NOSCM
NEW ORLEANS SUMMER CANCER MEETING

UCLA Jonsson Comprehensive Cancer Center

Novel Radiotherapy Approaches in Prostate Cancer

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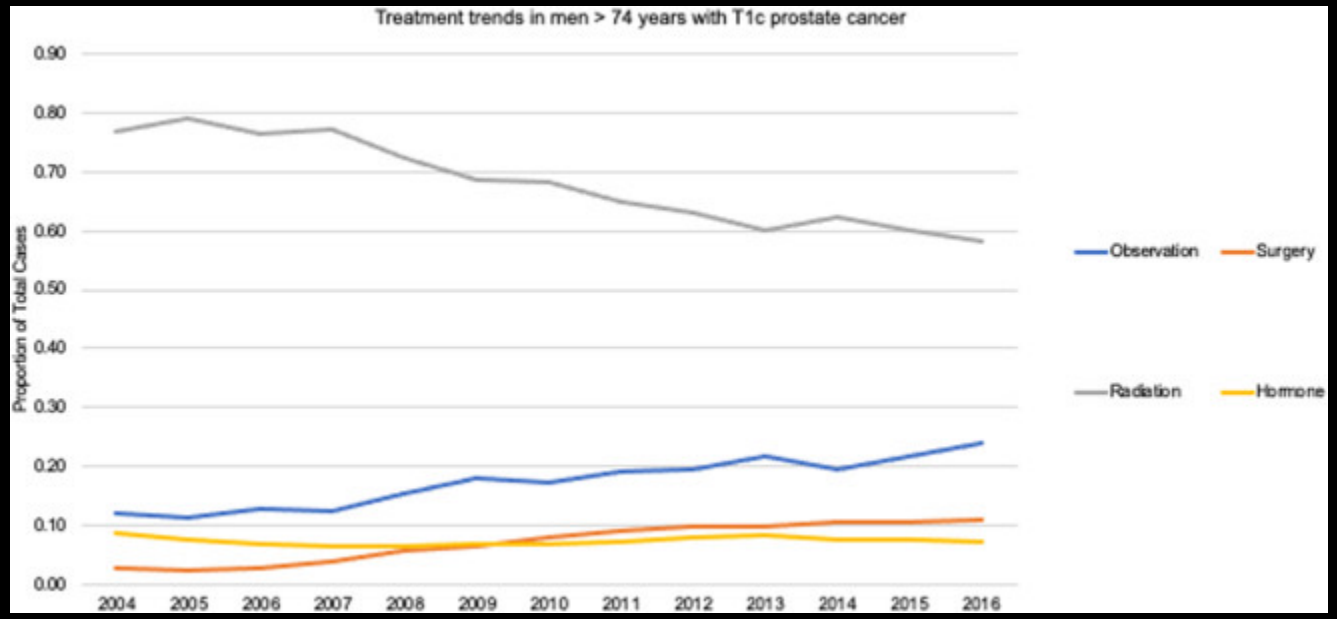
7/14/23

Outline

- **Age and Prostate Cancer: Trends and Relevance for ADT**
- **SBRT Overview**
- **Summary**

Trends in Older Individuals

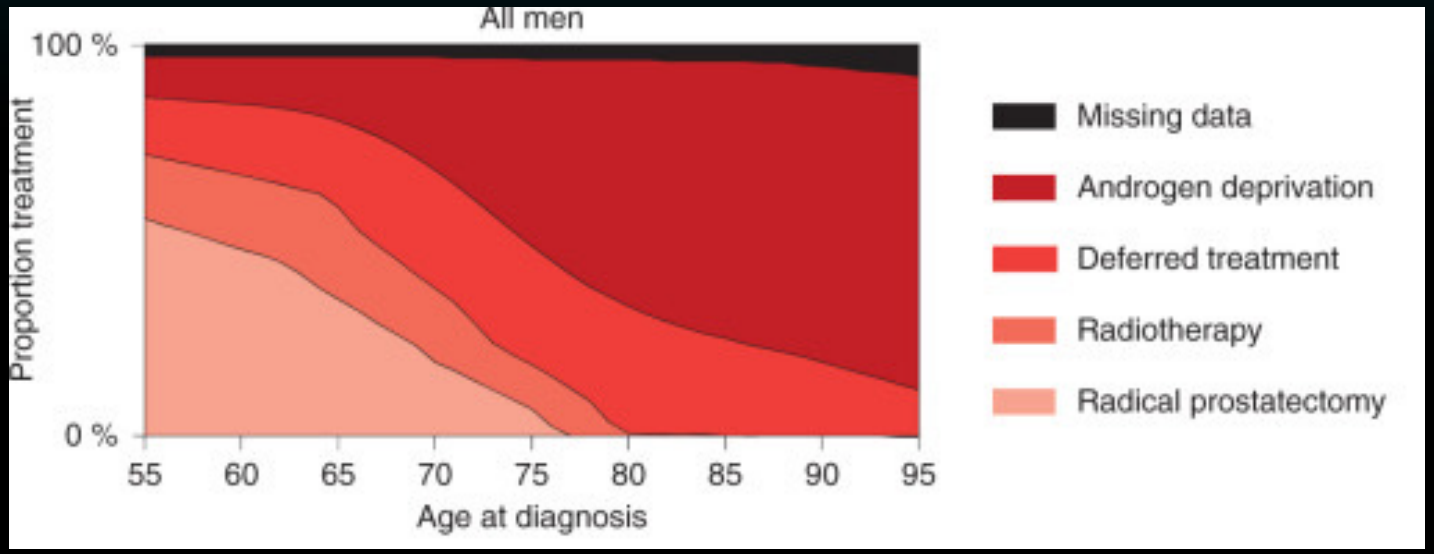
- NCDB study for patients with cT1c disease ≥75 years old from 2004-2016
- Trends indicate a significant decline in radiation and rise in observation and surgery



Clin Genitourin Cancer. 2023 Feb;21(1):16-23.

Is Age An Adverse Prognostic Factor?

- 121,392 Swedish men aged 55–95, of which 15,893 received RT

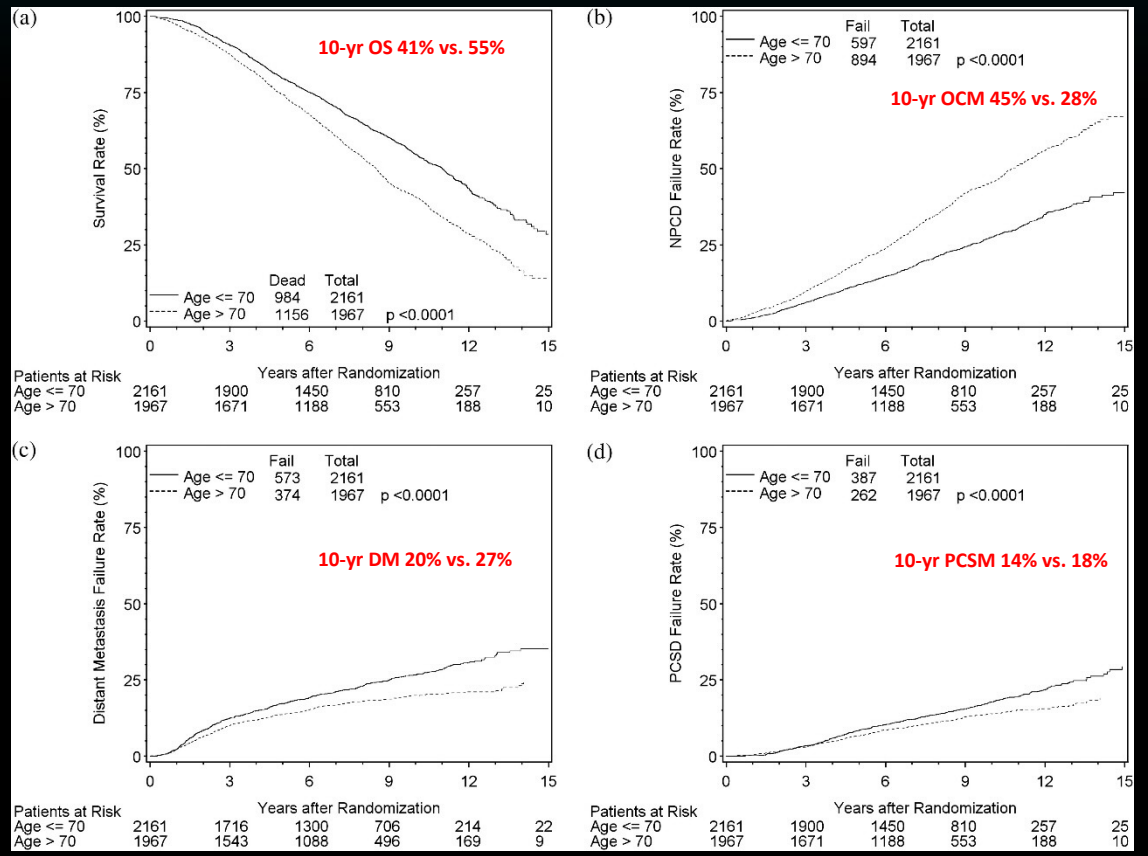


- There was no association between age and risk of prostate cancer death after radiotherapy: HR 1.03 (95% CI: 0.81–1.30) among men age 55–59 and HR 1.08 (95% CI: 0.76–1.53) among men above 75 (reference group age men 60-64).

Ann Oncol. 2018;29(2):377-85.

Prognostic Impact of Age

- Meta-analysis of four NRG/RTOG trials (n=1967 >70, of 4128 patients)



Int J Radiat Oncol Biol Phys. 2011 Dec 1;81(5):1293-301.

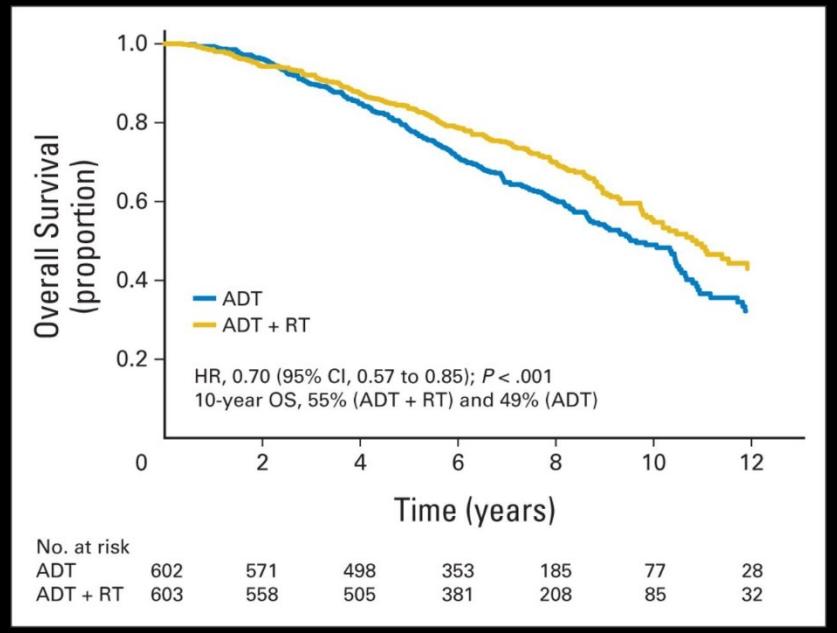
	Number of patients	Hazard ratio (95% CI)	p value	$p_{interaction}$
ADT use				
NCCN risk group	..	..	..	0·091
High	1647	0·72 (0·64–0·82)	<0·0001	..
Intermediate	2427	0·84 (0·75–0·93)	0·0014	..
Radiotherapy dose	..	..	..	0·96
High (≥74 Gy)	1018	0·83 (0·68–1·01)	0·063	..
Low (<74 Gy)	4118	0·83 (0·76–0·89)	<0·0001	..
Age, years	..	..	..	0·088
<70	2419	0·77 (0·69–0·87)	<0·0001	..
≥70	2716	0·88 (0·80–0·97)	0·0080	..
Neoadjuvant ADT extension*				
NCCN risk group	..	..	..	0·92
High	848	0·95 (0·78–1·16)	0·63	..
Intermediate	1356	0·97 (0·81–1·18)	0·79	..
Age, years	..	..	..	0·56
<70	1118	0·98 (0·80–1·21)	0·88	..
≥70	1095	0·91 (0·75–1·09)	0·29	..
Adjuvant ADT prolongation				
NCCN risk group	..	..	..	0·72
High	2688	0·85 (0·77–0·93)	0·0005	..
Intermediate	969	0·81 (0·69–0·94)	0·0058	..
Radiotherapy dose	..	..	..	0·41
High (≥74 Gy)	856	0·90 (0·76–1·06)	0·20	..
Low (<74 Gy)	2918	0·83 (0·76–0·91)	0·0004	..
Age, years	..	..	..	0·72
<70	1841	0·83 (0·74–0·94)	0·0019	..
≥70	1930	0·85 (0·76–0·94)	0·0024	..

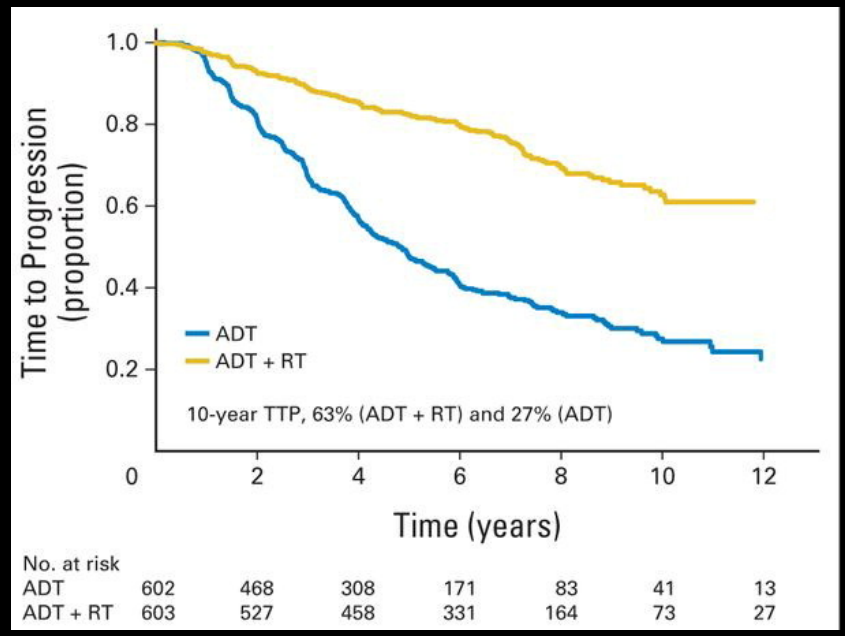
- Large individual patient data meta-analysis of 12 trials evaluating various intensification strategies with RT-based definitive therapy
- The impact of adding ADT or prolonging adjuvant ADT does not significantly vary with age

Lancet Oncol. 2022 Feb;23(2):304-316.

NCIC PR.3/MRC Trial

- Eligibility: T3-4 or T1-2 and PSA>40 or GS 8-10+ PSA 20-40
- 64-69 Gy with lifelong ADT vs. ADT alone
- 78% were aged 65 or older

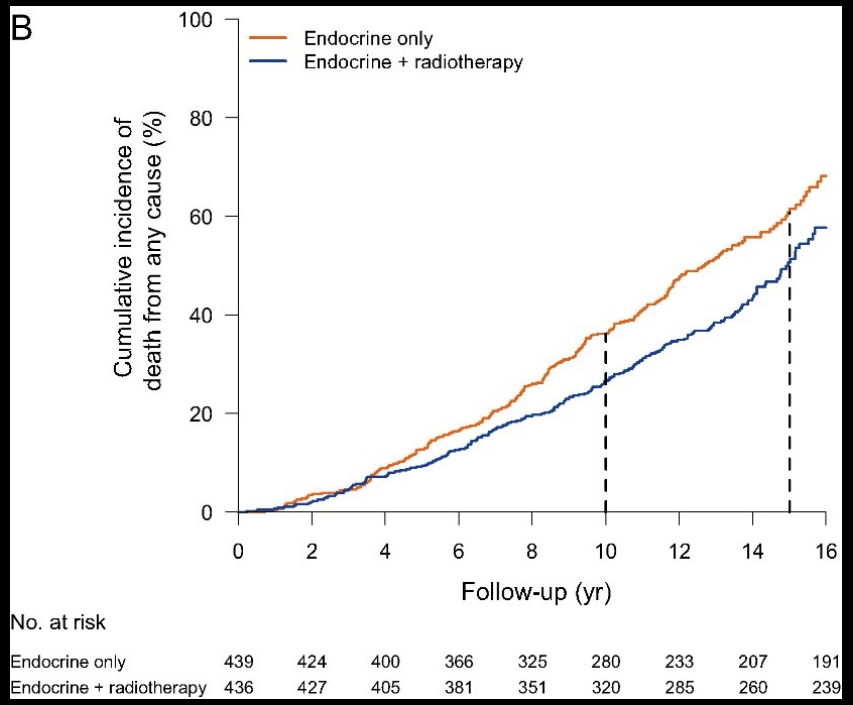


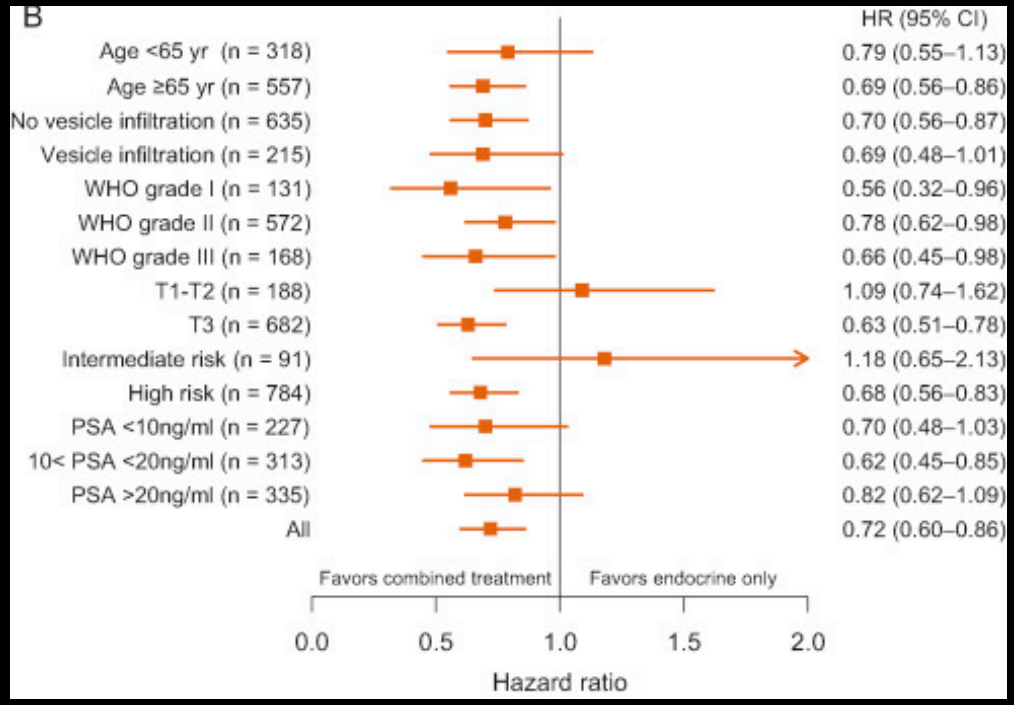


Lancet. 2011 Dec 17;378(9809):2104-11, *J Clin Oncol*. 2015 Jul 1;33(19):2143-50.

SPCG-07

- Eligibility: <75 year, T1-2 grade II or T3 with PSA ≤70
- 70-78 Gy with lifelong ADT vs. ADT alone
- Median age 66.7





Lancet. 2009 Jan 24;373(9660):301-8., *Eur Urol*. 2016 Oct;70(4):684-691.

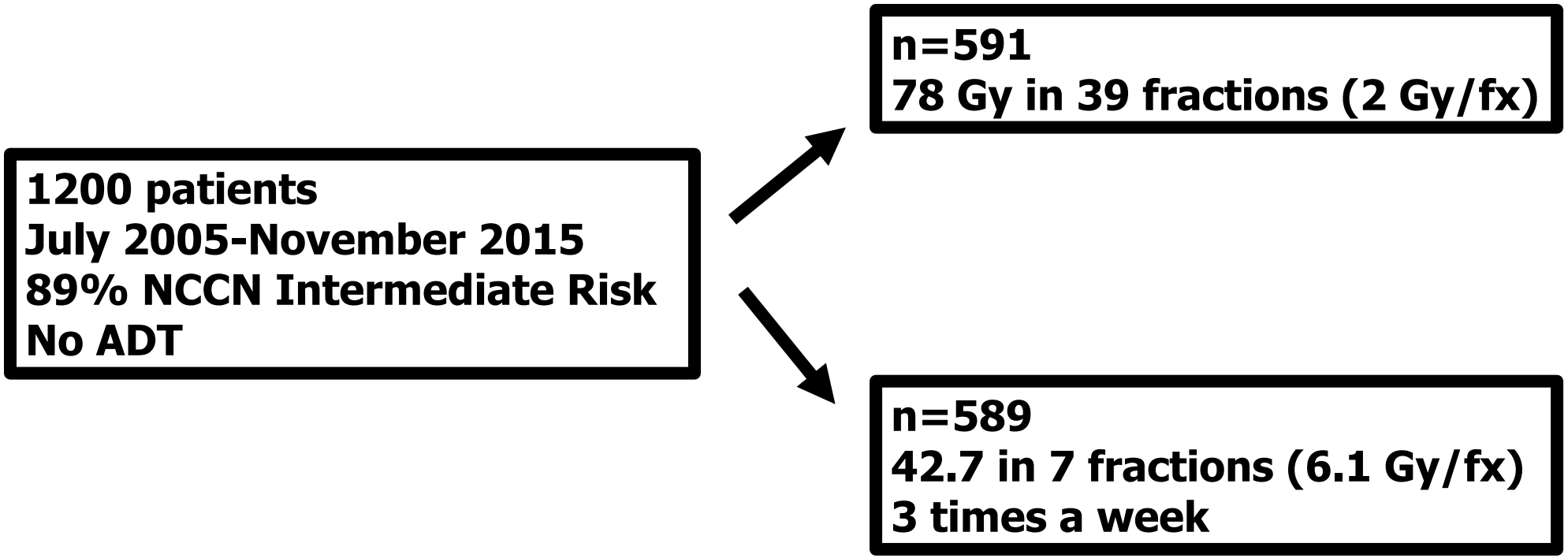
NCCN Guidelines

Table 1: Below are examples of regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions, voiding symptoms and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.

√ indicates an appropriate regimen option if radiation therapy is given. See PROS-3, PROS-4, PROS-5, PROS-6, PROS-7, PROS-9, PROS-13, and PROS-G for other recommendations, including recommendations for neoadjuvant/concomitant/adjuvant ADT.

Regimen	Preferred Dose/Fractionation	NCCN Risk Group (✓ indicates an appropriate regimen option if radiation therapy is given)					
		Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High[c]	Regional N1	Low Volume M1[a]
EBRT							
Moderate Hypofractionation (Preferred)	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓	✓	
	2.75 Gy x 20 fx						✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓	✓	
Ultra-Hypofractionation	7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	✓	✓	✓	✓		
	6 Gy x 6 fx						✓

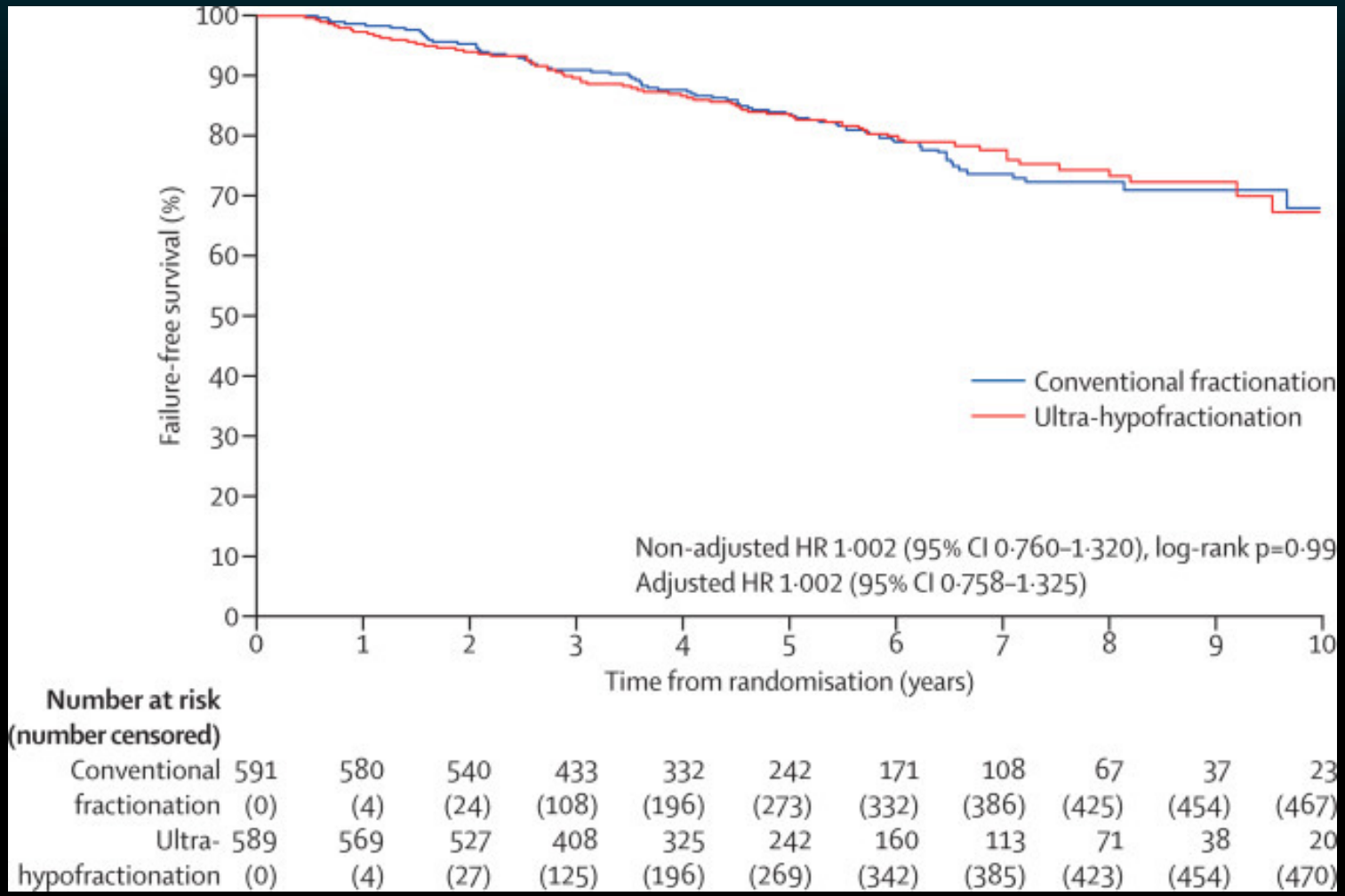
HYPO-RT-PC



Originally a superiority trial, but then re-designed as a non-inferiority trial (assuming α/β=2.95)
20% received IMRT

Lancet. 2019 Aug 3;394(10196):385-395

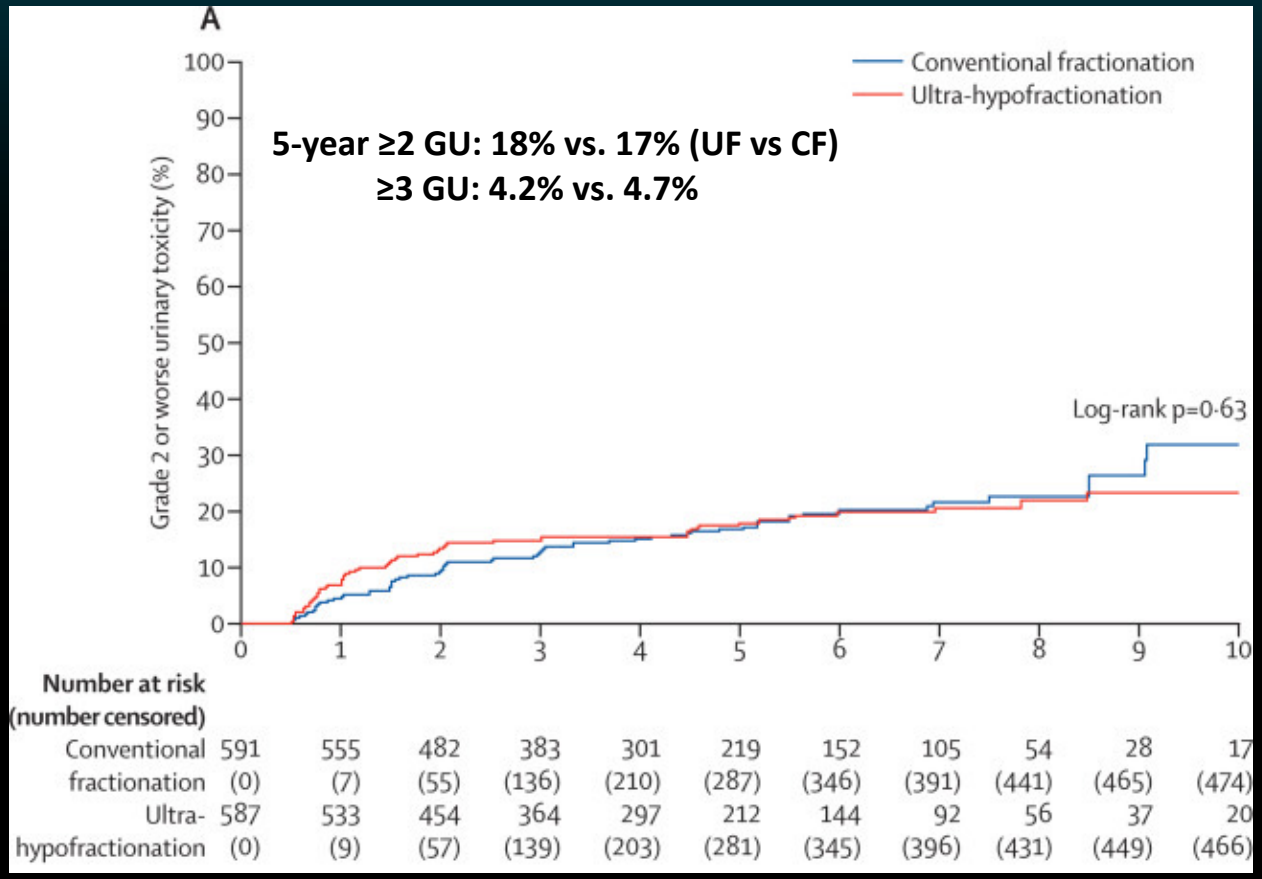
HYPO-RT-PC

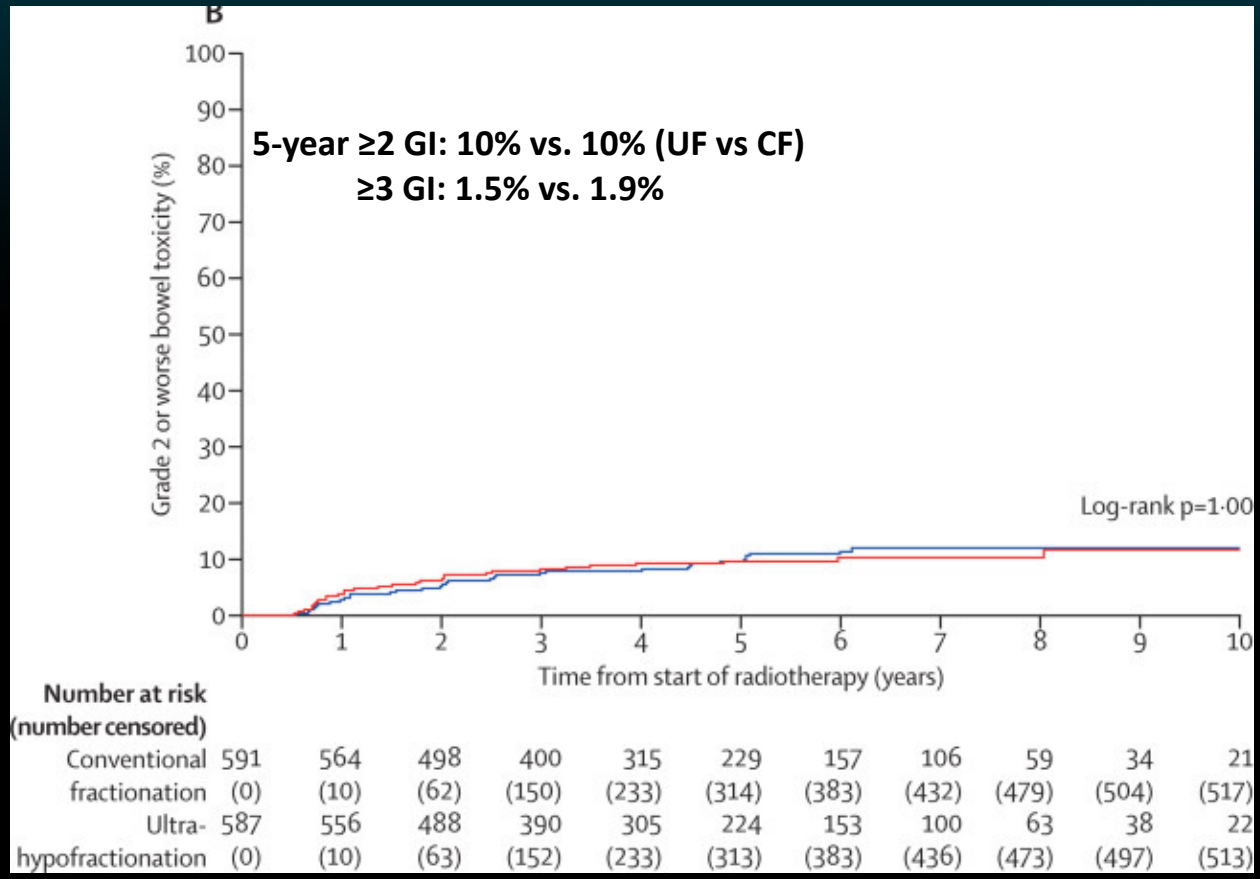


Median followup 5 years
5-year FFS was 84% in both arms
5-year OS 96% vs 94%, w/ 1-2% PCSM

Oncologically non-inferior!

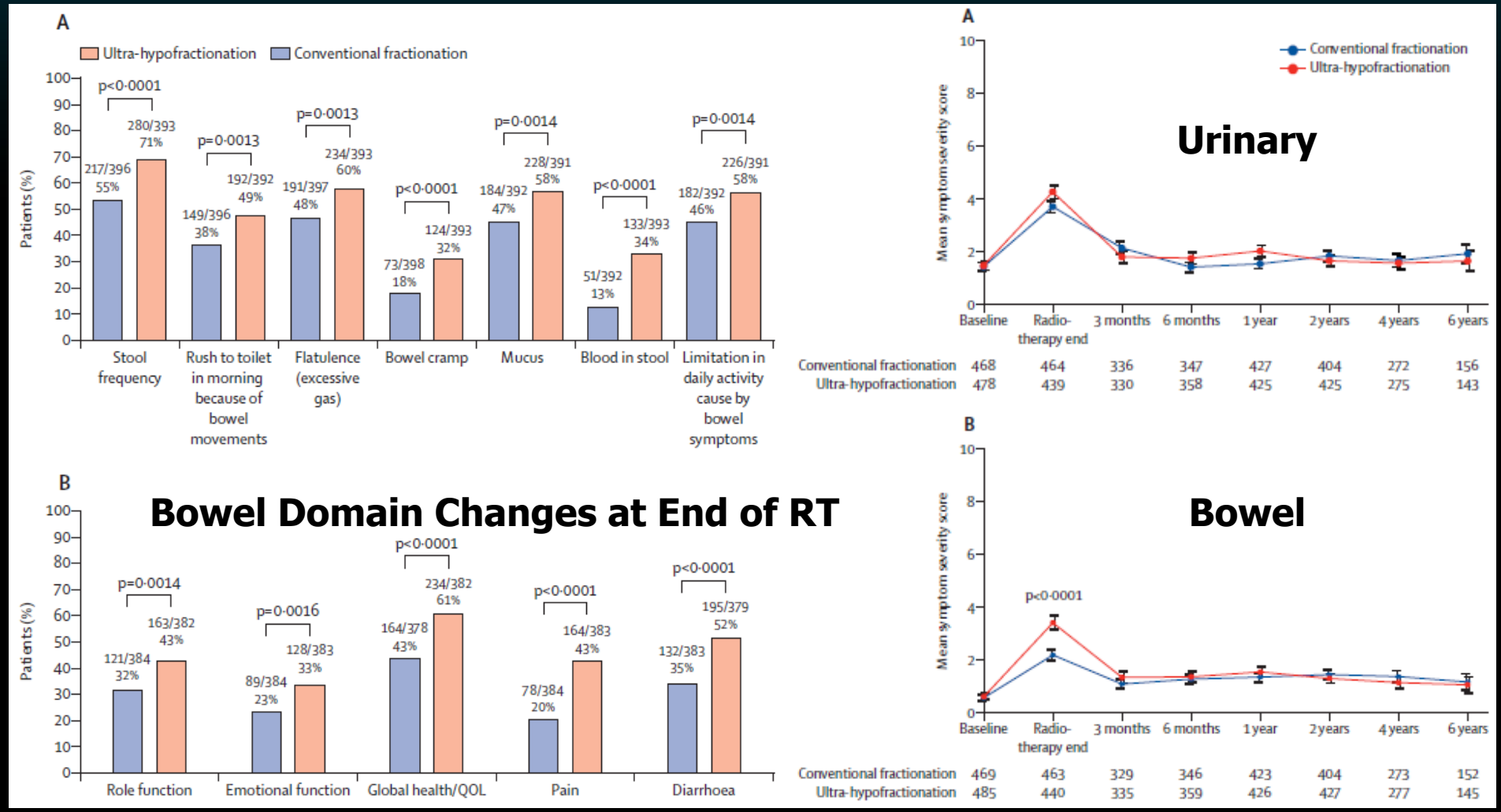
HYPO-RT-PC





- Acute RTOG grade ≥2 GU toxicity favors CF arm (28% vs. 23%, p=0.057)
- Prevalence of late RTOG grade ≥2 GU toxicity at 1-year favors the CF arm (6% vs 2%, p=0.0037), but no differences manifest at 5 years (5% vs 5%), or for GI toxicity

Patient-Reported Outcomes



Lancet Oncol. 2021 Jan 11;S1470-2045(20)30581-7

PACE-B

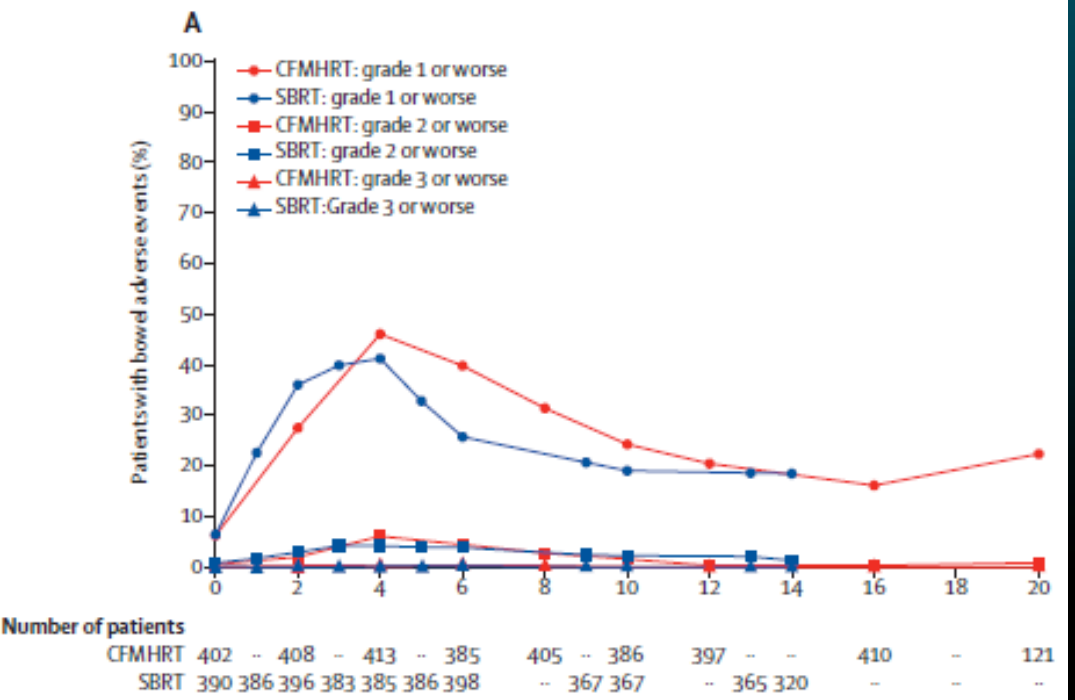
874 patients
August 2012-January 2018
90% NCCN Intermediate Risk (GG1 and GG 2)
No ADT

n=415
78 Gy in 39 fractions (2 Gy/fx; 31%)
62 Gy in 20 fractions (3.1 Gy/fx; (69%)

n=432
36.25 Gy in 5 fractions (7.25 Gy/fx)
20.7% consecutive days

Designed as a non-inferiority trial assuming (assuming $\alpha/\beta=3$)
58.3% VMAT 41% stereotactic radiosurgery

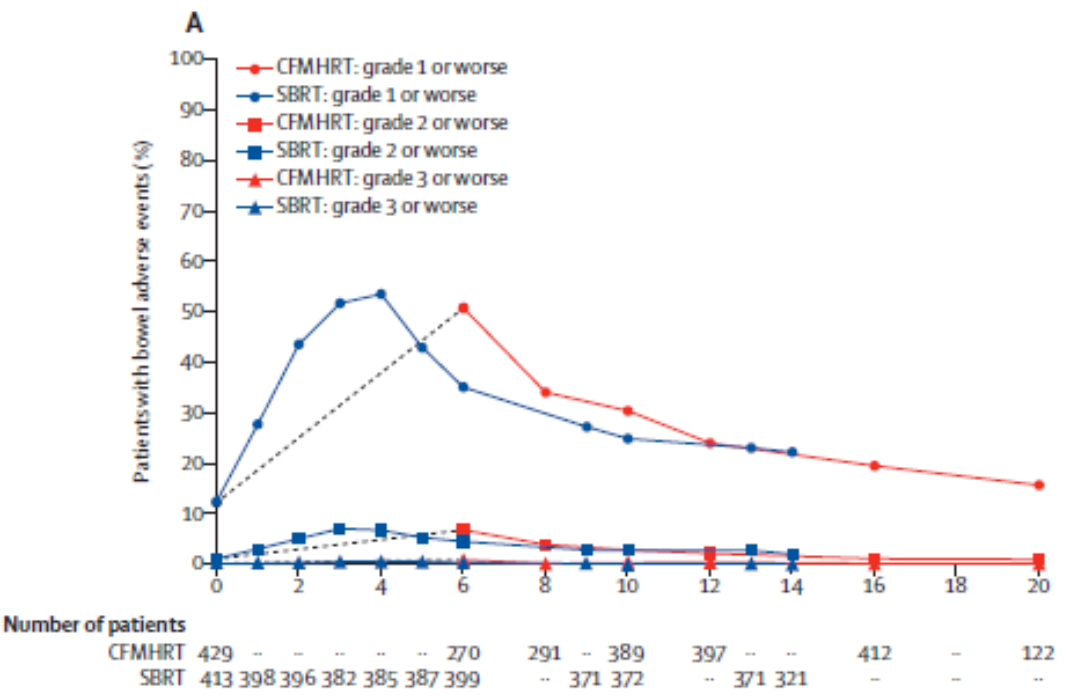
Lancet Oncol. 2019 Nov;20(11):1531-1543

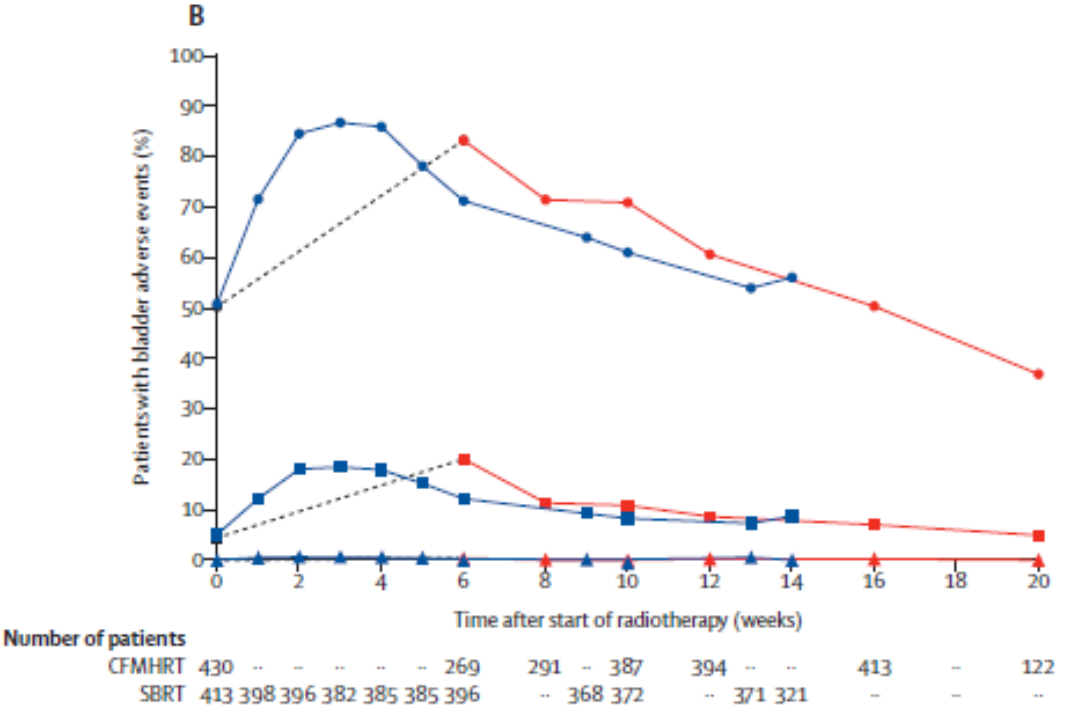


RTOG GI	CF/Mod HF	SBRT
1	61%	53%
2	11%	10%
3	1%	<1%
4	0.0%	0.0%

RTOG GU	CF/Mod HF	SBRT
1	59%	57%
2	26%	21%
3	1%	2%
4	<1%	<1%

- No significant difference in RTOG GU or GI toxicity

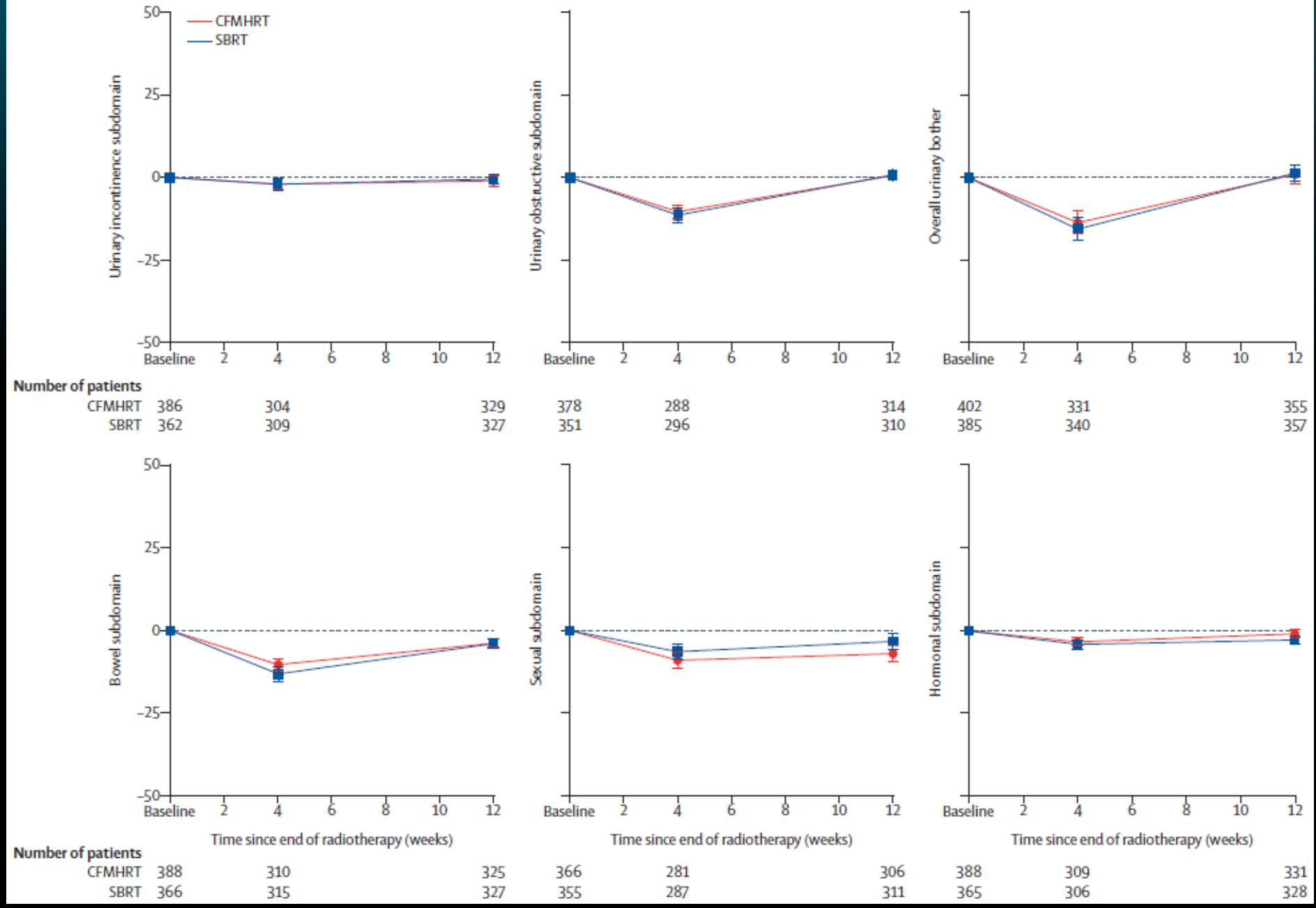




Worst CTCAE GI	CF/Mod HF	SBRT
0	42.1%	26.3%
1	49.5%	58.1%
2	**7.7%**	**14.9%**
3	0.7%	0.7%
4	0.0%	0.0%

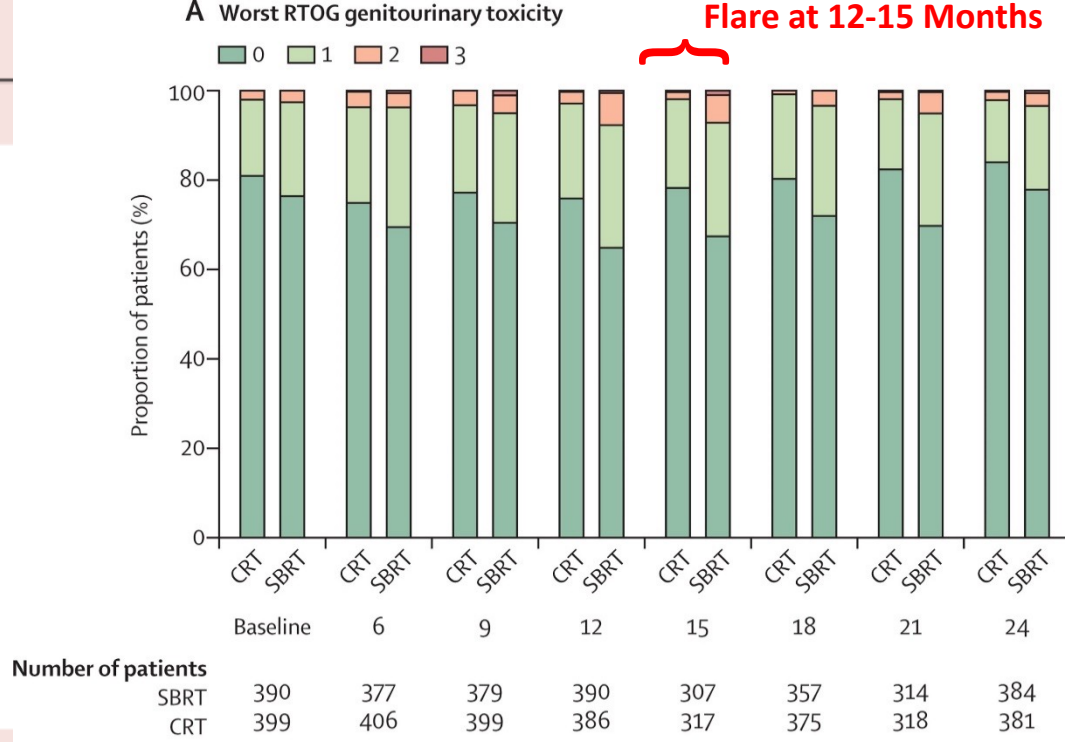
Worst CTCAE GU	CF/Mod HF	SBRT
0	11.2%	3.6%
1	65.8%	65.5%
2	22.3%	29.2%
3	0.7%	1.7%
4	0	0

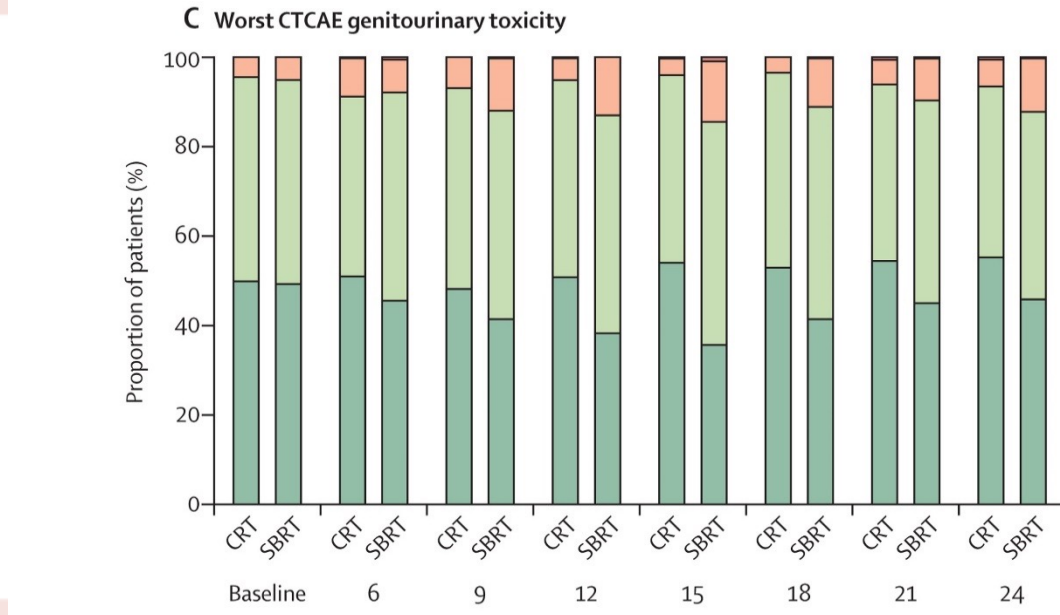
- Significantly greater "worst" acute CTCAE GI grade 2 toxicity, drive by more grade 2 diarrhea (6.5% vs. 1.4%) and proctitis (5.7% vs. 2.5%)



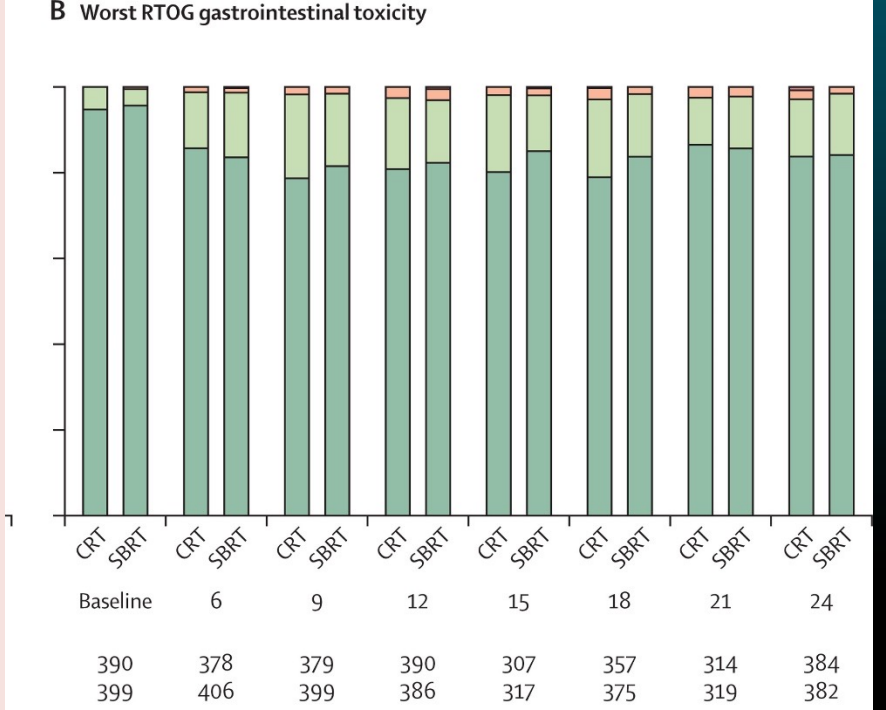
No differences in patient-reported outcomes at any point acutely

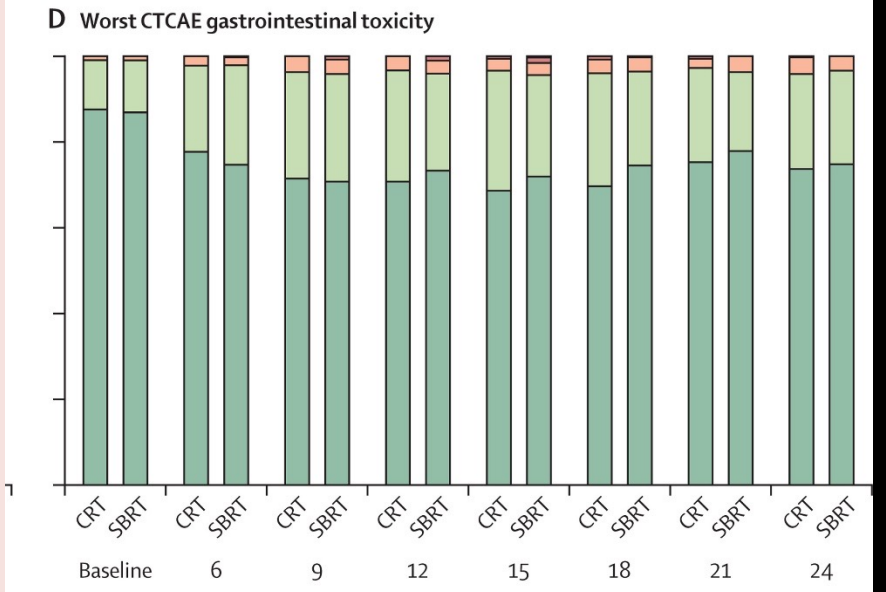
	CRT (n=430)	SBRT (n=414)	p value*
Genitourinary RTOG			
0	320 (84%)	299 (78%)	..
1	53 (14%)	72 (19%)	..
2	7 (2%)	11 (3%)	..
3	1 (<1%)	2 (<1%)	..
4	0	0	..
5	0	0	..
Missing data	49	30	..
Genitourinary RTOG grade ≥2			0·39
Yes	8 (2%)	13 (3%)	..
No	373 (98%)	371 (97%)	..
Genitourinary CTCAE			
0	211 (55%)	176 (46%)	..
1	146 (38%)	161 (42%)	..
2	23 (6%)	46 (12%)	..
3	2 (<1%)	1 (<1%)	..
4	0	0	..
5	0	0	..
Missing	48	30	..
Genitourinary CTCAE grade ≥2			0·010
Yes	25 (7%)	47 (12%)	..
No	357 (93%)	337 (88%)	..

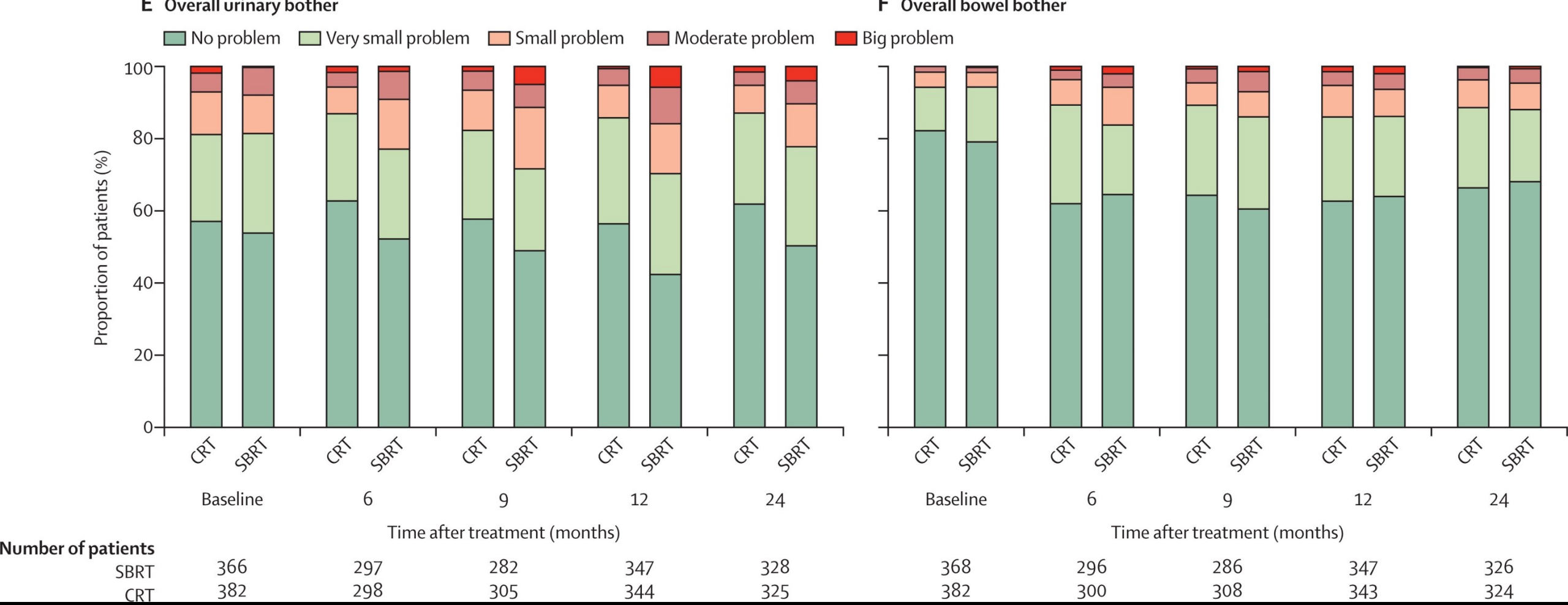




Gastrointestinal RTOG			
0	320 (84%)	323 (84%)	..
1	51 (13%)	55 (14%)	..
2	8 (2%)	6 (2%)	..
3	3 (1%)	0	..
4	0	0	..
5	0	0	..
Missing	48	30	..
Gastrointestinal RTOG grade ≥2			0·32
Yes	11 (3%)	6 (2%)	..
No	371 (97%)	378 (98%)	..
Gastrointestinal CTCAE			
0	283 (74%)	288 (75%)	..
1	85 (22%)	84 (22%)	..
2	15 (4%)	13 (3%)	..
3	1 (<1%)	0	..
4	0	0	..
5	0	0	..
Missing	46	29	..
Gastrointestinal CTCAE grade ≥2			0·70
Yes	16 (4%)	13 (3%)	..
No	368 (96%)	372 (97%)	..







- A numerically greater, but not significantly greater, proportion of patients getting SBRT had a minimally detectable decline in urinary incontinence scores (32% vs. 23%, p=0.01)
- A significantly smaller portion of patients getting SBRT had a minimally detectable decline in bowel scores (24% vs. 34%, p=0.0076)

PACE B: Summary

- No difference in RTOG grade ≥2 GU or GI toxicity at 2 years between arms; however, CTCAE grade ≥2 GU toxicity was significantly more frequent after SBRT, likely driven by a flare of urinary symptoms 12-15 months after SBRT
- Patient-reported urinary quality of life decrements were not significantly different between arms, and the decrement in bowel function was significantly lower with SBRT
- Overall, suggests the safety of SBRT while highlighting the need to further reduce GU toxicity (e.g., with urethral dose-limitation, margin reduction etc.)

SBRT Consortium Study

Single Institution Trials
Virginia Mason
Stanford
Flushing
21st Century Oncology
Sunnybrook (2 trials)
BIDMC
UCLA
Genesis Healthcare
Georgetown

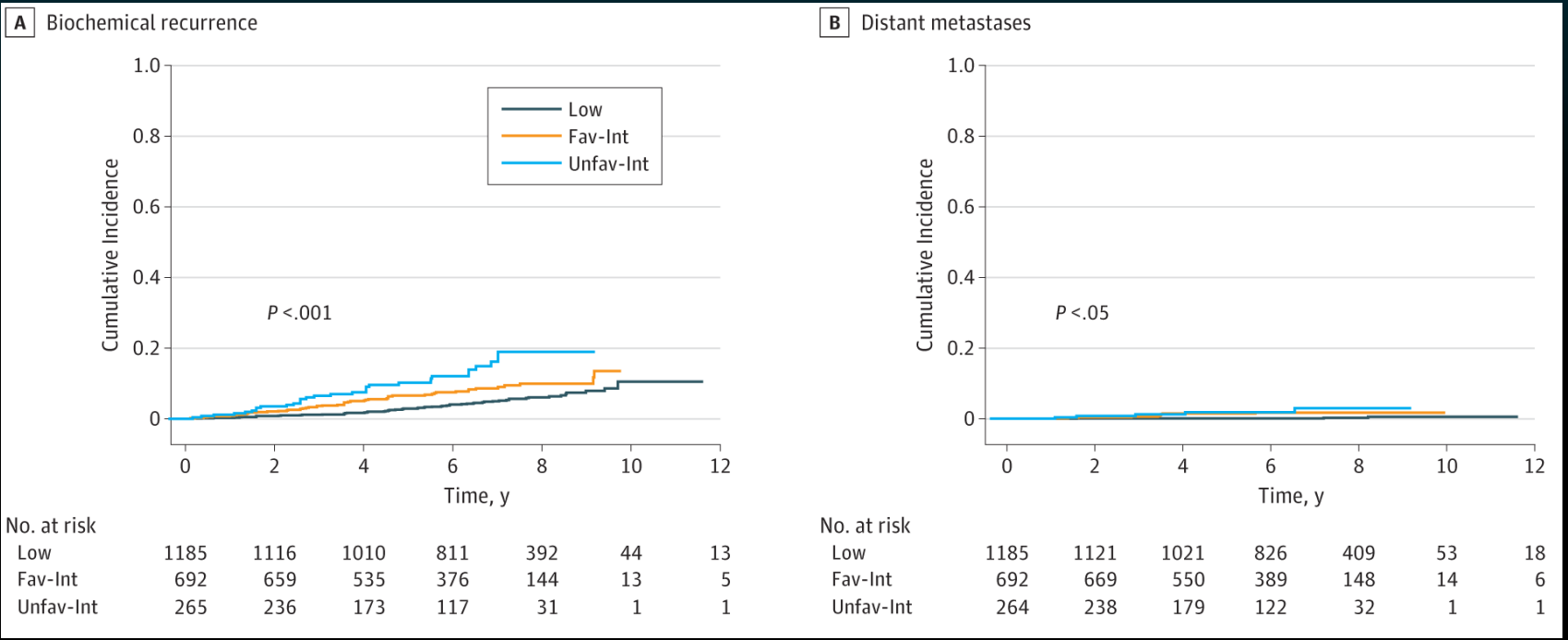
Multicenter Trials
NCT00643994
NCT00643617

2142 patients treated with SBRT
between 2000-2012
Median f/u of 6.9 years
45% NCCN Intermediate Risk

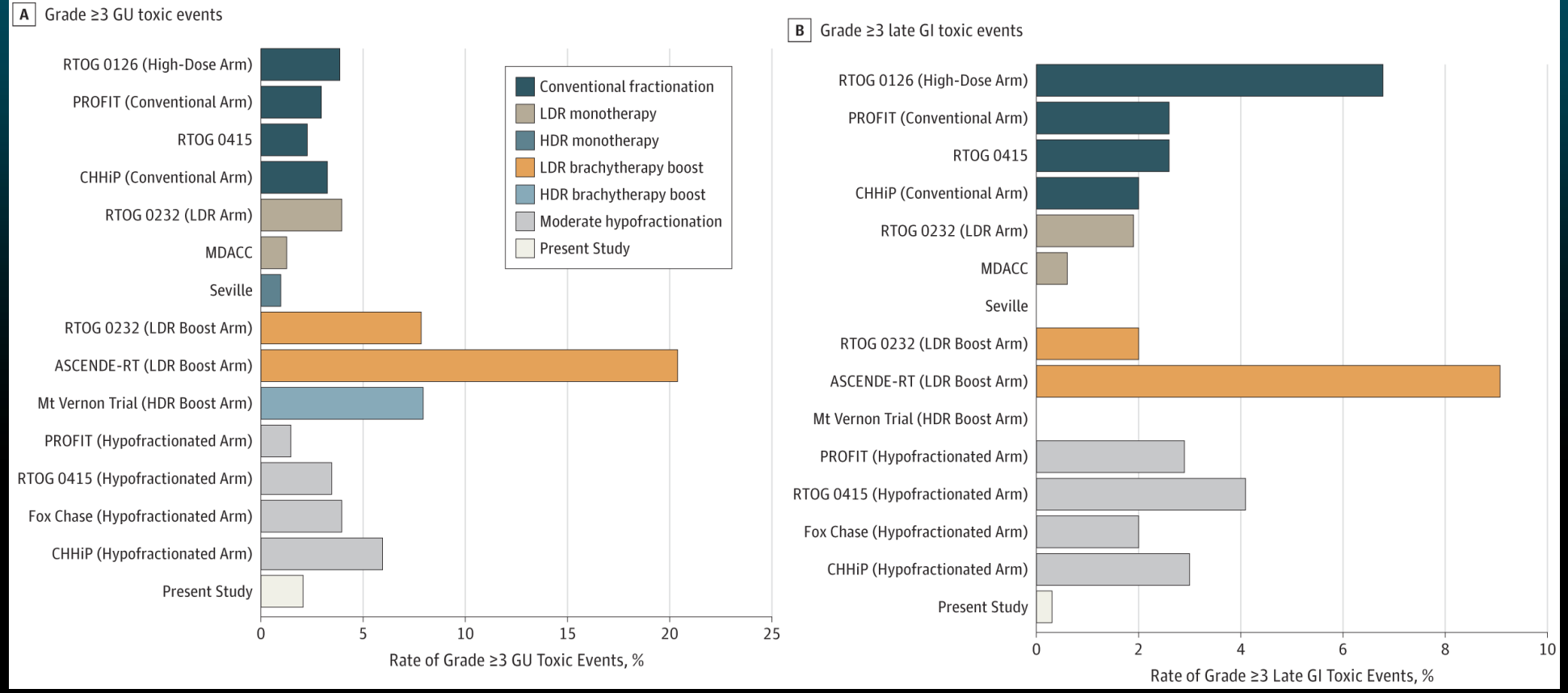
- Incidence of BCR and DM
- Incidence of severe RTOG/CTCAE toxicities

JAMA Netw Open. 2019 Feb 1;2(2):e188006

Clinical Outcomes



7-year BCR
Low: 4.5%
Fav-Int: 8.6%
Unfav-Int: 14.9%
All Int: 10.2%



	Crude Incidence	Cumulative Incidence Estimate (95% Confidence Interval)		
		5-Years	7-Years	10-Years
Acute Grade ≥3 GU	0.6%			
Acute Grade ≥3 GI	0.1%			
Late Grade ≥3 GU	2.1%	1.7% (1.2%-2.3%)	2.3% (1.6%-3.0%)	3.0% (1.9%-4.1%)
Late Grade ≥3 GI	0.2%	0.4% (0.1%-0.7%)	0.4% (0.1%-0.7%)	0.4% (0.1%-0.7%)

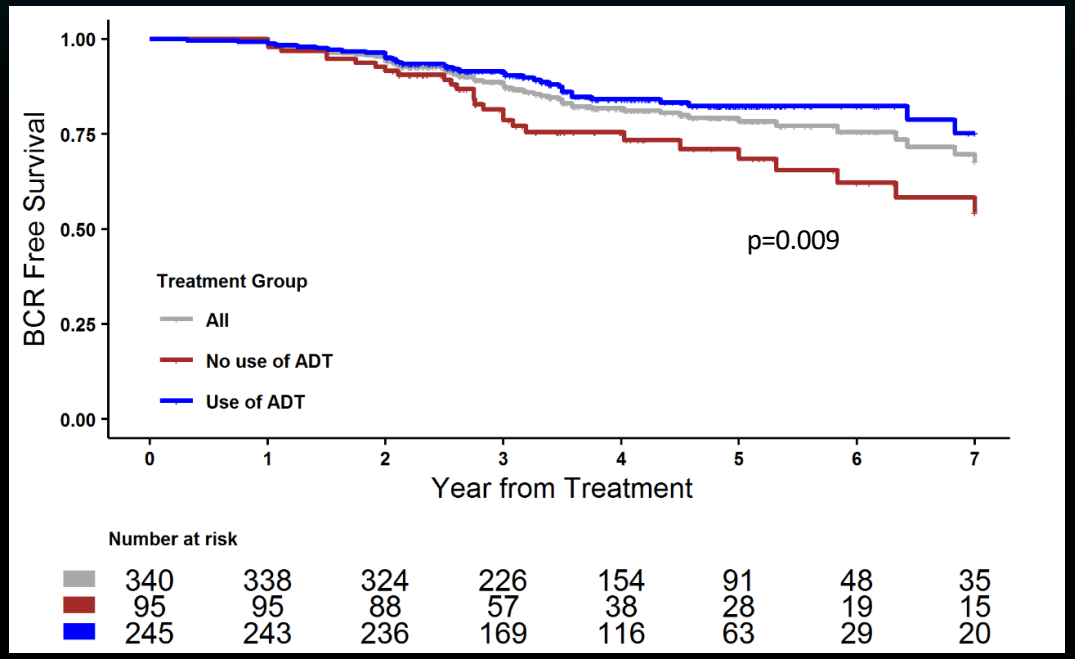
SHARP Consortium

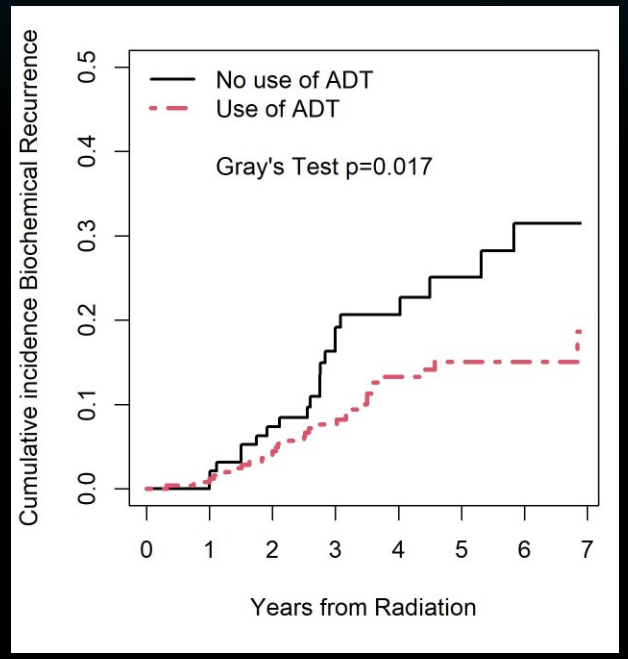
Parameter	Distribution
Age (median, IQR)	72.3 (67-78.5)
iPSA (median, IQR)	11 (7-21.3)
T stage	
T1-2	299 (87%)
T3-4	45 (13%)
Gleason grade group	
1	25 (7%)
2	43 (12%)
3	38 (11%)
4	156 (45%)
5	82 (24%)
Androgen deprivation therapy	
Use	248 (72%)
Duration (median, IQR)	9 (9-18)
Nodal radiotherapy	66 (19%)
Dose per fraction	
7	67 (19%)
7.5	124 (36%)
8	153 (44%)

- Individual patient data for 344 patients enrolled on 7 prospective studies
- Median follow-up of 49 months (minimum follow-up 24 months)
- 72% received ADT (median duration of 9 months)
- 19% received nodal radiotherapy

Int J Radiat Oncol Biol Phys. 2021 Jan 23;S0360-3016(21)00068-7

SHARP Consortium





SBRT Evidence Overview

- HYPO-RT-PC provides randomized data supporting the oncologic non-inferiority of UHF-RT, along with evidence of equivalent late toxicity. However, outdated technology limits extrapolation of toxicity rates.

- PACE-B provides randomized evidence of equivalent acute toxicity for modern SBRT versus longer courses of radiation. At the two-year time point, urinary toxicity may be slightly greater with SBRT, and bowel toxicity may be slightly lower

- SBRT is an option for high-risk prostate cancer, at this point supported mainly by phase II data (and a small amount of phase III data)
  - **SBRT is allowed on NRG GU-009 (high risk trial) as a standard of care option**

Techniques to Further Reduce Toxicity

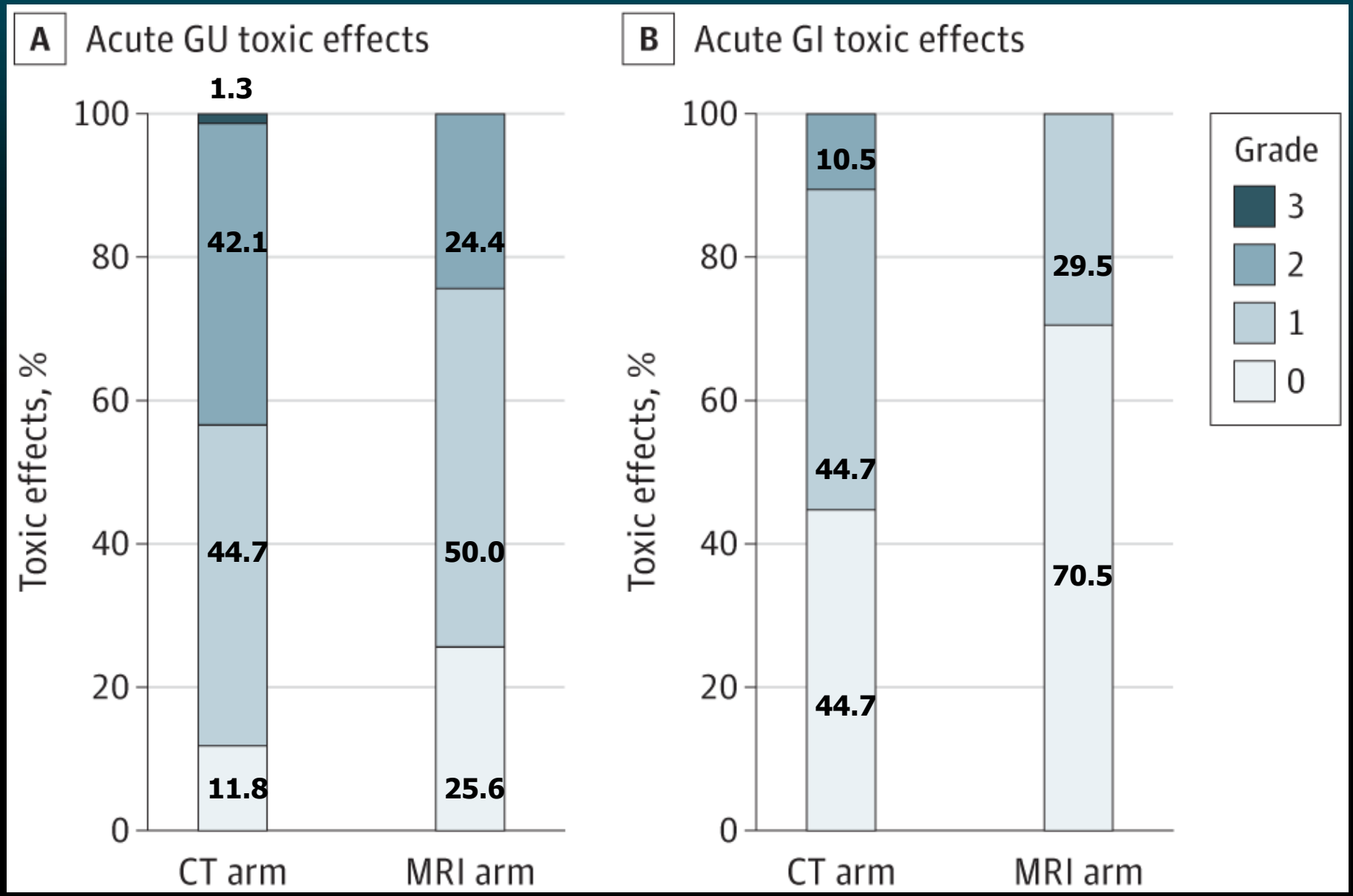
- Use of rectal spacers
- Radiogenomics to identify good candidates
- MRI-guided radiotherapy

MIRAGE Trial Design

- Hypothesis: Aggressive PTV margin reduction (4 mm→2 mm) will reduce acute grade ≥2 GU toxicity from 29% to 15%

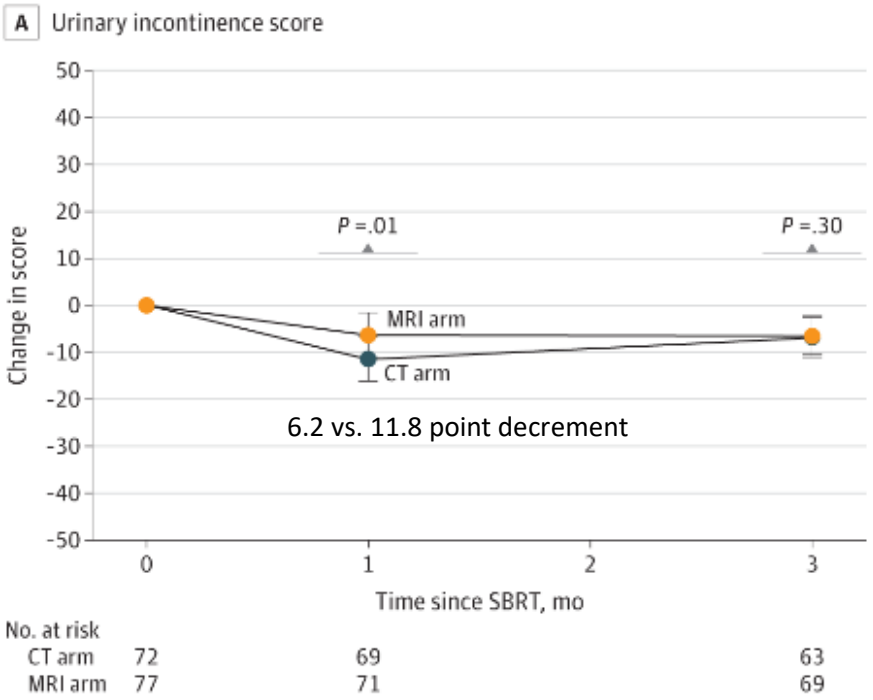
- Estimated a sample size of 300 patients to have 83.7% power to detect this difference using a one-sided Z test at a p-value threshold of 0.025
  - Interim analysis was stipulated after 100 patients were eligible, since doses used here (40 Gy) were higher than those used in prior studies

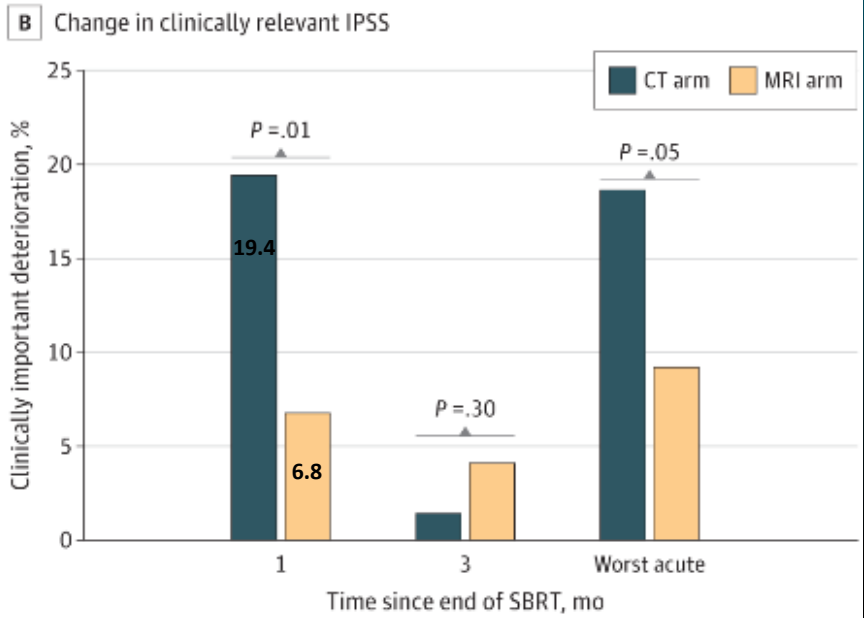
Parameter	CT (n=77)	MRI (n=79)
Age (median, IQR)	71 (67-77)	71 (68-75)
Risk Group		
Imaging N0		
Favorable Intermediate	15 (19%)	14 (18%)
Unfavorable Intermediate	25 (32%)	40 (51%)
High Risk	21 (27%)	15 (19%)
Very High Risk	9 (12%)	5 (6%)
Imaging N+	7 (9%)	5 (6%)
ADT Use	57 (74%)	49 (62%)
Nodal Radiation	19 (25%)	18 (23%)
GTV Boost	22 (29%)	19 (24%)
Rectal Spacer	32 (42%)	37 (47%)
Prior TURP/HOLEP	3 (4%)	5 (6%)
Prostate Size (mL, median, IQR)	41 (33-59)	39 (30-54)
IPSS (median, IQR)	6 (3-11)	7 (4-12.5)
Urinary medications at baseline	27 (35)	30 (38)
Baseline GI comorbidity	18 (23)	12 (15)
Hip Replacement	3 (4)	6 (8)

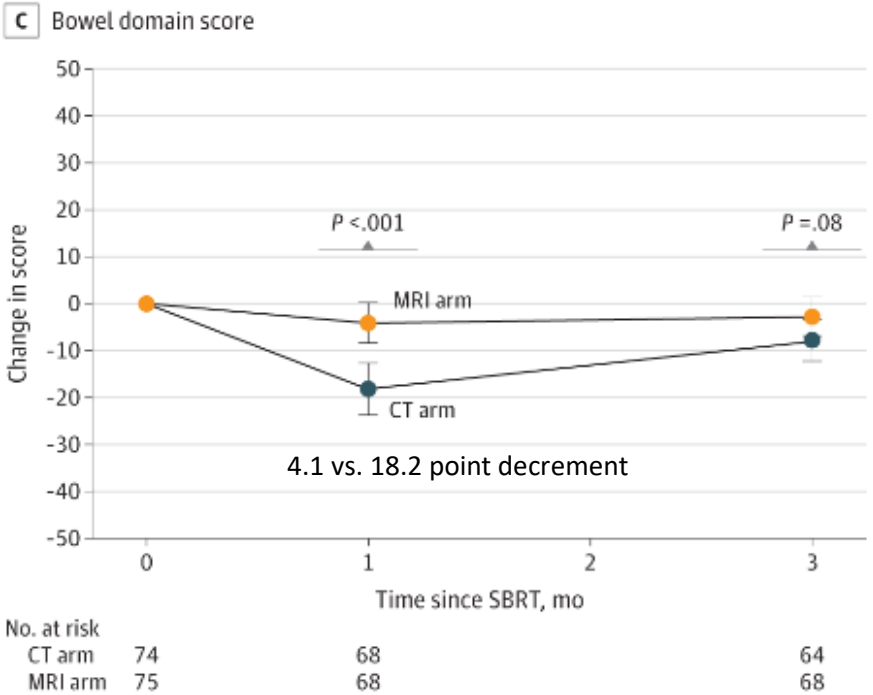


Acute grade ≥2 GU 43.4% vs. 24.4% (p=0.01)

Acute grade ≥2 GI 10.5% vs. 0% (p=0.003)


A
Urinary incontinence score
Change in score
P =.01
P =.30
MRI arm
CT arm
6.2 vs. 11.8 point decrement
Time since SBRT, mo
No. at risk
CT arm 72 69 63
MRI arm 77 71 69


B
Change in clinically relevant IPSS
CT arm
MRI arm
Clinically important deterioration, %
P =.01
P =.05
P =.30
19.4
6.8
Worst acute
Time since end of SBRT, mo


C
Bowel domain score
Change in score
P <.001
P =.08
MRI arm
CT arm
4.1 vs. 18.2 point decrement
Time since SBRT, mo
No. at risk
CT arm 74 68 64
MRI arm 75 68 68

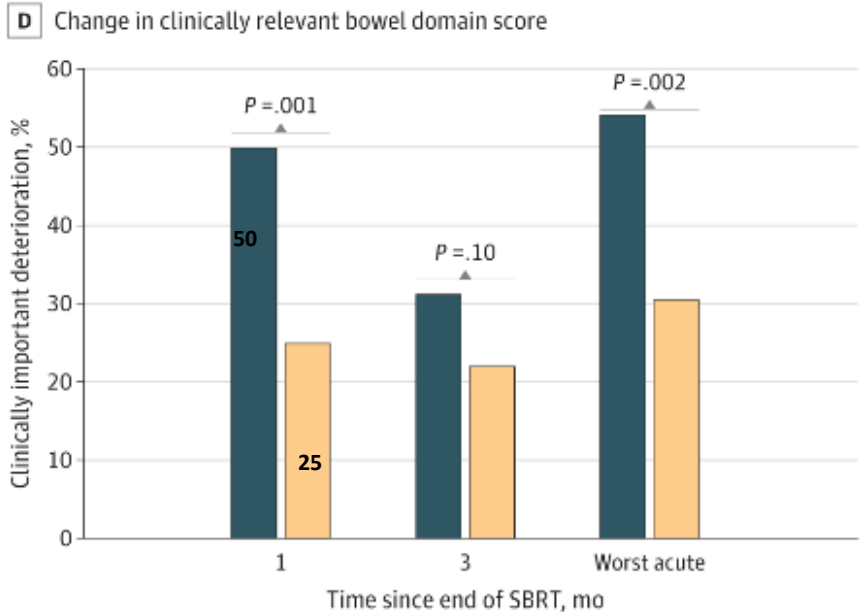
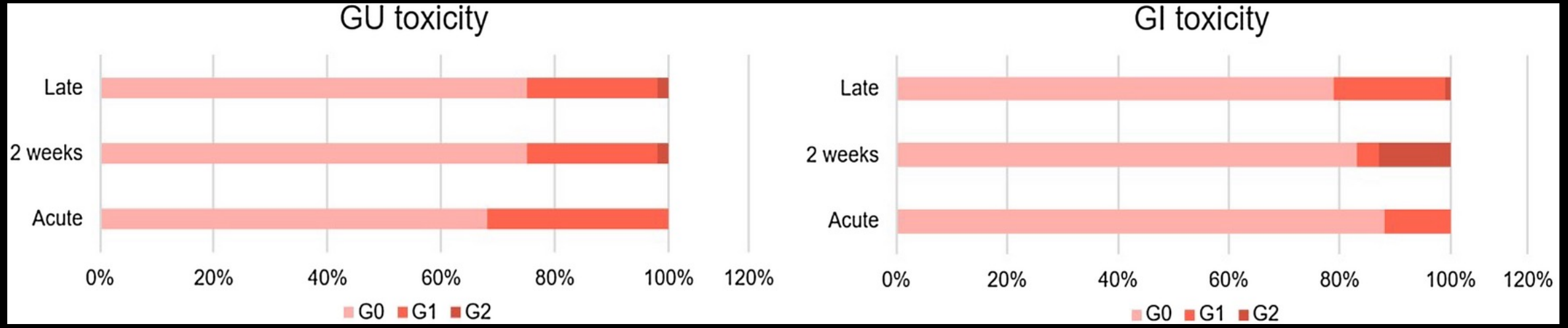

D
Change in clinically relevant bowel domain score
Clinically important deterioration, %
P =.001
P =.002
P =.10
50
25
Worst acute
Time since end of SBRT, mo

Table 2. Incidence of Acute Highest-Grade Treatment-Related Toxic Effects 3 Months or Less After SBRT[a]

	Patients, No. (%) (N = 154)								
	CT-guided SBRT (n = 76)				MRI-guided SBRT (n = 78)				
Adverse event	Grade 1	Grade 2	Grade 3	Grade ≥2	Grade 1	Grade 2	Grade 3	Grade ≥2	*P* value[b]
Genitourinary									
Any[c]	34 (44.7)	32 (42.1)	1 (1.3)	33 (43.4)	39 (50.0)	19 (24.4)	0	19 (24.4)	.006
Cystitis	2 (2.6)	2 (2.6)	0	2 (2.6)	0	0	0	0	.12
Hematuria	1 (1.3)	1 (1.3)	0	1 (1.3)	2 (2.6)	1 (1.3)	0	1 (1.3)	.50
Urinary frequency	32 (42.1)	24 (31.6)	0	24 (31.6)	28 (35.9)	12 (15.4)	0	12 (15.4)	.01
Urinary incontinence	9 (11.8)	3 (3.9)	0	3 (3.9)	4 (5.1)	2 (2.6)	0	2 (2.6)	.34
Urinary retention	10 (13.2)	20 (26.3)	1 (1.3)	21 (27.6)	7 (9.0)	9 (11.5)	0	9 (11.5)	.006
Urinary tract infection	0	0	0	0	0	0	0	0	.50
Urinary urgency	20 (26.3)	9 (11.8)	0	9 (11.8)	19 (24.4)	5 (6.4)	0	5 (6.4)	.14
Dysuria	9 (11.8)	5 (6.6)	0	5 (6.6)	1 (1.3)	5 (6.4)	0	5 (6.4)	.50
Gastrointestinal									
Any[c]	34 (44.7)	8 (10.5)	0	8 (10.5)	23 (29.5)	0	0	0	.001
Colitis	1 (1.3)	2 (2.6)	0	2 (2.6)	0	0	0	0	.12
Constipation	3 (3.9)	0	0	0	3 (3.8)	0	0	0	.50
Diarrhea	22 (28.9)	5 (6.6)	0	5 (6.4)	15 (19.2)	0	0	0	.01
Nausea	0	0	0	0	0	0	0	0	.50
Proctitis	15 (19.7)	5 (6.6)	0	5 (6.4)	9 (11.5)	0	0	0	.01
GI hemorrhage	4 (5.3)	3 (3.9)	0	3 (3.8)	1 (1.3)	0	0	0	.06
Rectal pain	2 (2.6)	2 (2.6)	0	2 (2.6)	1 (1.3)	0	0	0	.12
Sexual									
Any[c]	2 (2.6)	0	0	0	0	0	0	0	.50
Erectile dysfunction	2 (2.6)	0	0	0	0	0	0	0	.50

SBRT Trial in Elderly Men

- Prospective study of 35 Gy/5 fractions in 111 men aged ≥70
- No grade ≥23 GU or GI toxicities were seen, and prevalence of grade 2 GU/GI toxicities at last followup was <1%



Radiol Med. 2023 Apr;128(4):501-508.

Summary

- Definitive RT improves survival for men with localized prostate cancer when compared with ADT alone
- Age is not a negative prognostic factor in the context of definitive RT, and standard ADT practices should be followed
- SBRT appears to be safe and effective based on high-level data (including phase III clinical trial data)
- Emerging technologies, such as MRI-guided radiation, can further improve the therapeutic ratio

Acknowledgments

- Dr. Edgardo Santos
- NOSCM team and staff
- Dr. Michael Steinberg, Dr. Minsong Cao, and the UCLA GU Team
- My patients

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