Amethyst
RADIOTHERAPIE

10th edition
GLOBAL CONGRESS ON PROSTATE CANCER
JUBILEE EDITION

Radiotherapy in Very High-Risk Prostate Cancer

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Conflicts of interest

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research supports	---
Receipt of honoraria or consultation fees	Astellas, BMS, Elekta, Ipsen, Janssen, Myovant
Stock shareholder	---
Other support (please specify):	---

RT for High-Risk PCa: what we know…

RT for High-Risk PCa: what we know…

High prostate dose (= dose/response relationship)
IMRT-IGRT / BT boost (LDR, HDR)

Trial	n	PCa stage	RT Dose	Follow-up	Outcome	Results
MD Anderson study 2011	301	T1-**T3**, N0, M0, PSA 10 ng/mL vs. PSA > 10 ng/mL	**70 vs.78 Gy**	9 yr.	DSM vs. other cause of death	High risk/PSA > 10 16% vs 4% DSM Higher risk: 15% vs 2% DSM
PROG 95-09 2010	393	T1b-T2b PSA 15 ng/mL 75% ISUP grade < 1	**70.2 vs.79.2 Gy**	8.9 yr.	10-year ASTRO BCF	32% vs 17% BFailure
MRC RT01 2014	843	T1b-**T3a**, N0, M0 PSA < 50 ng/mL neoad ADT	**64 vs. 74 Gy**	10 yr.	BFS; OS	43% vs 55% BFreeSurv
Dutch RCT 2014	664	T1b-**T4** 143 pts. with (neo) adj ADT	**68 vs. 78 Gy**	110 mo.	Phoenix BCF and/or clinical failure at 10 yr..	43% vs 49% FFF
GETUG 06 2011	306	T1b-**T3a**, N0, M0 PSA < 50 ng/mL	**70 vs. 80 Gy**	61 mo.	BCF (ASTRO)	39% vs 28% BFailure
RTOG 0126 2018	1532	T1b-T2b ISUP grade 1 + PSA 10-20 ng/mL or **ISUP grade 2/3** + PSA < 15 ng/mL	**70.2 vs. 79.2 Gy**	100 mo.	OS / DM BCF (ASTRO)	75% vs 76% OS 6% vs 4% DM 47% vs 31% BFailure

RT for High-Risk PCa: what we know…

High prostate dose (= dose/response relationship)
IMRT-IGRT / BT boost (LDR, HDR)

RT + ADT better than RT alone:
RTOG 92.02, EORTC 22861

Adjuvant ADT to RT: Phase III trials of EBRT +/- Androgen Deprivation

	Number of patients	Characteristics	Hormone therapy	Results
RTOG **85**-31[1]	977	**T3/N+**	Goserelin life-long	OS, *P* < 0.004
EORTC 22**86**1[2]	415	T1-2, **G3** **T3-4**	Goserelin, **3 years** (AA, 1 month)	OS, *P* < 0.001
RTOG **92**-02[3]	1,514	**T2c-4**, N0 PSA < 150 ng/mL	4 months TAB or Goserelin, **2 years**	Gleason 8-10 OS, *P* = 0.04
RTOG **94**-13[4]	1,292	T1c-4, PSA ≤ 100 ng/dL, **risk N+ >15%**	PORT vs. WPRT, NHT vs. AHT	WPRT+ NHT, better PFS

OS: overall survival; AA: antiandrogen; TAB: total androgen blockade; PORT: prostate-only RT; WPRT: whole-pelvic RT; NHT: neoadjuvant hormone therapy; PFS: progression-free survival

[1]Pilepich MV, et al. Proc Am Soc Clin Oncol 2003; [2]Bolla M, et al. Lancet 2002; [3]Hanks GE, et al. J Clin Oncol 2003; [4]Roach M, et al. J Clin Oncol 2003

MARCAP Meta-Analysys: 12 eligible trials that provided individual patient data (10 853 patients) with a median follow-up of 11·4 years (IQR 9·0–15·0).

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate Cancer

6.2.3.4 *Guidelines for radical treatment of high-risk localised disease*

Recommendations
Radical prostatectomy (RP)
Offer RP to selected patients with high-risk localised PCa as part of potential multi-modal therapy.
Extended pelvic lymph node dissection (ePLND)
Perform an ePLND in high-risk PCa.
Do not perform a frozen section of nodes during RP to decide whether to proceed with, or abandon, the procedure (see Section 6.2.4.1).
Radiotherapeutic treatment
In patients with high-risk localised disease, use intensity-modulated radiation therapy (IMRT) /volumetric modulated arc therapy (VMAT) plus image-guided radiation therapy (IGRT) with 76–78 Gy in combination with long-term androgen deprivation therapy (ADT) (2 to 3 years).
In patients with high-risk localised disease and good urinary function, use IMRT/VMAT plus IGRT with brachytherapy boost (either high-dose rate or low-dose rate), in combination with long-term ADT (2 to 3 years).
Therapeutic options outside surgery or radiotherapy
Do not offer either whole gland or focal therapy to patients with high-risk localised disease.
Only offer ADT monotherapy to those patients unwilling or unable to receive any form of local treatment if they have a prostate-specific antigen (PSA)-doubling time < 12 months, and either a PSA > 50 ng/mL or a poorly-differentiated tumour.

RT for High-Risk PCa: what we do know…

High prostate dose (= dose/response relationship)
IMRT-IGRT / BT boost (LDR, HDR)

RT + ADT better than RT alone:
RTOG 92.02, EORTC 22861

RT + ADT better than ADT alone:
SPGC-7, INT:T94-0110

ADT alone vs RT + ADT for locally advanced PCa

Intergroup T94-0110 RCT (NCIC, SWOG, MRC)

Randomised phase III trial, **1205 pts**: T3 – T4
T2 and iPSA > 40 ng/ml
T2 and iPSA > 20 ng/ml and GS > 7

Lifelong ADT + / - RT (65 – 69 Gy)
Median follow-up : 8 years

Mason, JCO, 2015

ADT alone vs RT + ADT for locally advanced PCa

Intergroup T94-0110 RCT (NCIC, SWOG, MRC)

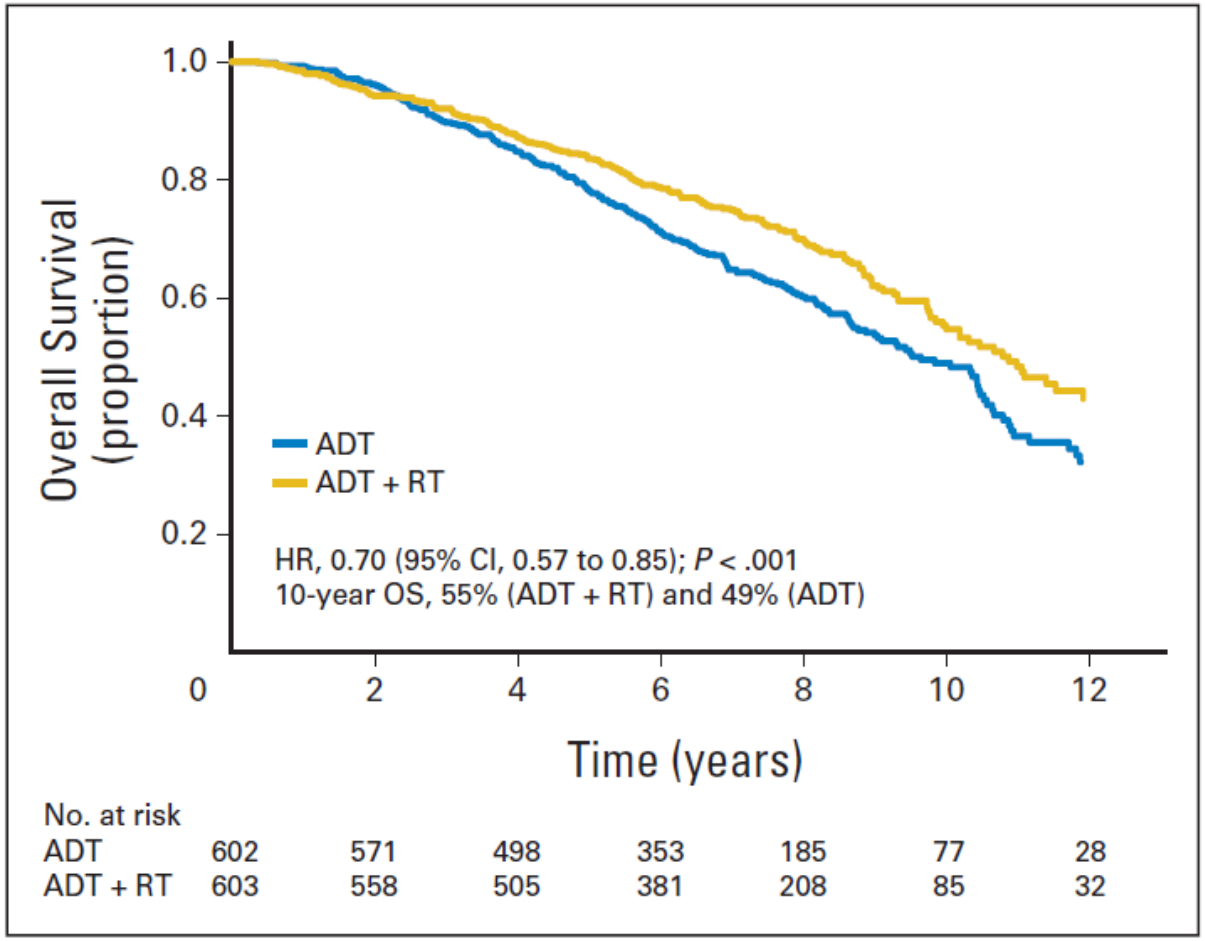


Fig 2. Overall survival (OS). ADT, androgen-deprivation therapy; HR, hazard ratio; RT, radiotherapy.

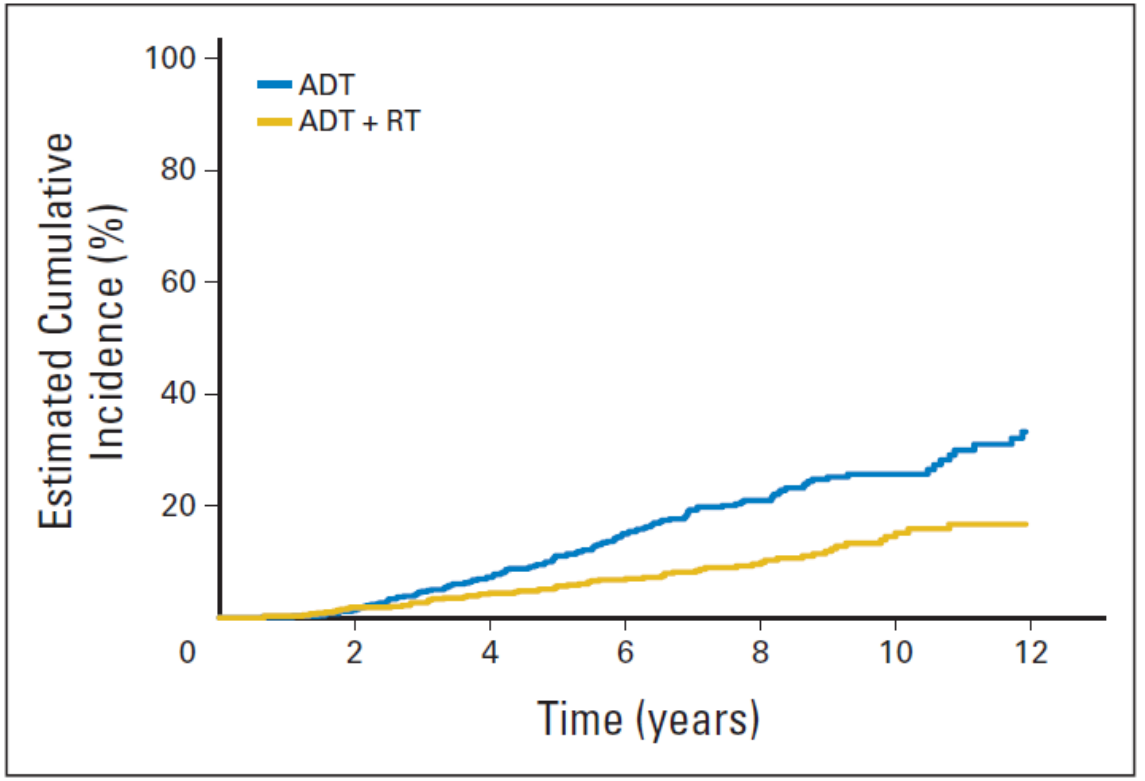


Fig 3. Deaths from prostate cancer. ADT, androgen-deprivation therapy; RT, radiotherapy.

Mason, JCO, 2015

RT for HR-PCa: what we ***do not*** **know**…

Which (high) total dose in the prostate ?

Which technique ?

ADT: how long ?

Pelvic RT: yes/no ?

RT for HR-PCa: what we *do not* know…

Which (high) total dose in the prostate ?

Which technique ?

ADT: how long ?

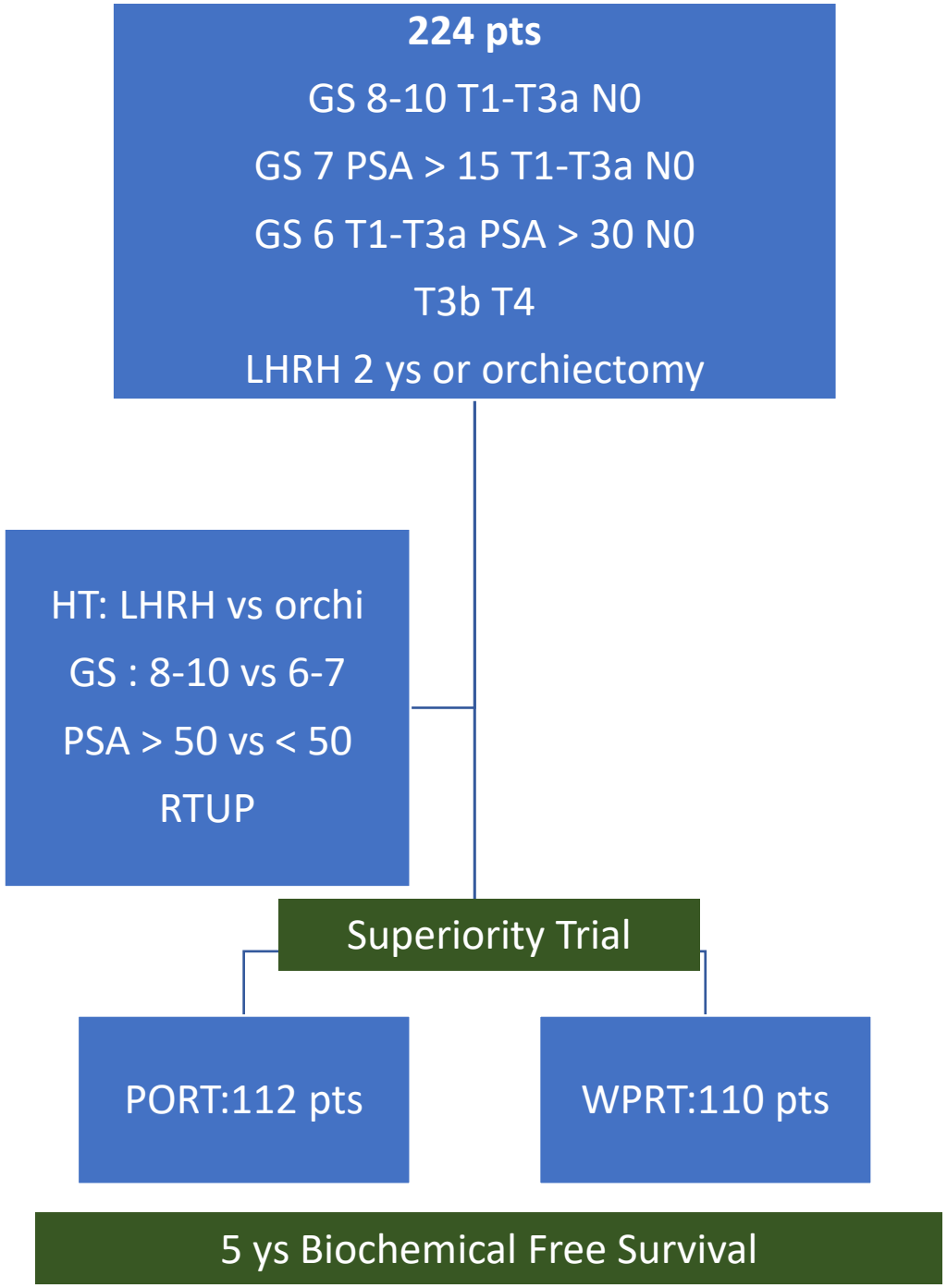
Pelvic RT: yes/no ?

… RT + ADT *vs* Surg (+/- RT +/- ADT) ?

POP RT Trial

Murthy et al **J Clin Oncol 39:1234-1242. © 2021**

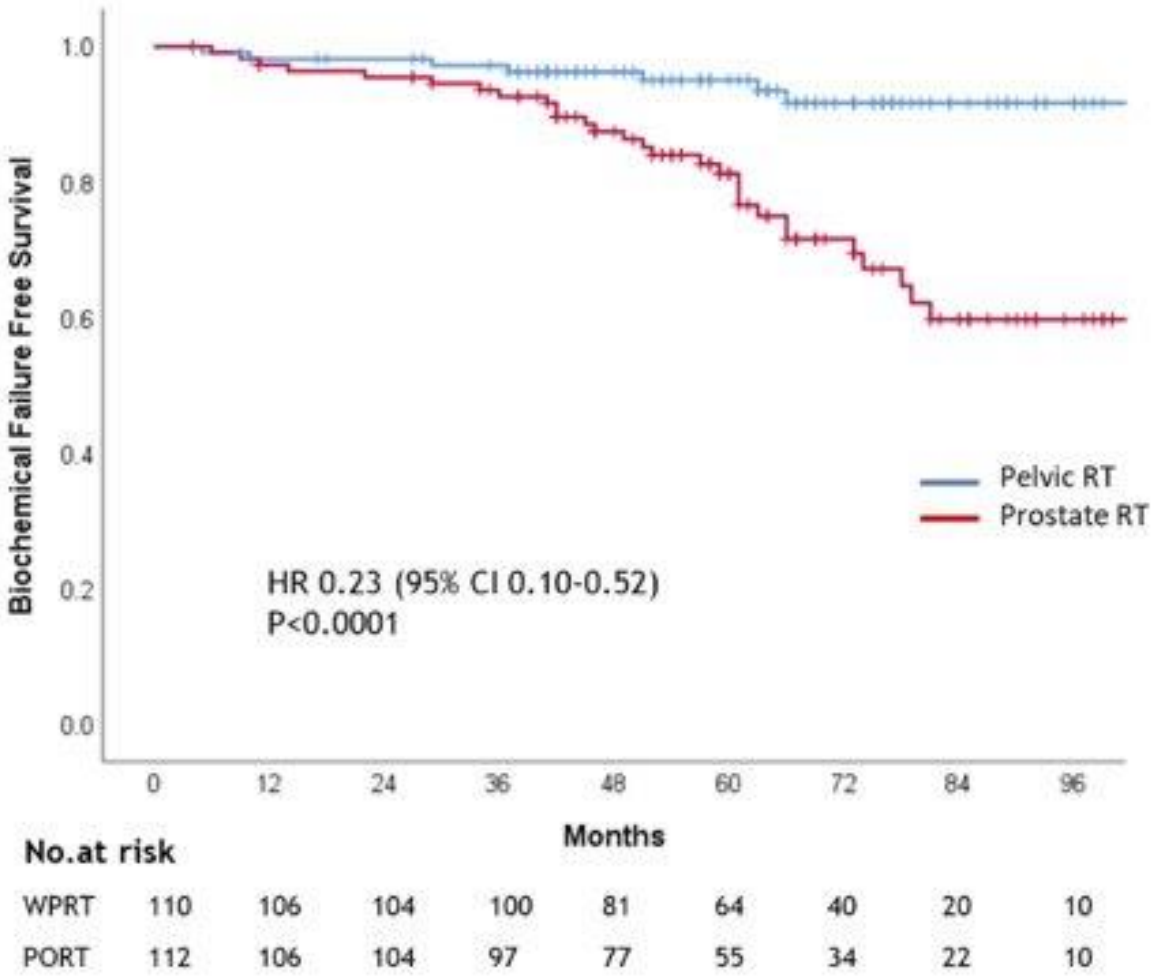
	POP RT
N+ Risk (Roach > 20)	**Med.:** 38% **> 35%:** 55% **> 50%:** 29%
Gleason	**8-10:** 49.1%
Staging	IRM pelv, TEP CT, **PSMA TEP (80 %)**
Pelvis	**50Gy /25 fr**
Prostate dose	**68Gy / 25 fr SIB**
Technique	**IG-IMRT**



Biochemical Failure-Free Survival

ESTRO 2020

V Murthy et al, India



Median Follow up: 68 Months

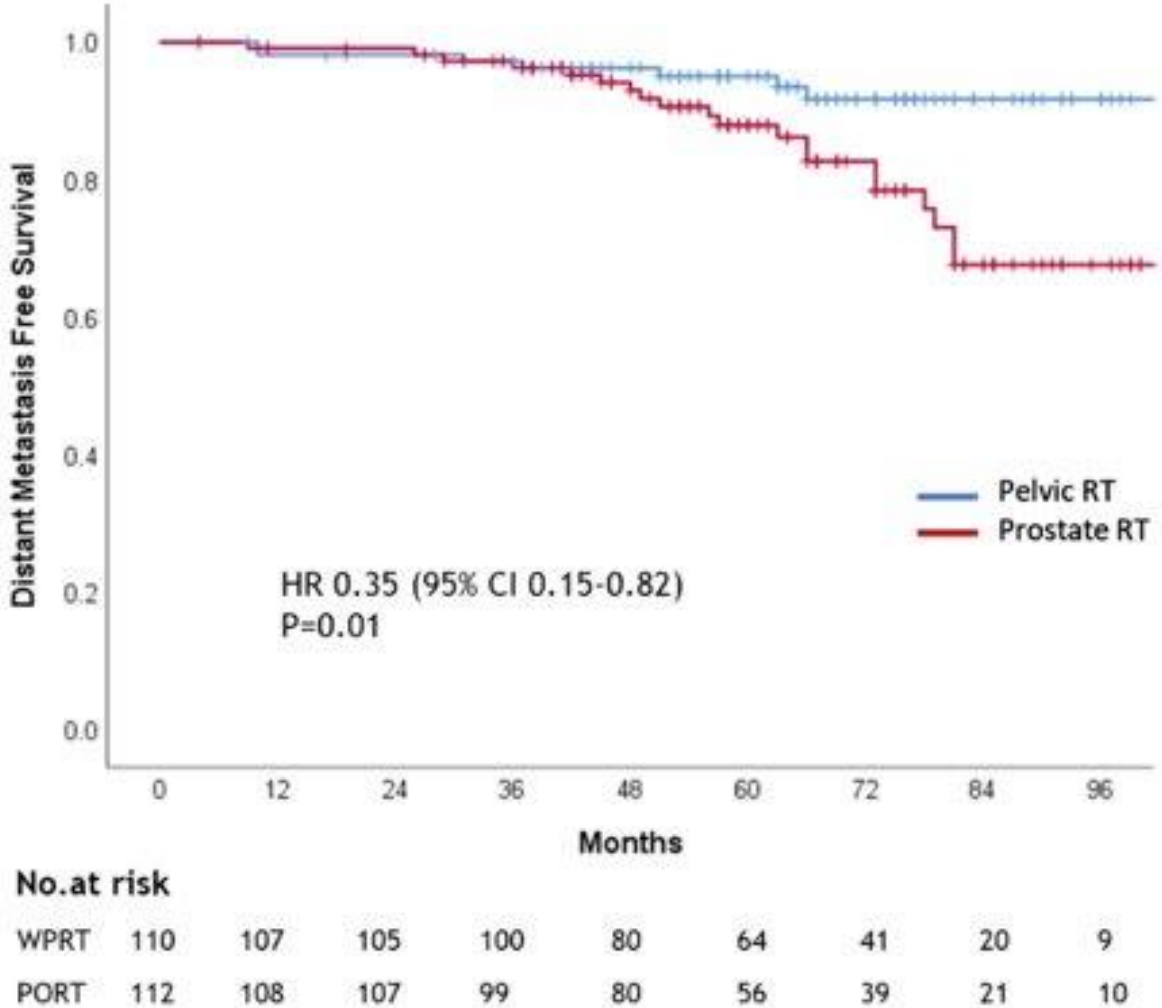
	WPRT	PORT
No. of events	7	29
5-yr BFFS	95.0%	81.2%

J Clin Oncol 39:1234-1242. © 2021

Distant Metastasis-Free Survival (Post Hoc)

ESTRO 2020

V Murthy et al, Indi



Median Follow up: 68 Months

	WPRT	PORT
No. of events	7	20
5-yr DMFS	95.0%	87.9%

J Clin Oncol 39:1234-1242. © 2021

Patterns of disease recurrence at biochemical failure

Site of recurrence	WPRT	PORT
Regional pelvic nodes (With/without Distant Metastasis)	1	15
Distant metastases only	5	7
Local recurrence only	0	1
No radiological disease (only BCF)	0	2
Pattern unknown	2	4
Total	7	29

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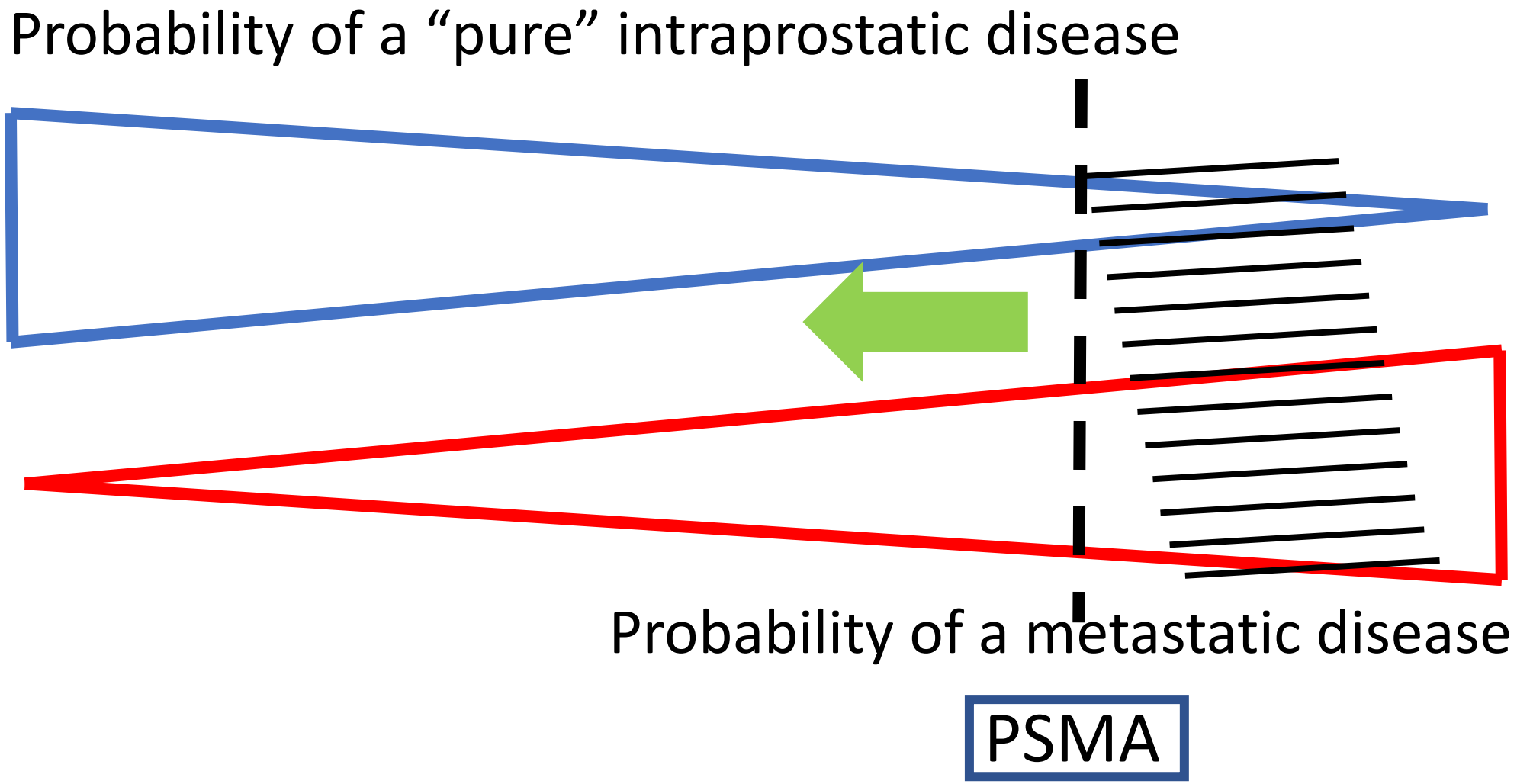
The “sliding window” of WPRT



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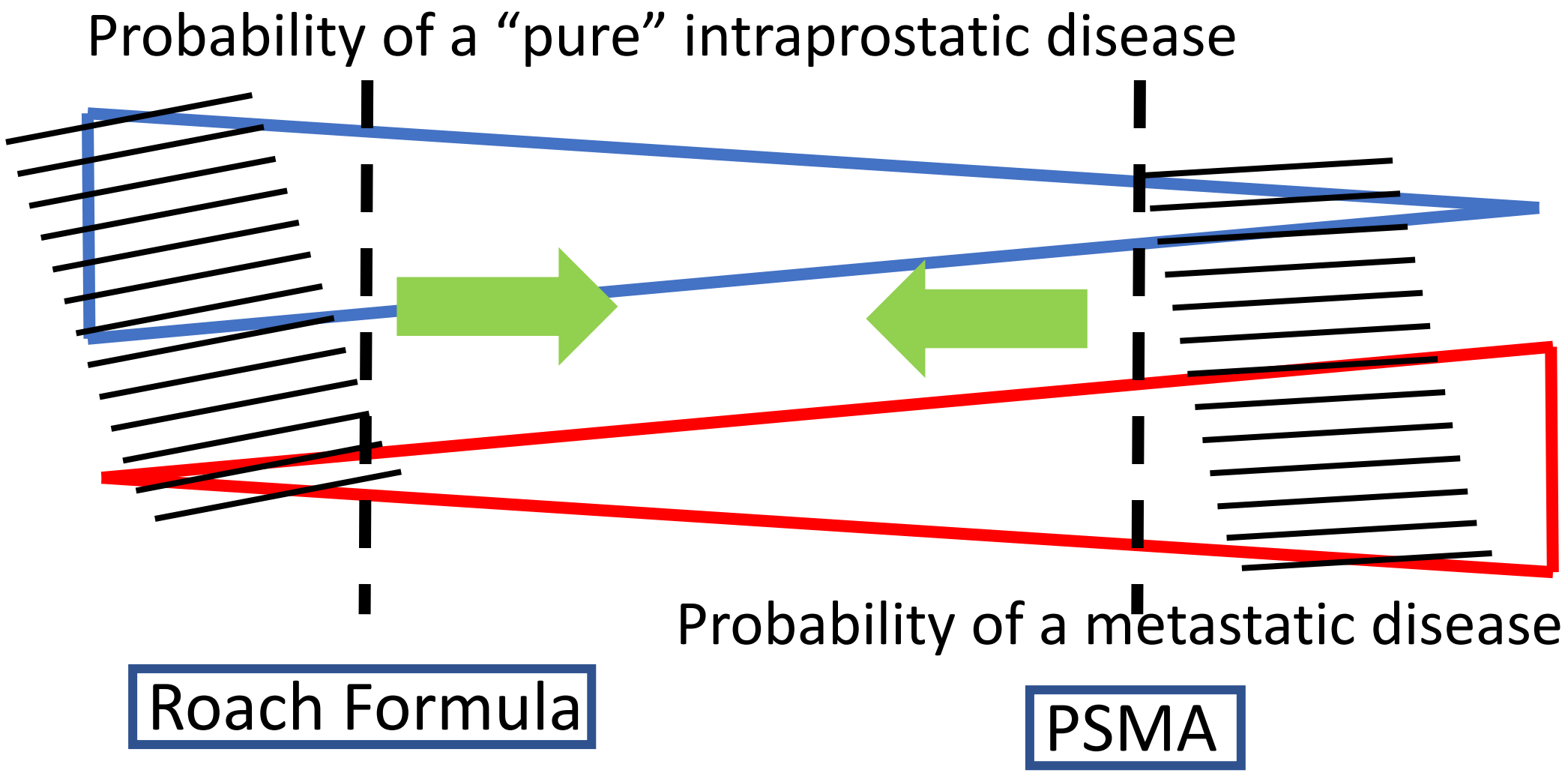
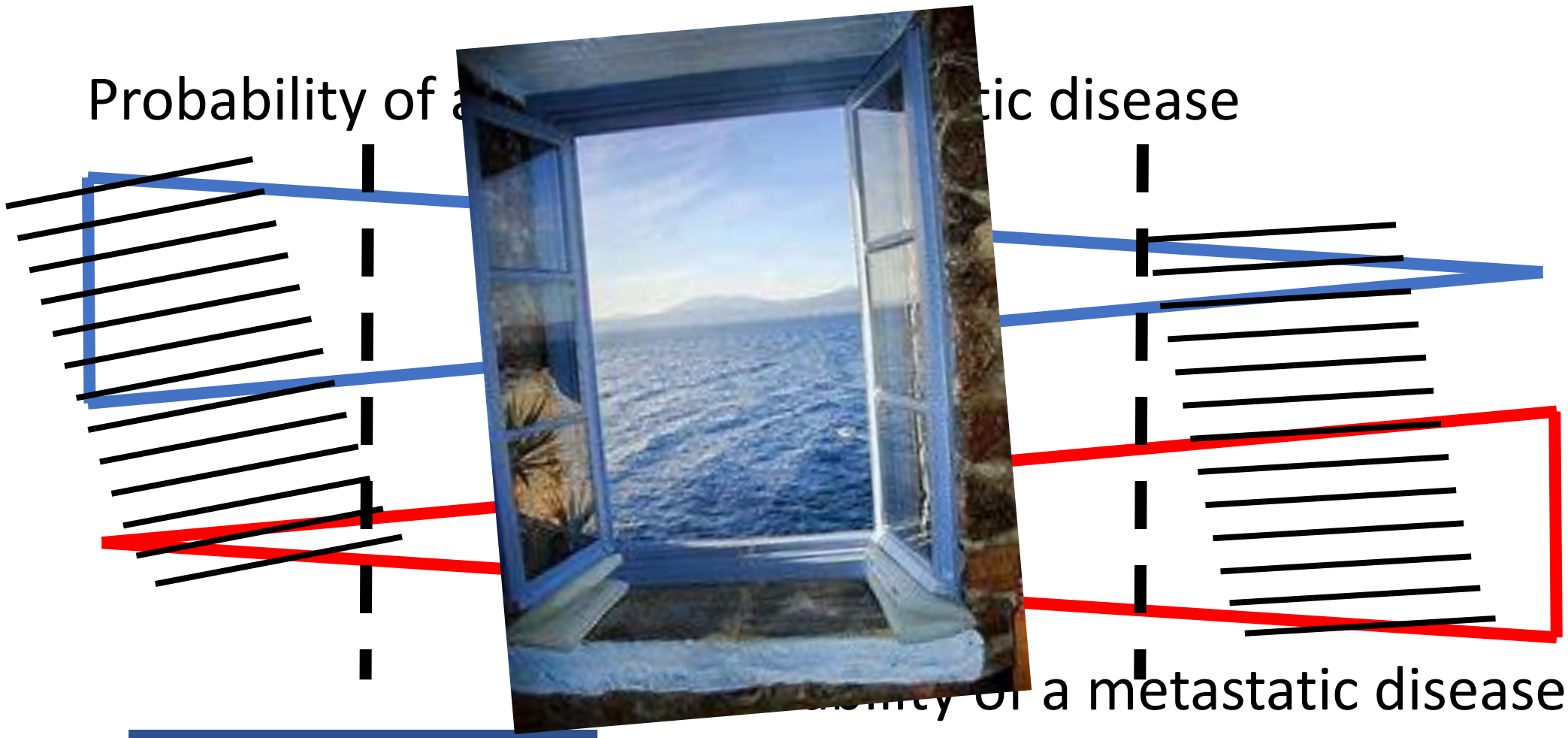
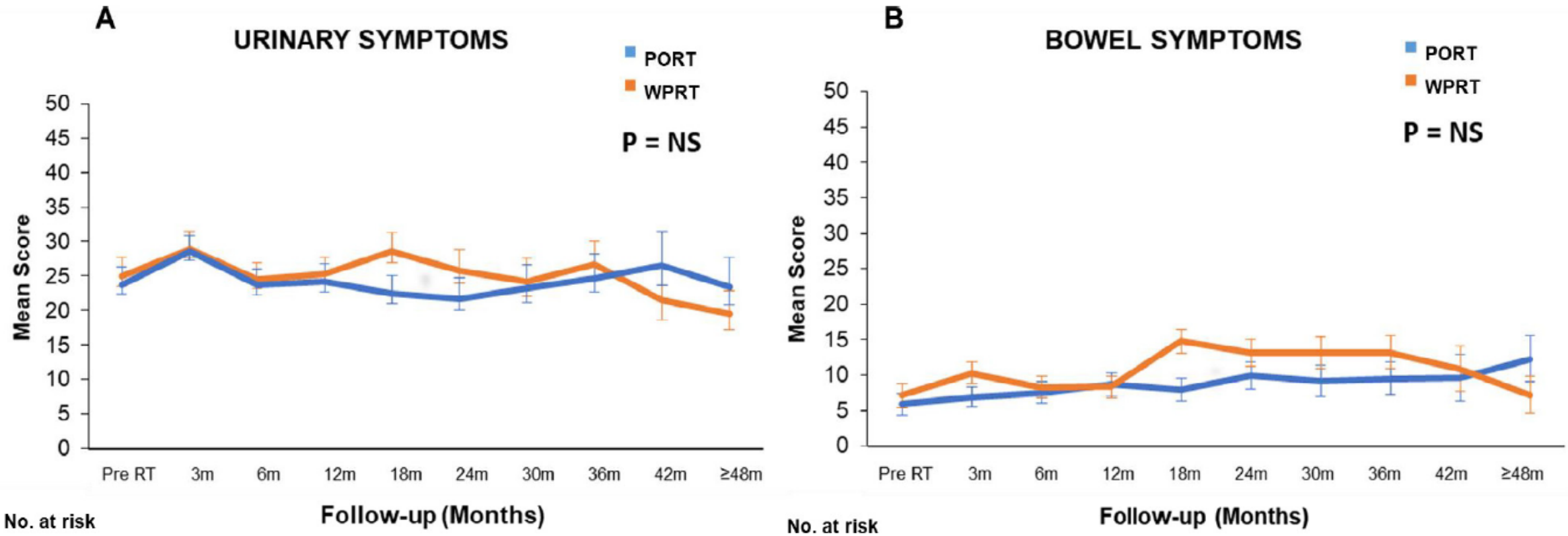


The “sliding window” of WPRT



Patient-reported quality of life outcomes for EORTC PR-25 urinary and bowel symptom domains.



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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

W. James Morris, MD, FRCPC,[*,†] Scott Tyldesley, MD, FRCPC,[*,†] Sree Rodda, MBBS, MRCP, FRCR,[*] Ross Halperin, MD, FRCPC,[*,‡] Howard Pai, MD, FRCPC,[*,§] Michael McKenzie, MD, FRCPC,[*,†] Graeme Duncan, MB, ChB, FRCPC,[*,†] Gerard Morton, MB, MRCPI, FRCPC, FFRRCSI,[‖] Jeremy Hamm, MSC,[¶] and Nevin Murray, MD, FRCPC[†,#]

International Journal of Radiation Oncology biology • physics

Int J Radiation Oncol Biol Phys, Vol. 98, No. 2, pp. 275–285, 2017

NCCN intermediate (31%) and high-risk (69%)

Gleason ≥ 8	40%
iPSA > 20 ng/ml	19%
cT3a	29%

RANDOMISE (N=398)

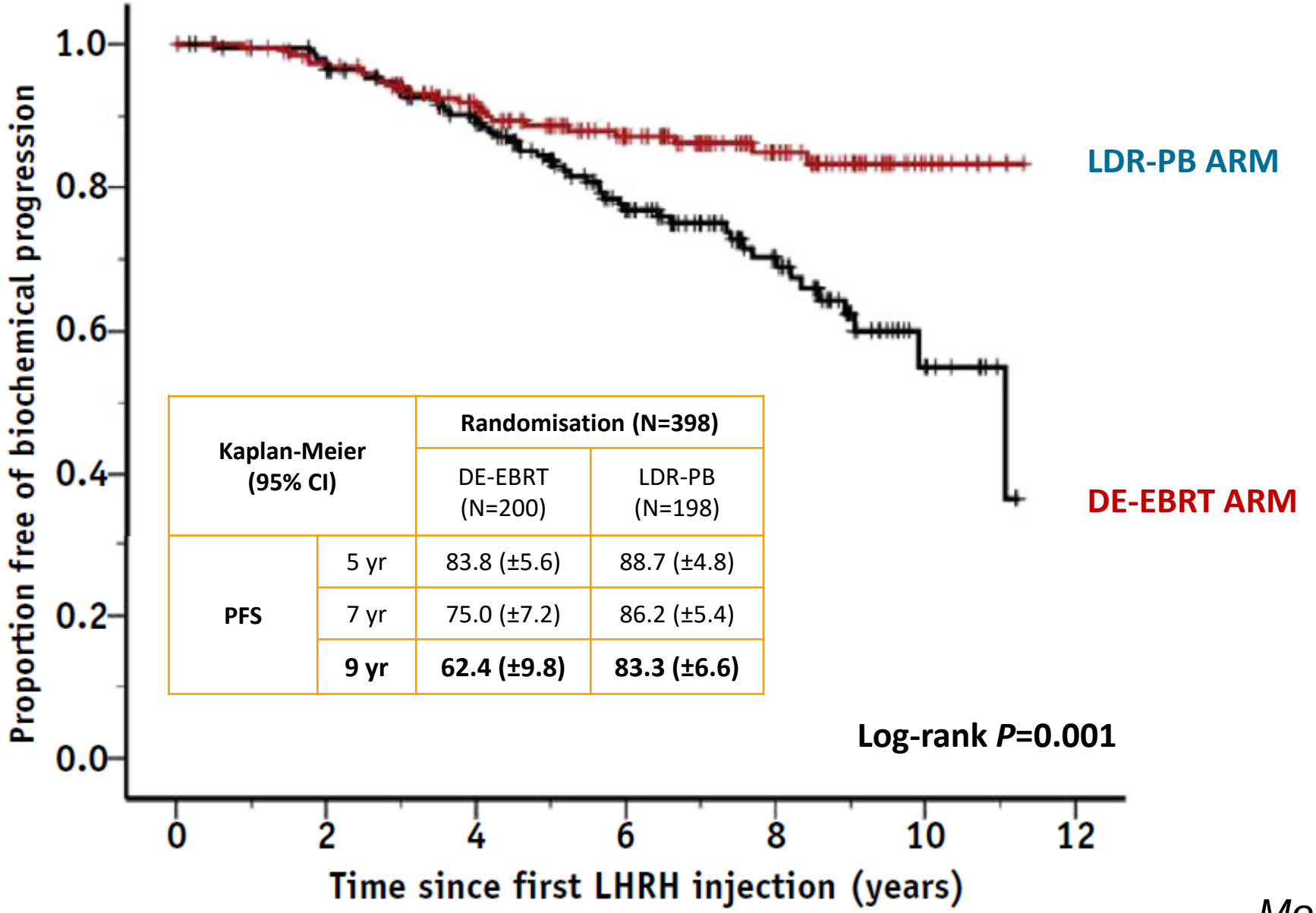
DE-EBRT arm (N=200)
12 mo ADT
46 Gy whole pelvis 3-DC-EBRT
32 Gy 3-DC-EBRT boost (=78 Gy tot)

LDR-PB arm (N=198)
12 mo ADT
46 Gy whole pelvis 3-DC-EBRT
LDR 115 Gy I^{125} boost

Median Follow-up: 6.5 yr

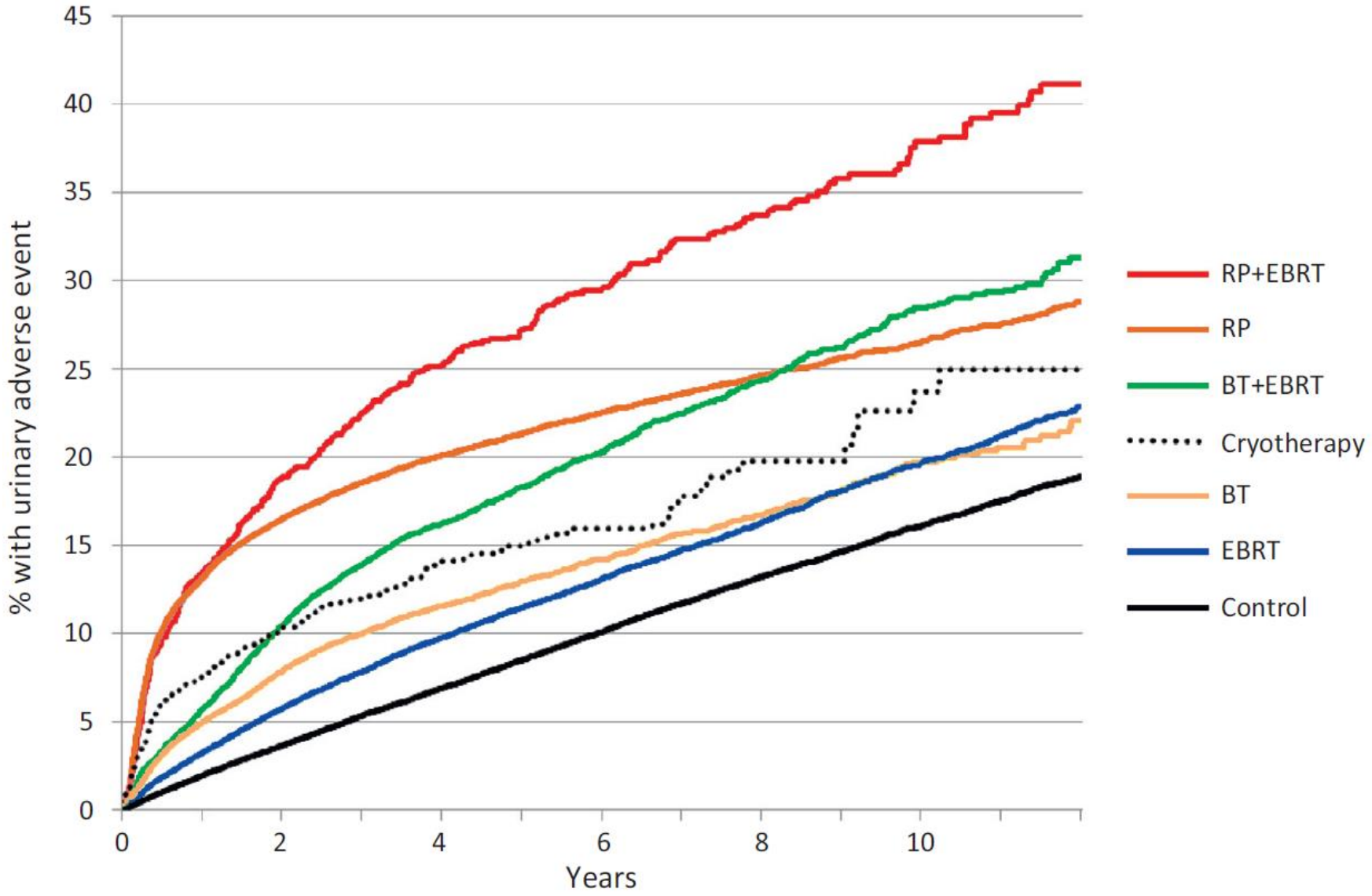
Primary endpoint: biochemical Progression Free Survival
(ASTRO PSA nadir+2 ng/ml)

Morris, 2017



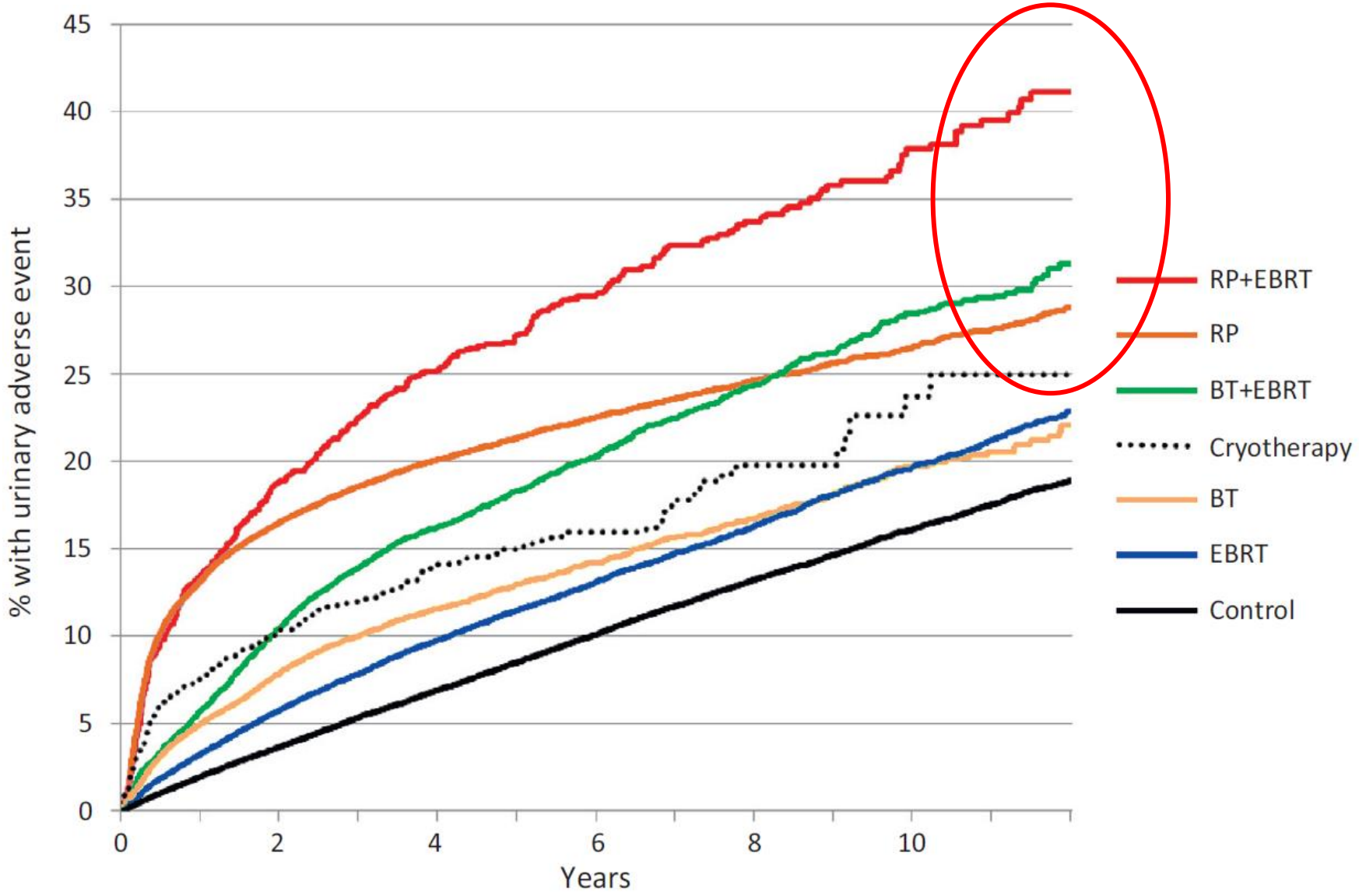
Kaplan-Meier (95% CI)		Randomisation (N=398)	
		DE-EBRT (N=200)	LDR-PB (N=198)
PFS	5 yr	83.8 (±5.6)	88.7 (±4.8)
	7 yr	75.0 (±7.2)	86.2 (±5.4)
	9 yr	**62.4 (±9.8)**	**83.3 (±6.6)**

Morris, 2017



Incidence of any Urinary Adverse Event by treatment group

Jarosek, Eur Urol, 2015



Incidence of any Urinary Adverse Event
by treatment group

Jarosek, Eur Urol, 2015

JAMA | Original Investigation

Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer

Kishan, Jama Oncol, 2018

Amar U. Kishan, MD; Ryan R. Cook, MSPH; Jay P. Ciezki, MD; Ashley E. Ross, MD, PhD; Mark M. Pomerantz, MD; Paul L. Nguyen, MD; Talha Shaikh, MD; Phuoc T. Tran, MD, PhD; Kiri A. Sandler, MD; Richard G. Stock, MD; Gregory S. Merrick, MD; D. Jeffrey Demanes, MD; Daniel E. Spratt, MD; Eyad I. Abu-Isa, MD; Trude B. Wedde, MD; Wolfgang Lilleby, MD, PhD; Daniel J. Krauss, MD; Grace K. Shaw, BA; Ridwan Alam, MPH; Chandana A. Reddy, MS; Andrew J. Stephenson, MD; Eric A. Klein, MD; Daniel Y. Song, MD; Jeffrey J. Tosoian, MD; John V. Hegde, MD; Sun Mi Yoo, MD, MPH; Ryan Fiano, MPH; Anthony V. D'Amico, MD, PhD; Nicholas G. Nickols, MD, PhD; William J. Aronson, MD; Ahmad Sadeghi, MD; Stephen Greco, MD; Curtiland Deville, MD; Todd McNutt, PhD; Theodore L. DeWeese, MD; Robert E. Reiter, MD; Johnathan W. Said, MD; Michael L. Steinberg, MD; Eric M. Horwitz, MD; Patrick A. Kupelian, MD; Christopher R. King, MD, PhD

- *"…large consortium of **1809 (very)-high risk PCa pts** from 12 tertiary US centers"*

- **RP** (*+ postop RT, 43%*): **639**
- **EBRT alone** (+ ADT, 22 m): **734**
- **EBRT+ BT- boost** (+ ADT, 12 m) : **436**
- **(HDR: 40 %)**
- median follow-up : 4.2 / 5.1 / 6.3 years

JAMA | Original Investigation

Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer

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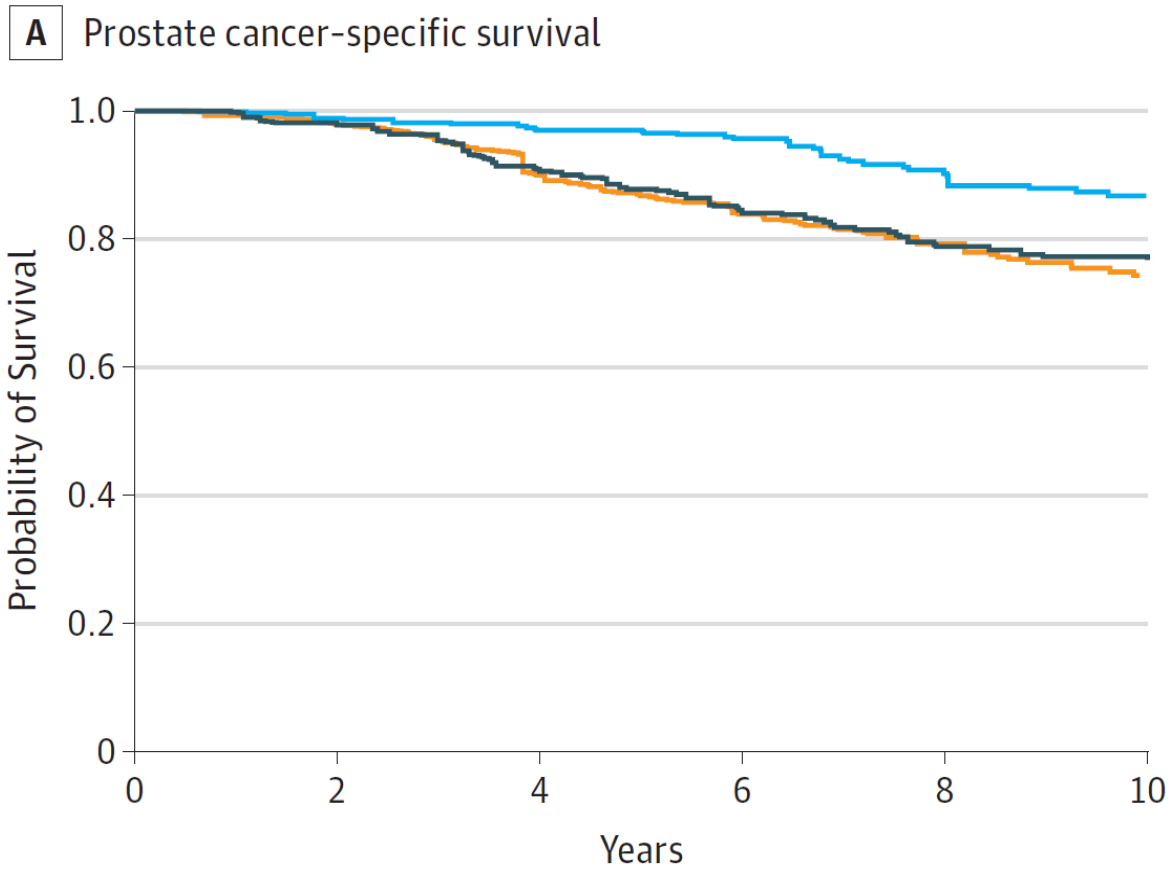

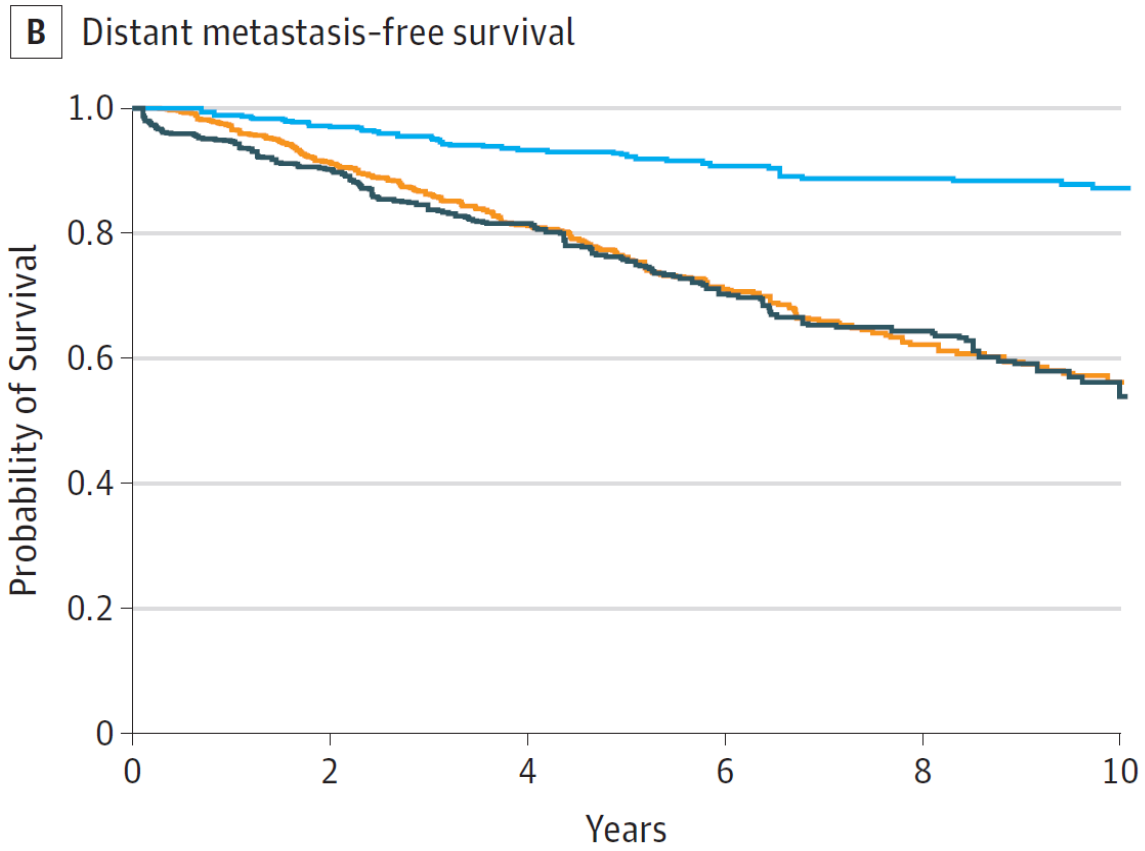

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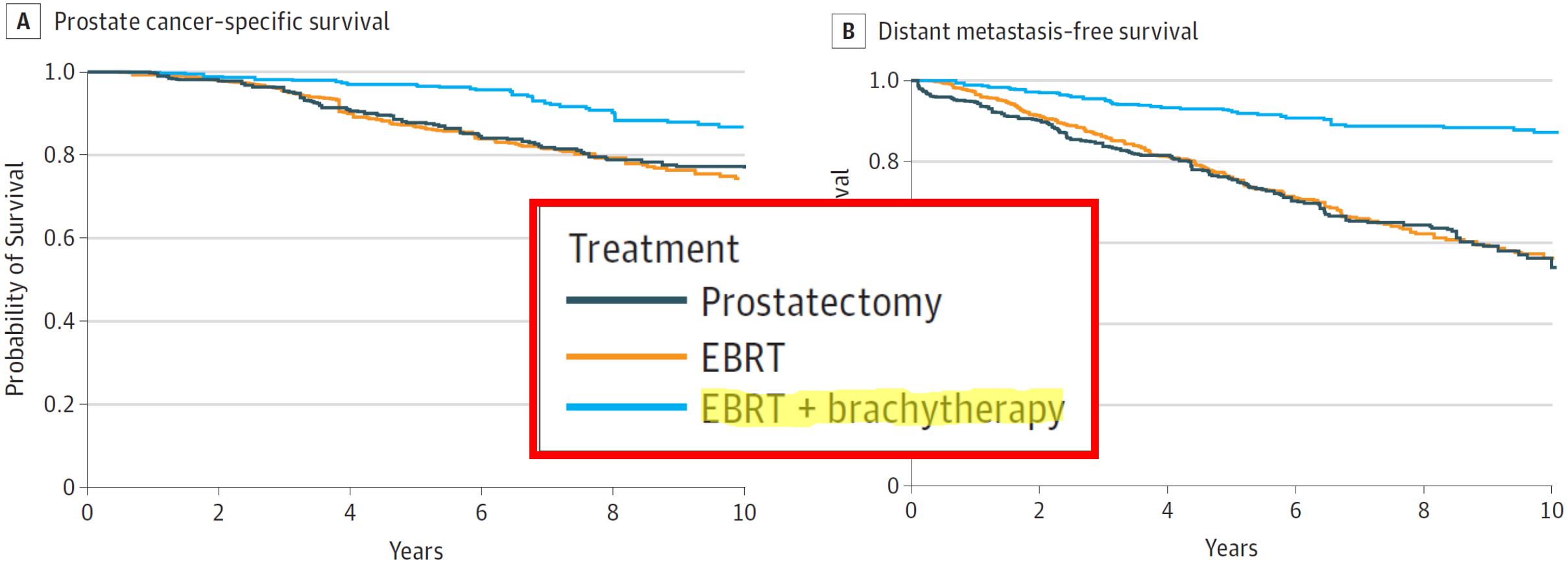


JAMA Oncology | Original Investigation

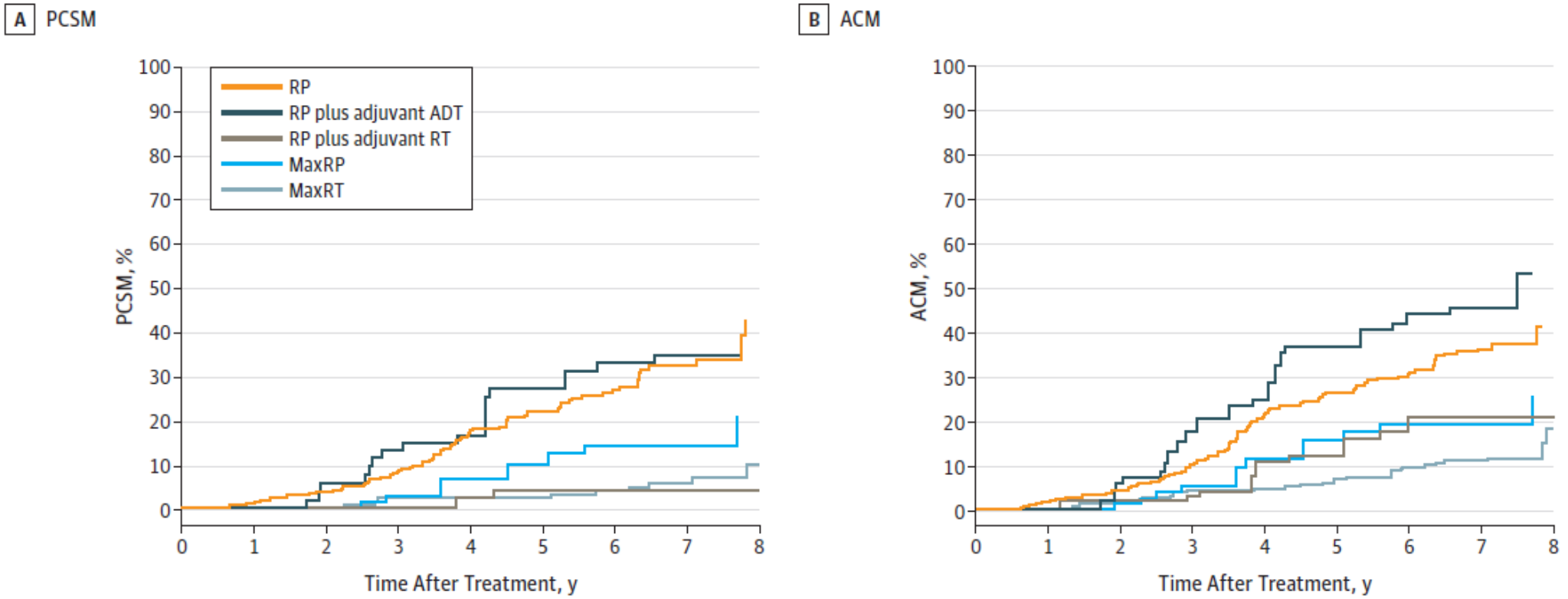
(very-) High Risk

Surgery vs Radiotherapy in the Management of Biopsy Gleason Score 9-10 Prostate Cancer and the Risk of Mortality

Derya Tilki, MD; Ming-Hui Chen, PhD; Jing Wu, PhD; Hartwig Huland, MD; Markus Graefen, MD, PhD; Michelle Braccioforte, MPH; Brian J. Moran, MD; Anthony V. D'Amico, MD, PhD

(treatment propensity score-adjusted risk, plausibility index)

JAMA Oncol. doi:10.1001/jamaoncol.2018.4836
Published online November 15, 2018.



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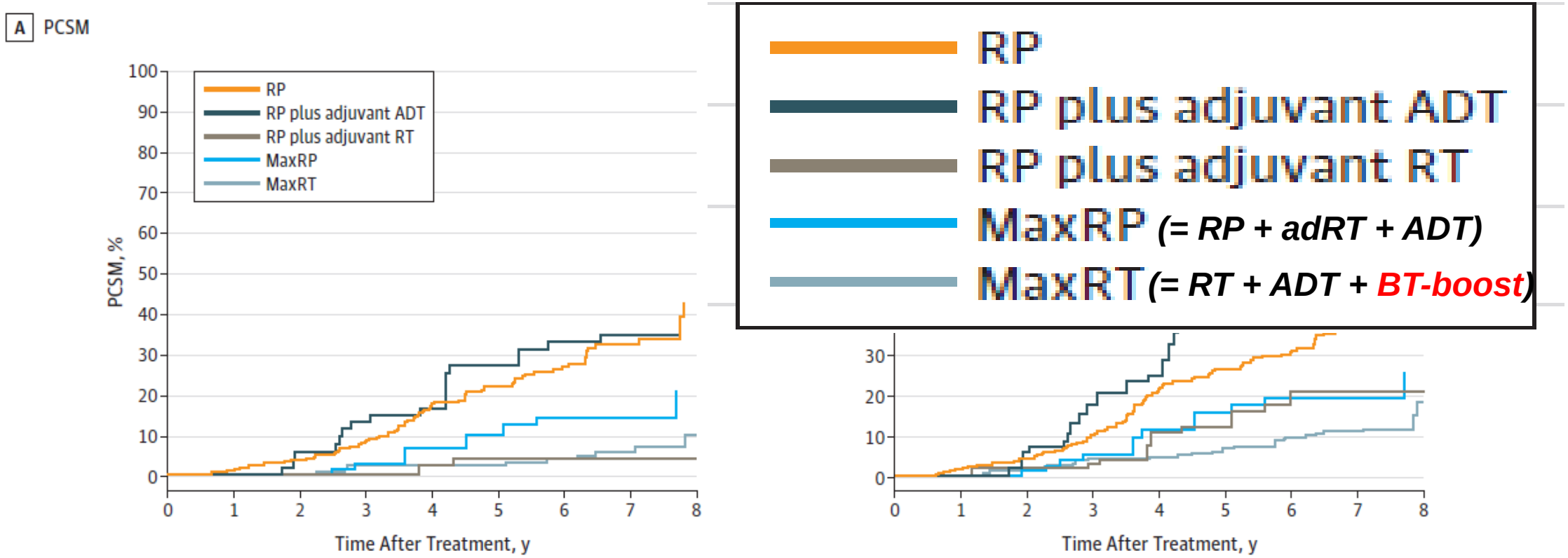

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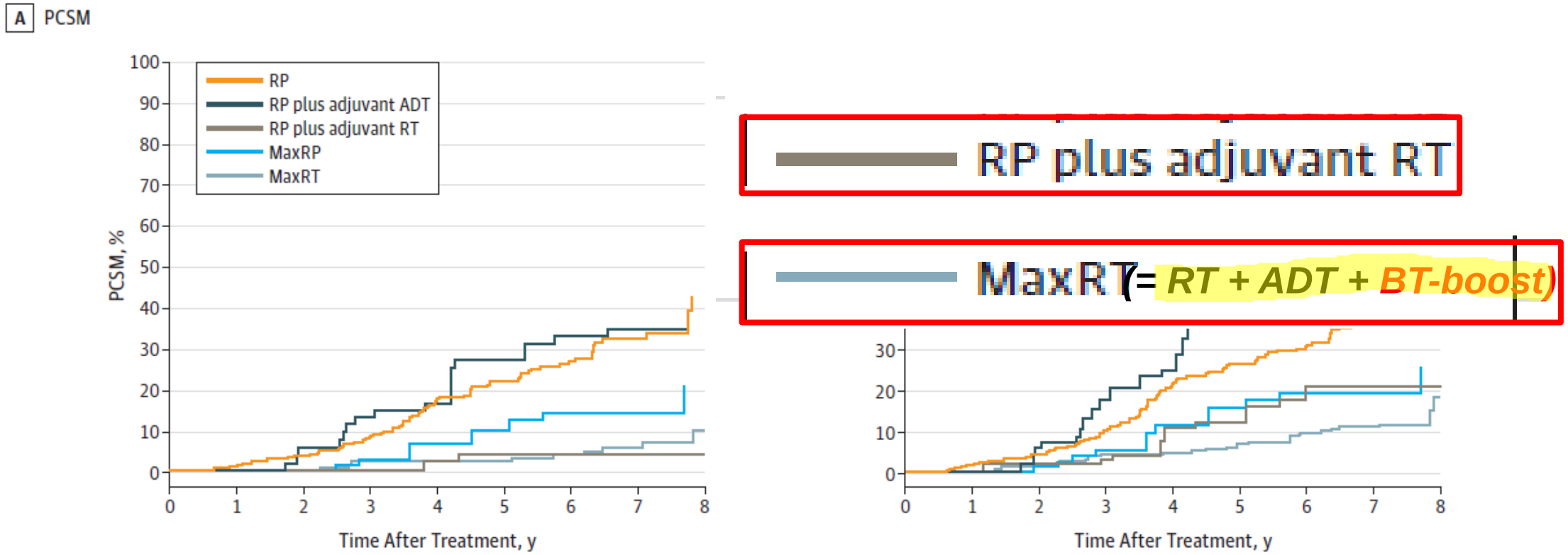


JAMA Oncology | Original Investigation

Interplay Between Duration of Androgen Deprivation Therapy and External Beam Radiotherapy With or Without a Brachytherapy Boost for Optimal Treatment of High-risk Prostate Cancer

A Patient-Level Data Analysis of 3 Cohorts

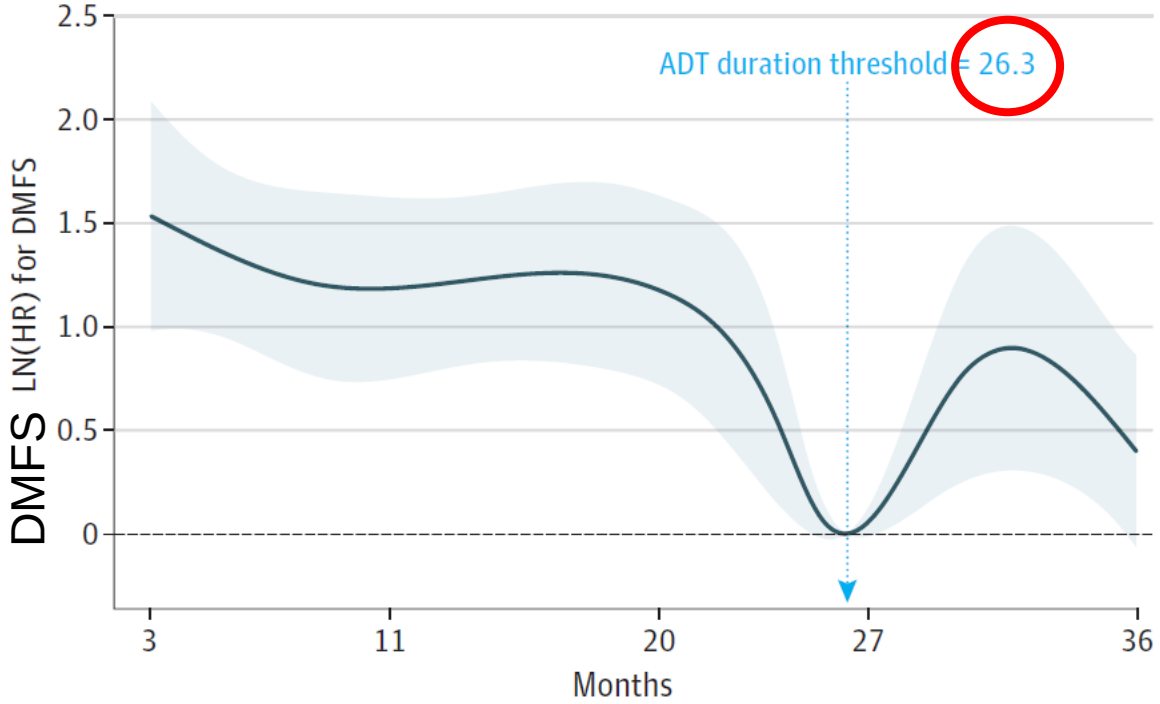
Amar U. Kishan, MD; Alison Steigler, BMath; James W. Denham, MD; Almudena Zapatero, MD; Araceli Guerrero, MD; David Joseph, MD; Xavier Maldonado, MD; Jessica K. Wong, MD; Bradley J. Stish, MD; Robert T. Dess, MD; Avinash Pilar, MD; Chandana Reddy, MS; Trude B. Wedde, MD; Wolfgang A. Lilleby, MD, PhD; Ryan Fiano, MPH; Gregory S. Merrick, MD; Richard G. Stock, MD; D. Jeffrey Demanes, MD; Brian J. Moran, MD; Phuoc T. Tran, MD; Santiago Martin, MD; Rafael Martinez-Monge, MD; Daniel J. Krauss, MD; Eyad I. Abu-Isa, MD; Thomas M. Pisansky, MD; C. Richard Choo, MD; Daniel Y. Song, MD; Stephen Greco, MD; Curtiland Deville, MD; Todd McNutt, PhD; Theodore L. DeWeese, MD; Ashley E. Ross, MD, PhD; Jay P. Ciezki, MD; Derya Tilki, MD; R. Jeffrey Karnes, MD; Jeffrey J. Tosoian, MD; Nicholas G. Nickols, MD, PhD; Prashant Bhat, BS; David Shabsovich, BS; Jesus E. Juarez, BS; Tommy Jiang, BS; T. Martin Ma, MD, PhD; Michael Xiang, MD, PhD; Rebecca Philipson, MD; Albert Chang, MD, PhD; Patrick A. Kupelian, MD; Matthew B. Rettig, MD; Felix Y. Feng, MD; Alejandro Berlin, MD, MSc; Jonathan D. Tward, MD, PhD; Brian J. Davis, MD, PhD; Robert E. Reiter, MD; Michael L. Steinberg, MD; David Elashoff, PhD; Paul C. Boutros, PhD; Eric M. Horwitz, MD; Rahul D. Tendulkar, MD; Daniel E. Spratt, MD; Tahmineh Romero, MS

published on-line, 20/1/2022

2935 pts,
High-Risk NCCN group

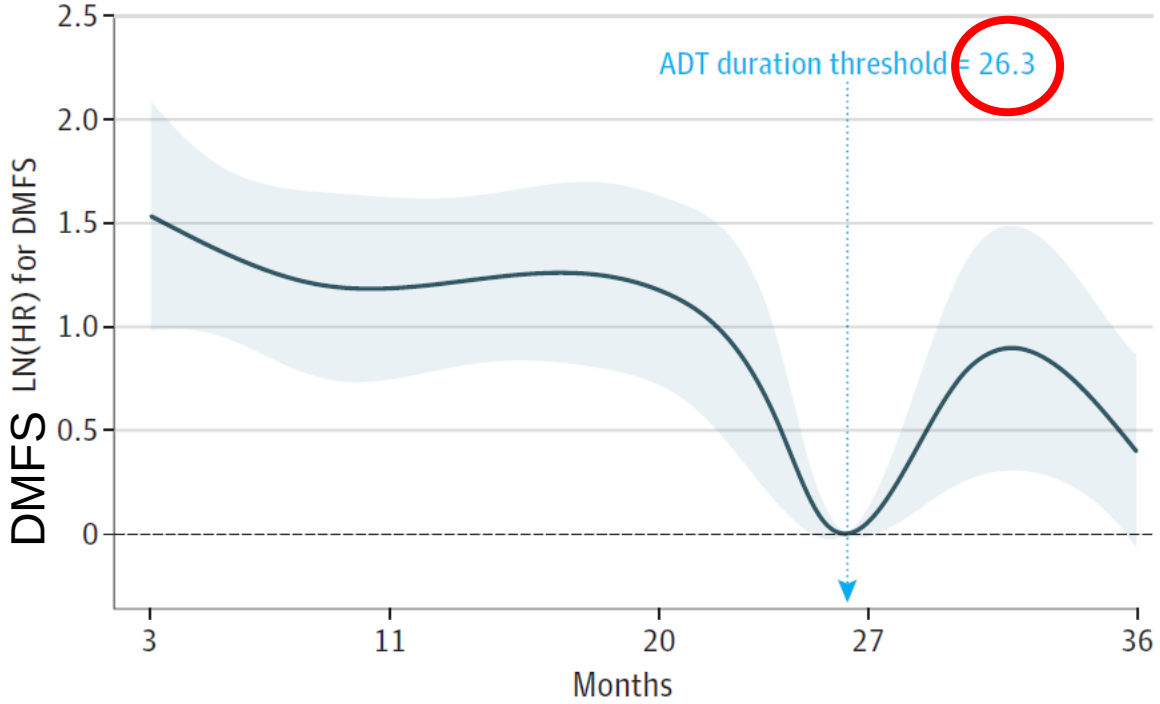
- EBRT ALONE:
  - no ADT
  - < 6 months ADT
  - 6 - <18 months ADT
  - ≥18 months ADT
- EBRT + **BT-boost**:
  - no ADT
  - < 6 months ADT
  - 6 - <18 months ADT
  - ≥18 months ADT

Kishan, Jama Oncol, 2022



EBRT ALONE = **26,3** months of ADT

Kishan, Jama Oncol, 2022



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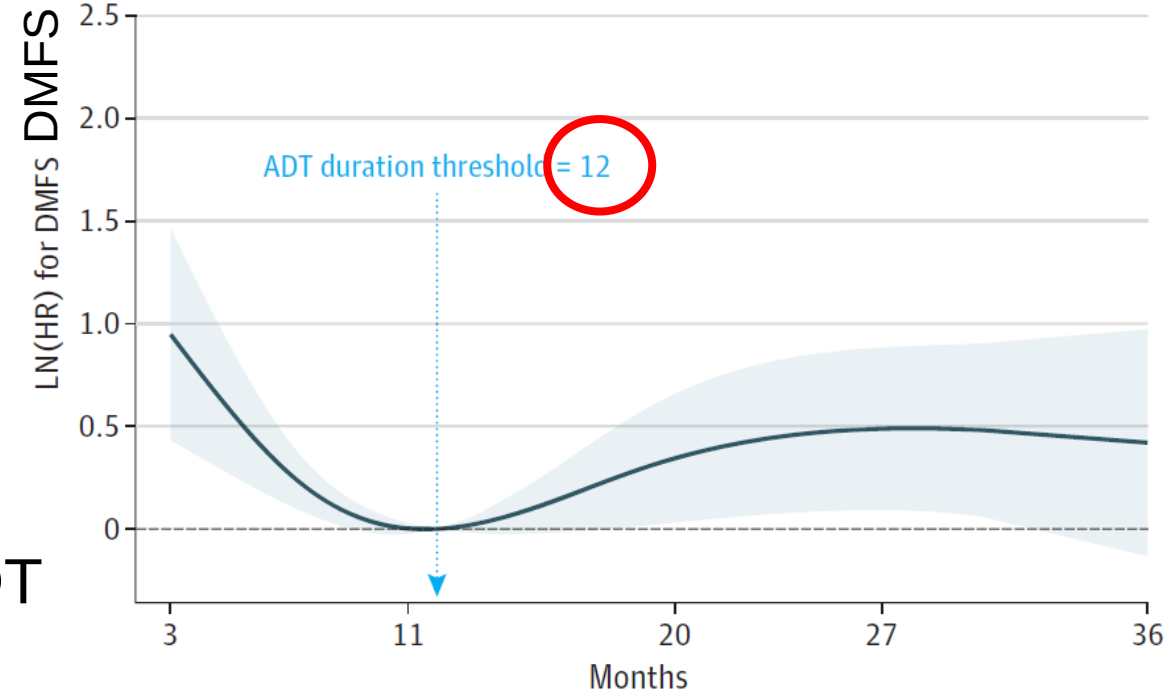
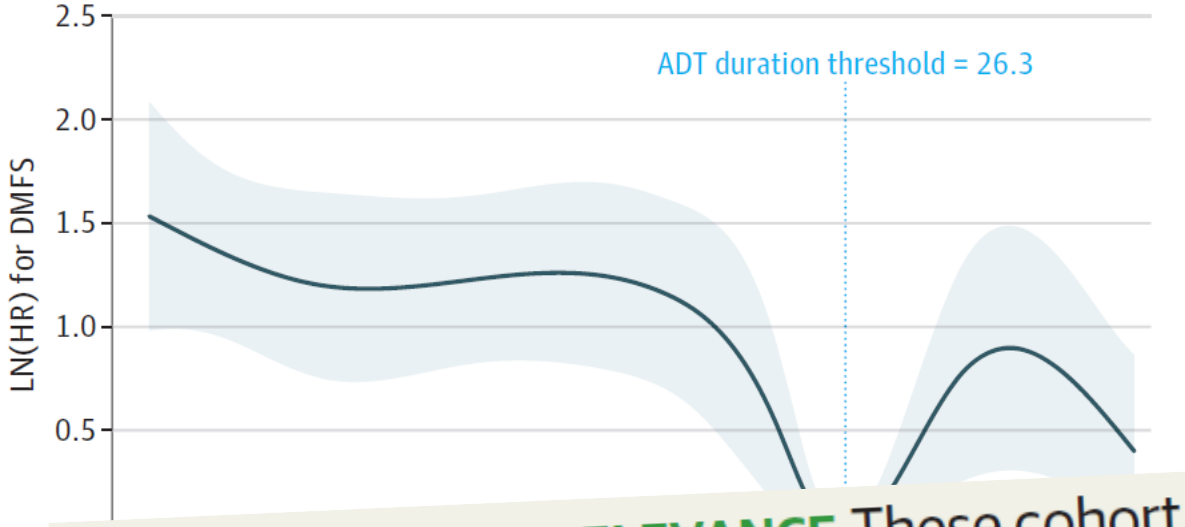
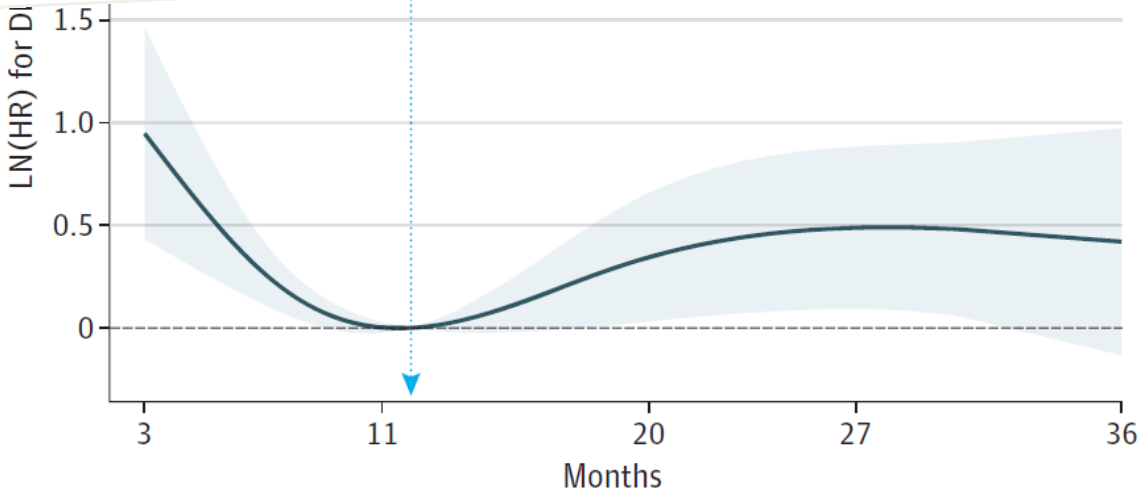


EBRT + **BT-boost** = **12** months of ADT

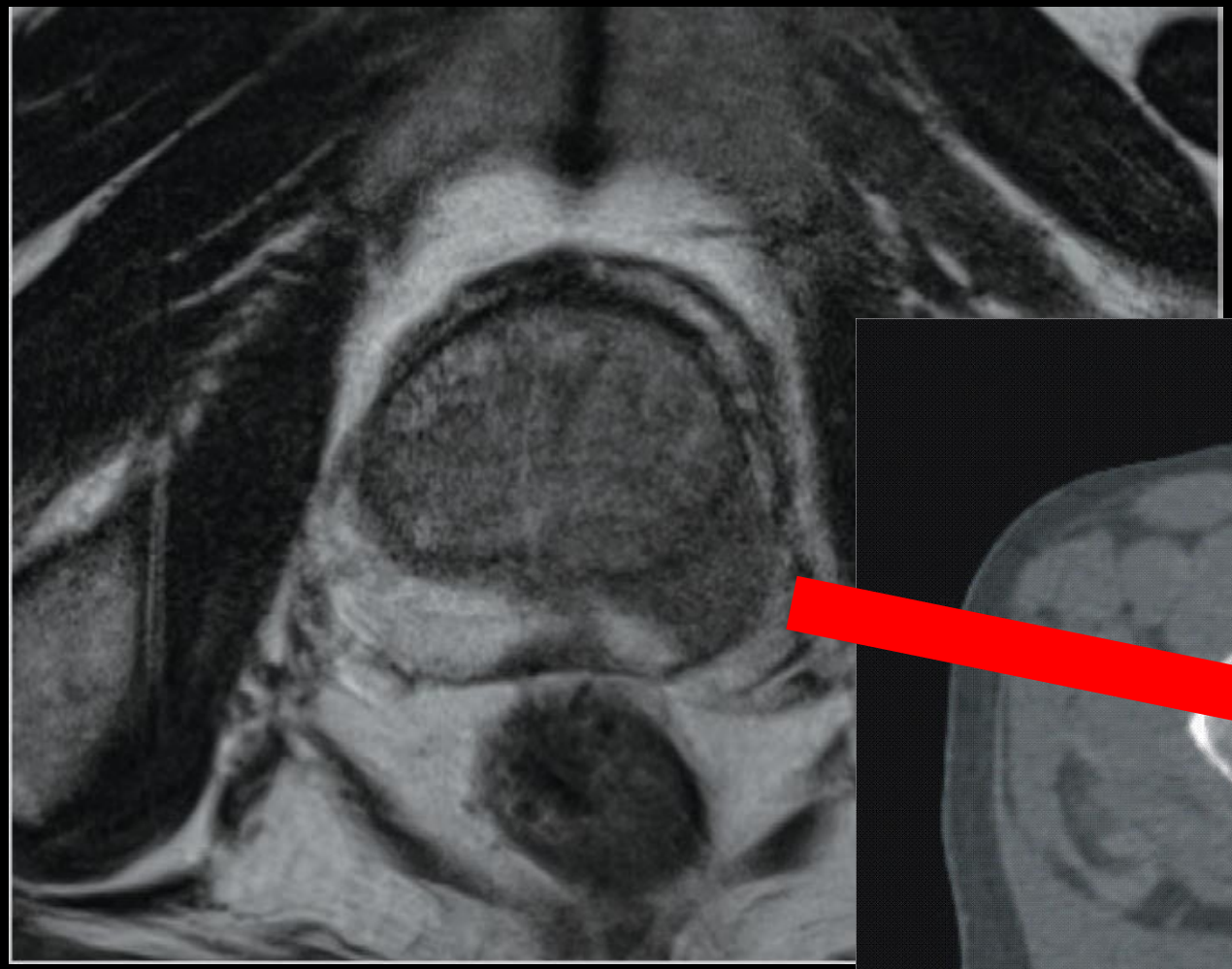
Kishan, Jama Oncol, 2022

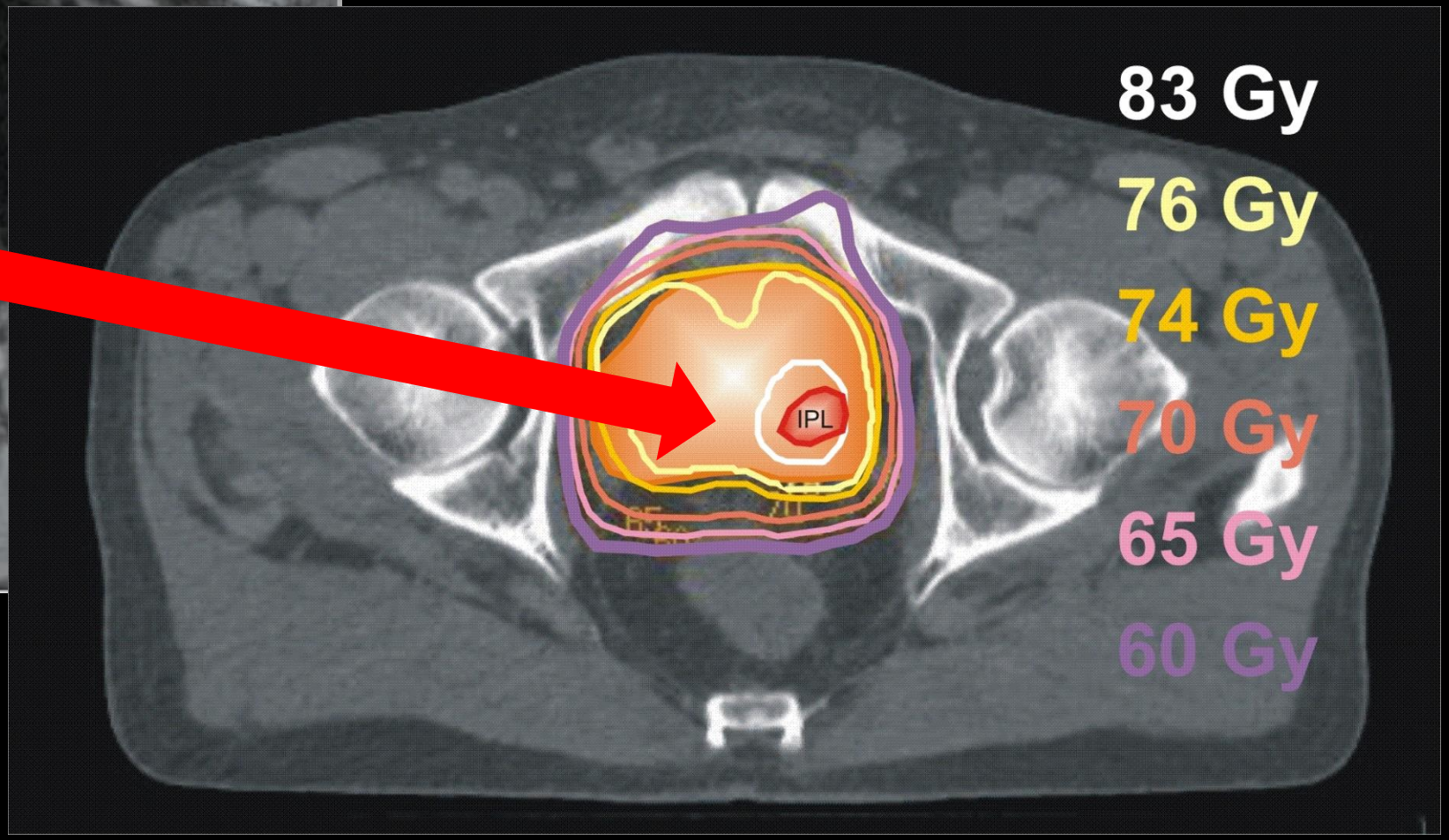


CONCLUSIONS AND RELEVANCE These cohort study findings suggest that the optimal minimum ADT duration for treatment with high-dose EBRT alone is more than 18 months; and for EBRT+BT, it is 18 months or possibly less.



Kishan, Jama Oncol, 2022





courtesy of G De Meerleer

original reports

Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial

Linda G. W. Kerkmeijer, MD, PhD[1,2]; Veerle H. Groen, MD[1]; Floris J. Pos, MD, PhD[3]; Karin Haustermans, MD, PhD[4]; Evelyn M. Monninkhof, PhD[5]; Robert Jan Smeenk, MD, PhD[2]; Martina Kunze-Busch, PhD[2]; Johannes C. J. de Boer, PhD[1]; Jochem van der Voort van Zijp, MD, PhD[1]; Marco van Vulpen, MD, PhD[6]; Cédric Draulans, MD, PhD[4]; Laura van den Bergh, MD, PhD[7]; Sofie Isebaert, PhD[4]; and Uulke A. van der Heide, PhD[3]

Focal Lesion Ablative Microboost in Prostate Cancer

Kerkmeijer et al, 2021

Journal of Clinical Oncology®

Baseline	Standard Treatment	Focal Boost Treatment
No. of subjects (n)	287	284
Mean age in years (SD)	70 (7)	70 (6)
Risk stratification (EAU criteria)	N (%)	N (%)
Low-risk	4 (1)	2 (1)
Intermediate-risk	43 (15)	43 (15)
High-risk	240 (84)	239 (84)

R

77 Gy, 35 fr (EQD2 81.8 Gy) +/- ADT

77 Gy, 35 fr (EQD2 81.8 Gy) +/- ADT
+ SIB on the mpMRI defined DIL of
95 Gy (EQD2 115.8 Gy) +/- ADT

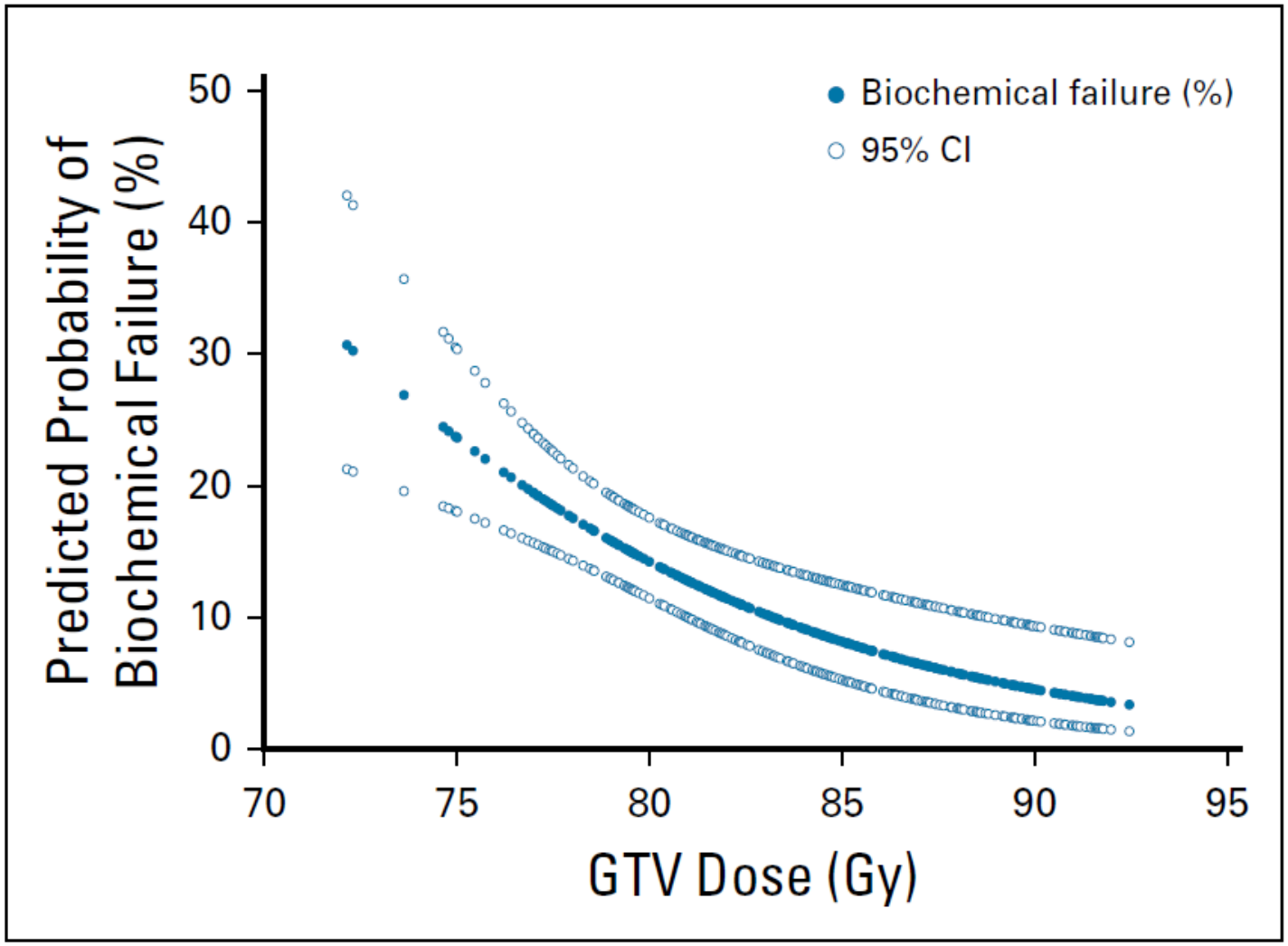


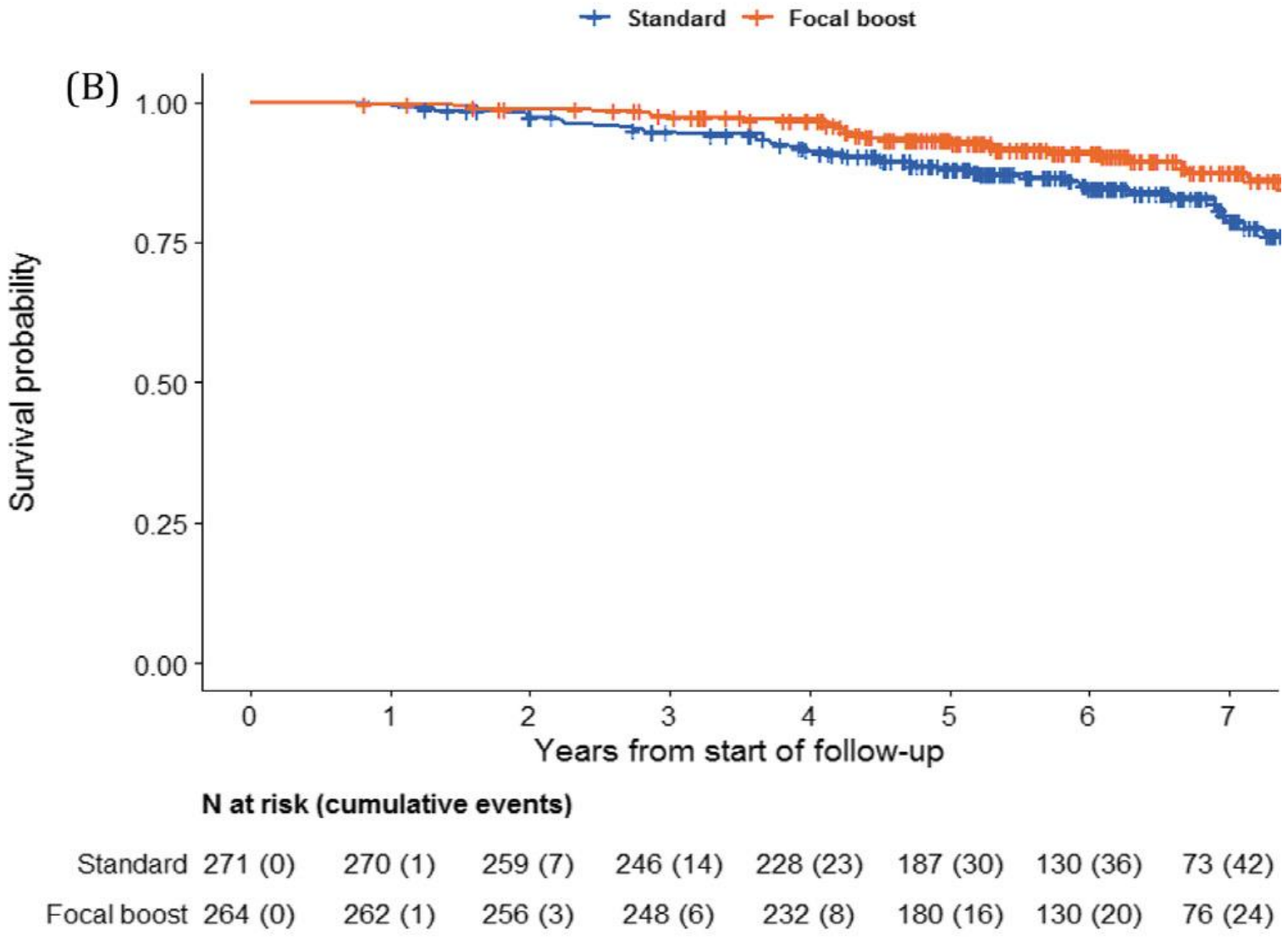
FIG 3. Predicted probability of biochemical failure up to 7 years as a function of achieved dose to the gross tumor volume (D98%; Gy).

FLAME

Single blind randomized Phase III trial to investigate the benefit of a focal lesion ablative microboost in prostate cancer (FLAME-trial): study protocol for a randomized controlled trial

Kerkmeijer et al, JCO 2021

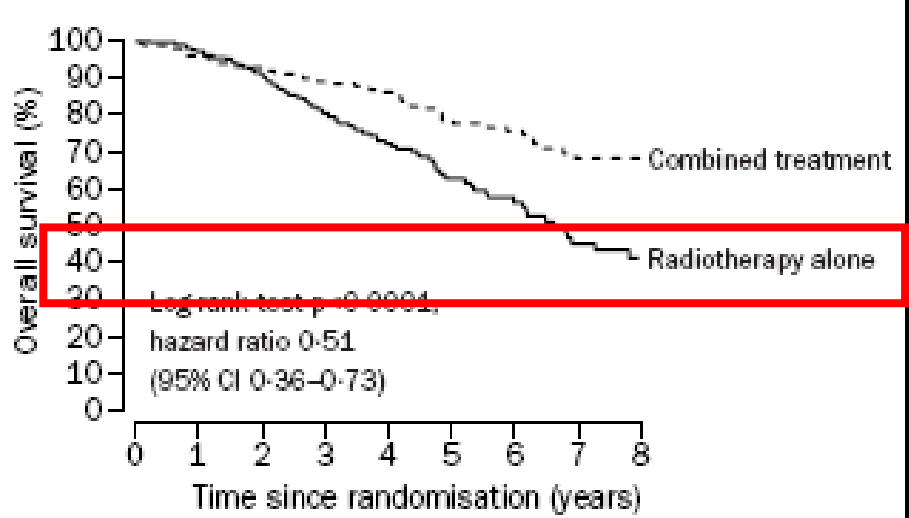
	HR	C.I.
Local Failure Free Survival	0.33	0.14 – 0.78
Regional + Distant Mets Free Survival	0.58	0.35 – 0.93



Groen et al, Eur Urol 2022

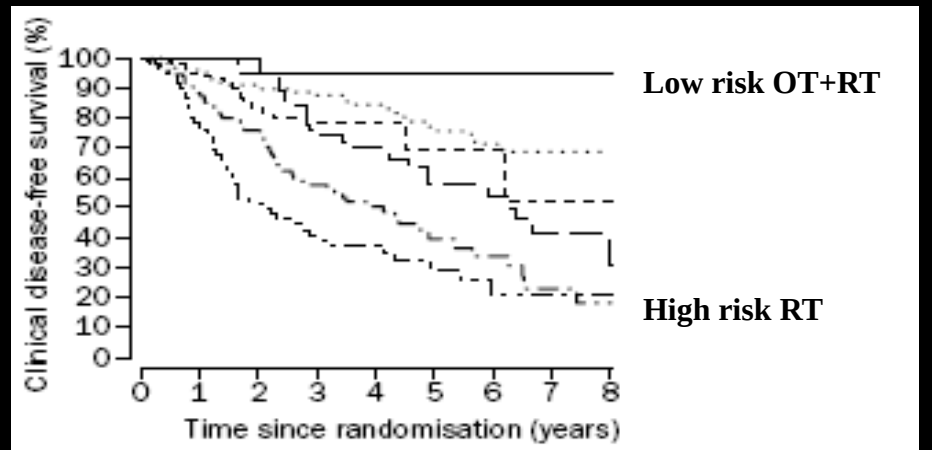
RT + ADT for HRPCa: ***the challenge***…

EORTC 22863 PHASE III TRIAL, Bolla, Lancet, 2002



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**
O=number of deaths; N=number of patients.



O	N	Number of patients at risk								Radiotherapy alone
6	20	20	18	14	11	8	4	3	3	Low risk
55	96	84	68	47	30	16	12	5	3	Intermediate risk
44	63	48	30	22	15	10	5	4	1	High risk
										Combined treatment
1	23	23	21	18	17	12	9	8	2	Low risk
26	99	94	89	84	71	46	33	17	10	Intermediate risk
27	64	59	47	40	34	20	15	8	3	High risk

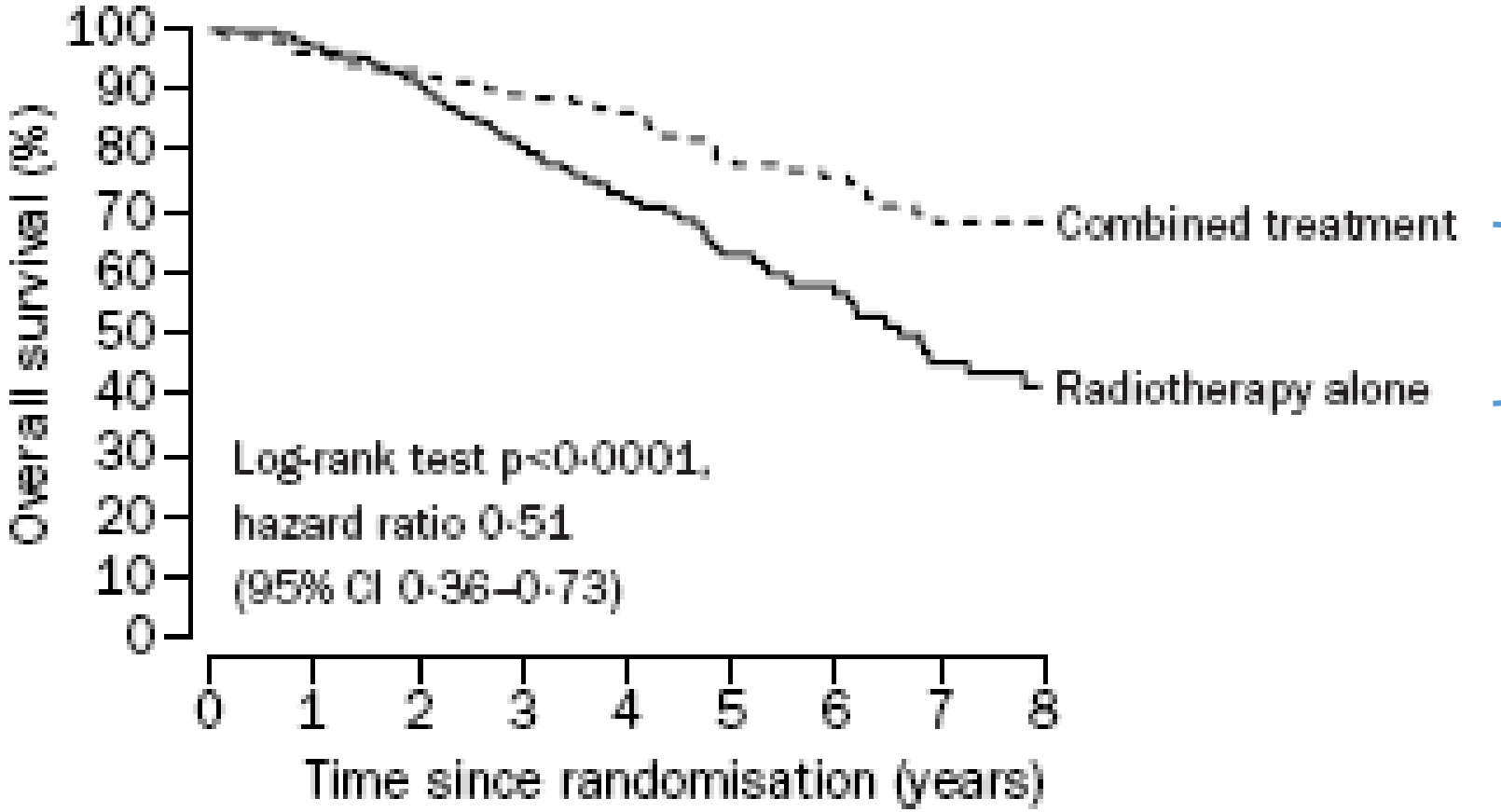
Figure 5: **Clinical disease-free survival by risk category and treatment group**
O=number of failures; N=number of patients.

Type of progression	Radiotherapy (n=208)	Combined treatment (n=207)
Any clinical progression	90	27
Local	15	3
Local and regional	3	0
Distant	56	22
Local and distant	13	2
Local, regional, and distant	3	0

Table 2: **Sites of disease progression**

"In our trial, the radiotherapy technique was conventional, far from being optimal. The contribution of radiotherapy to local control can be further improved by 3-D conformal radiotherapy…"

Bolla, 2002



O	N	Number of patients at risk							
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Benefit of RT+ADT *vs* RT alone (30% of pts at 10 ys)

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

O=number of deaths; N=number of patients.

Bolla, 2002

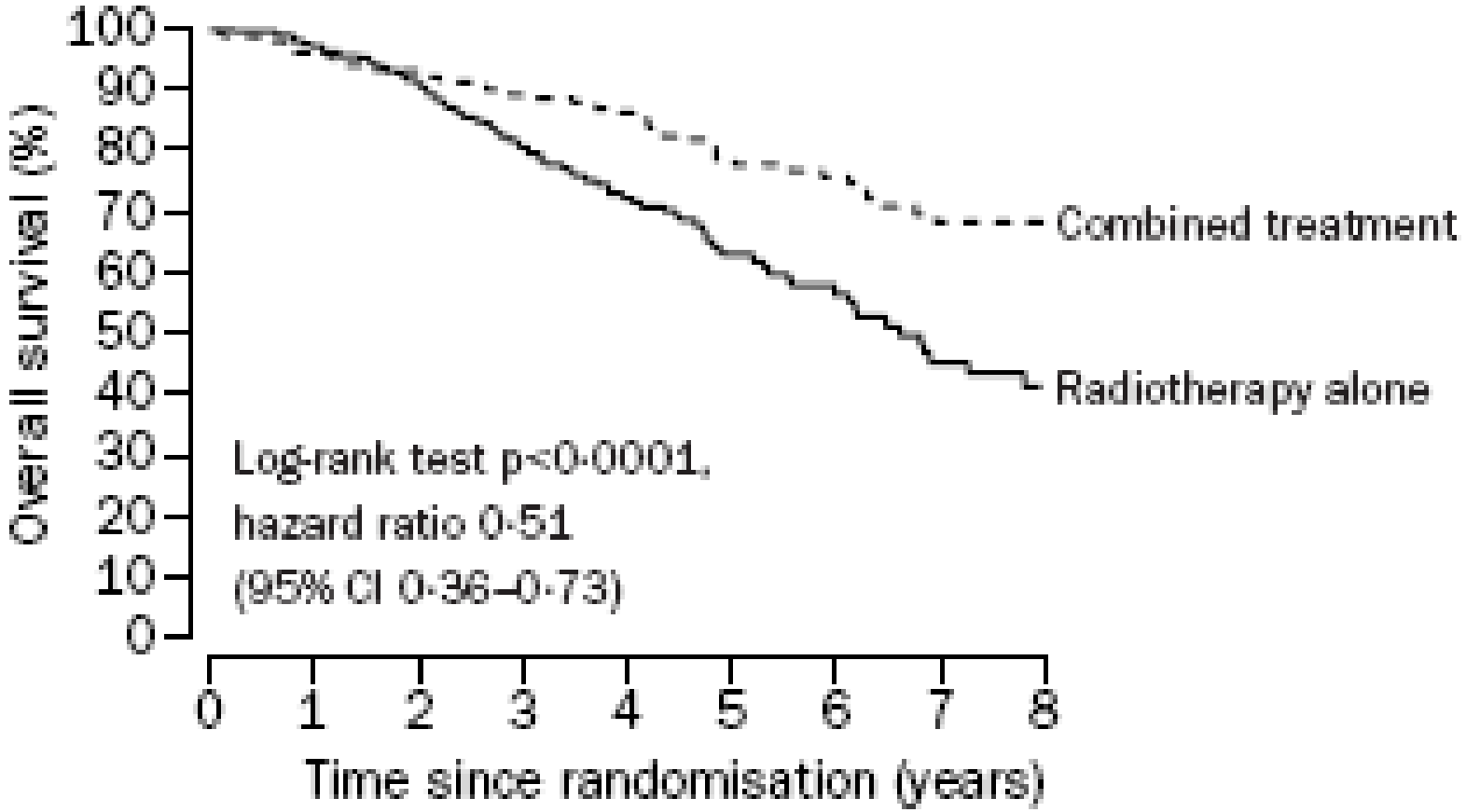

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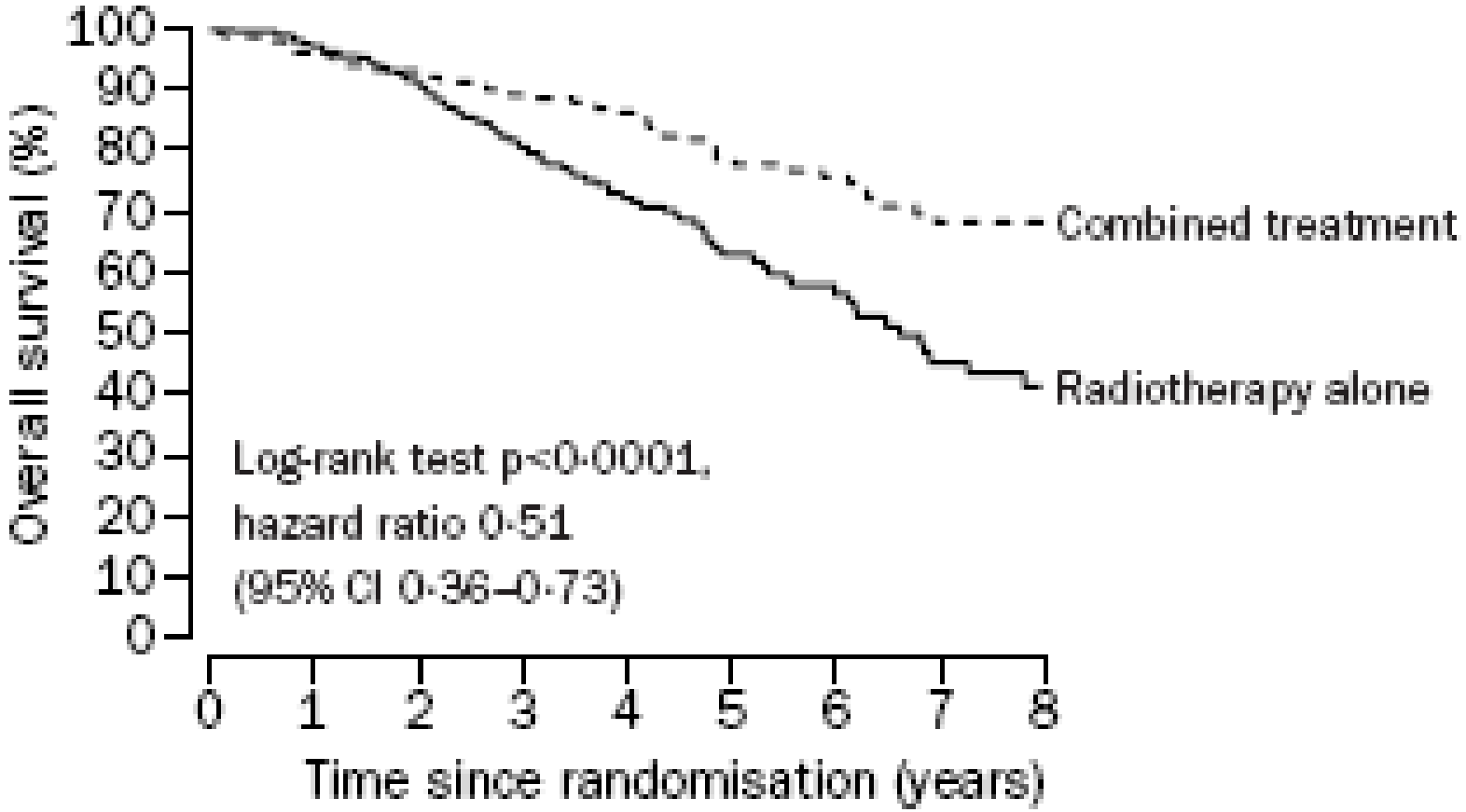
Figure 2: **Kaplan-Meier estimates of overall survival by treatment group**

O=number of deaths; N=number of patients.

Death despite RT+ADT (45% of pts at 10 ys)

Benefit of RT+ADT *vs* RT alone (30% of pts at 10 ys)

Bolla, 2002



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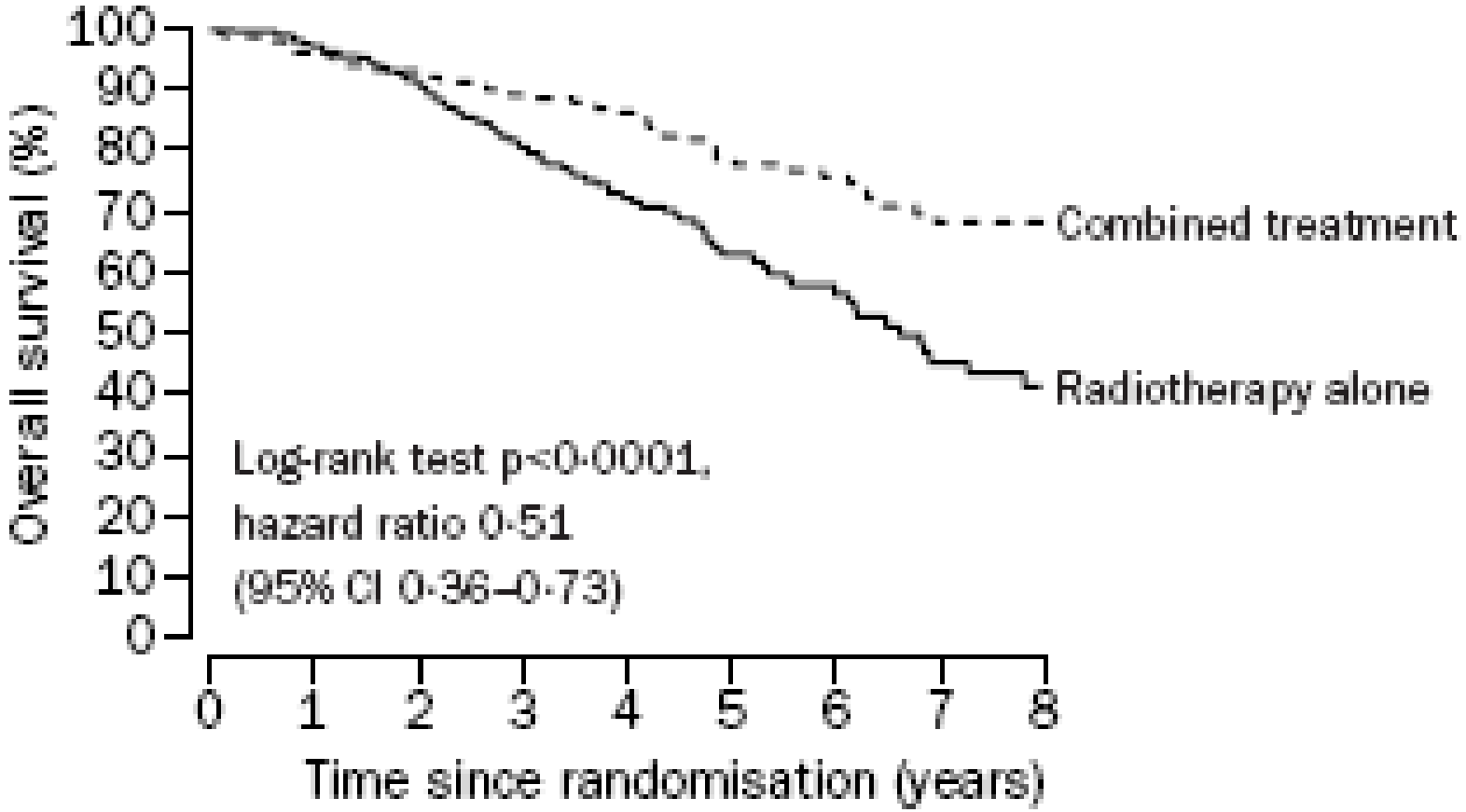
Death despite RT+ADT
(45% of pts at 10 ys)

Benefit of RT+ADT *vs* RT alone
(30% of pts at 10 ys)

Favourable outcome with RT alone
(25% of pts at 10 ys)

Bolla, 2002



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Death desp
(45%

under-treated

Benefit of RT+ADT *vs* RT alone
(30% of pts at 10 ys)

Favourabl T alone
(25% ys)

over-treated

Bolla, 2002

Take Home

- phase III RCT of the last 25-30 ys have tailored the role of RT in the management of High-Risk PCa.
- intensification strategy with long-term Androgen Deprivation Therapy should be the backbone of the RT management of High-Risk Pca.
- optimizing the local control with high-tech RT techniques seems essential to guarantee better results (role of EBRT+BT?, MRI-guided intra-prostatic boost?).
- de-intensification may also have a role in a well defined subgroup of High-Risk Pca patients.

@AlbertoBossial