Radiotherapie voor prostaatkanker anno 2018

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Alumni 02/05/2018

- Inleiding
- Evolutie in de externe radiotherapie:
  - » Zietecontrole
  - » Toxiciteit
  - » Toekomst

Inleiding

Therapeutische opties

- < 3 factoren:
  1) PSA
  2) Tumoruitgebreidheid (T)
  3) Gleason score

  $\Rightarrow$ 3 prognostische groepen

Therapeutische opties

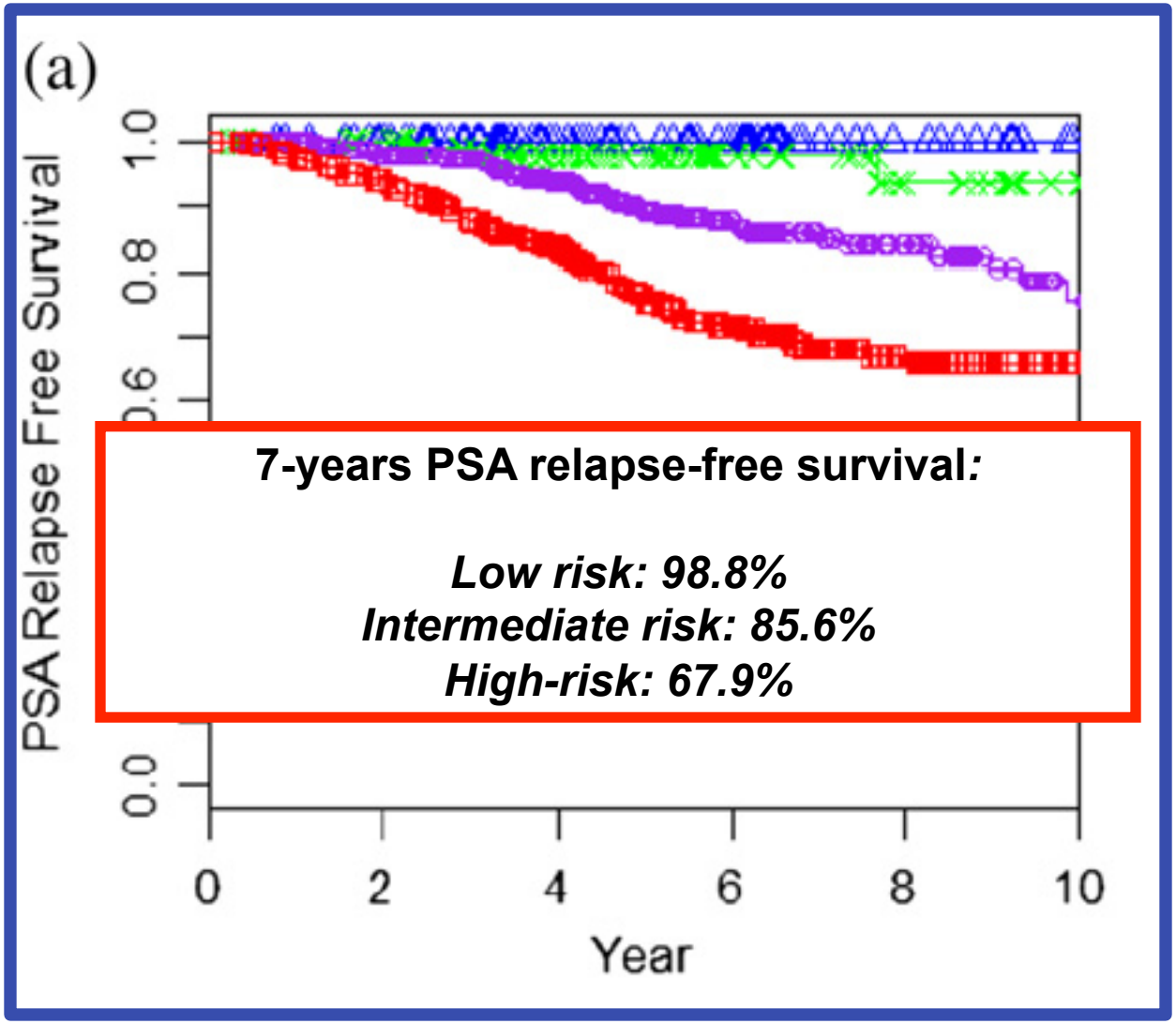
Risico groep	PSA	cT	Gleason	Therapeutische optie
Laag risico	≤10 ng/ml	≤T2a	6 (3+3)	- Active surveillance - Brachytherapie - ***Externe radiotherapie*** - heelkunde
Intermediair risico	>10 en ≤20 ng/ml	T>2a en <3	7 (3+4) of (4+3)	- Brachytherapie - ***Externe radiotherapie + 6 maanden ADT*** - heelkunde
Hoog risico	>20 ng/ml	T≥3	8-10	- ***Externe radiotherapie + 18-24 maanden ADT*** - heelkunde

Evolutie in de externe radiotherapie: *ziektecontrole*

Dosis escalatie: Evidentie

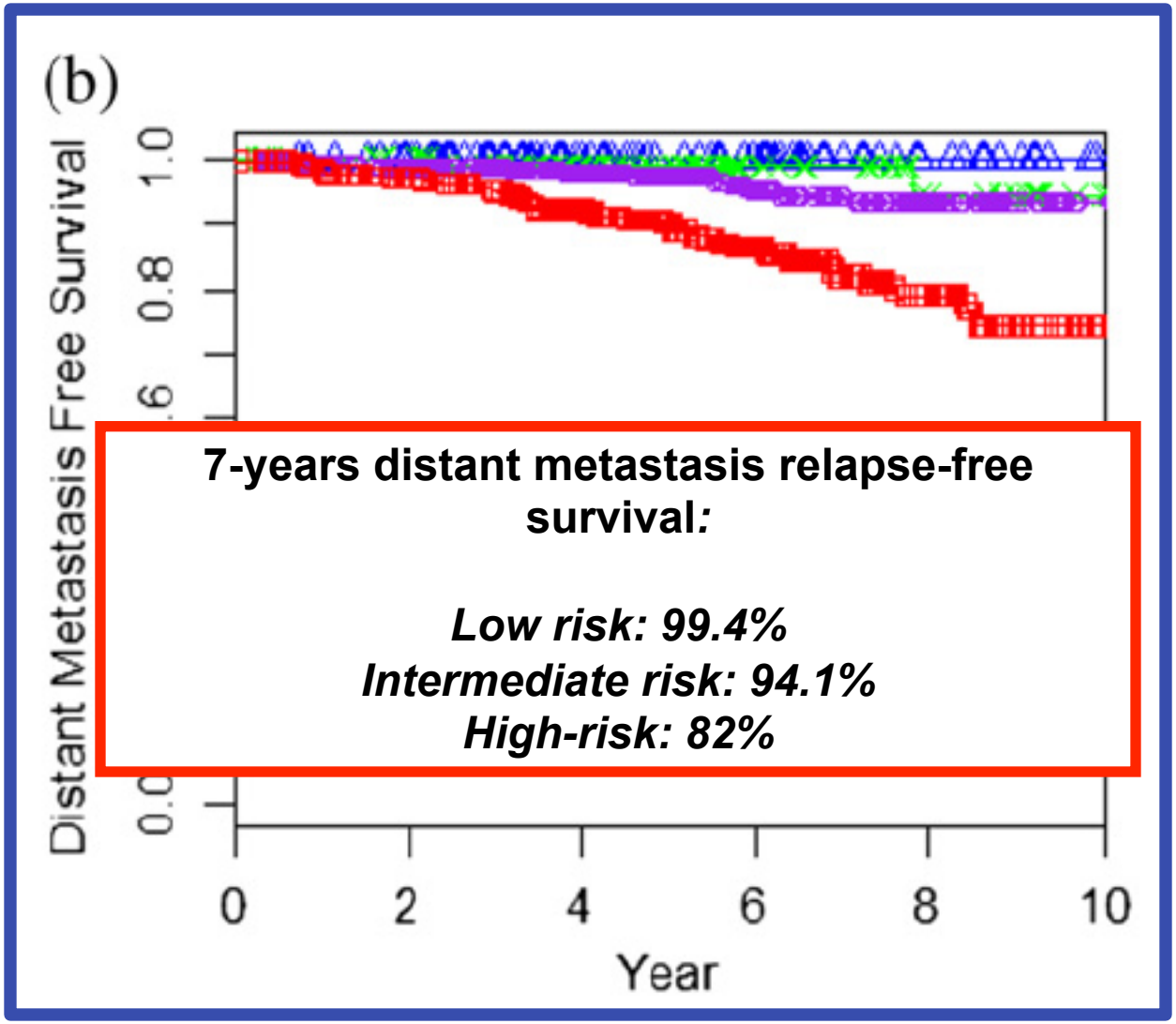
Study	*Dose (Gy)*	*N*	*Follow up*	*bRFS*	*P-value*
Zietman	70.2 GyE	197	8.9	61	0.0012
	79.2 GyE	196		80	
Peeters	68	331	8.9	54	0.02
	78	333		64	
Dearnaley	64	421	5.3	60	0.0007
	74	422		71	
Kuban	70	150	8.7	59	0.004
	78	151		78	
Beckendorf	70	153	5.1	68	0.09
	80	153		77	

Dosis escalatie: Evidentie



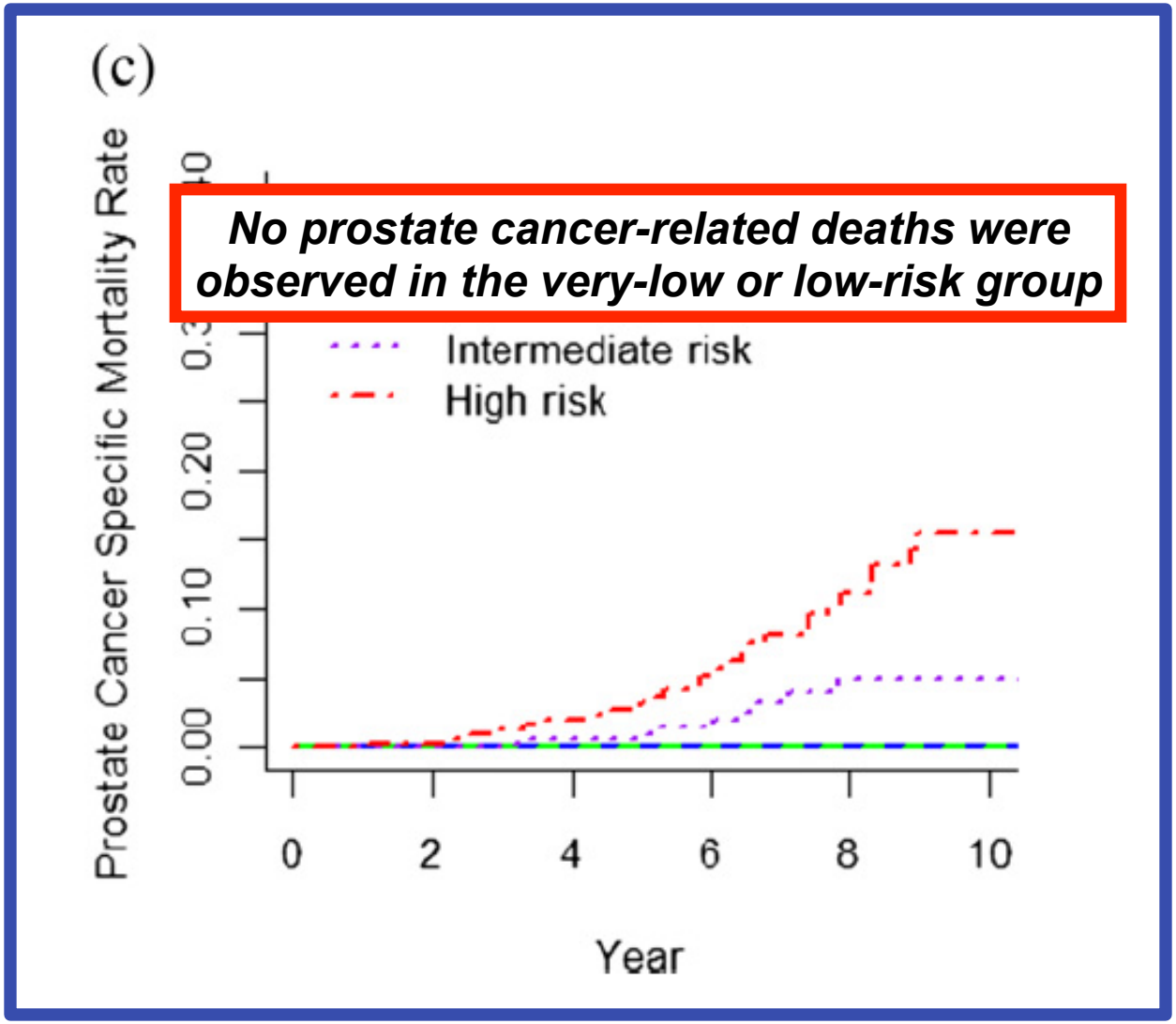
Spratt et al, Int J Radiat Oncol Biol Phys, 2013

Dosis escalatie: Evidentie

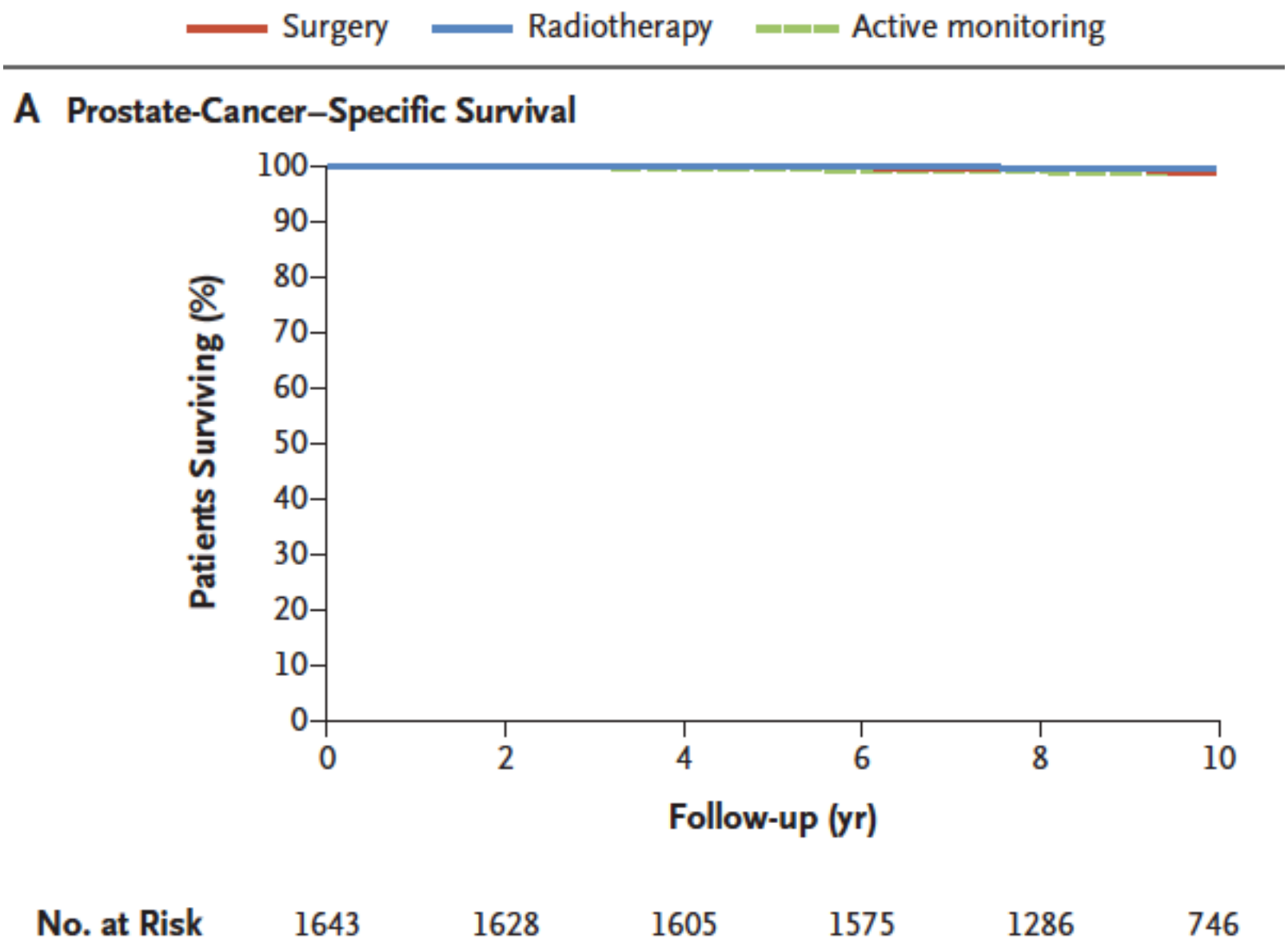


Spratt et al, Int J Radiat Oncol Biol Phys, 2013

Dosis escalatie: Evidentie



Spratt et al, Int J Radiat Oncol Biol Phys, 2013



Hamdi et al, New Engl J Med, 2016

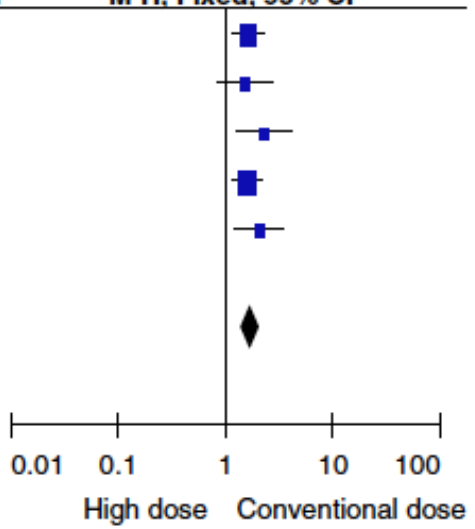
Evolutie in de externe radiotherapie: *toxiciteit*

Rectale toxiciteit

Study or Subgroup	High dose Events	Total	Conventional dose Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
DUTCH 2008	116	331	83	333	32.6%	1.63 [1.16, 2.27]
GETUG06 2011	30	153	21	153	10.2%	1.53 [0.83, 2.82]
MD Anderson 2008	39	151	20	150	9.0%	2.26 [1.25, 4.10]
MRC RT01 2007	119	422	83	421	36.2%	1.60 [1.16, 2.20]
PROG9509 2010	47	196	26	197	12.0%	2.07 [1.22, 3.51]
Total (95% CI)		**1253**		**1254**	**100.0%**	**1.72 [1.42, 2.08]**
Total events	351		233			

Heterogeneity: $Chi^2 = 1.75$, $df = 4$ ($P = 0.78$); $I^2 = 0\%$

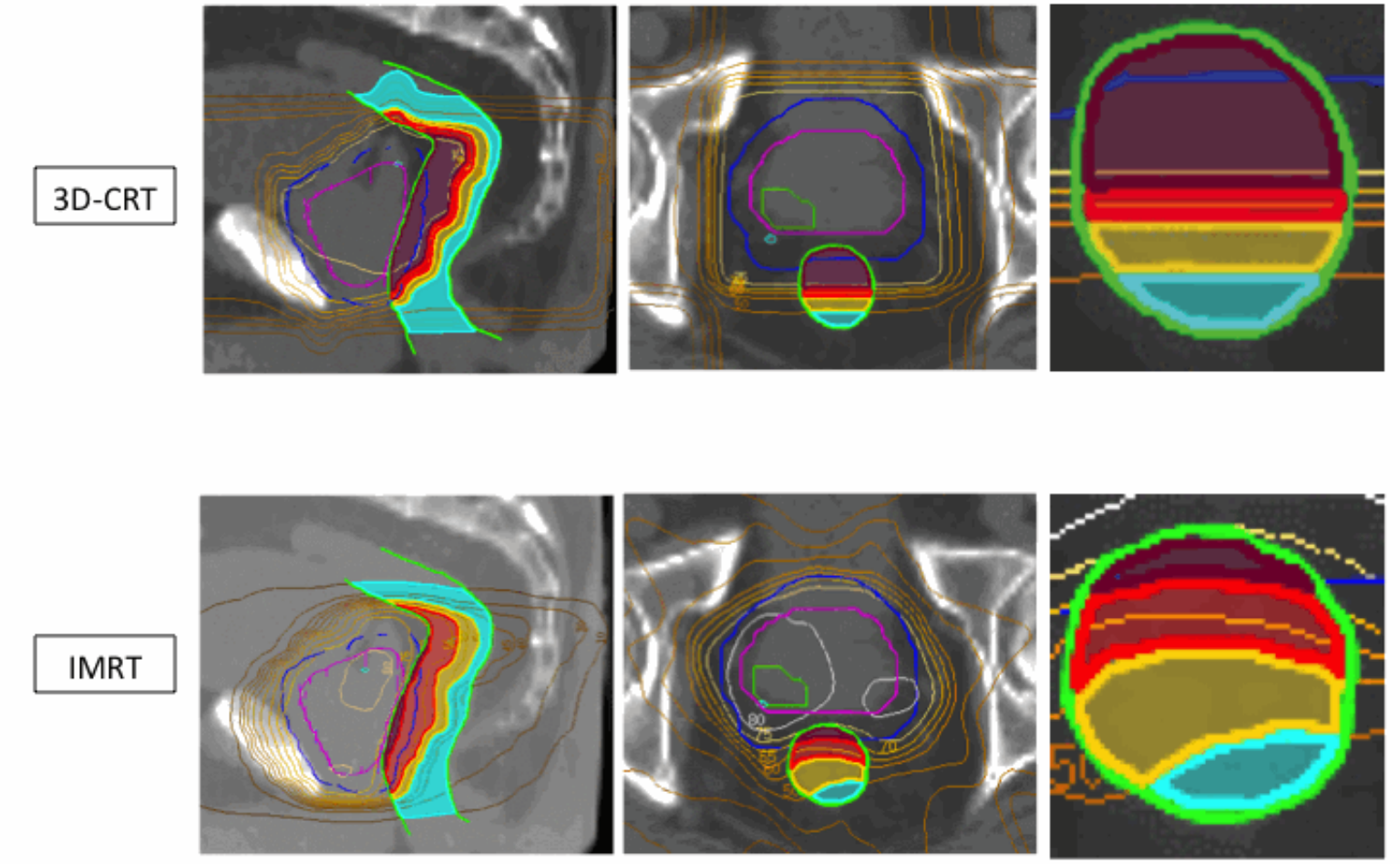
Test for overall effect: $Z = 5.59$ ($P < 0.00001$)



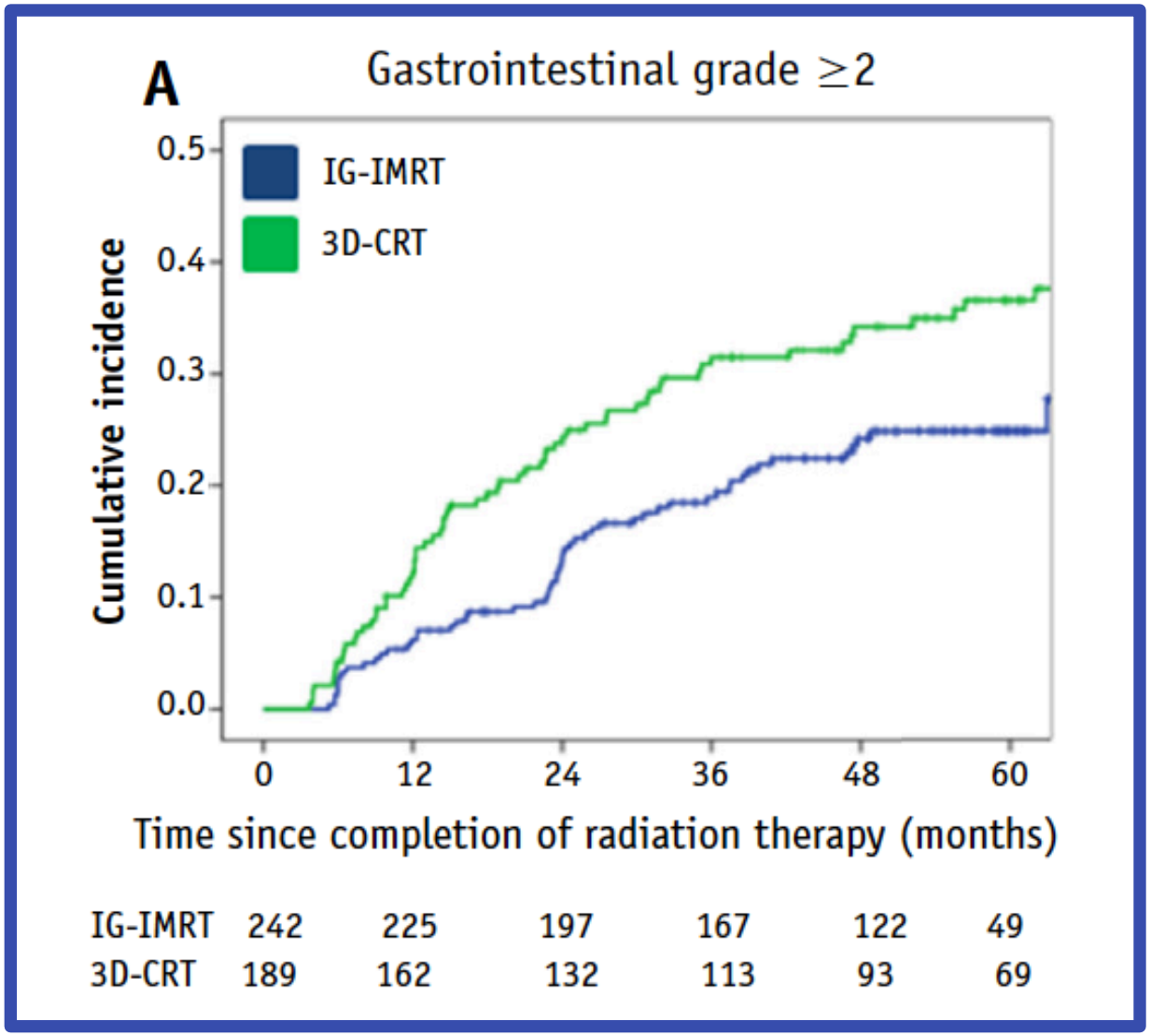
Late grade ≥2 rectal toxicity:
Conventional dose radiotherapy: 18.6%
High dose radiotherapy: 28%

Hou et al, J Cancer Res Clin Oncol, 2014

Rectale toxiciteit

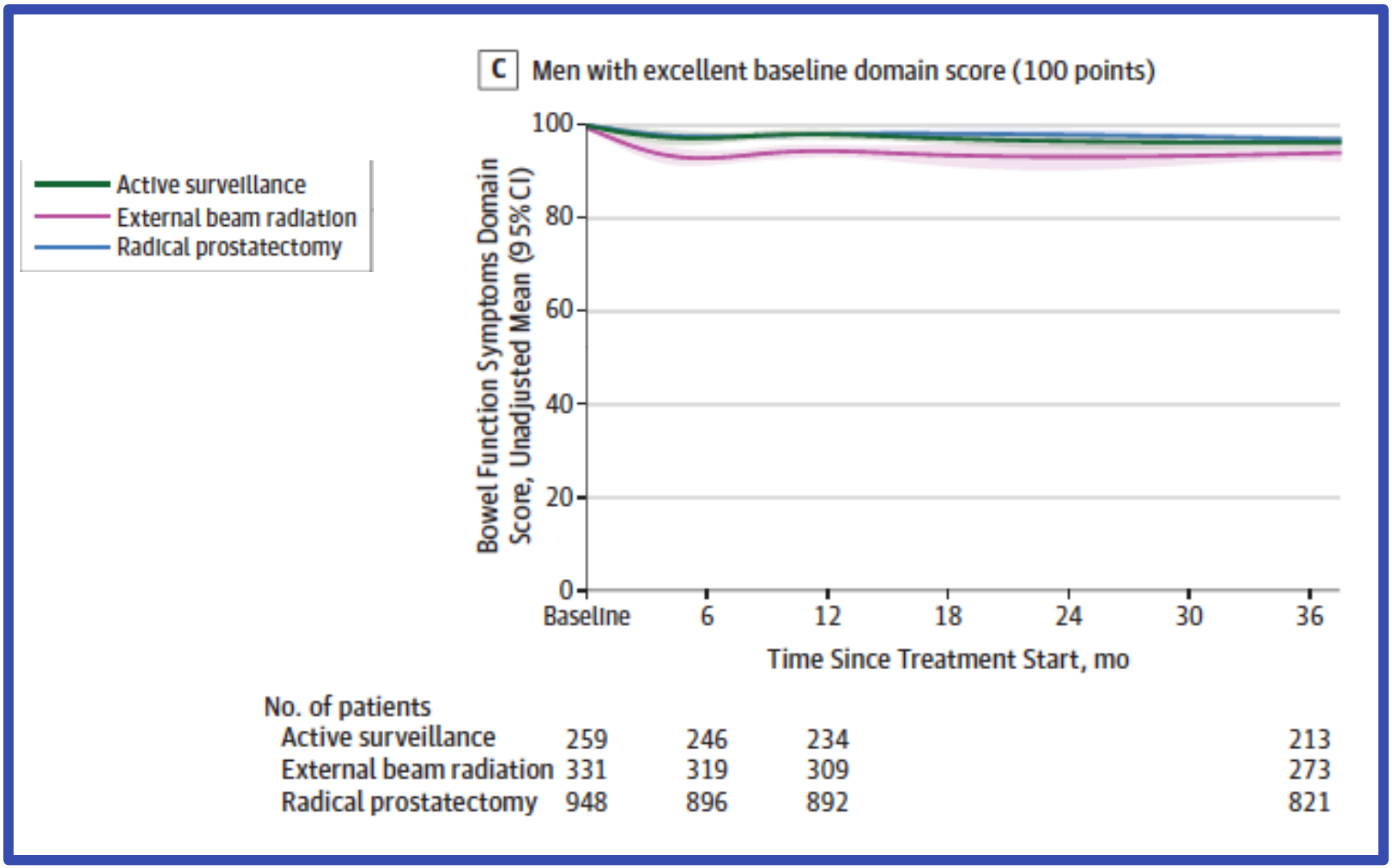


Rectale toxiciteit



Wortel et al, 2016. Int J Radiot Oncol Biol Phys

Patient reported outcome voor rectale toxiciteit



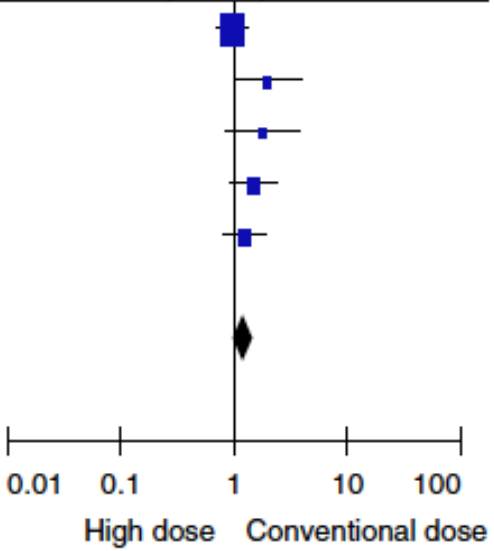
Barocas et al, Jama, 2017

Urinaire toxiciteit

Study or Subgroup	High dose Events	Total	Conventional dose Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
DUTCH 2008	133	331	136	333	48.5%	0.97 [0.71, 1.33]
GETUG06 2011	27	153	15	153	7.4%	1.97 [1.00, 3.88]
MD Anderson 2008	20	151	12	150	6.3%	1.76 [0.83, 3.73]
MRC RT01 2007	46	422	32	421	17.1%	1.49 [0.93, 2.39]
PROG9509 2010	57	196	49	197	20.7%	1.24 [0.79, 1.94]
Total (95% CI)		**1253**		**1254**	**100.0%**	**1.24 [1.01, 1.52]**
Total events	283		244			

Heterogeneity: Chi² = 5.54, df = 4 (P = 0.24); I² = 28%

Test for overall effect: Z = 2.06 (P = 0.04)



Late grade ≥2 urinary toxicity:
Conventional dose radiotherapy: 19.5%
High dose radiotherapy: 22.6%

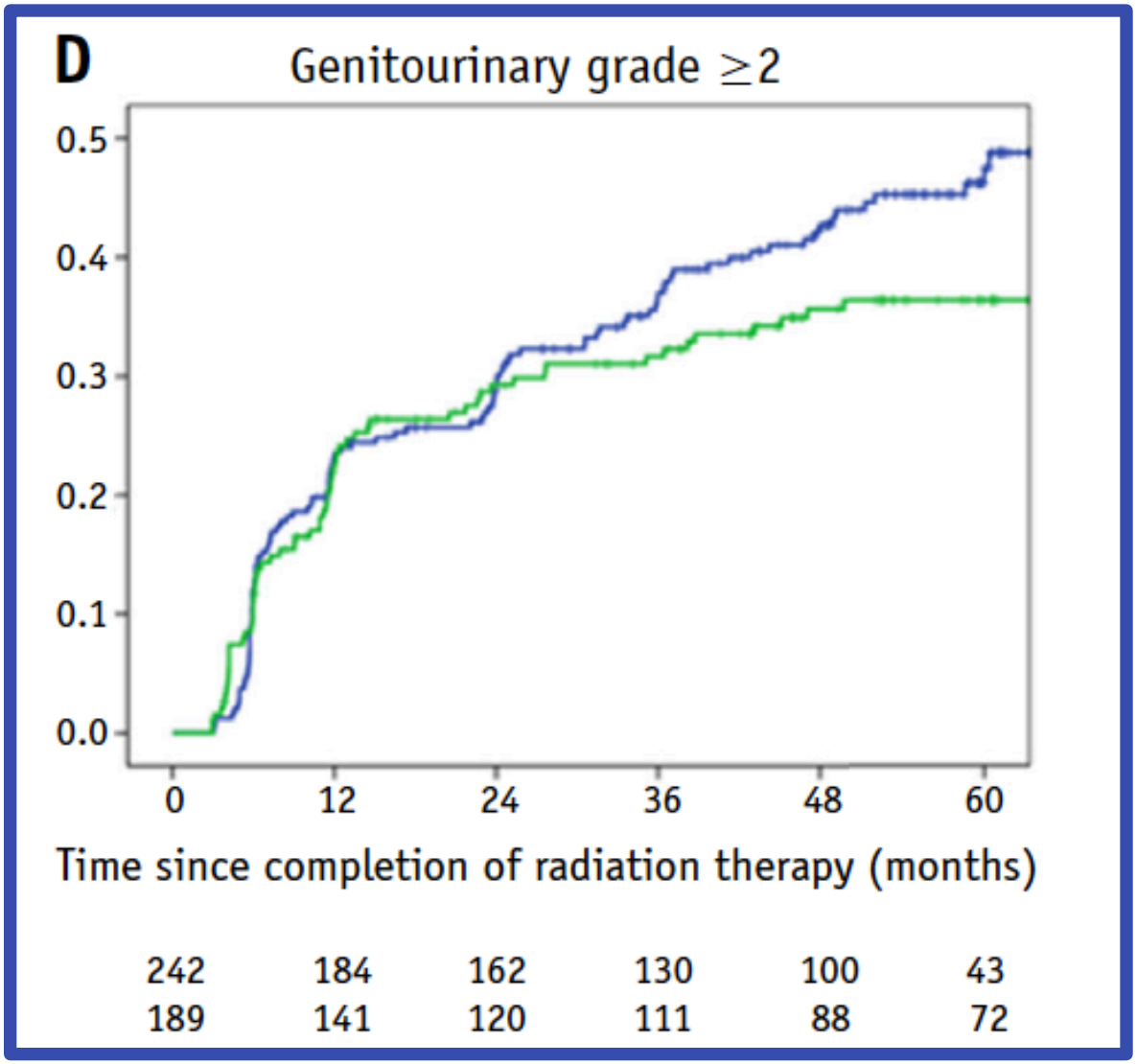
Hou et al, J Cancer Res Clin Oncol, 2014

Urinaire toxiciteit

Whole bladder	RTOG	UTHSCSA	Univ Miami	MSKCC
80 Gy	15%	-	-	-
75 Gy	25%	-	-	-
70 Gy	35%	25%	-	-
65 Gy	50%	-	25%	-
60-50 Gy	-	-	-	-
45 Gy	-	-	-	53% (V47)
40 Gy	-	-	50%	-

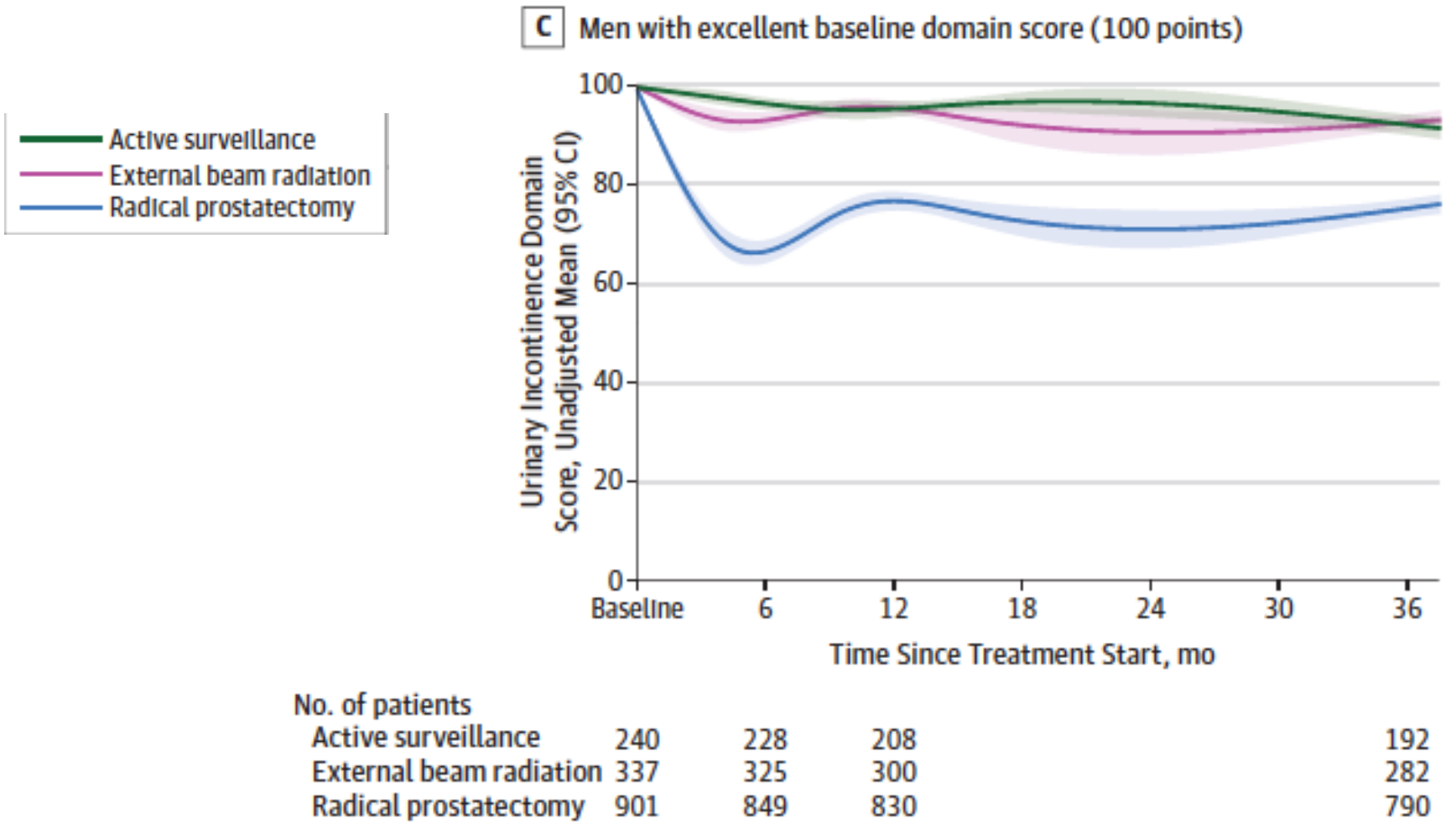
Swanson et al, Am J Clin Oncol, 2011

Rectale toxiciteit



Wortel et al, 2016. Int J Radiot Oncol Biol Phys

Patient reported outcome voor urinaire toxiciteit



Barocas et al, Jama, 2017

Erectiele dysfunctie

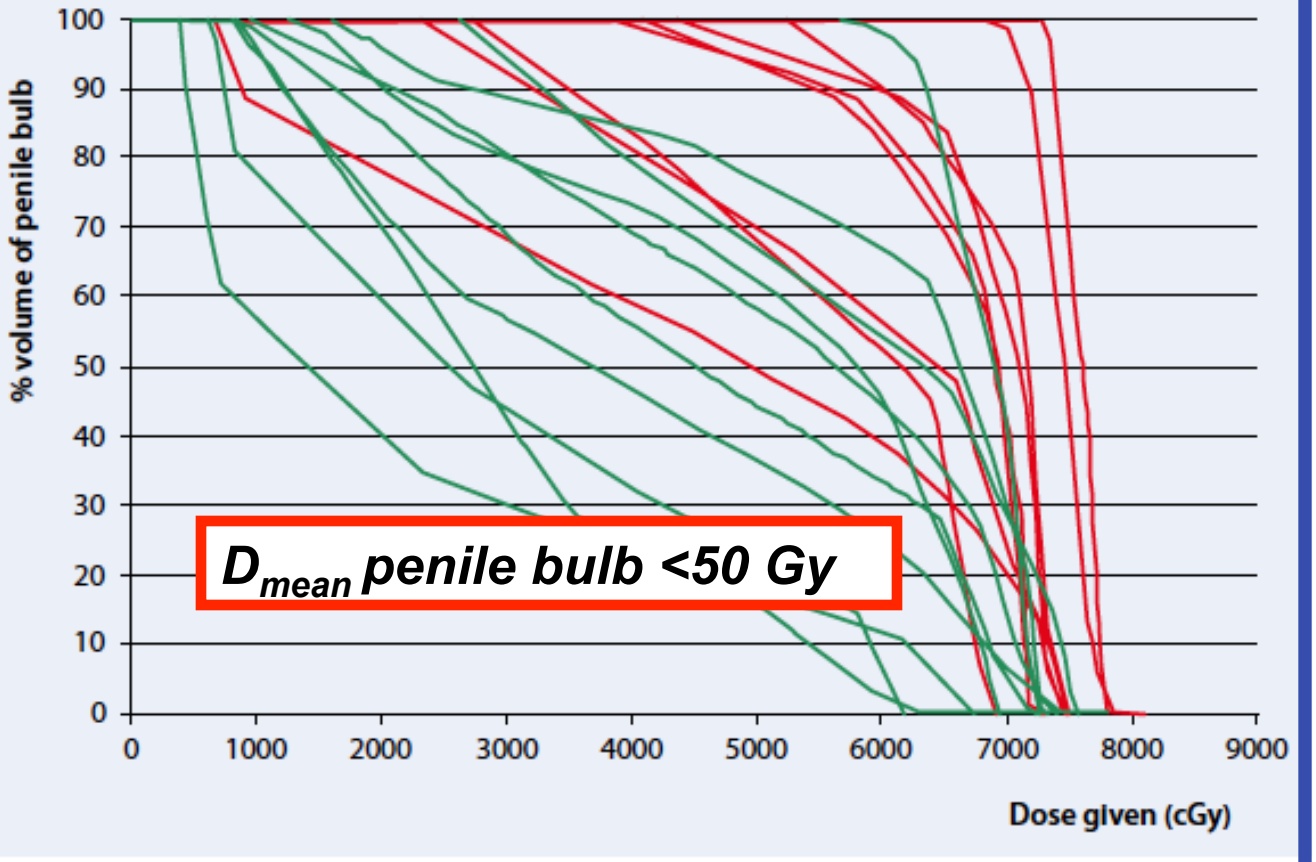
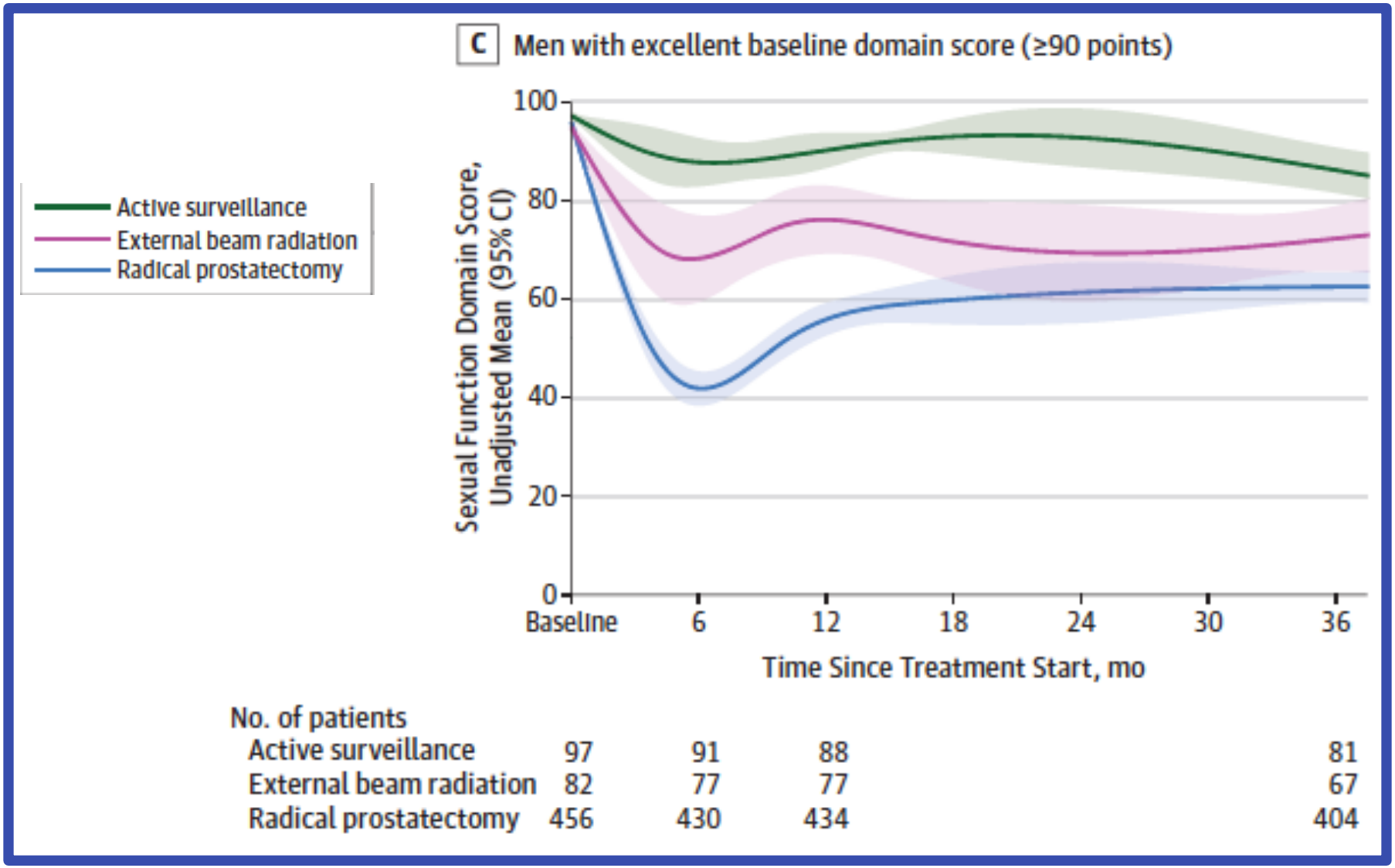


Fig. 1 ▲ Comparison of the dose–volume histograms of the penile bulb in potent (*green*) and impotent (*red*) patients

N= 19
3D-CRT to 72-76 Gy
No ADT

Magli et al, Strahlenther Onkol, 2012

Patient reported outcome voor erectiele dysfunctie



Barocas et al, Jama, 2017

Evolutie in de externe radiotherapie: *toekomst*

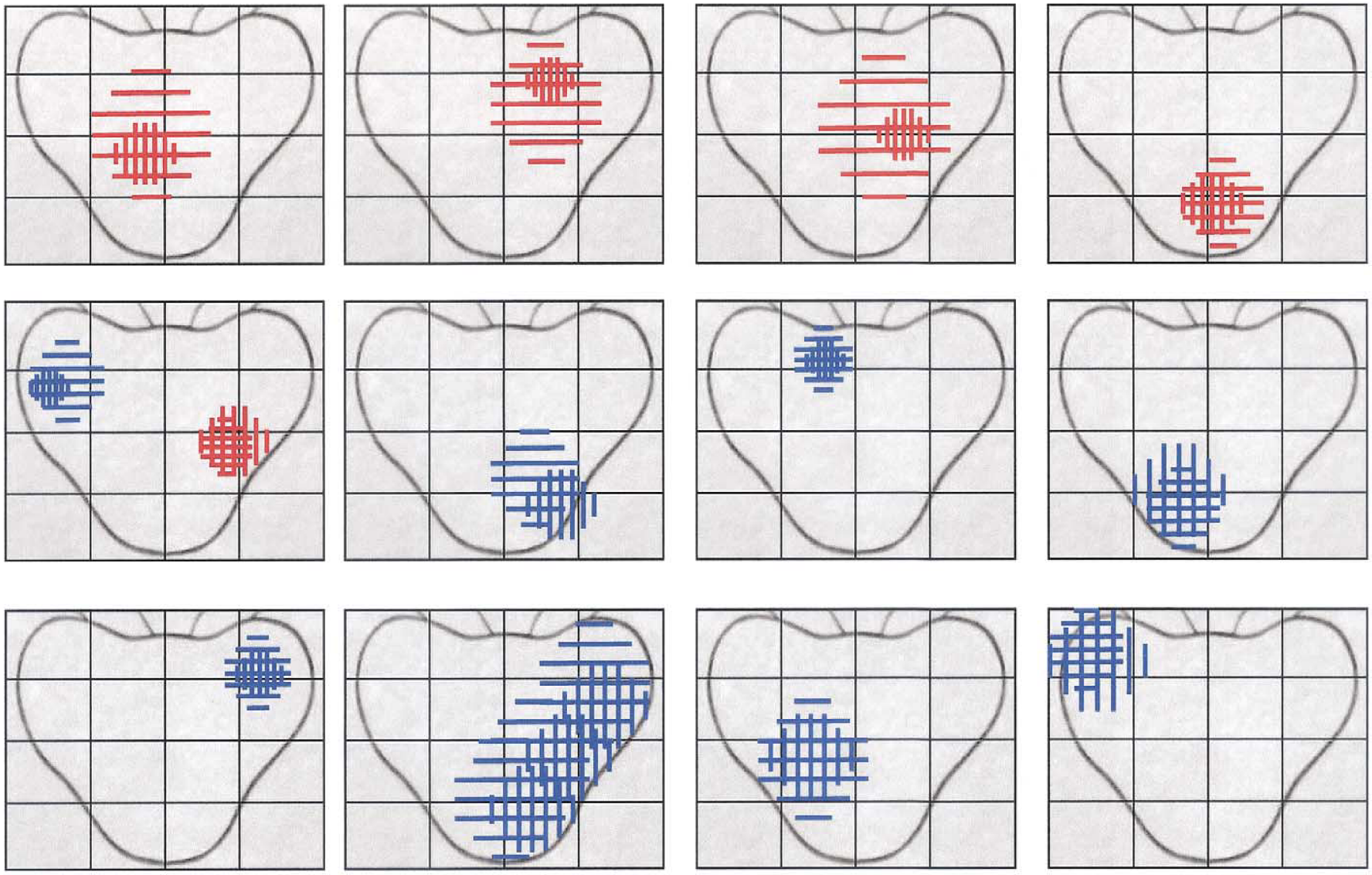
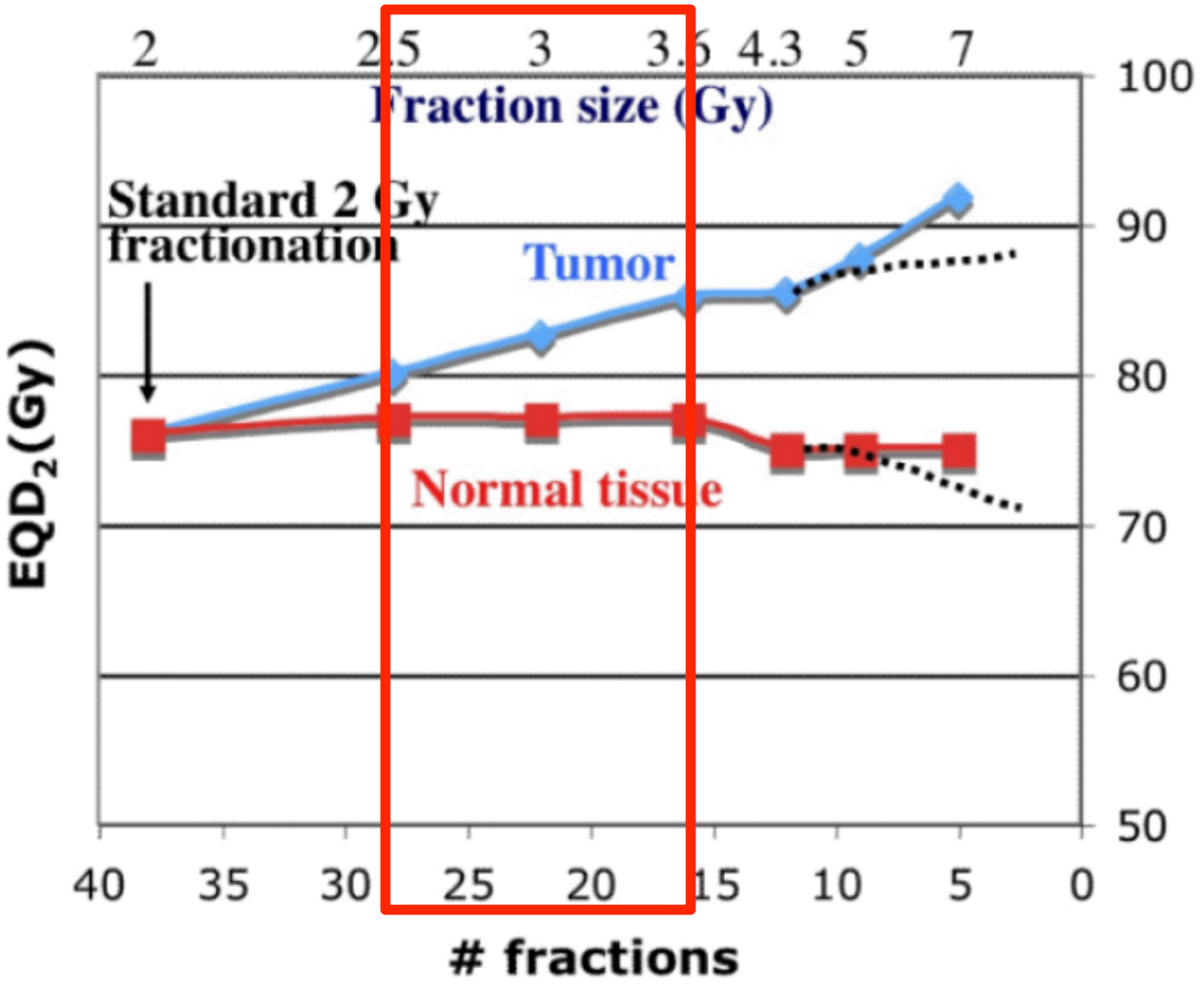


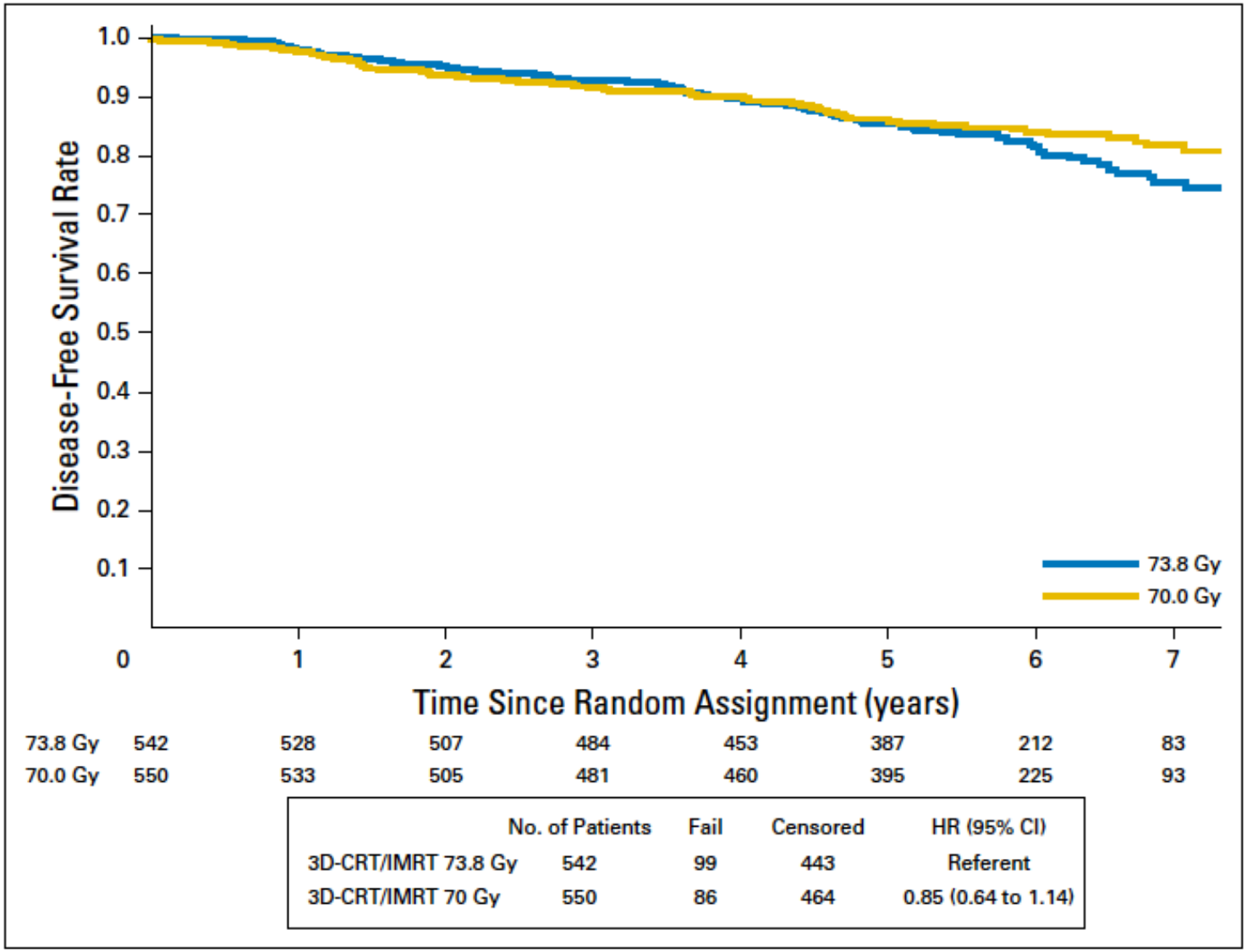
Fig. 3. Initial tumor extent (indicated with horizontal lines) and extent of disease progression at its identification (indicated with vertical lines) in 12 patients with local failure. Red lines indicate tumors with a complete response; blue lines indicate tumors with no or a partial response.



Ritter et al, Cancer J, 2009

Non inferiority trials of moderate hypofractionation in prostate cancer			
Sponsor	**Sample size**	**Risk group**	**Regimens tested**
RTOG 0415	1067	Low	73.8/1.8 Gy v 70/2.5 Gy
OCOG (Canada)	1204	Intermediate	78/2 Gy v 60/3 Gy
HYPRO (Dutch)	820	Int/High	78/2 Gy v 64.6/3.4 Gy (3 fractions/ week)
CHHIP (UK)	3216	Low/Intermediate/ High	74/2 Gy v 57/3 Gy v 60/3 Gy

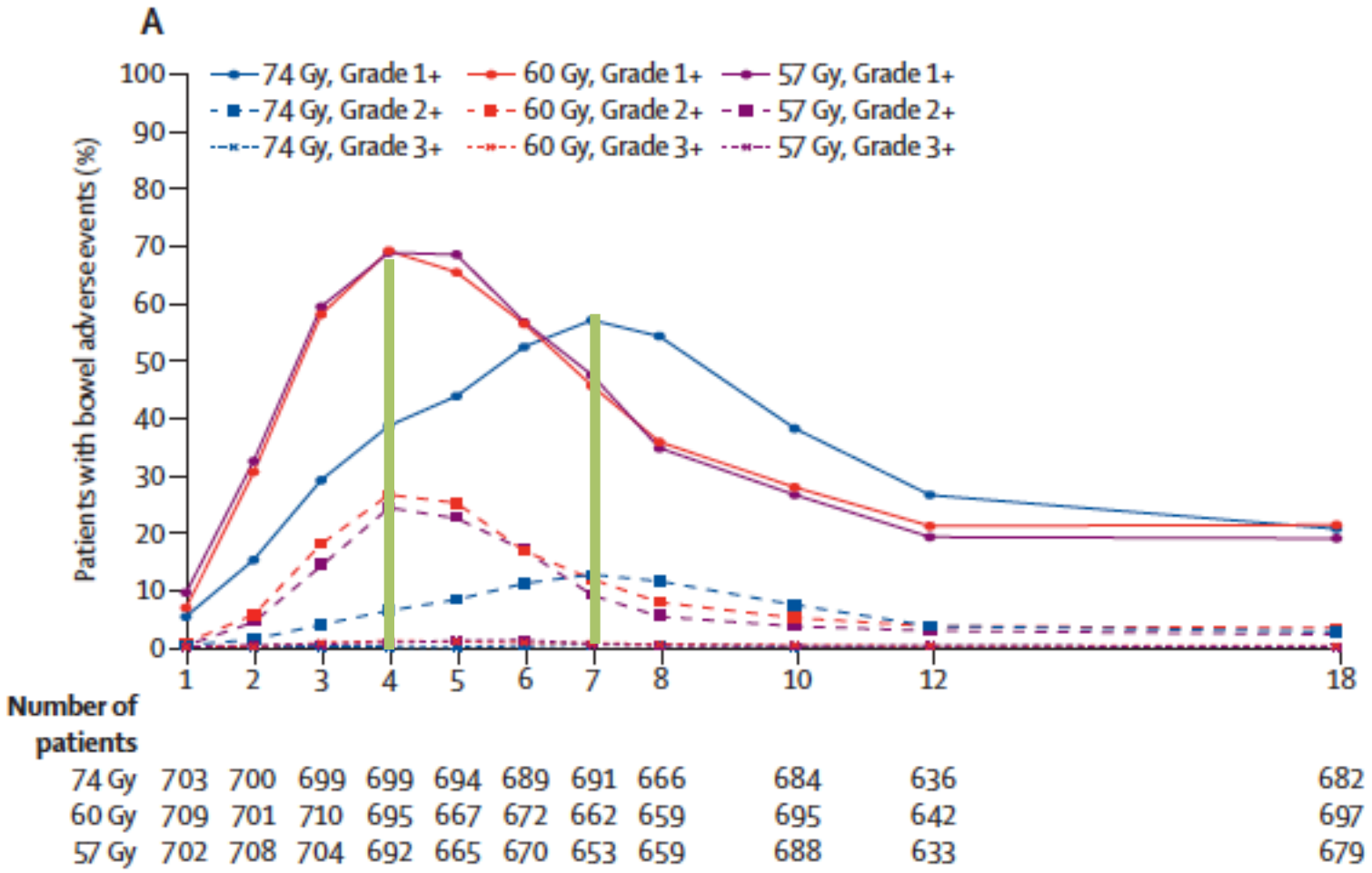
RTOG 0415 trial



Lee et al, JCO, 2016

CHHiP trial

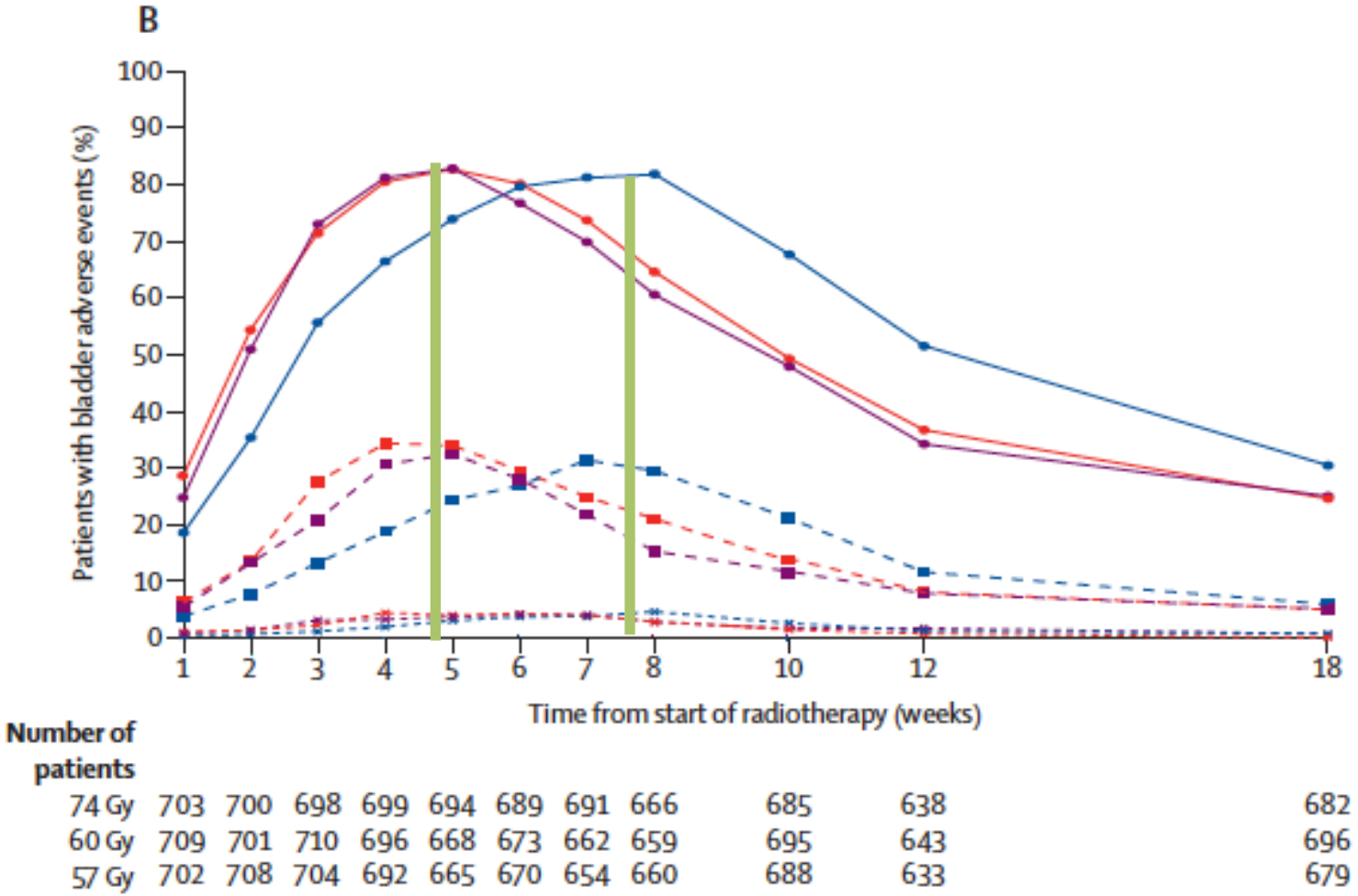
Acute Bowel toxicity



Dearnaley et al, Lancet Oncol, 2016

CHHiP trial

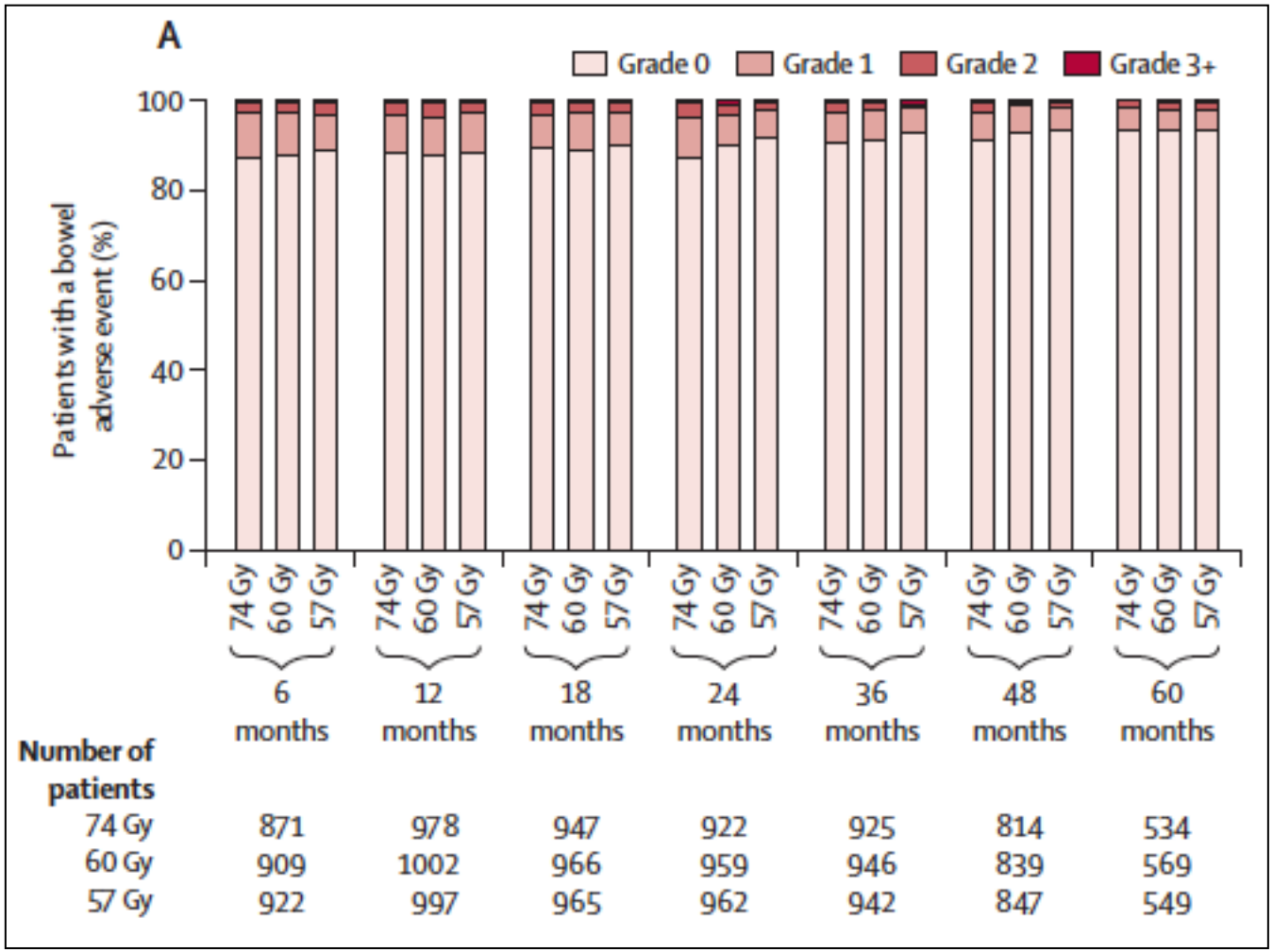
Acute Bladder toxicity



Dearnaley et al, Lancet Oncol, 2016

CHHiP trial

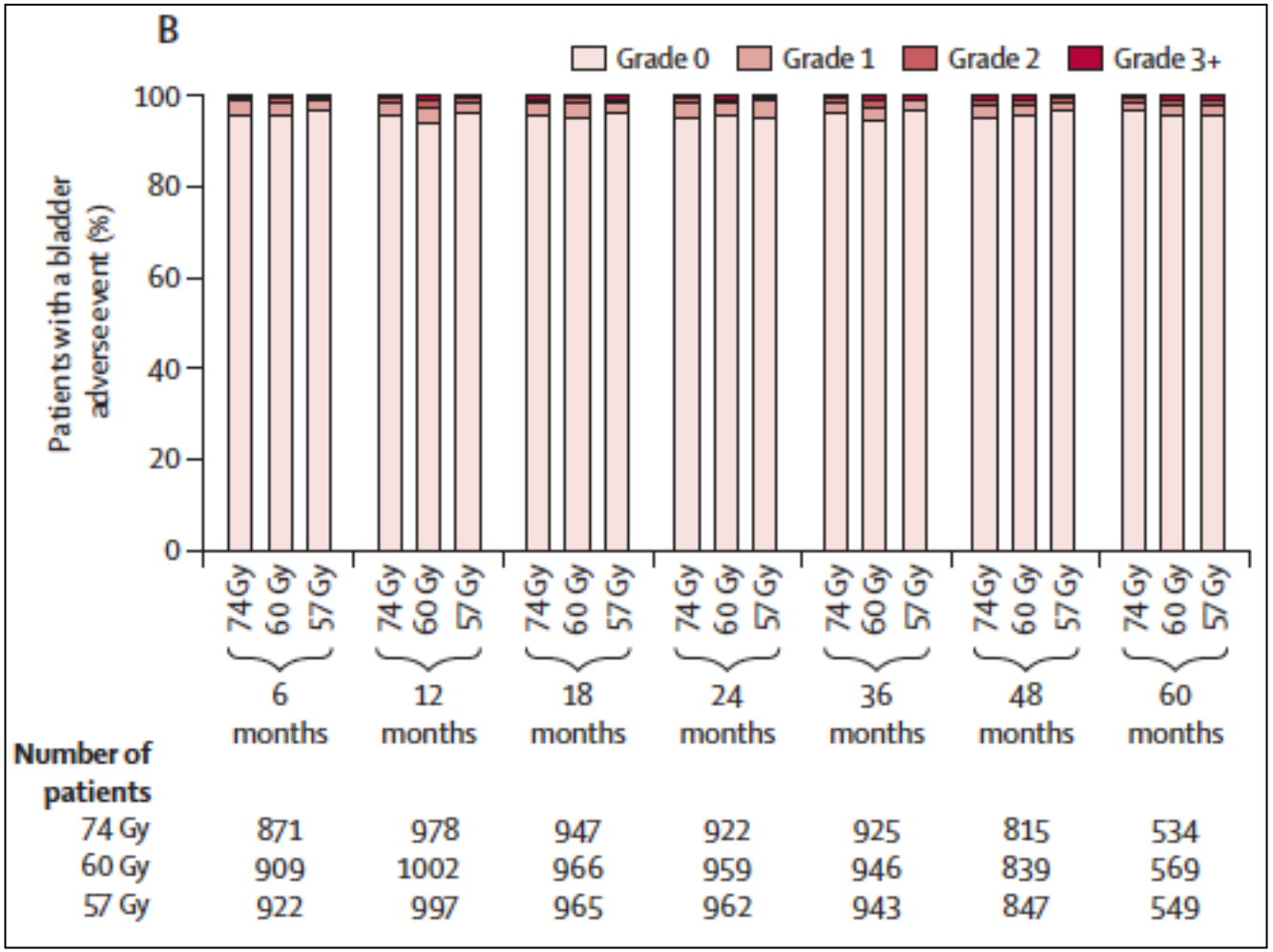
Late Bowel toxicity



Dearnaley et al, Lancet Oncol, 2016

CHHiP trial

Late Bladder toxicity



Dearnaley et al, Lancet Oncol, 2016

Extreme hypofractionation in prostate cancer	
Sponsor	**Regimens tested**
HYPO trial	78 Gy/39 F v 43.7 Gy/7 F
PACE trial	78 Gy/39 F v 36.25 Gy/5F

Conclusie

EUROPEAN UROLOGY 70 (2016) 21–30

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Prostate Cancer

Editorial by Martin Spahn, Alan Dal Pra, Daniel Aebersold and Bertrand Tombal on pp. 31–32 of this issue

Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis

Christopher J.D. Wallis [a,b,c], Refik Saskin [c,d], Richard Choo [e], Sender Herschorn [a,b], Ronald T. Kodama [a,b], Raj Satkunasivam [a,b], Prakesh S. Shah [c,f,g], Cyril Danjoux [h], Robert K. Nam [a,b,c,]*

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Risk category	Adjusted HR	p
Low risk	1.47 (1.19-1.83)	0.0004
Intermediate risk	1.50 (1.24-1.82)	<0.0001
High risk	1.88 (1.64-2.16)	<0.00001

Risk category	Adjusted HR	p
Low risk	1.70 (1.36-2.13)	<0.00001
Intermediate risk	1.80 (1.45-2.25)	<0.0001
High risk	1.83 (1.51-2.22)	0.0001

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European Association of Urology

Letter to the Editor

**Re: Christopher J.D. Wallis, Refik S
Choo, et al. Surgery Versus Radiot
Clinically-localized Prostate Cance
Review and Meta-analysis. Eur Ur**

Wallis et al compared the outcomes
patients treated with either surgery
prostate cancer [1]; however, a fla
flawed, no matter how large.

While nonrandomised compari
known confounders (eg, age, smok
to control for unknown confounder
RT are very different from those tre
residual confounding cannot be exc

Examining the data for low-risk
indicates that the analysis is not a fa
two well-matched groups. The
overall mortality for patients treat
surgery, with a hazard ratio of
interval, 1.19–1.83); however, low
almost never lethal within 10–15
survival of up to 99.9% even wi
treatment [2]. If mortality among R

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journal homepage: www.europeanurology.com

European Association of Urology

Letter to the Editor

Re: Christopher J.D. Wallis, Refik Saskin, Richard Choo, et al. Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol 2016;70:21–30

It is not without deep concern about the overinterpretation and misuse of data that we have read the systematic review and meta-analysis published by Wallis and colleagues on the comparative effectiveness of surgery and radiotherapy for the treatment of prostate cancer [1]. While the analysis of large databases can provide insights in several settings, they usually carry intrinsic biases that do not allow for accurate comparisons among competitive interventions [2]. Rather than providing arguments for treatment guidance and selection, such analyses merely demonstrate the biases intrinsic to the databases. Giordano and colleagues, for example, reported that patients undergoing radical prostatectomy (RP) included in the Surveillance Epidemiology and End Results (SEER) database had higher survival rates than a matched population *without* cancer. Surprisingly enough, RP had at least as much effect on deaths from diseases like pneumonia and cardiovascular disease as it had on deaths from prostate cancer, showing the tremendous bias in the operated population. Last but not least, these results remained unchanged even after statistical adjustment for all measured confounders or use of propensity score analysis [3].

That being said, it is commonly accepted that meta-analyses provide the highest level of evidence, but this is true only for meta-analyses of high-quality randomized trials. Meta-analyzing *biased* studies provides only a biased summary and does not increase the level of evidence. In this review, the authors evaluated the quality of the included studies using the Newcastle Ottawa Scale, which was designed to score case–control studies and was also shown to have low reliability between individual reviewers [4]. The authors did not mention clearly that the studies synthesized provided level 3 evidence; the level of evidence provided by the meta-analysis should be considered.

Furthermore, we are concerned by the fact that publishing biased research can mislead not only health care professionals but also, and more importantly, patients and their families. This is even more true in the setting of prostate cancer, given its prevalence. Authors should be quite aware that strong messages like the one in the patient summary of the paper by Wallace et al—"we demonstrated consistently higher mortality for patients treated with radiotherapy rather than surgery"—may be immediately echoed by media and reported by generalist Web sites without mention of the potential for bias. This would ultimately generate the (false) impression that the final word has been said on this topic. The public should be warned when treatment recommendations are not based on level 1 evidence, and this should be reflected in the abstract and the patient summary.

As clinicians involved in prostate cancer patient care, we deeply believe that improving our knowledge about the comparative effectiveness of and the selection criteria for surgery or radiotherapy is a major goal. But such a goal should be reached by the performance of high-quality and evidence-based research such as randomized trials or randomized registries rather than by repeating or compiling, over and over, the same biased studies. Only then will we provide patients with unbiased tools for shared decision making.

Conflicts of interest: The authors have nothing to disclose.

References

[1] Wallis CJ, Saskin R, Choo R, et al. Surgery versus radiotherapy for clinically-localized prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;70:21–30.

[2] Abdollah F, Sun M, Thuret R, et al. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988–2006. Eur Urol 2011;59:88–95.

[3] Giordano SH, Kuo Y-F, Duan Z, Hortobagyi GN, Freeman J, Goodwin JS. Limits of observational data in determining outcomes from cancer therapy. Cancer 2008;112:2456–66.

MAAR?


Study results included
Patients treated with
or salvage therapies
studies irrespective
tive. We included
of radiotherapy. In
Surgery Versus Radiotherapy for Clinically-localized Prostate Cancer: A Systematic Review and Meta-analysis


"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."