ICR The Institute of Cancer Research

in partnership with

CANCER RESEARCH UK

The ROYAL MARSDEN NHS Foundation Trust

Prostate Cancer Radiotherapy; Past, present and future

Prof David Dearnaley

Oslo 4th February 2016

- Background
- Dose
- Fractionation
- Systemic treatment
- Pelvic treatment
- Post–operative treatment
- Side-effects
- Blue skies

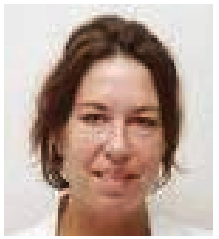
Technology

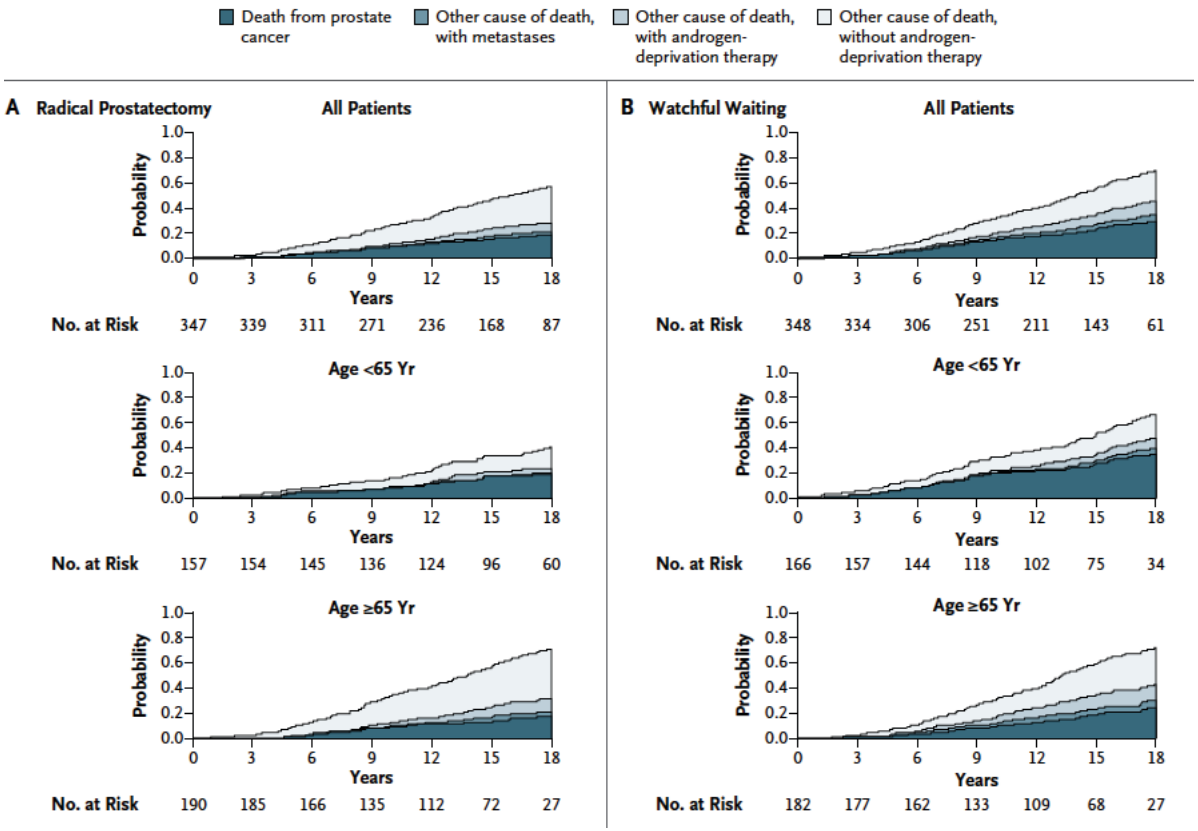
Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

The NEW ENGLAND JOURNAL of MEDICINE

Anna Bill-Axelson, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Garmo, Ph.D.,

2014,370,932





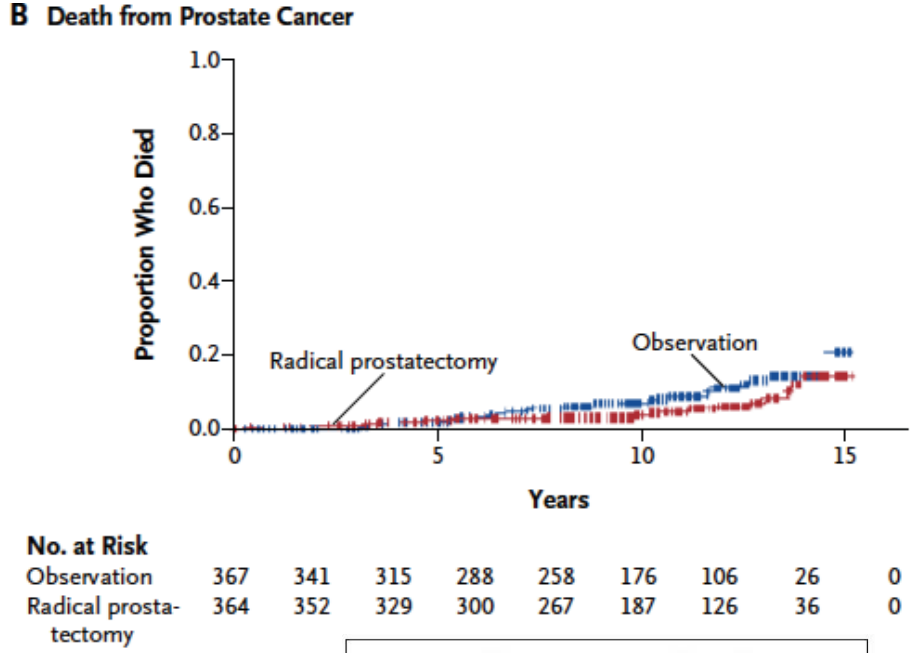
- 695 men 1989-99
- Follow up 23 years
- 11% reduction in CaP deaths
- RR 0.56
- NNT 8
- Benefit in men < 65 years

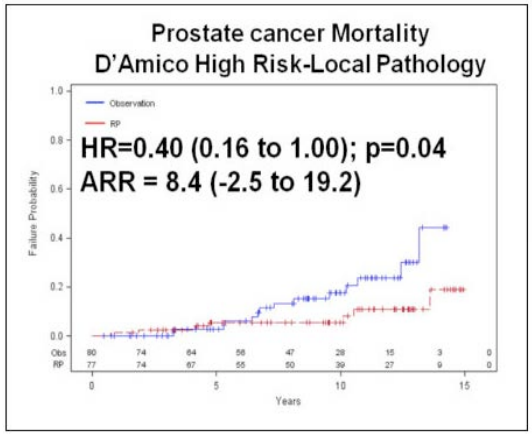
Radical Prostatectomy versus Observation for Localized Prostate Cancer

Timothy J. Wilt, M.D., M.P.H., Michael K. Brawer, M.D., Karen M. Jones, M.S., Michael J. Barry, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

2012,367,203





- 731 men 2002-10
- Follow up 10 years
- 2.6% reduction in CaP deaths (NS)
- RR 0.88 (NS)

- Sub group analysis: Int /High risk
10% reduction in CaP deaths
HR 0.45

Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial

Lancet 2009 373 301-8

Anders Widmark, Olbjørn Klepp, Arne Solberg, Jan-Erik Damber, Anders Angelsen, Per Fransson, Jo-Åsmund Lund, Ilker Tasdemir, Morten Hoyer,

- 875 men 1996-2002
- Initial PSA19.8
- Follow up 7.6years
- H.R 0.44
- 12% reduction in CaP deaths
- NNT 8.3 to prevent CaP death

Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial

Lancet 2011 378 2104-11

Padraig Warde*, Malcolm Mason*, Keyue Ding, Peter Kirkbride, Michael Brundage, Richard Cowan, Mary Gospodarowicz, Karen Sanders, Edmund Kostashuk, Greg Swanson, Jim Barber, Andrea Hiltz, Mahesh K B Parmar, Jinka Sathya, John Anderson, Charles Hayter, John Hetherington, Matthew R Sydes†, Wendy Parulekar†, for the NCIC CTG PR.3/MRC UK PR07 investigators

- 1057 men 1995-2005
- Initial PSA 27.5
- Follow up 6.0 years
- H.R 0.77
- 11% reduction in CaP deaths
- NNT 9.0 to prevent CaP death

2012 BJU International | 111, 381–388 | Urological Oncology

Treatment with curative intent and survival in men with high-risk prostate cancer. A population-based study of 11 380 men with serum PSA level 20–100 ng/mL

Sam Ladjevardi, Anders Berglund*, Eberhard Varenhorst†, Ola Bratt‡, Anders Widmark§ and Gabriel Sandblom¶

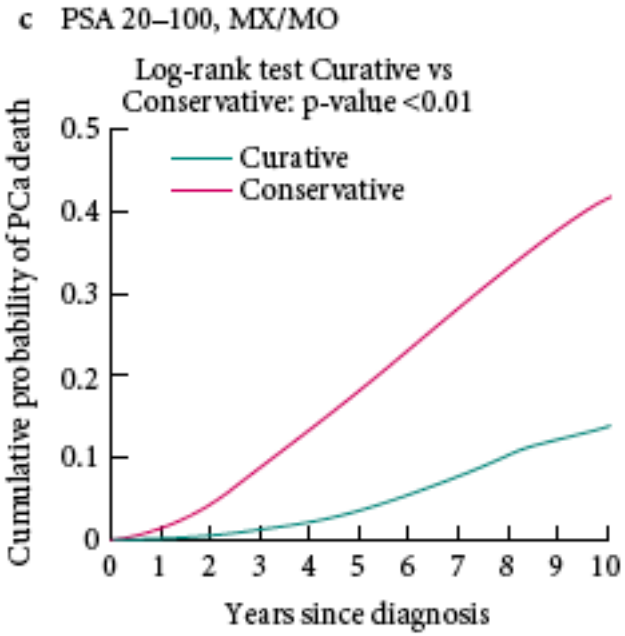
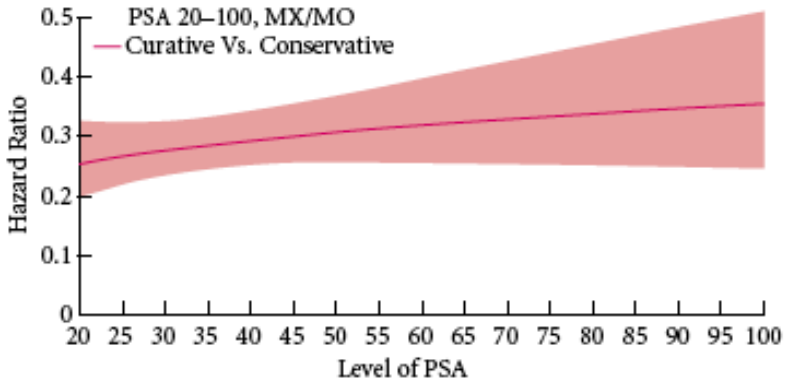


Fig. 3 Hazard ratio for death from prostate cancer for men undergoing treatment with curative intent, with adjustment for age at diagnosis, T category, serum prostate-specific antigen (PSA) level, co-morbidity and Gleason Score, and men receiving only palliative treatment as reference group. The shaded field indicates 95% confidence interval.



Surgery 30% Radiotherapy 70%

Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial

J Athene Lane*, Jenny L Donovan*, Michael Davis, Eleanor Walsh, Daniel Dedman, Liz Down, Emma L Turner, Malcolm D Mason, Chris Metcalfe, Tim J Peters, Richard M Martin, David E Neal*, Freddie C Hamdy*, for the ProtecT study group†

Lancet Oncol 2014; 15: 1109–18

Screen detected prostate cancer

- 228,955 men invited for screening
- 82,428 PSA test
- 2896 diagnosed with CaP
- 2417 localised CaP
- 1643 men randomised between Active monitoring (545) vs high dose conformal RT(545) vs RP(553)

Primary endpoint prostate cancer specific mortality at 10years

10 year median follow-up to be reported in 2016

Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions

Isabelle Soerjomataram, Joannie Lortet-Tieulent, D Maxwell Parkin, Jacques Ferlay, Colin Mathers, David Forman, Freddie Bray

Lancet 2012; 380: 1840–50

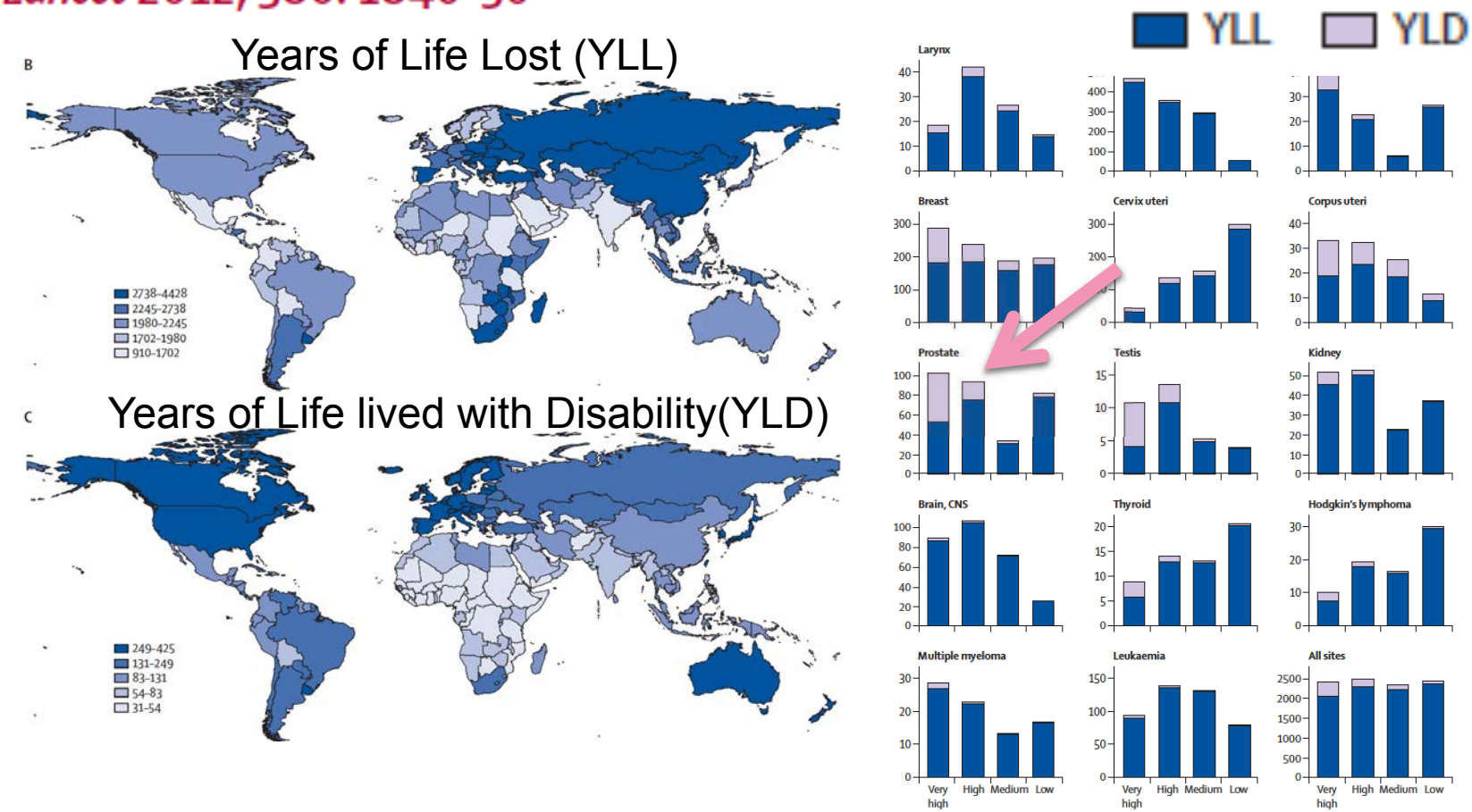


Figure 2: **Age-adjusted DALYs per 100 000 population by cancer site and level of HDI**

DALYs=disability-adjusted life-years. YLL=years of life lost. YLD=years of life lived with disability. HDI=Human Development Index.

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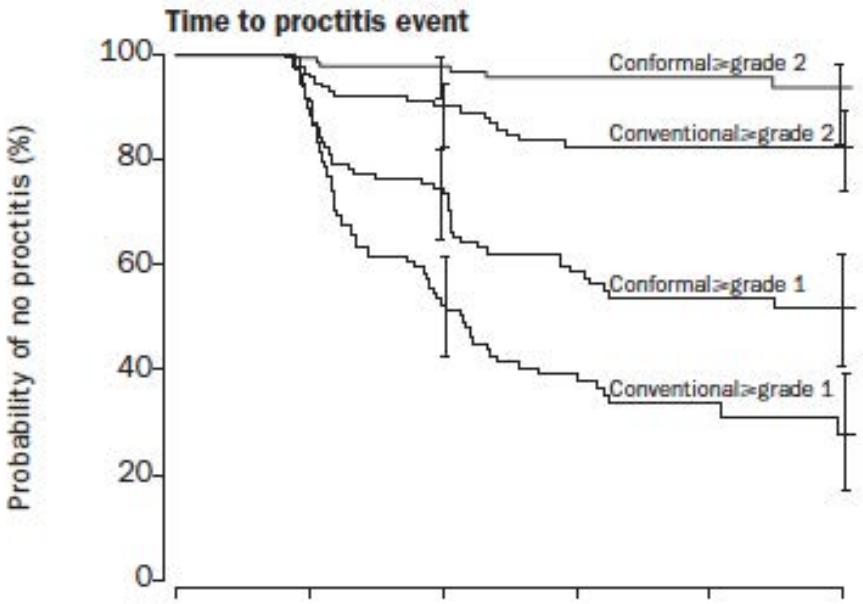
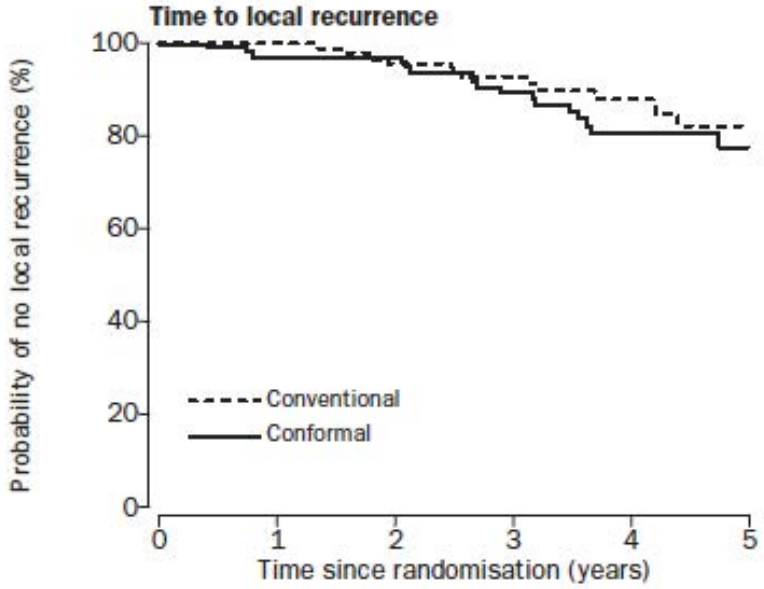
Technology

Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial

Lancet 1999; **353**: 267–72

David P Dearnaley, Vincent S Khoo, Andrew R Norman, Lesley Meyer, Alan Nahum, Diana Tait, John Yarnold, Alan Horwich



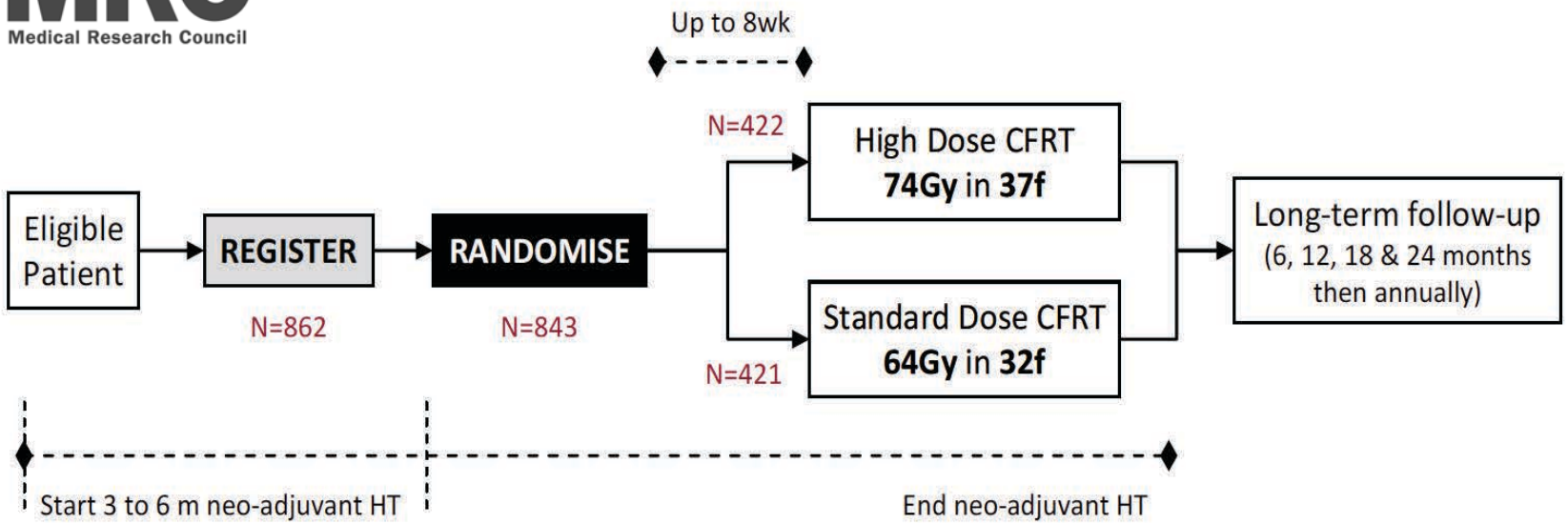


No.225 Dose 64Gy 32f T3 – 55% PSA median 19

Dose-Escalation Studies: Where have we got to?

Trial	Std	Esc	Hormones	N Pts	Accrual
MDACC (Kuban)	70Gy--35f	78Gy--39f	None	305	1993-1998
ICR/RMH (Dearnaley)	64Gy--32f	74Gy--37f	All	125	1995-1997
PROG 95-09 (Zeitman)	70.2CGE	79.2CGE	None	390	1996-2000
NKI(Lebesque)	68Gy--34f	78Gy--39f	Some	668	1997-2003
MRC RT01 (Dearnaley)	64Gy--32f	74Gy--37f	All	843	1998-2001
GETUG 06 (Beckendorf)	70Gy--35f	80Gy--40f	None	306	2000-2002
CCF(Kupelian)	70Gy--35f	78Gy--39f	None	130	???
RTOG-0126 (Michalski)	70.2Gy--39f	79.2Gy—44f	None	1520	2002-2008

RT01: 10yr results Dearnaley et al Lancet Oncol 2014,15,464-73



- Median age 67 yrs
- Median PSA = 12.8 ng/ml
- T stage: 75% palpable disease (cT2/3)
- NCCN Risk Group - Low 23%, Int 32%, High 44%
- Recruitment 1998 – 2001
- CFRT all patients

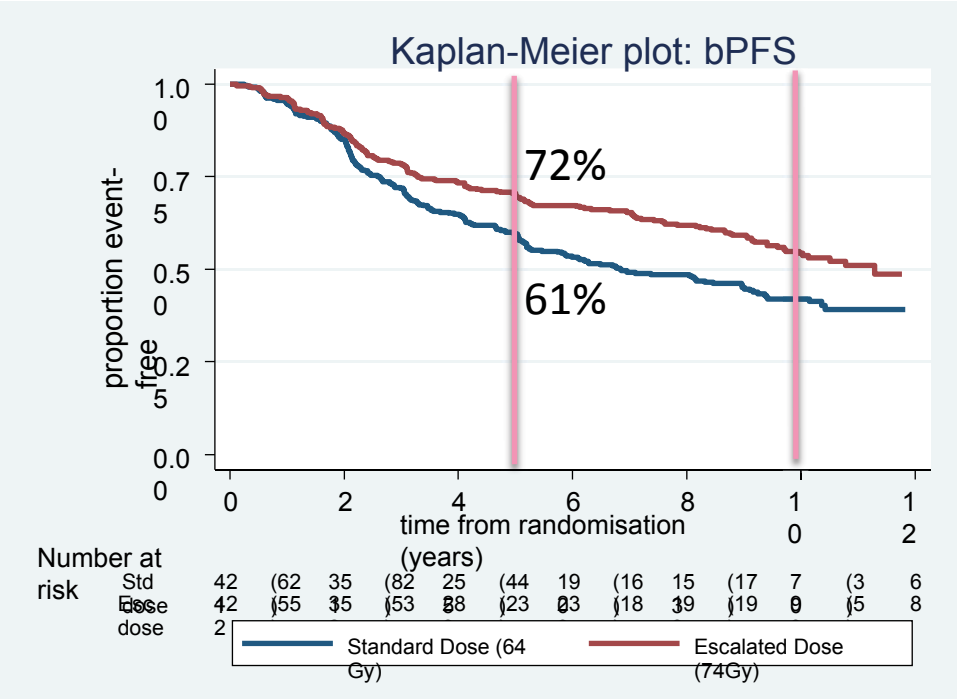
RT01 Trial: bPFS –10yr results Lancet Oncol 2014

MRC
Medical Research Council

397 bPFS: 224 Std and 173 Esc

HR=0.69, 95%CI=(0.57-0.84), p<0.001

Median FU 10 years



10yrs bPFS

54% in 74Gy group

42% in 64Gy group

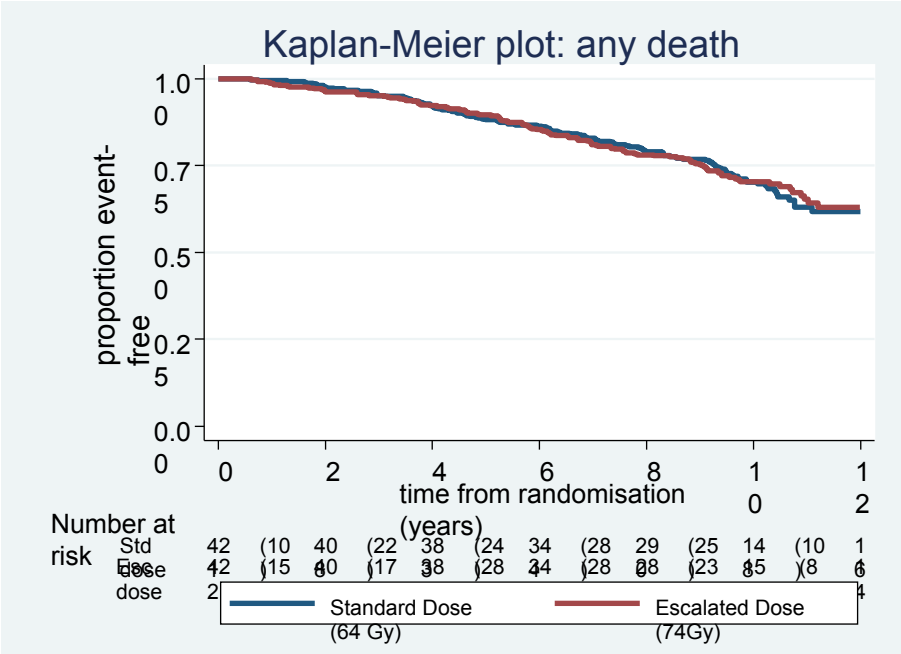
*adjusted for risk group and hospital

Reduced need for salvage hormone treatment by 6%

RT01 Trial: Overall survival –10yr results Lancet Oncol 2014

MRC
Medical Research Council

- 239 deaths: 120 Std and 119 Esc
- Median FU 10 yrs
- HR=0.99*, 95%CI=(0.77-1.28), p=0.94



10yrs OS

70% in both groups

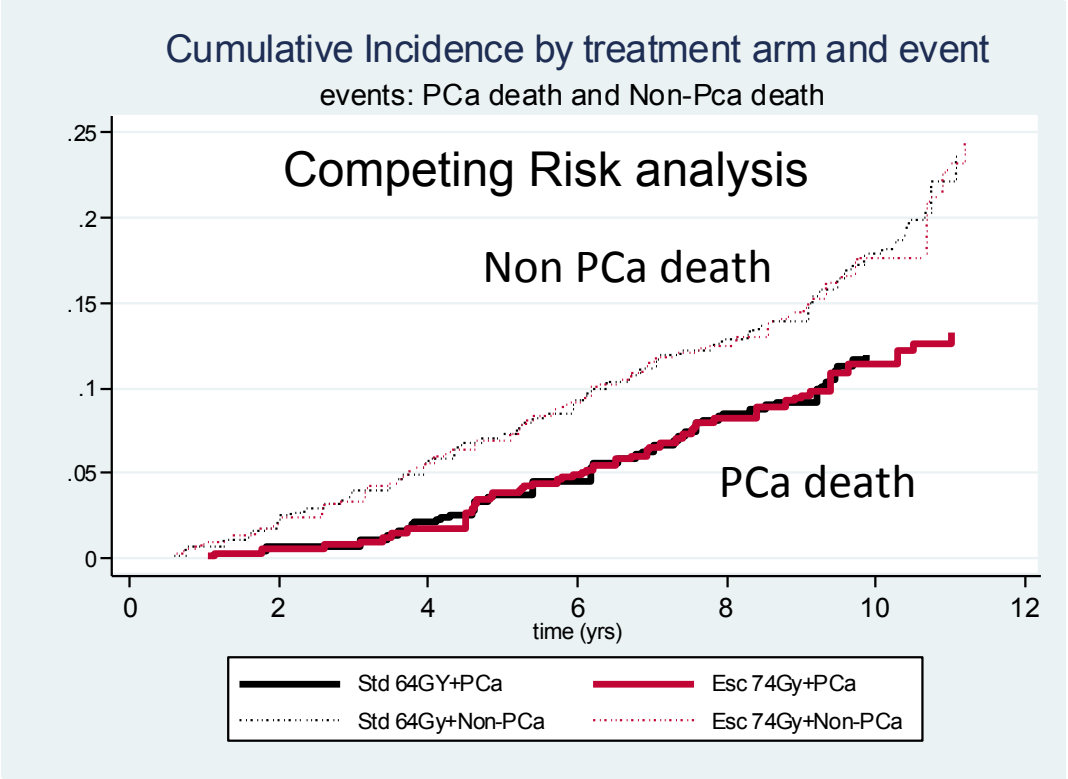
*adjusted for risk group and hospital

RT01 Trial: Prostate Ca.Survival: 10yr results Lancet Oncol 2014

MRC Medical Research Council

PCa death (91): sub-HR*=1.02 95%CI=(.07-1.53) p=.93

non-PCa death (148): sub-HR*=0.96 95%CI=(.70-1.33) p=.83



PCa deaths vs deaths other causes = 2:3

*Grey's test applied

ICR/RMH Dose Escalation Trial: (Creak BJC 2013.109.651-7)

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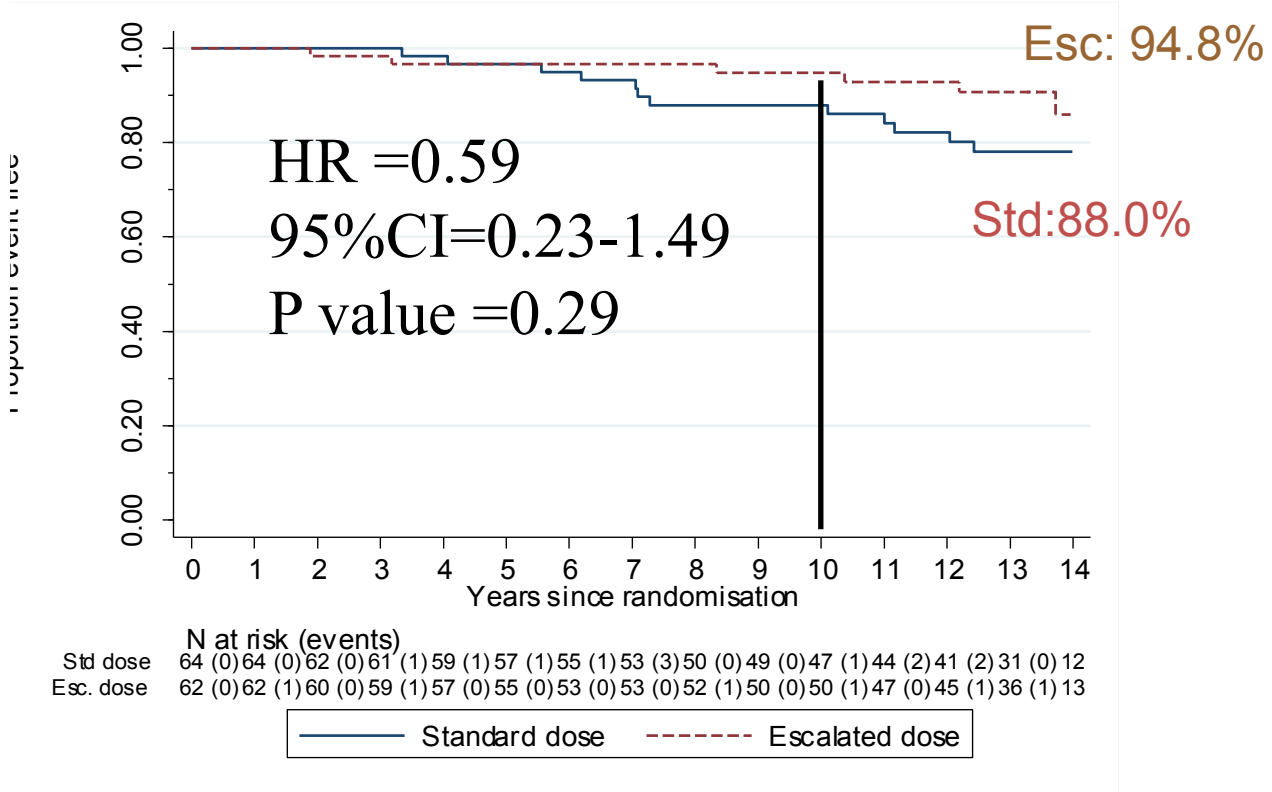
No. 127 Median follow up 14 yrs



CaP Deaths in RCT's of Dose Escalation

Trial	No.	FU	High Risk	CAP deaths
PROG	393	9yr	5%	4(1%)
MDA	305	9yr	33%	10 (3%)
NKI	669	5.8yr	55%	87(13%)
RT01	843	10yr	44%	91 (11%)
ICR/ RMH	126	14yr	59%	19 (15%)

Zietman JCO 2010, 28, 1106
Dearnaley Lancet Oncol 2007, 8, 475
Creak ESTRO May 2011,
Kuban IJROBP 2011, 79, 1310
Al-Mamgani IJROBP 2008,72,980
Dearnaley ECCO Sept 2011

From MDA and ICR/RMH dose escalation RCT–86%

CaP deaths occurred in men with high risk disease

High dose versus conventional dose in EBRT of prostate cancer: a meta-analysis of long-term follow-up

Zan Hou, Guangjun Li, Sen Bai

Journal of Cancer Research and Clinical Oncology 2015, 141, 6, 1063-1071

64Gy-70.2Gy vs 74Gy-78Gy

- 6 RCT 2822 patiens
- 10 yr OS 73.4% vs 74.3% OR 1.05
- 10y PCSS 90.7% vs 91.6% OR 1.11
- 10 yr BF 34.5% vs 24.7% OR 0.61 (p< 0.00001)

- Late ≥2 GI toxicity 28.0% vs 18.6% OR 1.72 (p<0.00001)
- Late ≥ 2 GU toxicity 22.6% vs 19.5% OR 1.24 p=0.04

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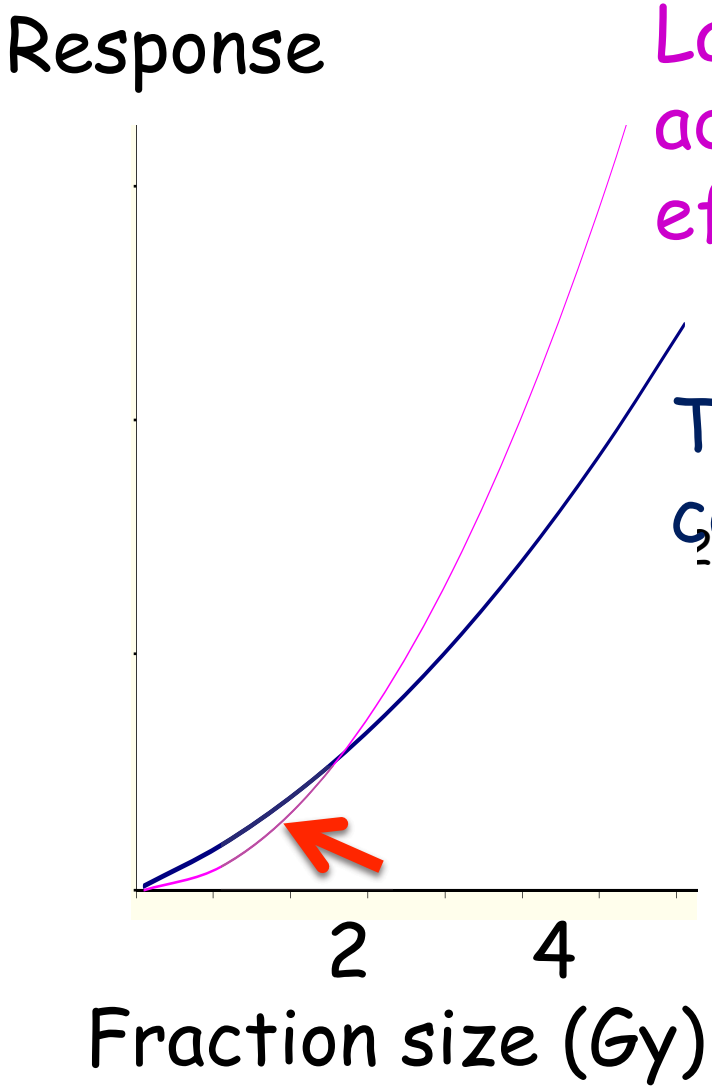
Technology

Traditional Model of Fractionation

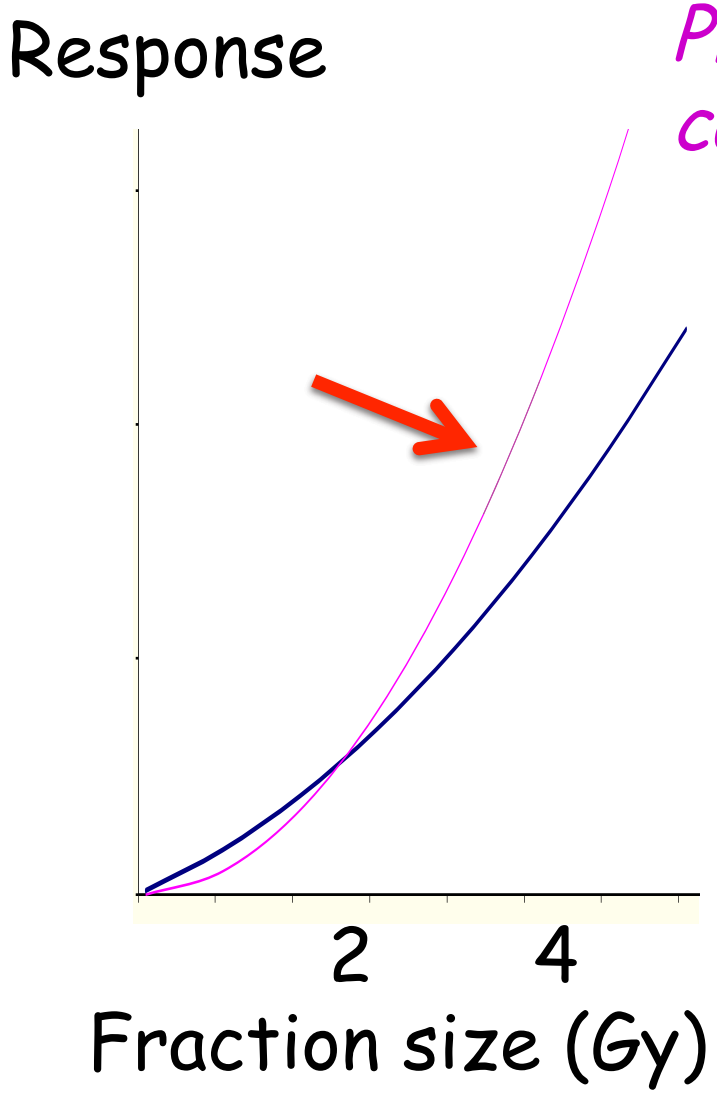


α/β<10Gy

α/β≥10Gy

adapted from Prof. Yarnold / Dr Somaiah

New Model of Tumour Fractionation



Prostate cancer

α/β<10Gy

Other tumours

α/β≥10Gy

adapted from Prof. Yarnold / Dr Somaiah

What's the fraction sensitivity of Ca prostate?

LATER OUTCOMES AND ALPHA/BETA ESTIMATE FROM HYPOFRACTIONATED CONFORMAL THREE-DIMENSIONAL RADIOTHERAPY VERSUS STANDARD FRACTIONATION FOR LOCALIZED PROSTATE CANCER

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 3, pp. 1200–1207, 2012

FELIX LEBORGNE, M.D.,* JACK FOWLER, D.SC., PH.D.,† JOSÉ H. LEBORGNE, M.D.,* AND JULIETA MEZZERA, B.SC.*

1.8 Gy

DOSE-FRACTIONATION SENSITIVITY OF PROSTATE CANCER DEDUCED FROM RADIOTHERAPY OUTCOMES OF 5,969 PATIENTS IN SEVEN INTERNATIONAL INSTITUTIONAL DATASETS: α/β = 1.4 (0.9–2.2) GY

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. e17–e24, 2012

RAYMOND MIRALBELL, M.D.,*† STEPHEN A. ROBERTS, PH.D.,‡ EDUARDO ZUBIZARRETA, M.D.,§ AND JOLYON H. HENDRY, PH.D.‖

1.4Gy

CONFIRMATION OF A LOW α/β RATIO FOR PROSTATE CANCER TREATED BY EXTERNAL BEAM RADIATION THERAPY ALONE USING A POST-TREATMENT REPEATED-MEASURES MODEL FOR PSA DYNAMICS

Int. J. Radiation Oncology Biol. Phys., Vol. 79, No. 1, pp. 195–201, 2011

CÉCILE PROUST-LIMA, PH.D.,*† JEREMY M. G. TAYLOR, PH.D.,‡§ SOLÈNE SÉCHER, PH.D.,*†

1.55 Gy

ASTRO Online CME

CLINICAL INVESTIGATION Prostate

USE OF INDIVIDUAL FRACTION SIZE DATA FROM 3756 PATIENTS TO DIRECTLY DETERMINE THE α/β RATIO OF PROSTATE CANCER

Int. J. Radiation Oncology Biol. Phys., Vol. 68, No. 1, pp. 24–33, 2007

SCOTT G. WILLIAMS, F.R.A.N.Z.C.R.,* JEREMY M. G. TAYLOR, PH.D.,†‖ NING LIU, M.S.,†

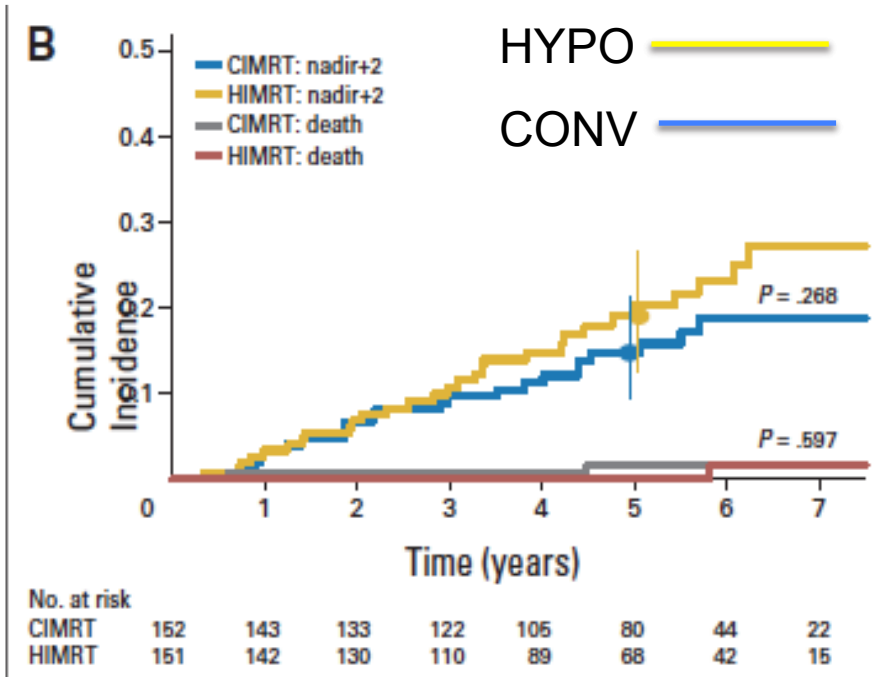
3.7 Gy

Randomized Trial of Hypofractionated External-Beam Radiotherapy for Prostate Cancer Pollack et al JCO 2013.381.3860

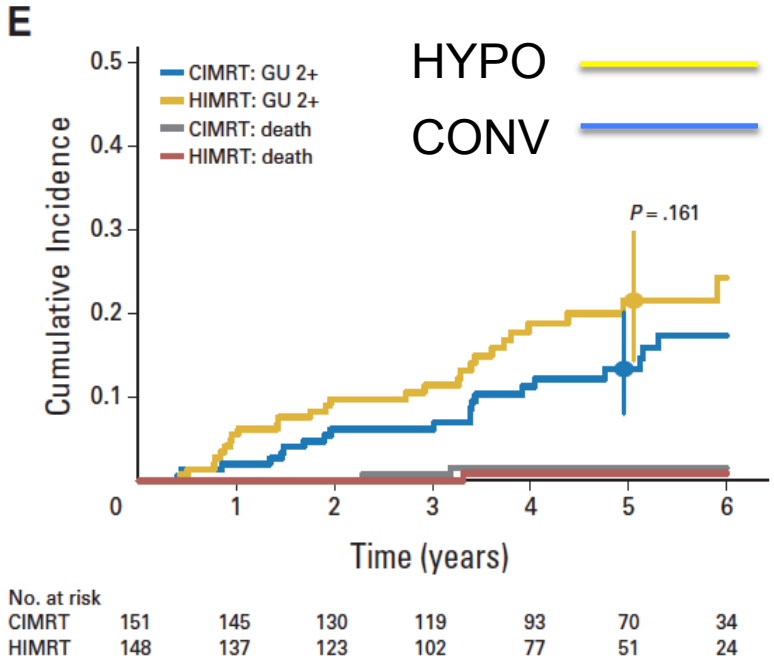
- No. 303; Favourable to high risk; 5.5 yrs FU
- 76 Gy 38F 2Gy/F vs 70.2Gy 27F 2.7Gy/F
- Calculated to be equivalent to 84Gy for alpha/beta 1.5Gy and 76Gy for alpha/beta 5Gy

Randomized Trial of Hypofractionated External-Beam Radiotherapy for Prostate Cancer Pollack et al JCO 2013.381.3860

PSA Control and death



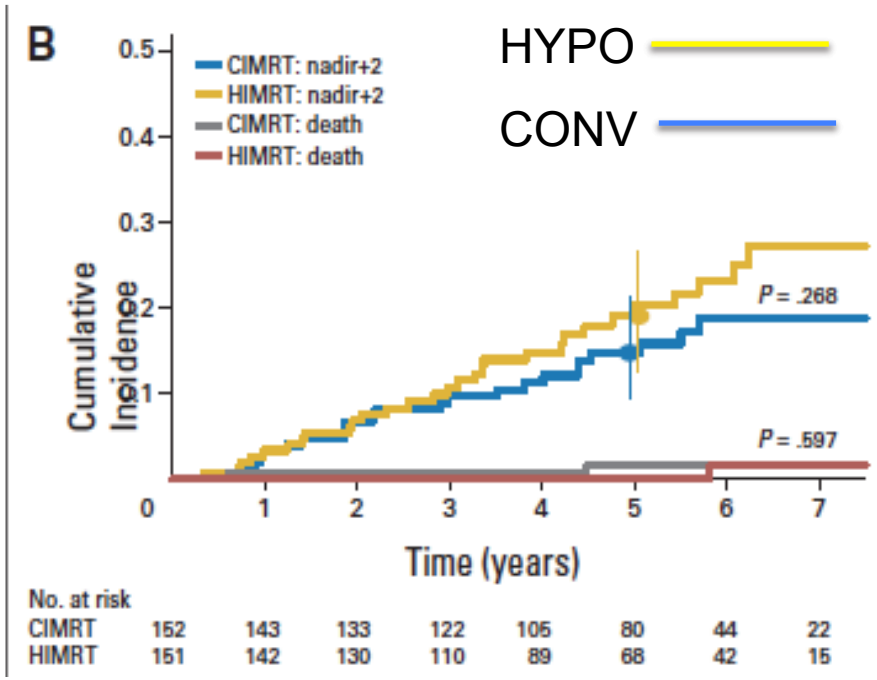
GU side effects



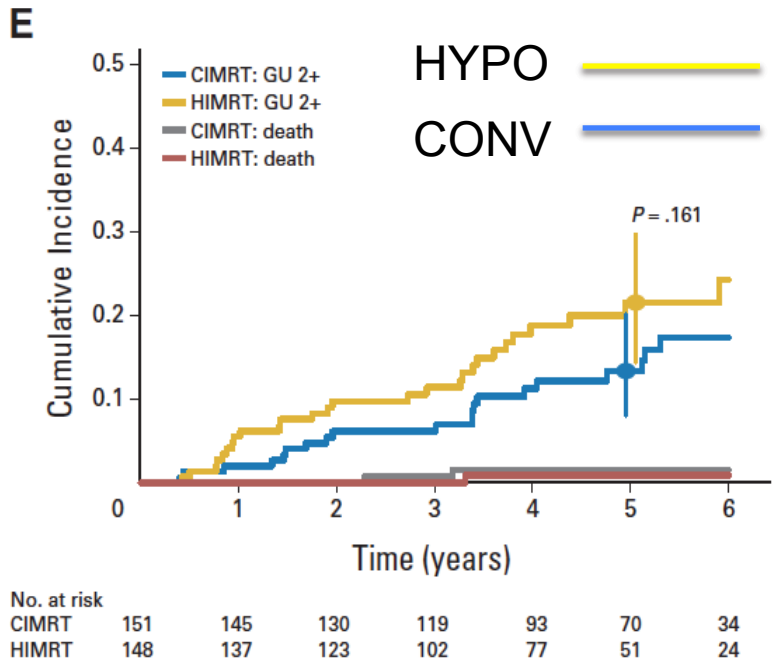
Randomized Trial of Hypofractionated External-Beam Radiotherapy for Prostate Cancer

Pollack et al JCO 2013.381.3860

PSA Control and death



GU side effects



Definitive RCT's awaited !

Clinical Hypothesis

- Prostate cancer is as (or more) sensitive to fraction size as the dose-limiting normal tissues
- 2Gy fractions spare prostate cancer as much as they spare normal tissues (no advantage)
- Larger fractions are worth testing

ICR The Institute of Cancer Research

Department of Health

CANCER RESEARCH UK

Biomedical Research Centre
at The Royal Marsden NHS Foundation Trust
and The Institute of Cancer Research, London

The ROYAL MARSDEN
NHS Foundation Trust

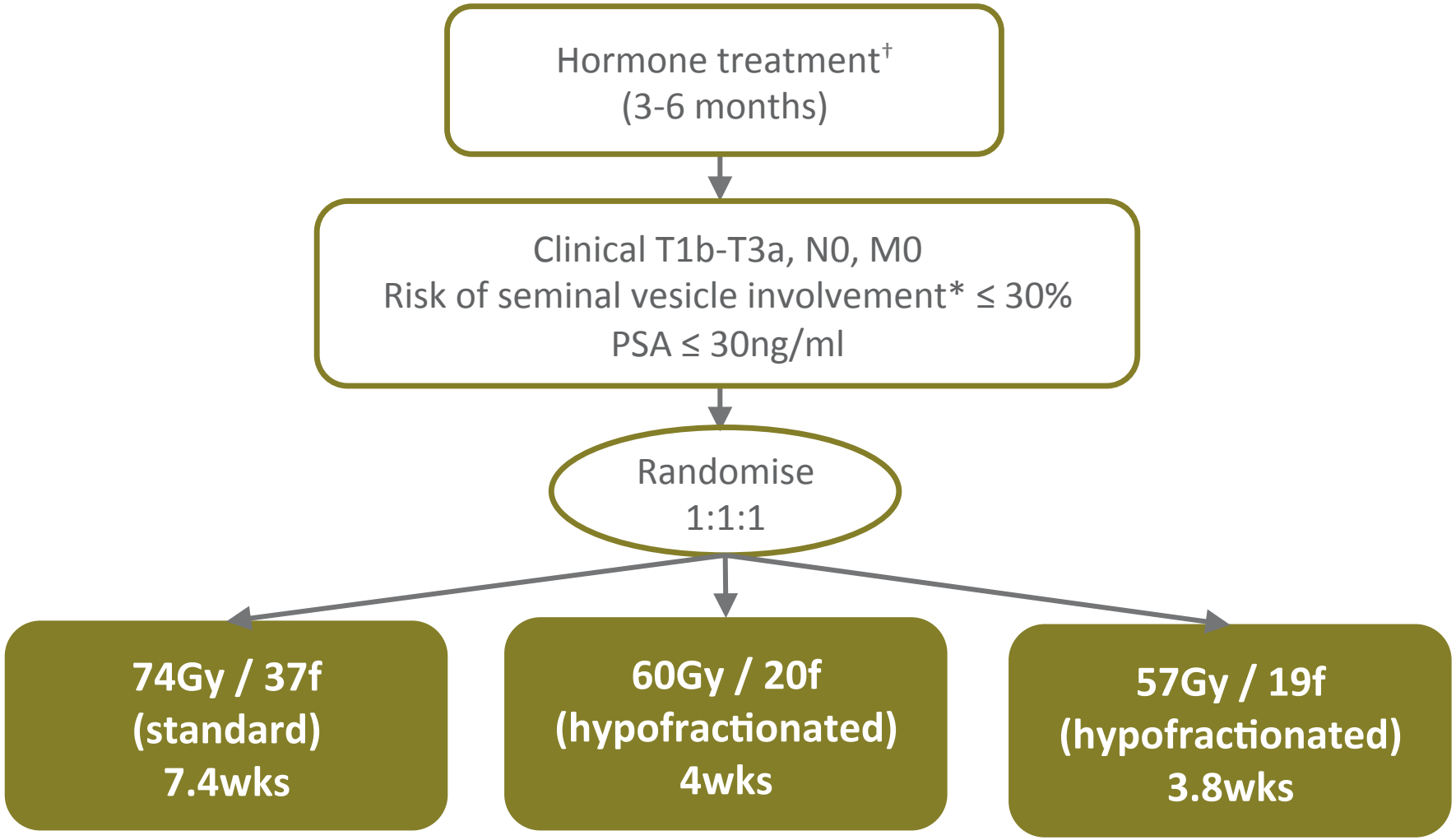
NHS
National Institute for Health Research

CHHiP

Conventional or Hypofractionated High-dose intensity-modulated radiotherapy for Prostate cancer: Results from the phase III randomized CHHiP trial (CRUK/06/016)

NCRI Urological CSG's Trials Meeting Jan 27th 2016

Trial schema



† optional for patients with low risk disease (T1c/T2a & Gleason score ≤6 & PSA ≤10ng/ml)

* PSA +([Gleason score-6] x10)

Endpoints

Primary Endpoint

- Biochemical (PSA) failure or prostate cancer recurrence

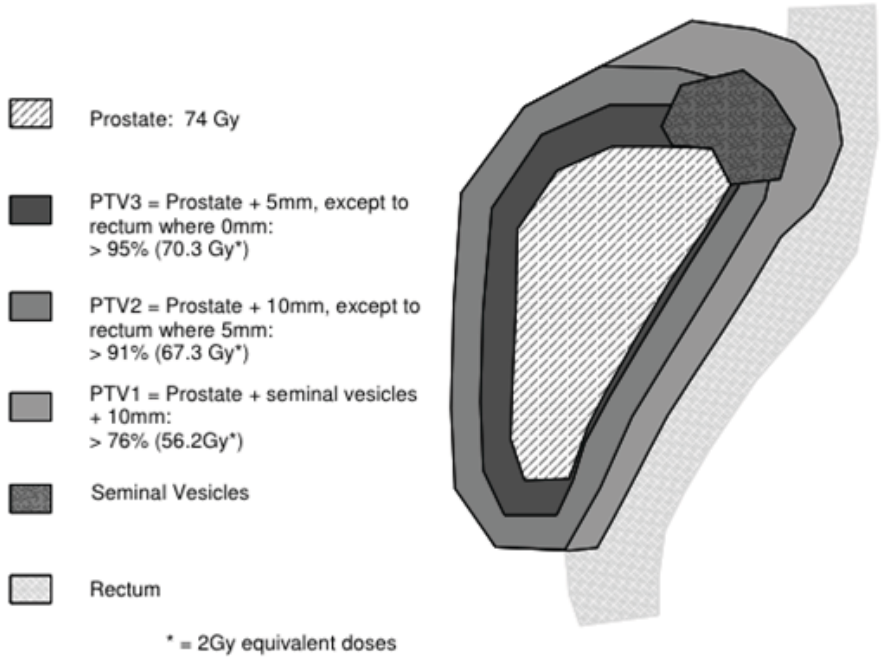
Secondary Endpoints

- Acute and late radiation induced side effects (RTOG, LENTSOM, RMH)
- Aspects of quality of life (UCLA-PCI, EPIC, FACT-P)
- Overall survival

- Cause specific survival
- Development of metastases
- Recommencement of hormonal treatment for disease recurrence
- Aspects of health economics
- Models of normal tissue and tumour control

Radiotherapy treatment technique

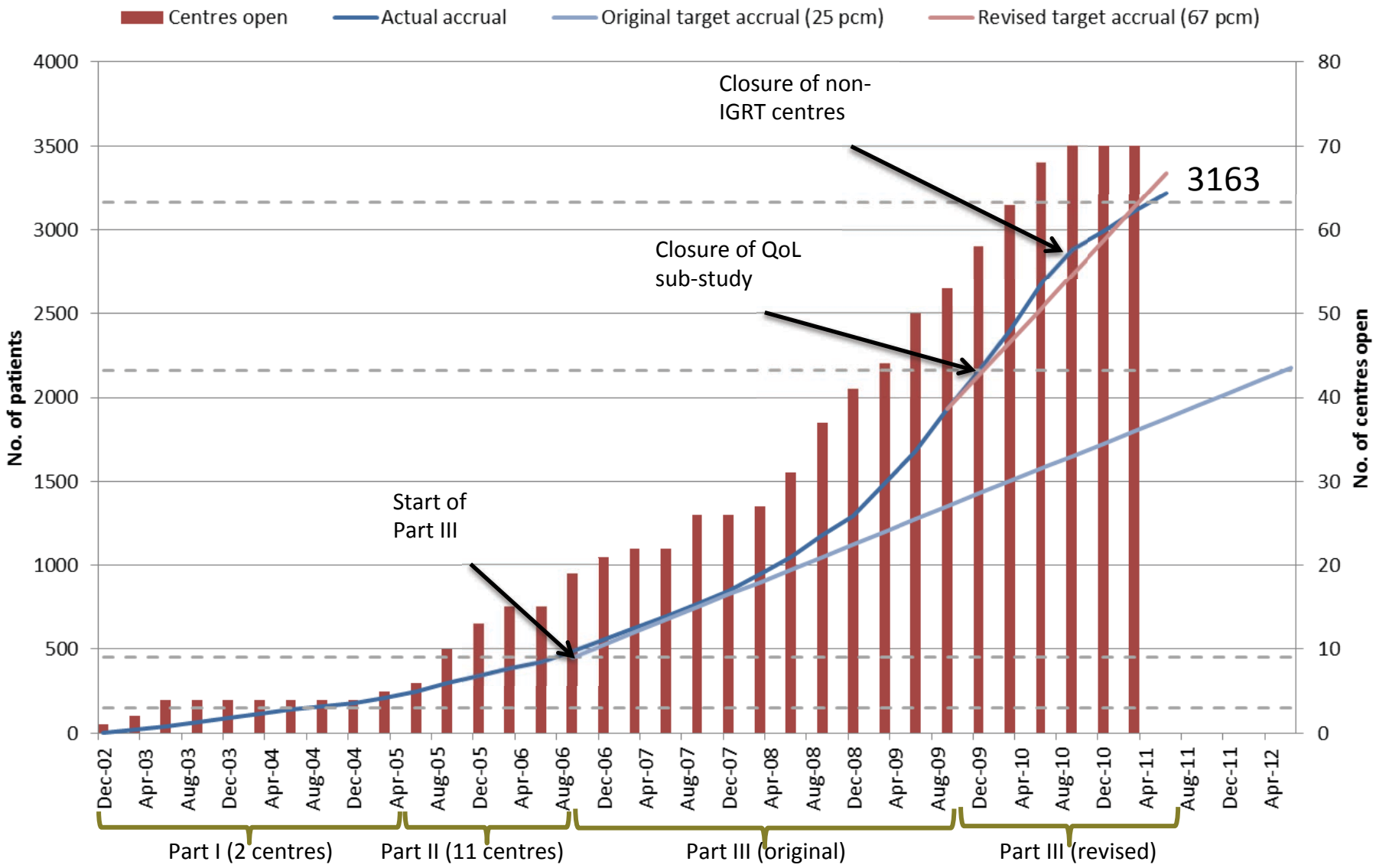
- Forward or inverse planned IMRT
- Simultaneous integrated boost technique to include Prostate and SV
- Mandatory normal tissue dose constraints
- National QA program



Normal Tissue Dose Constraints

	Dose for 2Gy/# Prescribed Dose	Dose (%)	Max Vol (% or cc)
Rectum	30	41	80%
	40	54	70%
	50	68	60%
	60	81	50%
	65	88	30%
	70	95	15%
	74	100	3%
Bladder	50	68	50%
	60	81	25%
	74	100	5%
Femoral Heads	50	68	50%
Bowel	50	68	17cc
Urethral Bulb	50	68	50%
	60	81	10%

Accrual



Funding:	CR UK programme grant	Department of Health	Cancer Research UK

Baseline characteristics

	74Gy/37f (N=1065)	60Gy/20f (N=1074)	57Gy/19f (N=1077)	Total (N=3216)
	%	%	%	%
Age				
Median (IQR)	69 (65, 73)	69 (64, 73)	69 (64, 73)	69 (64, 73)
Risk group				
High Risk	12	12	12	12
Intermediate Risk	73	73	73	73
Low risk	15	15	15	15
Pre-hormone [illegible] (ng/ml)				
Median (IQR)	10 (7, 14)	10 (7, 15)	10 (7, 14)	10 (7, 14)

Radiotherapy

	74Gy/37f (N=1065)	60Gy/20f (N=1074)	57Gy/19f (N=1077)	Total (N=3216)
	%	%	%	%
Radiotherapy received	98	98	98	98
Days of radiotherapy				
Median (IQR)	52 (50, 54)	28 (27, 28)	27 (26, 27)	28 (27, 50)
Received allocated fractions and dose	96	97	97	97
Treatment extended by more than one week	1	1	0	1

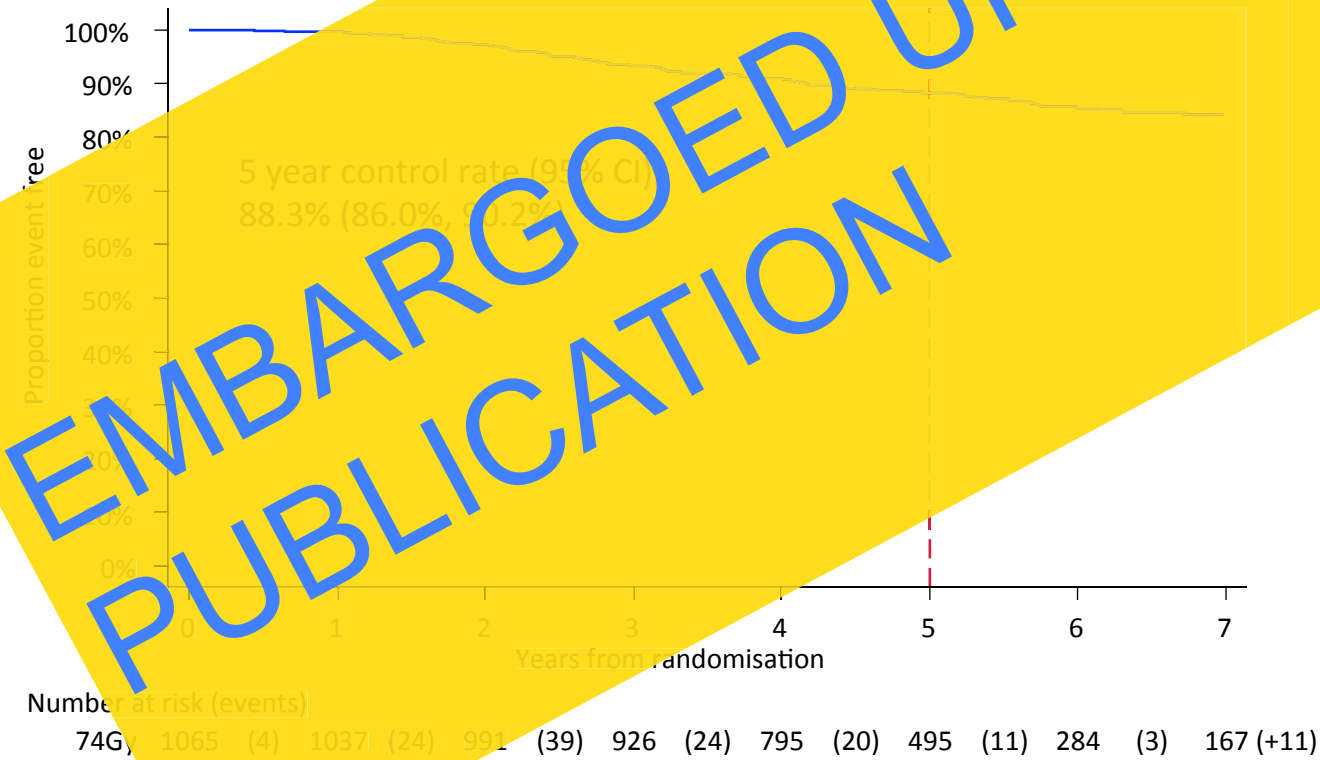
What is an acceptable non-inferiority margin?

- 5% non-inferiority margin around 70% control rate corresponding to a critical hazard ratio (HR) of 1.208.

- Trial Management Group (TMG) agreed that 5% non-inferiority margin around a control rate of 85-90% was too wide and the critical hazard ratio of 1.208 should be maintained accepting that this was “tight” if control rates were high (2.8%-1.9% for control rate of 85% -90% in standard 2Gy/F group).

- Greater confidence in interpretation of non-inferiority if intention to treat and per protocol analysis are consistent (CONSORT guidelines).

Time to biochemical failure and prostate cancer recurrence
Control arm

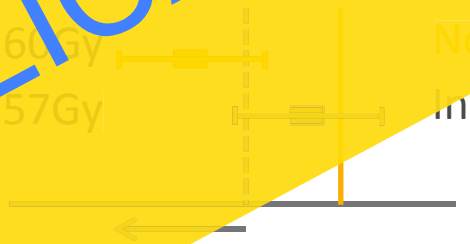


Time to biochemical failure and prostate cancer recurrence

Primary analysis

Non-inferiority analysis (ITT)

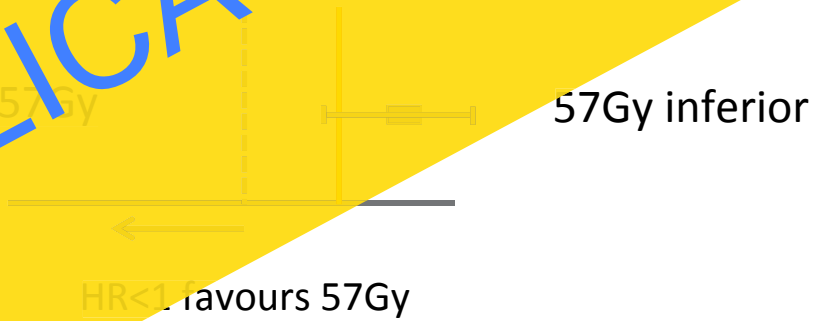
Biochemical failure or prostate cancer recurrence	74Gy/37f (N=1065)	60Gy/20f (N=1074)	57Gy/19f (N=1077)
Number of events	136	116	163
KM 5 year proportion event-free estimate (95% CI)	88.3 (86.0, 90.2)	90.6 (88.5, 92.3)	85.9 (83.4, 88.0)
Hazard ratio (90% CI)		0.84 (0.68, 1.03)	1.20 (0.99, 1.46)
Pr(HR<1.08)		p=0.004	p=0.96
Log rank p-value		p=0.16	p=0.11



HR<1 favours hypofractionation

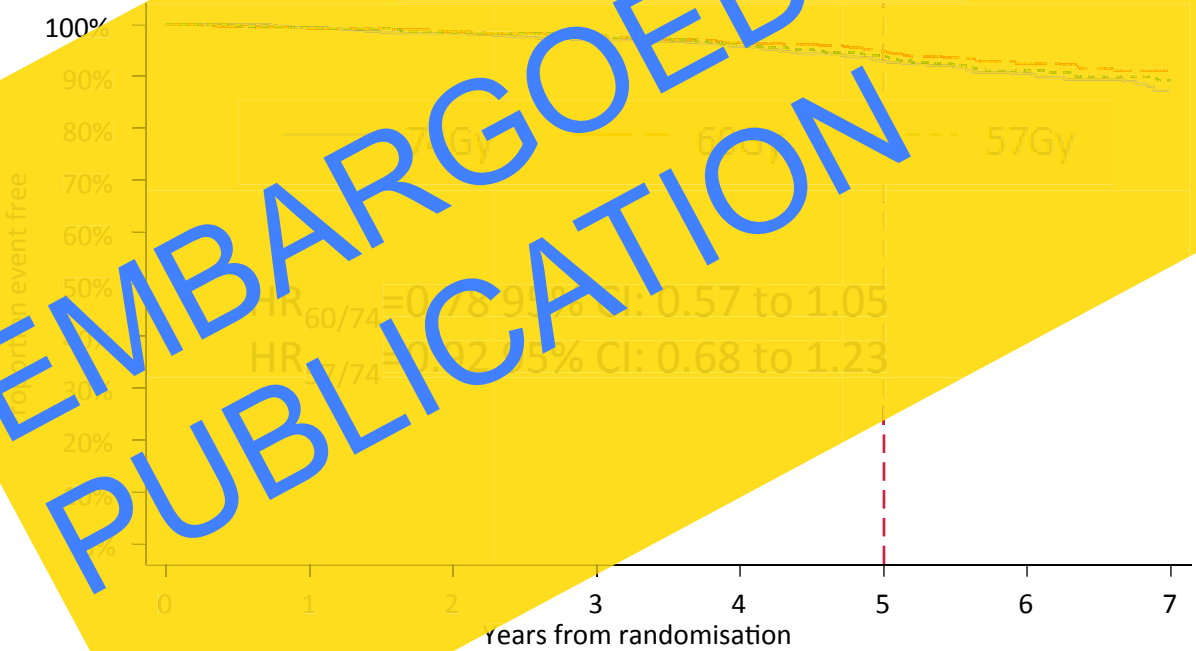
60Gy vs 57Gy analysis (ITT)

Biochemical failure or prostate cancer recurrence	60Gy/20f (N=1074)	57Gy/19f (N=1077)
Number of events	118	163
KM 5 year proportion event-free estimate (95% CI)	90.6 (88.5, 92.3)	85.9 (83.4, 88.0)
Hazard ratio (95% CI)		1.46 (1.13, 1.82)
Log rank p-value		p=0.003



Secondary endpoints: deaths

Deaths as reported	74Gy/37f (N=1065)		60Gy/20f (N=1074)		57Gy/19f (N=1077)		Total (N=3216)	
	No.	%	No.	%	No.	%	No.	%
Death	92	8.6	73	6.8	87	8.1	252	7.8
Prostate cancer related	13	1.2	9	0.8	18	1.7	40	1.2
Unrelated to prostate cancer	79	7.4	64	6.0	69	6.4	212	6.6



Number at risk (events)

74Gy	1065	(6)	1045	(13)	1025	(11)	996	(13)	889	(23)	585	(10)	337	(9)	201	(+7)
60Gy	1074	(8)	1049	(6)	1035	(11)	1011	(10)	896	(14)	608	(10)	339	(4)	224	(+10)
57Gy	1077	(7)	1053	(9)	1041	(7)	1021	(18)	910	(17)	606	(14)	336	(5)	217	(+10)

Side effects of prostate radiotherapy

Acute Late

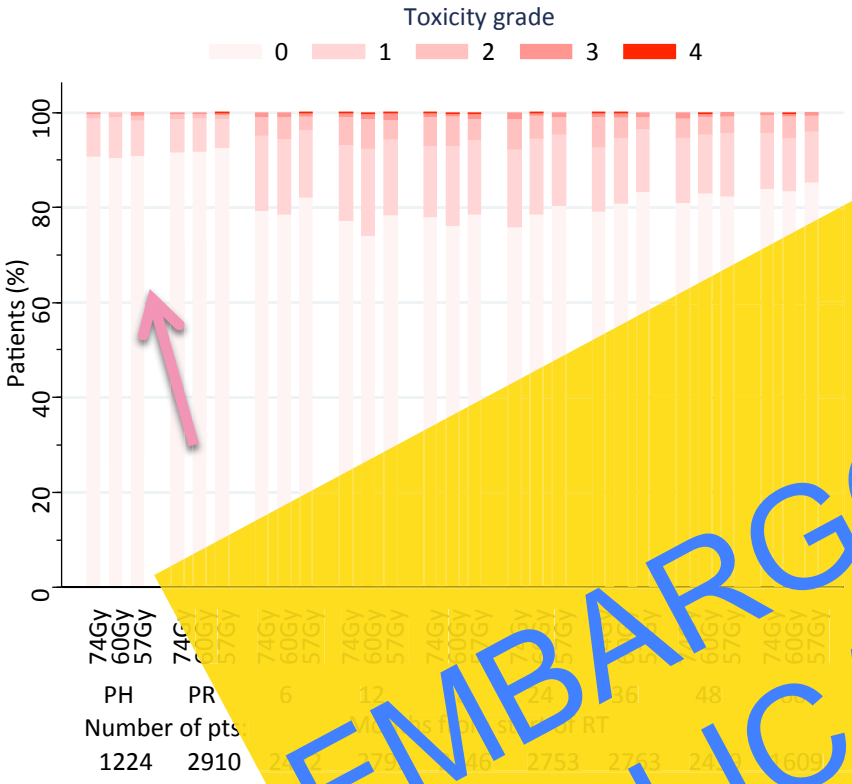
- Bowel
- Bladder
- Erectile dysfunction (ED)

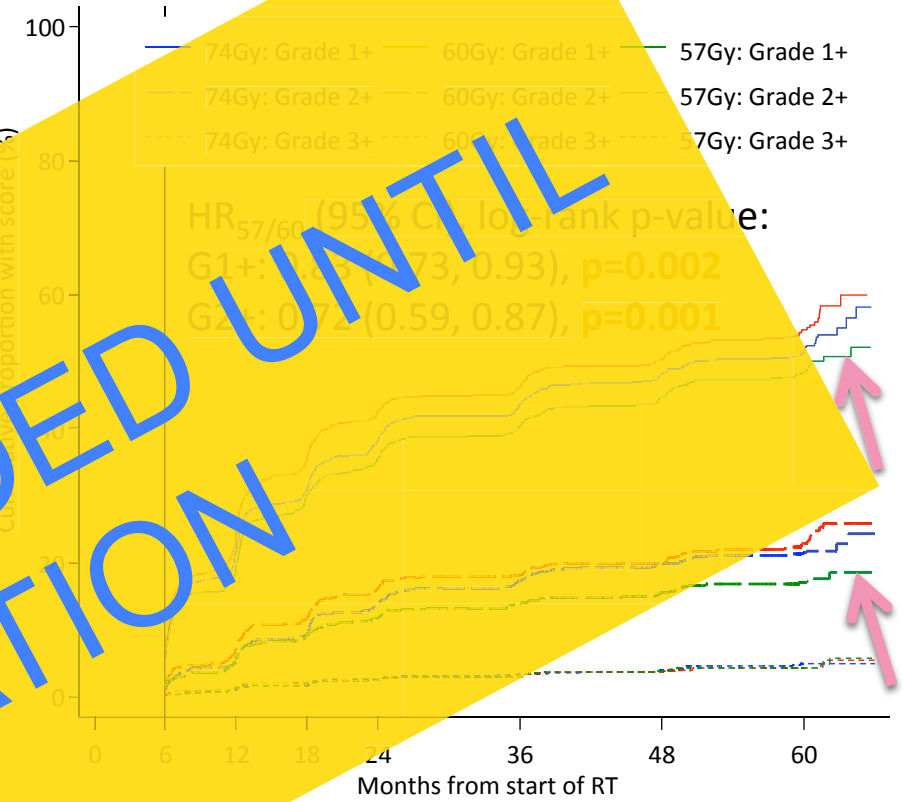
Acute toxicity – RTOG bowel and bladder

Worst bowel toxicity	74Gy/37f (N=715)		60Gy/20f (N=720)		57Gy/19f (N=713)	
	No.	%	No.	%	No.	%
0	186	26.0	137	19.0	122	17.1
1	353	49.4	306	42.5	321	45.0
2	170	23.8	260	36.1	254	35.6
3	6	0.8	17	2.4	16	2.2
4	0	0.0	0	0.0	0	0.0
Mann-Whitney			p<0.001		**p<0.001**	
			p=0.82			

Worst bladder toxicity	74Gy/37f (N=715)		60Gy/20f (N=720)		57Gy/19f (N=713)	
	No.	%	No.	%	No.	%
0	68	9.5	73	10.1	65	9.1
1	316	44.2	291	40.4	321	45.0
2	273	38.2	290	40.3	261	36.6
3	49	6.9	59	8.2	59	8.3
4	9	1.3	7	1.0	7	1.0
Mann-Whitney			p=0.34		p=0.90	
			p=0.41			

Late toxicity – LENT-SOM bowel





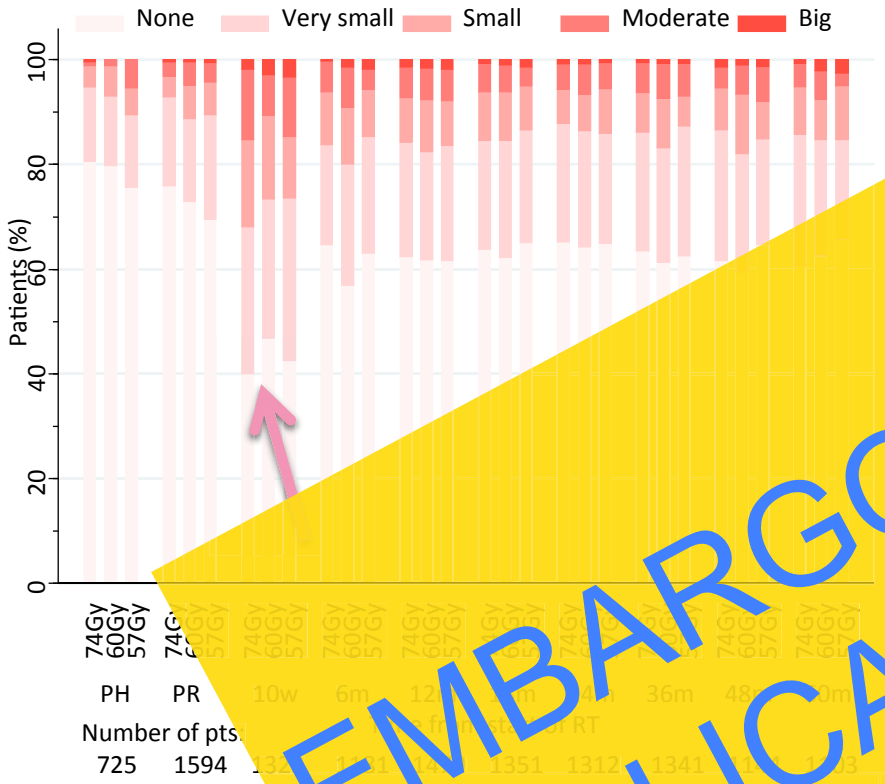
Gd 2+:

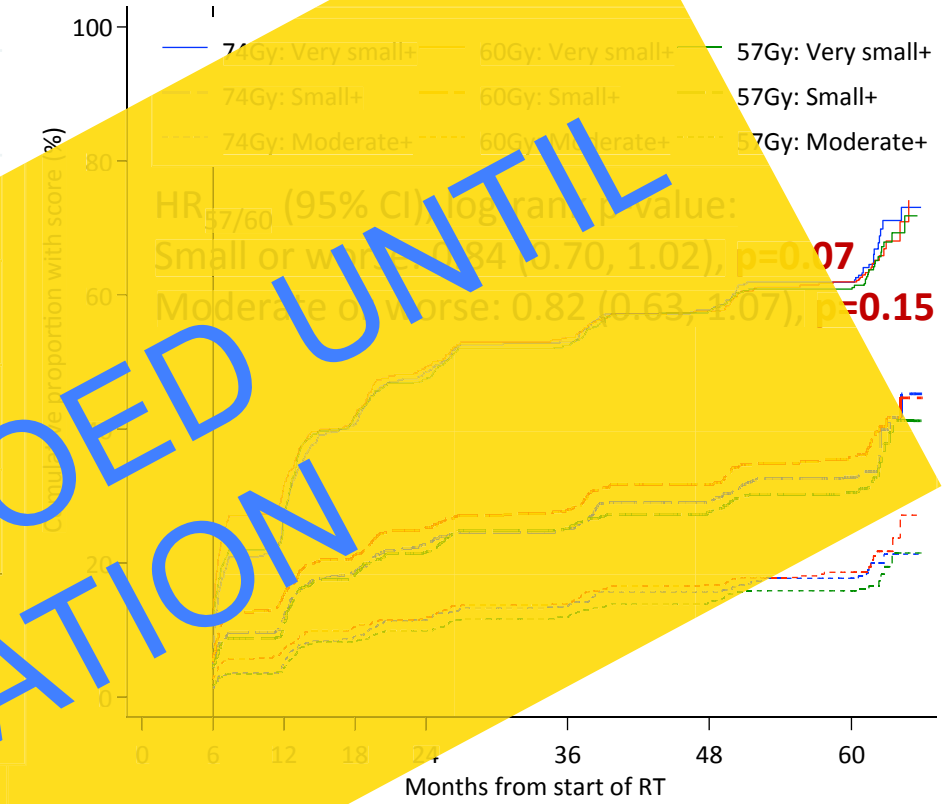
74Gy	60Gy	57Gy
4.2%	5.2%	3.9%
	p= ns	p= ns

Gd 2+: KM 5 year estimate

74Gy	60Gy	57Gy
24.3%	25.9%	18.5%
	p= ns	p= ns

Quality of Life – Bowel bother





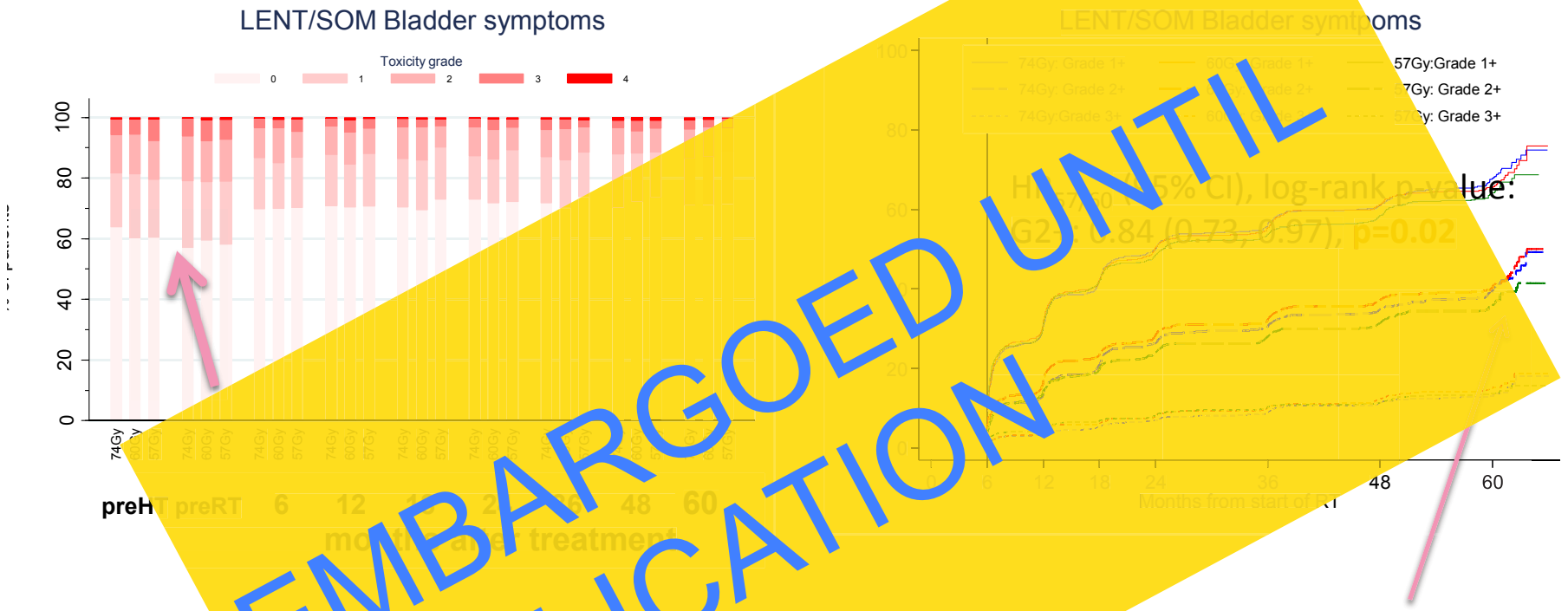
Small or worse: 5 year incidence

74Gy	60Gy	57Gy
14.4%	15.2%	15.2%
	p= ns	p= ns

Small or worse: KM 5 year estimate

74Gy	60Gy	57Gy
45.2%	44.7%	41.2%
	p= ns	p= ns

Late toxicity – LENT-SOM bladder



Gd 2+: 5 year incidence

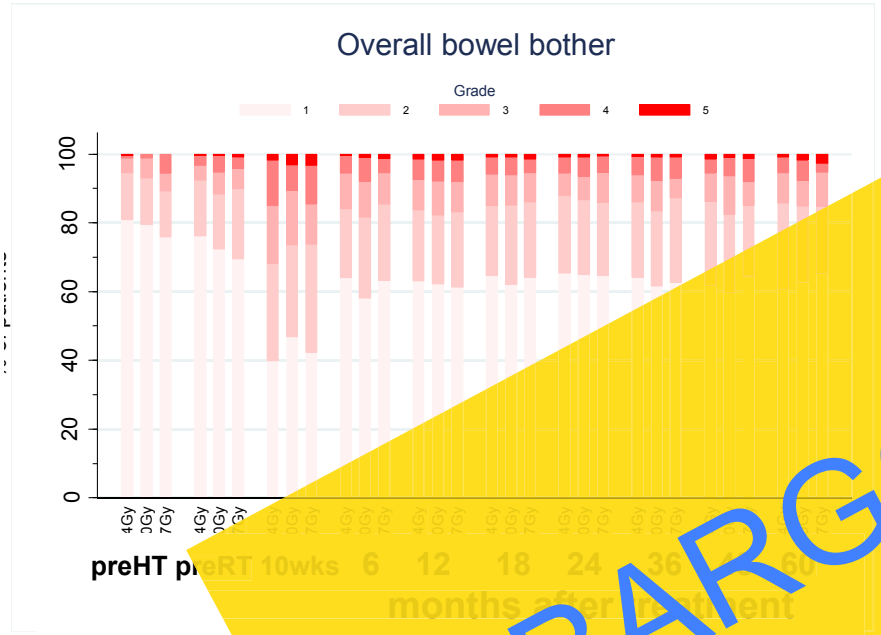
74Gy	60Gy	57Gy
13.5%	13.2%	11.2%
	p= ns	p= ns

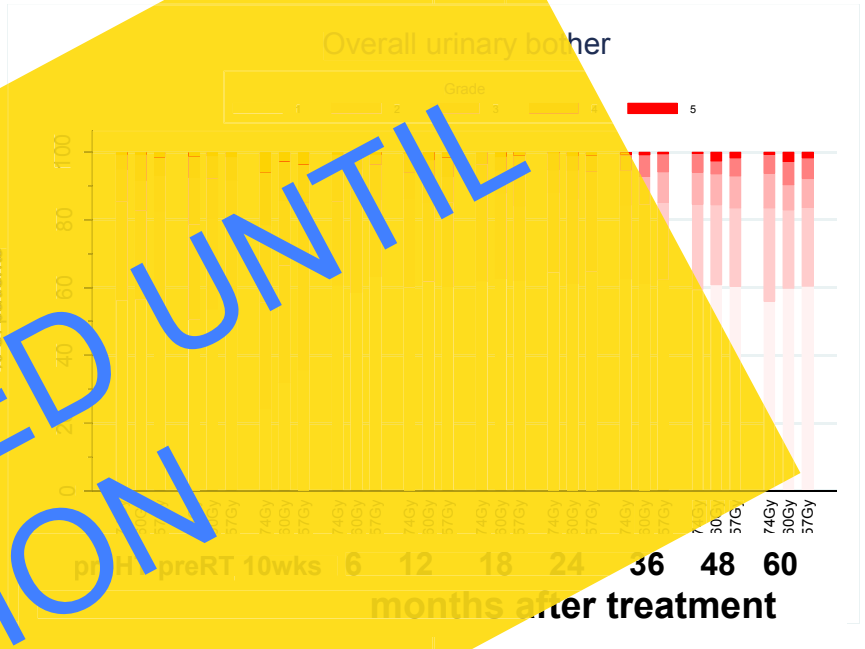
Gd 2+: KM 5 year estimate

74Gy	60Gy	57Gy
49.3%	50.0%	41.4%
	p= ns	**p= ns**

Comment: bladder symptoms less common at 6m - 5 years than pre-treatment

Quality of Life – Bowel and bladder bother





Moderate (4) or more bother: 5 year incidence

Bowel

74Gy	60Gy	57Gy
5.4%	7.6%	5.2%

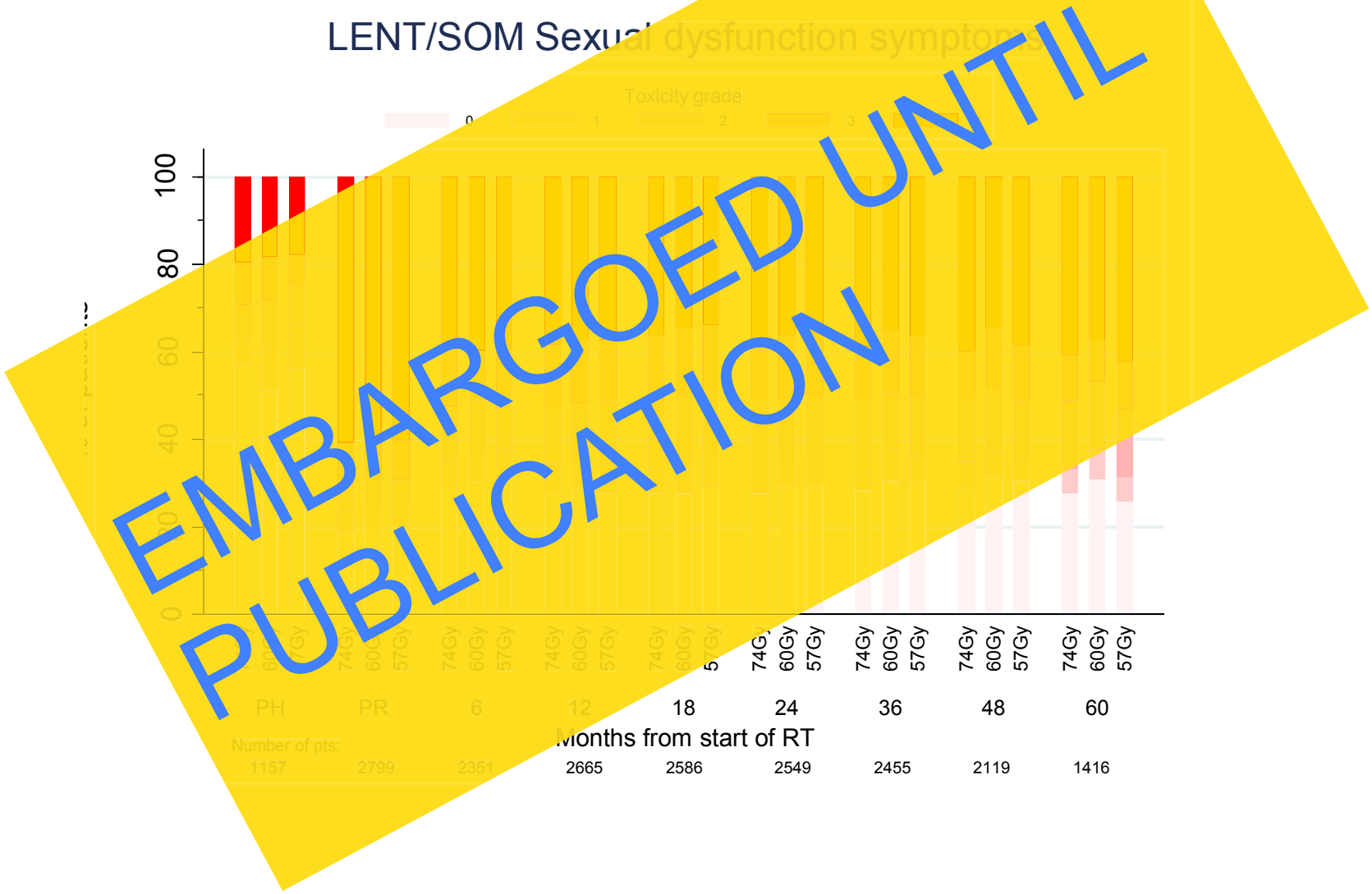
ptrend=0.75/0.77

Bladder

74Gy	60Gy	57Gy
6.5%	9.6%	7.9%

ptrend=0.74/0.83

Late toxicity – LENT/SOM sexual dysfunction



Comparison of QoL in National RT studies

CHHiP vs MRC Trial RT01 (74Gy groups)

A.Wilkins et al *Lancet Oncol* Sept 2015

	Bowel bother (%)		Bowel distress (%)	
Severity	Moderate	Severe	Moderate	Severe
RT01	3.5	3.1	11.8	0.7
CHHiP	4.6	1.0	4.2	0.0

Benefit from IMRT technique and dose constraints used in CHHiP

Conclusions

- With a median follow up of 62 months, hypofractionated treatment of 60Gy in 20F is non-inferior to 74Gy in 37F and superior to hypofractionated treatment of 57Gy in 19F
- Treatment of 60Gy in 20 fractions is associated with a small increase in late bowel side effects compared to 57Gy.
- The overall low side effect profile observed reflects the treatment technique chosen for use in this trial.
- Estimate of the alpha/beta ratio is 1.8Gy (provided no time factor)

Impact

- Modest hypofractionation using 60Gy in 20 fractions delivered with high quality RT techniques can be recommended as a new standard of care.

Impact on NHS Service Provision

NATCANSAT NHS

Chris Ball Head of NATCANSAT **National Clinical Analysis & Specialised Applications Team**
The Clatterbridge Cancer Centre NHS Foundation Trust

- Prostate cancer RT – 27% of workload of RT depts
- 14,364 patients treated in 2014/15
- 455,638 attendances
- Uniform change to 20 fraction schedule would save over 200,000 attendances annually
- NHS cost saving ~ £20-30M/year

Department of Health

CANCER RESEARCH UK

NHS National Institute for Health Research

Clinical Research Network Cancer

Acknowledgements

- Patients and investigators and research support staff at the 71 participating centres in the UK, Ireland, Switzerland, New Zealand

PI	Patients	PI	Patients	PI	Patients	PI	Patients
David Dearnaley	371	Zafar Malik	71	Fiona McKinna	29	Pierre Thirion	10
Isabel Syndikus	294	Daniel Ford	69	Robert Huddart	28	Maria Vilarino-Varela	8
Vincent Khoo	159	Robert Wade	66	Mark Beresford	26	Daniel Zwahlen	7
Miguel Panades	155	Chinnamani Eswar	64	Anjali Zarkar	24	Sharon Beesley	6
Christopher Scrase	153	Robert Thomas	61	Jo Hamilton	23	Joseph Davies	6
David Bloomfield	116	Cathryn Woodward	59	Richard Shaffer	22	Nishi Gupta	5
Alison Birtle	107	Paula Wells	58	Ann Henry	22	Peter Jenkins	5
John Logue	102	Gail Horan	57	Audrey Cook	19	Paul Elliot	5
Julian Money-Kyrle	100	Christine Elwell	54	Richard Brown	16	Anna Lydon	5
Helen Patterson	100	Stephen Mangar	53	Omi Parikh	16	John Glaholm	3
Joe O'Sullivan	92	Rana Mahmood	46	Robert Hughes	13	Jacqueline Livsey	2
Andrew Stockdale	89	Catherine Coyle	34	Stephanie Gibbs	11	Duncan McLaren	2
John Staffurth	86	Azman Ibrahim	33	Hugh Newman	11	Perric Crellin	1
Peter Kirkbride	81	Fawzi Adab	32	Joseph Martin	10	Al-Samarraie	1
John Graham	79	Ian Pedley	29	Chakiath Jose	10		

- Trials unit staff at ICR-CTSU and Bob Champion Unit
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What's the fraction sensitivity of prostate cancer ?

Ongoing Phase III Trials of Hypofractionated RT in Prostate Cancer

Modest 3Gy

Toronto (1204)	60Gy 20F (4w) vs 78Gy 39F
NKI (800)	64.6Gy 19F (7w) vs 78Gy 39F
UK CHHiP (3160)	**57Gy 19F (4w) vs 60Gy 20F (4w) vs 74Gy 37F (NAD all int/high risk)**

Extreme ≥6Gy

HYPO Scandinavia (1200) 42.7Gy 7F (15-19d) vs 78Gy 39F

PACE (Cyberknife consortium) 36.25Gy 5F vs 78Gy 39F

What's the fraction sensitivity of Ca prostate?

Phase III Trials of extreme hypofractionation

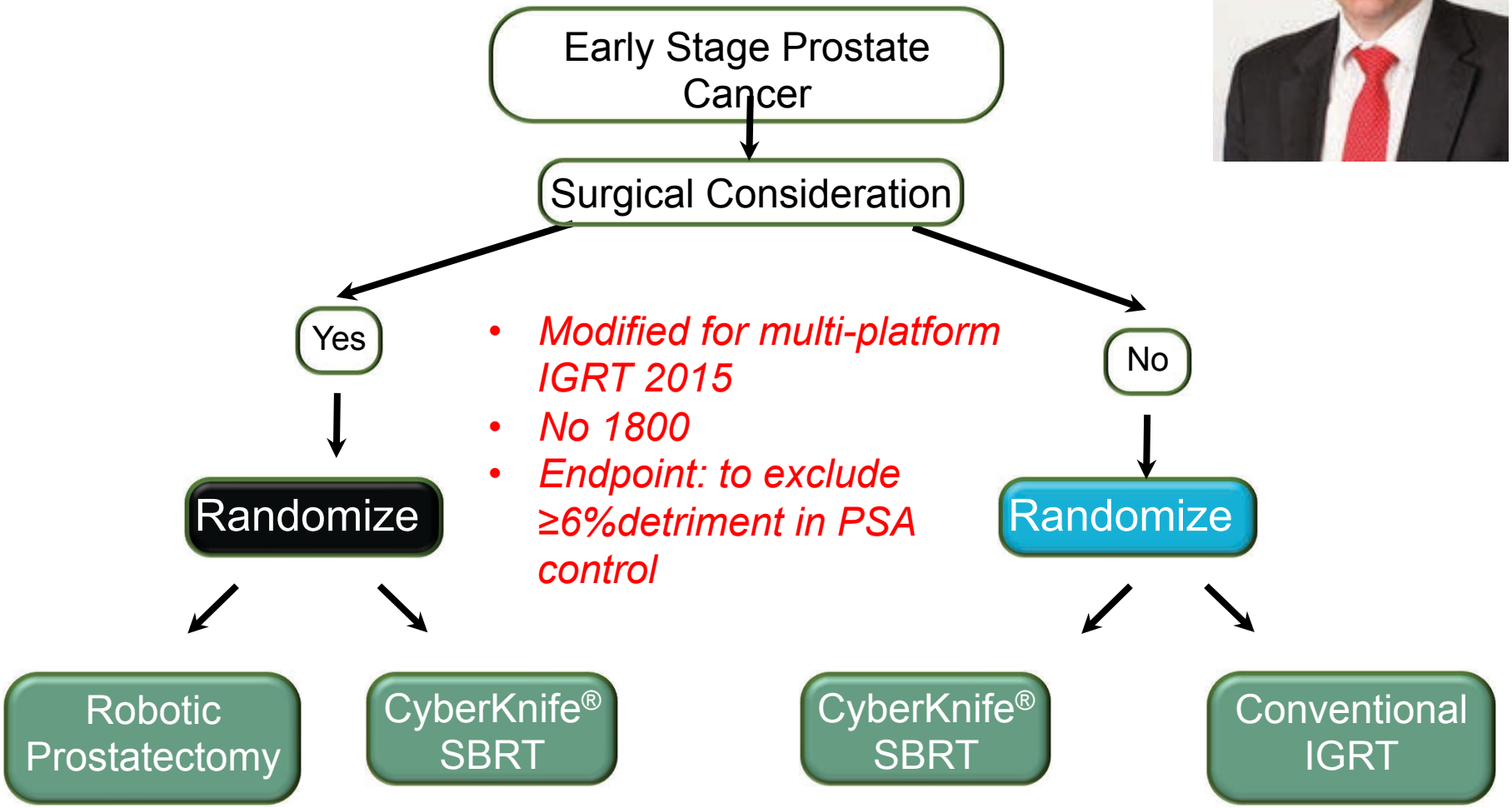
1. HYPO Trial: Scandinavia

- 42.7Gy in 7F of 6.1 Gy vs 78Gy in 39F of 2Gy
- IGRT in all patients
- Hormone therapy permitted

Collaboration: modified protocol with NADT approved by CTAAC 2014 for UK component - no. 1800

Endpoint: to exclude ≥ 6% detriment in PSA control

PACE: International Phase III Trial of extreme hypofractionation



- *Modified for multi-platform IGRT 2015*
- *No 1800*
- *Endpoint: to exclude ≥6%detriment in PSA control*

Daily Mail

Tuesday 12th January 2016

http://www.dailymail.co.uk/health/article-3394700/High-dose-prostate-therapy-halves-trips-hospital-Having-just-20-sessions-intensity-modulated-radiotherapy-effective-save-NHS-millions.html

High-dose prostate therapy that halves trips to hospital

By OONA MASHTA

AFTER the initial shock of being diagnosed with prostate cancer, David Parker just wanted to get the treatment over and done with.

'Fortunately, the cancer was still confined to my prostate, but I was advised to have radiotherapy because it could otherwise spread,' says David, 73, a retired engineer from Surbiton, Surrey.

'The problem is that radiotherapy is usually done in 37 sessions; you have it five days a week for seven-and-a-half weeks. And going to hospital nearly every day for nearly two months seemed like a long time to me.'

So when he was offered the chance to take part in a trial that meant just 20 sessions of radiation — at higher doses — he didn't hesitate.

David was diagnosed with prostate cancer five years ago. He'd been going to the loo up to six times a night, which can be a symptom of the disease, but had initially dismissed this as a natural part of ageing. But when his younger brother, Barry, was diagnosed with advanced prostate cancer at 63, doctors advised David to get tested, as the disease can run in families.

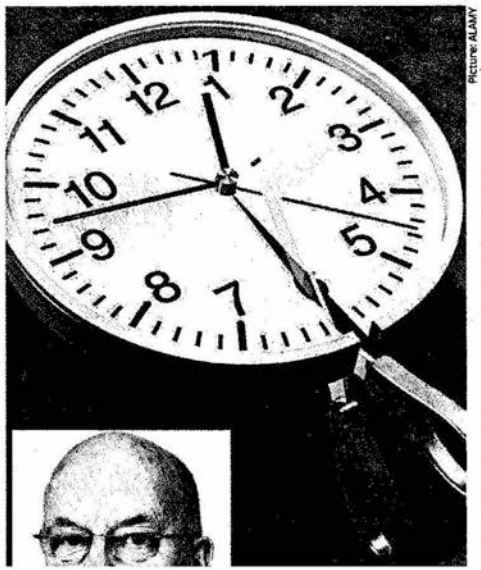
'Obviously I did so immediately and it was a good job I did, too, as I know that prostate cancer is very treatable in the early stages,' says David.

A blood test revealed he had high levels of prostate-specific antigen (PSA) in his blood; raised levels can be a sign of prostate cancer. A biopsy confirmed the diagnosis. Every year more than 41,000 men are diagnosed with prostate cancer; about 11,000 men die from it.

The main treatments are surgery and radiotherapy; every year, about 15,800 prostate cancer patients have radiotherapy, often alongside hormone therapy, which works to shrink the cancer, delay its growth and reduce symptoms.

Radiotherapy uses high-energy X-rays (usually delivered from outside the body) to destroy the DNA inside the cancer cells, causing them to die. The problem is that healthy cells can also be damaged, though modern techniques aim to target the dose very precisely in order to avoid this.

Typical damage might be to the bowel, resulting in loose



Picture: ALAMY

radiotherapy in high doses is safe and causes no more side-effects than standard, longer-term treatment.

Before his radiotherapy, David underwent a month of hormone treatment — two fortnightly injections — to reduce the amount of testosterone (which can fuel prostate cancer) in his body, helping to shrink the cancer.

Then followed the course of radiotherapy. 'For the first three months I had problems with my bowels,' he says. 'I had less control and I was going a couple of times a day.

'The doctors said the radiotherapy must have hit my bowel, which is why I suffered for the first few weeks, but it's now fine.' Five years on, he remains cancer free.

Professor David Dearnaley, from the Institute of Cancer Research and The Royal Marsden Hospital in London, and the lead researcher in the trial, says: 'Our results make a compelling case to change practice within the NHS and move from a 37-day regimen to one that lasts 20 days.

'Apart from saving patients repeated hospital visits it could save the NHS tens of millions of pounds a year.

- Background
- Dose
- Fractionation
- **Systemic treatment**
- Pelvic treatment
- Post–operative treatment
- Side-effects
- Blue skies

Technology

Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial

James W Denham, Allison Steigler, David S Lamb, David Joseph, Sandra Turner, John Matthews, Chris Atkinson, John North, David Christie, Nigel A Spry, Keen-Hun Tai, Chris Wynne, Catherine D'Este

Lancet Oncol 2011; 12: 451–59

RT to prostate and SV - 66Gy

Randomisation:

RT alone vs RT and 3 months NAD

vs RT and 6 months NAD

No. 802, median FU 10.6 yrs

Median PSA 15, Int. Risk 16% High Risk 84%

TROG 96.01

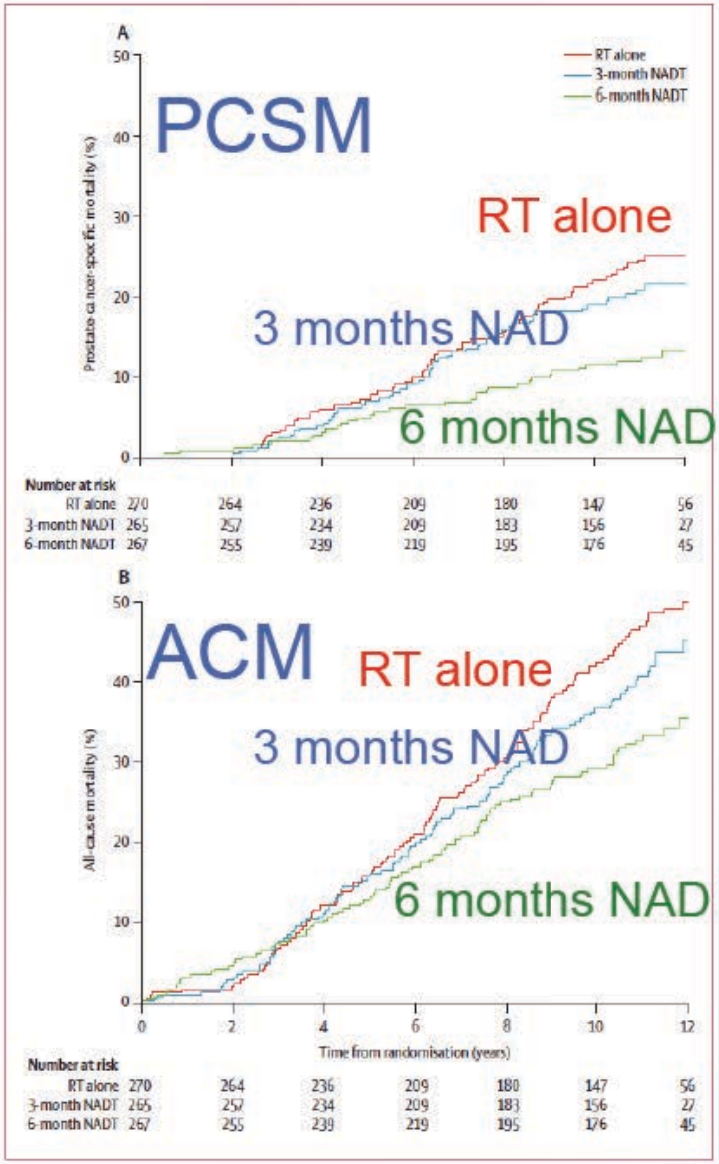
Lancet Oncol 2011; 12: 451–59

Prostate cancer specific mortality (10yrs)

- RT alone 22.0%
- RT and 3 months NAD 18.9%
- RT and 6 months NAD 11.4%

All cause mortality (10yrs)

- RT alone 42.5%
- RT and 3 months NAD 36.7%
- RT and 6 months NAD 29.2%



TROG 96.01

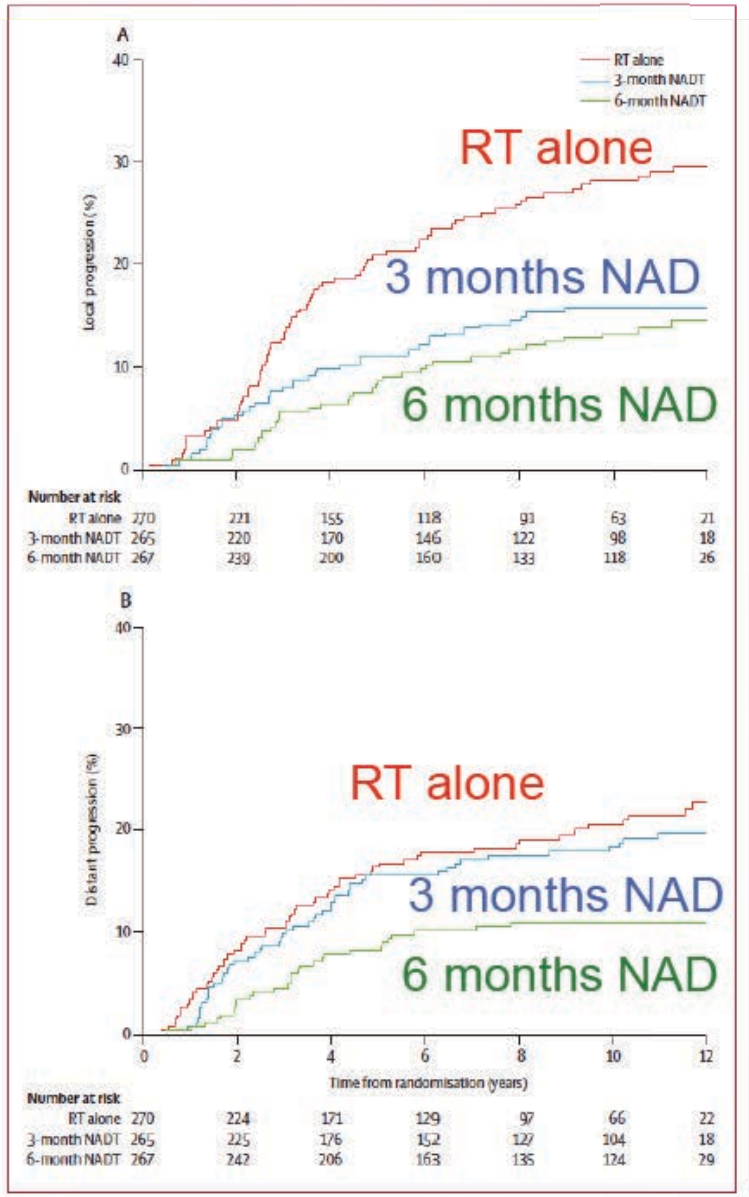
Lancet Oncol 2011; 12: 451–59

Local progression free

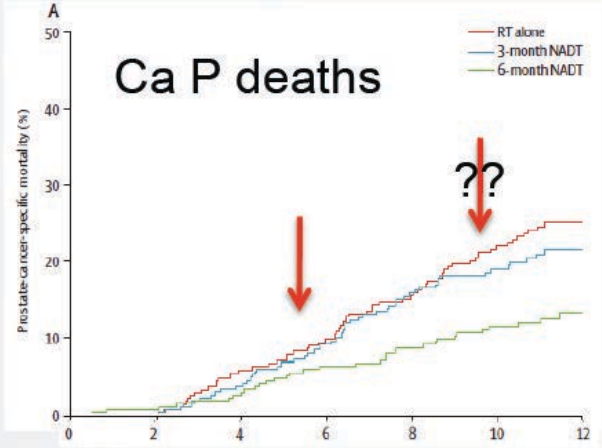
- RT alone 86
- RT and 3 months NAD 53
- RT and 6 months NAD 40

Distant metastases free

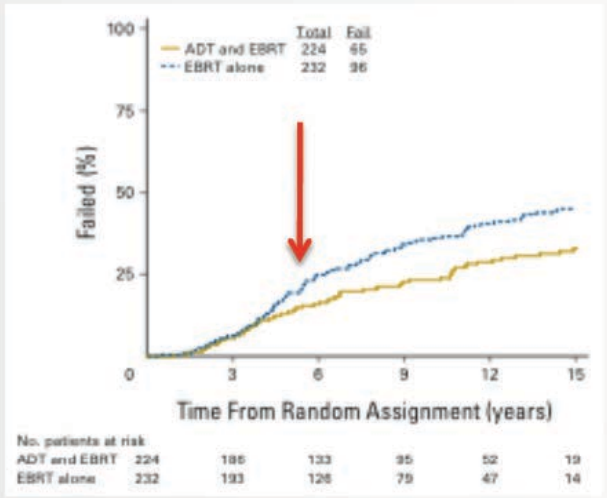
- RT alone 98
- RT and 3 months NAD 79
- RT and 6 months NAD 49



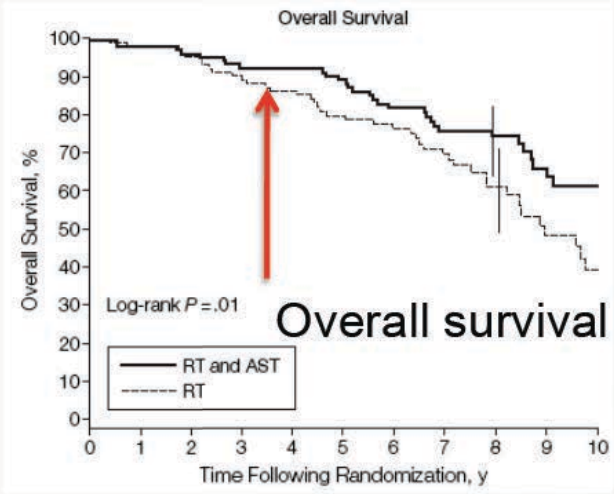
Time to separation of survival curves with neo/adjuv.hormone treatment



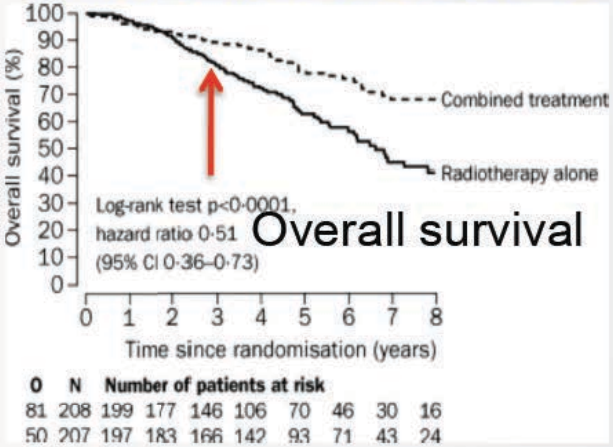
Denham Lancet Oncol 2011 12 451



Roach JCO 2008 26 585-91

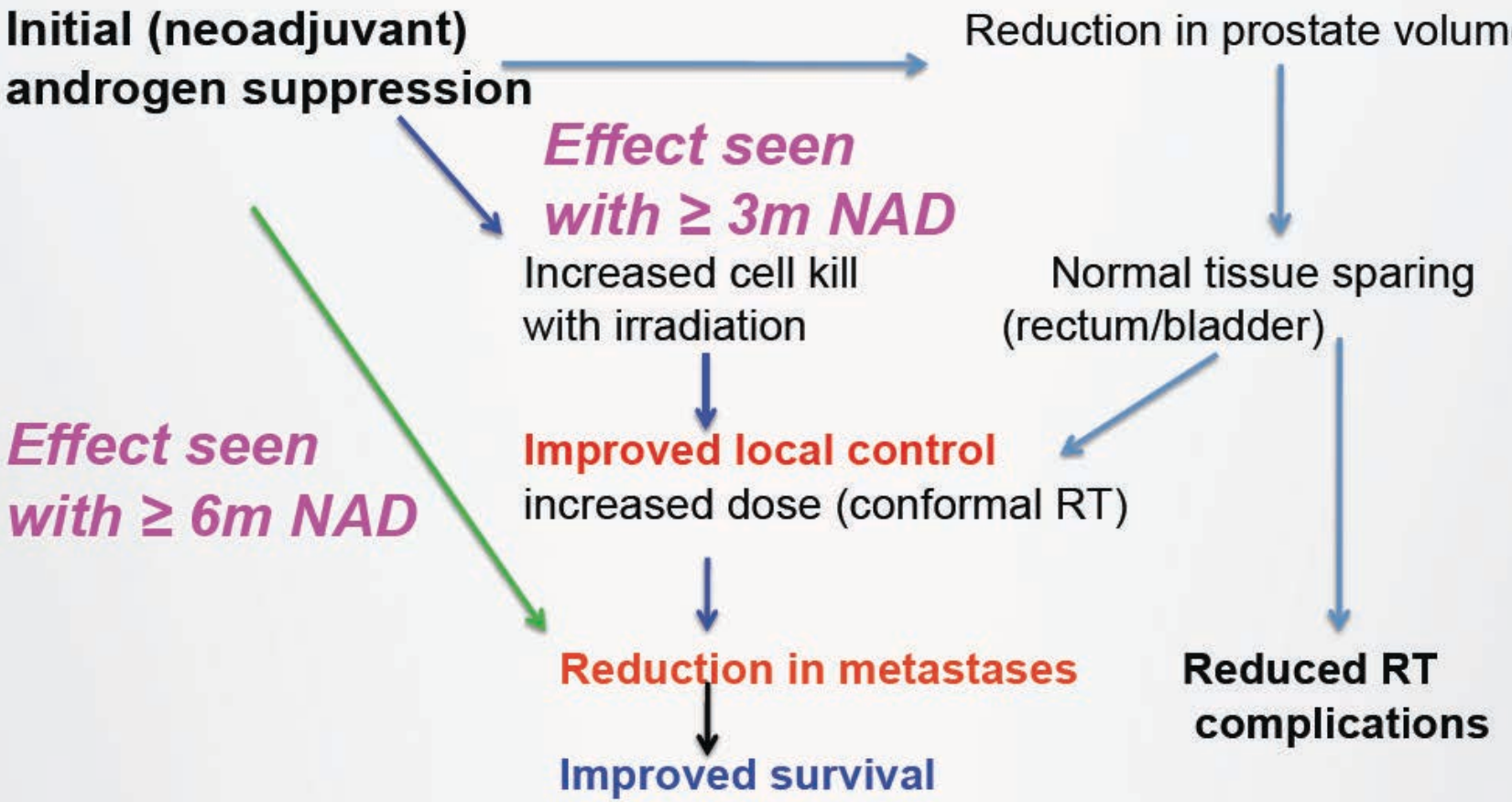


D'Amico JAMA 2008 299 289-95



Bolla Lancet 2002 360 103

Combined modality treatment using androgen suppression and radiotherapy

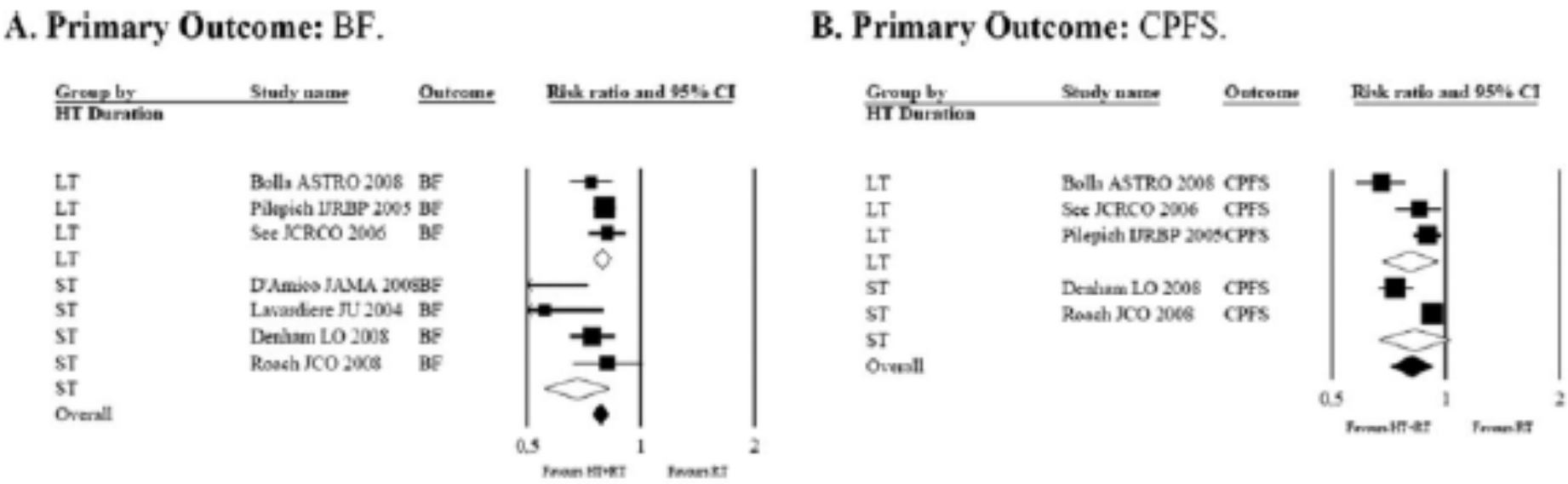


Metaanalysis of homones and RT

Bria Cancer 2009 115 3446

7 trials - 4387 patients - 3 long /4 short course

HR 0.76 for PSA failure 0.81 for CPFS

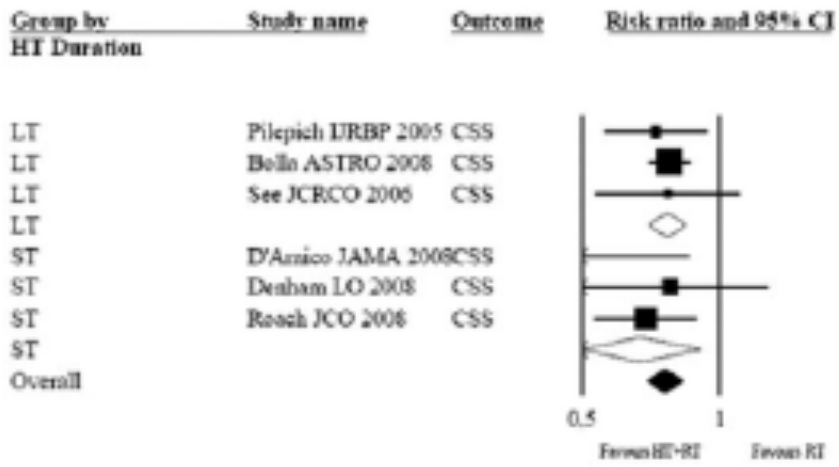


Metaanalysis of homones and RT

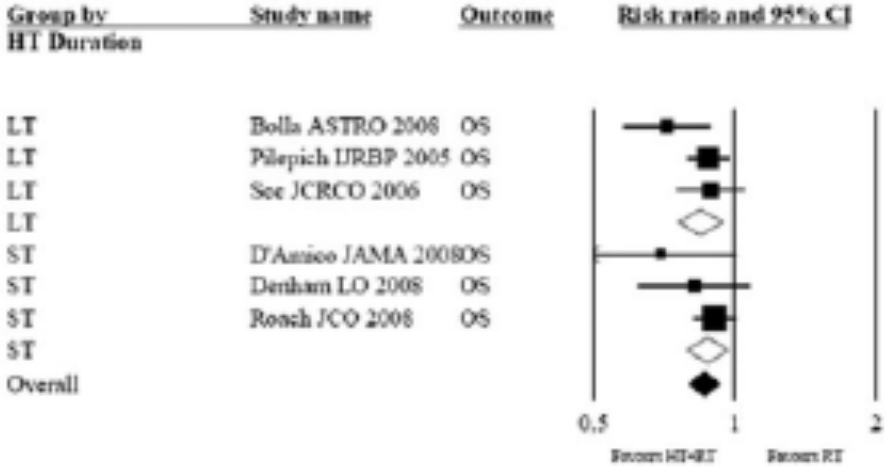
Bria Cancer 2009 115 3446

HR 0.76 for CSS and 0.86 for OS

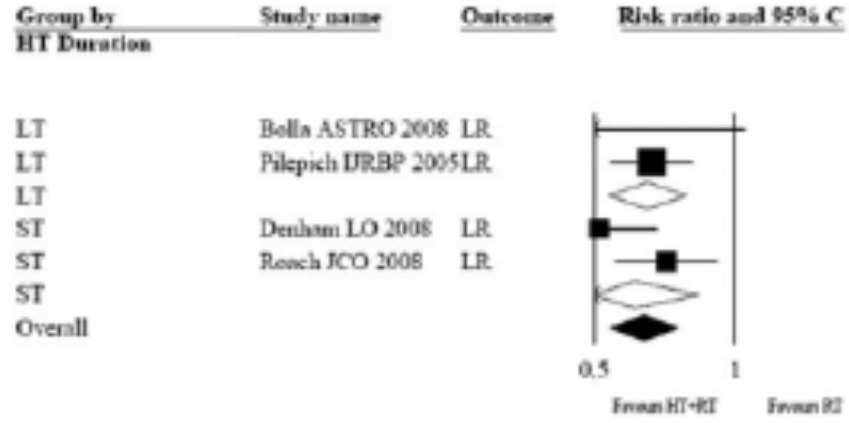
C. Secondary Outcome: CSS.



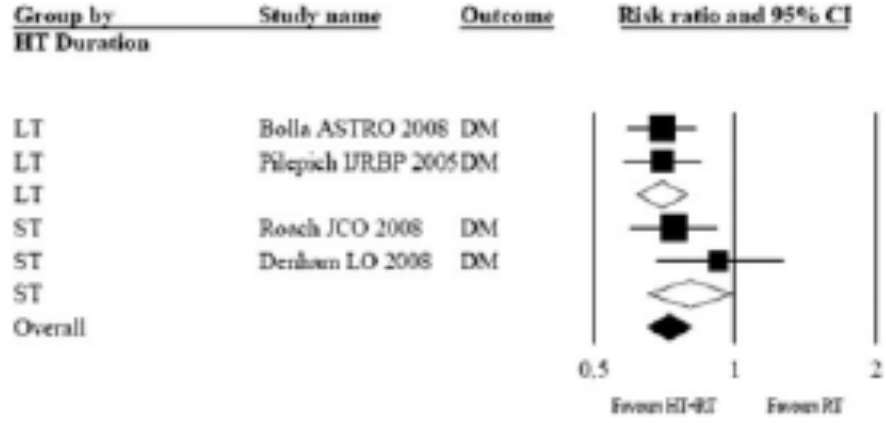
D. Secondary Outcome: OS.



E. Secondary Outcome: LR.



F. Secondary Outcome: DM.



Metaanalysis of homones and RT Bria Cancer 2009 115 3446

NO increase of GU / GI toxicity or Cardiac deaths

Table 3. Combined Toxicity and Cardiac Deaths Results

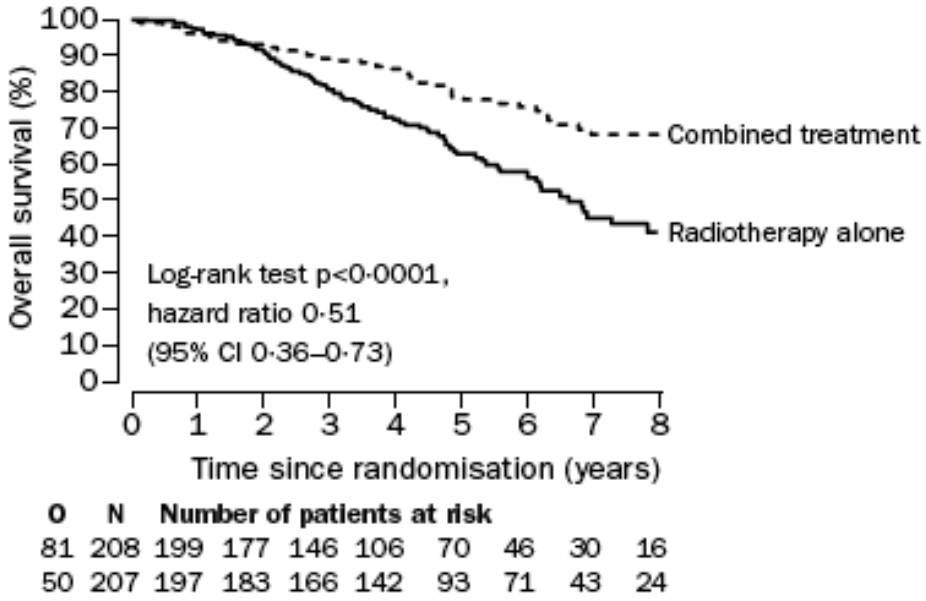
Outcomes	Pts (RCTs)	RR (95% CI)	*P*	Heterogeneity *P*
Overall toxicity	2050 (4)	0.92 (0.87-1.11)	.41	.55
GU toxicity	2050 (4)	0.66 (0.36-1.22)	.19	.05
GI toxicity	2050 (4)	0.69 (0.46-1.03)	.07	.71
Cardiac deaths	4266 (6)	0.87 (0.70-1.09)	.24	.69

Pts indicates patients; RCT, randomized clinical trial; RR, relative risk; CI, confidence interval; GU, genitourinary; GI, gastrointestinal.

Articles

Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial

Michel Bolla *Lancet* 2002 ;360: 103-08



O	N	Number of patients at risk							
81	208	199	177	146	106	70	46	30	16
50	207	197	183	166	142	93	71	43	24

Figure 2: **Kaplan-Meier estimates of overall survival by treatment group**

NNT treat is 6.7 to prevent 1 CaP death at 5 yrs

NNT treat is 2.9 to prevent 1 PSA recurrence at 5yrs

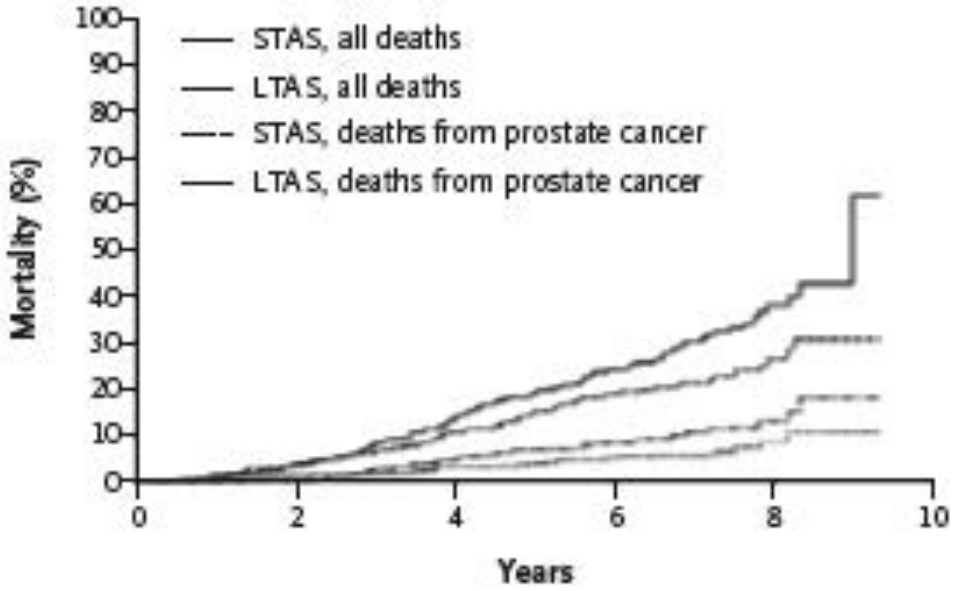
The NEW ENGLAND JOURNAL of MEDICINE

N Eng J Med 2009;360:2516-7

ORIGINAL ARTICLE

Duration of Androgen Suppression in the Treatment of Prostate Cancer

Michel Bolla, M.D., Theodorus M. de Reijke, M.D., Ph.D.,



EORTC Trial

RT+ 6m AD vs 36m AD

No. 970 FU 6.4yrs

5 yr Overall Deaths19.0% vs 15.2%

Absolute difference 3.8% HR 1.42

5 yr CaP Deaths 4.7% vs 3.2%

Absolute difference 1.5% HR 1.42

“Number needed to” (NNT) estimates

Short (6m) or long (3yrs) adjuvant AS with RT in advanced localised disease

NNT treat (3yrs AS) is 66.7 to prevent
1 CaP death at 5 yrs

NNT treat (3yrs AS) is 26.3 to prevent
1 death from any cause at 5 yrs

RTOG 92-02:Radiotherapy and duration of androgen suppression

Change in outcome using LTAD compared with STAD

	5 year disease specific survival	5 year overall survival
All cases	+5%	-1%
Gleason 8-10	+12%	+11% (p=.02)
Gleason 4-7	+3%	-5%

Hanks IJROBP 2000 48 112
Parker and Dearnaley JNCI 2002 94 8661-2

Diabetes and cardiovascular disease during androgen deprivation for prostate cancer Keating JCO 2006 24 4448

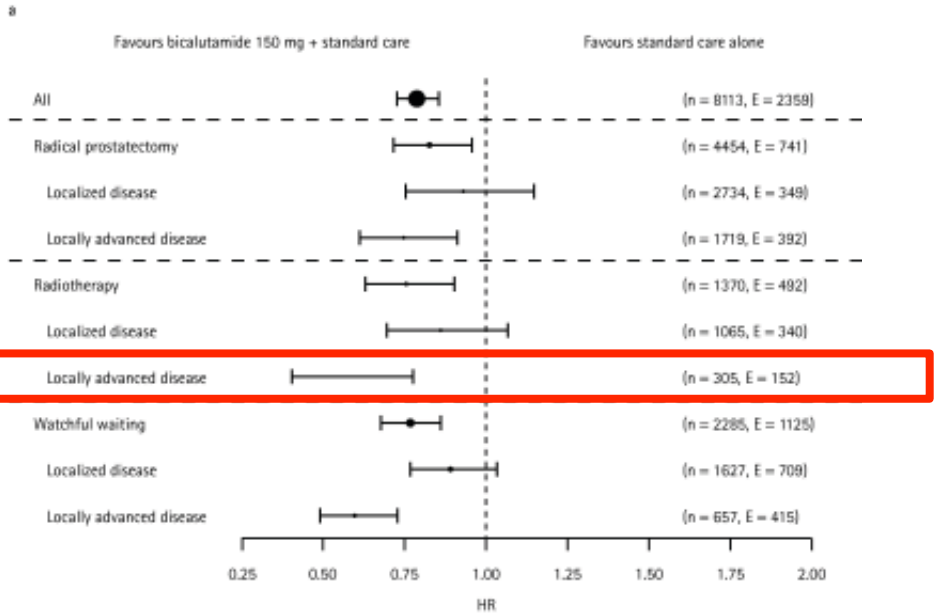
Total No. 73,196 Age ≥66 LHRHa 37% Orchidectomy 7% Adjusted H.R. Rate of event/1000 patient years and adjusted Hazard Ratio								
	Diabetes		Incident CHD		M1		Sudden Cardiac Death	
No Treatment	21	-	61	-	11	-	9	9
LHRHa	29	1.4	72	1.2	14	1.1	13	1.2
Orchidectomy	25	1.3	63	1.0	13	1.0	13	1.0
HR 1.1 p<.05; ≥1.2 p<0.001								

What should we advise?

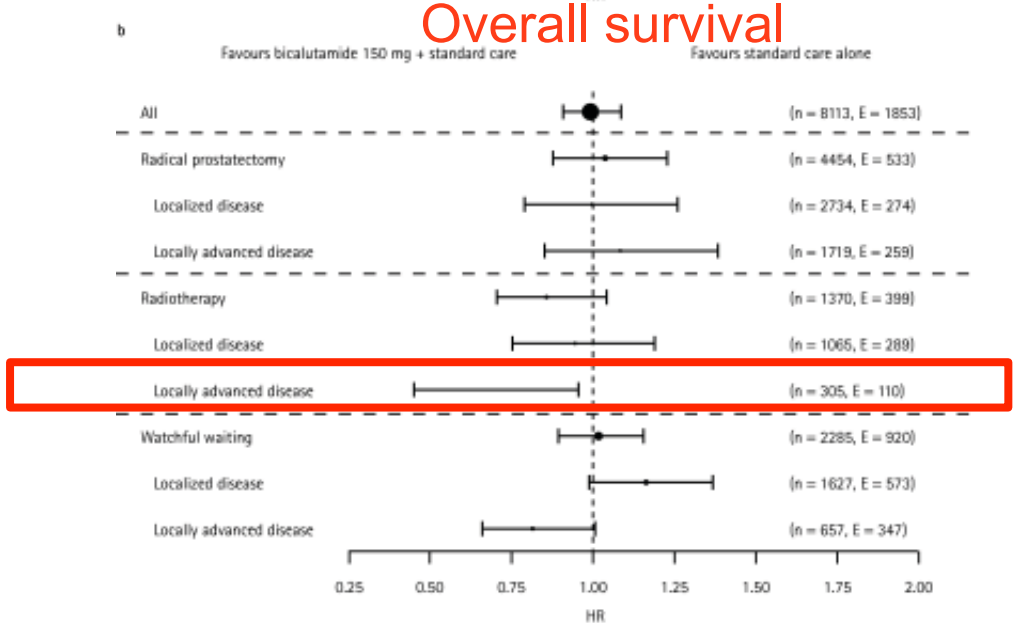
Address risk factors

- Diabetes , Cholesterol, Hypertension
- Aspirin
- Exercise
- Bone health
- Consider testosterone replacement

Progression free survival (n=no. patients in subgroup E= no. of events)



Overall survival

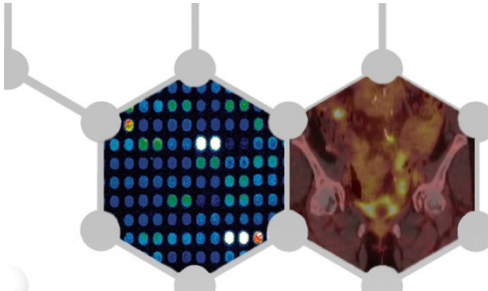


The size of the HR circle is proportional to the number of events included in the analysis

Bicalutamide 150mg plus standard care vs standard care alone for early prostate cancer (EPC). Mcleod *BJU Int 2006* 9 247

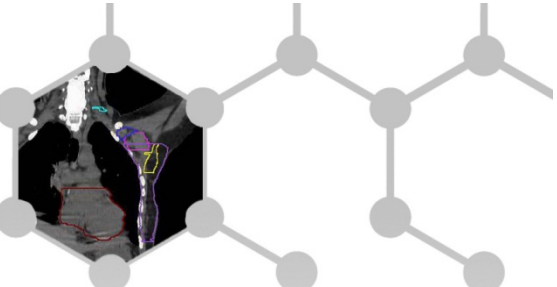
Questions for use of adjuvant androgen suppression

- How long?
- Where is “dividing line” between long and short course treatment?
- Are anti-androgens as effective?
- Can additional agents improve on LHRHa alone? Abiraterone ?? Enzalutamide ?? Docetaxel???



NRG ONCOLOGY

Advancing Research. Improving Lives.™



NRG Oncology/RTOG 96-01

A Phase III trial in patients following Radical Prostatectomy (RP) with pT2-3, pN0 prostate cancer and elevated PSA levels: Anti-Androgen Therapy (AAT) with Bicalutamide during and after *salvage* Radiation Therapy (RT) compared to Placebo + *salvage* RT.

RTOG 96-01 Schema

Pre-randomization Stratifications

Surgical margins: positive or not
Nadir PSA level: < 0.5: yes or no
Entry PSA level: < 1.6 or 1.6 – 4.0
Pre RP neoadjuvant STAD: yes or no

RANDOMIZE

Arm 1 → RT (64.8 Gy) plus AAT (Bicalutamide 150 mg) QD**

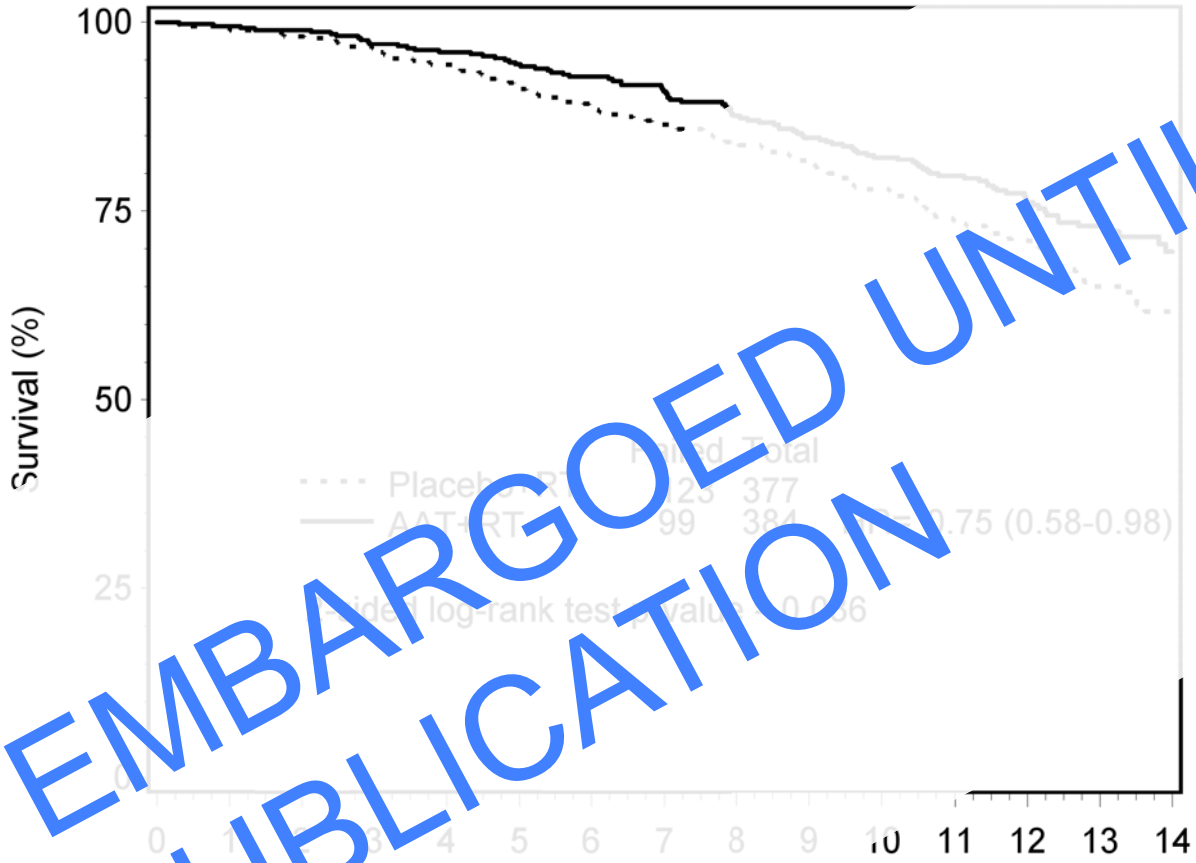
Arm 2 → RT (64.8 Gy) plus placebo QD**

** During and after RT for 24 months

- No. 761, age 65 yrs
- Median entry PSA was 0.6 ng/ml
- follow-up 12.6 yrs

NRG ONCOLOGY™

Overall Survival



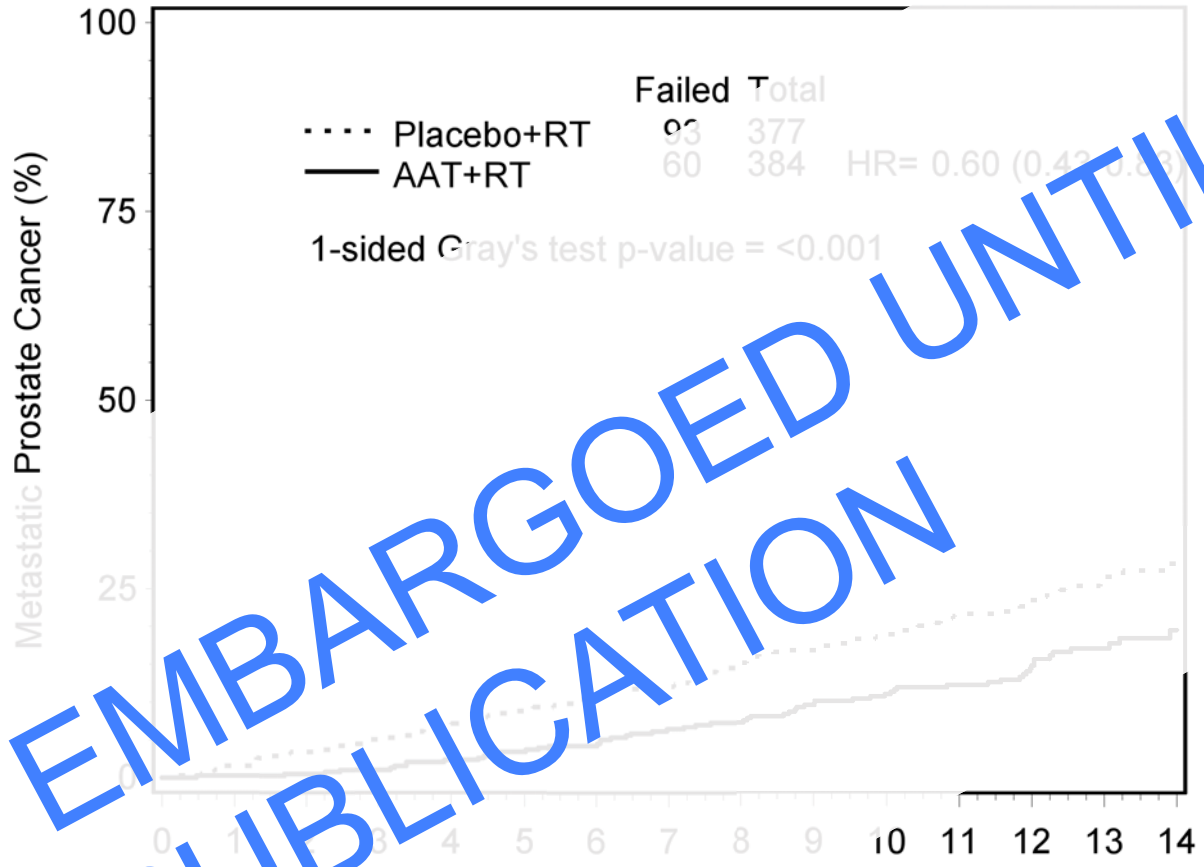
EMBARGOED UNTIL PUBLICATION

OS at 10 yrs:
82% vs 78%

Patients at Risk															
Placebo+RT	377	373	369	360	351	333	320	308	295	281	261	234	174	99	48
AAT+RT	384	382	376	368	362	347	337	326	308	294	279	253	190	123	60

NRG ONCOLOGY™

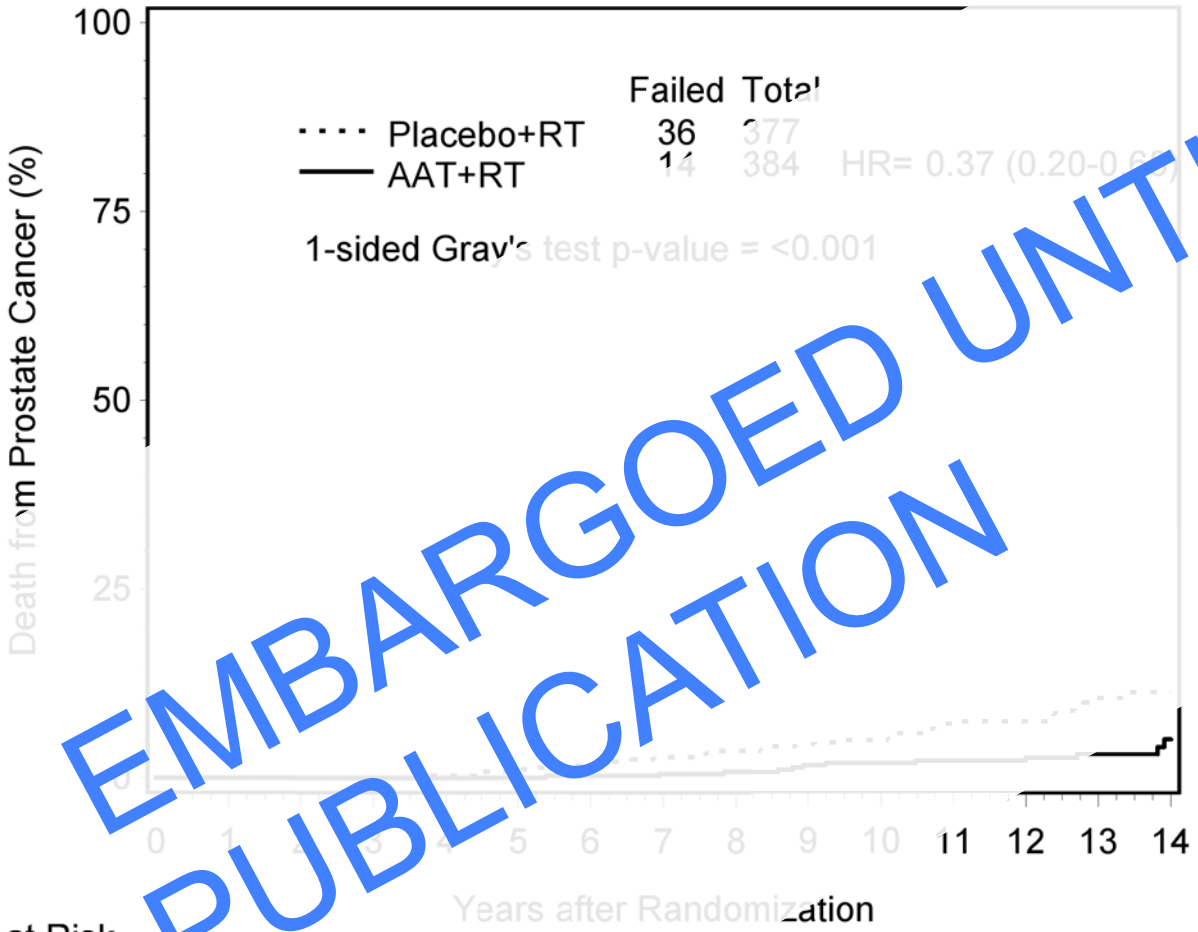
Time to Metastatic Prostate Cancer



DM from PC
at 12 yrs
14% vs 23%

NRG ONCOLOGY™

Time to Death from Prostate Cancer



Patients at Risk

Placebo+RT	377	373	369	360	351	333	320	306	295	281	261	234	174	99	48
AAT+RT	384	382	376	368	362	347	337	326	308	294	279	253	190	123	60

Death from PC at 12 yrs 2.3% vs 7.5%

NNT=17

NRG ONCOLOGY™

Other events during treatment*

	AAT +RT	Placebo + RT
Cardiac events ≥Grade 2	4%	3%
Cardiac events ≥Grade 3	2%	2%
Gynecomastia -- all Grades	**70%**	**11%**

* No cardiac deaths during AAT or Placebo Treatment

NRG ONCOLOGY™

MRC STAMPEDE TRIAL 2014

Patient group

>> Histologically confirmed PCa

>> Starting long-term hormone therapy for **first time**

>> From one of 4 groups:

1. Newly diagnosed M+
2. Newly diagnosed N+
3. Newly diagnosed high-risk N0M0
4. High-risk hormone-naïve failing after previous local treatment

Comparison Lead Investigator

>> Dr Gert Attard, London

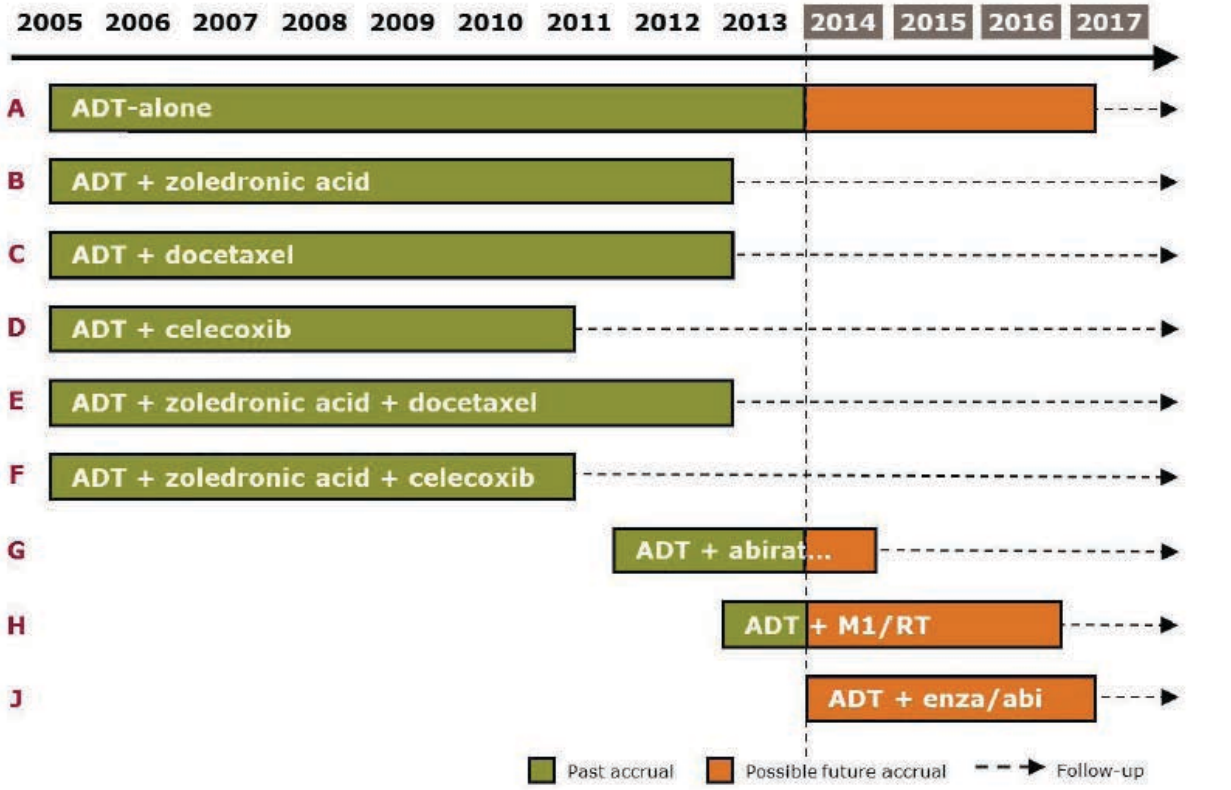
Chief Investigator

>> Prof Nick James, Birmingham

Sponsor

>> UK Medical Research Council

Figure 1: Actively recruiting trial over time and possible projection



For more information on STAMPEDE: www.stampedetrial.org

ISRCTN78818544
NCT00268476

MRC STAMPEDE TRIAL 2014

Patient group

>> Histologically confirmed PCa

>> Starting long-term hormone therapy for **first time**

>> From one of 4 groups:

1. Newly diagnosed M+
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3. Newly diagnosed high-risk N0M0
4. High-risk hormon… failing after previo… treatment

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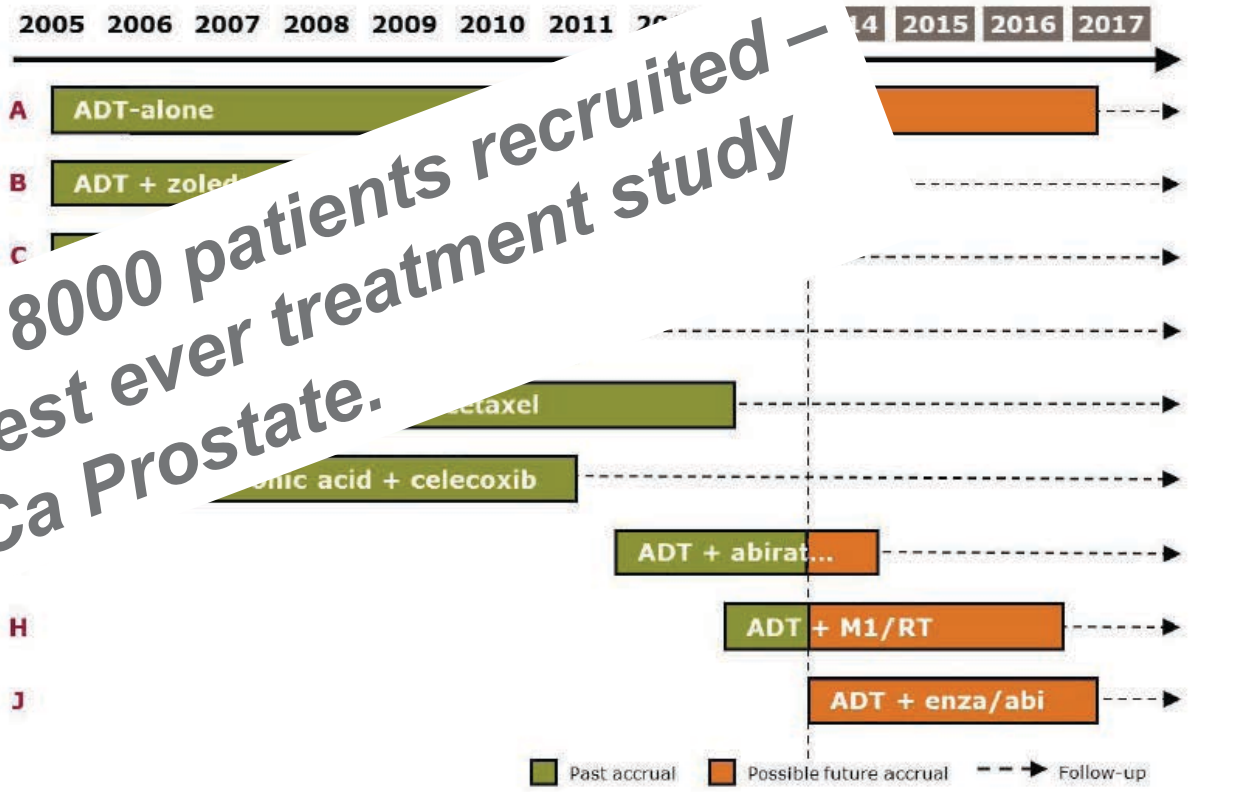


Over 8000 patients recruited – largest ever treatment study in Ca Prostate.

For more information on STAMPEDE: www.stampedetrial.org

ISRCTN78818544
NCT00268476

Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial

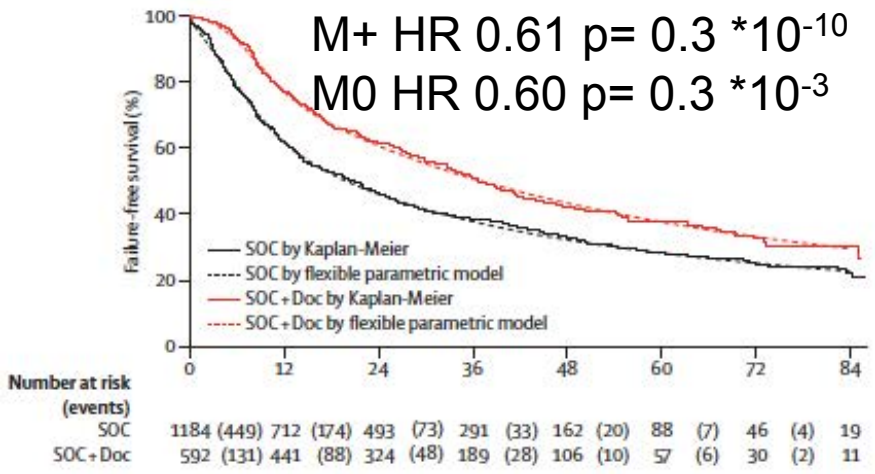
Published on line Dec 22nd 2015

*Nicholas D James, Matthew R Sydes, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Melissa R Spears, Alastair W S Ritchie, Christopher C Parker, J Martin Russell, Gerhardt Attard, Johann de Bono, William Cross, Rob J Jones, George Thalmann, Claire Amos, David Matheson, Robin Millman, Mymoona Alzouebi, Sharon Beesley, Alison J Birtle, Susannah Brock, Richard Cathomas, Prabir Chakraborti, Simon Chowdhury, Audrey Cook, Tony Elliott, Joanna Gale, Stephanie Gibbs, John D Graham, John Hetherington, Robert Hughes, Robert Laing, Fiona McKinna, Duncan B McLaren, Joe M O'Sullivan, Omi Parikh, Clive Peedell, Andrew Protheroe, Angus J Robinson, Narayanan Srihari, Rajaguru Srinivasan, John Staffurth, Santhanam Sundar, Shaun Tolan, David Tsang, John Wagstaff, Mahesh K B Parmar, for the STAMPEDE investigators**

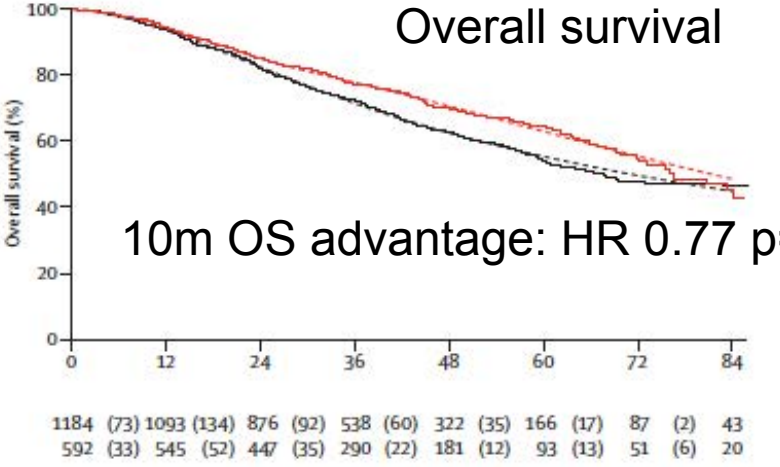
Failure free survival

M+ HR 0.61 p= 0.3 *10^{-10}

M0 HR 0.60 p= 0.3 *10^{-3}



Overall survival



10m OS advantage: HR 0.77 p= 0.05

- Background
- Dose
- Fractionation
- Systemic treatment
- **Pelvic treatment**
- Post–operative treatment
- Side-effects
- Blue skies

Technology

Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial *Lancet* 2009; 373: 301–08

Anders Widmark, Olbjørn Klepp, Arne Solberg, Jan-Erik Damber, Anders Angelsen, Per Fransson, Jo-Åsmund Lund, Ilker Tasdemir, Morten Hoyer,

After 10 years 12% improvement CaP deaths
10% improvement in overall survival RR 0.68

Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial *Lancet* 2011; 378: 2104–11

Padraig Warde*, Malcolm Mason*, Keyue Ding, Peter Kirkbride, Michael Brundage, Richard Cowan, Mary Gospodarowicz, Karen Sanders,

After 7 years 11% improvement CaP deaths
8% improvement in overall survival RR 0.77

RT to prostate and SV only
No pelvic RT
(obt. LN biopsy if psa ≥11)

Pelvic RT recommended

Trials in locally advanced prostate cancer using pelvic and prostate RT

EORTC 22866
RTOG 85-31

EORTC 22961
RTOG 92-02

Is there a role for pelvic RT?

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Is There a Role for Pelvic Irradiation in Localized Prostate Adenocarcinoma? Preliminary Results of GETUG-01

Pascal Pommier, Sylvie Chabaud, Jean Leon Lagrange, Pierre Richaud, François Lesaunier, Elisabeth Le Prise,

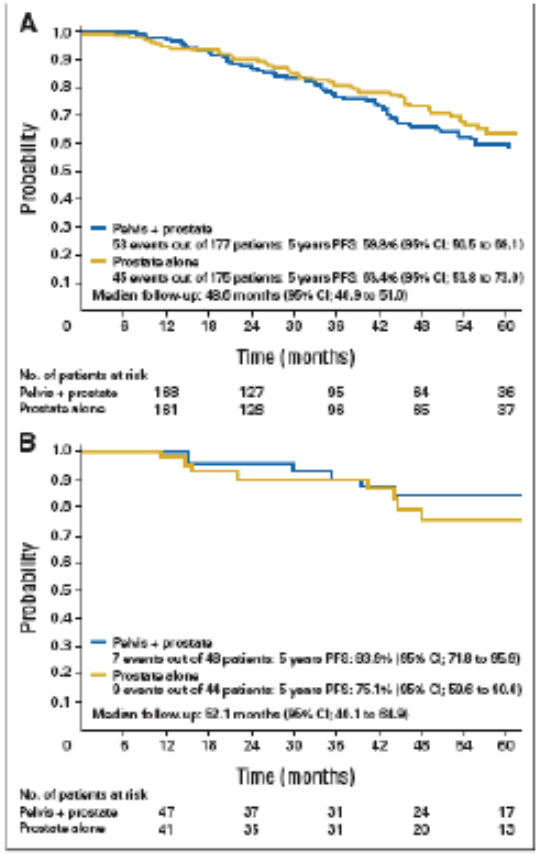
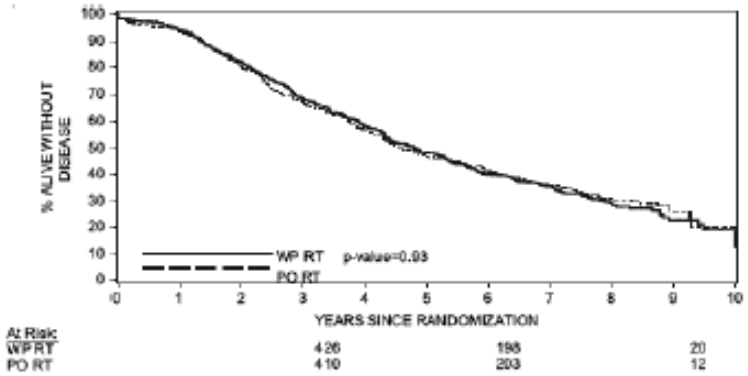


Fig 2. Progression-free survival (PFS) according to the stratified groups. (A) High-risk group. (B) Low-risk group.

UPDATED ANALYSIS OF RTOG 94-13



COLLEEN A. LAWTON, M.D.,* MICHELLE DESILVIO, PH.D.,† MACK ROACH III, M.D.

Int. J. Radiation Oncology Biol. Phys., Vol. 69, No. 3, pp. 646–655, 2007

What were the problems with these trials ?

- Recruitment of patients with low risk of LN mets (GETUG)
- Low doses of RT to prostate and pelvis approx. 66-70GY and 46-48Gy
- Inadequate treatment of some LN groups
- Interaction with scheduling of hormone treatment (RTOG)
- Some favourable subgroup analyses for LN RT

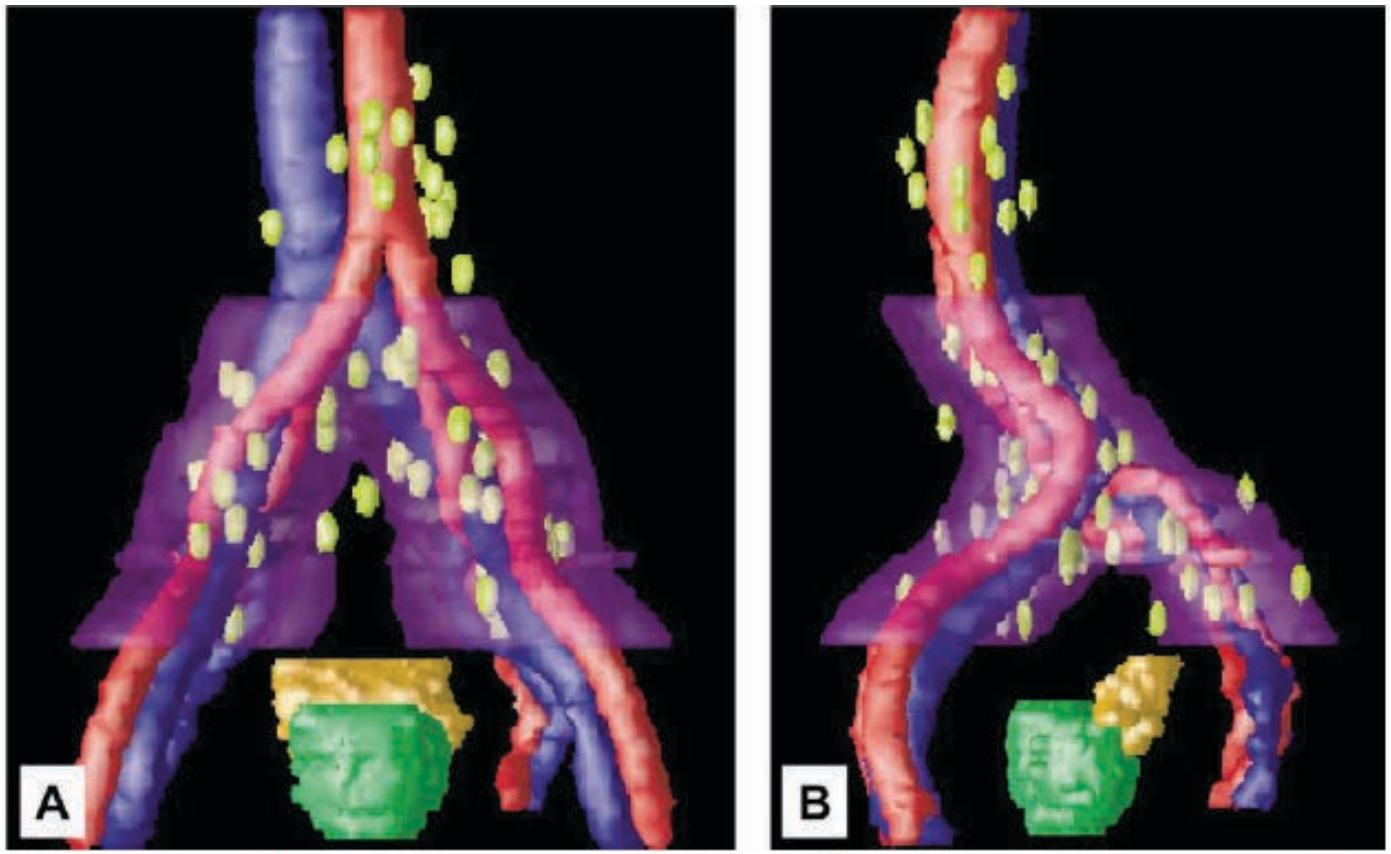
Lymph node involvement in prostate cancer

	Patients (N=)	Extent of PLND	Number of lymph nodes removed	Prevalence of LNI
Cagiannos et al	7014	Limited	NR	3.7%
Bhojani et al	3101	Limited	NR	2.2%
Klein et al	4693	Limited	5.8	2.1%
Toujier et al	144	Limited	9 (6-13)	4%
Makarov et al	5730	Limited	NR	1%
Heidenreich et al	103	Extended	28 (21-42)	26.2%
Briganti A et al	1020	Extended	19.1 (7-63)	11.8%
Bader A et al	365	Extended	21 (6-50)	24%
Toujier et al	595	Extended	13 (9-18)	14.3%
Toujier et al	471	Extended	13.1	11.4%

NR: not reported

Roach equation LN risk = 2/3 PSA + (GI score – 6)*10 is reasonably accurate

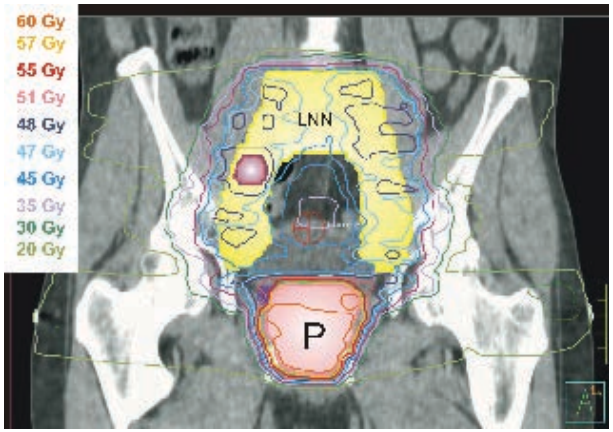
Target volume for Treatment of pelvic lymph nodes



Metastatic nodes referenced to pelvic vessels with a 2.0-cm clinical target volume expansion to the region

Radiotherapy development pipeline for CaP: Phase 1-2 Trials: lymph node radiotherapy

- Phase1/2 Dose Escalation Study: No.480
- Prostate dose 70 – 74Gy
- LN Dose 50 – 55 - 60 Gy with 5Gy boost if involved LN
- Hypofractionation cohort: 60 Gy Pr 47Gy LN (cf CHHiP)

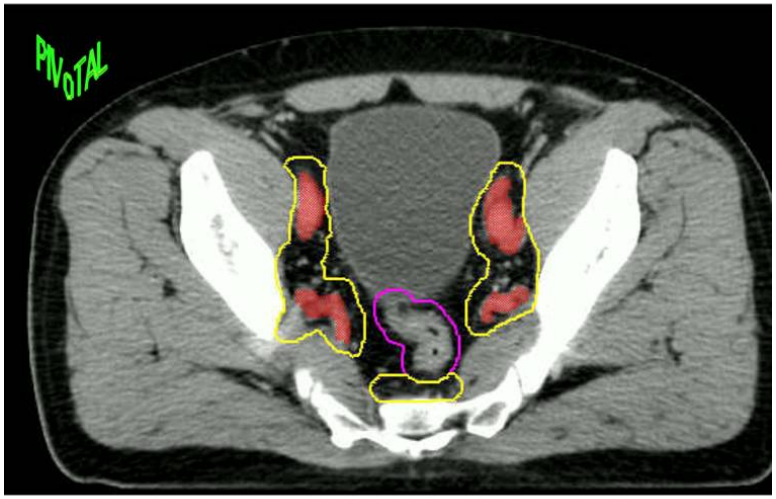


PIVOTAL

Phase 2 Pilot RCT: 2011-2013

- Prostate/SV IMRT vs P/SV and Pelvis IMRT
- 8 centres no.125
- End point 18 week toxicity

8. Expand bowel by 3mm isotropically (shown in pink) ensuring it does not overlap with the blood vessels. Edit the LN CTV to exclude the expanded bowel volume (as well as bladder & rectum) using the planning software. **Please note, the LN CTV may need to be manually edited if the expanded bowel volume compromises the LN CTV.**



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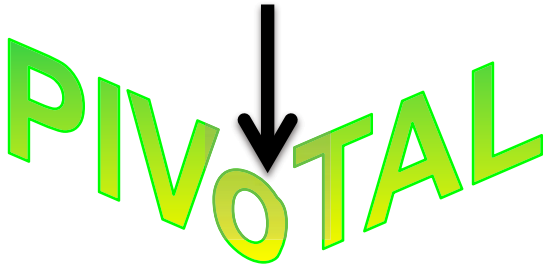


Phase 2 Pilot RCT: 2011-2013

- Prostate/SV IMRT vs P/SV and Pelvis IMRT
- 8 centres no.125
- End point 18 week toxicity

Impacts

•National QA for pelvic IMRT

• Vascular expansion outlining method

Future Impacts

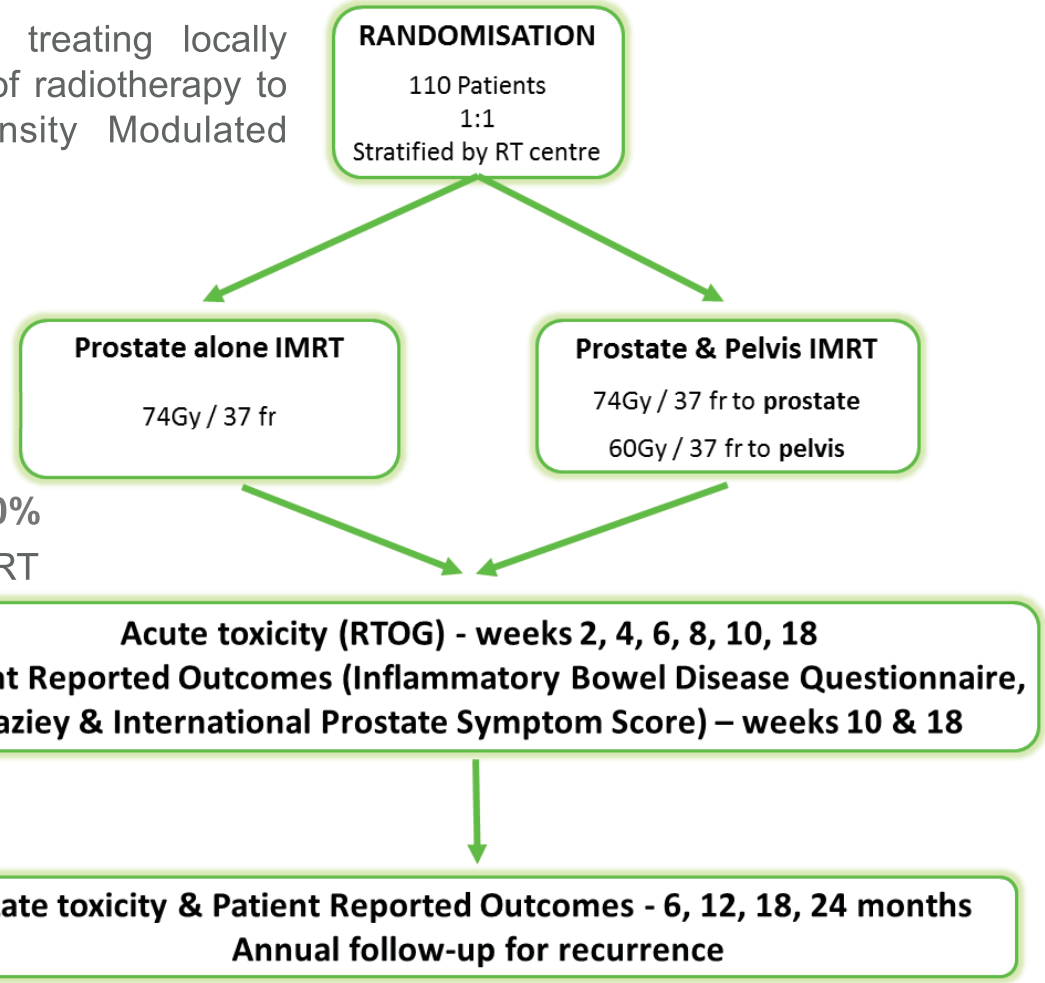
•New Dose Constraints

•MAMS study

PIVOTAL Design

Aim :

To determine the **feasibility** and **toxicity** of treating locally advanced prostate cancer with escalated doses of radiotherapy to the **prostate and pelvic nodes** using Intensity Modulated Radiotherapy (IMRT)



Inclusion criteria:

- Histologically confirmed, previously untreated, non-metastatic adenocarcinoma of the prostate
- **T3b/T4 or risk of pelvic node involvement ≥30%**
- LHRH analogue therapy for 6-9 months prior to RT
- WHO performance status 0 or 1
- Written informed consent

Exclusion criteria:

- Radiologically positive LN
- Castrate resistant prostate cancer
- Prior pelvic radiotherapy or major pelvic surgery
- Bilateral hip prosthesis or fixation

Target Definition

Clinical Target Volume	Organ At Risk
Prostate	Bladder
Prostate + Seminal Vesicles	Bowel
	Rectum
Pelvic Lymph Nodes	Femoral Heads

Pelvic Nodal CTV:

•Inferior border L5 vertebra to 1cm cranial to pubic symphysis

•Pelvic vasculature identified, margin of 7mm applied radially

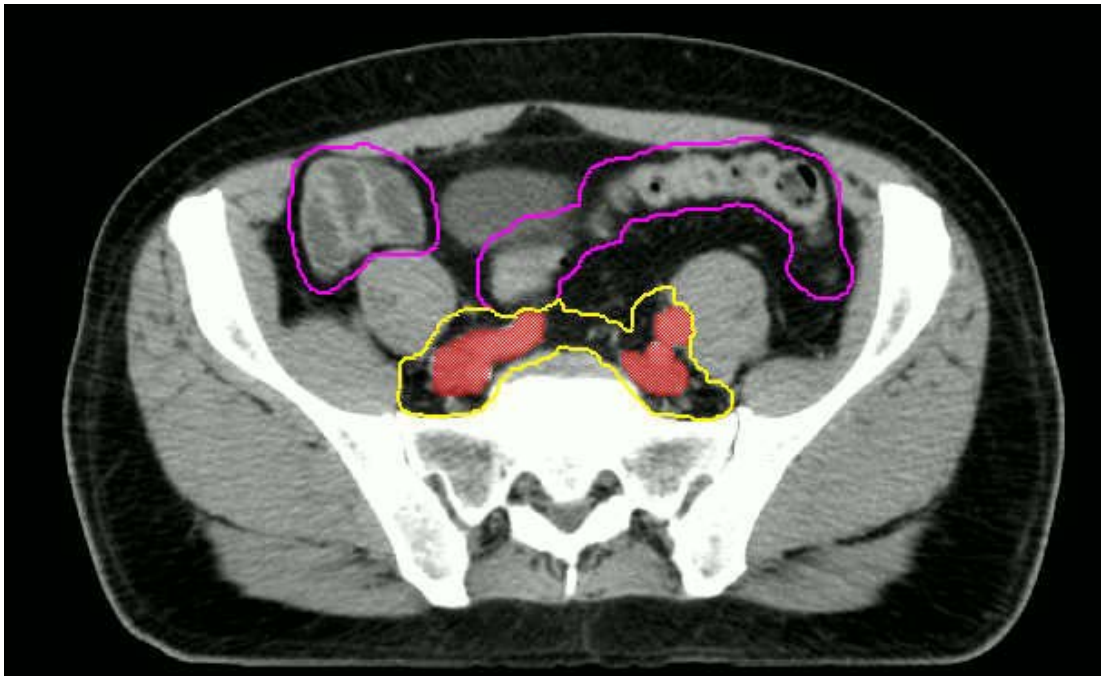
•Manually edited to exclude bone, muscle and bladder

•12mm presacral strip (S1-S3 inc.)

•Internal & external iliac volumes connected by 18mm strip inside bony pelvic side wall

•Bowel expanded by 3mm isotropic margin, LN CTV edited to exclude the expanded bowel volume ensuring LN CTV not compromised

•Editing permitted to ensure all areas thought to be LN were included in CTV



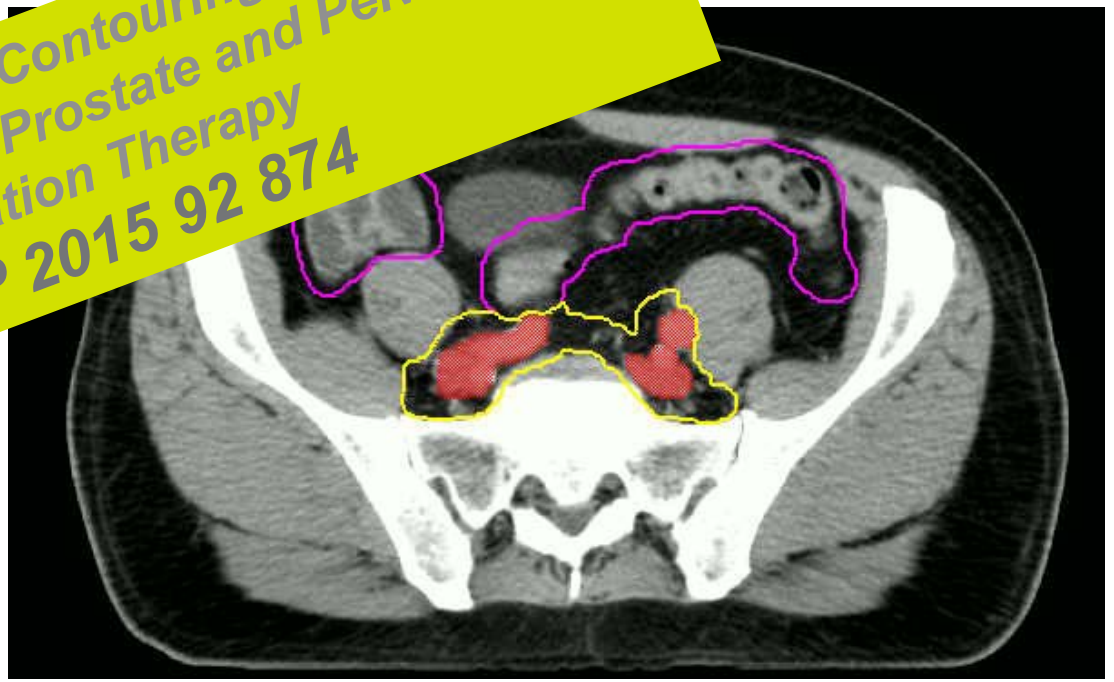
Target Definition

Pelvic Nodal CTV:

- Inferior border L5 vertebra to 1cm cranial to pubic symphysis
- Pelvic vasculature identified, margin of 7mm applied radially
- Manually edited to exclude bone, muscle and bladder
- 12mm presacral strip (S1-S3 inc.)
- Internal & external iliac vol
by 18mm strip inside
- Bowel exp
LN C
bow
comp
- Editin all areas
thought e included in CTV

Clinical Target Volume	Organ At Risk
Prostate	Bladder
Prostate + Seminal Vesicles	Bowel
	Rectum
Pelvi	Femoral Heads

Consensus Guidelines and Contouring Atlas for Pelvic Node Delineation in Prostate and Pelvic Node Intensity Modulated Radiation Therapy
Vicki Harris IJROBP 2015 92 874

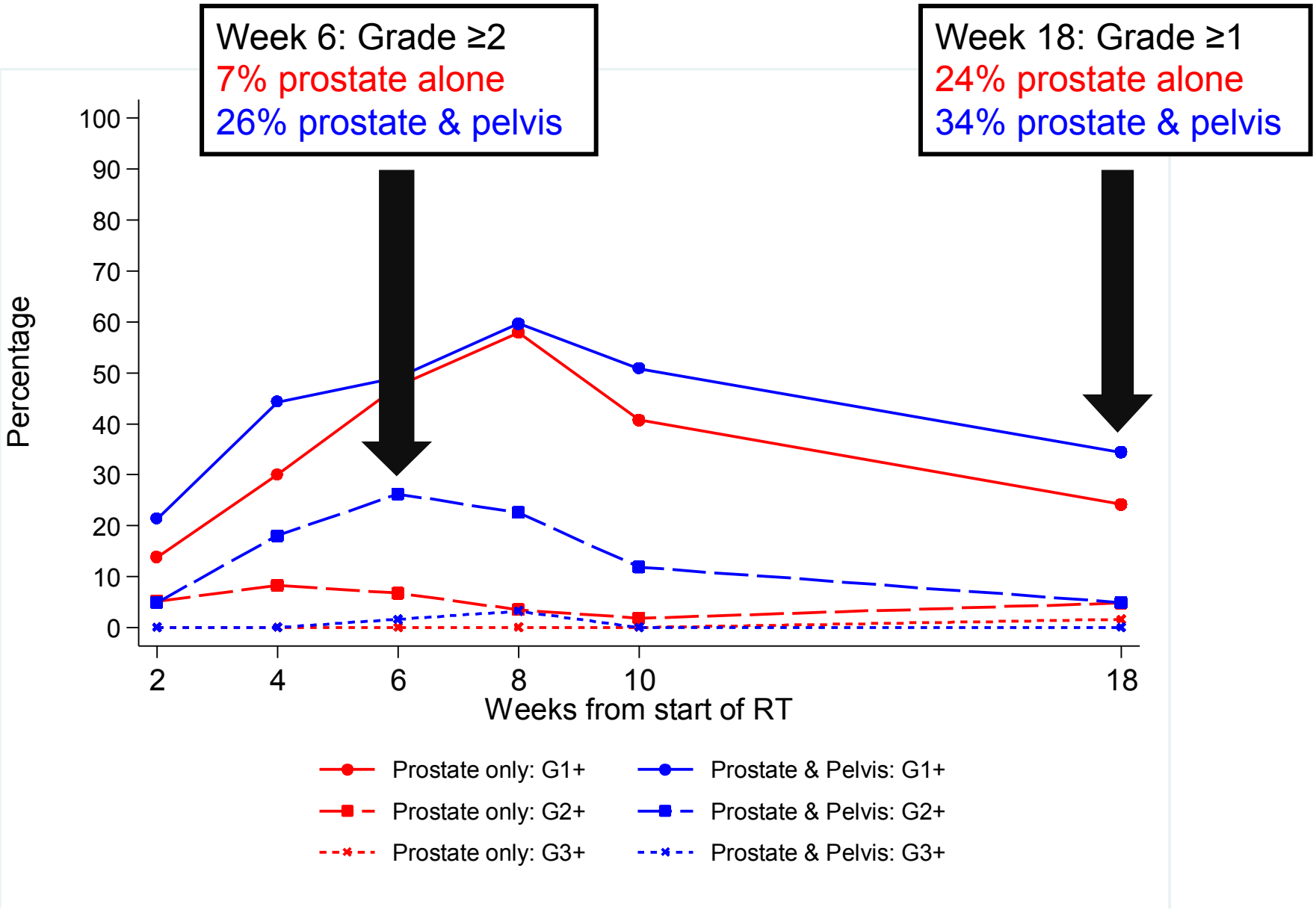


Treatment

- LHRHa + short term AA for 6-9 months pre RT and total duration 2-3 years recommended

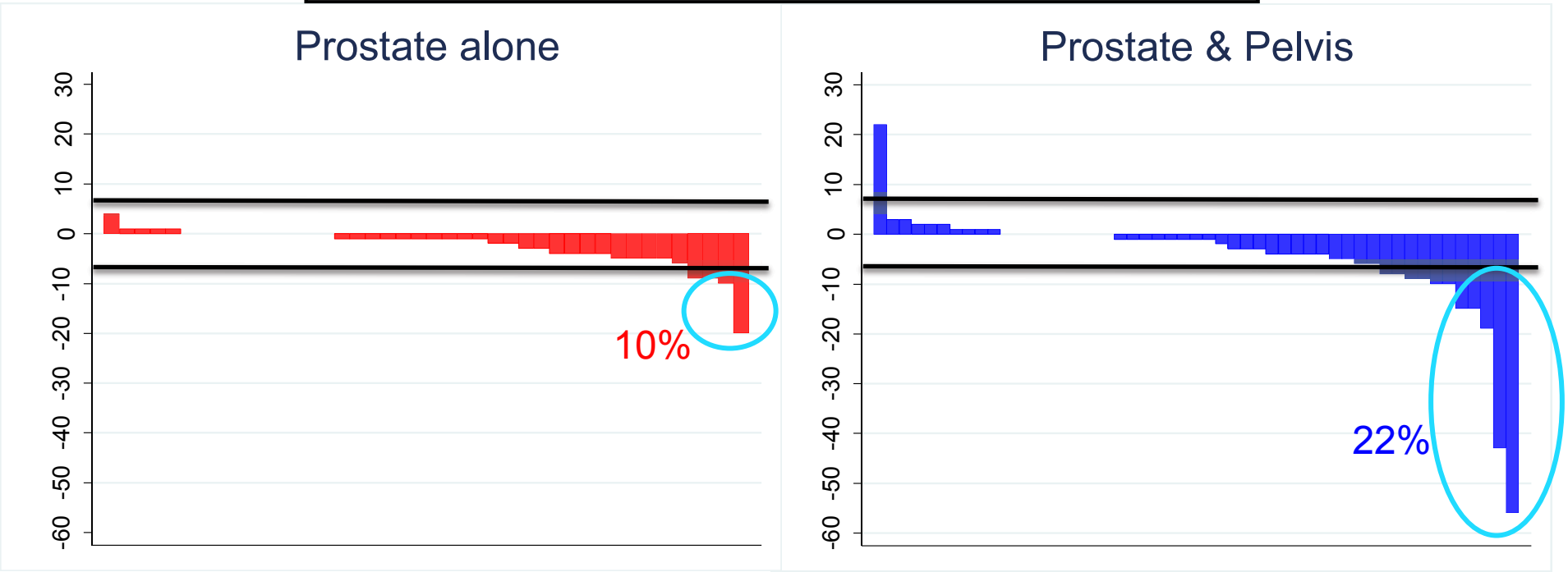
	Prostate only N=62 n (%)	Prostate & Pelvis N=62 n (%)
Prostate RT dose given		
55Gy/20fr	1 (1)	0
64Gy/32fr	1 (1)	1 (1)
74Gy/37fr	60 (98)	61 (99)
Pelvis RT dose given		
0	62 (100)	1 (1)
50Gy/37fr	0	1 (1)
55Gy/37fr	0	11 (19)
60Gy/37fr	0	49 (79)

Acute toxicity – lower GI



IBDQ Bowel Domain – change from pre-RT to week 18

- 10 bowel items
- Range 10 (worst symptoms) to 70 (no symptoms)



IBDQ Bowel Domain		Pre-RT	Week 18	Change pre-RT to week 18
Prostate alone	Median IQR	69 67 to 70	68 65 to 70	-1 -4 to 0
Prostate & Pelvis	Median IQR	69 67 to 70	66 62 to 69	-1 -6 to 0

Pelvic LN RT: Questions

- Is LN RT needed with prolonged courses of ADT and improved systemic treatment?
- What dose is needed?
- Can hypofractionation be used?
- What is the real level of ongoing side-effects?

Probable survival advantage in Breast Ca about 5%

- Background
- Dose
- Fractionation
- Systemic treatment
- Pelvic treatment
- **Post–operative treatment**
- Side-effects
- Blue skies

Technology

Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term Followup of a Randomized Clinical Trial

Ian M. Thompson,*,† Catherine M. Tangen, Jorge Paradelo, M. Scott Lucia,

THE JOURNAL OF UROLOGY® Vol. 181, 956-962, March 2009

No. 425 F.U 12.6yrs

- 10yr Metastases free survival 71% vs 61% HR 0.71 p=0.016 NNT 12.2
- 10 yr OS 74% vs 66% HR 0.72 p=0.023 NNT 9.1
- PSA failure NNT 3.4

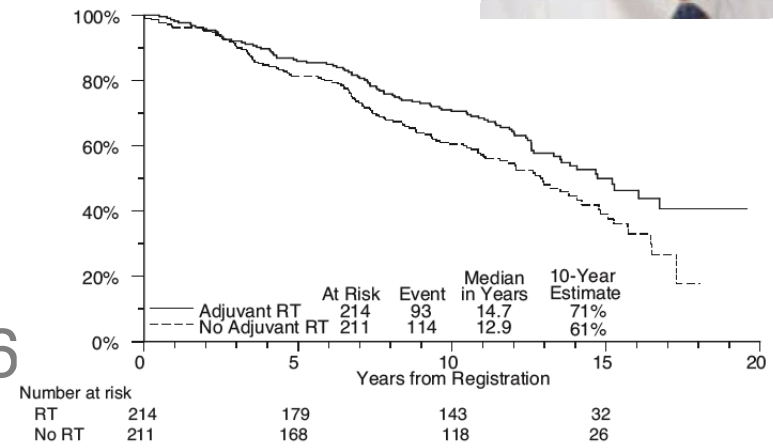


Figure 1. Metastasis-free survival by treatment arm

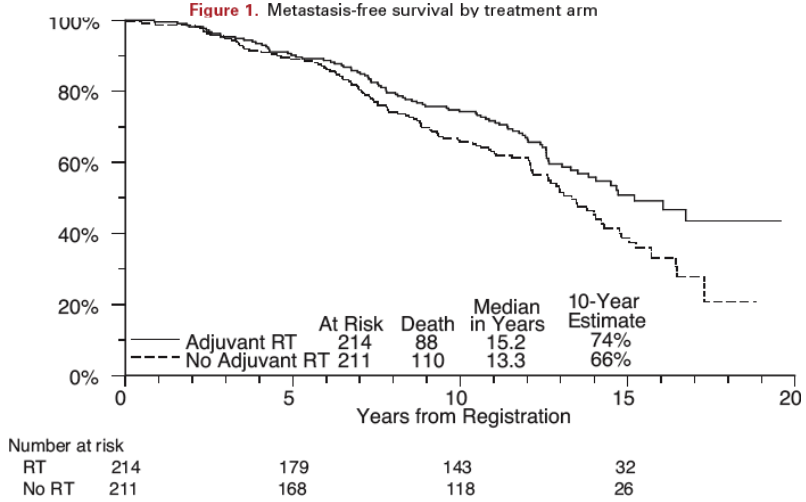


Figure 2. Survival by treatment arm

Platinum Priority – Collaborative Review – Prostate Cancer
Editorial by Adam S. Kibel on pp. 452–454 of this issue

Postoperative Radiation Therapy for Pathologically Advanced Prostate Cancer After Radical Prostatectomy

EUROPEAN UROLOGY 61 (2012) 443–451

Andrew J. Stephenson[a,], Michel Bolla[b], Alberto Briganti[c], Cesare Cozzarini[d], Judd W. Moul[e], Mack Roach III[f], Hein van Poppel[g], Anthony Zietman[h]*

EORTC (no 1005) 10 year data (Eur Urol suppl 2011 abstract 227)

- PSA progression free HR 0.5 p<0.001
- Clinical progression free survival HR=0.8 p=0.054
- Overall 10 yr survival 81% vs 77% p>0.1

ARO 96-02 (No 388) 5 year data (Wiegel JCO 2009 27 294)

- 5 yr progression free 72% vs 54% HR 0.53 p=0.002
- Too few deaths /metastases to analyse

Platinum Priority – Collaborative Review – Prostate Cancer
Editorial by Adam S. Kibel on pp. 452–454 of this issue

Postoperative Radiation Therapy for Pathologically Advanced Prostate Cancer After Radical Prostatectomy

EUROPEAN UROLOGY 61 (2012) 443–451

Andrew J. Stephenson[a,], Michel Bolla[b], Alberto Briganti[c], Cesare Cozzarini[d], Judd W. Moul[e], Mack Roach III[f], Hein van Poppel[g], Anthony Zietman[h]*

Conclusions:

- RT reduces PSA and local recurrence – no certain impact on metastases and survival

Questions:

- Immediate or early salvage treatment ?
- Adjuvant systemic treatment ?
- Treatment volume and dose ?

RADICALS

MRC Clinical Trials Unit

Radiotherapy and Androgen Deprivation In Combination After Local Surgery

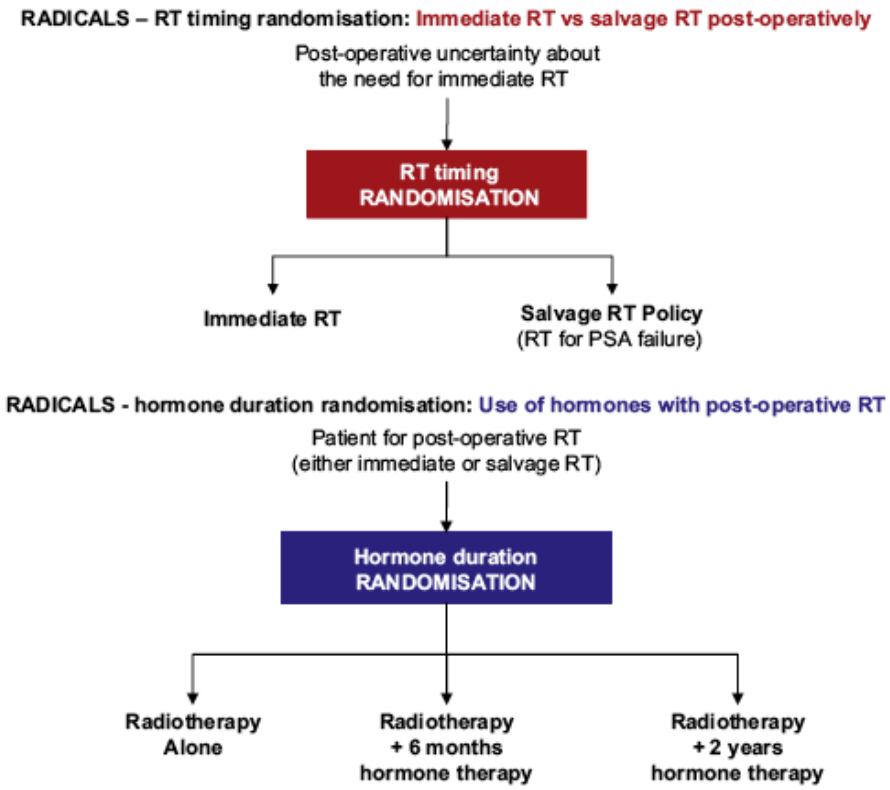
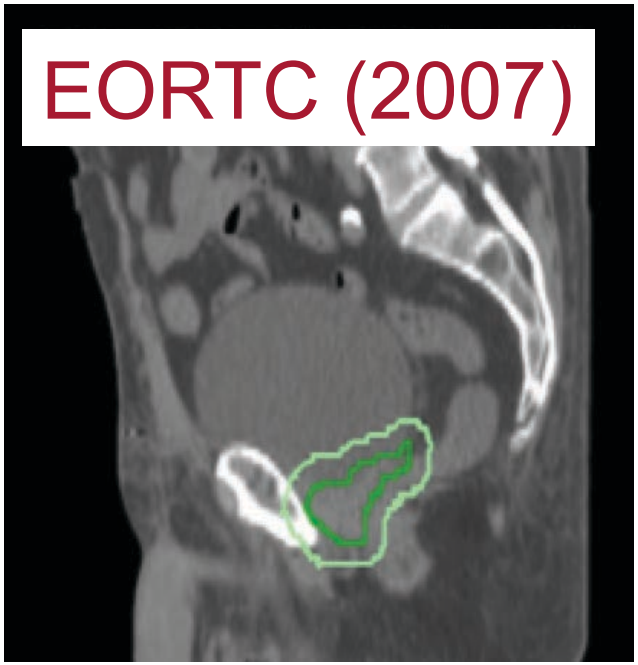
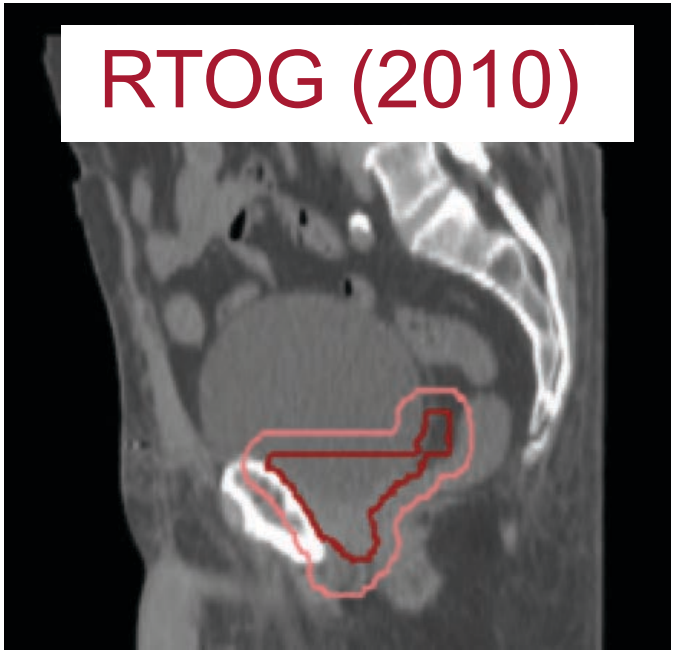
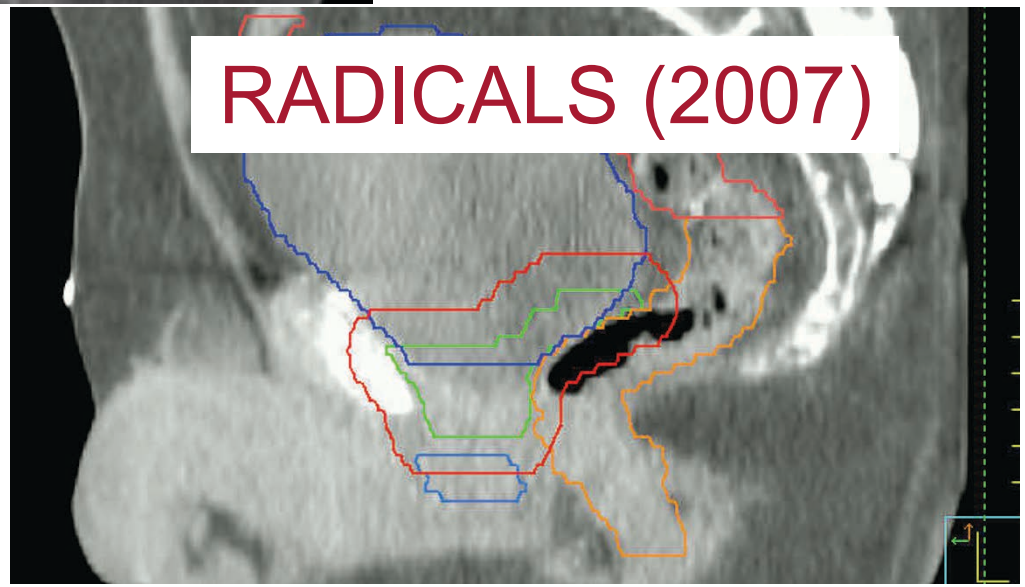


Fig. 1 – The RADICALS trial has two separate randomisations. Patients may take part in one or both.

Prostate bed contouring guidelines



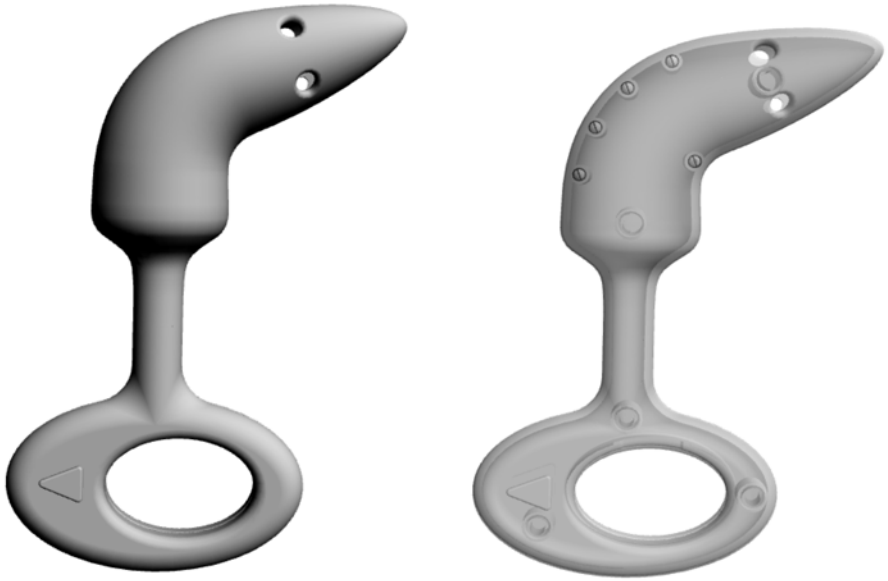




Malone et al. 2012

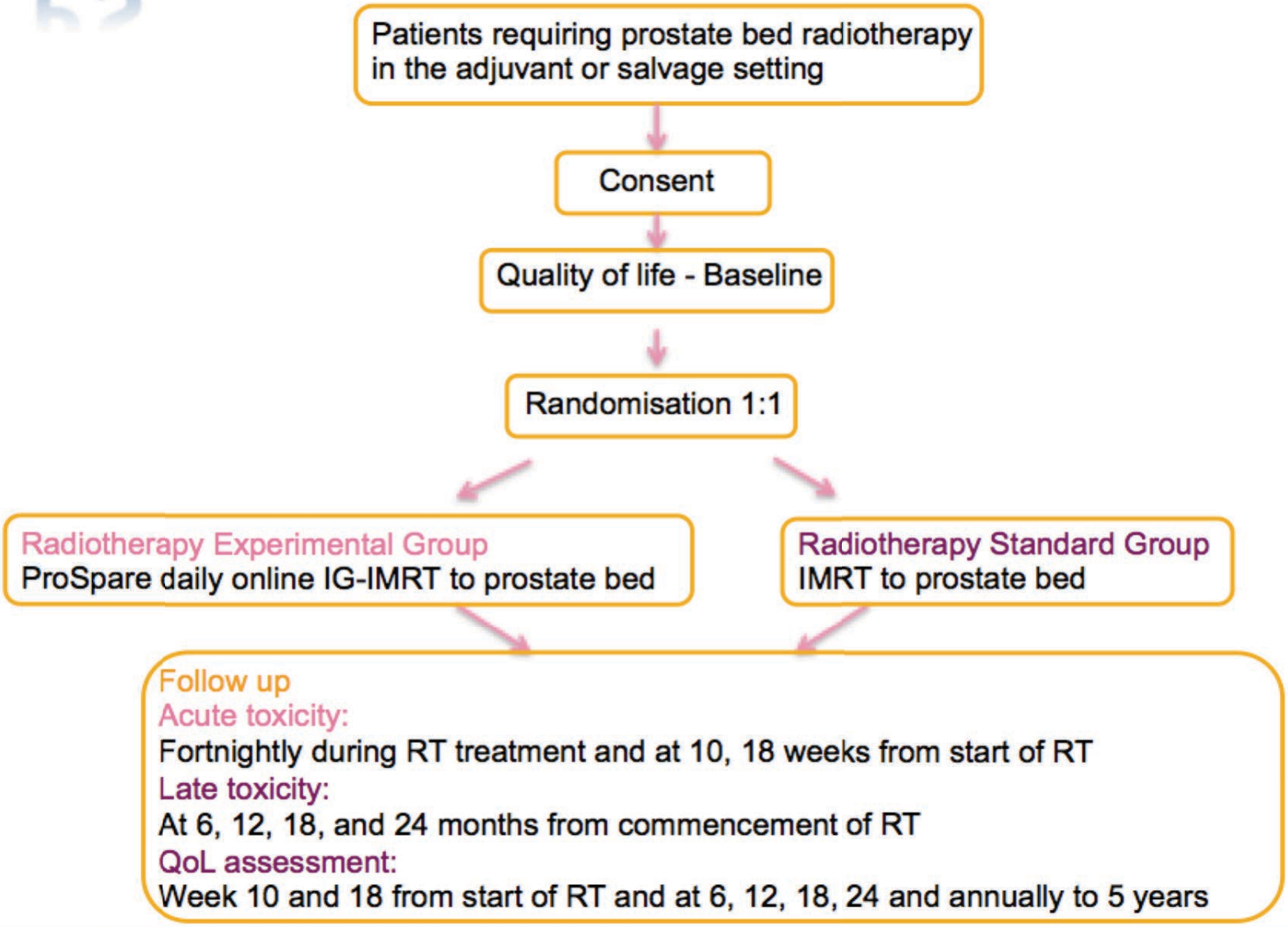
Overview

A multicentre randomised phase II trial assessing Post-Operative use of ProSpare™, a rectal obturator in prostate cancer radiotherapy.

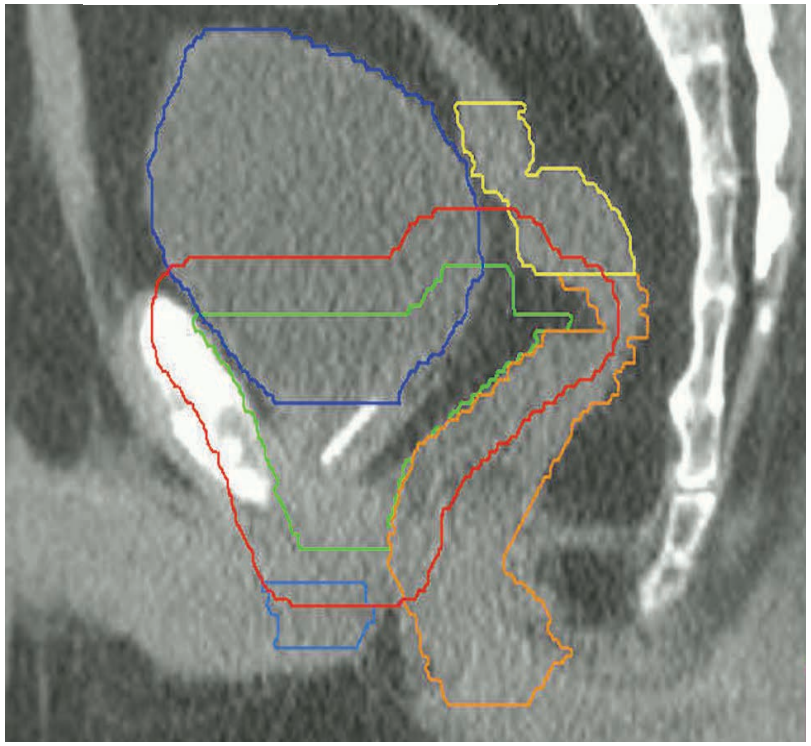


- Self-insertable rectal obturator
- Single-use
- Radio-opaque markers in wall
- Venting holes in the tip

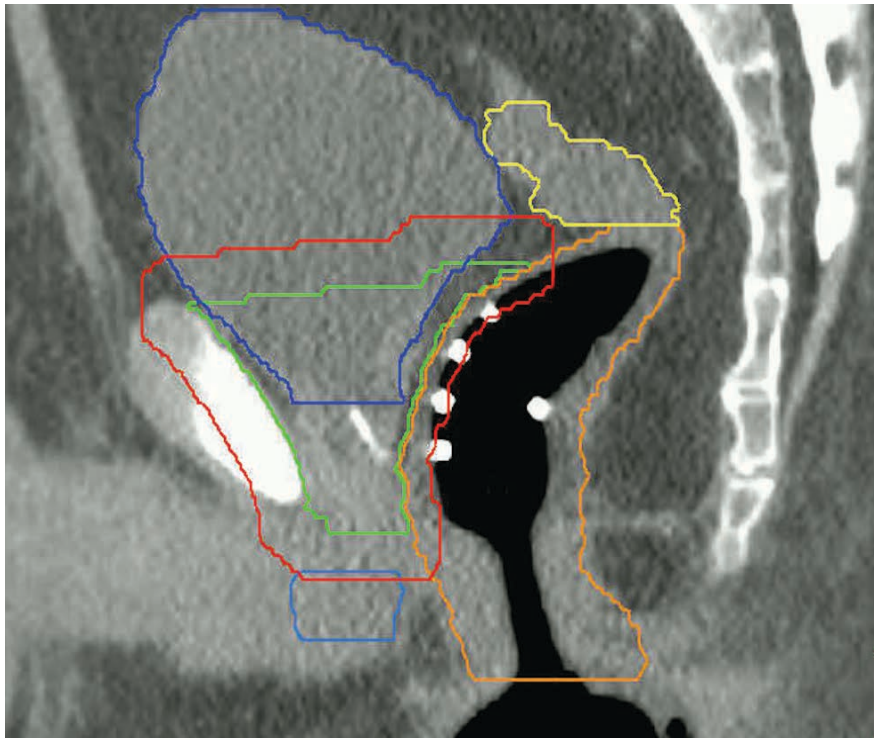
Trial Schema



CTV – PTV1 Margins



STANDARD ARM



EXPERIMENTAL ARM

- Background
- Dose
- Fractionation
- Systemic treatment
- Pelvic treatment
- Post–operative treatment
- **Side-effects**
- Blue skies

Technology

Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions

Isabelle Soerjomataram, Joannie Lortet-Tieulent, D Maxwell Parkin, Jacques Ferlay, Colin Mathers, David Forman, Freddie Bray

Lancet 2012; 380: 1840–50

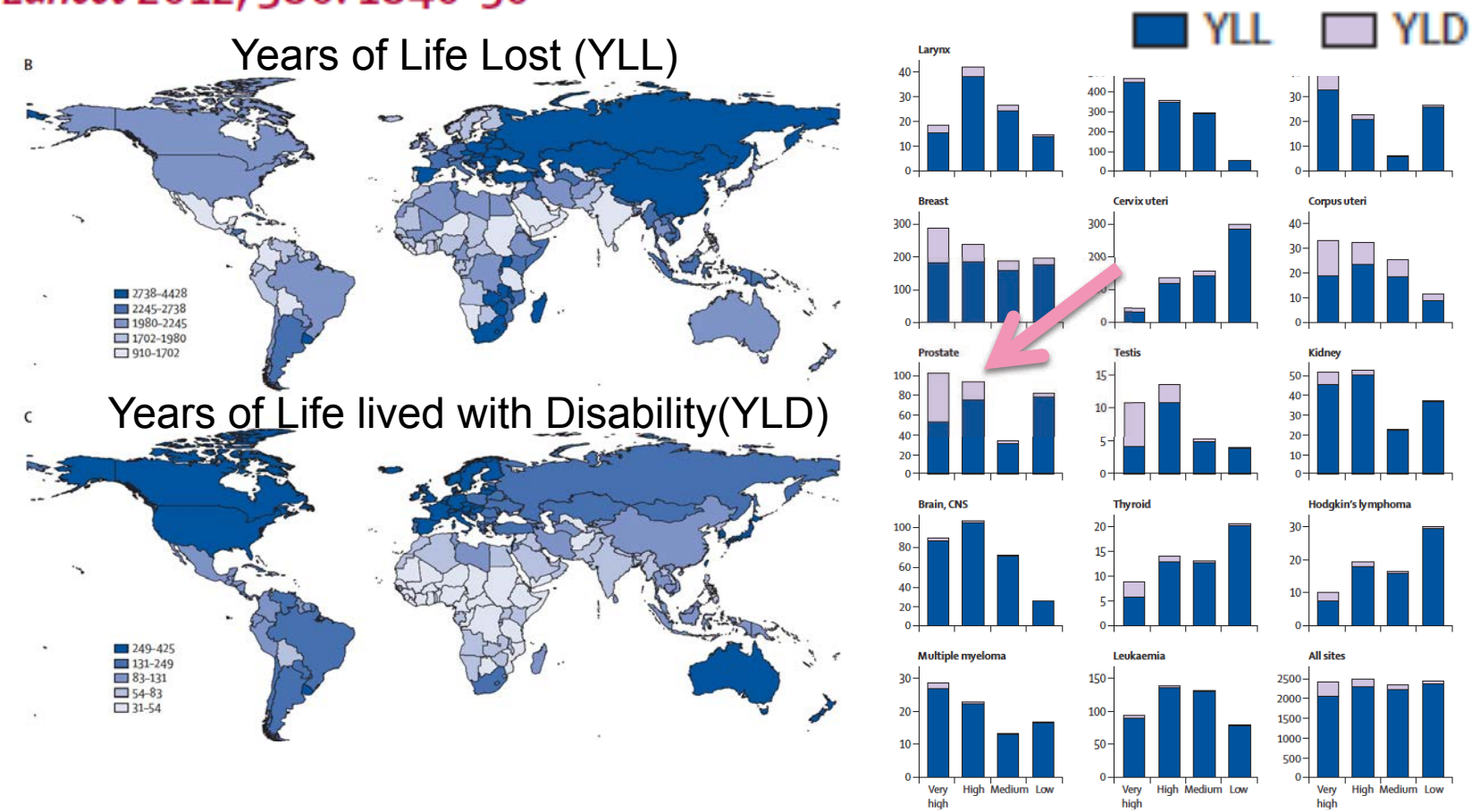


Figure 2: **Age-adjusted DALYs per 100 000 population by cancer site and level of HDI**

DALYs=disability-adjusted life-years. YLL=years of life lost. YLD=years of life lived with disability. HDI=Human Development Index.

Predictive factors in radiotherapy induced toxicity

- **Physics (of dose distribution)**
- Patient related (clinical/co-morbid conditions)
- Genome related – radiogenomics
- Microbiome related

Comparison of QoL in National RT studies

CHHiP vs MRC Trial RT01 (74Gy groups)

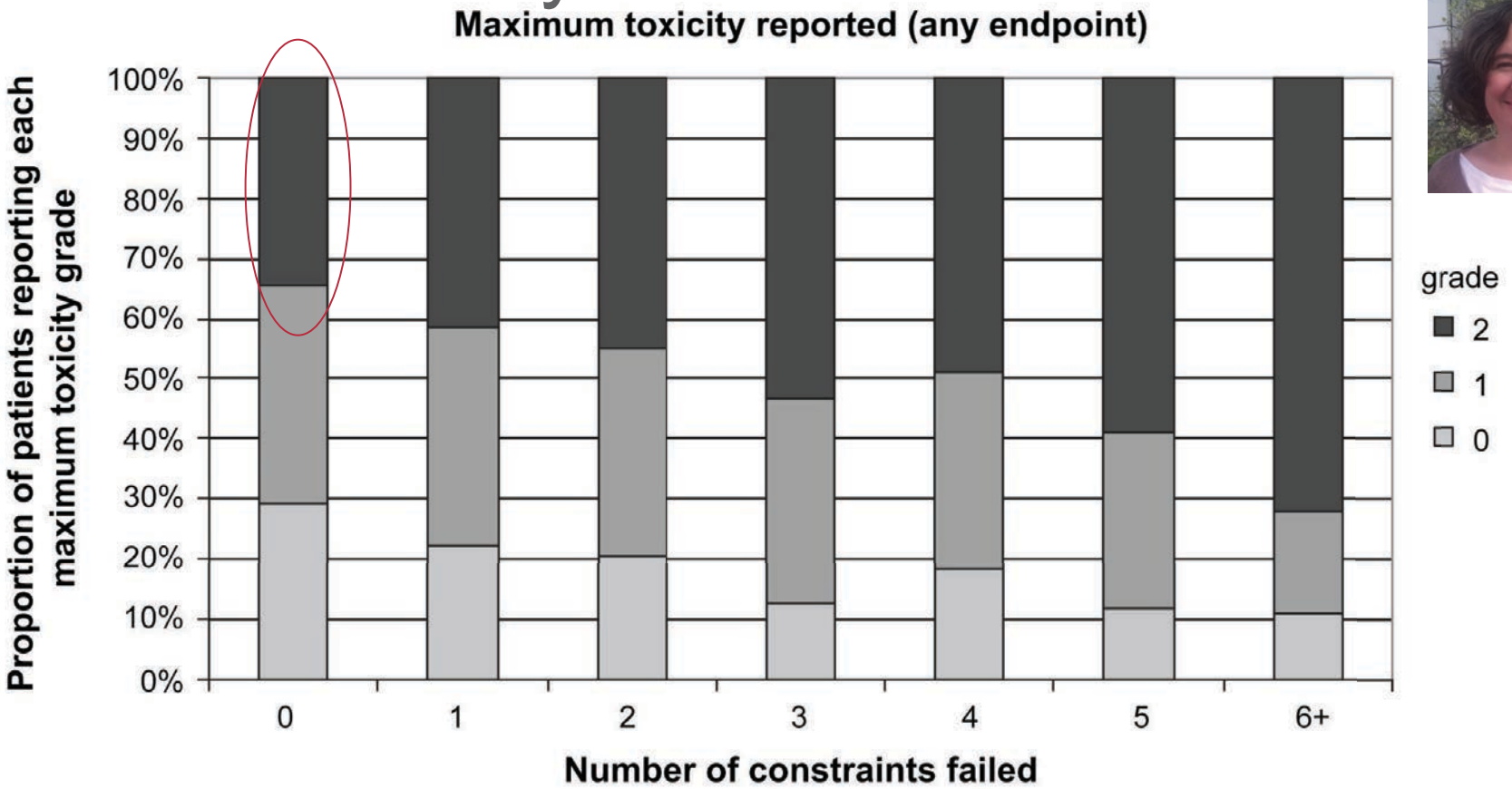
A.Wilkins et al *Lancet Oncol* Sept 2015

	Bowel bother (%)		Bowel distress (%)	
Severity	Moderate	Severe	Moderate	Severe
RT01	9.3	3.1	11.8	0.7
CHHiP	4.6	1.0	4.2	0.0

Benefit from IMRT technique and dose constraints used in CHHiP

Summary: Number of constraints failed vs maximum toxicity recorded

Gulliford IJROBP 2010



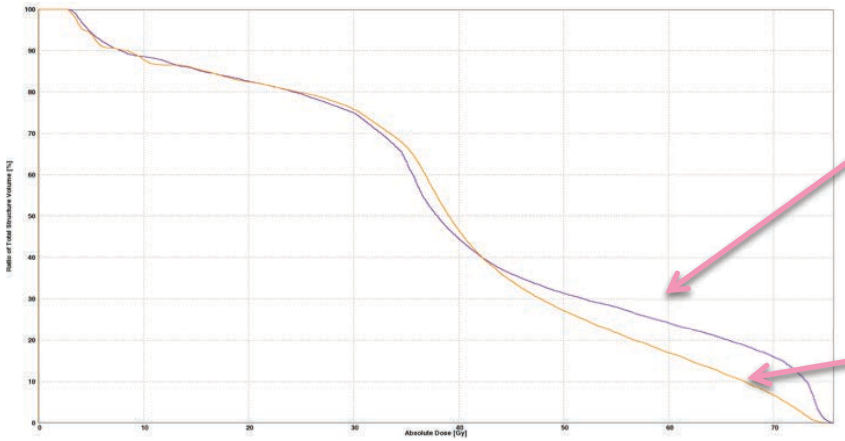
Endpoint	Grading scale	Endpoint	Grading scale
Rectal bleeding	RMH	Mgmt. sphincter control	LENT/SOM
Proctitis	RTOG	Loose stools	UCLA PCI
Subj. sphinchter control	LENT/SOM	Rectal urgency	UCLA PCI
Subj. stool frequency	LENT/SOM		

Why do DVH's not give the full story?

- Loss of spatial information in DVH
- Analyses usually based on single planning CT scan.
- Limitations to toxicity scoring systems

- Pre-treatment patient factors
- Intrinsic differences in patient radiosensitivity
- Microbiome related

Dose Surface Maps (DSM): Rectum unfolding

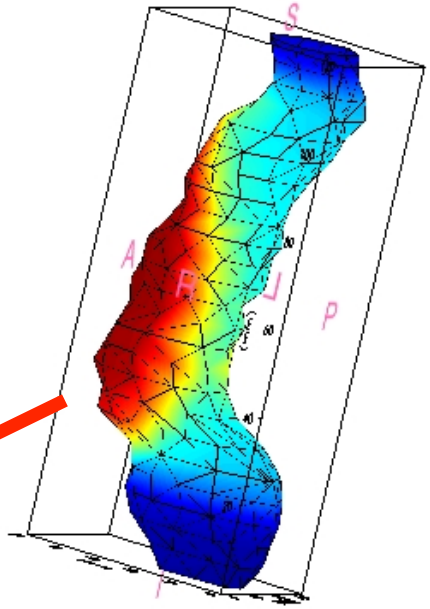


1D dose distribution:

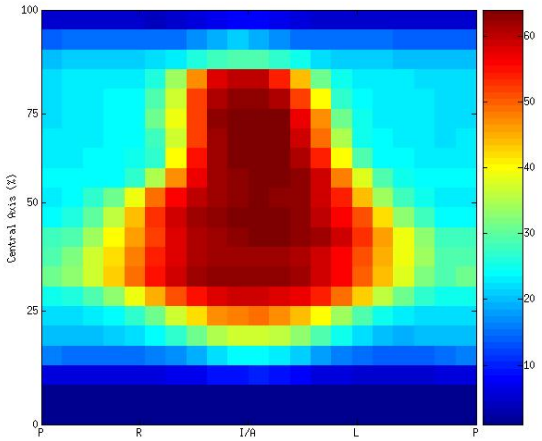
Dose surface histogram

Dose volume histogram

3D DSM



2D DSM



VODCA (MSS GmBH, Hagendorn, CH)

Results of dose surface map analysis

Rectal bleeding:

- High doses most important
- Lateral extent and circumferential irradiation strongest correlation to rectal bleeding

Loose stools:

- Low and medium doses most relevant
- Longitudinal extent at low doses important particularly to superior rectum

Rectal Incontinence

- Dose to anal region

Inter fraction motion

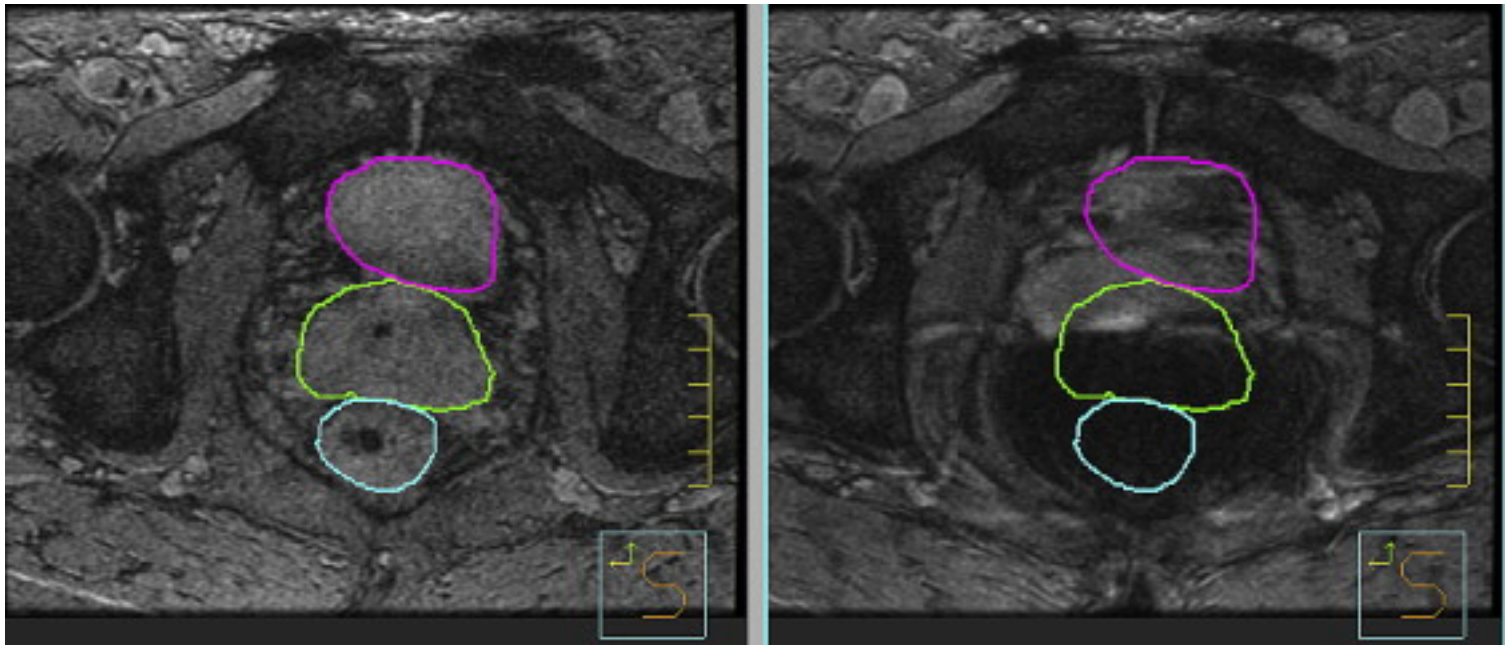


Fig. 7 Repeat magnetic resonance images obtained for the example prostate patient. The bladder (pink), prostate (green), and rectum (blue) contoured on the first image (left) are overlaid onto the second magnetic resonance image (right) for reference.

Kristy K. Brock

Results of a Multi-Institution Deformable Registration Accuracy Study (MIDRAS)

International Journal of Radiation Oncology*Biology*Physics, Volume 76, Issue 2, 2010, 583 - 596

http://dx.doi.org/10.1016/j.ijrobp.2009.06.031

Difference between planned and delivered dose

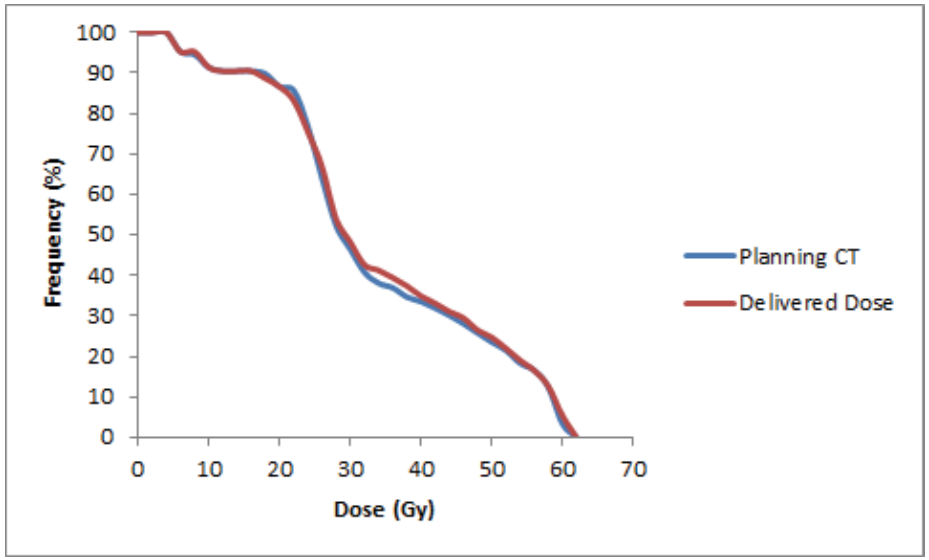


Fig 1. Cumulative dose surface histogram (patient A)

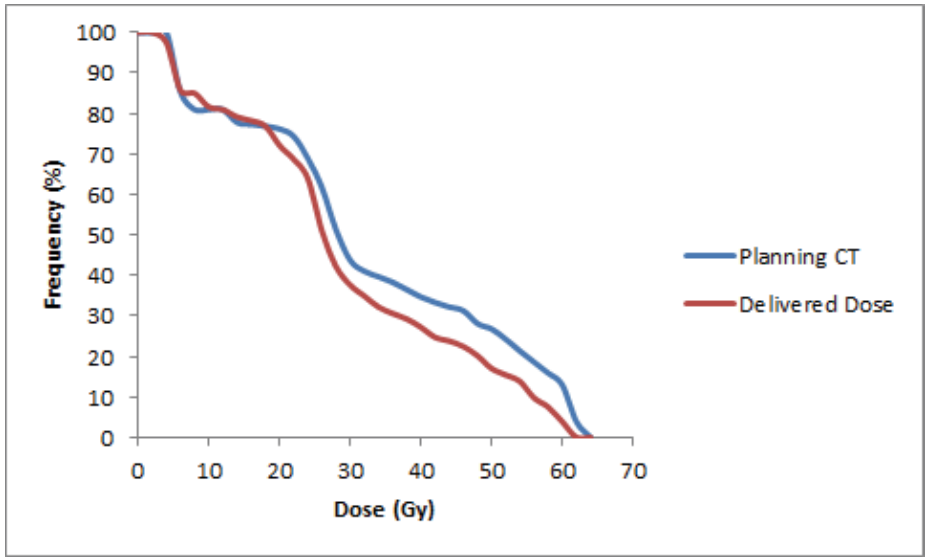
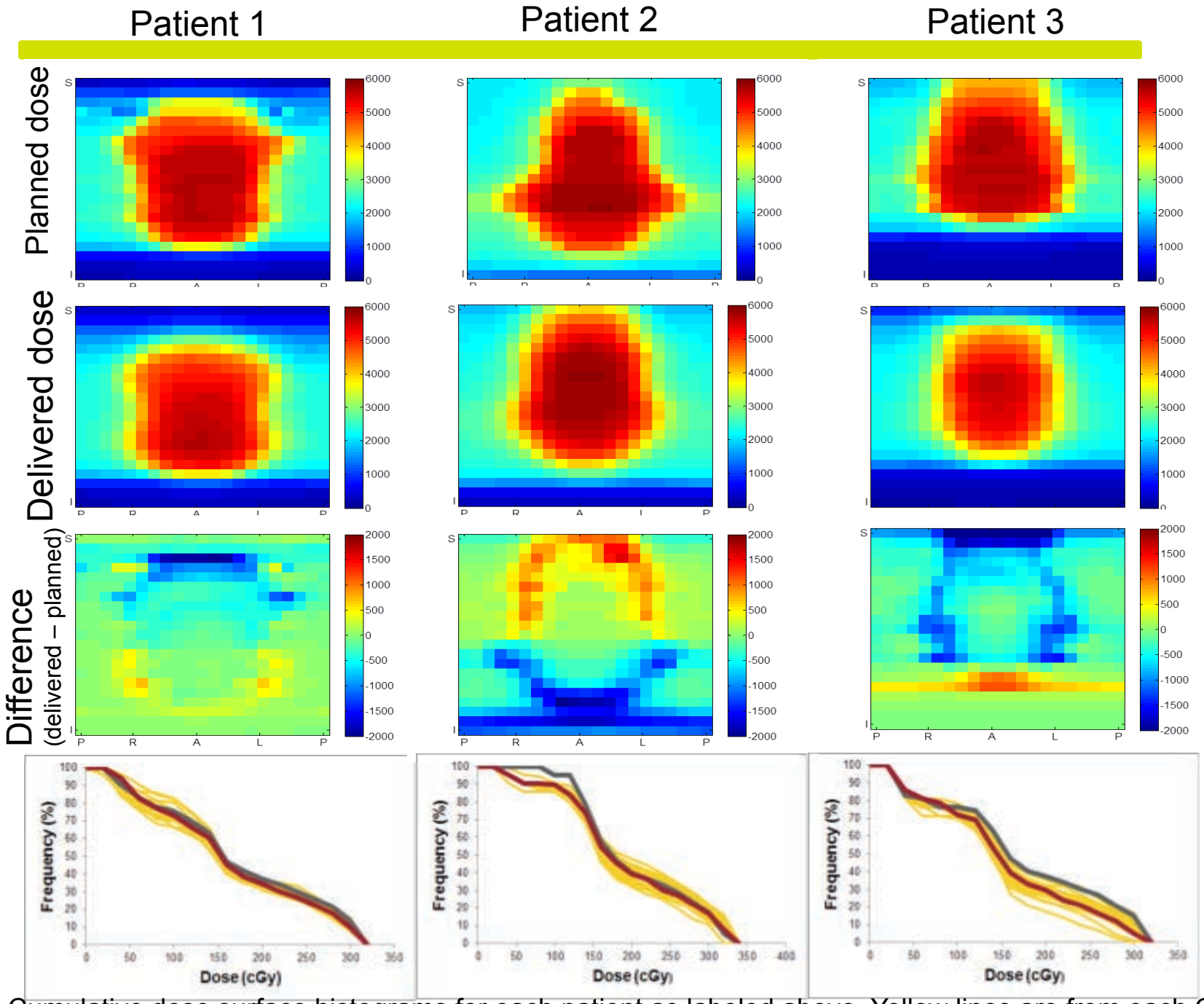
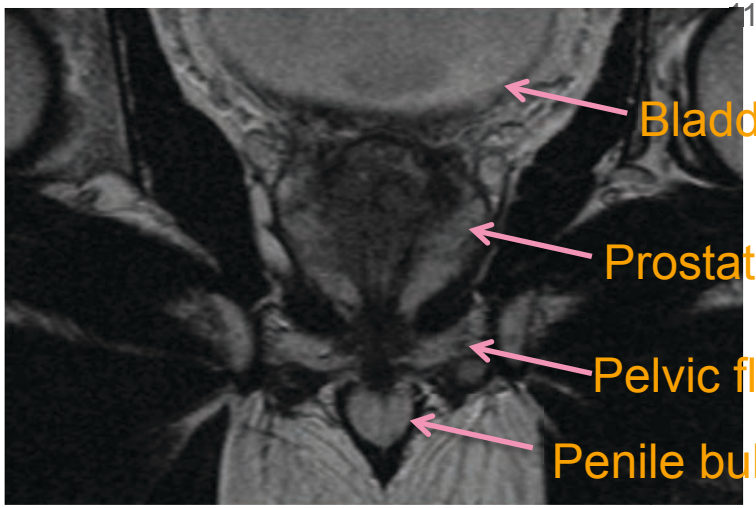


Fig 2. Cumulative dose surface histogram (patient B)



Cumulative dose surface histograms for each patient as labeled above. Yellow lines are from each CBCT, red line is the mean of the CBCT and the grey line is from the planning CT

CHHiP IGRT subTrial
Dose distribution analysis
Penile bulb



290 patients eligible for analysis

42 patients no DICOM files received

248 patients penile bulb outlined

79 DICOM files incompatible with in house code

169 plans converted into equivalent dose in 2Gy/F (α/β = 3Gy)

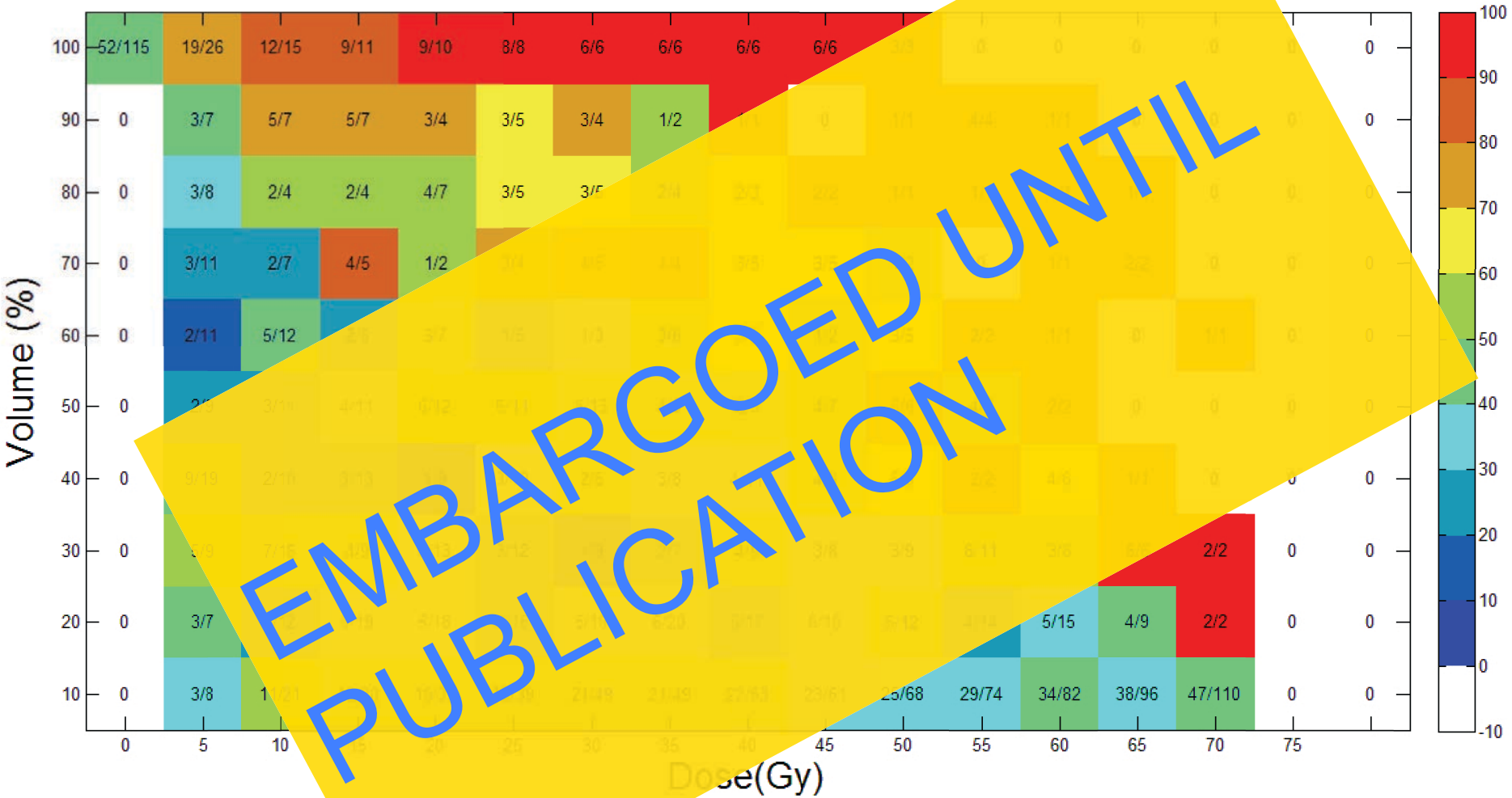
20 patients treated with no IGRT

20 patients had no baseline or 2 year EP data

14 patients had Grade 2 EP at baseline

115 patients included in analysis

Toxicity map for impotence



Absent erectile function at 2 years:
27/52 (52%) men treated with standard margins
25/63 (40%) men treated with reduced margins

Dr Julia Murray Accepted for oral presentation, ESTRO 2016

What matters to patients: "Bother" and "Distress"

Independent predictors of ***patient*** reported bother and distress - physician and patient reported instuments

RTOG
- Diarrhoea
- Proctitis

LENTSOM
- sphyncter control
- tenesmus
- bleeding

PRO scales: UCLA-PCI, EPIC, EORTC, IBDQ, Vaizey incont. score
- loose stools
- rectal urgency
- crampy pain
- incontinence

Predictive factors in radiotherapy induced toxicity

- Physics (of dose distribution)
- **Patient related (clinical/co-morbid conditions)**
- Genome related – radiogenomics
- Microbiome related

Original Article Clinical Oncology 23 (2011) 613–624

The Impact of Clinical Factors on the Development of Late Radiation Toxicity: Results from the Medical Research Council RT01 Trial (ISRCTN47772397)

G.C. Barnett *†, G. De Meerleer ‡, S.L. Gulliford §, M.R. Sydes ||, R.M. Elliott ¶, D.P. Dearnaley **

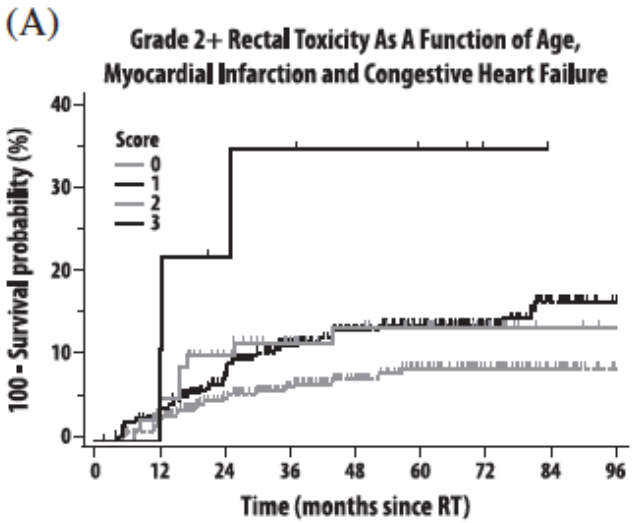
Multivariate analysis of factors related to radiation induced proctitis

	Hazard ratio	P value
Age	1.06	0.04
Dose V30	1.13	0.02
Acute bowel toxicity	1.65	0.05

Age and Comorbid Illness Are Associated With Late Rectal Toxicity Following Dose-Escalated Radiation Therapy for Prostate Cancer Hamstra et al IJROBP 85 (2013) 1246-1253,

Development and validation of age and comorbidity model

	Hazard ratio	P value
Age	1.04	< 0.03
MI	1.8	<0.02
CCF	2.2	0.09



Does hypertension or its treatment protect against late RT side effects ?

IMPACT OF NEOADJUVANT ANDROGEN ABLATION AND OTHER FACTORS ON LATE TOXICITY AFTER EXTERNAL BEAM PROSTATE RADIOTHERAPY

IJROBP 2004 58 59-67

MITCHELL LIU, M.D.C.M., F.R.C.P.C.,* TOM PICKLES, M.D., F.R.C.P.C.,†

Hypertension RR 0.5 for development of late GI toxicity p=0.004 (no.1192)

PREDICTORS FOR RECTAL AND INTESTINAL ACUTE TOXICITIES DURING PROSTATE CANCER HIGH-DOSE 3D-CRT: RESULTS OF A PROSPECTIVE MULTICENTER STUDY

IJROBP 2007 67 1401-10

VITTORIO VAVASSORI, M.D.,* CLAUDIO FIORINO, PH.D.,† TIZIANA RANCATI, PH.D.,‡

Hypertension RR 0.4 for development of late GI toxicity p=0.03 (no.1132)

LATE RECTAL TOXICITY ON RTOG 94-06: ANALYSIS USING A MIXTURE LYMAN MODEL

IJROBP 2010

SUSAN L. TUCKER, PH.D.,* LEI DONG, PH.D.,† WALTER R. BOSCH, D.SC.,‡§ JEFF MICHALSKI, M.D.,§

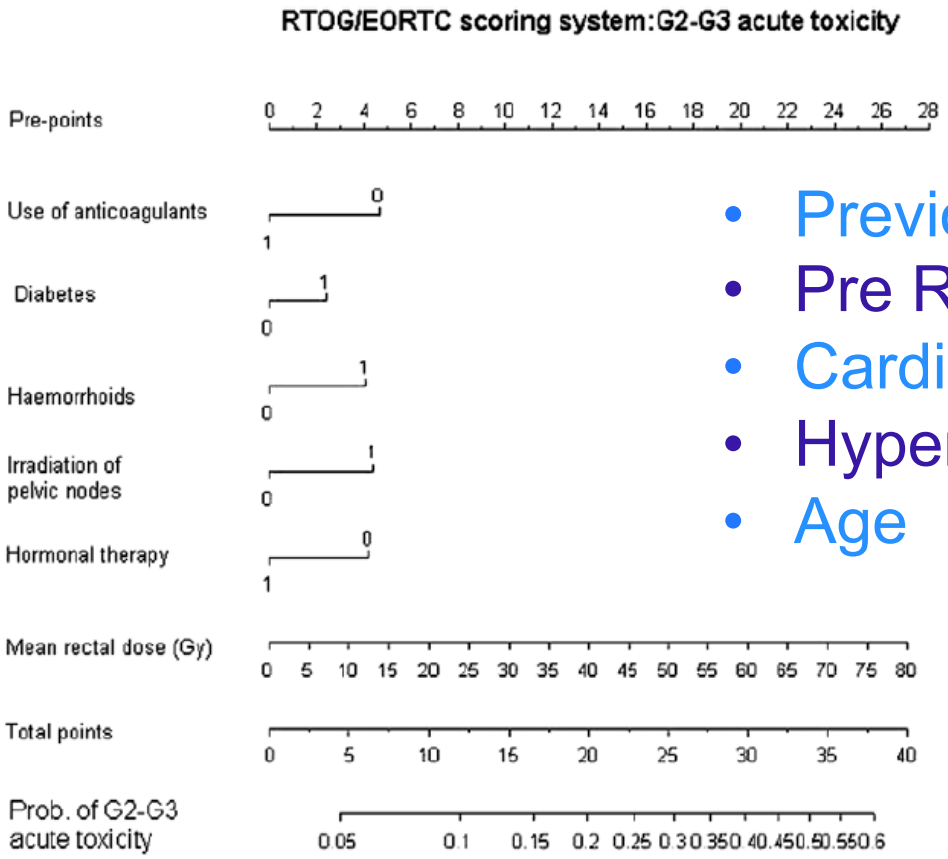
Hypertension no relationship to late GI toxicity (no.1100)

Patient factors related to bowel disorder after RT

Dose–volume effects for normal tissues in external radiotherapy: Pelvis

Claudio Fiorino [a,*], Riccardo Valdagni [b], Tiziana Rancati [b], Giuseppe Sanguineti [c]

2009 93 153-67



- Previous abdomen/ pelvic surgery
- Pre RT bowel symptoms
- Cardiovascular disease
- Hypertension
- Age

Predictive factors in radiotherapy induced toxicity

- Physics (of dose distribution)
- Patient related (clinical/co-morbid conditions)
- **Genome related – radiogenomics**
- Microbiome related

Independent validation of genes and polymorphisms reported to be associated with radiation toxicity: a prospective analysis study

Lancet Oncol 2012; 13: 65–77

Gillian C Barnett, Charlotte E Coles, Rebecca M Elliott, Caroline Baynes, Craig Luccarini, Don Conroy, Jennifer S Wilkinson, Jonathan Tyrer, Vivek Misra, Radka Platte, Sarah L Gulliford, Matthew R Sydes, Emma Hall, Søren M Bentzen, David P Dearnaley, Neil G Burnet, Paul D P Pharoah, Alison M Dunning, Catharine M L West

Genome-wide association study identifies a region on chromosome 11q14.3 associated with late rectal bleeding following radiation therapy for prostate cancer ☆

Radiotherapy and Oncology 107 (2013) 372–376

Sarah L. Kerns [a,b], Richard G. Stock [a], Nelson N. Stone [a,c], Seth R. Blacksburg [a], Lynda Rath [a], Ana Vega [d] Laura Fachal [d], Antonio Gómez-Caamaño [e], Dirk De Ruysscher [f,g], Guido Lammering [g], Matthew Parliament [h], Michael Blackshaw [h], Michael Sia [i], Jamie Cesaretti [j], Mitchell Terk [j], Rosetta Hixson [j], Barry S. Rosenstein [a,k,l,m,*,1], Harry Ostrer [b,n,1]

NATURE GENETICS VOLUME 46 | NUMBER 8 | AUGUST 2014

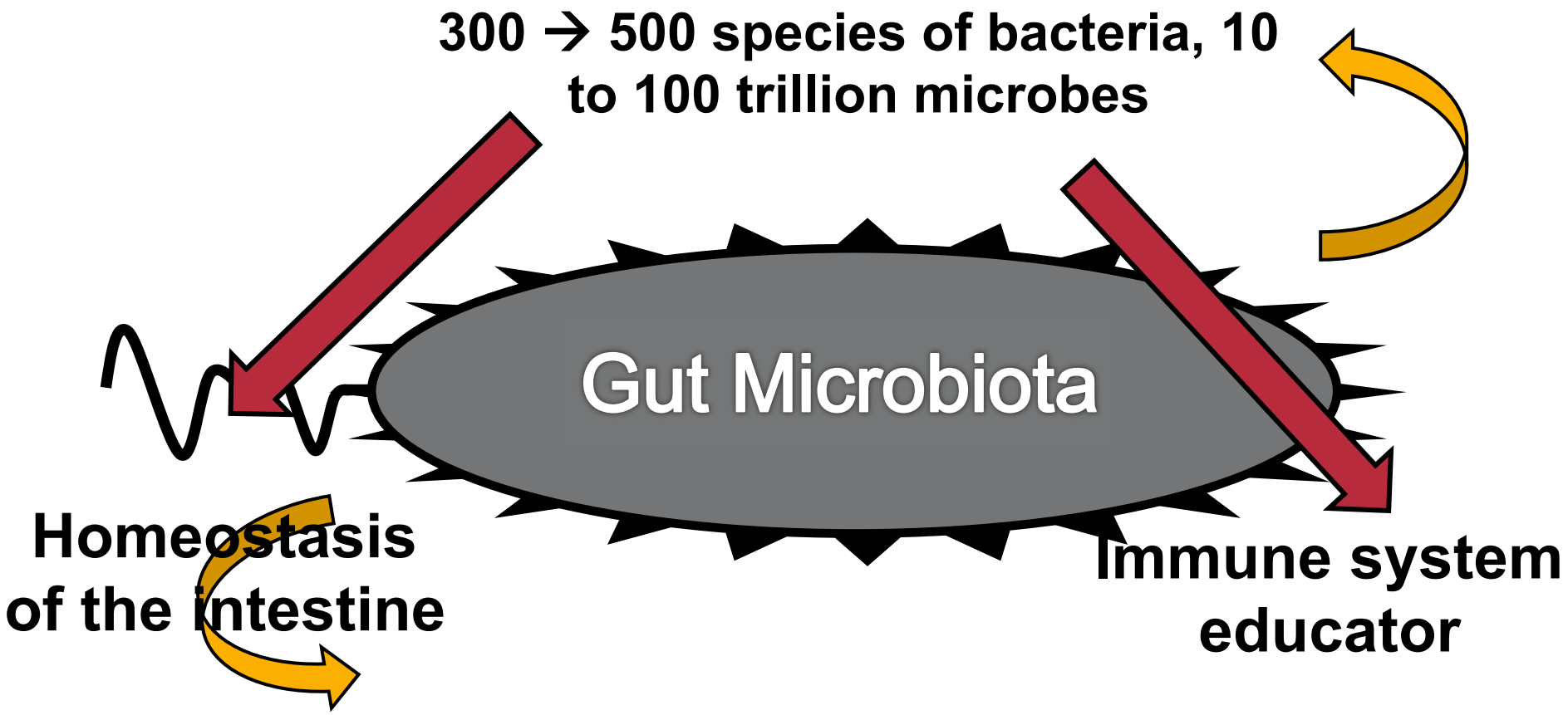
A three-stage genome-wide association study identifies a susceptibility locus for late radiotherapy toxicity at 2q24.1

Laura Fachal[1,2], Antonio Gómez-Caamaño[3], Gillian C Barnett[4], Paula Peleteiro[3], Ana M Carballo[3], Patricia Calvo-Crespo[3], Sarah L Kerns[5], Manuel Sánchez-García[6], Ramón Lobato-Busto[6], Leila Dorling[4], Rebecca M Elliott[7], David P Dearnaley[8], Matthew R Sydes[9], Emma Hall[10], Neil G Burnet[11], Ángel Carracedo[1,2,12], Barry S Rosenstein[5], Catharine M L West[7], Alison M Dunning[4] & Ana Vega[1,2]

Predictive factors in radiotherapy induced toxicity

- Physics (of dose distribution)
- Patient related (clinical/co-morbid conditions)
- Genome related – radiogenomics
- **Microbiome related**

The microbiota

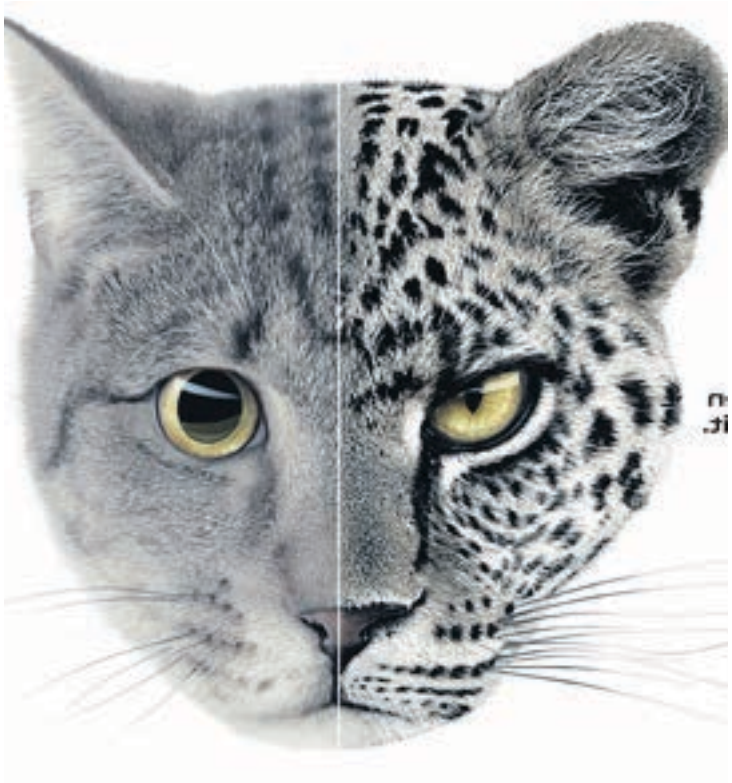


The 2nd human genome, known as the GUT MICROBIOME

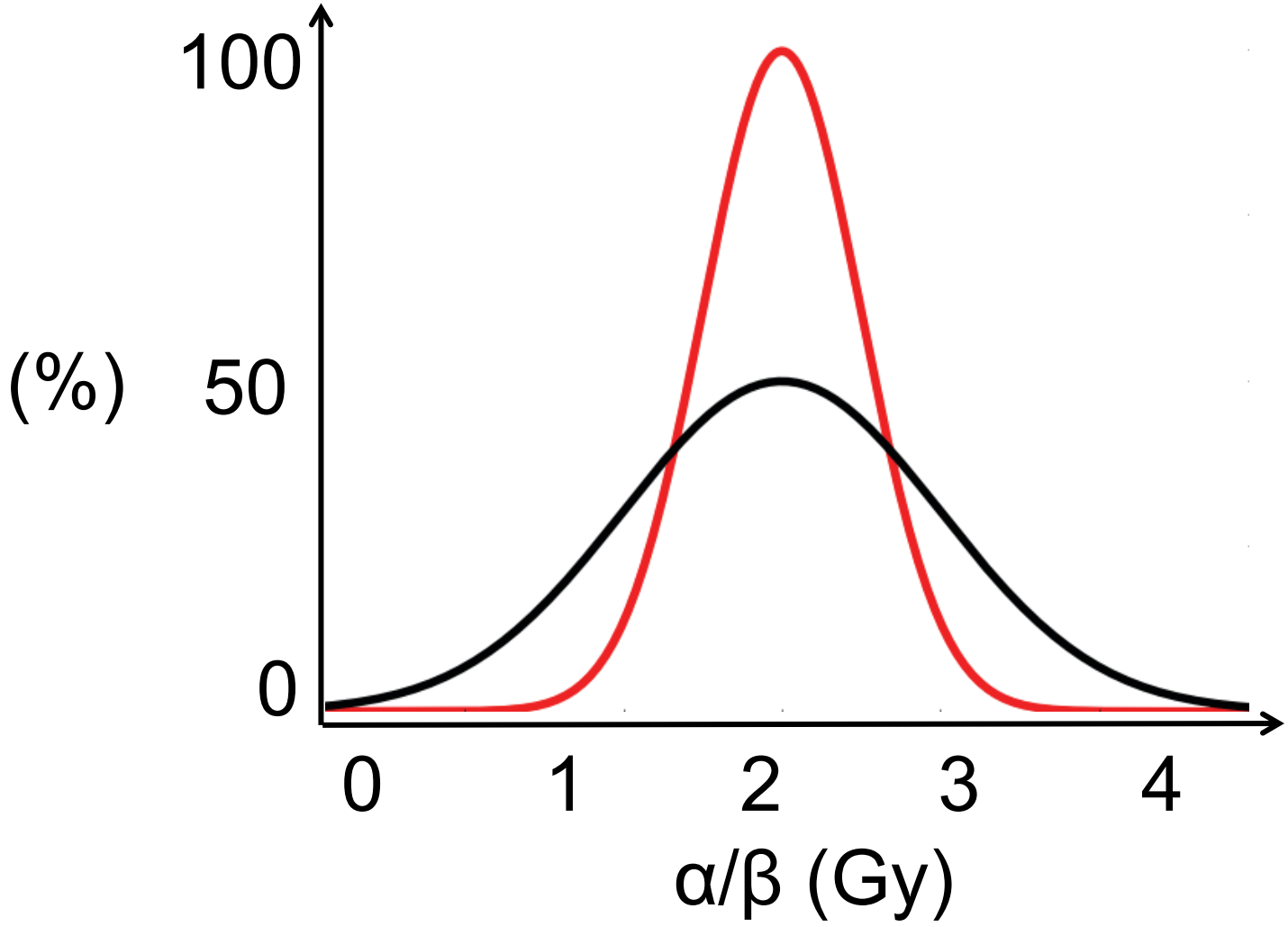
- Background
- Dose
- Fractionation
- Systemic treatment
- Pelvic treatment
- Post–operative treatment
- Side-effects
- **Blue skies**

Technology

Towards precision and personalised radiotherapy



Do Prostate Cancers Vary in Sensitivity to Fraction Size?



Tissue microarray (TMA) and biomarker characterisation in localised prostate cancer

CHHiP Trans study

Potential Markers

Proliferation: Ki67,PKA type1

Hypoxia: HIF1alpha,VEGF,osteopontin

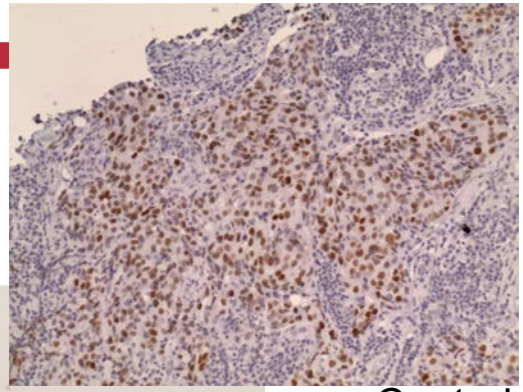
DNA repair pathways: p53,p16,MRE 11,

Apoptosis: BCL2,BAX

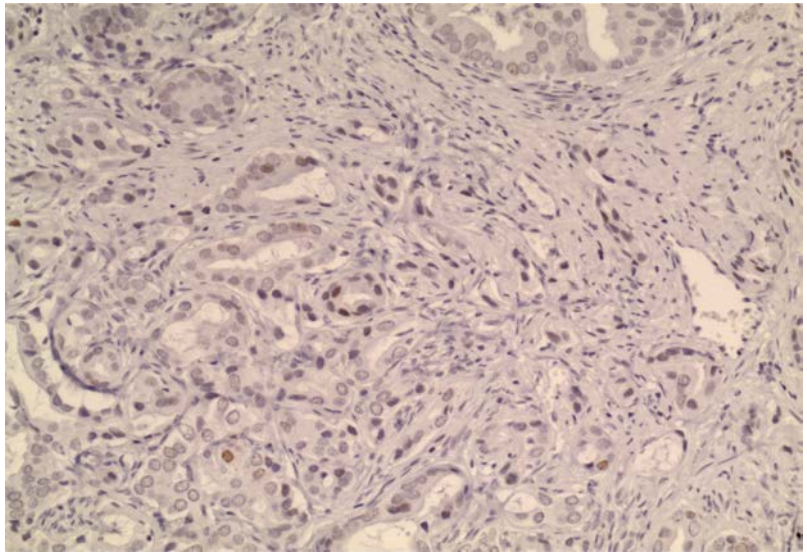
Other prognostic candidates: ERG gene rearrangements, nuclear AR, PTEN loss, EZH2, E-cadherin, hepsin, p27, PDZK-3, Hsp27, PKC-zeta, PRL-19, beta-catenin, pRb, MDM2, SOX9, p21, AMACR and p63. E2F3, TEAD1,C-Cbl,SPINK1.

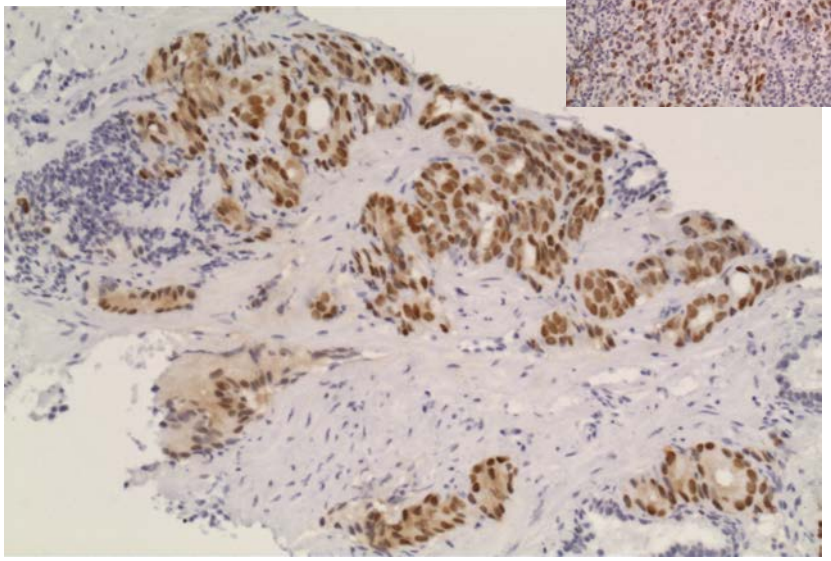
Stats: Aprox 600 events for HR 0.5 for biomarker positive vs negative with 80% power

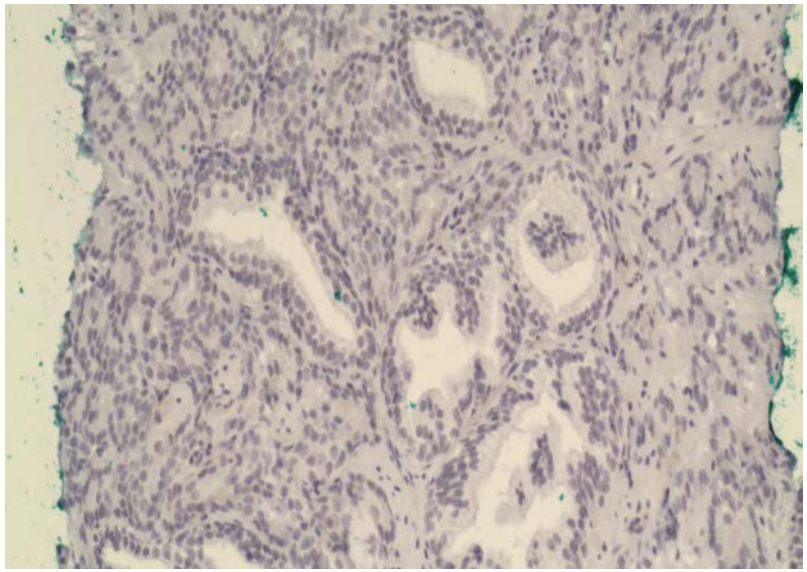
IHC for p53 (4 prostate tumours)

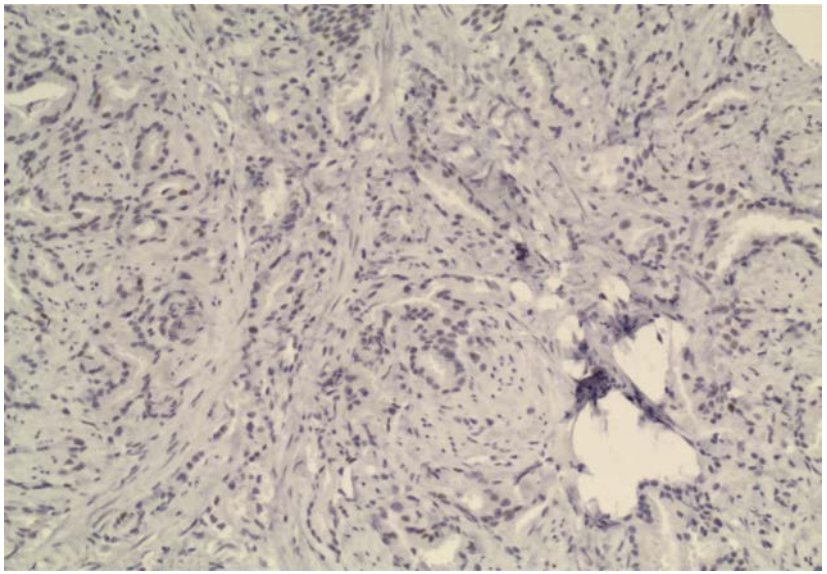


Control







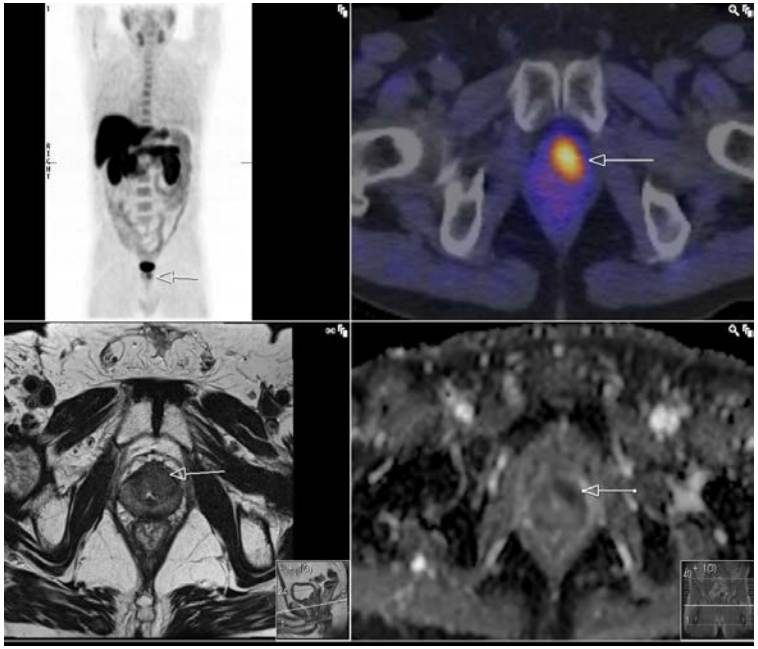


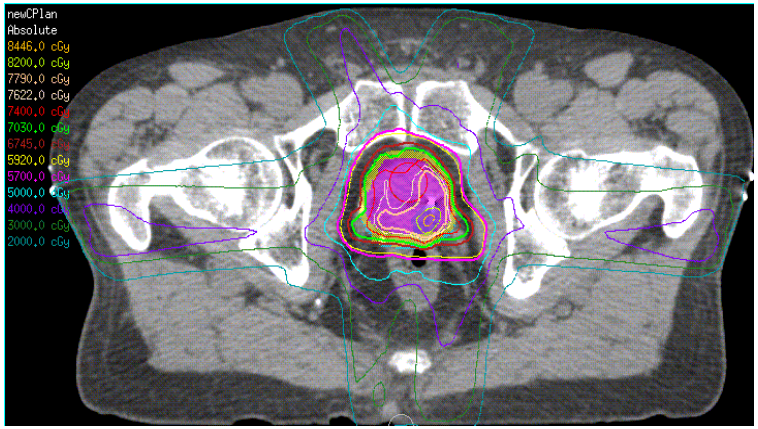
Multifunctional Image guidance for image guided radiotherapy

- Hypothesis 1:
  multiparametric MR and choline PET accurately define DIL

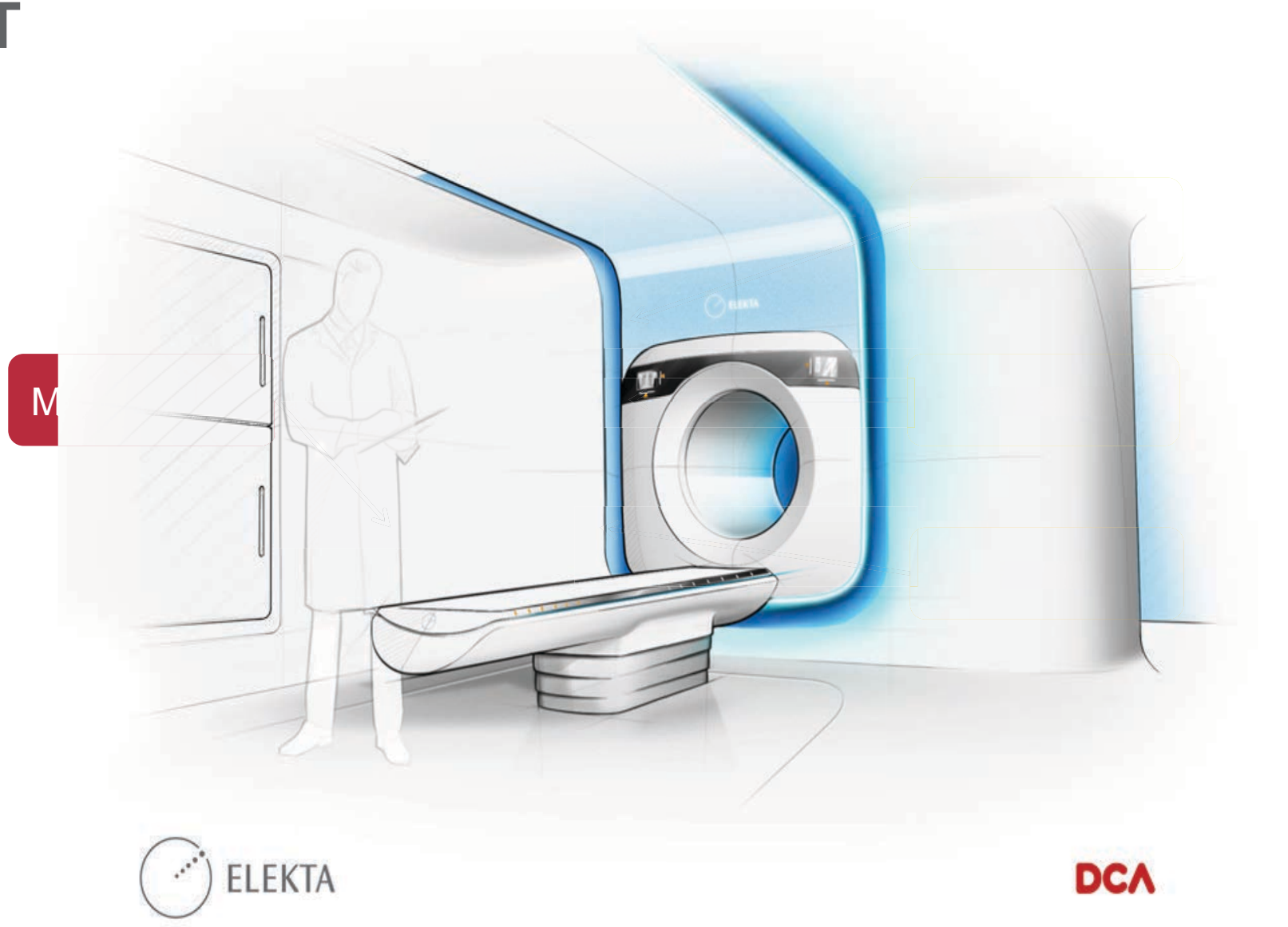
- Hypothesis 2:
  DIL boost can be safely given with conventional, modest and extreme hypofraction.

- Hypothesis 3:
  Phase 3 trials will show improved outcomes and reduced or similar toxicity





Development and Optimization of MR-Guided RT

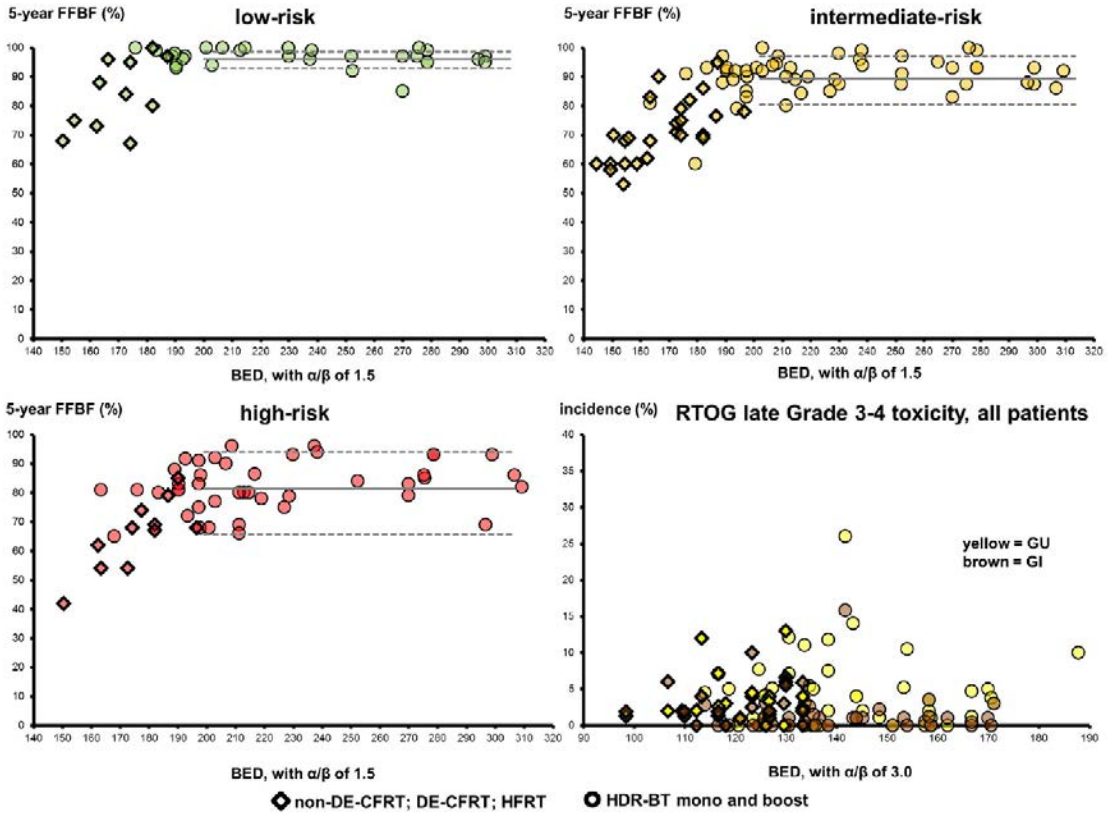


Systematic review

Radiotherapy and Oncology 115 (2015) 295–300

What is the ideal radiotherapy dose to treat prostate cancer? A meta-analysis of biologically equivalent dose escalation

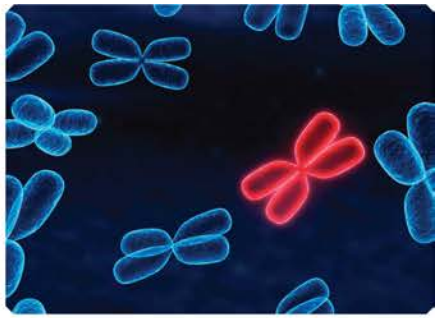
Nicholas G. Zaorsky [a,b,*], Joshua D. Palmer [b], Mark D. Hurwitz [b], Scott W. Keith [c], Adam P. Dicker [b], Robert B. Den [b]



- Dose escalation to BED of 200Gy for alpha/beta of 1.5Gy associated with improved biochemical disease control – but with increased toxicity
- Equivalent to a dose of 86Gy in 2Gy/f or 66Gy in 3Gy/f or 40.1Gy in 5.85Gy/f or 35.25Gy in 7.05Gy/f

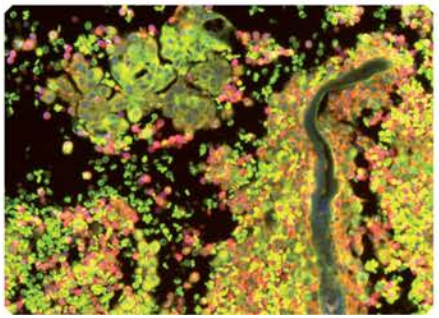
Unrivalled track record

ICR The Institute of Cancer Research



Making the discoveries that defeat cancer

ICR



One of the world's most influential cancer research institutes