EBRT and LDR brachytherapy boost.
ASCENDE RT Summary

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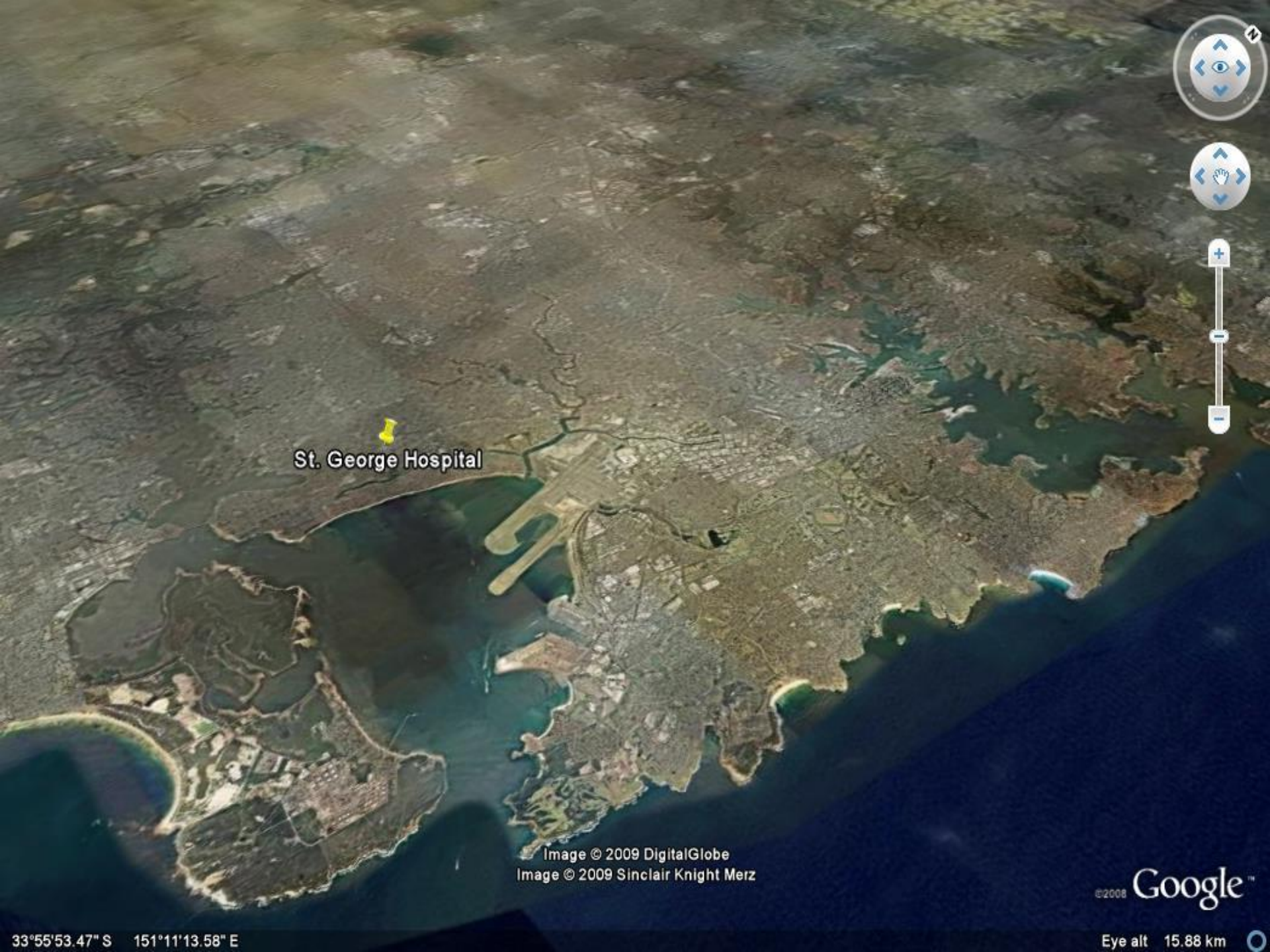
St. George Hospital
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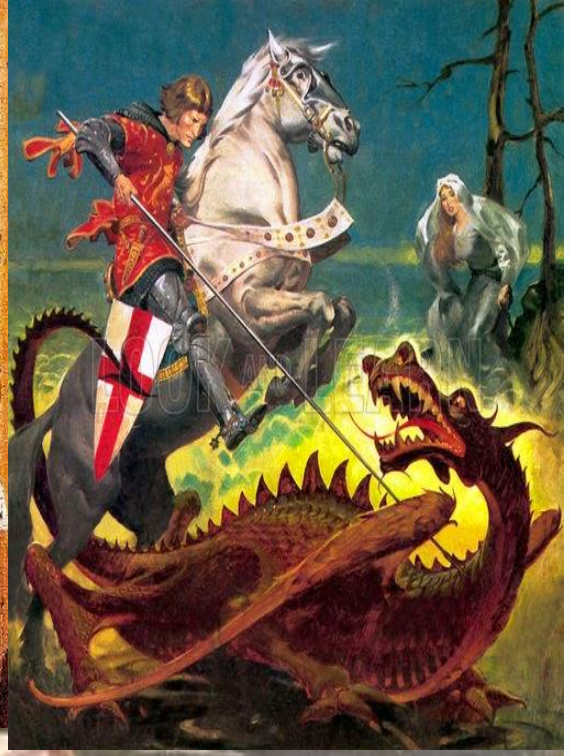
33°55'53.47" S 151°11'13.58" E
Eye alt 15.88 km



THE ST GEORGE HOSPITAL
TU SOUFFRES CELA SUFFIT



BC Cancer Agency
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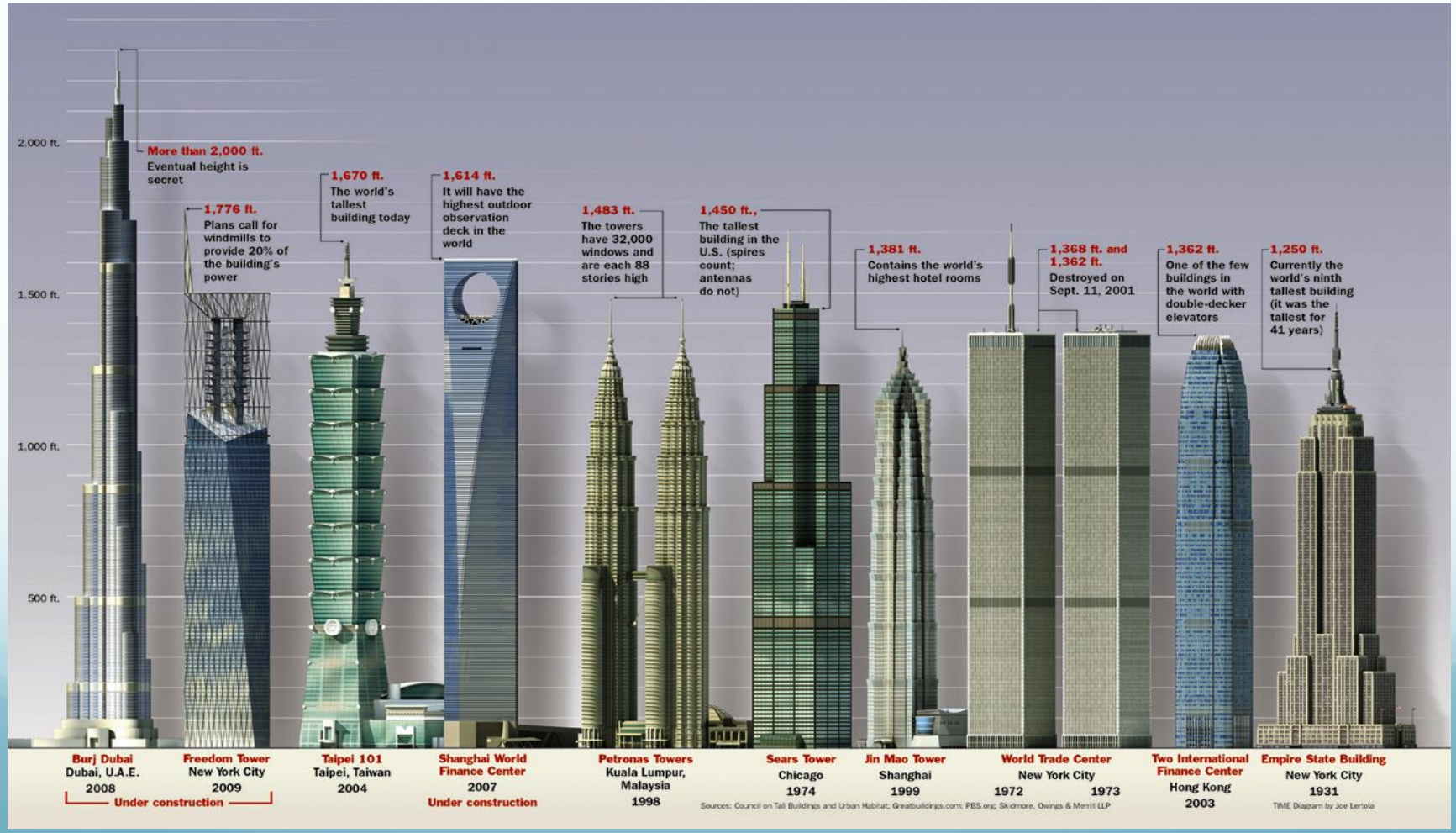
Background

- Multiple randomized studies of dose-escalated-EBRT
  - associated with improved b-PFS compared with standard dose EBRT using PSA endpoints
- 2 randomized trials comparing EBRT + brachytherapy boost vs EBRT alone
  - neither used DE-EBRT for the standard arm
  - no low-dose-rate prostate brachytherapy (LDR-PB) for the experimental arm

Higher doses improve control….

But how high is enough?



If higher doses improve control….

What about toxicity?

HIGHER-THAN-CONVENTIONAL RADIATION DOSES IN LOCALIZED PROSTATE CANCER TREATMENT: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

GUSTAVO ARRUDA VIANI, M.D., EDUARDO JOSE STEFANO, M.D., AND SERGIO LUIS AFONSO, M.D.

- More G2+ GU toxicity after dose escalation:
- OR 1.2
- P = 0.054

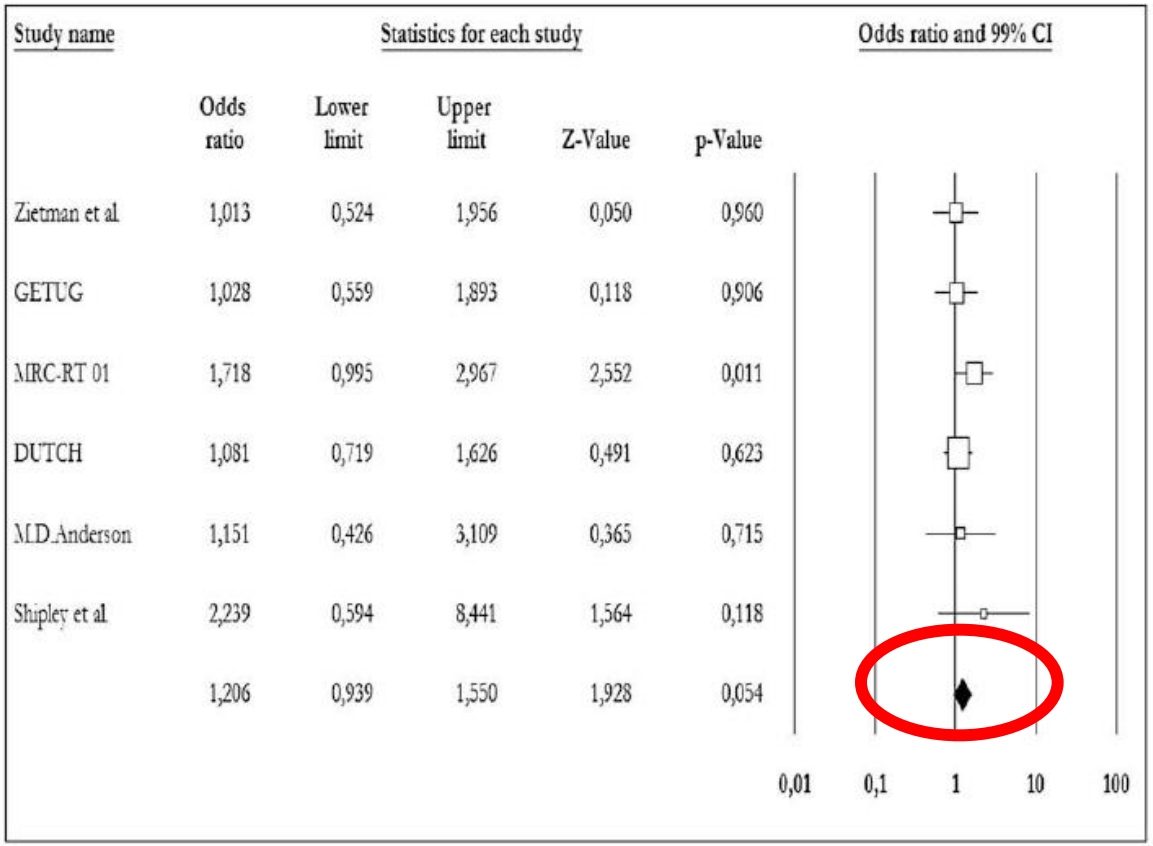


Fig. 8. Gastrointestinal toxicity of Grade ≥2 in the trials comparing high-dose radiotherapy with conventional-dose radiotherapy. CI = confidence interval.

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 5, pp. 1405–1418, 2009

HIGHER-THAN-CONVENTIONAL RADIATION DOSES IN LOCALIZED PROSTATE CANCER TREATMENT: A META-ANALYSIS OF RANDOMIZED, CONTROLLED TRIALS

GUSTAVO ARRUDA VIANI, M.D., EDUARDO JOSE STEFANO, M.D., AND SERGIO LUIS AFONSO, M.D.

- More G2+ GI toxicity after dose escalation:
- OR 1.58
- P < 0.001

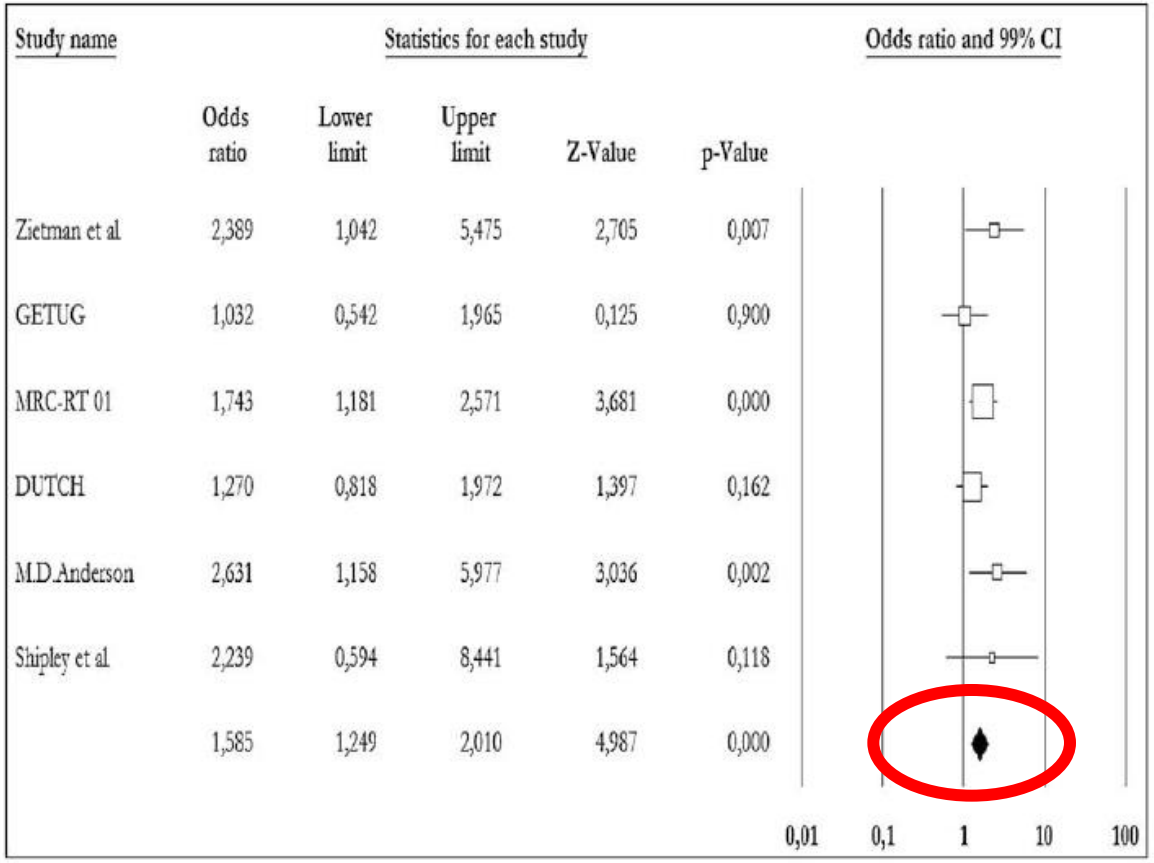
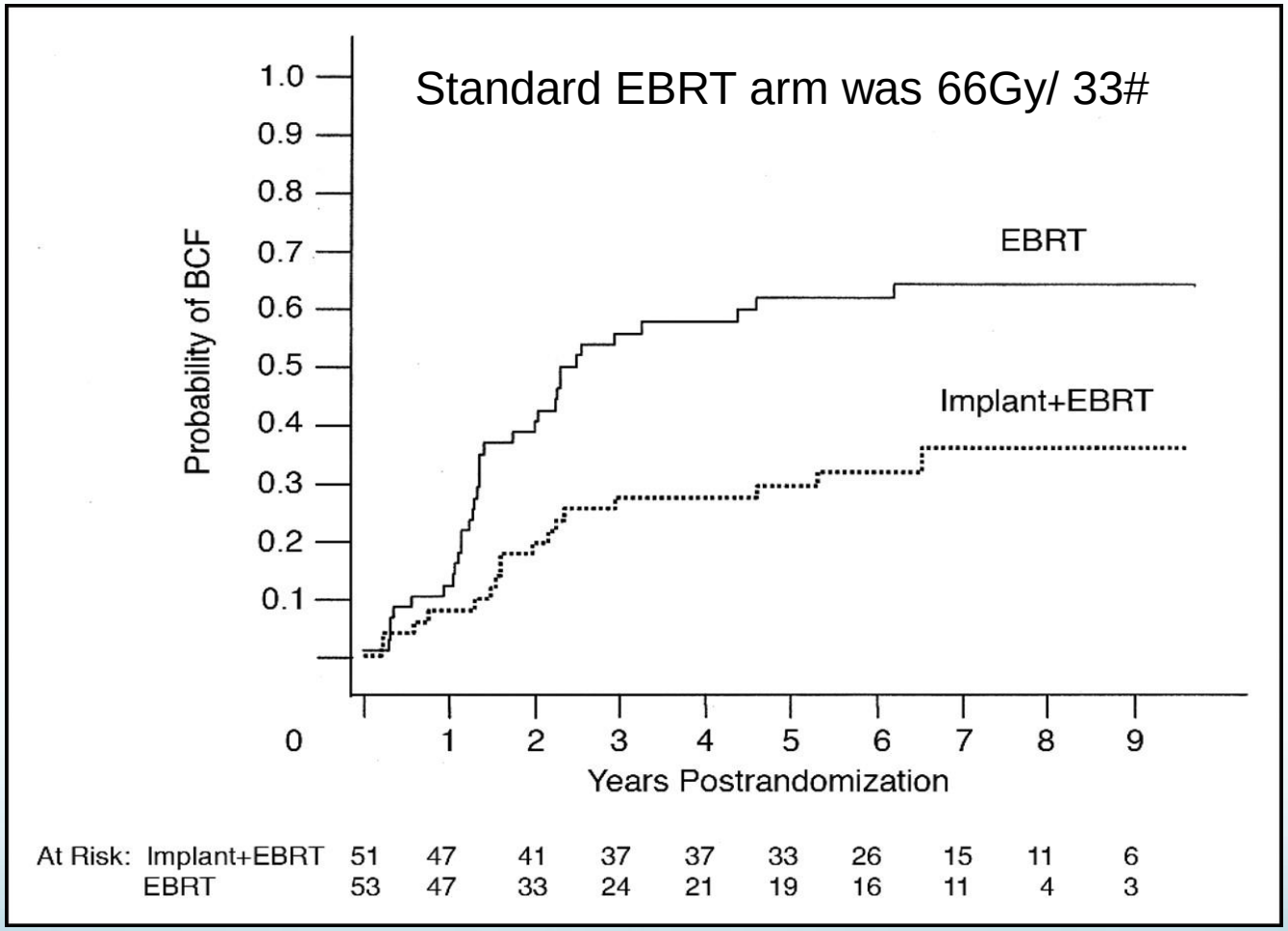


Fig. 9. Genitourinary toxicity of Grade ≥2 in the trials comparing comparing high-dose radiotherapy with conventional-dose radiotherapy. CI = confidence interval.

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 5, pp. 1405–1418, 2009

Probability of biochemical or clinical failure (BCF) by randomized treatment arm.



Sathya J R et al. JCO 2005;23:1192-1199

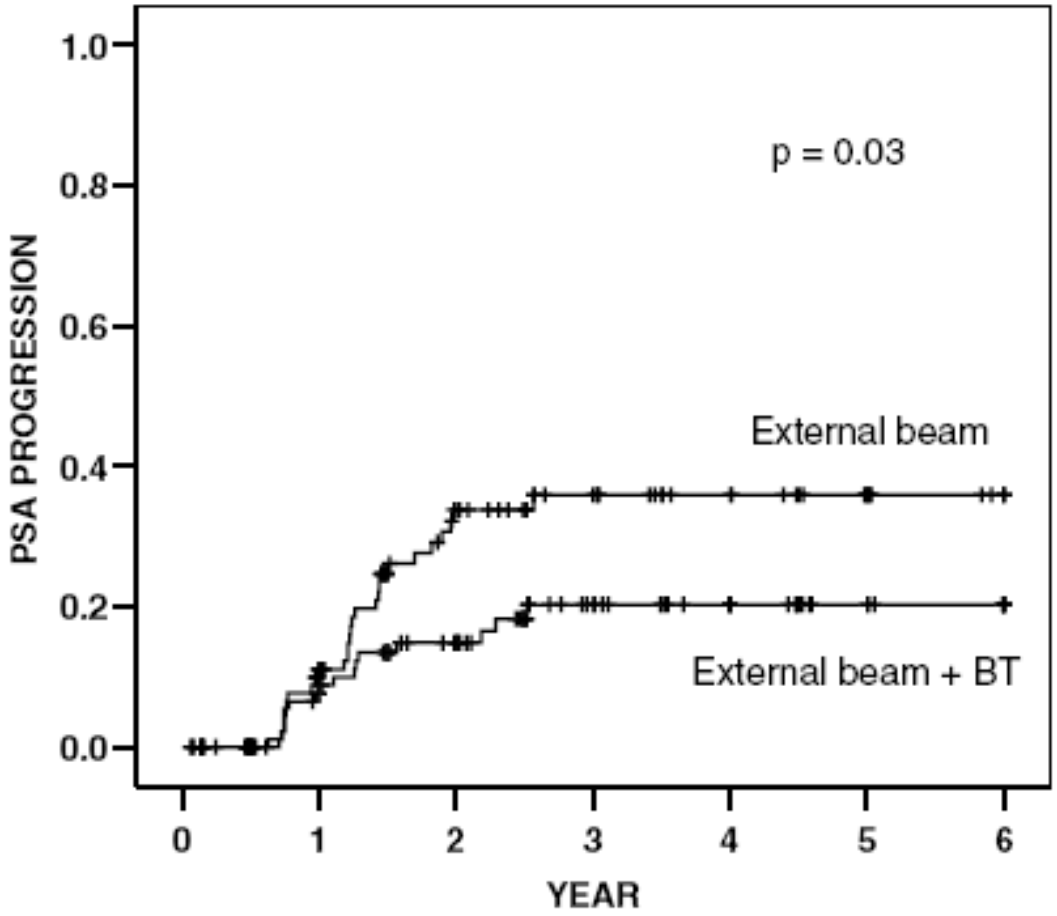
High dose rate brachytherapy in combination with external beam radiotherapy in the radical treatment of prostate cancer: initial results of a randomised phase three trial

Peter J. Hoskin*, Kate Motohashi, Peter Bownes, Linda Bryant, Peter Ostler

220 pts. randomised to:
- 55Gy/20# EBRT, or
- 37.5Gy/13# + 17Gy/2# HDR

30 mths follow up
- Equivalent acute and late toxicity

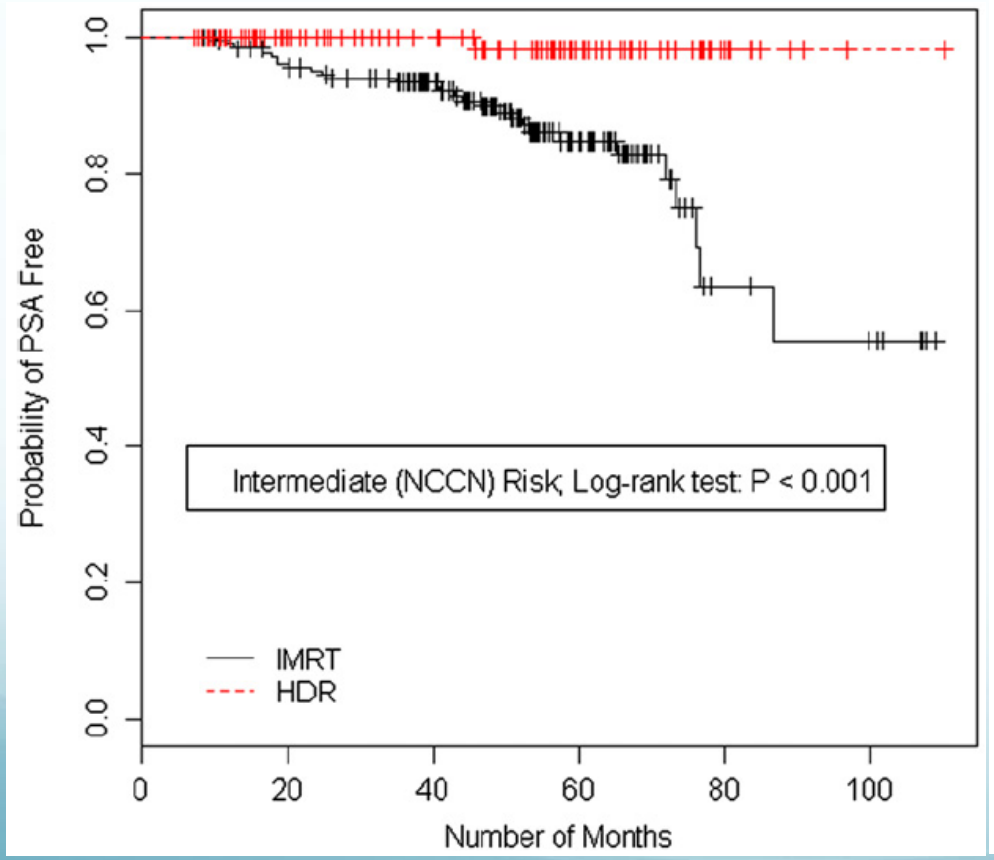
Improved biochemical control in HDR group

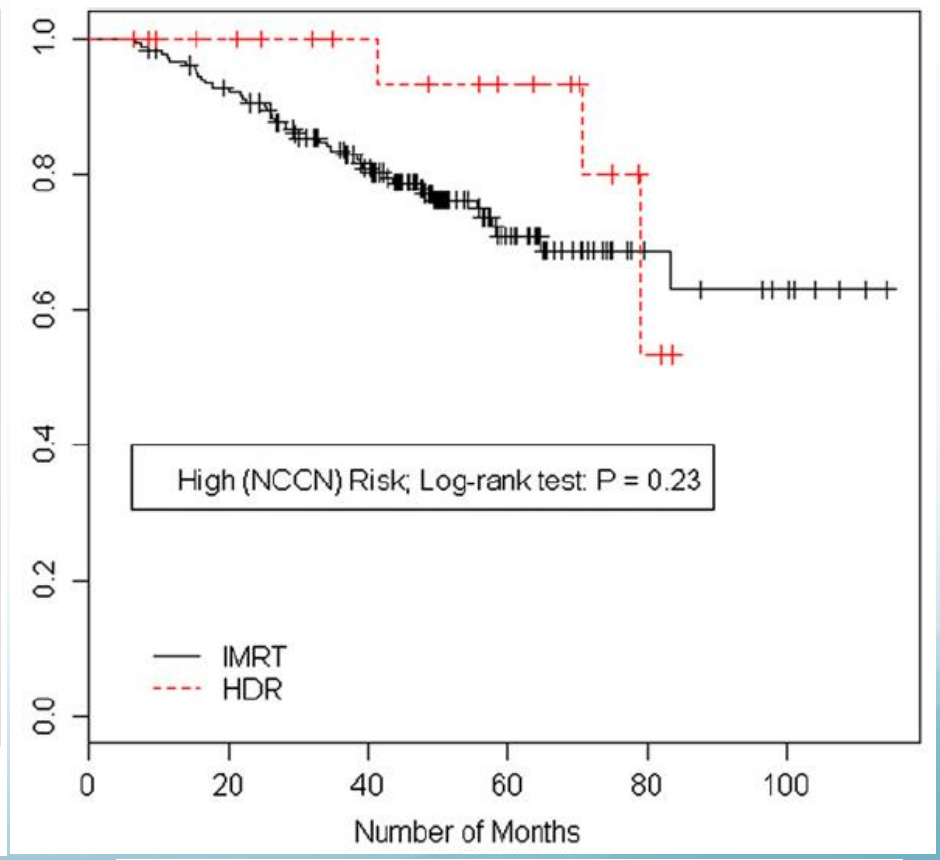


Radiotherapy and Oncology 84 (2007) 114–120

Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT

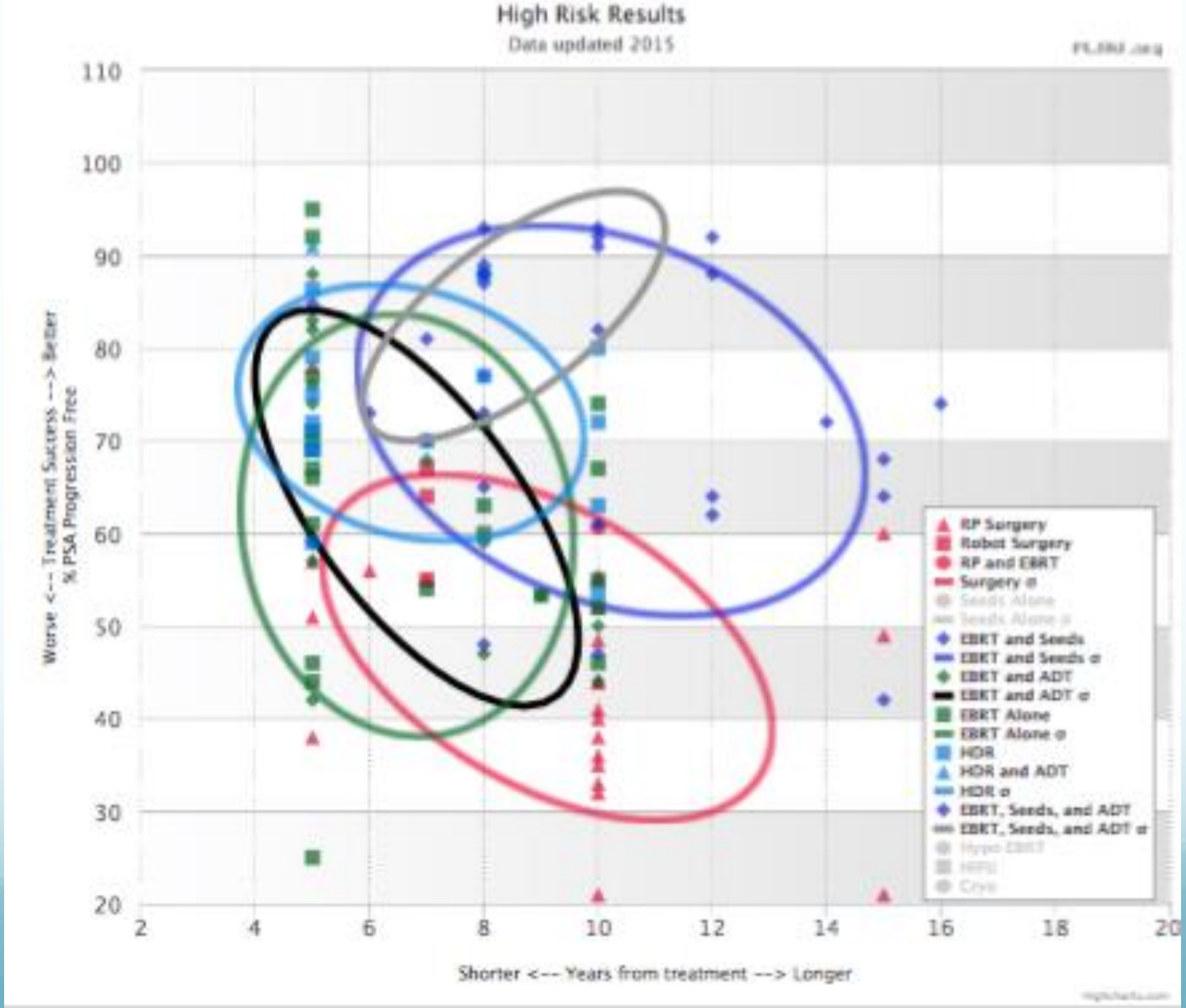
Israel Deutsch[1], Michael J. Zelefsky[1], Zhigang Zhang[2], Qianxing Mo[2], Marco Zaider[3], Gil'ad Cohen[3], Oren Cahlon[1], Yoshiya Yamada[1,*]





Brachytherapy 9 (2010) 313–318

Comparative analysis:High risk



Clinical Investigation

Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer

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*Departments of *Surgery, and #Medicine, University of British Columbia; †BC Cancer Agency—Vancouver Centre; ‡BC Cancer Agency—Centre for the Southern Interior; §BC Cancer Agency—Vancouver Island Centre; ¶Department of Population Oncology, BC Cancer Agency, Vancouver, British Columbia; and ‖Department of Radiation Oncology, University of Toronto, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada*

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ASCENDE-RT Landmark trial

- Combined modality therapy for NCCN high and intermediate-risk prostate cancer
- 12 months of androgen deprivation therapy
  - buserelin acetate [Suprefact] or leuprolide acetate [Eligard] concurrent with 4 weeks of nonsteroidal antiandrogen
  - Whole pelvic irradiation to 46Gy/23# (IMRT)
- Randomised comparison of
  - I^{125} brachytherapy boost (115Gy)
  - 32Gy/16# EBRT boost (total 78Gy/32#)

Endpoints and trial design

- Primary endpoint was
  - b-PFS (nadir >2 ng/mL)
- Secondary endpoints
  - overall survival (OS)
  - metastasis-free survival (MFS)
  - prostate cancer-specific survival (PCSS)
  - The incidence and prevalence of treatment-related adverse effects

Factor	All patients (n=398)	DE-EBRT (n=200)	LDR-PB (n=198)
Age (y)			
Median	68	69	67
Mean ± SD	67.6 ± 7.5	67.9 ± 7.5	67.4 ± 7.4
Range	45-86	45-86	49-84
NCCN risk stratum			
Intermediate	122 (30.7)	63 (31.5)	59 (29.8)
High	276 (69.3)	137 (68.5)	139 (70.2)
Clinical T stage			
T1c-T2c	282 (70.9)	143 (71.5)	139 (70.2)
T3a	116 (29.1)	57 (28.5)	59 (29.8)
iPSA (ng/mL)			
<5	35 (8.8)	18 (9.0)	17 (8.6)
5-10	156 (39.2)	76 (38.0)	80 (40.4)
10-20	132 (33.2)	66 (33.0)	66 (33.3)
>20	75 (18.8)	40 (20.0)	35 (17.7)
Median	10.7	11.0	10.1
Mean ± SD	13.3 ± 8.2	13.4 ± 8.3	13.2 ± 8.1
Range	2.4-40.0	2.7-39.1	2.4-40.0
Gleason sum			
6	22 (5.5)	10 (5.0)	12 (6.1)
7	214 (53.8)	110 (55.0)	104 (52.5)
8-10	162 (40.7)	80 (40.0)	82 (41.4)

Post implant dosimetry

D_{90}	
Median	108.7
Mean ± SD	109.6 ± 12.8
Range	81-154.3
V_{100}	
Median	94.4
Mean ± SD	93.1 ± 5.2
Range	69.9-100

Multivariate analysis - biochemical control

Table 3 Univariate and multivariable analyses (Cox model; backwards: conditional) for

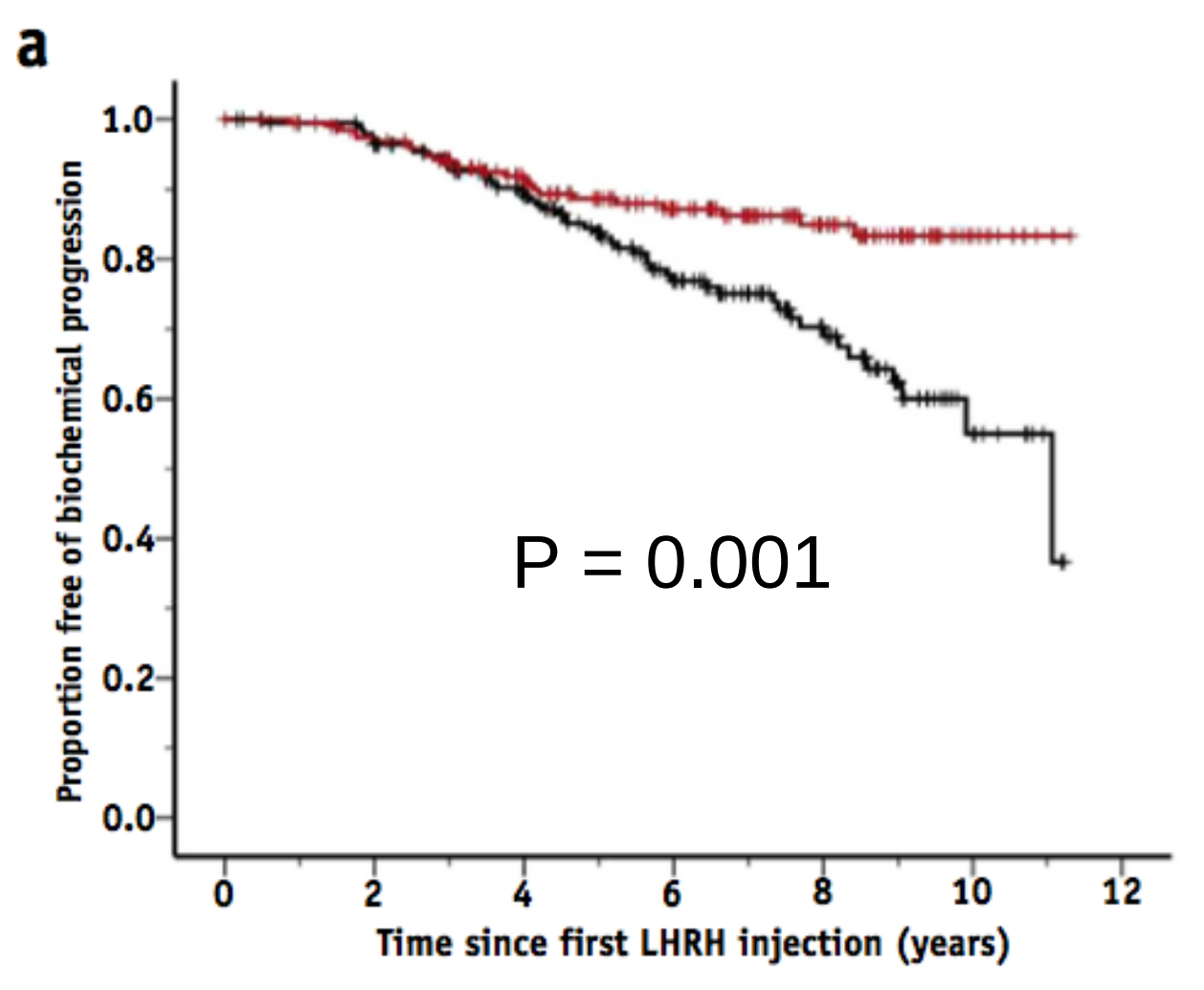
Variable	MVA Cox model		
	HR	95% CI	*P* value
Randomization arm*† (DE-EBRT vs LDR-PB)	**2.04**	**1.25-3.33**	**.004**‡
PPC* (unit = 1%)	**1.01**	**1.00-1.02**	**.006**‡
Clinical T stage*† (T3a vs T1-T2b)	**1.97**	**1.24-3.13**	**.004**‡
Log iPSA* (unit = 1 log)	**1.62**	**1.11-2.36**	**.01**‡
Risk code†§ (high vs intermediate)	NA	NA	NA
Number of high-risk features†§ (≥3 vs ≤2)	NA	NA	NA
Gleason sum*† (8-10 vs ≤7)	1.38	0.87-2.19	.17
Age (unit = 1 y)	NA		

Multivariate analysis - all cause mortality

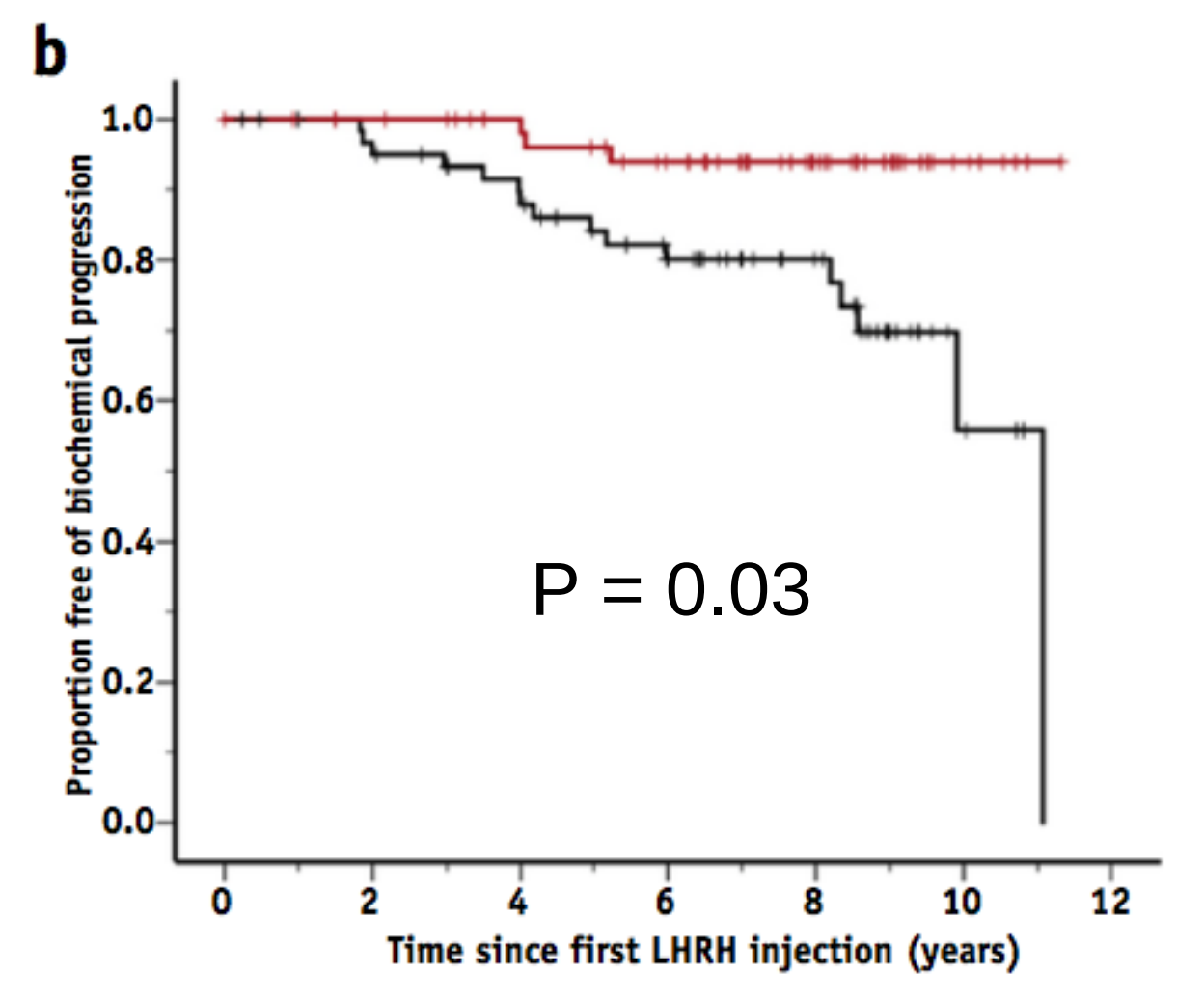
Table 4 Univariate and multivariable analysis (Cox model; backwards: conditional) for

Variable	MVA Cox model		
	HR	95% CI	*P* value
Randomization arm*† (DE-EBRT vs LDR-PB)	1.13	0.69-1.84	.62
PPC (unit = 1%)	NA	NA	NA
Clinical T stage† (T3a vs T1-T2)	NA	NA	NA
Log iPSA* (unit = 1 log)	1.18	0.80-1.73	0.42
Risk code†‡ (high vs intermediate)	NA	NA	NA
Number of high-risk features†‡ (≥3 vs ≤2)	NA	NA	NA
Gleason sum† (8-10 vs ≤7)	NA	NA	NA
Age* (unit = 1 y)	**1.05**	**1.02-1.09**	**.006**§
Disease status*† (relapse vs no relapse)	**6.30**	**3.62-10.9**	**< .001**§

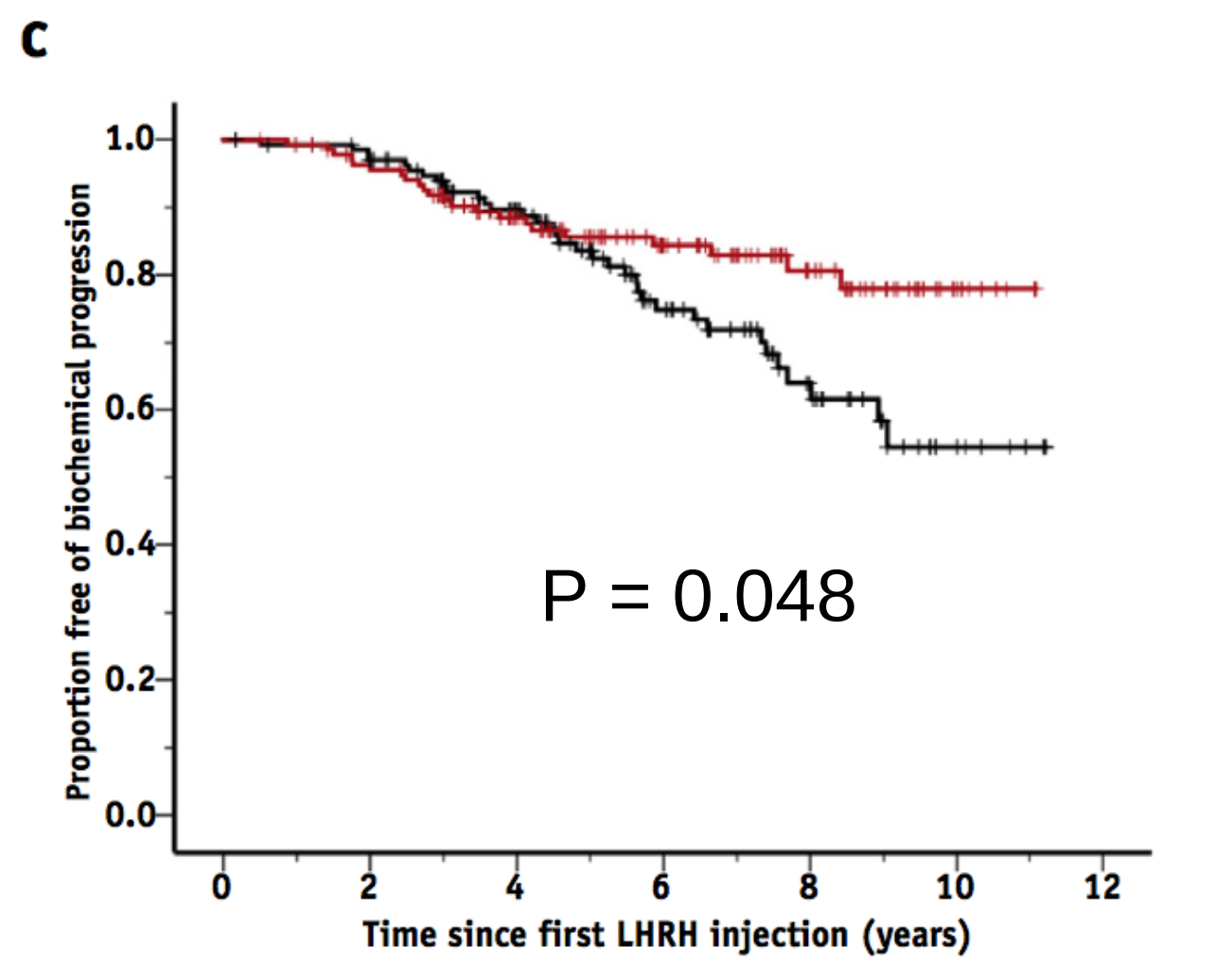
Biochemical progression-free survival



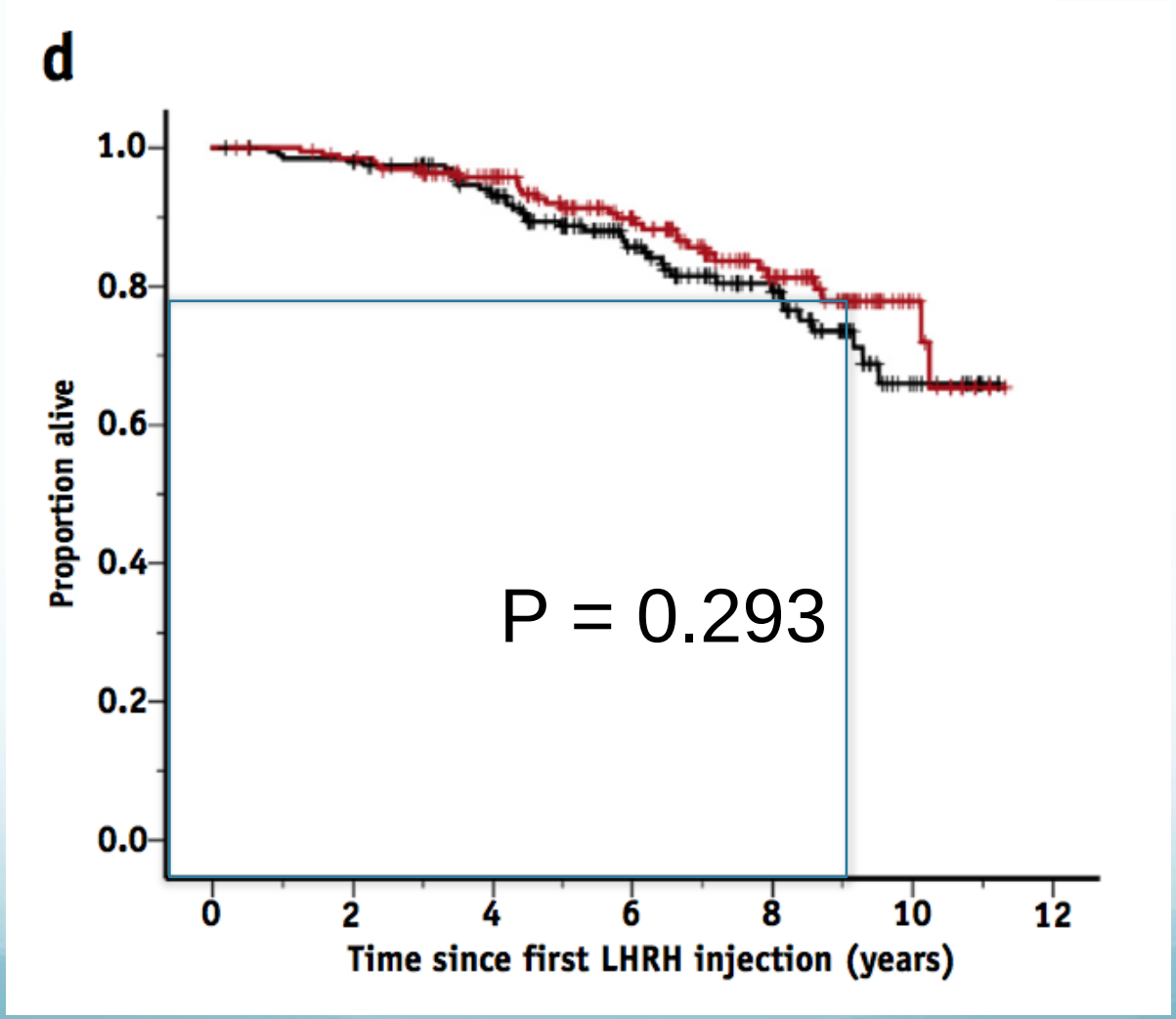
b-PFS for NCCN intermediate-risk



b-PFS for the NCCN high-risk



Overall survival



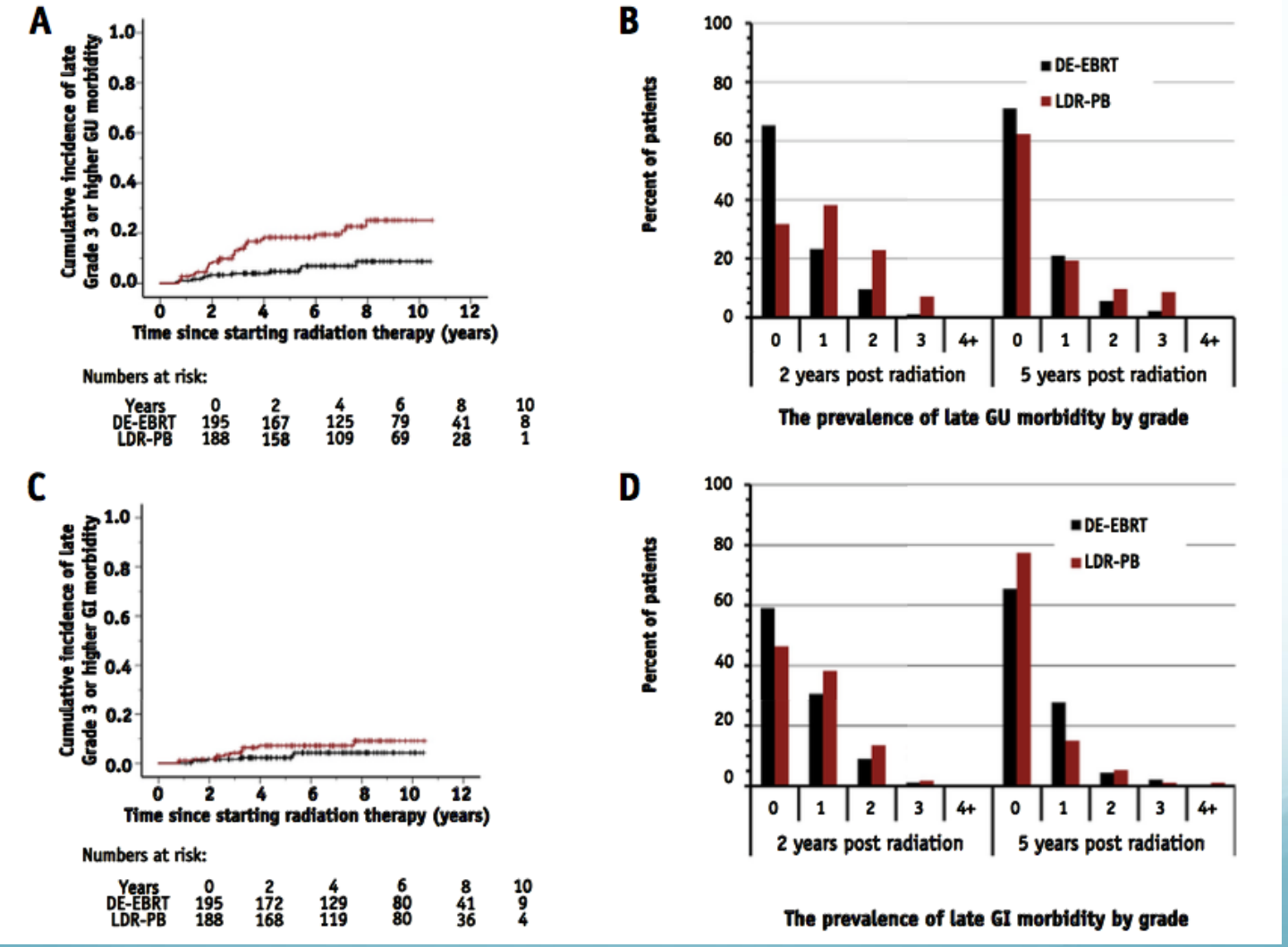
ASCENDE-RT

- Overall survival was
  - 77.9% in the brachytherapy group compared with 73.6% in the EBRT group.
- “Surgical definition" of b-PFS (PSA level > 0.2 ng/mL). extremely profound difference between arms
  - 31.5% in the EBRT vs 82.2% in the brachytherapy group

ASCENDE-RT Toxicity

5yr results	EBRT +LDR Brachy boost	Dose Escalated EBRT (78Gy)	P value
Cumulative incidence of Grade 3 GU	18.4%	5.2%	<0.001
Prevalence of Grade 3 GU	8.6%	2.2%	0.058
Cumulative incidence of Grade 3 GI	8.1%	3.2%	0.124
Prevalence of Grade 3 GI	1%	2.2%	ns
Adequate erectile function	45%	37%	0.30

Cumulative incidence vs. Prevalence



ASCENDE-RT Toxicity

Table 4 Comparing late grade 3 GU and GI toxicity reported for radiation dose-escalation studies for prostate cancer

Study	Median follow-up (y)	Late GU toxicity grade 3 (%)	Late GI toxicity grade 3 (%)
EBRT + LDR-PB studies: combination arm			
Albert et al (8)	2.8	N/A	30 (rectal bleeding)
Wong et al (9)	4.8	18	5
Spratt et al (10)	5.3	1.4	1.4
CALGB 99809 phase 2 study (11)	6.0	3	0
RTOG 00-19 phase 2 study* (12)	8.2	~15	~15
ASCENDE-RT (LDR-PB arm)	6.5	18.4	8.1
HDR + EBRT studies: combination arm			
Aluwini et al (13)	6.2	4	1
Sathya et al (14)	8.2	13.7	3.9
Hoskin et al (15)	7.3	31	7
Agoston et al (19)	5.1	14	2
Ghadjar et al (20)	5.1	10.9	0
EBRT alone dose-escalation studies: dose-escalation group			
M. D. Anderson (1)	8.7	4	7
MRC RT01 (2)	5.2	4	10
Dutch CKVO96-10 (3)	5.8	13	5
PROG95-09 (18)	8.9	2	1
ASCENDE-RT (DE-EBRT arm)	6.5	5.2	3.2

ASCENDE-RT Toxicity

- Technical changes may have the potential to reduce the incidence and severity of adverse effects
  - MRI for treatment planning
  - Improved image quality of new ultrasound equipment.
  - Reducing the prescription dose
  - Reducing the V150%
  - Dominant intraprostatic lesion boost
  - Smaller volumes with EBRT or ?omitting EBRT

ASCENDE-RT - summary

- b-PFS was profoundly different between groups
  - 5 yrs. 88.7% vs 83.8% 5% difference
  - 7 yrs. 86.2% vs 75.0% 11% difference
  - 9 yrs. 83.3% vs 62.4% 20% difference
    - HR 0.49 P = 0.001
- **Seed brachytherapy boost should be the standard of care!**

Brachytherapy under siege!