Amethyst
RADIOTHERAPIE

10th edition
GLOBAL CONGRESS ON PROSTATE CANCER
JUBILEE EDITION

External-Beam-Radiotherapy, What's the future?

Alberto Bossi

Radiation Oncologist

Amethyst Radiotherapy, Paris, France

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):	---

RE: Please reply_Your role during PROSCA 2022

A: BOSSI Alberto
Cc: Stefanie Smolders; Luc Van Ruysevelt
Oggetto: Please reply_Your role during PROSCA 2022

Dear Alberto,
We hope you are doing fine.
We are contacting you regarding the scientific programme of PROSCA 2022. As follow-up to the communication below, we hereby provide you with detailed information about your role during the PROSCA congress.
We would like to ask for your contribution to 2 sessions of the meeting:

1. Speaker in the session "High-risk & very high-risk PCa" taking place on Tuesday 18 October, 16.30-18.00 (local time in Greece).
   We would like to ask you to discuss RT in very high-risk PCa, including the role of brachytherapy boost. This would be a 15-minute presentation entitled "RT in very high-risk PCa".

2. Speaker in the session "Back to the future" taking place on Wednesday 19 October, 15.00-16.00 (local time in Greece).
   This session refers to the 10th edition of PROSCA. The idea of every presentation in this session is to talk about where we were 10 years ago, where are we now, and where will we be in the next 10 years. We would like to ask you to do this for RT. This would be a 15-minute presentation entitled "EBRT: what's the future?".

RE: Please reply_Your role during PROSCA 2022

2. Speaker in the session "Back to the future" taking place on Wednesday 19 October, 15.00-16.00 (local time in Greece).

   This session refers to the 10th edition of PROSCA. The idea of every presentation in this session is to talk about where we were 10 years ago, where are we now, and where will we be in the next 10 years. We would like to ask you to do this for RT. This would be a 15-minute presentation entitled "EBRT: what's the future?".

sessions of the meeting:

1. Speaker in the session "High-risk & very high-risk PCa" taking place on Tuesday 18 October, 16.30-18.00 (local time in Greece).
   We would like to ask you to discuss RT in very high-risk PCa, including the role of brachytherapy boost. This would be a 15-minute presentation entitled "RT in very high-risk PCa".

2. Speaker in the session "Back to the future" taking place on Wednesday 19 October, 15.00-16.00 (local time in Greece).

   This session refers to the 10th edition of PROSCA. The idea of every presentation in this session is to talk about where we were 10 years ago, where are we now, and where will we be in the next 10 years. We would like to ask you to do this for RT. This would be a 15-minute presentation entitled "EBRT: what's the future?".

Institut de cancérologie GUSTAVE ROUSSY VILLEJUIF - www.igr.fr

Global Congress on Prostate Cancer, Brussels, June 2012
Key issues in Managing High-Risk Non-metastatic Disease

What is your evidence?… External Beam RadioTherapy What and How?

Alberto Bossi

Institut Gustave Roussy, Villejuif, France

Key issues for the Radiotherapy of High Risk Prostate Cancer ?

1. Dose (and Volumes….)

2. Androgen Deprivation Therapy

Key issues for the Radiotherapy of High Risk Prostate Cancer ?

1. Dose (and Volumes….)
2. Androgen Deprivation Therapy
3. Surgery *versus* RT…

Platinum Priority – Prostate Cancer

Editorial by Michel Bolla on pp. 1140–1141 of this issue

Dose Escalation for Prostate Cancer Radiotherapy: Predictors of Long-Term Biochemical Tumor Control and Distant Metastases–Free Survival Outcomes

*Michael J. Zelefsky *, Xin Pei, Joanne F. Chou, Michael Schechter, Marisa Kollmeier, Brett Cox, Yoshiya Yamada, Anthony Fidaleo, Dahlia Sperling, Laura Happersett, Zhigang Zhang*

Departments of Radiation Oncology, Medical Physics, and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Article info

Article history:
Accepted August 11, 2011
Published online ahead of print on August 22, 2011

2551 pts, 1988 – 2004

571, 22%, NCCN low-risk
1074, 42%, int-risk
906, 36%, high-risk

1249 pts, 49%, 6 m. ADT

Platinum Priority – Prostate Cancer
Editorial by Michel Bolla on pp. 1140–1141 of this issue

Dose Escalation for Prostate Cancer Radiotherapy: Predictors of Long-Term Biochemical Tumor Control and Distant Metastases–Free Survival Outcomes

Michael J. Zelefsky *, *Xin Pei*, *Joanne F. Chou*, *Michael Schechter*, *Marisa Kollmeier*, *Brett Cox*, *Yoshiya Yamada*, *Anthony Fidaleo*, *Dahlia Sperling*, *Laura Happersett*, *Zhigang Zhang*

Departments of Radiation Oncology, Medical Physics, and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Article info

Article history:
Accepted August 11, 2011
Published online ahead of print on August 22, 2011

2551 pts, 1988 – 2004

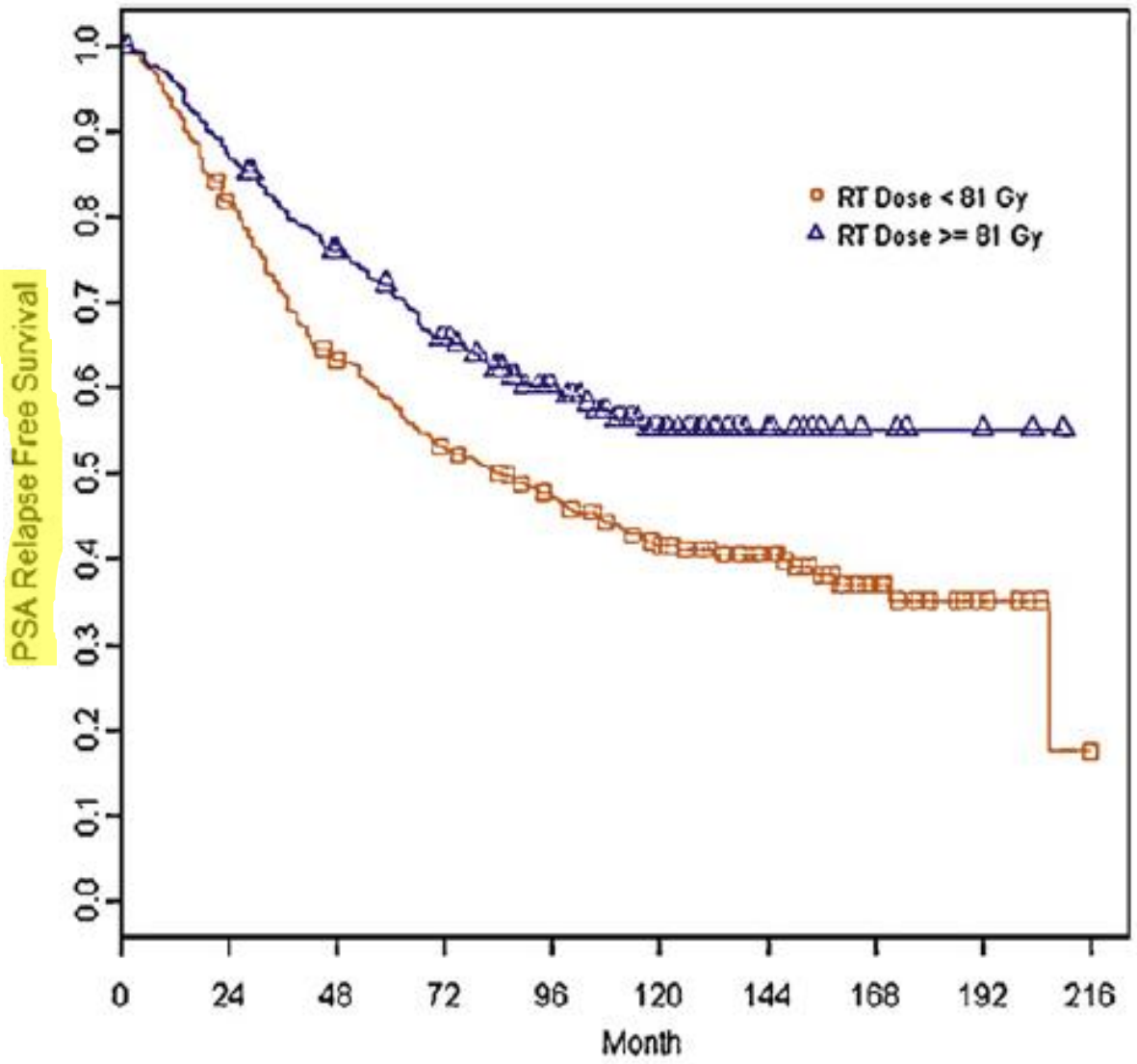
571, 22%, NCCN low-risk
1074, 42%, int-risk
906, 36%, high-risk

1249 pts, 49%, 6 m. ADT

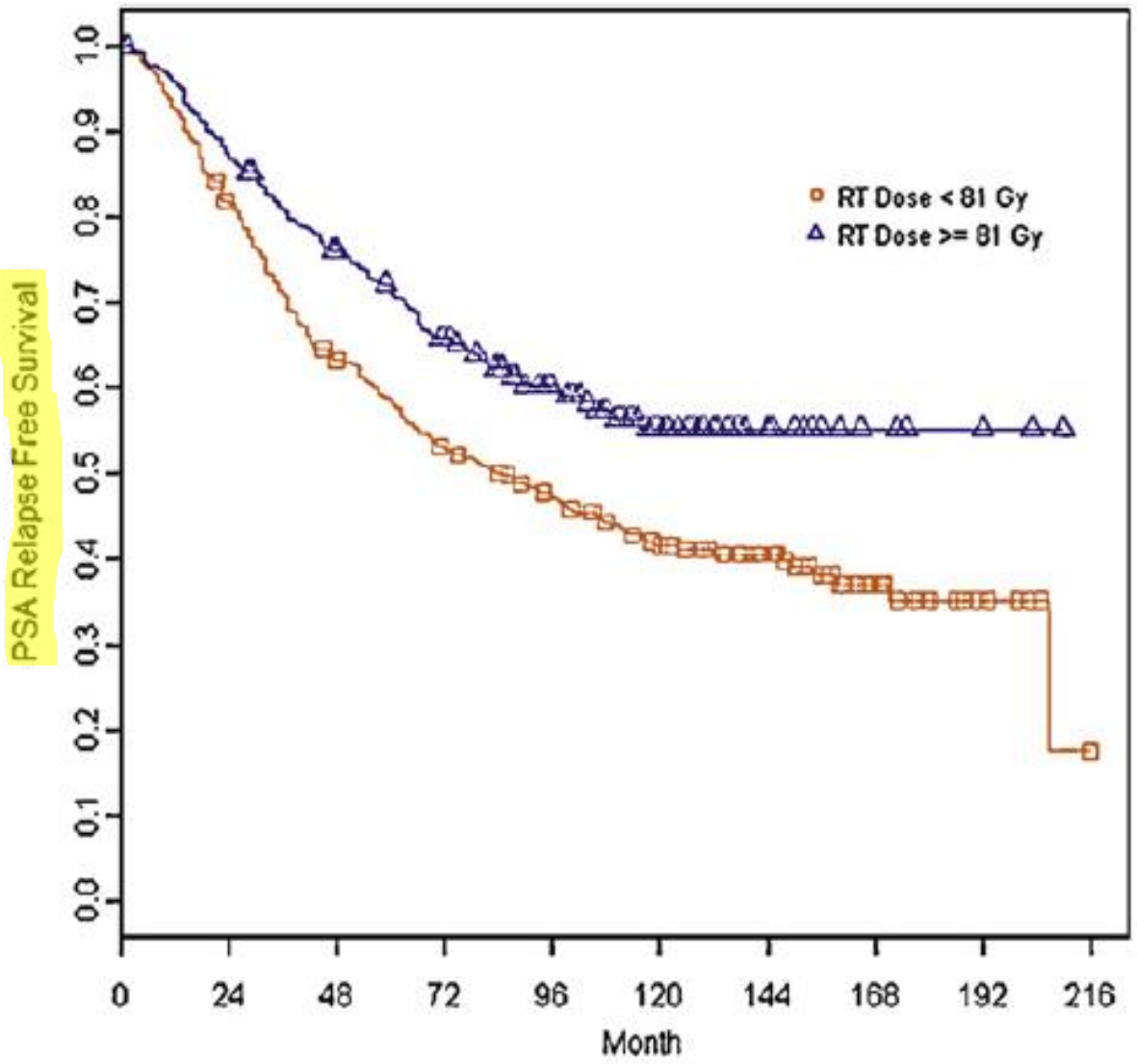
3D-CRT / IMRT
No pelvic RT

Different dose-level cut-offs:
- 70.2 Gy
- 75,6 Gy
- 81 Gy….

Zelefsky, Eur Urol, 2011



Zelefsky, Eur Urol, 2011



Radiation dose level and use of ADT in this population of patients did not influence PCa mortality or overall survival outcomes

Zelefsky, Eur Urol, 2011

Table 3 – Univariate and multivariate analysis of predictors for time to distant metastases

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
HT (yes vs no)	1.224	0.9796–1.529	0.075	0.7817	0.610–1.002	0.052
T stage			<0.0001			<0.0001
T1c/T2a	1.00			1.00		
T2b/T2c	1.93	1.459–2.575	<0.0001	1.6279	1.207–2.196	
T3a/T3b/T3c	5.06	3.895–6.575	<0.0001	3.2095	2.395–4.302	
Gleason	1.673	1.522–1.838	<0.0001	1.5069	1.367–1.661	<0.001
Pre-PSA	1.017	1.013–1.021	<0.0001	1.0107	1.006–1.015	<0.001
RT dose, Gy			<.0001			0.027
≥81 (reference)	1.00			1.00		
70.2–75.6	1.839	1.449–2.334	<0.0001	1.3528	1.044–1.752	0.022
<70.2	1.909	1.223–2.982	0.0044	1.6737	1.045–2.680	0.032

HR = hazard ratio; CI = confidence interval; HT = hormone therapy; PSA = prostate-specific antigen; RT = radiotherapy.

Zelefsky, Eur Urol, 2011

Table 3 – Univariate and multivariate analysis of predictors for time to distant metastases

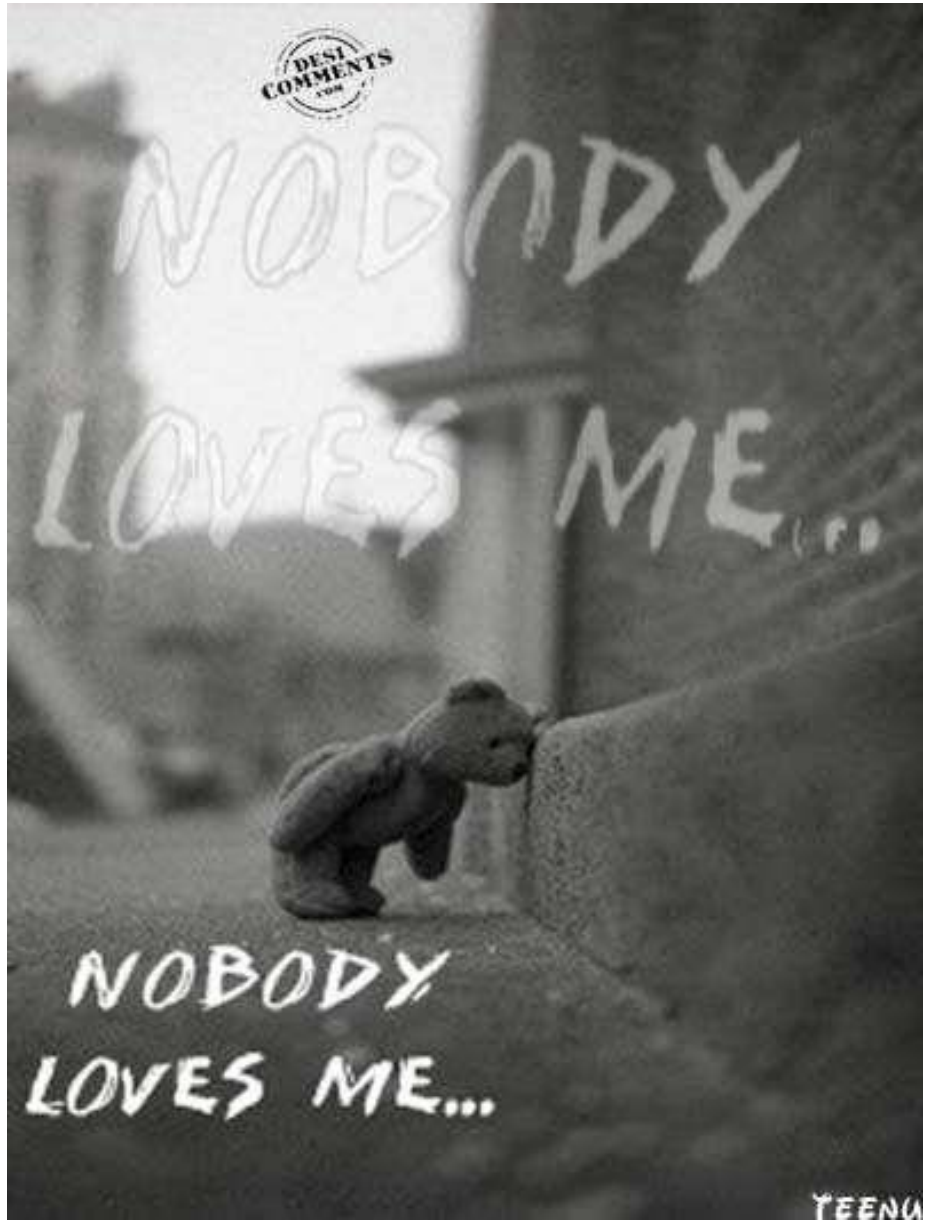
	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
HT (yes vs no)	1.224	0.9796–1.529	0.075	0.7817	0.610–1.002	0.052
T stage			<0.0001			<0.0001
T1c/T2a	1.00			1.00		
T2b/T2c	1.93	1.459–2.575	<0.0001	1.6279	1.207–2.196	
T3a/T3b/T3c	5.06	3.895–6.575	<0.0001	3.2095	2.395–4.302	
Gleason						<0.001
Pre-PSA						<0.001
RT dose, Gy						0.027
≥81 (reference)						
70.2–75.6						0.022
<70.2						0.032

HR = hazard rati

	Multivariate		
	HR	95% CI	*p* value
RT dose, Gy			0.027
≥81 (reference)	1.00		
70.2–75.6	1.3528	1.044–1.752	0.022
<70.2	1.6737	1.045–2.680	0.032

Why don’t surgeons like radiotherapy?

- It is less effective?
- It is toxic?
- It causes cancer?
- It is hard to perform surgery afterwards?
- It’s a hassle?
- It is expensive?
- It makes men have ADT?



courtesy of M Mason

The NEW ENGLAND JOURNAL of MEDICINE

Sept 2016

ORIGINAL ARTICLE

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

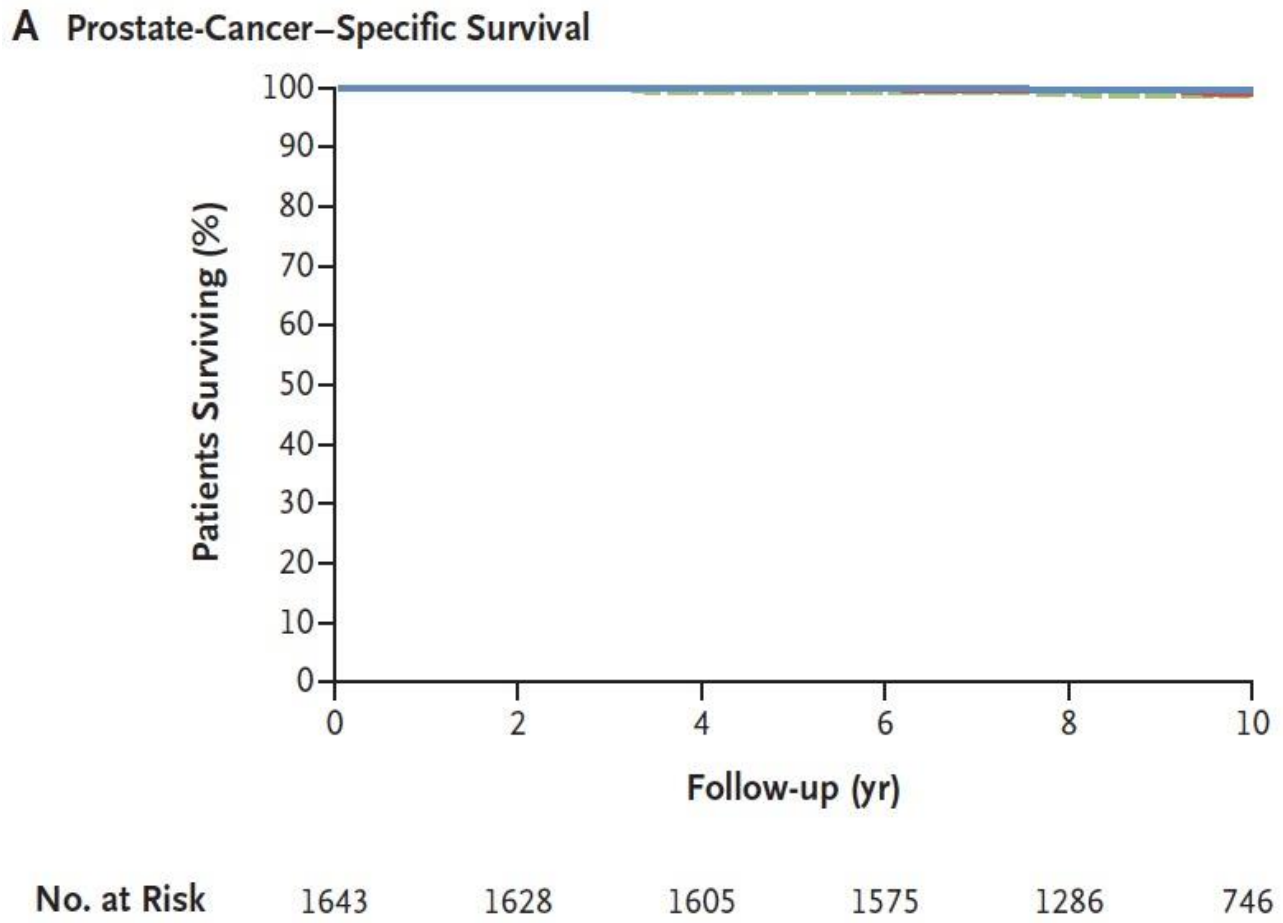
F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Turner, R.M. Martin, J. Oxley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherty, D. Gillatt, R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Prescott, D.J. Rosario, E. Rowe, and D.E. Neal, for the ProtecT Study Group*

1999 – 2009: 1643 pts (553 RP, 545 RT+ 6 m ADT, 545 Active Monitoring)

End-point: PCa mortality at 10 ys FU
clinical progression
metastasis
all-cause mortality

Quality of Life

58% Low risk - 40% intermediate - 2% high risk D'Amico



Hamdy, NEJM, 2016

Comparative effectiveness of AM, RP and EBRT

- PCa and mortality

	AM (N=545)	RP (N=553)	EBRT (N=545)	*P* value*
PCA-specific survival†				
5-yr (%)	99.4	100	100	
10-yr (%)	**98.8**	**99.0**	**99.6**	
Deaths from PCa† (per 1,000 person-years)	1.5	0.9	0.7	NS
Deaths from any cause (per 1,000 person-years)	10.9	10.1	10.3	NS

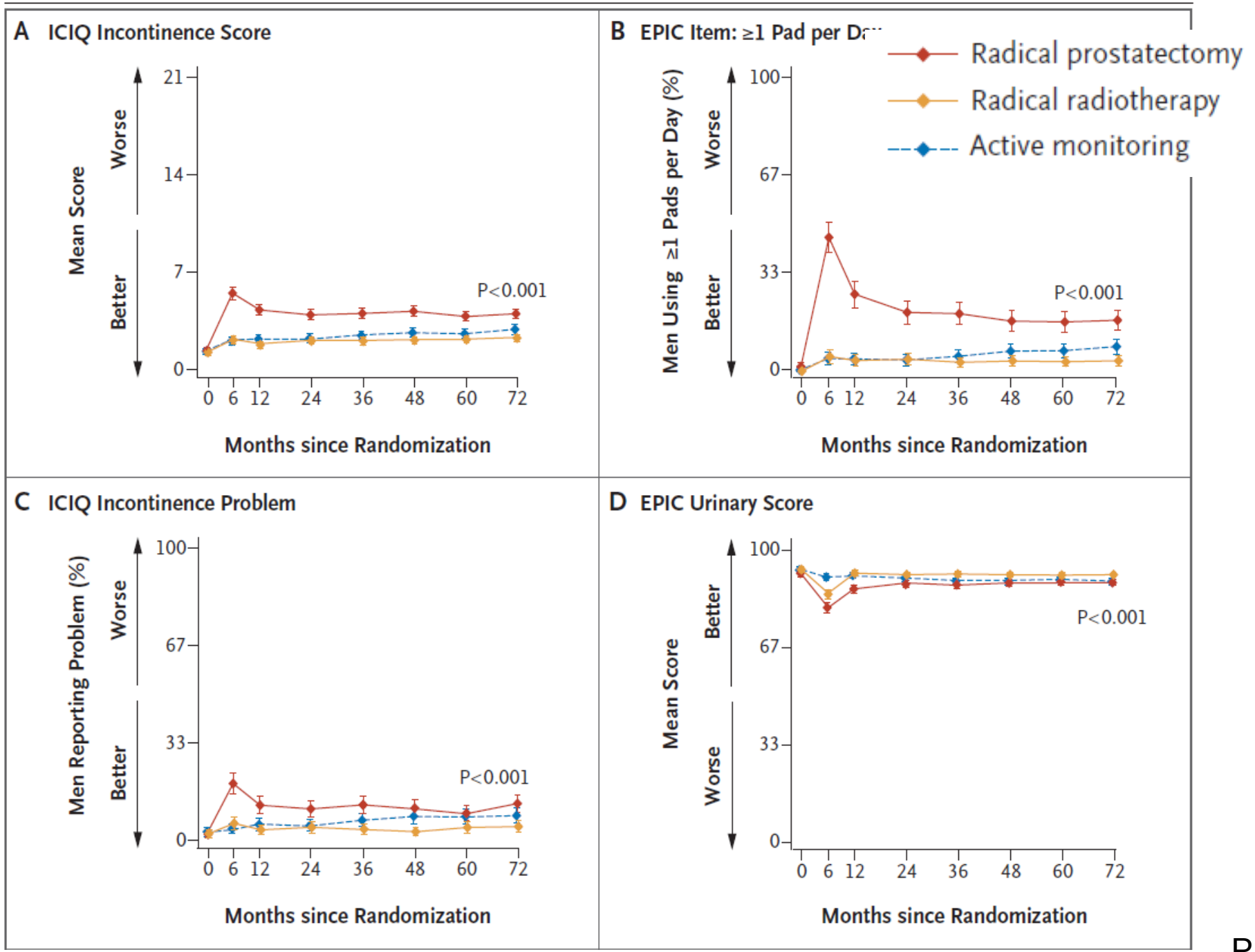
Hamdy, NEJM, 2016

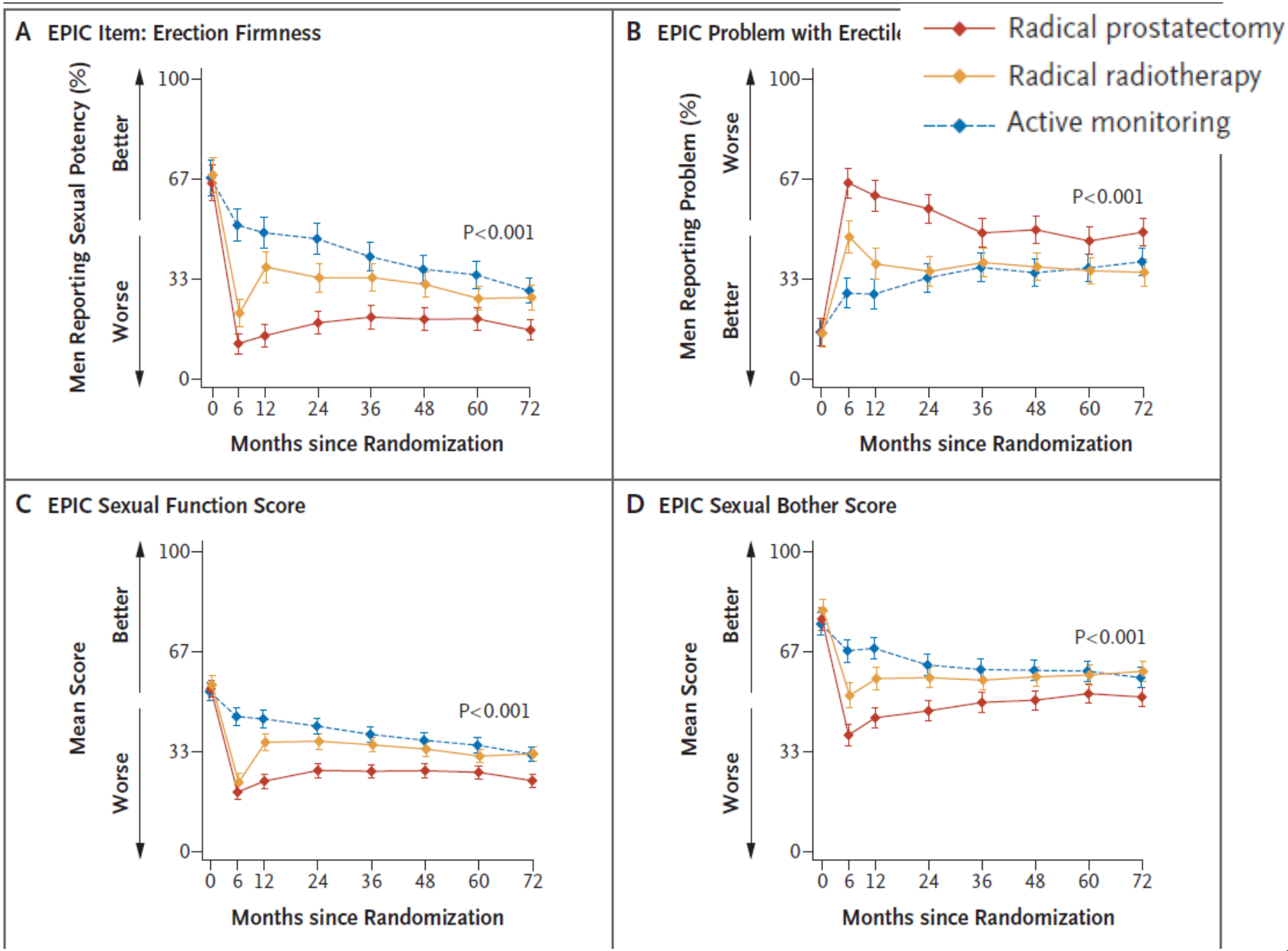
Comparative effectiveness of AM, RP and EBRT

- PCa and mortality

	AM (N=545)	RP (N=553)	EBRT (N=545)	*P* value*
PCA-specific survival†				
5-yr (%)	99.4	100	100	
10-yr (%)	**98.8**	**99.0**	**99.6**	
Deaths from PCa† (per 1,000 person-years)	1.5	0.9	0.7	NS
Deaths from any cause (per 1,000 person-years)	10.9	10.1	10.3	NS

Low PCa-specific mortality irrespective of treatment
Death from ANY cause NOT different


A ICIQ Incontinence Score
Mean Score
Worse
Better
21
14
7
0
P<0.001
0 6 12 24 36 48 60 72
Months since Randomization
B EPIC Item: ≥1 Pad per Da
Men Using ≥1 Pads per Day (%)
Worse
Better
100
67
33
0
P<0.001
0 6 12 24 36 48 60 72
Months since Randomization
Radical prostatectomy
Radical radiotherapy
Active monitoring
C ICIQ Incontinence Problem
Men Reporting Problem (%)
Worse
Better
100
67
33
0
P<0.001
0 6 12 24 36 48 60 72
Months since Randomization
D EPIC Urinary Score
Mean Score
Better
Worse
100
67
33
0
P<0.001
0 6 12 24 36 48 60 72
Months since Randomization


A EPIC Item: Erection Firmness
Men Reporting Sexual Potency (%)
Better
Worse
100
67
33
0
P<0.001
0 6 12 24 36 48 60 72
Months since Randomization
B EPIC Problem with Erectil
Men Reporting Problem (%)
Worse
Better
P<0.001
Months since Randomization
Radical prostatectomy
Radical radiotherapy
Active monitoring
C EPIC Sexual Function Score
Mean Score
P<0.001
D EPIC Sexual Bother Score
P<0.001

2010 – 2014…

VOLUME 28 · NUMBER 9 · MARCH 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Metastasis After Radical Prostatectomy or External Beam Radiotherapy for Patients With Clinically Localized Prostate Cancer: A Comparison of Clinical Cohorts Adjusted for Case Mix

Michael J. Zelefsky, James A. Eastham, Angel M. Cronin, Zvi Fuks, Zhigang Zhang, Yoshiya Yamada, Andrew Vickers, and Peter T. Scardino

VOLUME 28 · NUMBER 9 · MARCH 20 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

2010 – 2014…

Metastasis After Radical Prostatectomy or External Beam Radiotherapy for Patients With Clinically Localized Prostate Cancer: A Comparison of Clinical Cohorts Adjusted for Case Mix

Michael J. Zelefsky, Yoshiya Yamada,

Original Article

Comparative Risk-Adjusted Mortality Outcomes After Primary Surgery, Radiotherapy, or Androgen-Deprivation Therapy for Localized Prostate Cancer

Matthew R. Cooperberg, MD, MPH[1]; Andrew J. Vickers, PhD[2]; Jeanette M. Broering, RN, MS MPH[1]; and Peter R. Carroll, MD, MPH,[1] for the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) Investigators

2010 – 2014…

VOLUME 28 · NUMBER 9 · MARCH 20 2010

JOURNAL OF CLINICAL ONCOLOGY

BMJ

BMJ 2014;348:g1502 doi: 10.1136/bmj.g1502 (Published 27 February 2014)

RESEARCH

Original Article

Comparati
Outcomes
Radiothera
Therapy fc

Matthew R. Cooperberg, M
and Peter R. Carroll, MD, MPH,[I] for the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) Investigators

Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: observational study of mortality outcomes

OPEN ACCESS

Prasanna Sooriakumaran *assistant professor and senior clinical researcher*[1 2], Tommy Nyberg *statistician*[3], Olof Akre *associate professor*[4], Leif Haendler *consultant*[1], Inge Heus *statistician*[5], Mats Olsson *consultant*[1], Stefan Carlsson *consultant*[1], Monique J Roobol *associate professor*[5], Gunnar Steineck *professor*[3 6], Peter Wiklund *professor*[1]

VOLUME 28 · NUMBER 9 · MARCH 20 2010

JOURNAL OF CLINICAL

RESEARCH

Original Article

Comparati… Outcomes … Radiothera… Therapy fo…

tatectomy
rvational

Matthew R. Cooperberg, M…
and Peter R. Carroll, MD, MPH… Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) Investigators

Tommy Nyberg
…s statistician[5],
…que J Roobol associate professor[5],
…kland professor[1]

***Observational data-set analysis*:**

- are unable to account for the evolution of treatment modalities

- makes it impossible to adjust for confounders like PSA (SEER)

- do not include details on adjuvant or salvage therapies (SEER)

- suffer from lack of randomization…

Abdollah, Eur Urol 2011

Limits of Observational Data in Determining Outcomes From Cancer Therapy

Sharon H. Giordano, MD, MPH[1]
Yong-Fang Kuo, PhD[2]
Zhigang Duan, BMed, MS[1]
Gabriel N. Hortobagyi, MD[1]
Jean Freeman, PhD[2]
James S. Goodwin, MD[2]

[1] Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[2] Sealy Center on Aging, Department of Internal Medicine, The University of Texas Medical Branch at Galveston, Galveston, Texas.

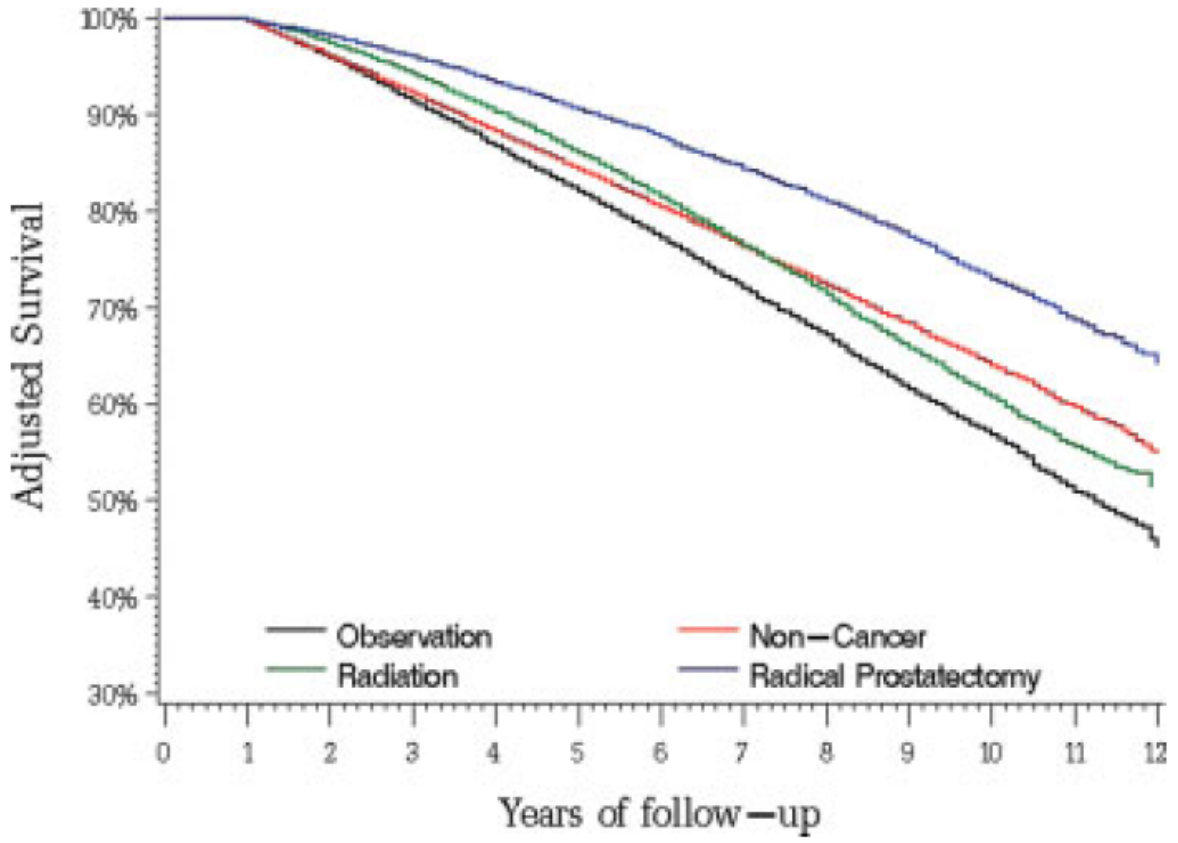


FIGURE 1. Adjusted overall survival curves from Cox models for men with localized prostate cancer stratified by therapy and for a matched noncancer control population.

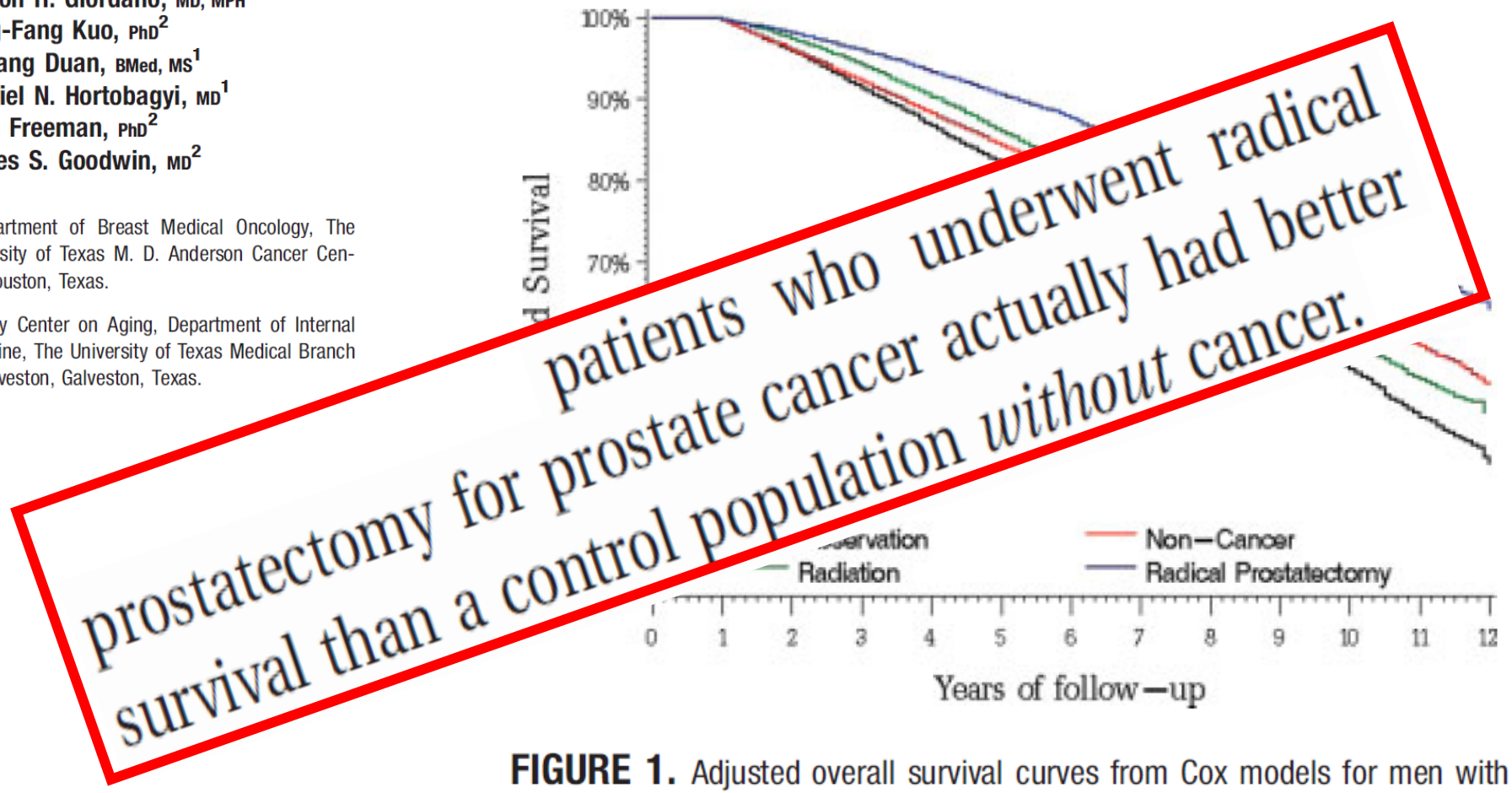
Cancer, 2008

Limits of Observational Data in Determining Outcomes From Cancer Therapy

Sharon H. Giordano, MD, MPH[1]
Yong-Fang Kuo, PhD[2]
Zhigang Duan, BMed, MS[1]
Gabriel N. Hortobagyi, MD[1]
Jean Freeman, PhD[2]
James S. Goodwin, MD[2]

[1] Department of Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[2] Sealy Center on Aging, Department of Internal Medicine, The University of Texas Medical Branch at Galveston, Galveston, Texas.



patients who underwent radical prostatectomy for prostate cancer actually had better survival than a control population *without* cancer.

FIGURE 1. Adjusted overall survival curves from Cox models for men with localized prostate cancer stratified by therapy and for a matched noncancer control population.

Cancer, 2008

‘ it’s only the fish that John West rejects that makes John West the best.’ .

EUROPEAN UROLOGY 72 (2017) 7–9

extreme hypo-fractionation

MRI-guided intra-prostatic boost

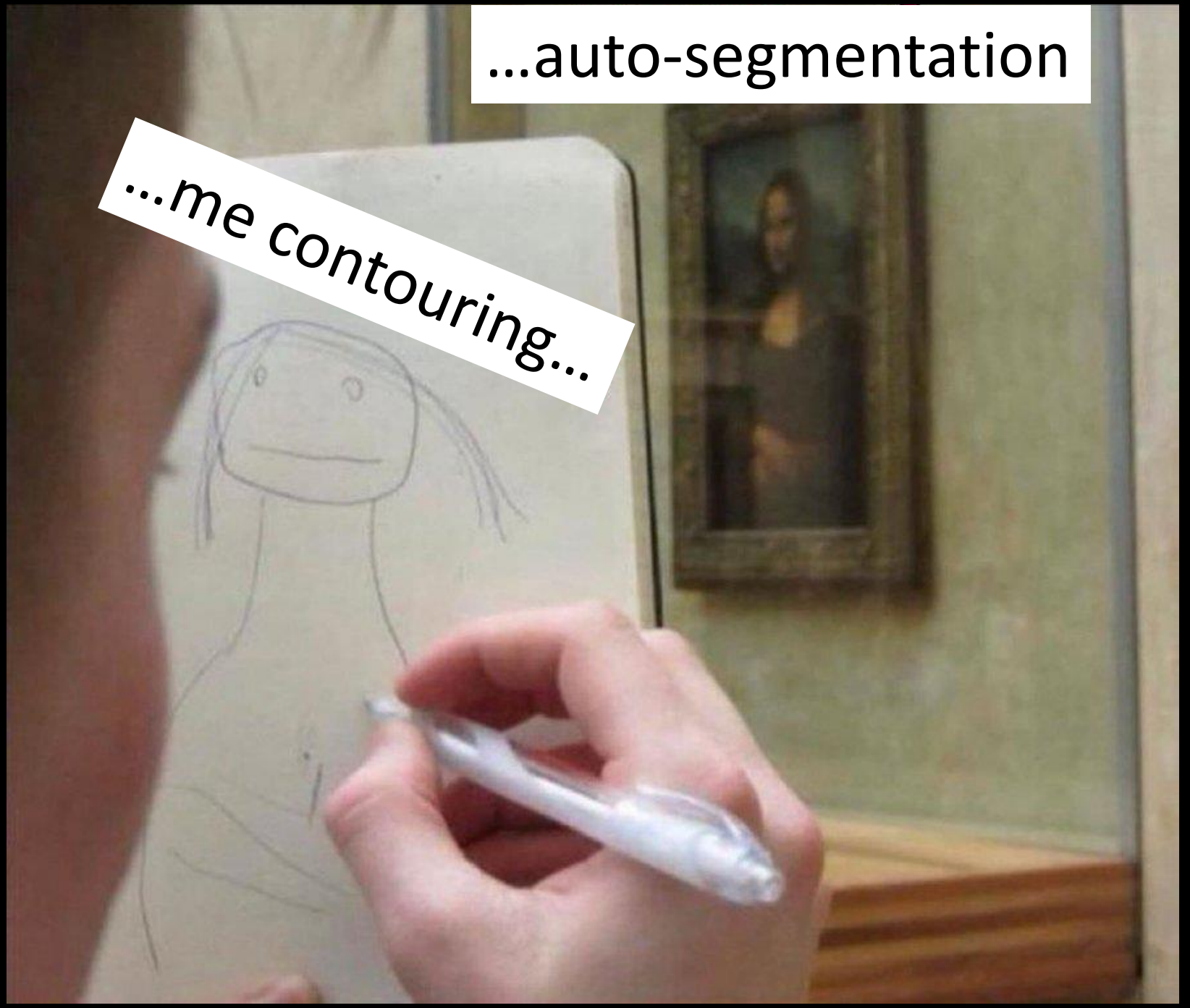
auto-segmentation

radiomics

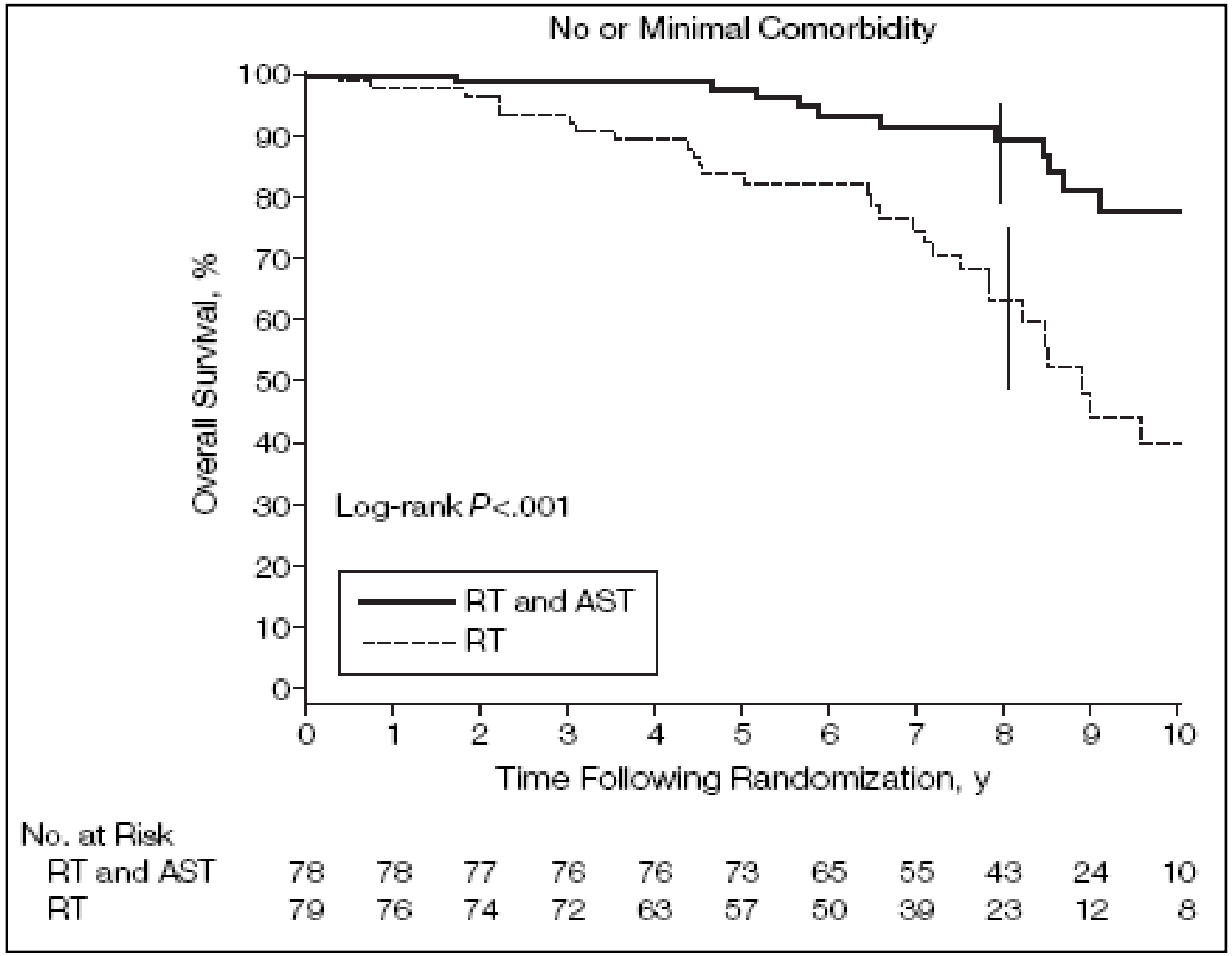
biomarkers

dose / ADT de-escalation

combined RT – ADT + ….

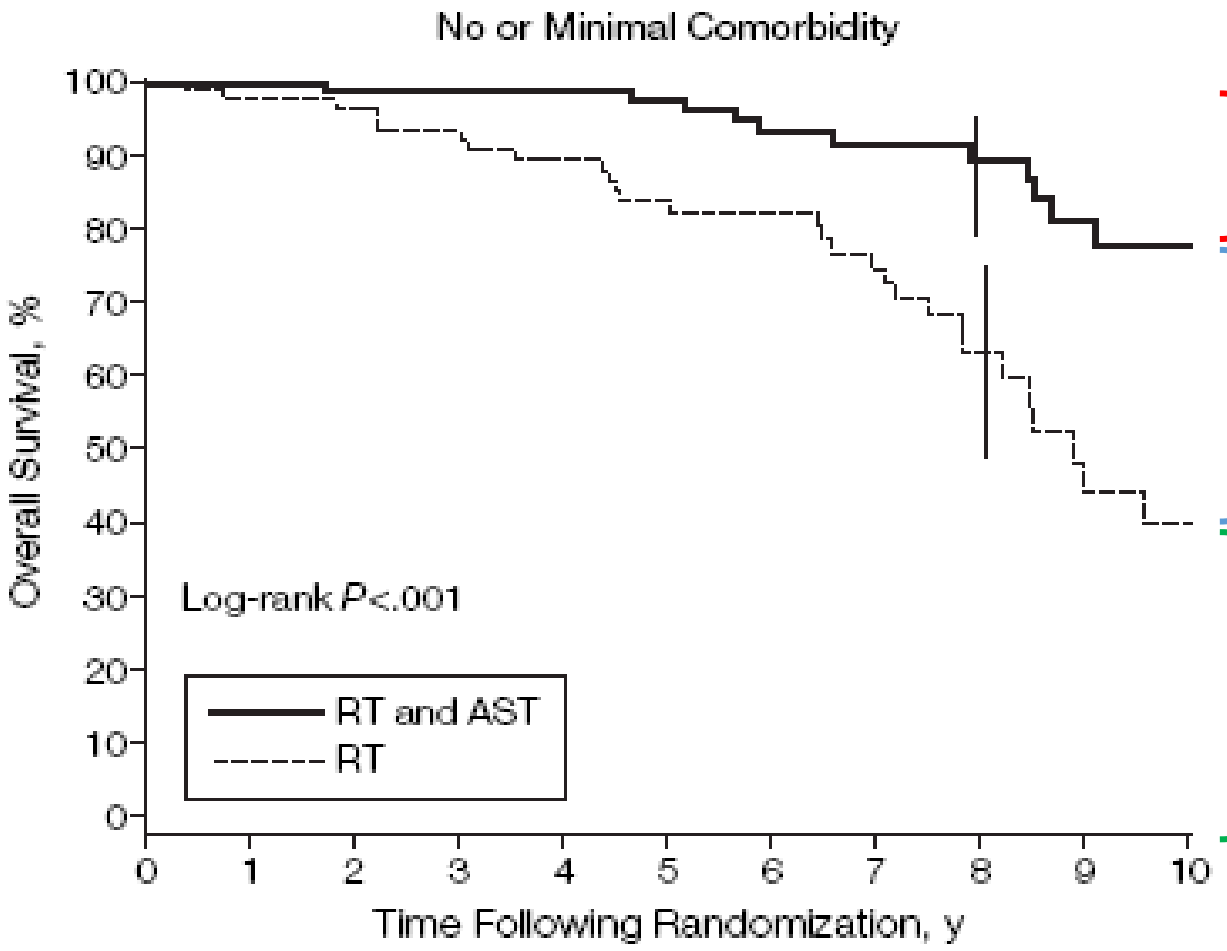

…auto-segmentation
…me contouring…

- DFCI 95-096, N = 206, localised but unfavourable-risk PCa, RT alone versus RT + HT



D'Amico et al. JAMA 2008

- DFCI 95-096, N = 206, localised but unfavourable-risk PCa, RT alone versus RT + HT



No. at Risk											
RT and AST	78	78	77	76	76	73	65	55	43	24	10
RT	79	76	74	72	63	57	50	39	23	12	8

Dead despite RT+ADT

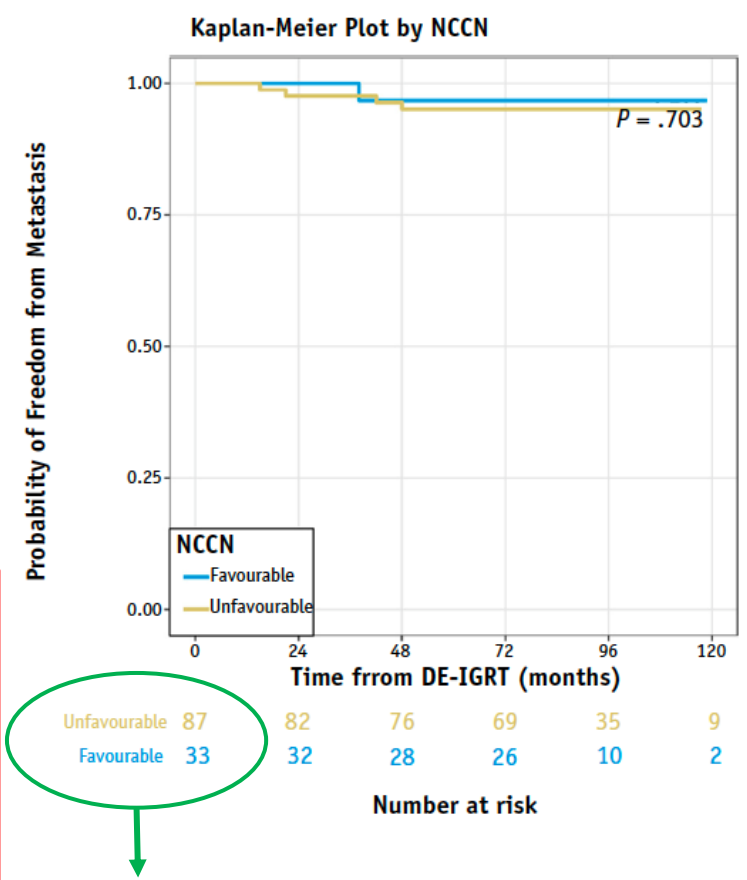
Benefit with RT+ADT *vs* RT alone

Alive with RT alone

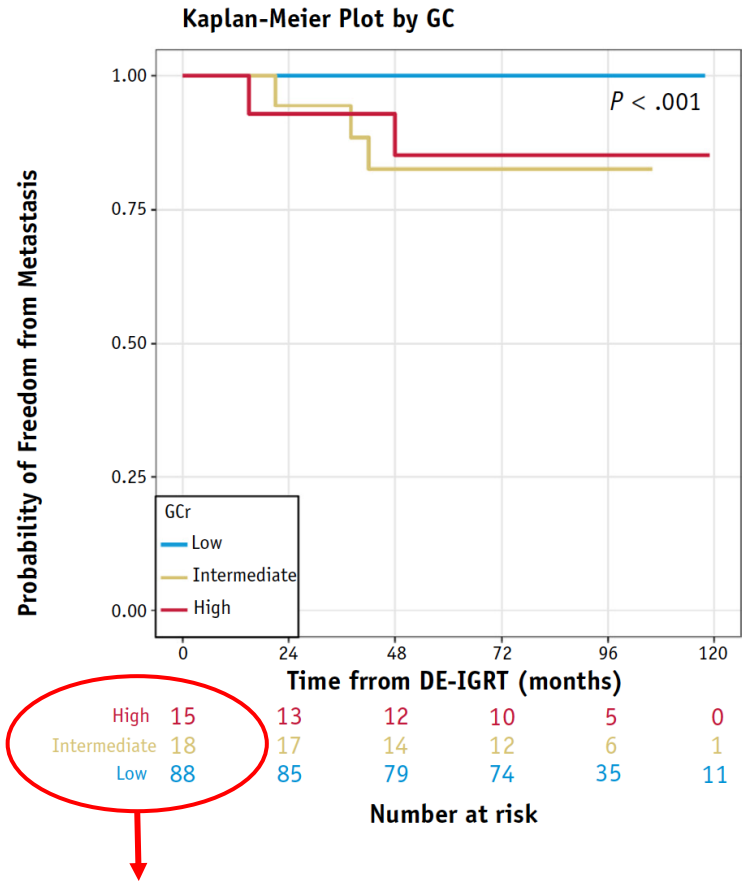
D'Amico et al. JAMA 2008

Potential Approaches for Personalizing ADT for Patients with Intermediate Risk Prostate Cancer

- Retrospective cohort of 121 patients with intermediate risk prostate cancer treated with RT alone
- 72% unfavorable int risk
- All underwent testing with the genomic classifier Decipher
- Decipher scores were more strongly associated with outcome vs NCCN subgroups



NCCN subgroup



Decipher scores

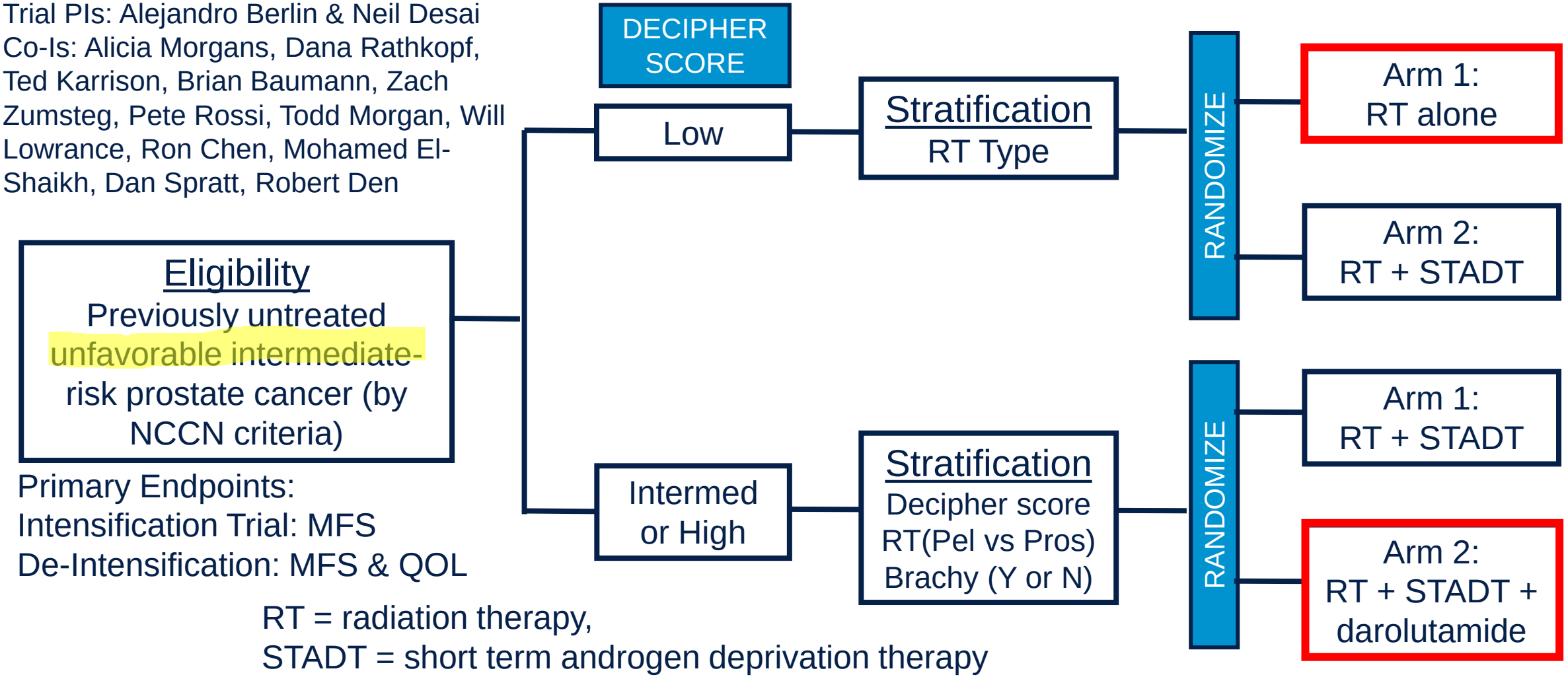
courtesy of F Feng

Berlin A et al, *International Journal of Rad Onc, Biology & Physics*, 2019

UCSF

NRG GU010: A Genomic-Risk Stratified Trial for Patients with Unfavorable Intermediate Risk PCa

Trial PIs: Alejandro Berlin & Neil Desai
Co-Is: Alicia Morgans, Dana Rathkopf, Ted Karrison, Brian Baumann, Zach Zumsteg, Pete Rossi, Todd Morgan, Will Lowrance, Ron Chen, Mohamed El-Shaikh, Dan Spratt, Robert Den

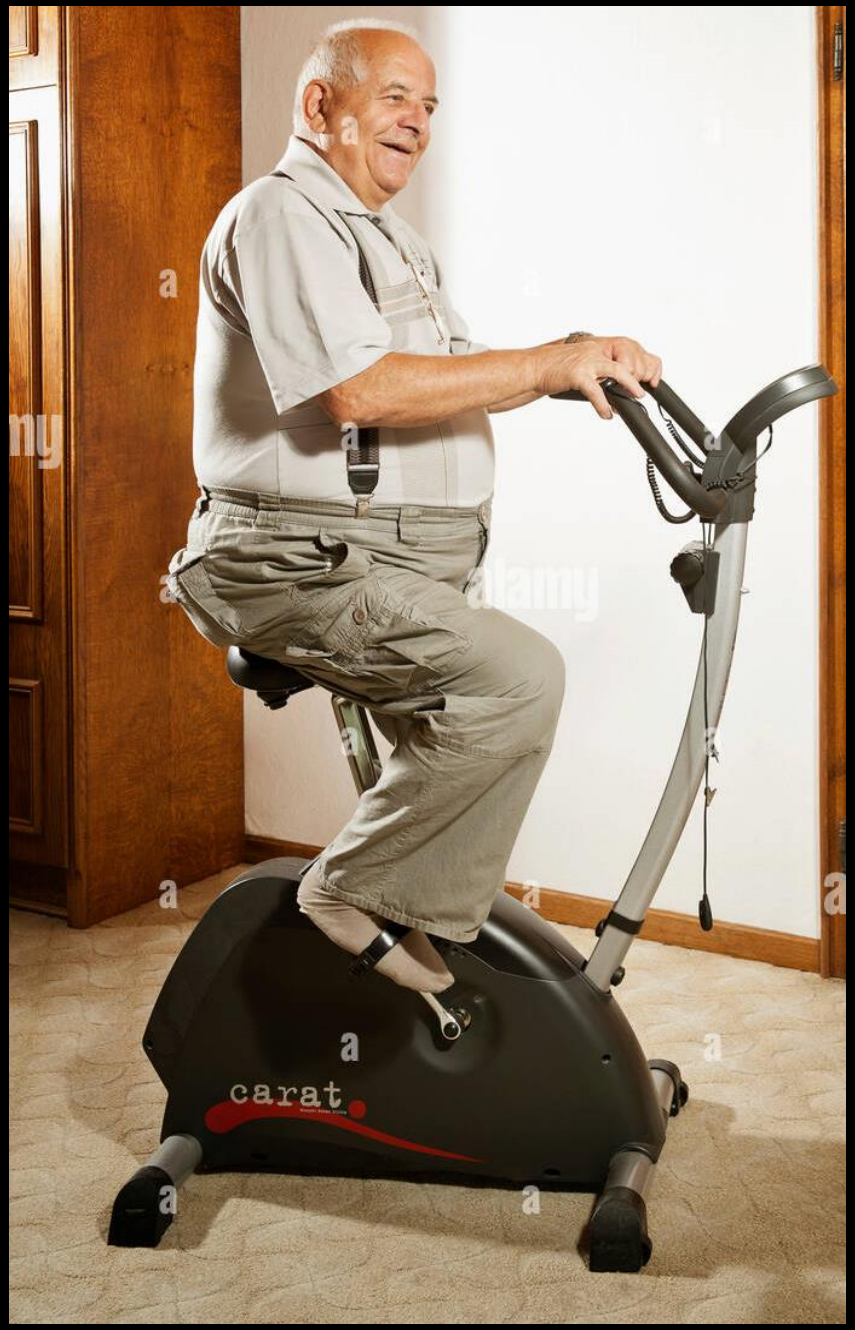


Primary Endpoints:
Intensification Trial: MFS
De-Intensification: MFS & QOL

RT = radiation therapy,
STADT = short term androgen deprivation therapy

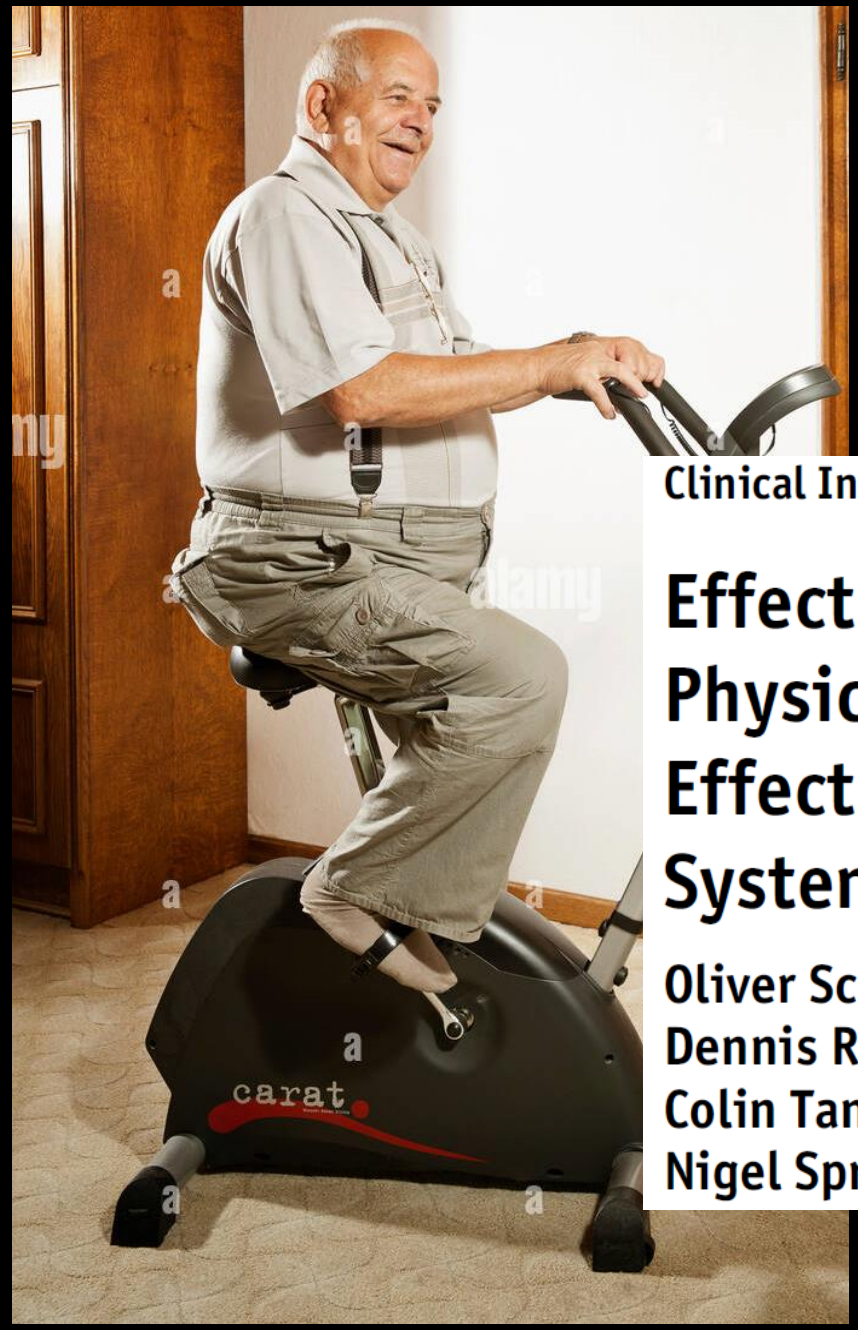
courtesy of F Feng

UCSF



A Bossi

Prosca 2022



Clinical Investigations

Effects of Exercise During Radiation Therapy on Physical Function and Treatment-Related Side Effects in Men With Prostate Cancer: A Systematic Review and Meta-Analysis

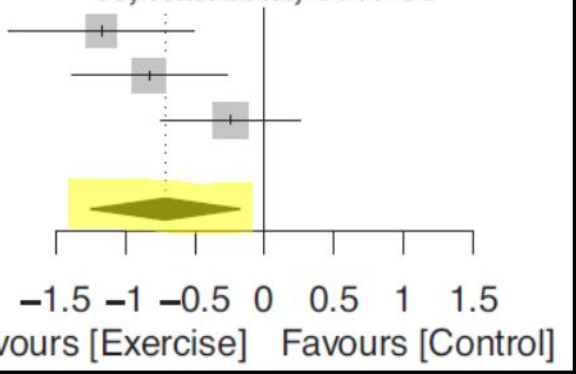
Oliver Schumacher, MSc,*,† Hao Luo, MEd,*,†
Dennis R. Taaffe, PhD, DSc, MPH,*,† Daniel A. Galvão, PhD,*,†
Colin Tang, MBBS, FRANZCR,*,‡ Raphael Chee, MBBS, FRANZCR,*,§
Nigel Spry, MBBS, PhD, FRANZCR,*,‖ and Robert U. Newton, PhD, DSc*,†

Schumacher, IJROBP, 2021

B. Urinary toxicity

Study	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
McQuade et al. (2017)	1.51	7.63	19	10.33	7.17	22	29.3%	−1.17 [−1.84; −0.50]
Hojan et al. (2016)	1.90	18.50	27	16.40	16.00	27	34.1%	−0.83 [−1.38; −0.27]
Kapur et al. (2010)	0.68	0.64	29	0.86	0.81	33	36.7%	−0.24 [−0.74; 0.26]
Total (95% CI)			**75**			**82**	**100.0%**	**−0.71 [−1.25; −0.18]**

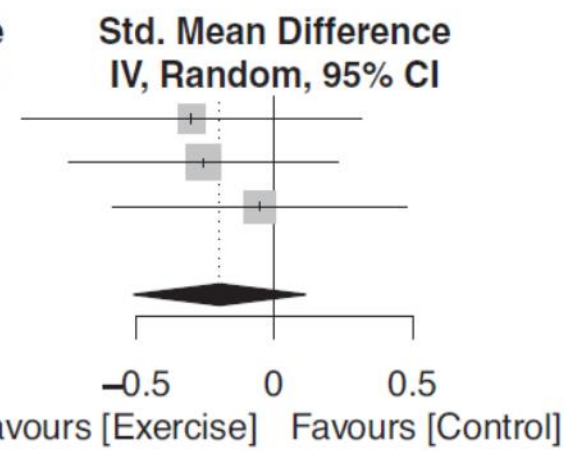
Heterogeneity: $Tau^2 = 0.1392$; $Chi^2 = 5.28$, df = 2 (P = 0.07); $I^2 = 62\%$
Test for overall effect: Z = −2.60 (P < 0.01)



C. Intestinal toxicity

Study	Exercise Mean	Exercise SD	Exercise Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
McQuade et al. (2017)	4.16	11.06	19	7.44	10.34	22	25.4%	−0.30 [−0.92; 0.32]
Kapur et al. (2010)	1.48	0.83	32	1.66	0.52	33	40.6%	−0.26 [−0.75; 0.23]
Hojan et al. (2016)	8.83	13.67	27	9.67	17.23	27	34.0%	−0.05 [−0.59; 0.48]
Total (95% CI)			**78**			**82**	**100.0%**	**−0.20 [−0.51; 0.11]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.45$, df = 2 (P = 0.80); $I^2 = 0\%$
Test for overall effect: Z = −1.25 (P = 0.21)



Schumacher, IJROBP, 2021

Take Home

- …
- …
- …

@AlbertoBossial