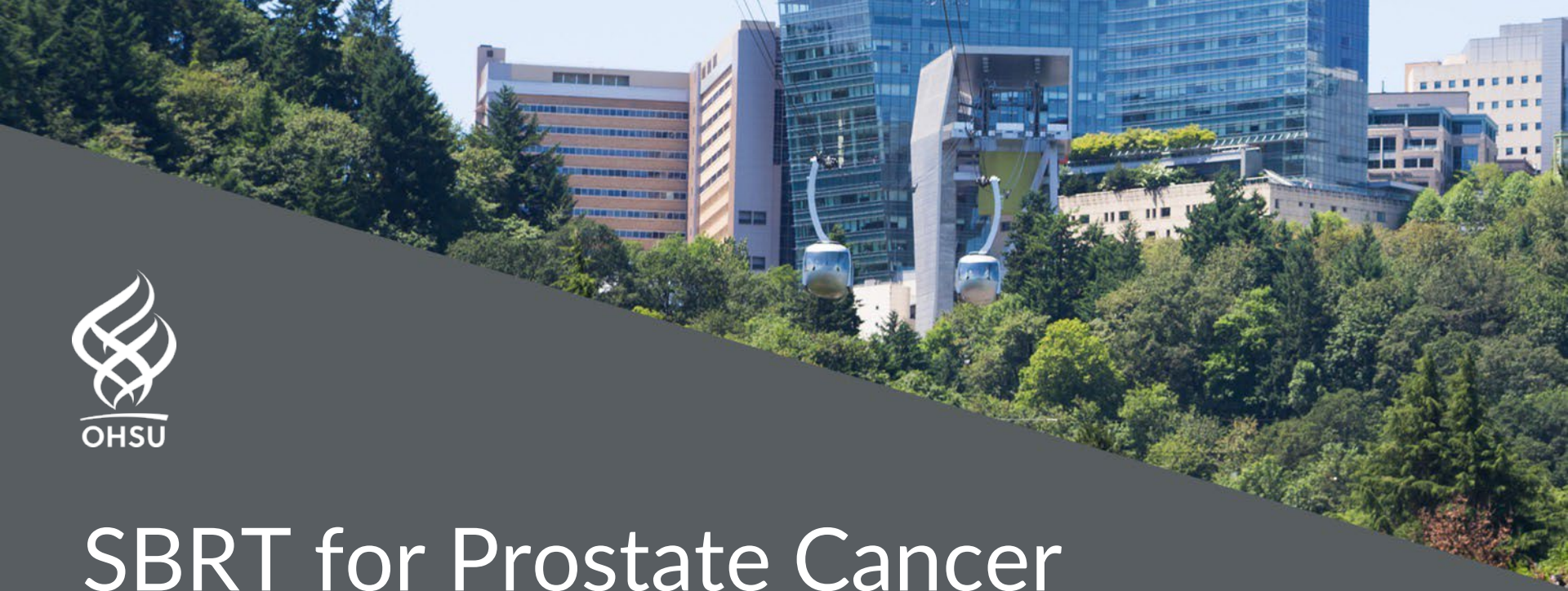

SBRT for Prostate Cancer

Casey Williamson, MD, MAS
Assistant Professor, Radiation Medicine @ OHSU

March 03, 2023

Disclosures

- Employment: OHSU

Learning Objectives

- Definition of, rationale for SBRT in prostate cancer
- Indications for definitive SBRT
- Efficacy and toxicity data
- SBRT for re-irradiation
- Upcoming directions and studies

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What is SBRT?

- Stereotactic Body Radiation Therapy
- Precise delivery of high dose to a localized target
- ≤5 treatment fractions
- Used routinely in other settings (lung, brain, GI, mets)
- Reliant on good imaging
- Close attention to dose to nearby organs (rectum, bladder, others)

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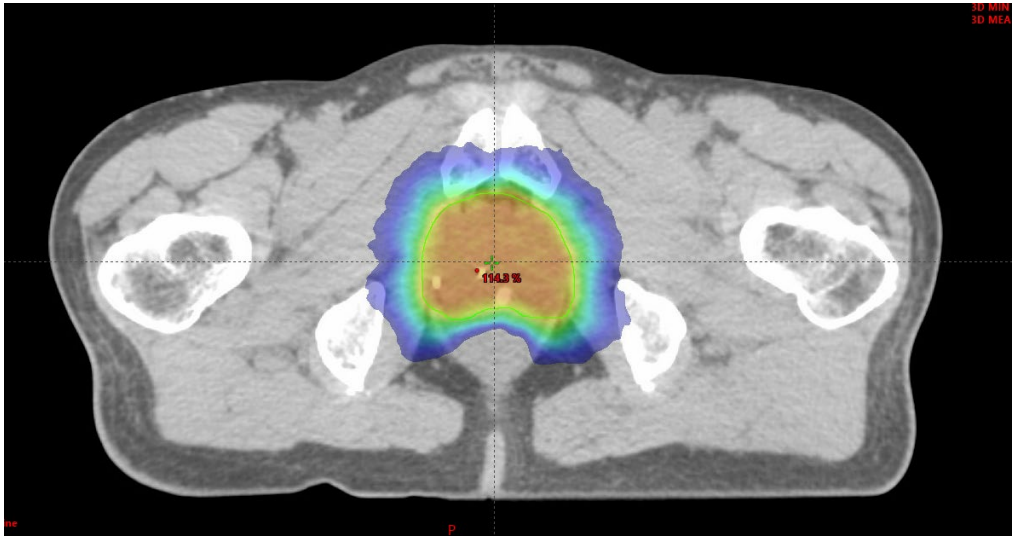
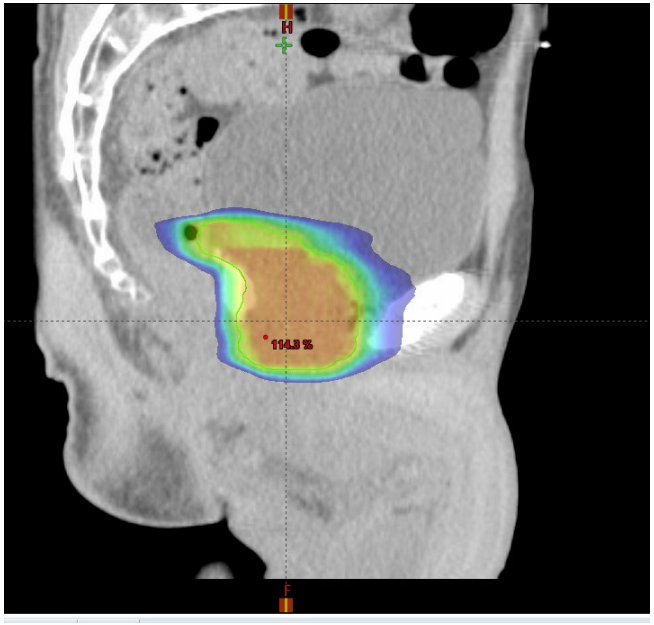
Conformal Dose Distribution





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Fractionation in Prostate Cancer

- **Conventional** fractionation: ~78 Gy in 39 fractions
- **Hypofractionation** = fewer fractions
  - **Moderate** hypofractionation: 70 Gy in 28 fractions, 60 Gy in 20 fractions
  - **Ultra**hypofractionation (AKA SBRT): 36.25 Gy in 5 fractions

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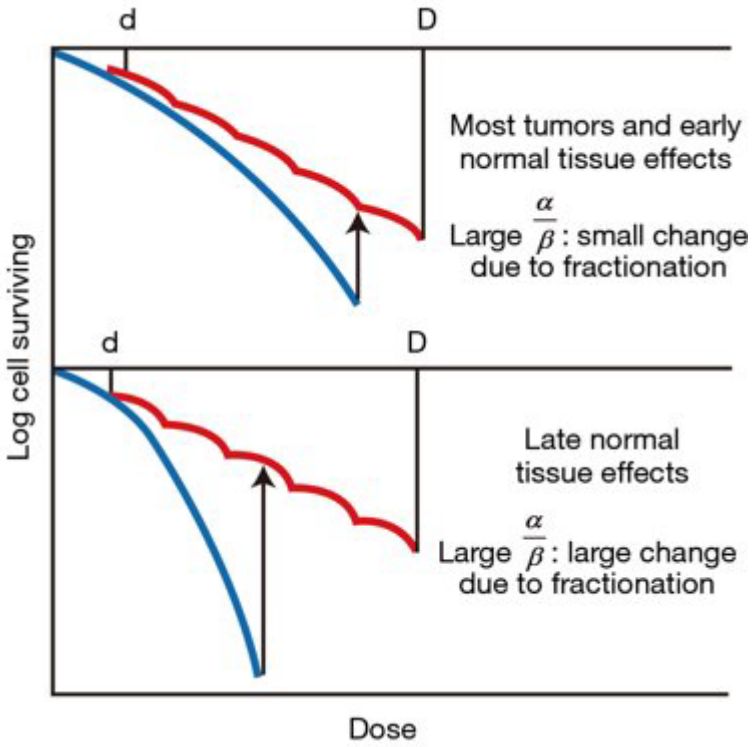
Rationale for Prostate SBRT

- Tissues have differential sensitivities to total dose and fractionation: α/β ratio
- Prostate cancer felt to have a low α/β; may imply benefit to hypofractionation
- Patient convenience, cost
- Highly conformal dose



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Hesitancy with SBRT

- Long-term follow-up not as robust
- Higher dose, fewer fractions → less room for error
- ? Relative toxicity
- Use by risk group

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NCCN & Prostate SBRT

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF RADIATION THERAPY

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.
See PROS-3, PROS-4, PROS-5, PROS-6, PROS-7, PROS-8, PROS-12, and PROS-I for other recommendations, including recommendations for neoadjuvant/concomitant/adjuvant ADT.

Regimen	Preferred Dose/Fractionation	NCCN Risk Group (✓ indicates an appropriate regimen option if RT is given)					
		Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High	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	✓	✓	✓	✓	✓	
	2.2 Gy x 35 fx + micro-boost to MRI-dominant lesion to up to 95 Gy (fractions up to 2.7 Gy)		✓	✓	✓		
SBRT Ultra-Hypofractionation	9.5 Gy x 4 fx 7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	✓	✓	✓	✓		
	6 Gy x 6 fx						✓
Brachytherapy Monotherapy							
LDR Iodine 125 Palladium 103 Cesium 131	145 Gy 125 Gy 115 Gy	✓	✓				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	✓	✓				
EBRT and Brachytherapy (combined with 45–50.4 Gy x 25–28 fx or 37.5 Gy x 15 fx)							
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			✓	✓		
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			✓	✓		

[a] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.

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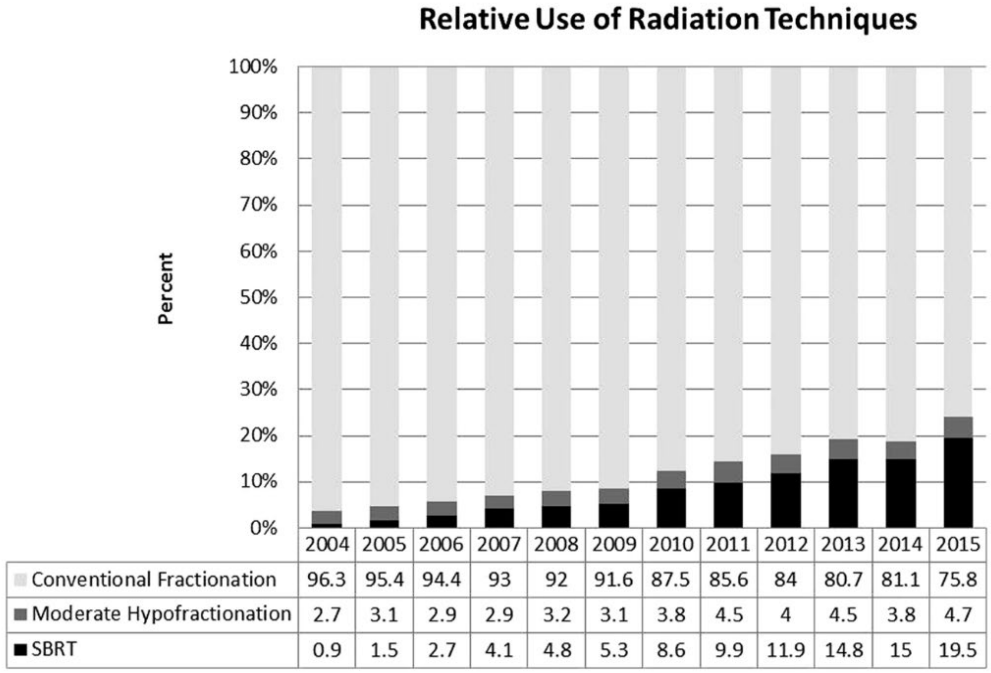
Utilization of Prostate SBRT

- National trends approach 20% utilization for low and intermediate risk



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Conventional Fractionation	96.3	95.4	94.4	93	92	91.6	87.5	85.6	84	80.7	81.1	75.8
Moderate Hypofractionation	2.7	3.1	2.9	2.9	3.2	3.1	3.8	4.5	4	4.5	3.8	4.7
SBRT	0.9	1.5	2.7	4.1	4.8	5.3	8.6	9.9	11.9	14.8	15	19.5

Malouff et al. PCPD 2019

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Review of Recent Data

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SBRT vs. Longer Course RT

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HypoRT

- Randomized, phase 3, non-inferiority trial
- 12 centers in Sweden and Denmark
- 1,200 men with mostly intermediate risk prostate cancer (small number of high risk)
- Treated with either:
  - SBRT 42.7 Gy in seven fractions every other day
  - Conventional RT: 78 Gy in 39 fractions
- No ADT allowed

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HypoRT

- Only 20% used IMRT/VMAT
- MRI recommended but not mandatory
- 4 mm posterior margin
- No hydrogel spacers

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Outcomes

- Median follow-up 5 years
- 5 yr FFS:
  - SBRT: 84%
  - RT: 84% (NS)
- 5 yr OS:
  - SBRT: 94%
  - RT: 96% (NS)

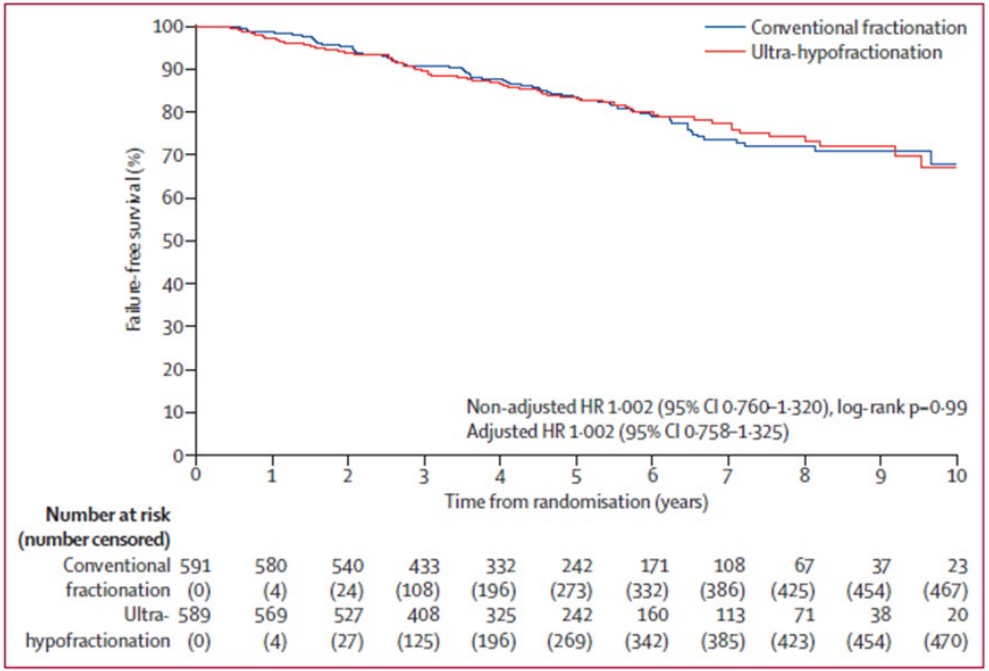
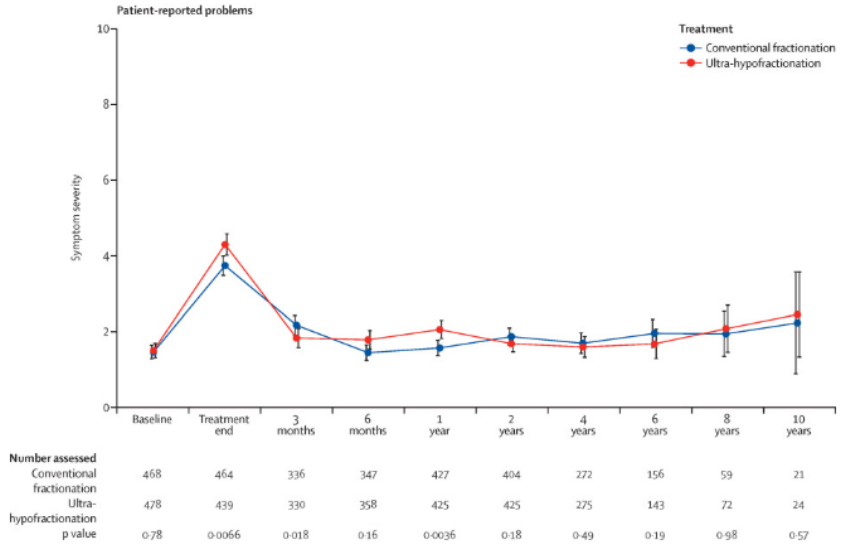


Figure 2: **Failure-free survival**
HR=hazard ratio.

Widmark et al. Lancet 2019

HypoRT – urinary toxicity

- Patient-reported higher GI and GU problems at end of treatment with SBRT
- Grade 2+ acute GU toxicity (p=0.057):
  - SBRT: 28%
  - RT: 23%
- Grade 2+ GU toxicity at 1 year (p=<0.01)
  - SBRT: 6%
  - RT: 2%
- No difference in grade 2+ GU toxicity at 5 yrs (5%)



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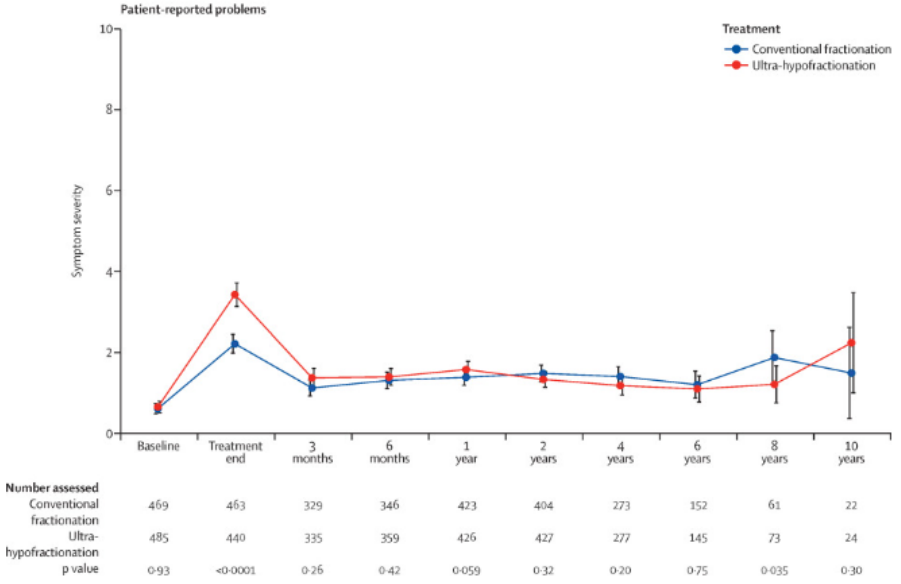
HypoRT – GI toxicity

- Grade 2+ acute GI toxicity:
  - SBRT: 28%
  - RT: 23%
- Grade 2+ GI toxicity at 1 year
  - SBRT: 1%
  - RT: 4%



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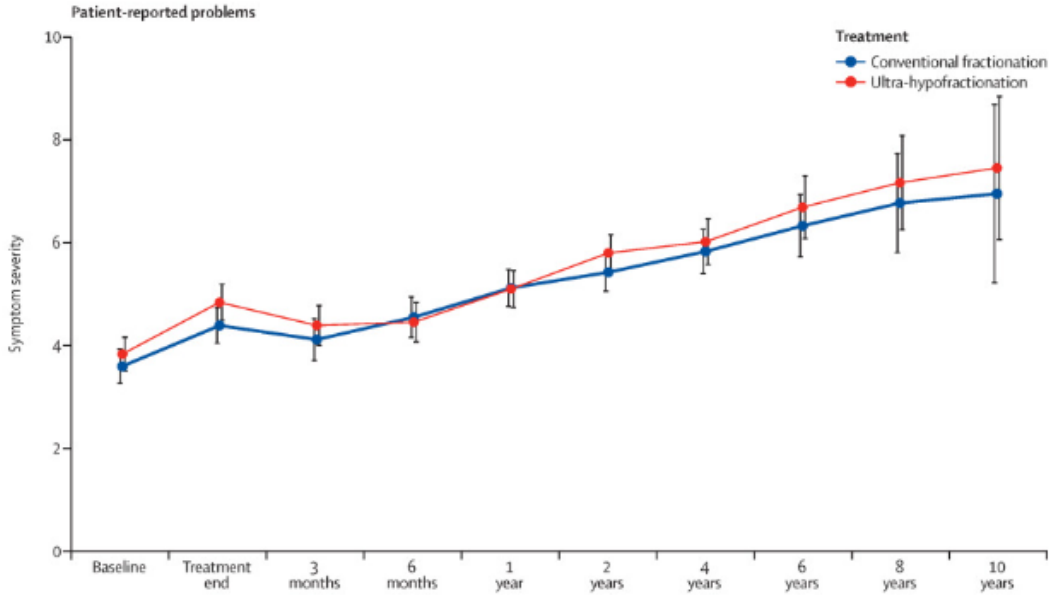
HypoRT – erectile function



Number assessed	Baseline	Treatment end	3 months	6 months	1 year	2 years	4 years	6 years	8 years	10 years
Conventional fractionation	453	443	318	331	412	396	266	153	61	21
Ultra-hypofractionation	470	414	319	346	410	405	260	135	66	22
p value	0·31	0·066	0·28	0·62	0·74	0·18	0·57	0·41	0·47	0·90

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HypoRT – conclusions & questions

- Noninferior failure-free survival
- Acute side effects more pronounced, late side effects similar
- Relatively short follow-up
- 11% high risk
- Applicability to 5 fraction US-style SBRT?
- Benefit to MRI, rectal spacer, smaller margins?

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ARTICLES | VOLUME 23, ISSUE 10, P1308-1320, OCTOBER 2022

Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial

Alison C Tree, MDRes • Peter Ostler, FRCR • Hans van der Voet, MD • William Chu, MD • Andrew Loblaw, MD • Daniel Ford, FRCR • et al. Show all authors • Show footnotes

Published: September 13, 2022 • DOI: https://doi.org/10.1016/S1470-2045(22)00517-4 • Check for updates

- Phase 3 trial at 35 hospitals in UK, Ireland, Canada
- Low/IM risk disease (but excluded GS 4+3)
- 874 men randomized between SBRT (**36.25 Gy/5 fractions**) vs. conventional fractionation (78 Gy in 39 fractions)
- Primary endpoint: freedom from biochemical or clinical failure @ 5 years
  - 2-year toxicity data published while primary outcome maturing

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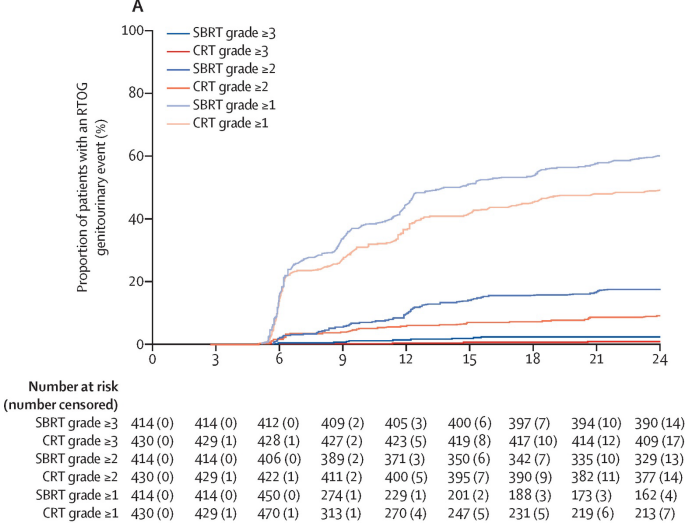
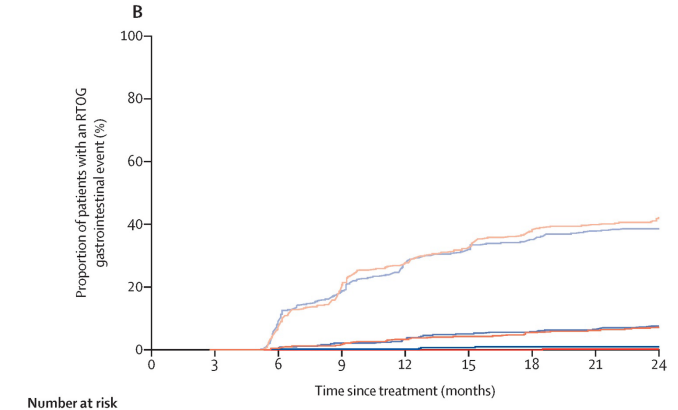
24 month results

- RTOG grade 2+ GU toxicity
  - CRT: 8 (2%) of 381
  - SBRT: 13 (3%) of 384
  - Absolute difference 1.3% [95% CI −1.3 to 4.0]; p=0.39)
- RTOG grade 2+ GI toxicity
  - CRT: 11 (3%)
  - SBRT: 6 (2%)
  - Absolute difference −1/3% [95% CI −3.9 to 1.1]; p=0.32)
- No serious adverse events (RTOG 4+) or treatment-related deaths
- Overall: 2-year toxicity similar



Number at risk (number censored)

SBRT grade ≥3	414 (0)	414 (0)	412 (0)	409 (2)	405 (3)	400 (6)	397 (7)	394 (10)	390 (14)
CRT grade ≥3	430 (0)	429 (1)	428 (1)	427 (2)	423 (5)	419 (8)	417 (10)	414 (12)	409 (17)
SBRT grade ≥2	414 (0)	414 (0)	406 (0)	389 (2)	371 (3)	350 (6)	342 (7)	335 (10)	329 (13)
CRT grade ≥2	430 (0)	429 (1)	422 (1)	411 (2)	400 (5)	395 (7)	390 (9)	382 (11)	377 (14)
SBRT grade ≥1	414 (0)	414 (0)	450 (0)	274 (1)	229 (1)	201 (2)	188 (3)	173 (3)	162 (4)
CRT grade ≥1	430 (0)	429 (1)	470 (1)	313 (1)	270 (4)	247 (5)	231 (5)	219 (6)	213 (7)

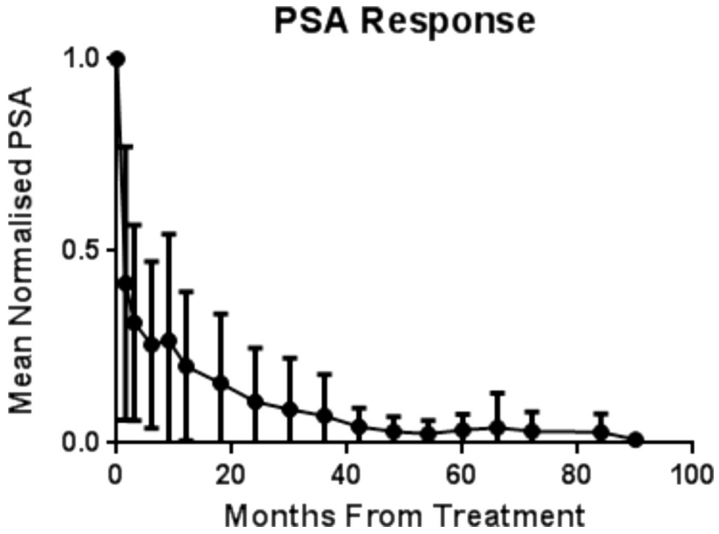


Number at risk (number censored)

SBRT grade ≥3	414 (0)	414 (0)	413 (0)	411 (2)	410 (3)	405 (6)	403 (7)	400 (10)	396 (14)
CRT grade ≥3	430 (0)	429 (1)	429 (1)	428 (2)	425 (5)	422 (8)	420 (10)	416 (13)	411 (18)
SBRT grade ≥2	414 (0)	414 (0)	412 (0)	403 (2)	398 (2)	388 (5)	384 (6)	378 (9)	370 (13)
CRT grade ≥2	430 (0)	429 (1)	427 (1)	421 (2)	411 (5)	404 (8)	397 (10)	391 (13)	382 (18)
SBRT grade ≥1	414 (0)	414 (0)	376 (0)	335 (2)	298 (2)	278 (4)	264 (5)	253 (5)	247 (8)
CRT grade ≥1	430 (0)	429 (1)	396 (1)	341 (2)	307 (4)	284 (7)	261 (8)	250 (10)	237 (14)

Higher Dose?

- 91 patients with low/IM risk, phase I/II dose escalation trial
- Doses: 45Gy, 47.5Gy, 50Gy (all in 5)
- 3mm margin, fiducials, rectal balloon daily
- 4mg dexamethasone prior to treatment, a-blocker (i.e. tamsulosin) for 6 weeks
- Primary endpoint phase II: late GU/GI toxicity
- Secondary endpoints: biochemical control, DSS, OS
- MTD not reached in Phase I →Phase II started at 50Gy/5fx



Hannan et al, EJC 2016

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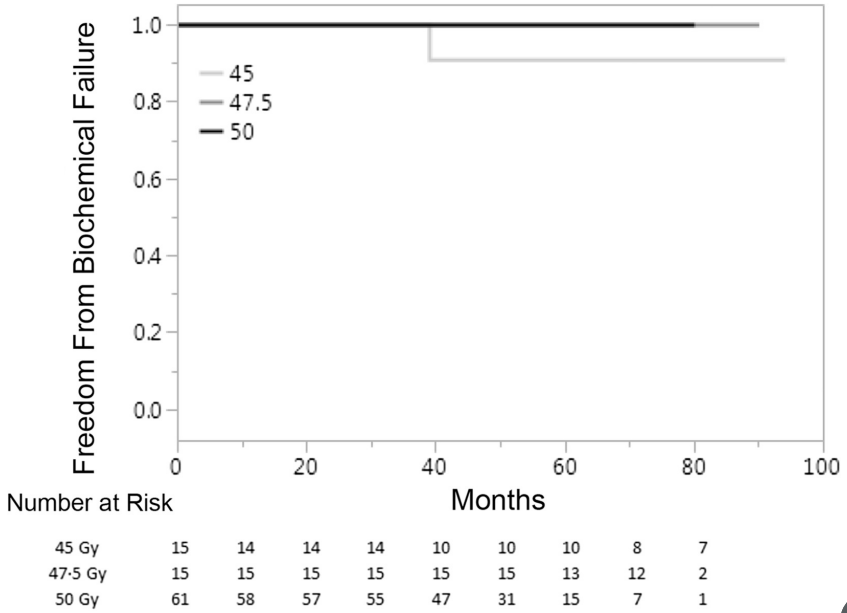
Outcomes

- FFBF 100% for all patients at 3 years
- One biochemical failure in the 45 Gy arm after 3 years
- No deaths from prostate cancer or treatment



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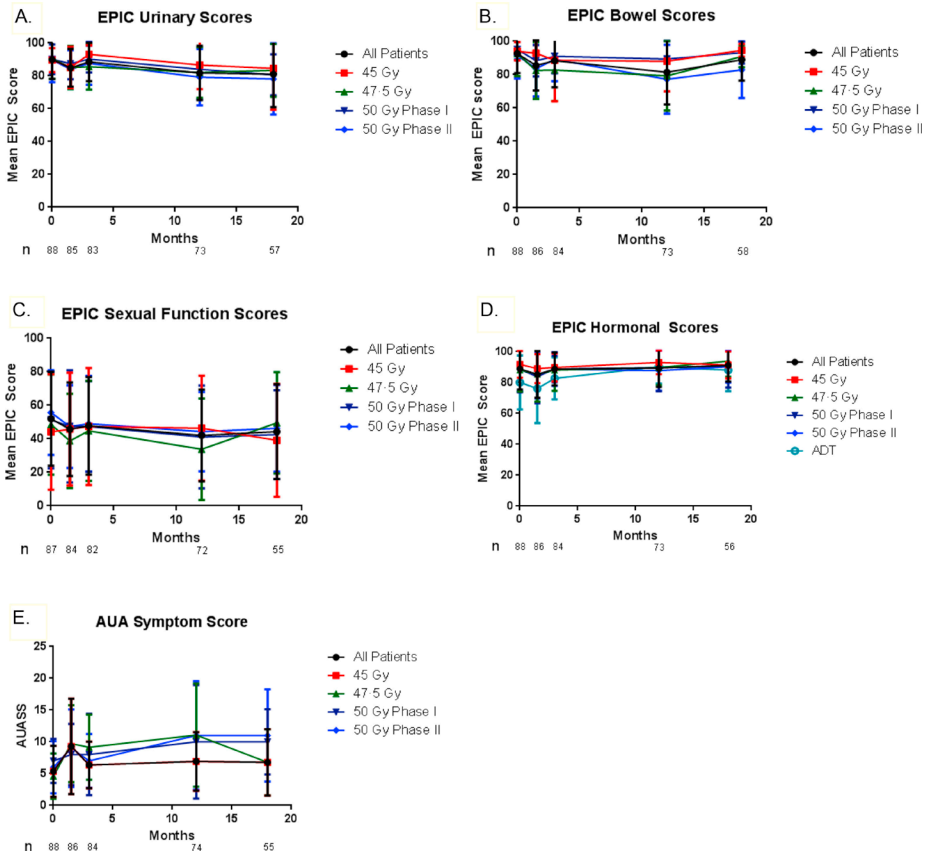
- **Toxicity**
  - Acute grade 2 GU tox: 22% (no grade 3 tox)
  - 14/20 reports were in 50Gy arm
  - Late grade 3+ GU tox: 4.4%, all within 50Gy arm
  - 50Gy arm had 1 acute grade 4 GI tox and 2 late grade 4 GI tox (ulceration of rectum requiring diverting colostomy)
- **Conclusions**:
  - Doses of 45 and 47.5 Gy in 5 fractions have high control rates and acceptable toxicity
  - 50 Gy: high rates of late toxicity



SBRT vs Surgery?

Hot off the presses from ASCO GU 2023

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PACE-A: An international phase 3 randomized controlled trial (RCT) comparing stereotactic body radiotherapy (SBRT) to surgery for localized prostate cancer (LPCa)—Primary endpoint analysis.

Nicholas J. Van As, Alison Tree, Peter J. Ostler, Hans van der Voet, Daniel Ford, Shaun Tolan, Paula Wells, Rana Mahmood, Mathias Winkler, Andrew Chan, Alan Thompson, Christopher Ogden, Stephanie Brown, Julia Pugh, Stephanie M. Burnett, Clare Griffin, Jaymini Patel, Olivia Naismith, **Emma Hall**

- Presented at ASCO GU 2023 (Feb 16 2023)

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PACE-A

- Phase 3: T1-T2, Gleason ≤ 3+4, PSA ≤ 20, suitable for surgery
- SBRT (36.25 Gy/5 fractions) vs laparoscopic or robot-assisted prostatectomy
- ADT not permitted
- Co-primary endpoints: expanded prostate index composite (EPIC-26) **number of pads per day** and EPIC **bowel subdomain score at 2 years**
- Analysis by treatment received
- 123 men from 10 centers randomized (goal sample size 234 but stopped recruitment after a 2-year gap during COVID)

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PACE-A Results

- Median follow-up 50 months
- At 2 years:
  - 2/43 (4.5%) SBRT patients used pads vs 15/32 (46.9%) in surgery, p<0.001
  - 7/45 (15.6%) SBRT patients vs 0/31 (0%) surgery patients reported moderate/big problem with bowel symptoms (p=0.04)
  - SBRT patients: significantly worse bowel subdomain score (mean 88.4 vs. 97.3)
  - SBRT patients: significantly better sexual subdomain score
  - No evidence of difference in urinary subdomain score
  - GU grade 2+ was seen in 5/54 (9.3%) SBRT vs 4/42 surgery (9.5%), NS
  - No GI G2+ in either group

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PACE-A

- SBRT associated with less urinary incontinence but worse bowel bother
- Awaiting further follow-up and publication

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Can we predict toxicity?

Patient Factors

Treatment Factors

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Predictors of Toxicity

- Patient Specific Factors
  - **Large prostate**: Late grade 2+ GU toxicity 15% for prostate > 60cc vs. 8%
  - **Prior TURP** increases risk of GU toxicity including hematuria, 21% vs 2%
  - **High baseline urinary symptoms** (IPSS > 15)
  - **Anticoagulant use** associated with late rectal bleeding, 47% vs 18%

Katz et al. Front Oncol 2014
Gurka et al. Radiat Oncol 2015
Jackson et al. PRO 2018
Musunuru et al. IJROBP 2016

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Predictors of Toxicity

- Treatment-Specific Factors
  - Higher Prescription Dose:
    - Grade 2+ urinary toxicity was 48% in patients receiving 40 Gy vs. 5% in patients receiving 35 Gy
    - In another study, 6 of 61 patients (10%) treated to 50 Gy in 5 fractions experienced high grade rectal toxicity, 5 of whom required temporary or permanent colostomy
  - Higher doses to the rectum, bladder, and probably urethra
  - Daily versus every other day treatment?
    - In one series QD was associated with increased rates of late grade 1-2 urinary (56% vs. 17%) and bowel (44% vs. 5%) toxicity

Helou et al. Radiother Oncol 2017
King et al. IJROBP 2012

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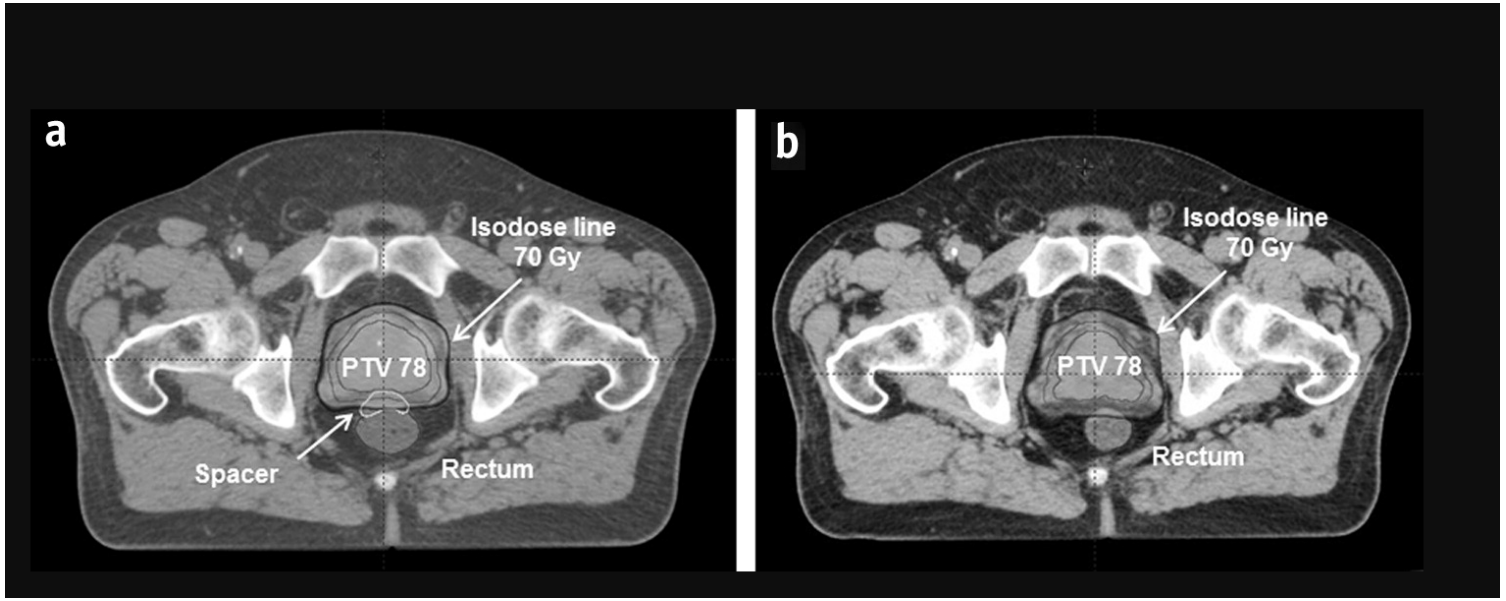
What about a rectal spacer?



Mok et al. IJROBP 2014

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Original Investigation

ONLINE FIRST

February 9, 2023

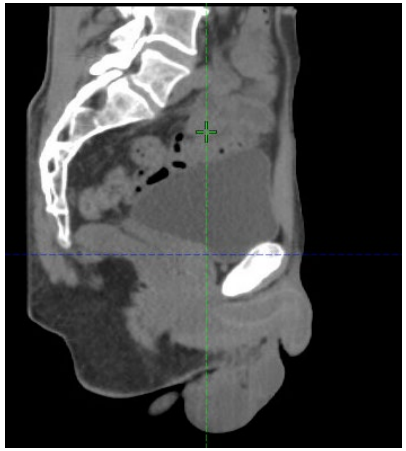
Hyaluronic Acid Spacer for Hypofractionated Prostate Radiation Therapy

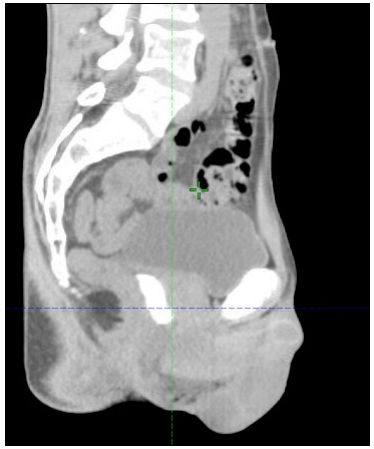
A Randomized Clinical Trial

Neil F. Mariados, MD[1]; Peter F. Orio III, DO, MS[2,3]; Zvi Schiffman, MD[4]; et al

» Author Affiliations | Article Information

JAMA Oncol. Published online February 9, 2023. doi:10.1001/jamaoncol.2022.7592





- Multicenter randomized trial, 260 patients
- 12 centers within the US, Australia, and Spain, with a 6-month follow-up
- T1 to T2 prostate cancer with a Gleason score 7 or less and prostate-specific antigen level of 20 ng/mL or less
- Stratified by intended 4-month androgen deprivation therapy use and erectile quality
- Patients received 60 Gy in 20 fractions – **first trial looking at moderately hypofractionated RT**
- Primary outcome: hypothesized that more than 70% of patients in the spacer group would achieve a 25% or greater reduction in the rectal volume receiving 54 Gy (V54)
- Secondary Outcome: hypothesized that the spacer group would have noninferior acute (within 3 months) grade 2+ GI toxic effects compared with the control group, with a margin of 10%

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Results

- 131 of 133 (98.5%) spacer group had a 25%+ reduction in rectum V54, greater than the minimally acceptable 70% ($P < .001$).
  - Mean reduction 85.0%
- Acute grade 2+ GI toxicity:
  - Spacer: 4 of 136 patients (2.9%)
  - Control: 9 of 65 patients (13.8%) in control group
  - Difference: -10.8%, p= 0.01
- Patient reported QOL similar

Table 3. Gastrointestinal and Genitourinary Toxic Effects by CTCAE, Version 5.0

	Acute toxic effect (within 3 mo)		6-mo Toxic effect	
CTCAE	Spacer	Control	Spacer	Control
No.	136	65	136	65
Gastrointestinal				
0	114 (84.4)	36 (55.4)	129 (99.2)	57 (91.9)
1	17 (12.6)	20 (30.8)	1 (0.8)	5 (8.1)
2	3 (2.2)	9 (13.8)	0	0
3	1 (0.7)	0	0	0
Genitourinary				
0	56 (41.5)	28 (43.1)	123 (94.6)	55 (88.7)
1	53 (39.3)	24 (36.9)	5 (3.8)	7 (11.3)
2	26 (19.3)	13 (20.0)	2 (1.5)	0
3	0	0	0	0

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Conclusions, Questions

- Rectal spacer can improve dosimetry, associated with small reduction in GI toxicity and is generally well-tolerated
- Applicability to SBRT?
- Relevance of primary endpoint?
- Larger margins used
- Consistent with other studies showing statistically significant but relatively small effect

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SBRT for locally recurrent disease?

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ELSEVIER

European Urology

Volume 80, Issue 3, September 2021, Pages 280-292

Platinum Priority – Review – Prostate Cancer – Editor's Choice

Editorial by Jack Zheng and Juanita Crook on pp. 293–294 of this issue

A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER)EU★ACME ☆

Luca F. Valle [a †], Eric J. Lehrer [b †], Daniela Markovic [c], David Elashoff [c], Rebecca Levin-Epstein [a], R. Jeffery Karnes [d], Robert E. Reiter [e], Matthew Rettig [f g], Jeremie Calais [h], Nicholas G. Nickols [a i], Robert T. Dess [j], Daniel E. Spratt [j], Michael L. Steinberg [a], Paul L. Nguyen [k], Brian J. Davis [l], Nicholas G. Zaorsky [m], Amar U. Kishan [a e]

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MASTER meta-analysis

- 150 studies included; salvage RP, HIFU, cryotherapy, SBRT, brachytherapy
- Adjusted 5-year RFS ranged from 50% after cryotherapy to 60% after brachytherapy and SBRT
- No significant differences between any modality and radical prostatectomy
- Less severe GU toxicity with cryo/brachy/SBRT vs. RP
- Less severe GI toxicity with brachytherapy vs. RP

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International Journal of Radiation Oncology*Biology*Physics
Volume 106, Issue 2, 1 February 2020, Pages 291-299

Clinical Investigation

Retreatment for Local Recurrence of Prostatic Carcinoma After Prior Therapeutic Irradiation: Efficacy and Toxicity of HDR-Like SBRT

Donald Fuller MD *, James Wurzer MD †, Reza Shirazi MD *, Stephen Bridge MD ‡, Jonathan Law DABR †, Tami Crabtree PhD §, George Mardirossian PhD *

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https://doi.org/10.1016/j.ijrobp.2019.10.014

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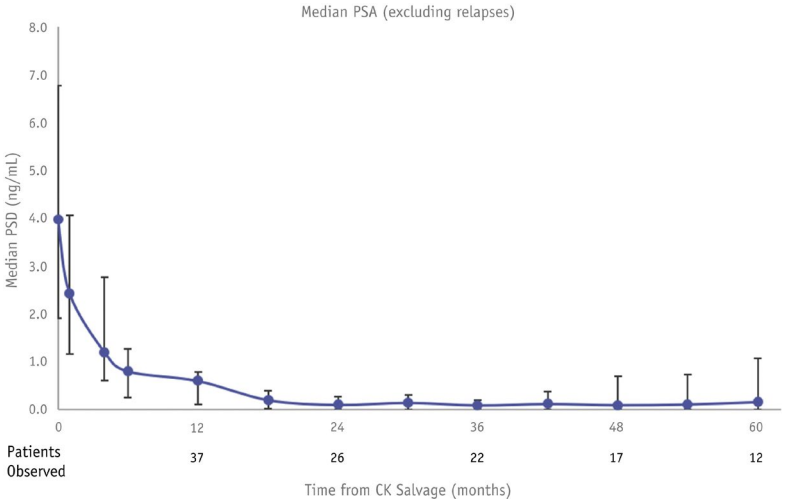
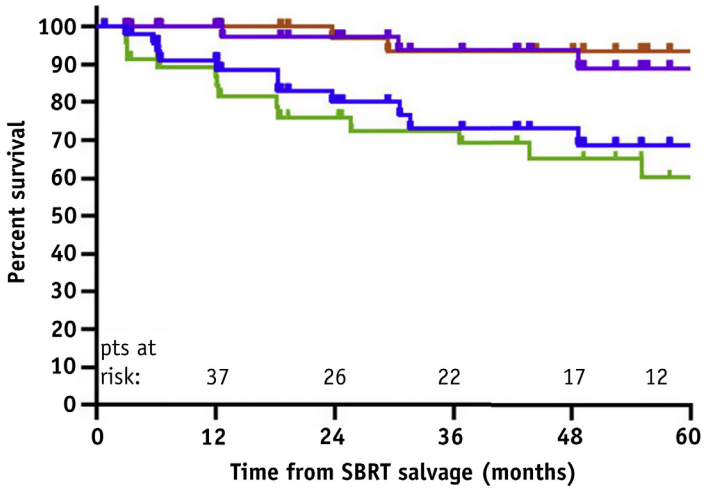
SBRT reirradiation

- Biopsy-proven locally recurrent disease at least 2 years out from initial RT, no evidence of disease elsewhere, no worse than G1 toxicity from initial course
- 50 patients, 43 treated with SBRT alone (no ADT)
- Median time to salvage 98 months
- 34 Gy in 5 consecutive daily treatments of 6.8 Gy





Patients at Risk at:	12 months	24 months	36 months	48 months	60 months
Freedom from Local Recurrence	41	33	27	22	16
Freedom from Distant Metastases	41	33	26	21	15
Freedom from Androgen Deprivation Therapy	38	26	22	17	12
Freedom from Biochemical Relapse	39	28	22	18	13

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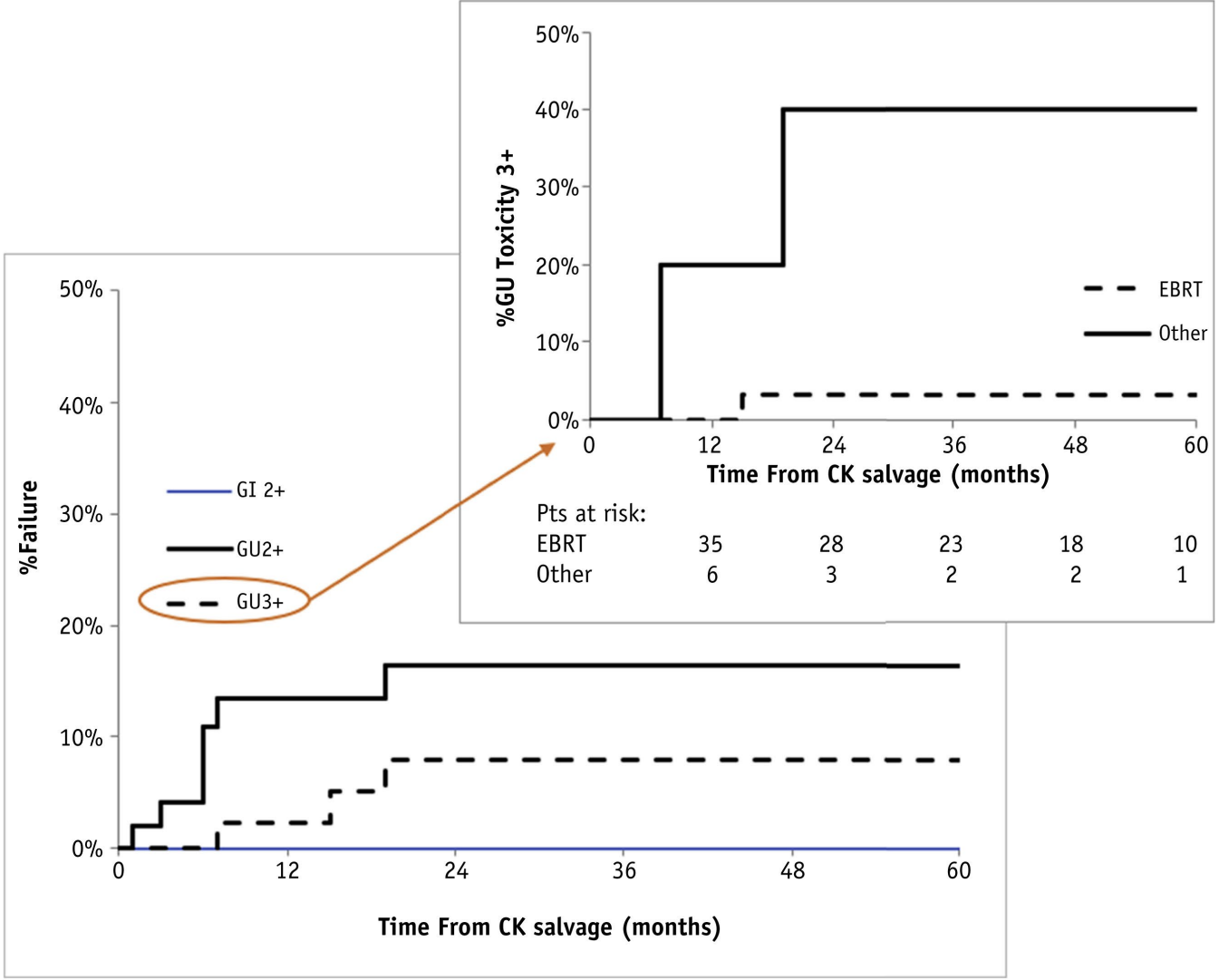
50%
40%
30%
20%
10%
0%
%GU Toxicity 3+
0
12
24
36
48
60
Time From CK salvage (months)
EBRT
Other
Pts at risk:
EBRT 35 28 23 18 10
Other 6 3 2 2 1
%Failure
GI 2+
GU2+
GU3+
Time From CK salvage (months)

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Future Directions, Ongoing Studies

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Ongoing Trials

- NRG-GU 005: SBRT (36.25 Gy/5 fractions vs. 70 Gy in 28 fractions)
- HYPO-RT-PC: SBRT (42.7 Gy/7 fractions) vs. 78 Gy in 39 fractions
- HEAT: SBRT (36.25 Gy/5 fractions) vs 70.2 Gy in 26 fractions

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NRG GU-06

- Patients:
  - Favorable intermediate risk PC
  - Prostate volume < 60 cc
  - IPSS <15
- Dose 36.25 Gy in 5 fractions every other day
- Target: Prostate +/- 1 cm SV defined on MRI
- PTV margin: 5 mm, 3 mm post
- Fiducials recommended but not required
- Hydrogel Spacer optional

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Areas of Interest

- Focal boost within prostate
- Spacer with SBRT
- Comparison to brachytherapy

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Conclusions

- SBRT is a safe and effective radiation modality for localized prostate cancer
  - Potentially appropriate for any risk group although less data for high risk and not for treating lymph nodes
  - Caution with very large prostates, significant obstructive urinary symptoms, prior TURP
  - Highly recommend MRI for treatment planning
- Awaiting longer follow-up and additional comparative studies
- Rectal spacer may reduce GI toxicity
- An option for locally recurrent disease after initial RT

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Thank You!