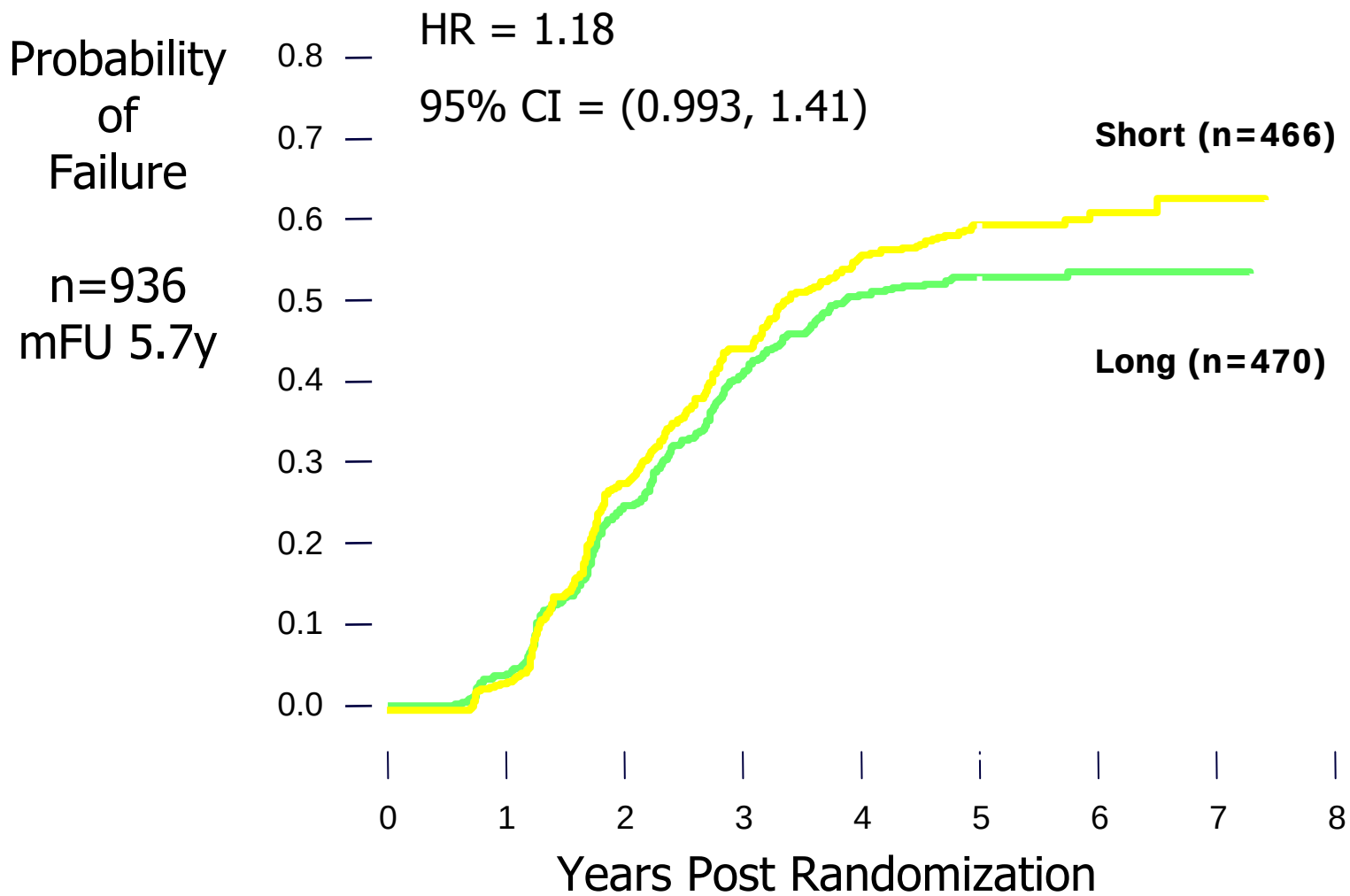


Fig 1. Probability of biochemical or clinical failure (BCF) by randomized treatment arm. EBRT, external-beam radiation therapy.

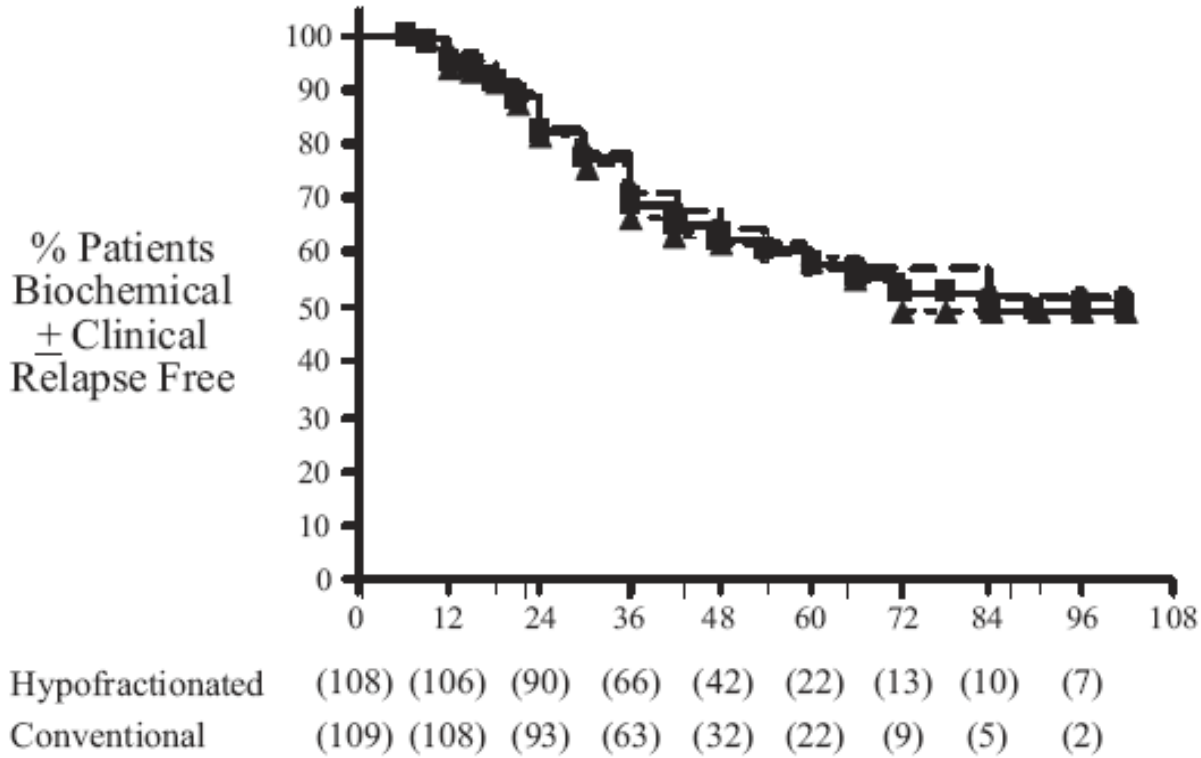


OCOG/NCIC PR5: RCT 66 Gy / 33f vs 52.5 Gy / 20f



Lukka et al. J Clin Oncol 2005

Australian RCT: 64 Gy/32f vs 55 Gy/20f



n = 217, median FU 48 mo

Yeoh et al. IJROBP 2006; 66(4):1072-83

What is the α/β of prostate cancer?

- Brenner and Hall, 1999 n=367
  - Ext beam vs I-125 implant
  - α/β **= 1.5** (95% C.I. 0.8-2.8)
- Fowler et al, 2001 n=735
  - Ext Beam vs I-125/Pd-103 vs HDR
  - α/β **= 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
  - α/β **= 0.9**
- Yeoh et al, 2003 n=120
  - Australian 64 Gy/32 vs 55 Gy/20 RCT
  - α/β **= 2.6**

Overall n = 2158

weighted α/β = 1.3

Loblaw DA, Cheung P. Cdn J Urol 13(Suppl 1):62-6; 2006

Little Punches
vs
One Big KO!

Conventional

HART

Hypofractionated Radiotherapy Protocol Menu

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
Adjuvant Post-op	pHART4	2	17 f / 3 wk

Prostate HART 3 STUDY

HYPOFRACTIONATED ACCELERATED RADIOTHERAPY FOR LOW RISK LOCALIZED PROSTATE CANCER

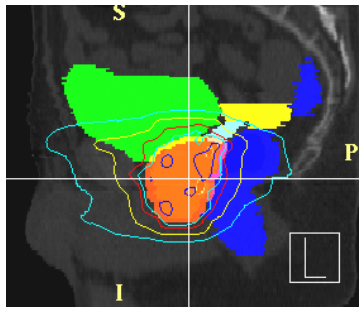
Andrew Loblaw, Patrick Cheung

Department of Radiation Oncology
Sunnybrook Health Sciences Centre
University of Toronto

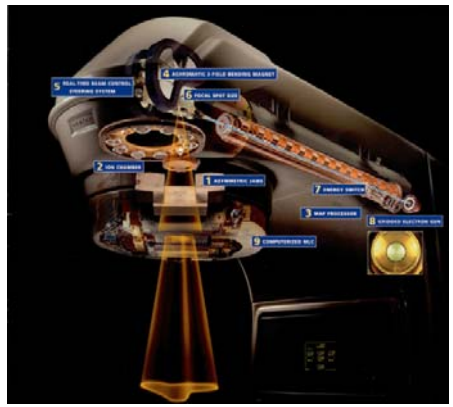
pHART3 Schema

Gold feducial marker insert

Helical Planning CT 1.5 mm slices



IMRT Plan



Treatment
On-Line Portal Imaging
35 Gy / 5 Fr
1 Fr / wk x 5 wk

Primary Outcome:	Acute GU/GI Toxicity
Secondary Outcomes:	Late GU/GI Toxicity at 3y
	Quality of Life (incl. ED)
	Positive 3y biopsy
	5y bDFS

Planning Objectives

<u>Target</u>

CTV D100% > 100%

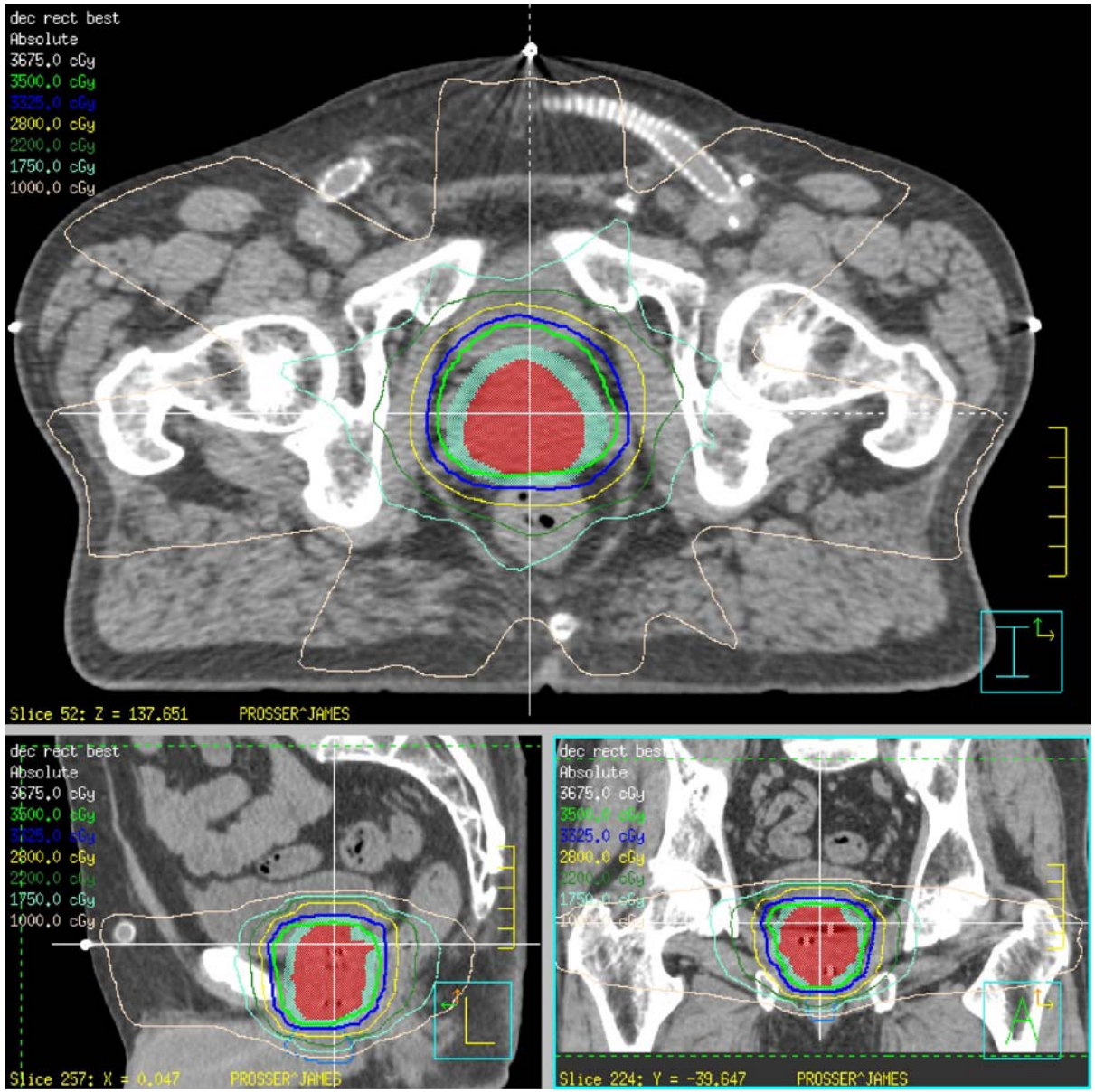
PTV D95% > 99%

<u>Normal Tissues</u>

Bladder V15% < 3300
V20% < 2800

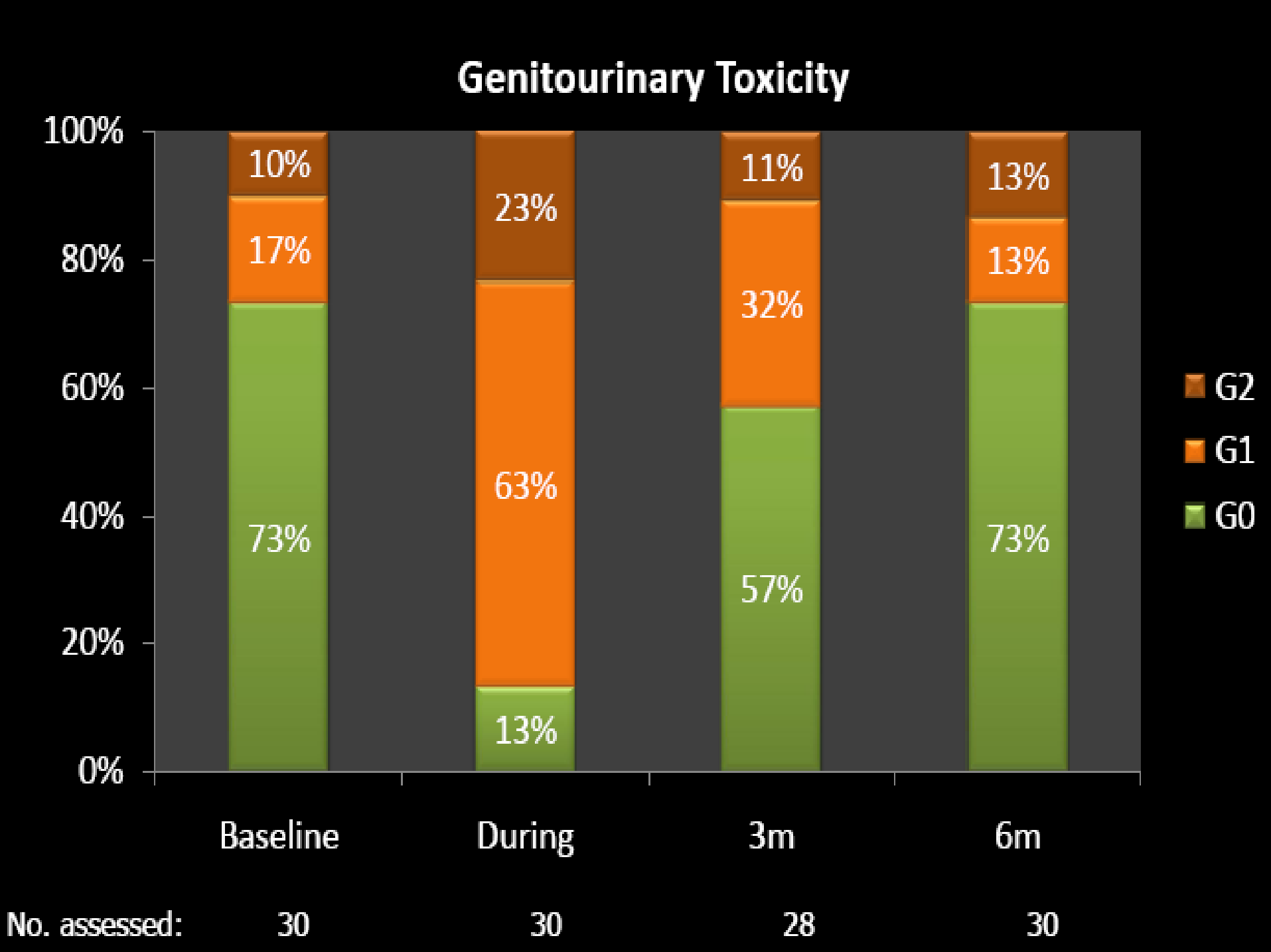
Rectum V15% < 3180
V20% < 2800

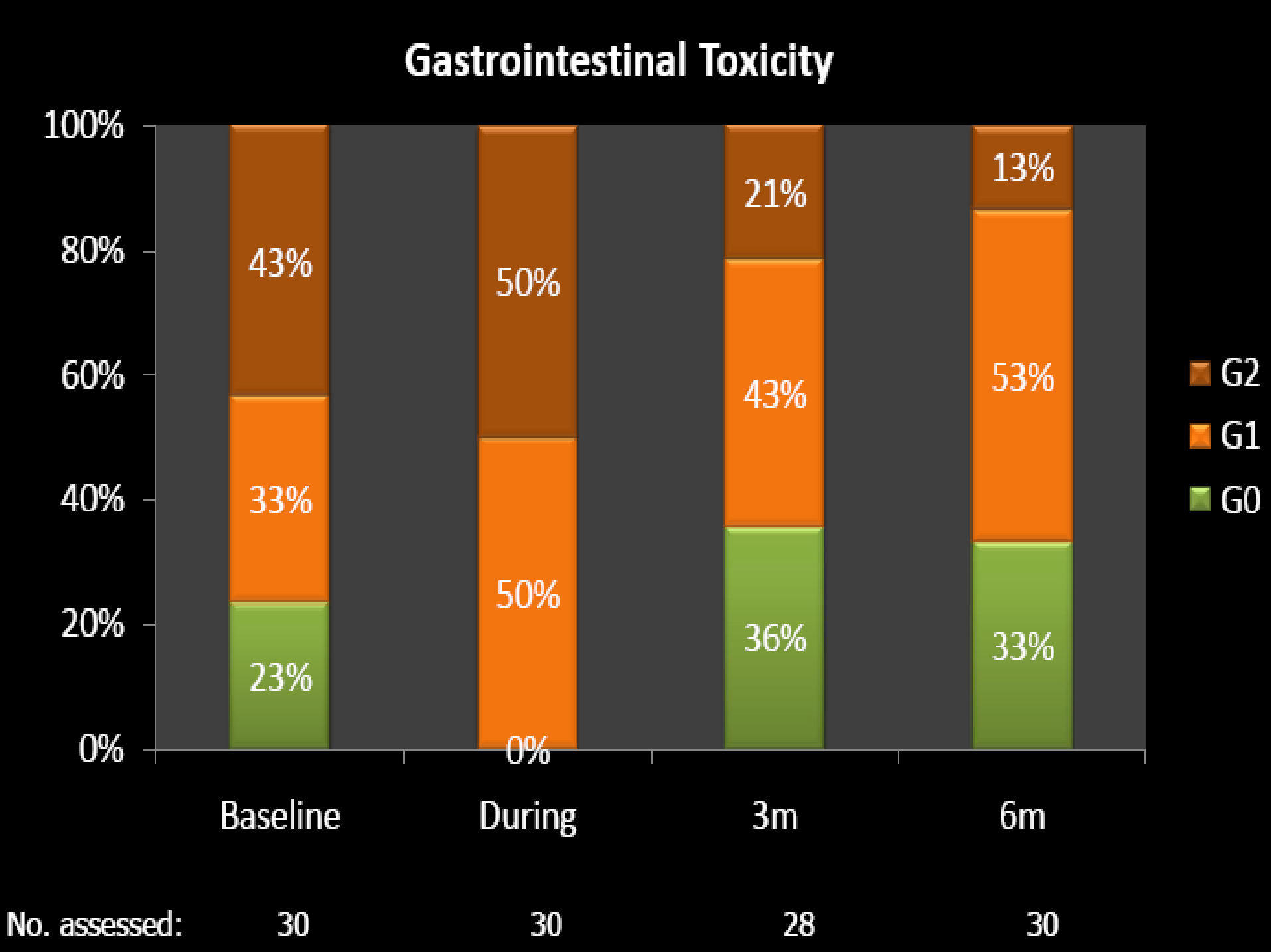
P Bulb V90% < 2000

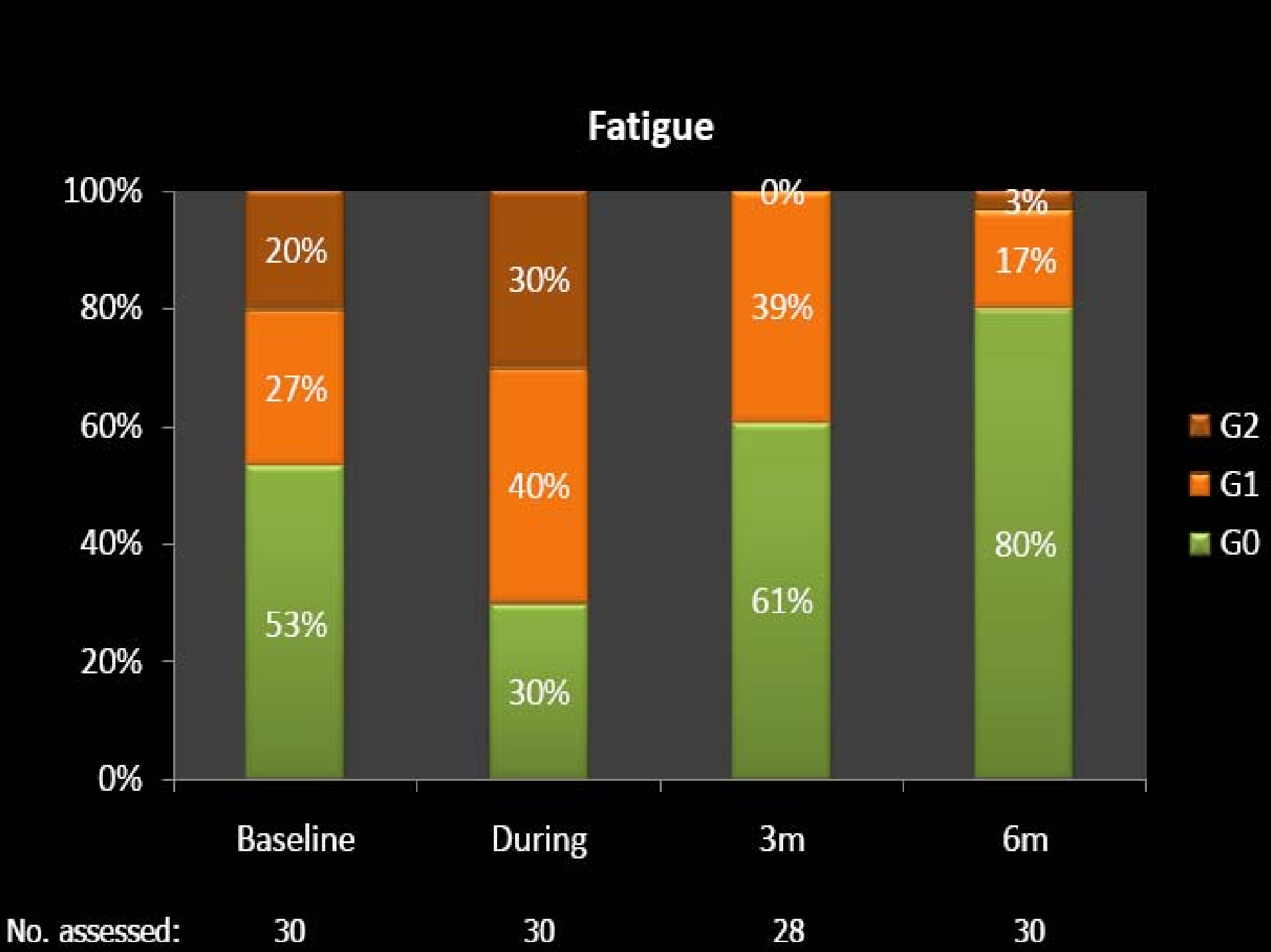


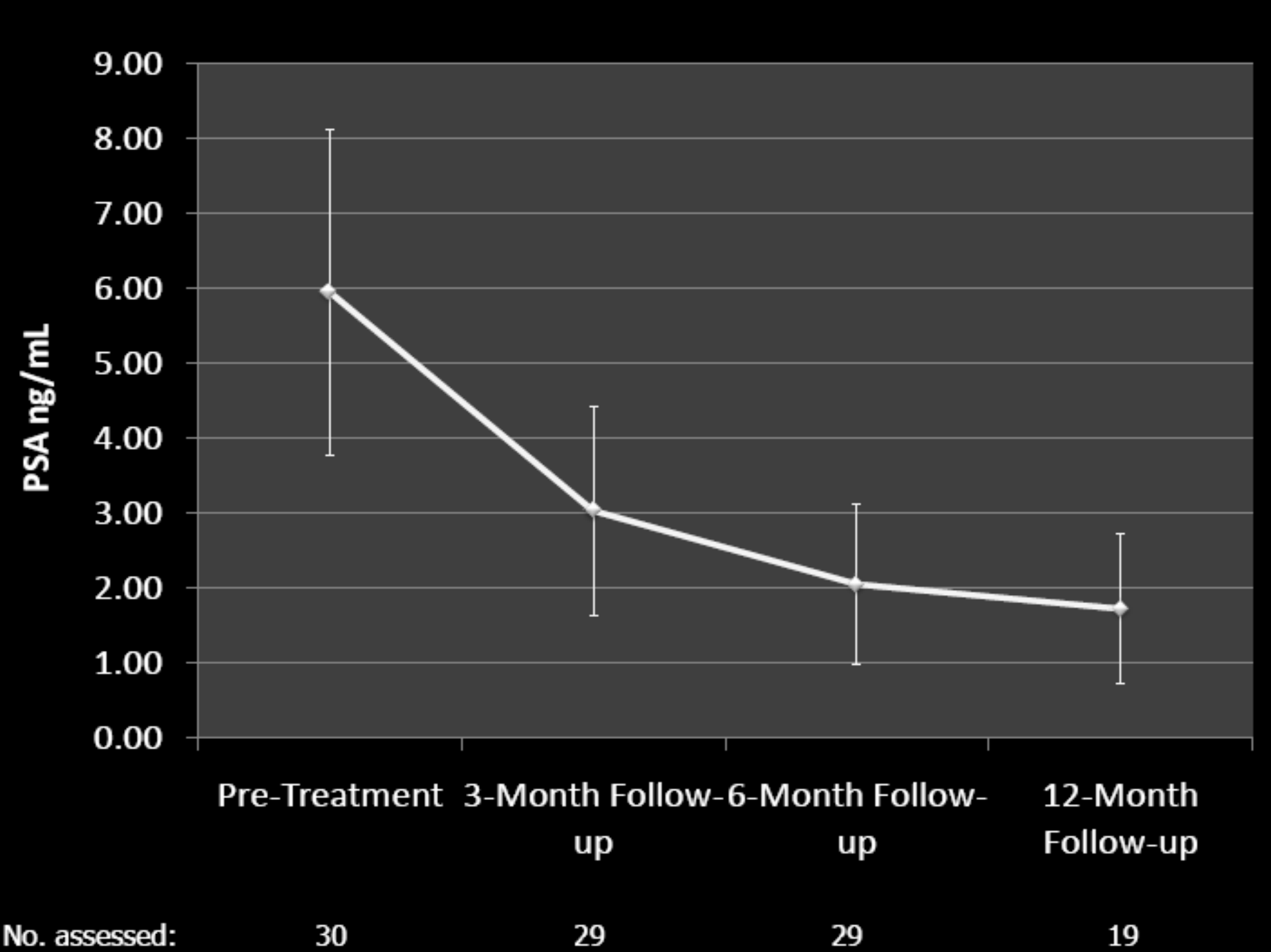
Accrual Statistics

- Opened October 2006
- As of Sept 2009:
  - 85 Consented
  - Median F/U ~ 2 y


Genitourinary Toxicity
100%
80%
60%
40%
20%
0%
10%
17%
73%
23%
63%
13%
11%
32%
57%
13%
13%
73%
G2
G1
G0
Baseline
During
3m
6m
No. assessed:
30
30
28
30


Gastrointestinal Toxicity
100%
80%
60%
40%
20%
0%
43%
33%
23%
50%
50%
0%
21%
43%
36%
13%
53%
33%
G2
G1
G0
Baseline
During
3m
6m
No. assessed:
30
30
28
30


Fatigue
100%
80%
60%
40%
20%
0%
20%
27%
53%
30%
40%
30%
0%
39%
61%
3%
17%
80%
G2
G1
G0
Baseline
During
3m
6m
No. assessed:
30
30
28
30


9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
PSA ng/mL
Pre-Treatment
3-Month Follow-up
6-Month Follow-up
12-Month Follow-up
No. assessed:
30
29
29
19

Virginia Mason HART Experience

- 33.5 / 5 / 1 wk
- 40 low risk patients
- Median follow-up 41 mo (21 – 67 mo)
- bDFS 90%

Toxicity	Grade 0	Grade 1-2	Grade 3
Acute GU	49%	49%	2%
Acute GI	61%	39%	0%
Late GU	55%	43%	2%
Late GI	63%	35%	2%
ED (new)			23%

Madsen BL. IJROBP 67(4):1099-1105; 2007

Stanford Cyberknife Experience

- 36.25 / 5f / 1-2 wks
- 41 low risk patients
- Median follow-up 33 mo (21 – 67 mo)
- bDFS 100%

Benign bounce 29%
G3 rectal less with qOD
(p = 0.003)

Toxicity	Grade 0	Grade 1-2	Grade 3
Acute GU (IPSS)	58%	0%	5%
Acute GI (EPIC)	37%	63%	0%
Late GU	71%	24%	5%
Late GI	85%	15%	0%
ED (new)			

King CR et al. IJROBP 73(4):1043-8; 2009

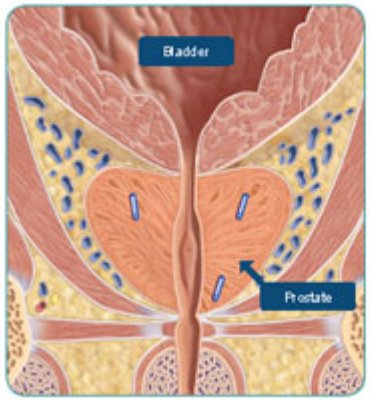
Naples Cyberknife Experience

- 35 / 5f / 5 days; LHRH 21/112
- 112 patients (82 G6-, 29 G7, 1 G9)
- Median follow-up 24 mo
- bDFS 97%

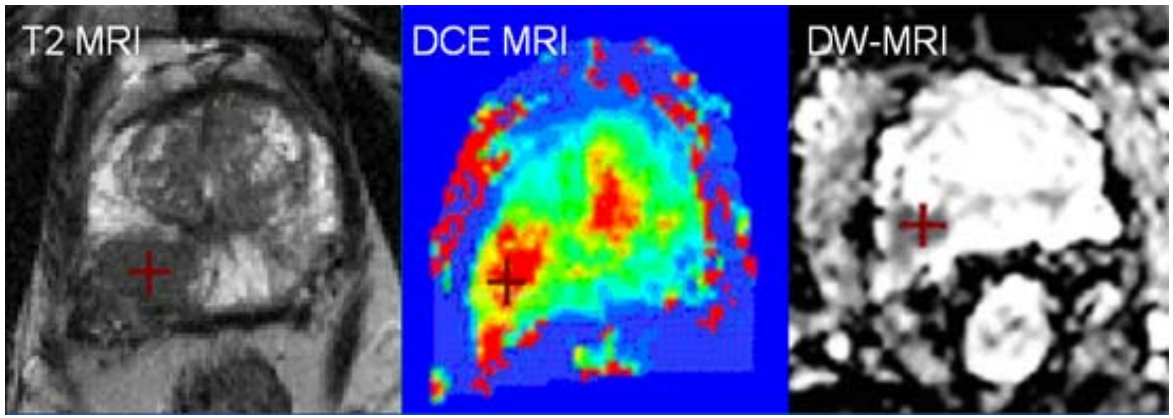
Toxicity	Grade 0	Grade 1-2	Grade 3
Acute GU (IPSS)			6%
Acute GI (RAS)			
Late GU			1%
Late GI			1%
ED (new)			82%

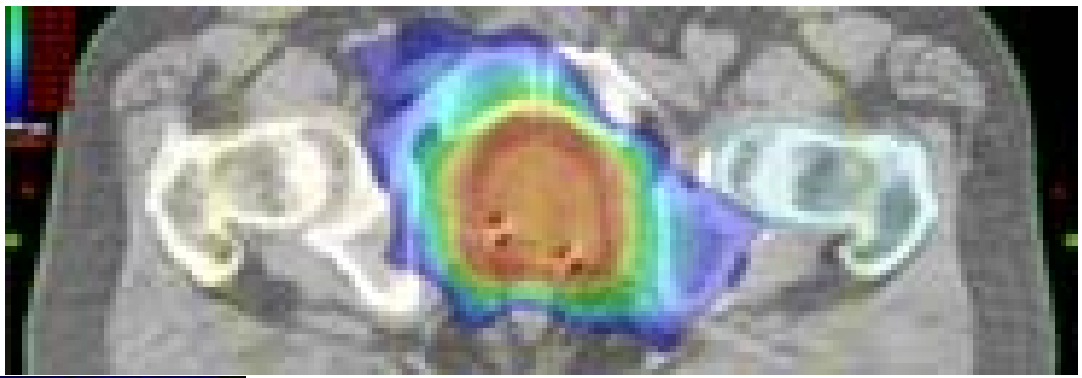
Friedland JL et al. Tech Ca Res Treat 8(5):387-92; 2009

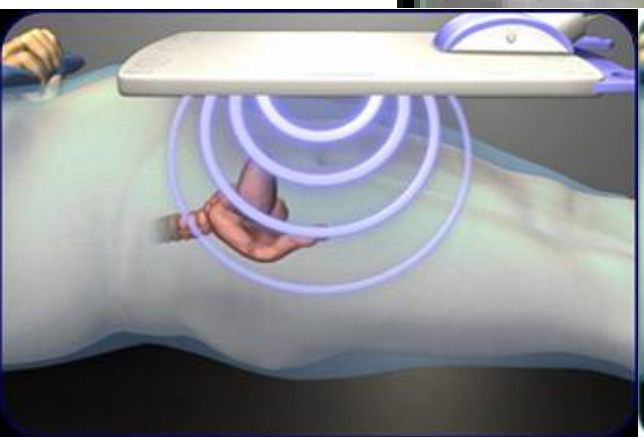
pHART3.3

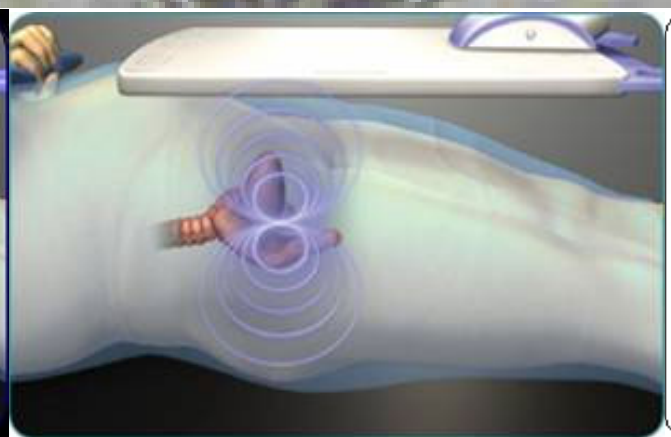


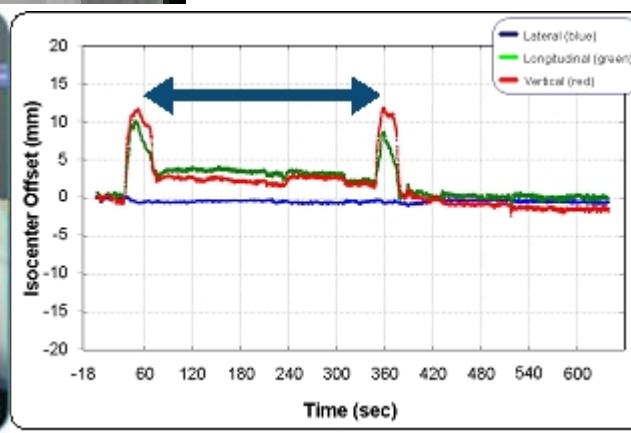
Three tiny Beacon® electromagnetic transponders are implanted into the prostate.











Seed Brachytherapy

SWOG 8794

pT3

Prostate Cancer

N=473
410 eligible

RANDOMIZE

Adjuvant RT

No RT*

Outcomes

bNED

- Cause specific survival
- Overall survival
- Freedom from Distant Metastasis

* 32% received delayed RT

Thompson et al JAMA 2006

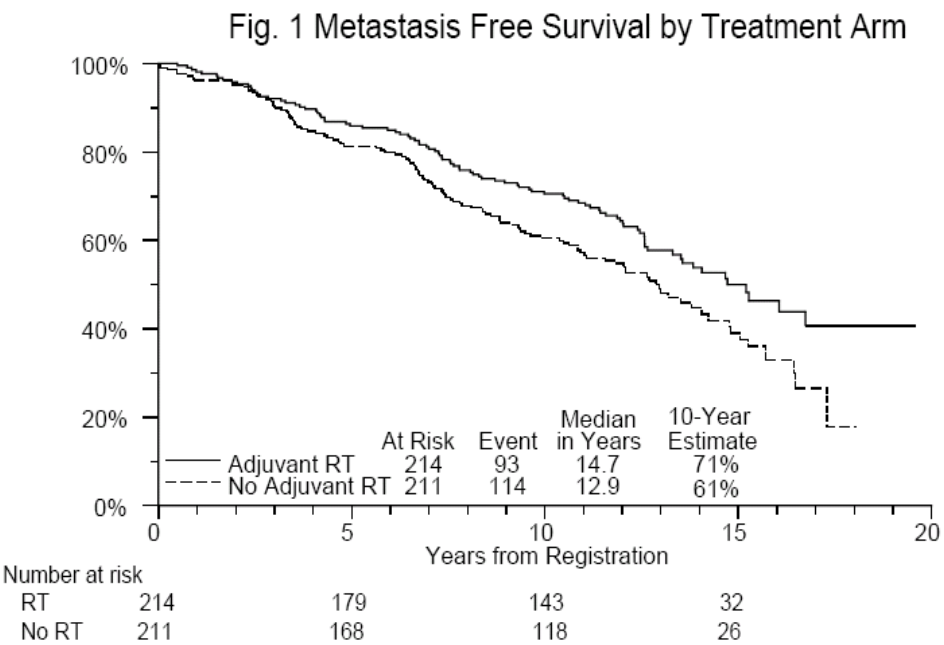
Adjuvant RT for pathologic T3 prostate cancer (SWOG 8794)

	Adjuvant RT	Observation	HR	P value
10-yr bNED	47%	23%	0.51 (0.39-0.67)	<0.0001
10-yr FFDM	71%	61%	0.80 (0.57-1.11)	0.17
10-yr OS	74%	63%	0.76 (0.54-1.07)	0.11

Thompson et al JAMA 2006

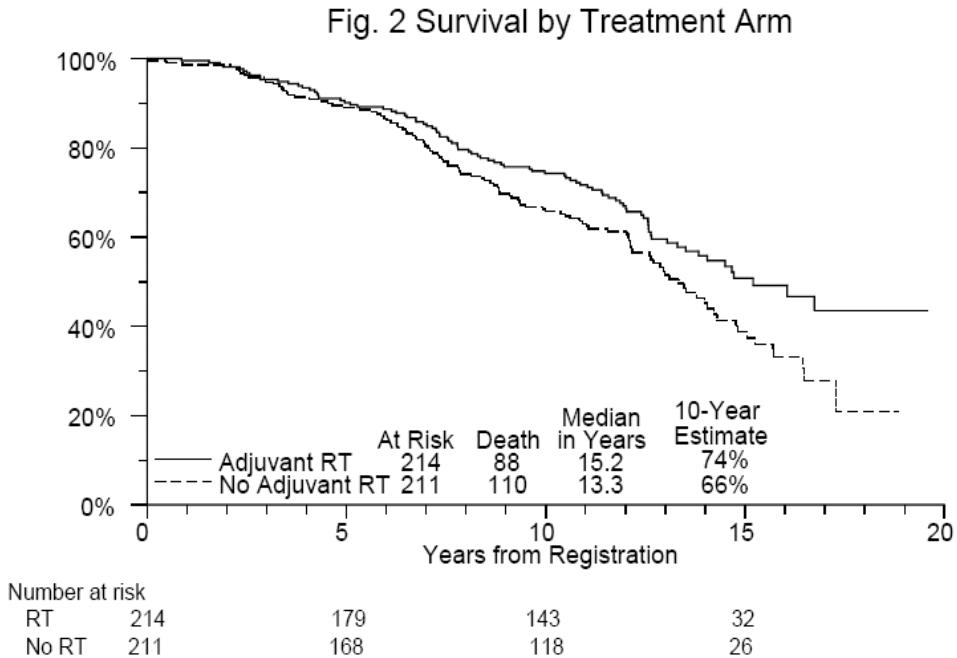
mFU = 10 years

SWOG 8794: mFU 12 years



HR 0.71 (95% CI 0.54 – 0.94), p = 0.016

HR 0.72 (95% CI 0.55 – 0.96), p = 0.023

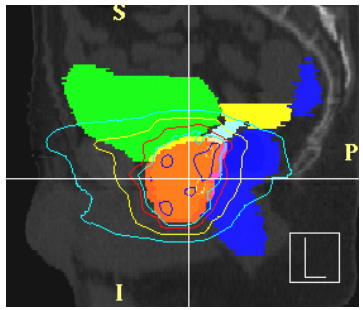


Thompson AUA, in press J Urol 2008

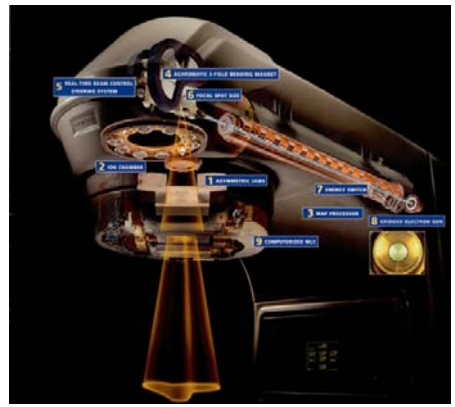
pHART4 Schema

Gold feducial marker insert

Helical Planning CT 1.5 mm slices



IMRT Plan

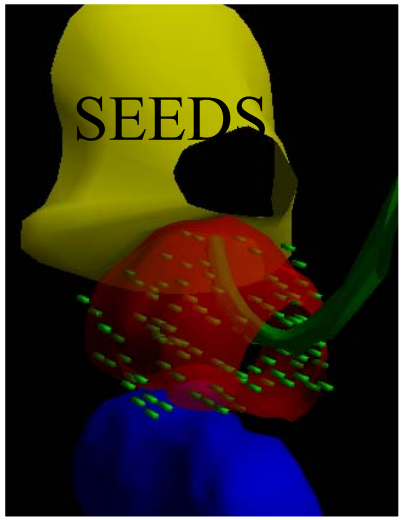


Treatment
On-Line Portal Imaging
51 Gy / 17 Fr
3.5 wk

Primary Outcome:	Acute GU/GI Toxicity
Secondary Outcomes:	Late GU/GI Toxicity at 3y
	Quality of Life (incl. ED)
	5y bDFS

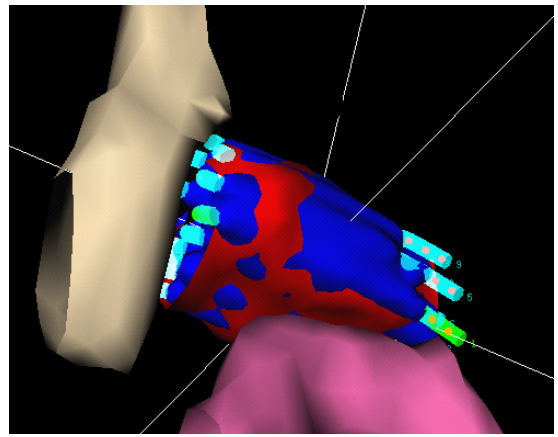
Seed Brachytherapy

Prostate Brachytherapy



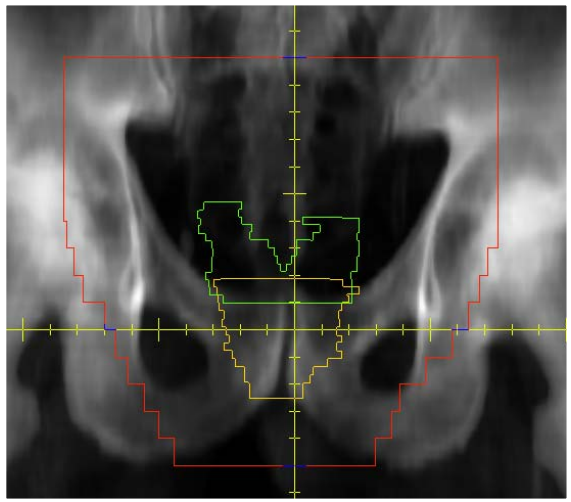
Permanent

Temporary



Monotherapy

Combined with External Beam



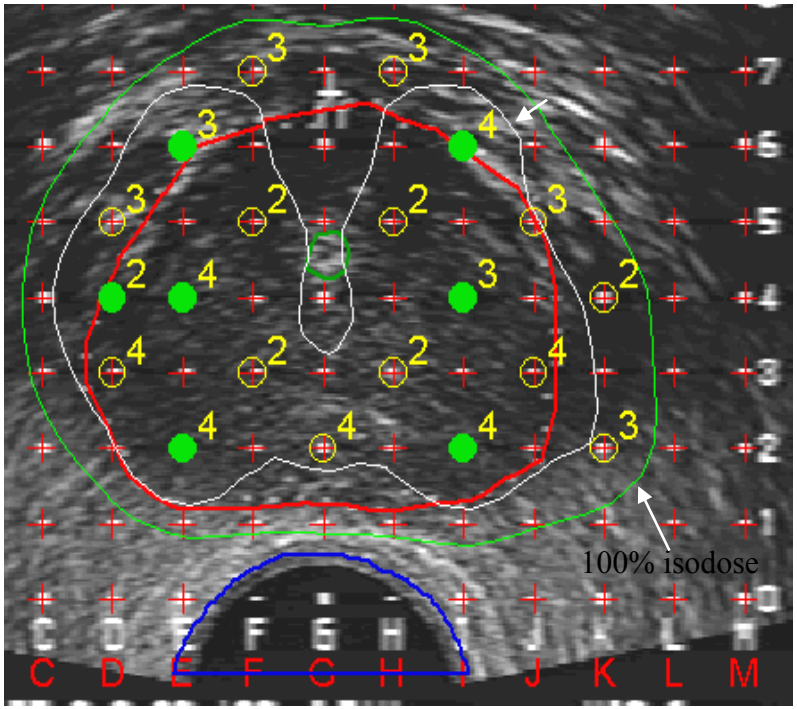
Low Risk Cancer

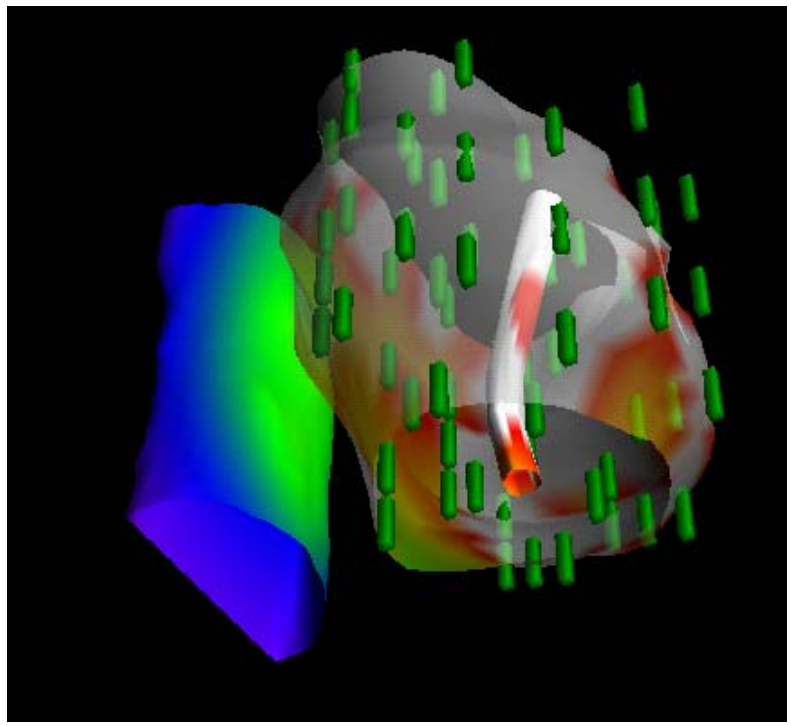
IPSS < 15, Vol < 50 cc

Intermediate / high risk

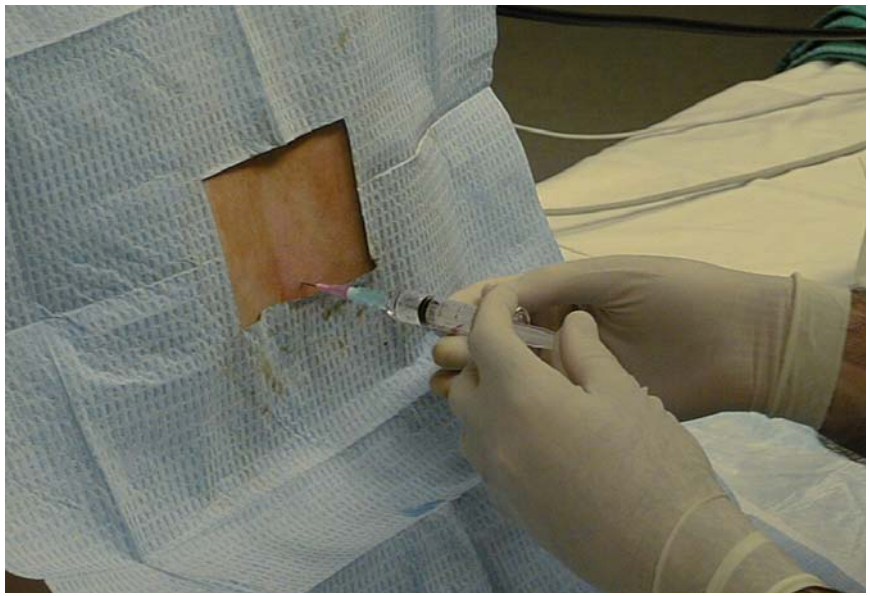
IPSS < 15, Vol < 50

Pre-Implant Planning





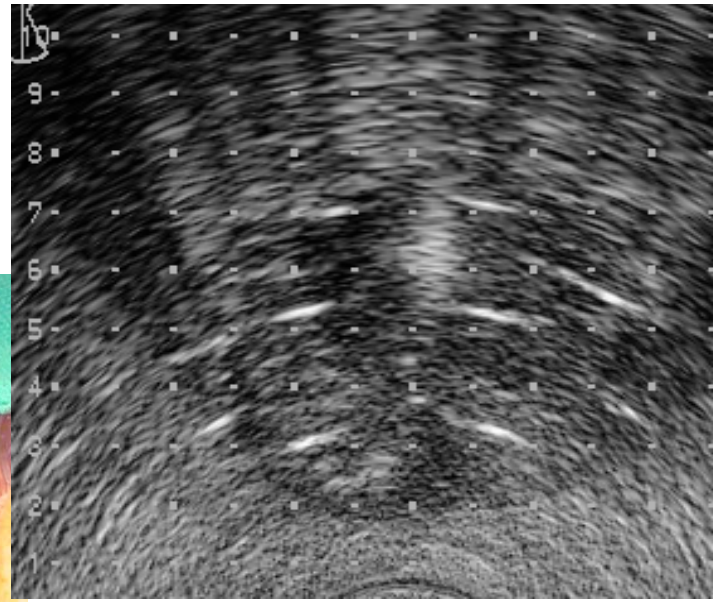
Anaesthesia and Positioning

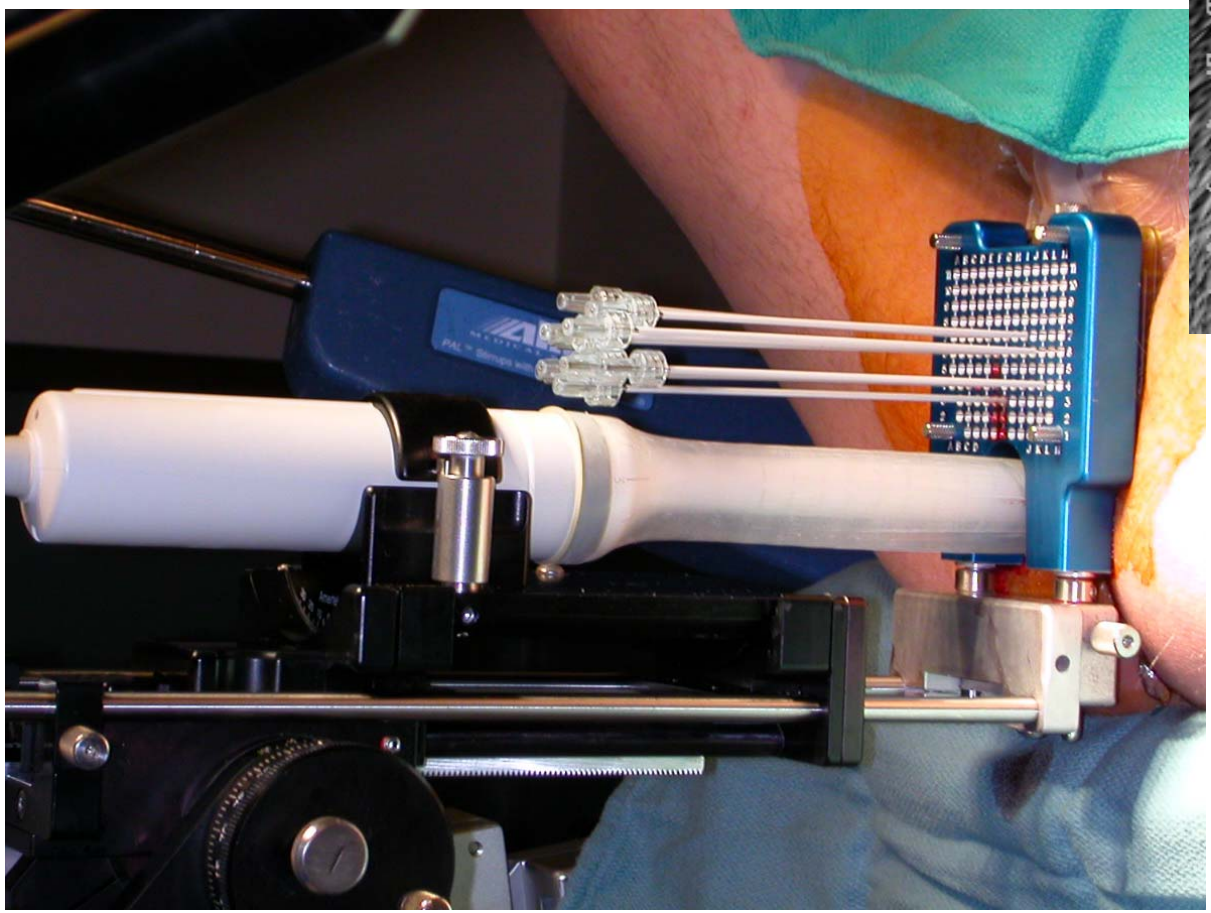


Spinal

Positioning

Needle Insertion





Seed Brachy Post-Implant Day 1

Thundering Waters, 11th Hole, Niagara Falls

Seattle Prostate Institute

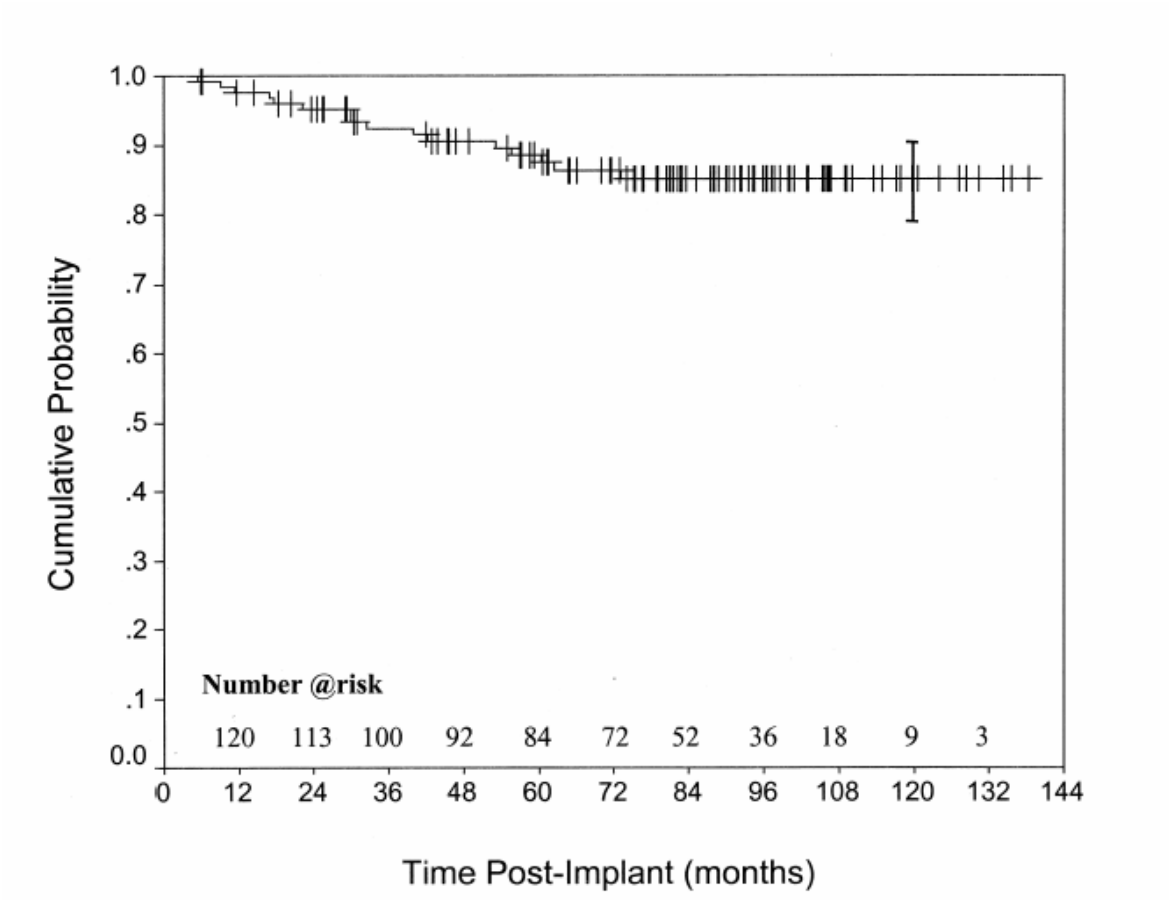


Fig. 1. Prostate-specific antigen progression-free survival for all 125 study patients.

Grimm,et al. Int J Radiat Oncol Biol Phys 51:31-40, 2001

Canadian Data

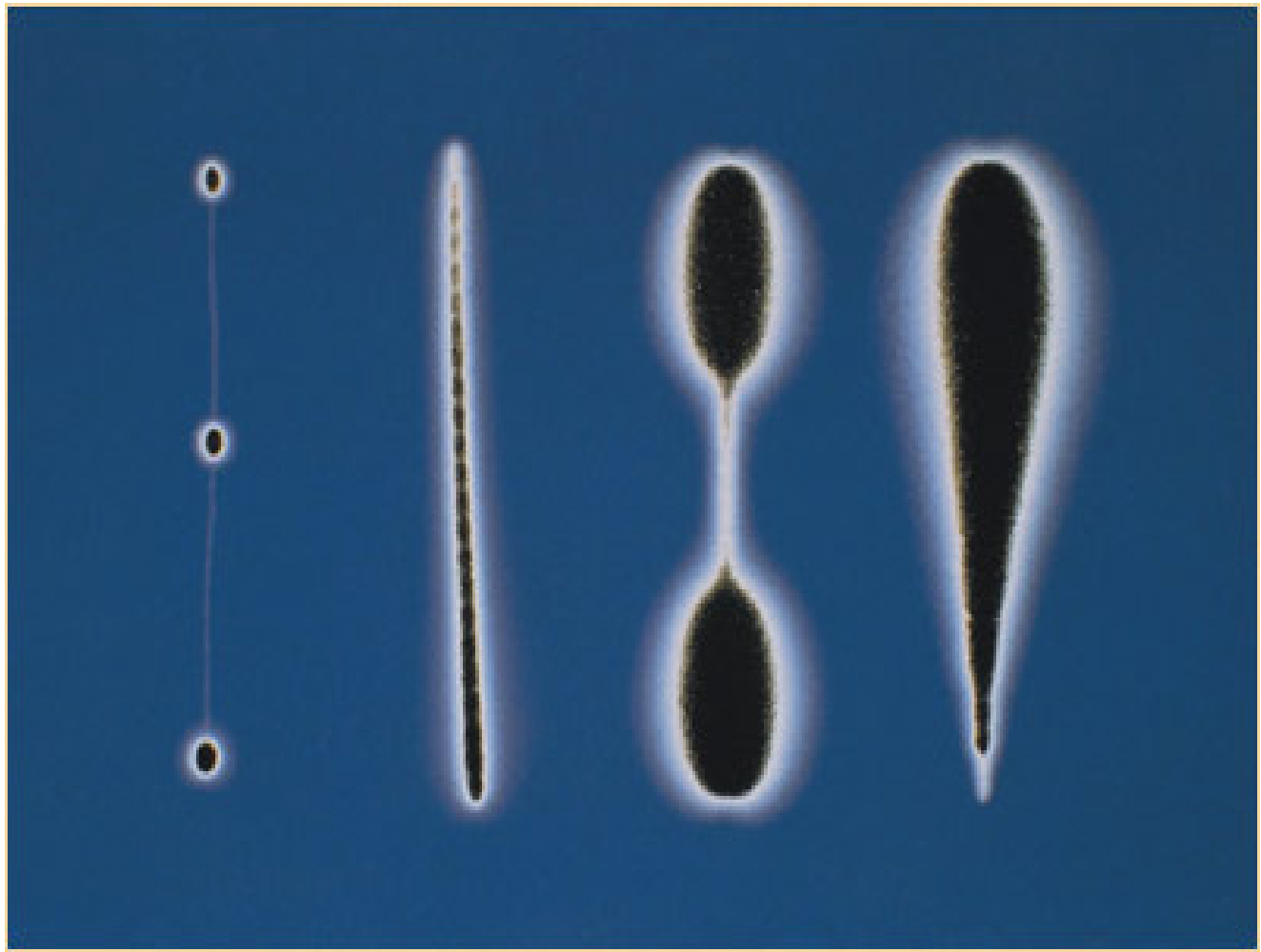
Centre	Started	5-yr bDFS
Quebec	1995	92%
Sunnybrook	1998	94%
BCCA	1998	96%
PMH	1999	95%

Disease Control (n=201)

- Median Follow-up = 69 months (4-102 months)
- 5-year Disease-Free Survival = 94%
- 18 failures
  - 5 distant metastases (2.5%)
    - 2 deaths from disease
  - 5 local recurrence (2.5%)
    - 3 salvage prostatectomy
    - 1 salvage cryotherapy
  - 8 biochemical failure only (nadir+2) (4%)

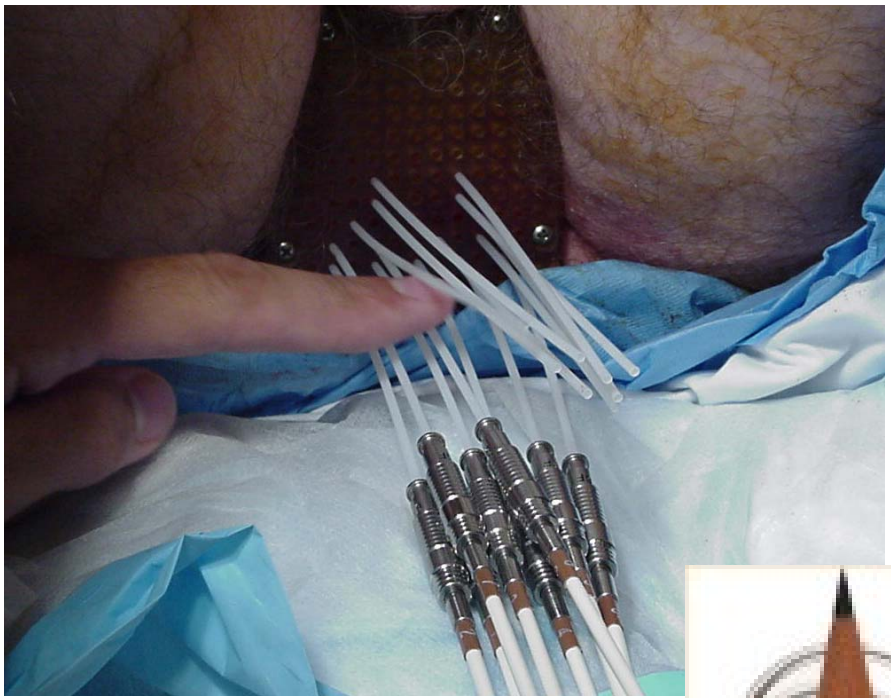
HDR Brachytherapy

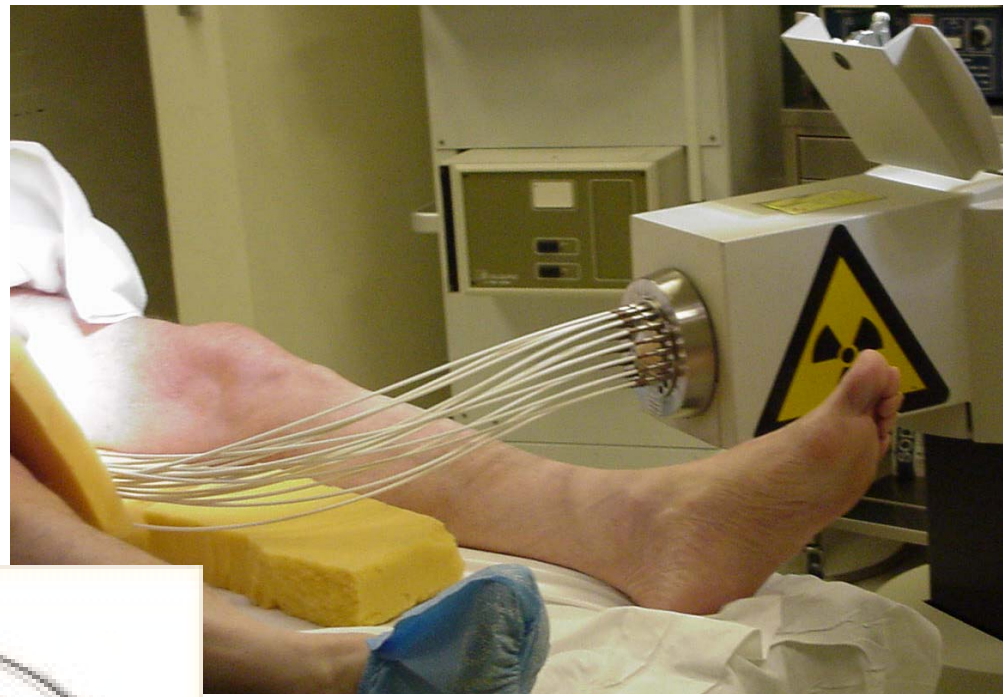
HDR Stepping Source



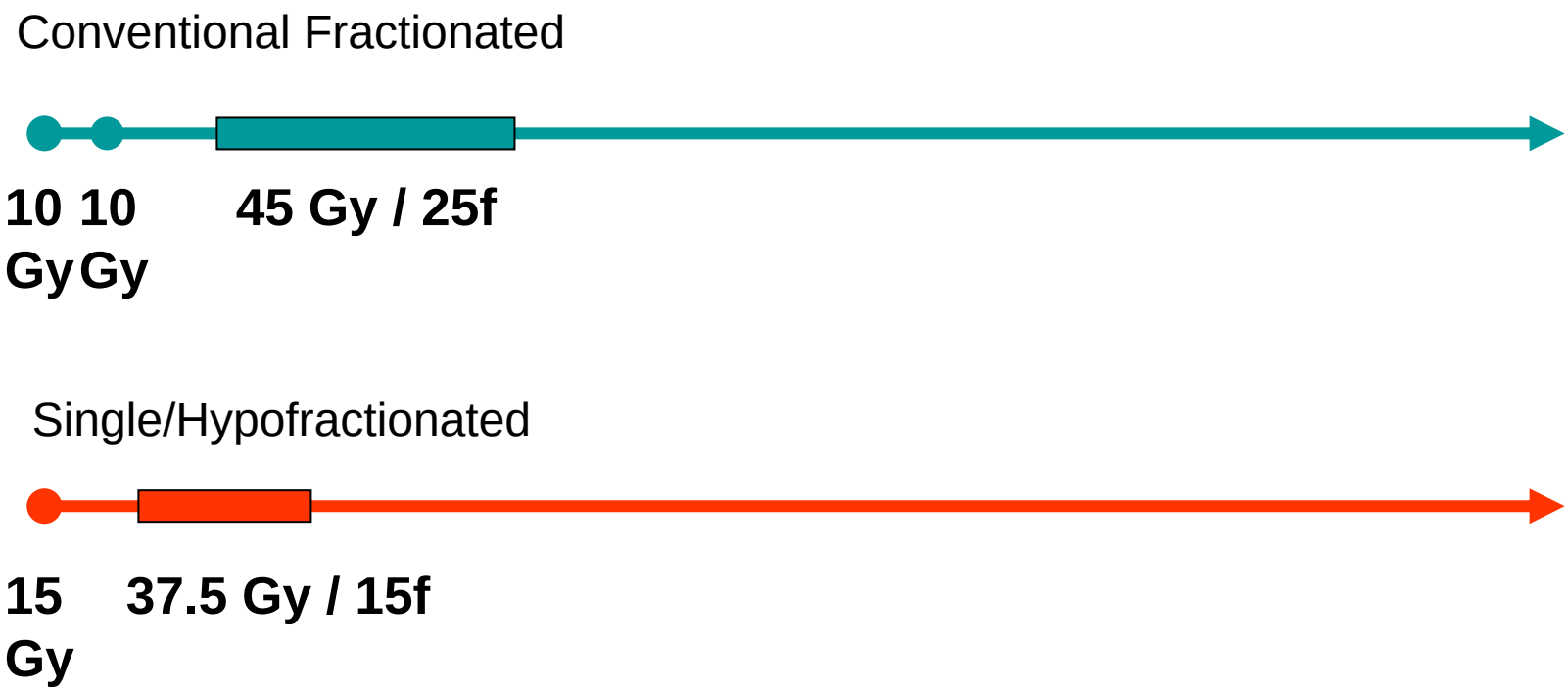
Dose Distributions along single catheter

Treatment Administered



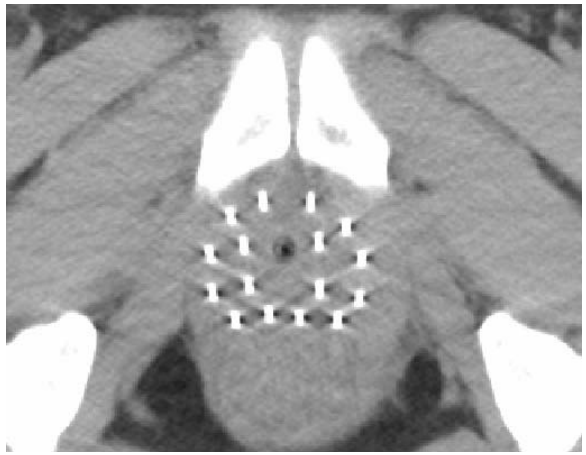


Study Schema

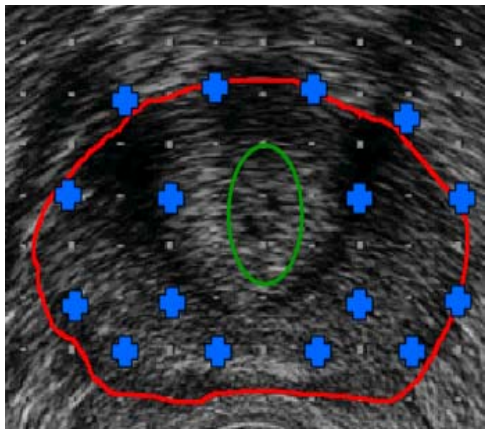


HDR Procedure: Outpatient, Spinal Anaesthesia

Catheter Insertion



CT Planning

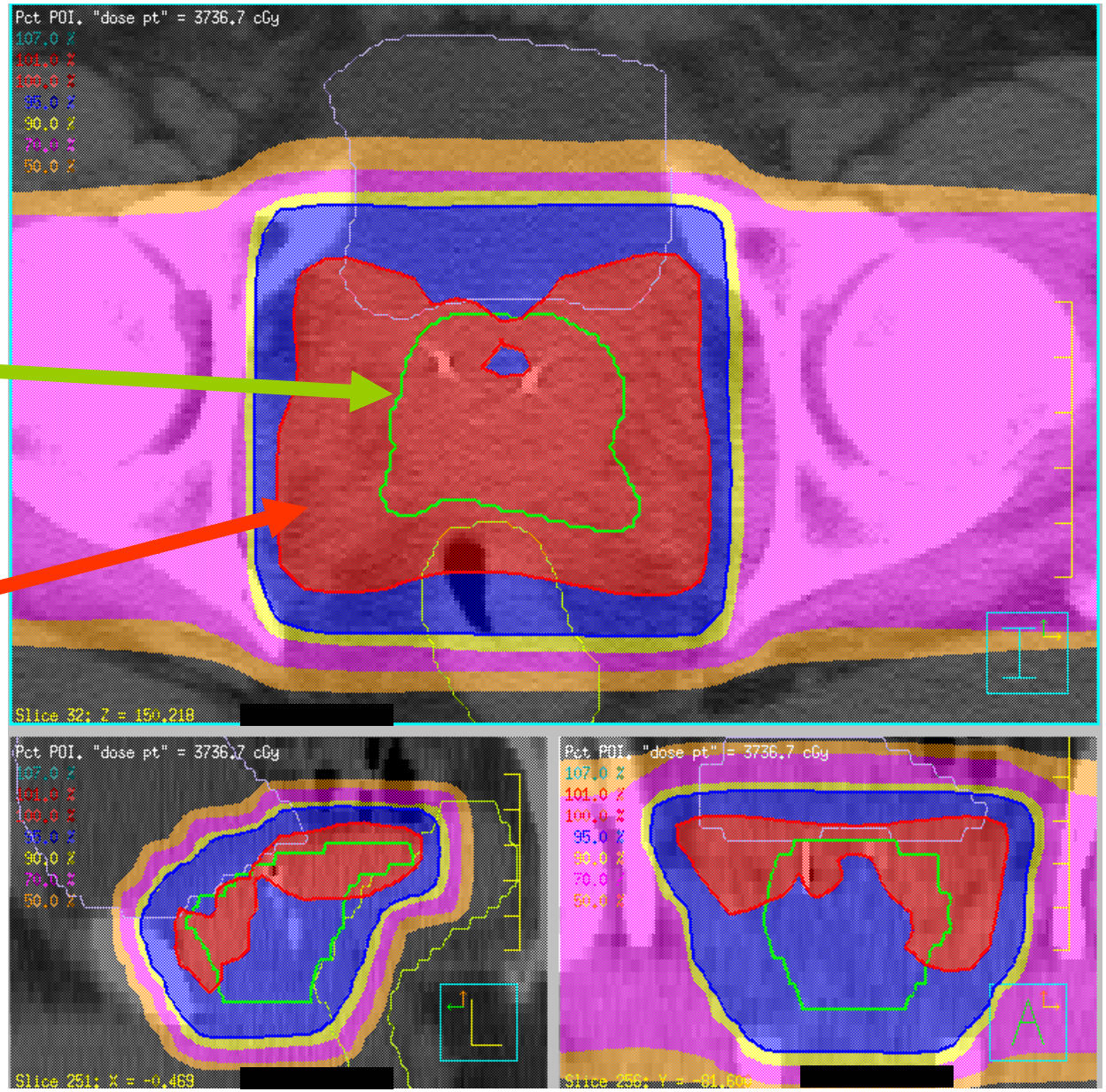


Dose Optimisation

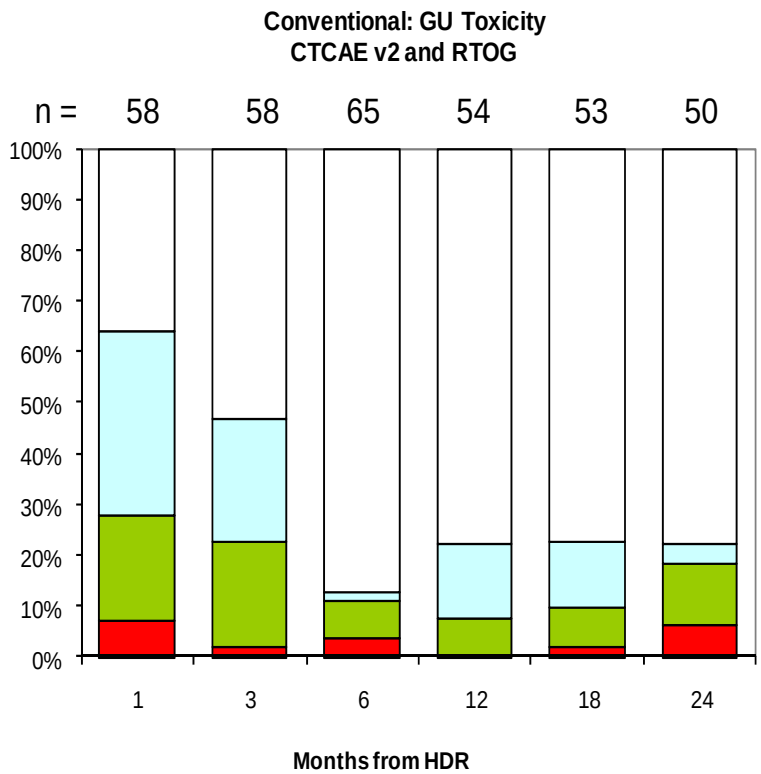
External Beam RT

Prostate

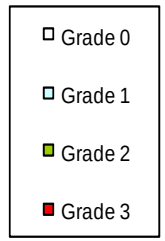
High Dose Region

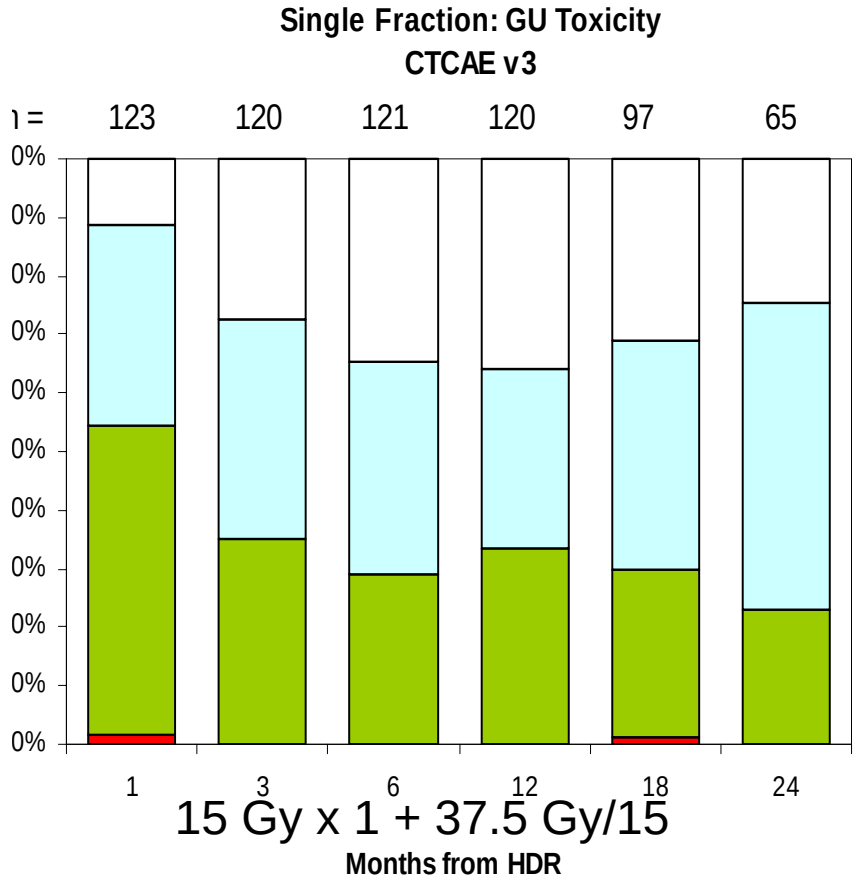


GU Toxicity



10 Gy x 2 + 45 Gy/25

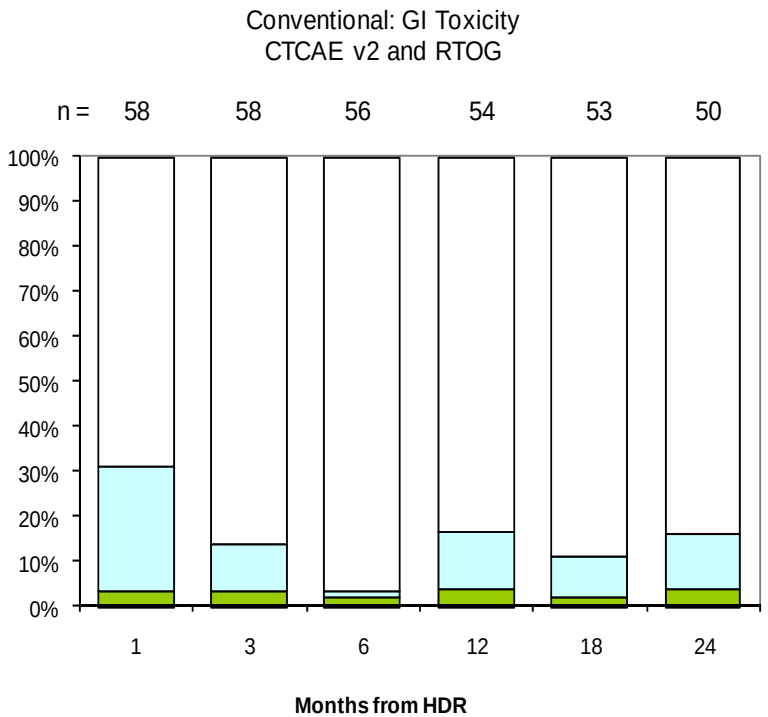




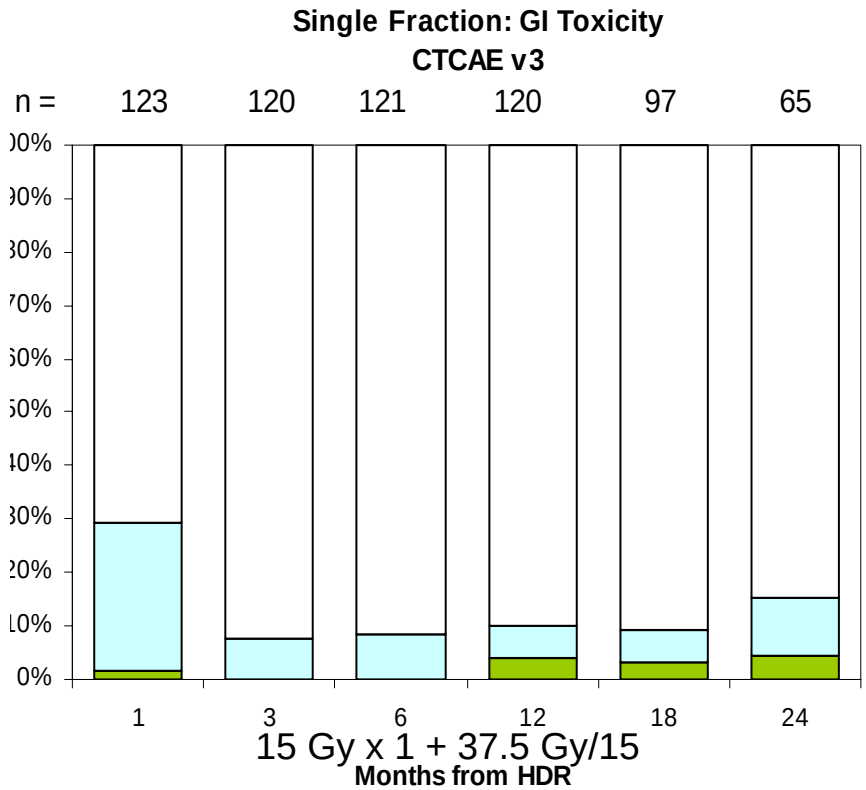
15 Gy x 1 + 37.5 Gy/15

Less Acute Grade 3 with Single Fraction
No difference in late effects, but different toxicity scales

GI Toxicity



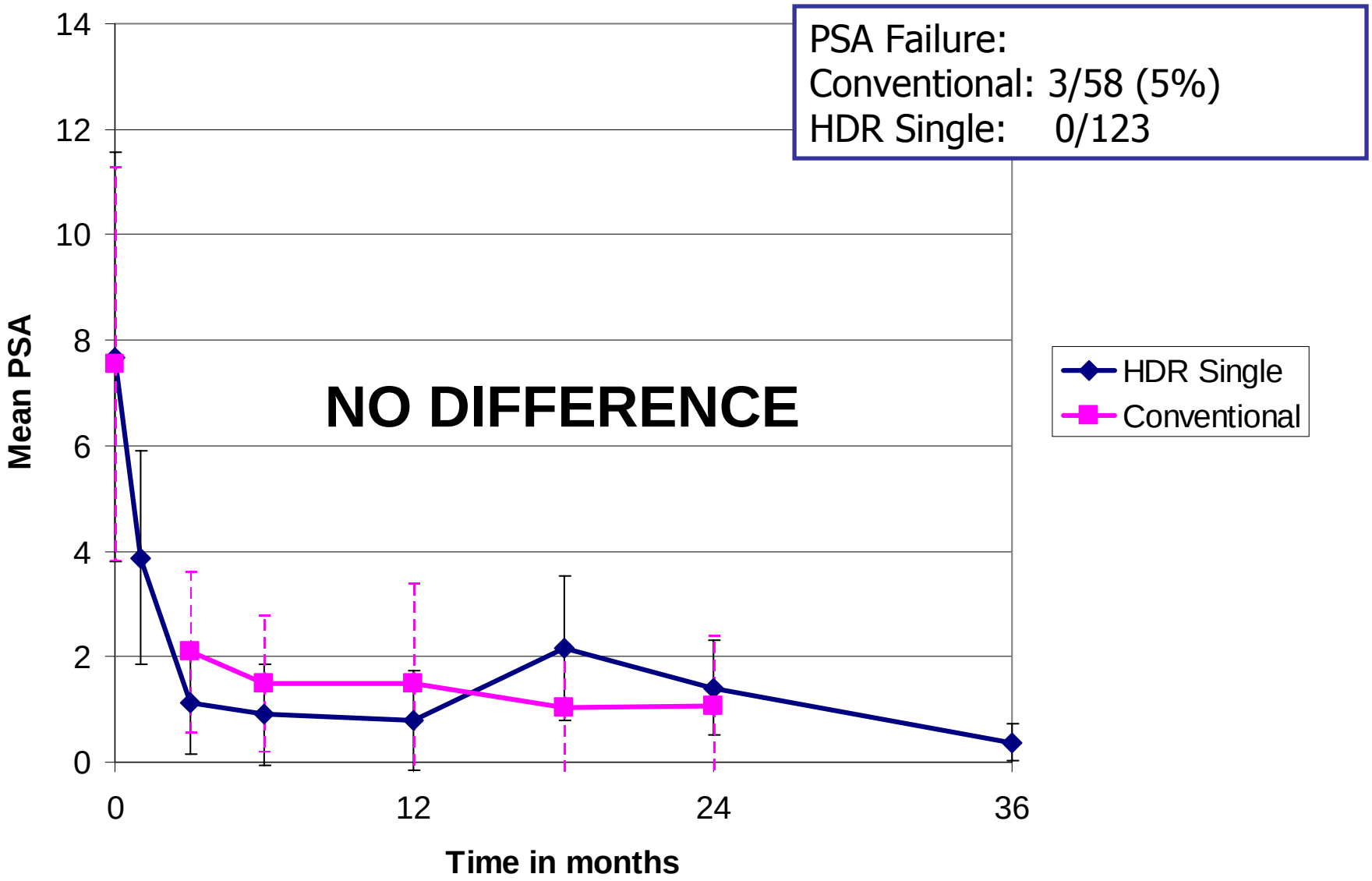
10 Gy x 2 + 45 Gy/25



15 Gy x 1 + 37.5 Gy/15

Minimal GI toxicity with either protocol
< 5% Grade 2 GI toxicity at 2 years

Efficacy- PSA



Efficacy: 2 year biopsy

	Conventional n=60	**Single HF n=123**	p
Negative	36 (73%)	24 (73%)	NS
Indeterminate	12 (25%)	8 (24%)	NS
Positive	1 (2%)	1 (3%)	NS
Total	49	33	

McGill HDR Experience

- 10 Gy + 50/20 EBRT (CTV + 7mm)
- Intermediate risk pr ca: n=137, 100 with FU > 2 y
- mFU = 59mo
- Biopsy: 95% negative (35/37)
- bDFS: 90% (7% mets)

Toxicity	Grade 2	Grade 3
Acute GU	n/r	0%
Acute GI	n/r	0%
Late GU	2%	1%
Late GI	2%	1%
Erectile Dys		31%

Cury F et al., CARO 2009 abstract 34

HDR RCTs

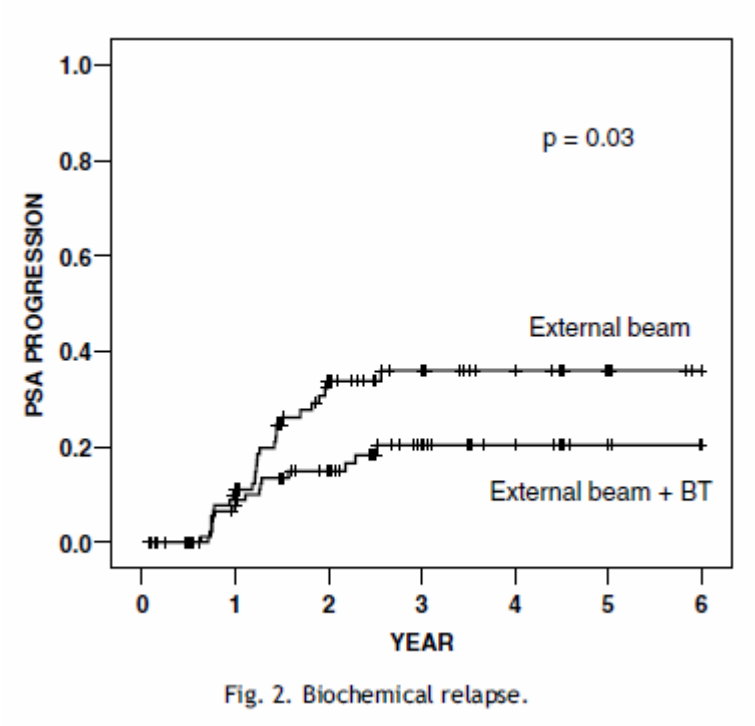
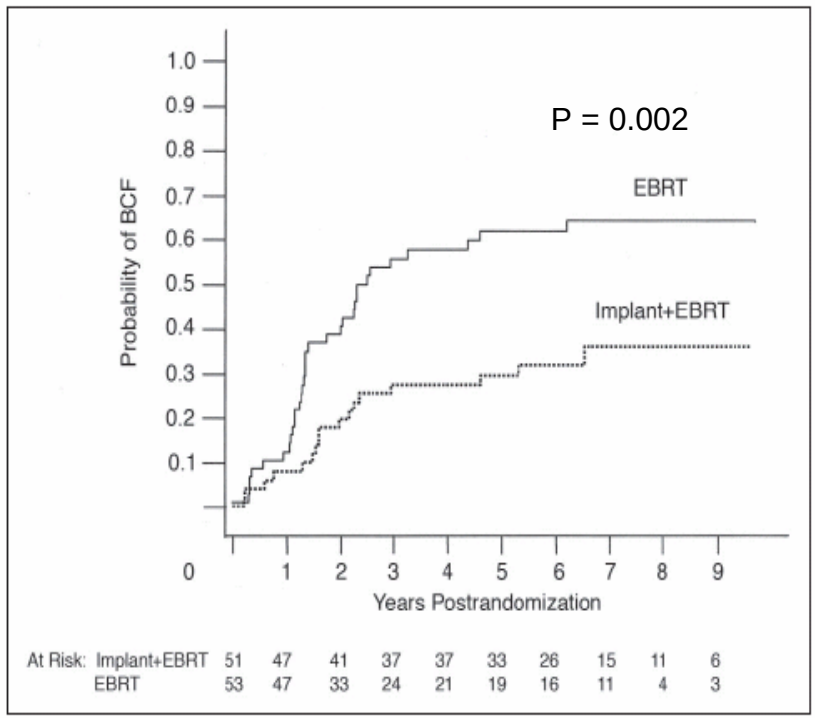


Fig. 2. Biochemical relapse.



Hoskin et al Radioth Oncol 2007
55/20 vs 36/13 + 17/2 HDR boost
N = 220, mFU = 30 mo

Sathya et al J Clin Oncol 2005
66/33 vs 40/20 + 35 Gy / 48 hrs
N=104, 60% HR, 40% IR
mFU = 8.2 y

HDR RCTs

Guix et al., Am Brachy Soc 2009

- 445 pts, mFU 55mo
- 76/38 vs 46/23 + 16/2 HDR boost

	EBRT n=223	**HDR Boost n=222**	p
Grade 2 late GI	12.5%	2.7%	<0.001
Grade 3 late GI	0.4%	0%	NS
Grade 2 late GU	8.5%	8.5%	NS
Grade 3 late GU	0%	0%	NS
5y BDFS Int Risk	92%	97%	
5y bDFS High Risk	91%	96%	< 0.06

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

Burden of Problem

Extent of disease	Incidence	
Localized	17,225	(85%)
Metastatic	3,151	(15%)

Skarsgard D, Tonita J. Ca Cause Control 2000; Cdn Cancer Stats 2006

Burden of Problem

Localized disease	Incidence	5 yr Biochemical Failure At risk (n)	Post-RT (n)
Low risk	5391 (31%)	970	485
Intermediate	4852 (28%)	1941	970
High risk	6982 (41%)	1745	873

30% overall (2570 post-RT)

Skarsgard D, Tonita J. Ca Cause Control 2000; Cdn Cancer Stats 2006

RCTs Timing of ADT Post Radical RT

TROG Timing of Androgen Deprivation (TOAD)

- ongoing

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

Skarsgard D, Tonita J. Ca Cause Control 2000; Cdn Cancer Stats 2006

ASCO Guidelines

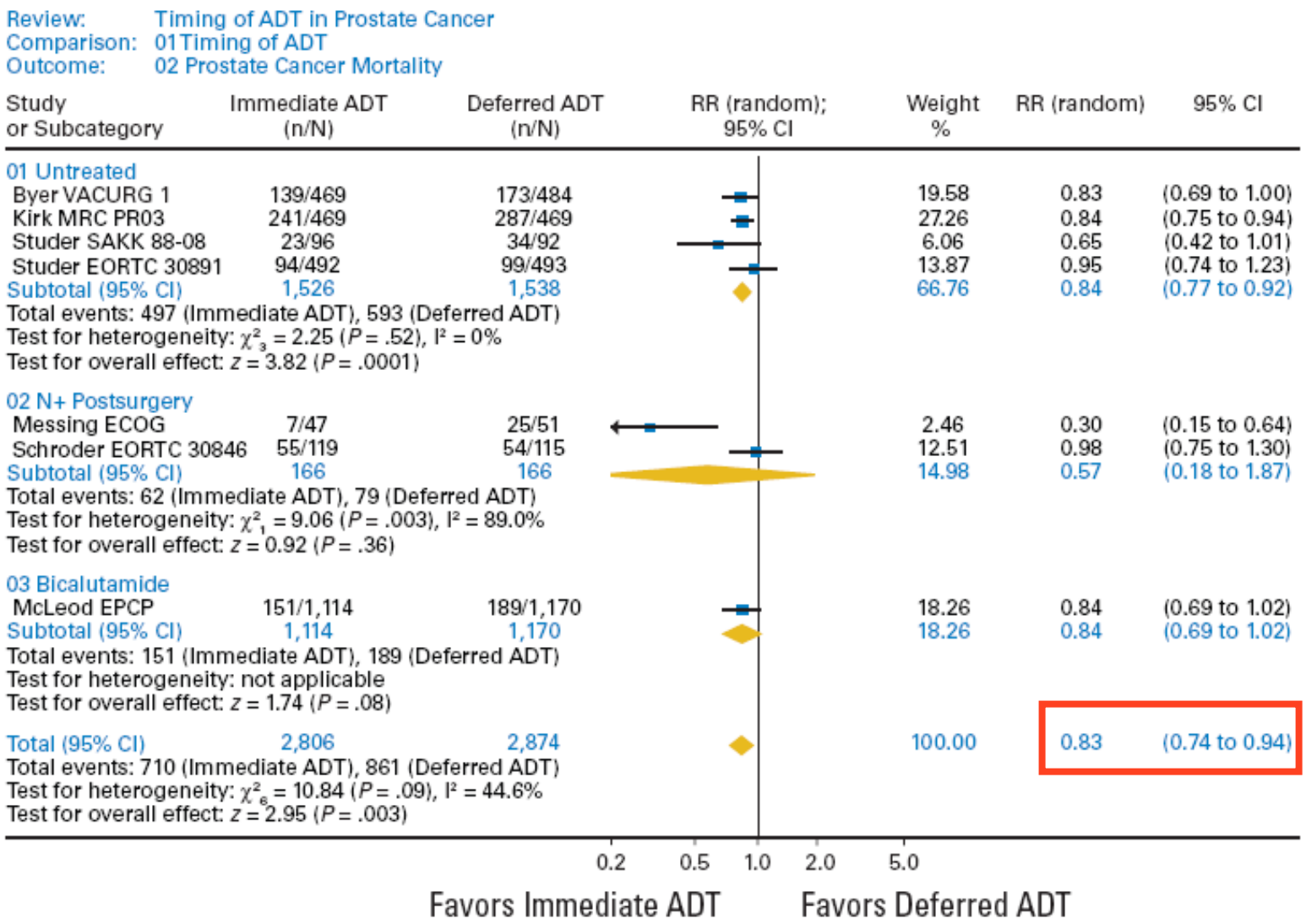
"Until data from studies using modern medical diagnostic/ biochemical tests and standardized follow-up schedules become available, no specific recommendations can be issued regarding the question of early versus deferred ADT. A discussion about the pros and cons of early versus deferred ADT should occur."

Loblaw DA et al
J Clin Oncol 2004;14: 2927- 41

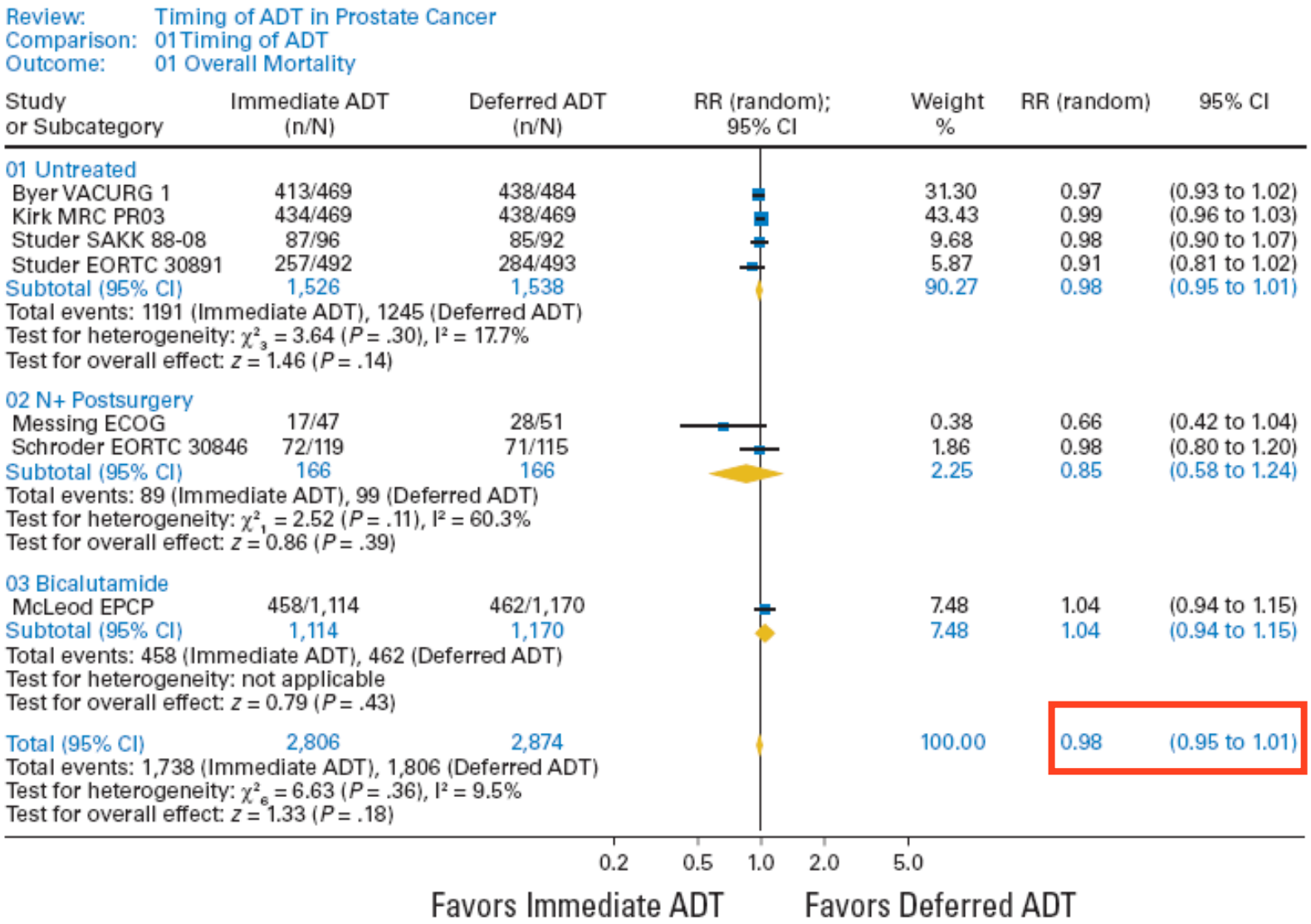
"In metastatic or progressive PCa, immediate versus symptom-onset institution of ADT results in a moderate decrease (17%) in relative risk (RR) for PCa-specific mortality, a moderate increase (15%) in RR for non–PCa-specific mortality, and no overall survival advantage. Therefore, the Panel cannot make a strong recommendation for early ADT initiation.... For patients electing to wait until symptoms for ADT, regular monitoring visits are indicated."

Loblaw DA et al
J Clin Oncol 2007; 25(12): 1596-1605

Prostate Cancer Mortality



Overall Mortality



Unanswered Questions

1. *What are the benefits of immediate ADT following radiation therapy*
   - *Can we extrapolate from Watchful Waiting / Metastatic patient data?*

2. *What is the magnitude of detriment on QOL?*

ADT Side Effects

- Vasomotor symptoms
- Decreased libido → erectile dysfunction
- Decreased muscle mass
- Decreased energy
- Metabolic syndrome
- Osteopenic effects

The NEW ENGLAND JOURNAL of MEDICINE

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.

- 50,613 men with Prostate Cancer in SEER database 1992-1997
- 19% vs 12% had (any) fracture (living >5 yr)
  — bone metastases not excluded

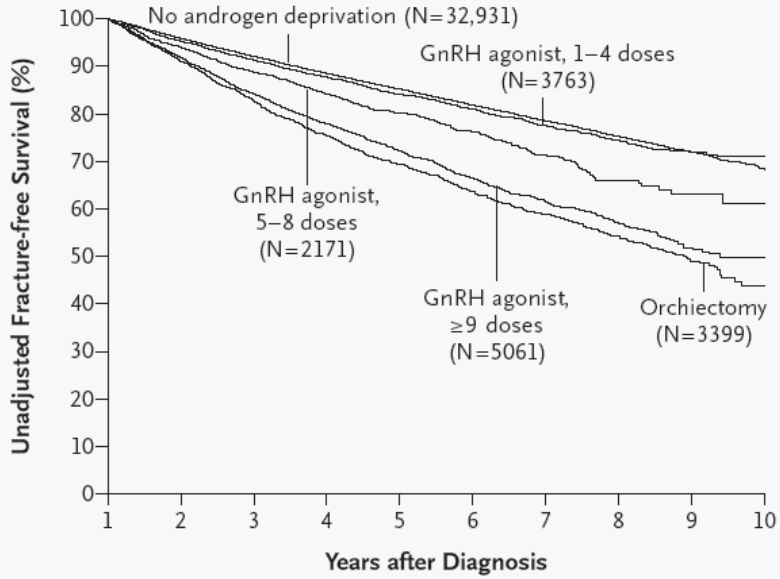


Figure 1. Unadjusted Fracture-free Survival among Patients with Prostate Cancer, According to Androgen-Deprivation Therapy.

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.

VOLUME 24 · NUMBER 27 · SEPTEMBER 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Diabetes and Cardiovascular Disease During Androgen Deprivation Therapy for Prostate Cancer

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

- 73,197 men > 66 yr in SEER, Medicare
- 1/3 had LHRH agonist
- Excluded prevalent M1, DM, CAD

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

In 10 years 9% 11% Events per 1,000 Person-Years 3% 4%

	Incident Diabetes			Incident CHD			Myocardial Infarction			Sudden Cardiac Death		
Treatment	No.	95% CI	*P**	No.	95% CI	*P**	No.	95% CI	*P**	No.	95% CI	*P**
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 62.4	< .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, gonadatropin-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.

Prognostic Factors

Predictors	Overall Mortality	Cause specific Mortality	Distant Metastases
PSAdt (< 6months)	D'Amico 2006	Kim-Sing 2004	Pound 1999
Gleason Score (8-10)			Pound 1999
PSA response to ADT	D'Amico 2006		
Age < 75yr		D'Amico 2006	

3. Does the effect of timing of ADT differ by PSAdt, Gleason?

Timing of ADT for Recurrent Prostate Cancer

ELAAT Survey

96 Canadian Specialists

- 42 GU Radiation Oncologists
- 50 Urologists
- 4 Medical Oncologists

Current Practice

- Trigger: PSAdt (28%), PSA (3%), both (69%)
- Start treatment if PSAdt < 12months (95%)
- Start treatment if PSA (ng/mL) <10 (53%), 10-20 (36%)
- Orchiectomy (0%)

ELAAT Survey

Trial comfort zones to start ADT

- Lowest PSA to start ADT: 4ng/mL (58%)
  5ng/mL (86%)
- Highest PSA to withhold ADT: 25ng/mL (61%)
- PSAdt trigger: < 12 months (71%)

Need for Trial

- Moderate to very important (86%)
- Very important (51%)
- Number of patients per year: 1500+

ELAAT STUDY

A Randomized Comparison of Immediate versus Deferred Androgen Deprivation Therapy using Goserelin for Recurrent Prostate Cancer after Radical Radiotherapy

Andrew Loblaw, Sergio Faria, Himu Lukka, Tom Pickles, Patrick Cheung, Lawrence Klotz, Kathy Pritchard, Martin Gleave, Tulay Koru-Singul, Mark Levine

ONTARIO CLINICAL ONCOLOGY GROUP

ELAAT Study Schema

Localized Prostate Cancer

Asymptomatic biochemical failure post RT

n = 1100

RANDOMIZE

Immediate LHRH

Deferred LHRH
(at symptom onset)
(or PSA>25ng/mL)

Outcomes

Time to Androgen Independent Disease

- Cause specific survival
- Overall survival
- Quality of Life
- Complications of Advanced Malignancy
- Bone Fractures

ELAAT Enrolment Does Not Preclude Enrolment in Any Other Clinical Trial

ELAAT Study Status

First Center Activated	May 2007
# Centers Activated	14
# Patients entered (Sept 09)	67