

Updates in Radiation Oncology: Of Brachytherapy and Beams

***David C. Beyer MD FACR, FACRO, FASTRO
Cancer Centers of Northern Arizona
Healthcare
Sedona, Arizona***



**Cancer Centers of
Northern Arizona Healthcare**
Sedona Campus

I have nothing to disclose



“It is difficult to see what
is genuinely new...,
harder still to admit
ignorance in the face of
it.”

-Mark Lilla



**Cancer Centers of
Northern Arizona Healthcare**

Sedona Campus

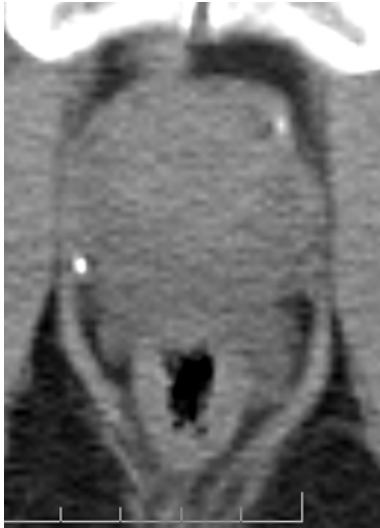
New York Review of Books March 24, 2016

Trends in Radiation Oncology 2017

- * External Beam
 - * Organ at Risk (OAR) protection
 - * Fractionation
 - * Field design and coverage
- * Brachytherapy
- * Androgen deprivation (ADT)

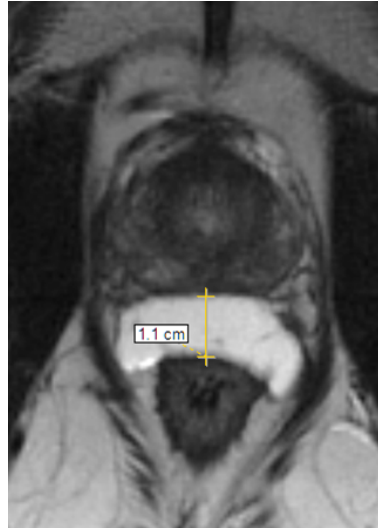
Hydrogel Space Creation, Maintenance and Absorption

Post Implant (1 week)
Axial CT image



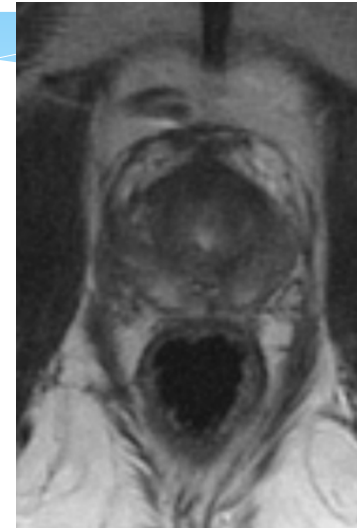
Post implant space

Post IMRT
Axial T2 MRI



**Space maintained for
about 3 months**

Six Months Post Implant
Axial T2 MRI



**Absorbed in about 6
months**

Bowel QOL with Hydrogel Spacer 5 Year Results

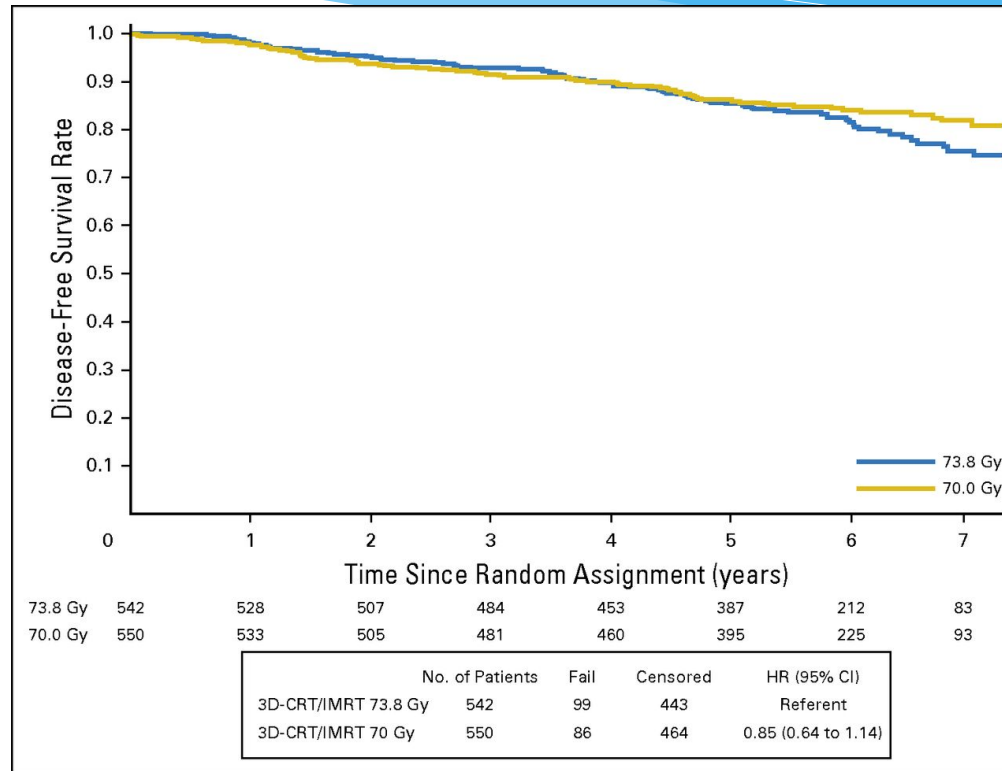
	With (n=54)	Without (n=60)
Age	73	73
PTV (cc)	126	123
Rectal Dose		
Volume in 90%	4%	13%
Volume in 70%	20%	32%
≥ Moderate Bowel Urgency	0%	14%
≥ Moderate Loss of Control	0%	7%
≥ Moderate Bowel Habits	0%	7%

NRG / RTOG 0415

Fractionation in Prostate Cancer

- * **Low risk prostate cancer**
 - * **T1b-T2c**
 - * **Gleason 2-6**
 - * **PSA<10**
- * **Stratified PSA, Gleason, and IMRT vs 3D**
 - * **Non-inferiority**
- * **Randomized 1:1**
 - * **73.8 Gy in 41 fractions over 8.2 weeks**
 - * **70 Gy in 28 fractions over 5-6 weeks**
- * **1092 evaluable men**
- * **Median F/U 5.8 years**

Estimates of disease-free survival (DFS) according to treatment assignment.



W. Robert Lee et al. JCO doi:10.1200/JCO.2016.67.0448

Biology of Extreme Hypofractionation

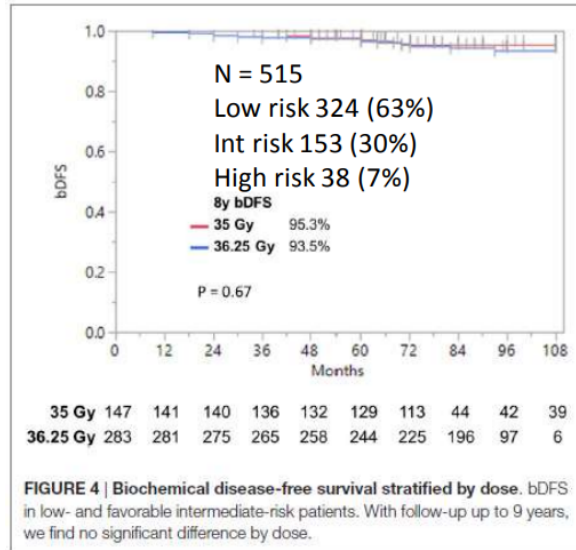
- * Basic laboratory data suggests α/β ratio favors large fractions
- * Mouse data suggests:
 - * Biologically more effective
 - * Slows rate of progression
 - * Cancer cells less likely to metastasize
- * Human data evolving showing equivalence

Cyberknife Data

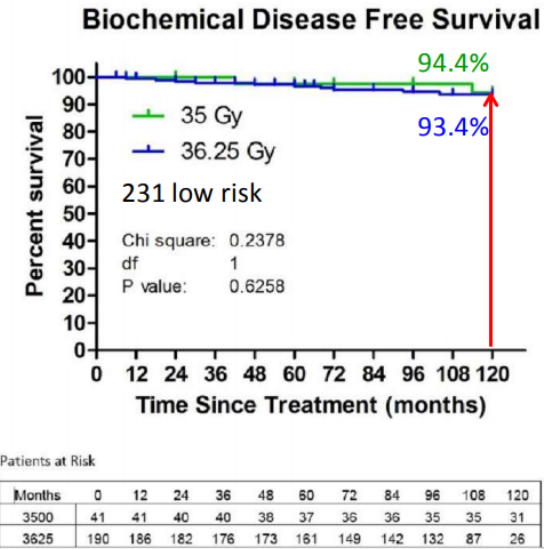
- * 515 men
- * 84 months median F/U
- * Risk groups
 - * 63% low
 - * 30% intermediate
 - * 7% high
 - * 14% ADT
- * 35-26.25 Gy / 5 daily fractions
 - * 5 mm expansion (3mm posterior)

SBRT

Flushing NY Experience

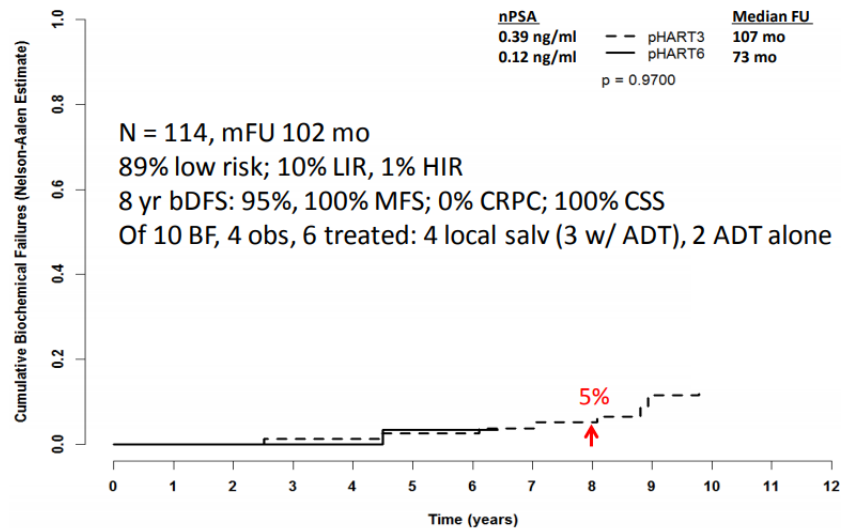


Katz A et al. Front Oncol 2016



Katz A. Cereus 2017

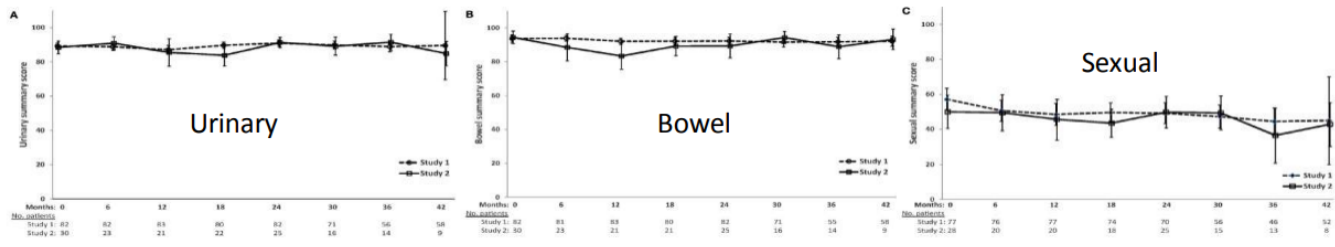
Sunnybrook SABR Experience



Medium Term SABR Outcomes

Study (yr)	Dose (Gy)/F/wk	EQD2 (Gy)	n	G6 (%)	Med FU(mo)	5y bDFS (%)	Acute G3+(%)		Late G3+(%)		
							GU	GI	GU	GI	ED
Pham et al. (2010)	34/5/1	82	40	100%	60	93%	2	0	3	0	50
Katz et al. (2013)	35–36.3/5/1	86.5–92.2	303	73%	60	95%	0	0	2	0	25
Kupelian et al. (2013)	35–40/4–5/1–2	86.5–110.6	135	80%	60	97%	NR	NR	NR	NR	NR
Mantz. (2014)	40/5/x	110.6	102	69%	>60	100%	2	0	NR	0	NR
Hannan et al. (2016)	45-50/5/2	138-168	91	47%	54	99%	0	2	5.4	6.8	26
Musunuru et al. (2016)	35/5/4	86.5	84	100%	74	97%	1	0	0	1	43
Zimmerman et al. (2016)	45/9/9	84.7	80	100%	83	96%	NR	NR	4	13%	NR
Total*			835	77%	63	97%	0.6%	0.3%	2.6%	1.0%	30%

No Effect of Dose of QOL

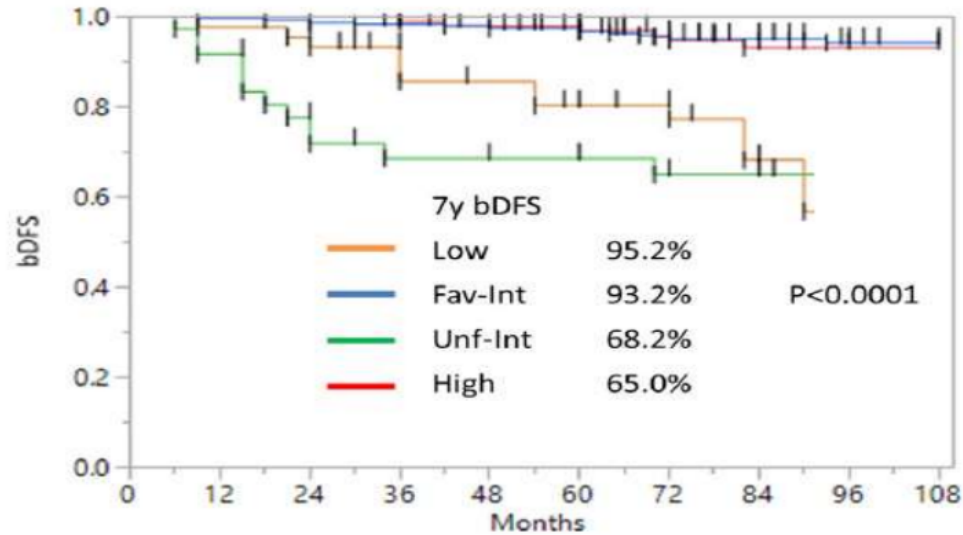


Summary domain	Average change			Worst change		
	Study 1 (35 Gy/5 F)	Study 2 (40 Gy/5 F)	p-Value	Study 1 (35 Gy/5 F)	Study 2 (40 Gy/5 F)	p-Value
Urinary			0.60			0.50
No MCIC	66 (80.5%)	22 (75.9%)		27 (32.9%)	12 (41.4%)	
MCIC	16 (19.5%)	7 (24.1%)		55 (67.1%)	17 (58.6%)	
Bowel			0.16			0.82
No MCIC	60 (73.2%)	17 (58.6%)		28 (34.2%)	11 (37.9%)	
MCIC	22 (26.8%)	12 (41.4%)		54 (65.9%)	18 (62.1%)	
Sexual			0.82			0.24
No MCIC	44 (57.1%)	16 (61.5%)		27 (35.1%)	13 (50.0%)	
MCIC	33 (42.9%)	10 (38.5%)		50 (64.9%)	13 (50.0%)	

QOL, quality of life; EPIC, Expanded prostate cancer index composite.

*Minimum clinically important change defined as a decrease in quality of life from baseline to follow-up which exceeds half of the standard deviation of the baseline value (10).

bDFS High Risk Prostate SBRT



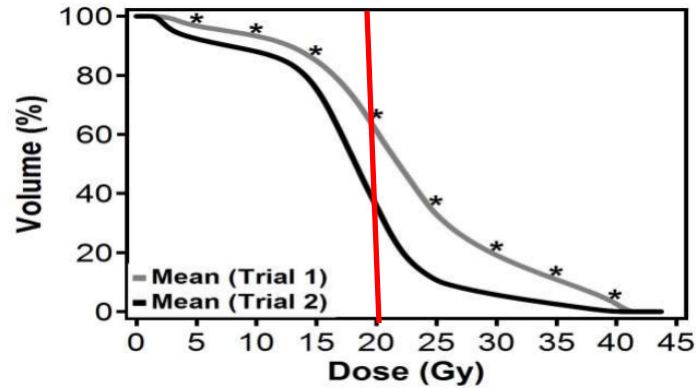
Low	324	318	313	301	293	278	251	179	103	35
Fav-Int	106	103	101	99	96	94	86	60	36	10
Unf-Int	47	45	42	37	33	29	27	15	5	2
High	38	35	27	22	21	20	18	10	4	1

SBRT High Risk PCa

- * **Combined trials**
 - * **FASTR (NCT01439542)**
 - * **SATURN (NCT01953055)**
- * **40 Gy/5 weekly Fx (25 Gy to lymph nodes)**
- * **Higher risk rectal bleeding**
 - * **5mm vs 3mm margin**
 - * **Seminal vesicle vs prostate only**
 - * **V40Gy 1.53cc vs. 0.69cc**
 - * **V20 Gy 55cc vs 40cc**

Rates of GI Bleeding: FASTR vs. SATURN

GI outcomes	N (15 total)	N (30 total)
Grade 1 bleeding	2	4
Grade 2 bleeding	2	0
Grade 3 bleeding	3	0
Grade 4 bleeding	1	0



High Risk SBRT at UCLA

- * Linac Based SBRT 40Gy prostate in 5 Fx
 - * +/- 25 Gy nodes
 - * +/- 9 months ADT
- * 73 men with 13.8 mos F/U
- * Nodal RT had “no significant association with either physician or patient reported toxicity”
- * 2.7% Biochemical failure

Watch for Hypofractionation Guidelines

Public comment through ASTRO, AUA, ASCO

NOT TO BE COPIED, DISSEMINATED OR REFERENCED

1 **Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO,**
2 **and AUA Evidence-Based Guideline**

3
4 Scott C. Morgan, MD, MSc, FRCPC,^a Karen Hoffman, MD, MHSc, MPH,^b D. Andrew Loblaw,
5 MD, MSc, FRCPC,^c Mark K. Buyyounouski, MD, MS,^d Caroline Patton, MA,^e Daniel Barocas,
6 MD, MPH,^f Soren Bentzen, DSc, PhD,^g Michael Chang, MD,^h Jason Efstathiou, MD, PhD,ⁱ
7 Patrick Greany, PhD,^j Per Halvorsen, MS,^k Bridget F. Koontz, MD,^l Colleen Lawton, MD,
8 FASTRO,^m C. Marc Leyrer, MD,ⁿ Daniel Lin, MD,^o Michael Ray, MD, PhD,^p Howard Sandler,
9 MD, MS, FASTRO, FASCO^{q*}

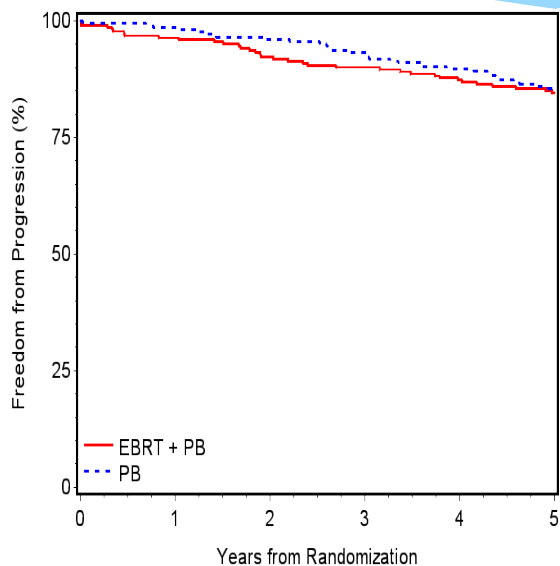
PSA Bounce with SBRT

Author	n=	Definition	%	Median ng/ml	Median months
King	41	≥ 0.2 ng/ml	29	0.39	18
Lee	29	≥ 0.2 ng/ml	28	0.69	9
McBride	45	≥ 0.4 ng/ml	20	1.07	12
Chen	100	≥ 0.2 ng/ml	31	0.5	15
Katz	304	≥ 0.2 ng/ml	17	0.55	30
Vu	120	≥ 0.2 ng/ml	28	0.5	9

RTOG 0232: Study Schema

S T R A T I F Y	Stage	R E C O R D	Isotope	R A N D O M I Z E	Arm 1: 45 Gy EBRT Partial pelvis (1.8 Gy/fraction M-F for five weeks) followed 2-4 weeks later by Pd-103 (100 Gy) or I-125 (110 Gy)			
	1. T1c 2. T2a – T2b					1. I-125 2. Pd-103	or	
	Gleason Score							Arm 2: Pd-103 (125 Gy) or I-125 (145 Gy)
	1. ≤ 6 2. 7							
	PSA							
	1. 0 - < 10 2. 10-20							
Neoadjuvant Hormonal Therapy								
1. No 2. Yes								

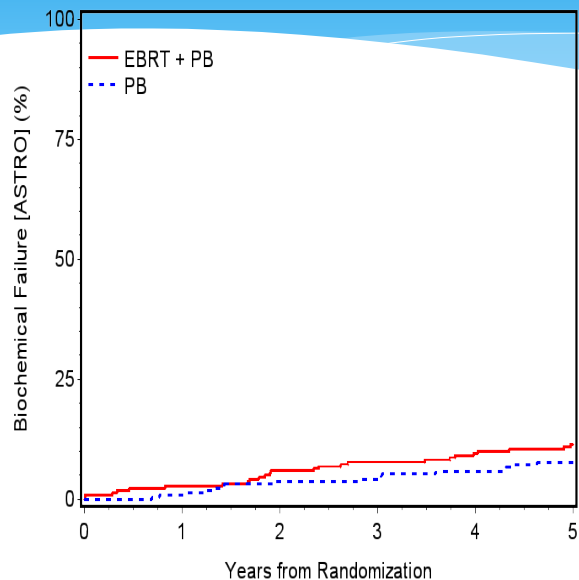
Freedom From Progression



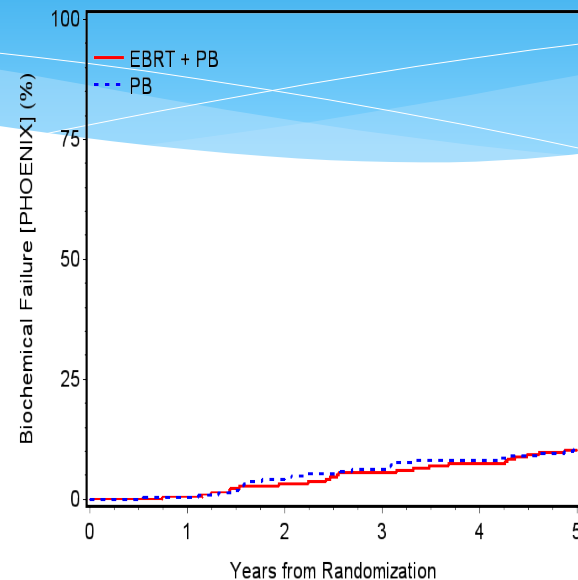
Patients at Risk						
EBRT + PB	220	212	203	198	192	183
PB	223	219	213	207	198	186

Biochemical Failure

ASTRO Definition



Phoenix Definition

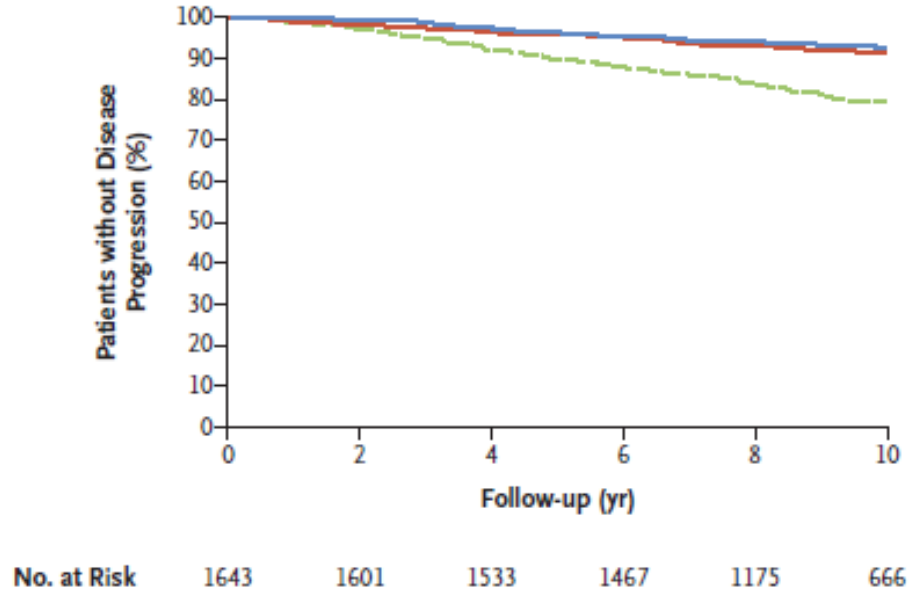


Patients at Risk						
EBRT + PB	220	212	203	198	192	183
PB	223	219	213	208	199	187

Patients at Risk						
EBRT + PB	220	213	204	198	191	178
PB	223	220	211	203	195	182

ProtecT Trial

B Freedom from Disease Progression



Adverse Events

		EBRT + PB (n=283)		PB (n=292)		p-value*
ACUTE	Any Grade \geq 2 Toxicity	n	%	n	%	0.68
	Yes	80	28.3	78	26.7	
	No	203	71.7	214	73.3	
	Any Grade \geq 3 Toxicity					0.97
	Yes	23	8.1	24	8.2	
	No	260	91.9	268	91.8	
LATE	Any Grade \geq 2 Toxicity					0.0001
	Yes	150	53.0	107	36.9	
	No	133	47.0	183	63.1	
	Any Grade \geq 3 Toxicity					0.039
	Yes	35	12.4	21	7.2	
	No	248	87.6	269	92.8	

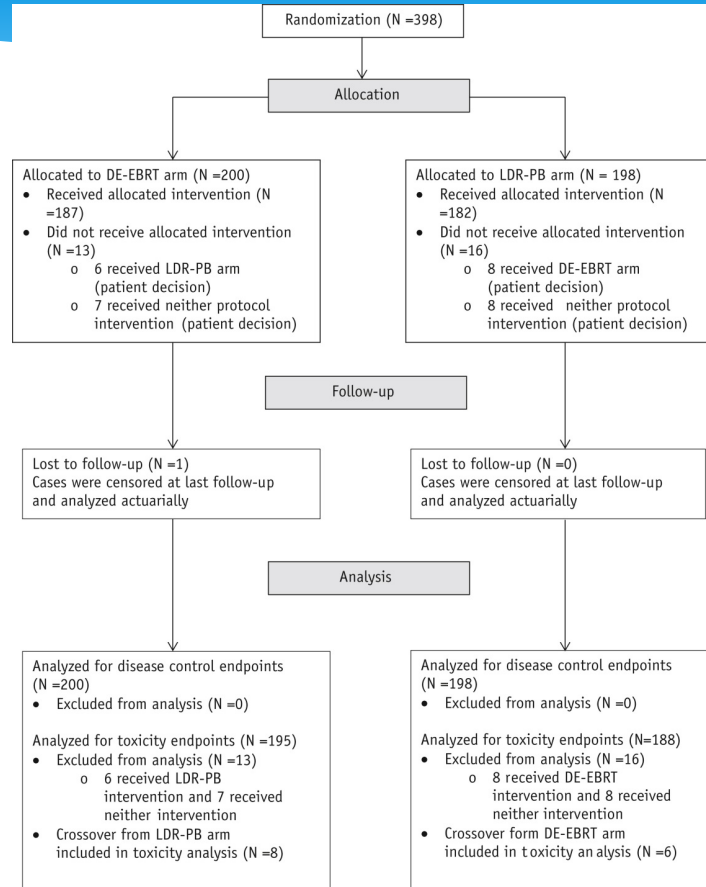
Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer

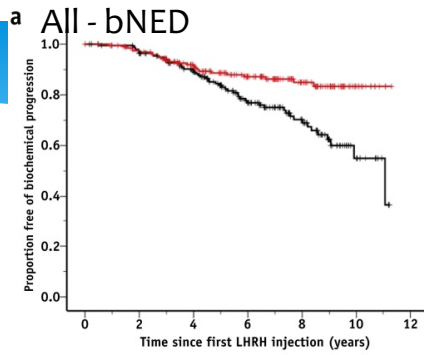
W. James Morris, MD, FRCPC, Scott Tyldesley, MD, FRCPC, Sree Rodda, MBBS, MRCP, FRCR, Ross Halperin, MD, FRCPC, Howard Pai, MD, FRCPC, Michael McKenzie, MD, FRCPC, Graeme Duncan, MB, ChB, FRCPC, Gerard Morton, MB, MRCPI, FRCPC, FFRRCSI, Jeremy Hamm, MSC, Nevin Murray, MD, FRCPC

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DOI: 10.1016/j.ijrobp.2016.11.026



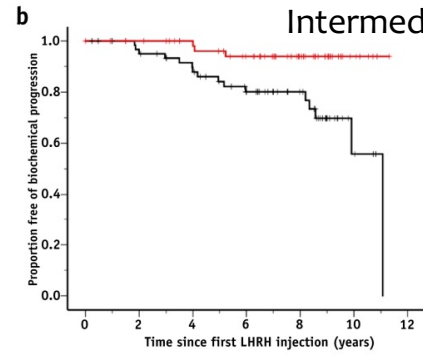
Fig. 1





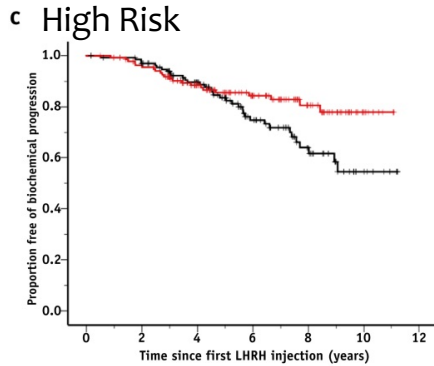
Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	200	186	168	145	119	93	74	52	27	11
LDR-PB	198	184	168	147	127	106	86	59	38	14



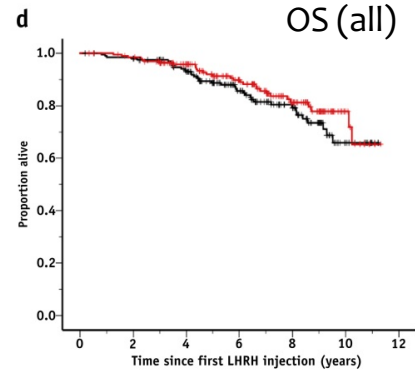
Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	63	57	54	49	43	38	30	25	12	4
LDR-PB	59	55	54	50	47	42	35	26	7	6



Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	137	129	114	96	76	55	44	27	15	7
LDR-PB	139	128	114	97	80	64	51	33	21	8



Numbers at risk:

Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	200	192	184	161	134	109	85	66	40	16
LDR-PB	198	191	182	160	137	116	94	65	41	15



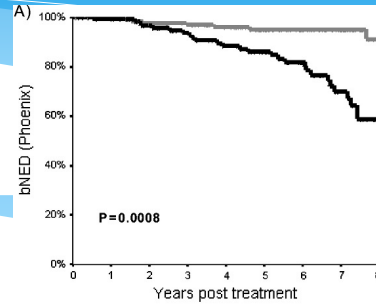
Surprised by the magnitude of
the difference?

Others have reported the exact same
finding without impacting on practice
patterns!

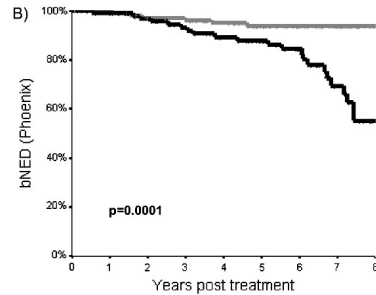
Single Institution Matched Pair

5 year biochemical control

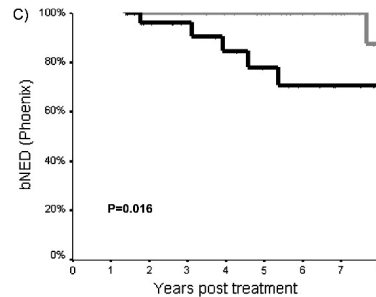
LDR Brachytherapy vs EBRT



All

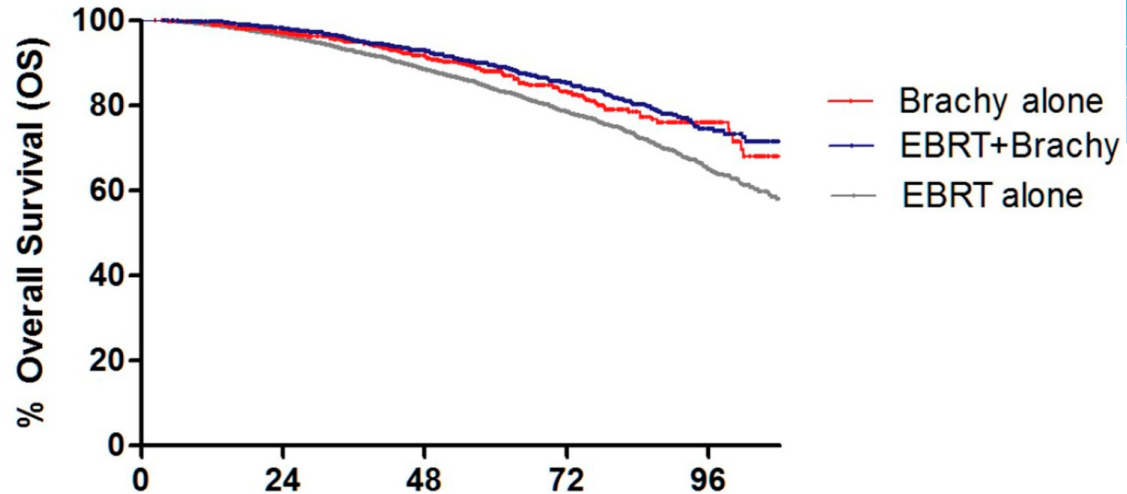


Low Risk



Intermediate
Risk

NCDB Favorable High Risk

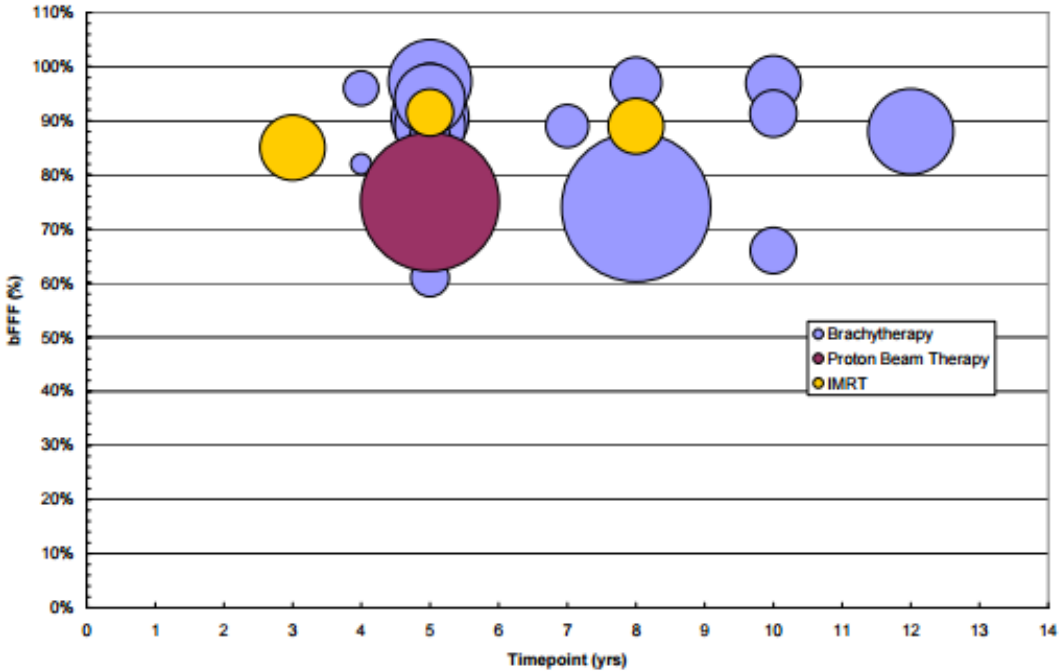


Number at Risk

	0	24	48	72	96
EBRT+Brachy	1530	1357	938	499	143
Brachy alone	703	610	422	231	67
EBRT alone	7169	5909	3582	1638	429



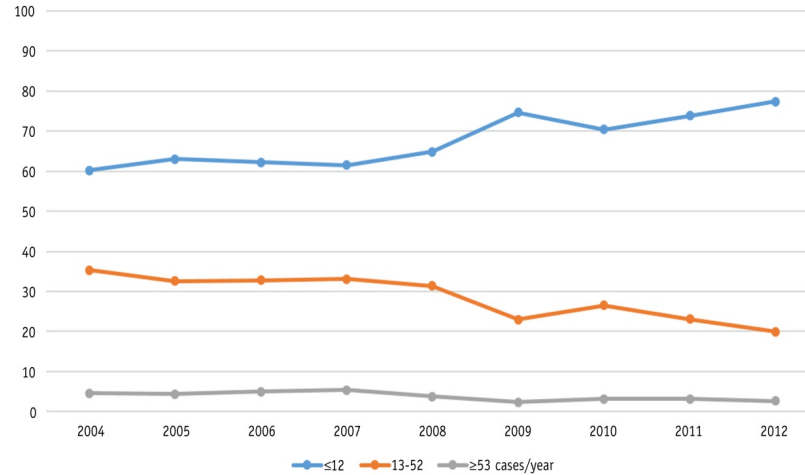
Institute for Clinical and Economic Review - ICER



Low Volume Brachytherapy

NCDB records of Non-Academic Practices

% of Non-academic Practices by Case Volume



Non-academic Practices(%)	2004	2005	2006	2007	2008	2009	2010	2011	2012
≤12	60.20	63.06	62.26	61.50	64.86	74.64	70.37	73.79	77.38
13-52	35.28	32.58	32.74	33.12	31.41	22.99	26.48	23.11	19.96
≥53 cases/year	4.52	4.35	5.00	5.38	3.74	2.37	3.15	3.11	2.66

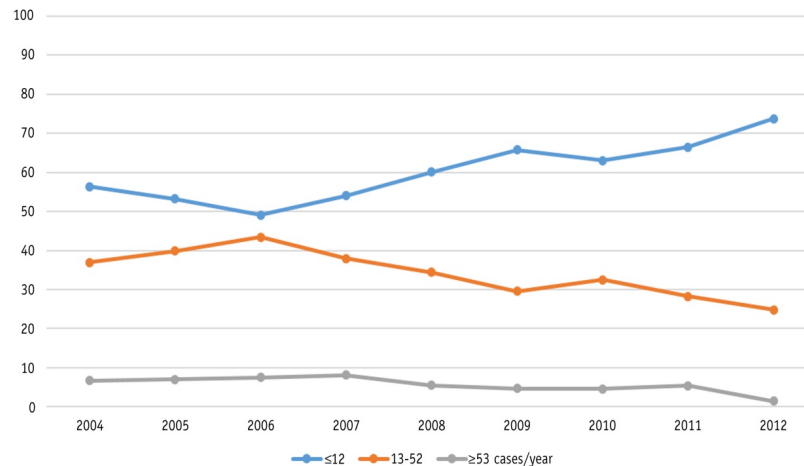
Training in Brachytherapy

NCDB records of Academic Medical Centers

73.7% perform ≤ 12 cases per year

1.46% perform ≥ 53 cases per year!

% of Academic Practices by Case Volume



Academic Practices(%)	2004	2005	2006	2007	2008	2009	2010	2011	2012
≤12	56.36	53.16	49.06	54.04	60.12	65.77	62.99	66.44	73.72
13-52	36.97	39.87	43.40	37.89	34.36	29.53	32.47	28.19	24.82
≥53 cases/year	6.67	6.96	7.55	8.07	5.52	4.70	4.55	5.37	1.46

ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer

Sree Rodda, MBBS, MRCP, FRCR, Scott Tyldesley, MD, FRCPC, W. James Morris, MD, FRCPC, Mira Keyes, MD, FRCPC, 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, Nevin Murray, MD, FRCPC

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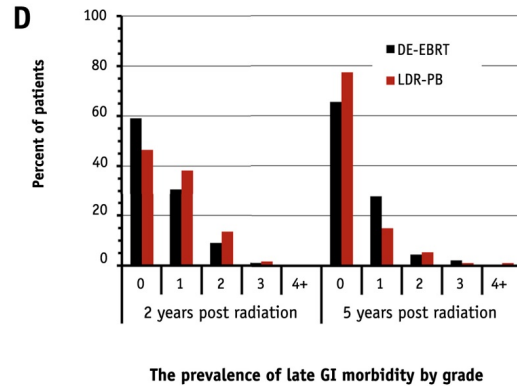
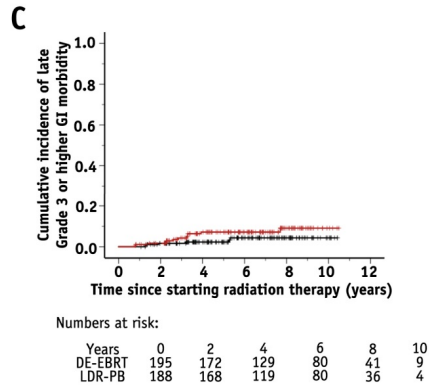
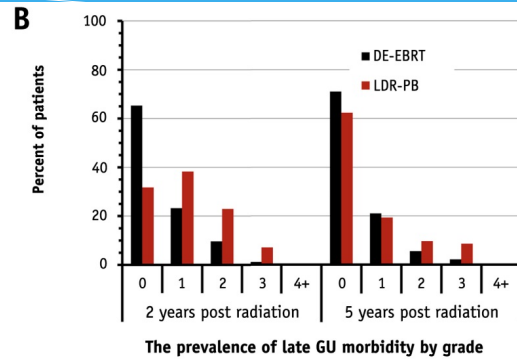
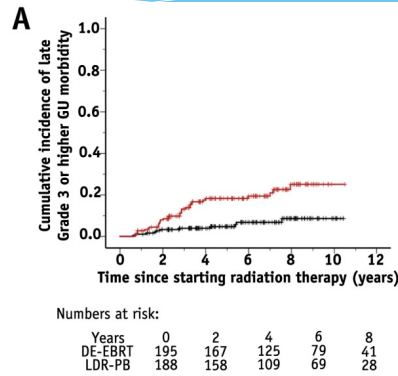


Fig. 1

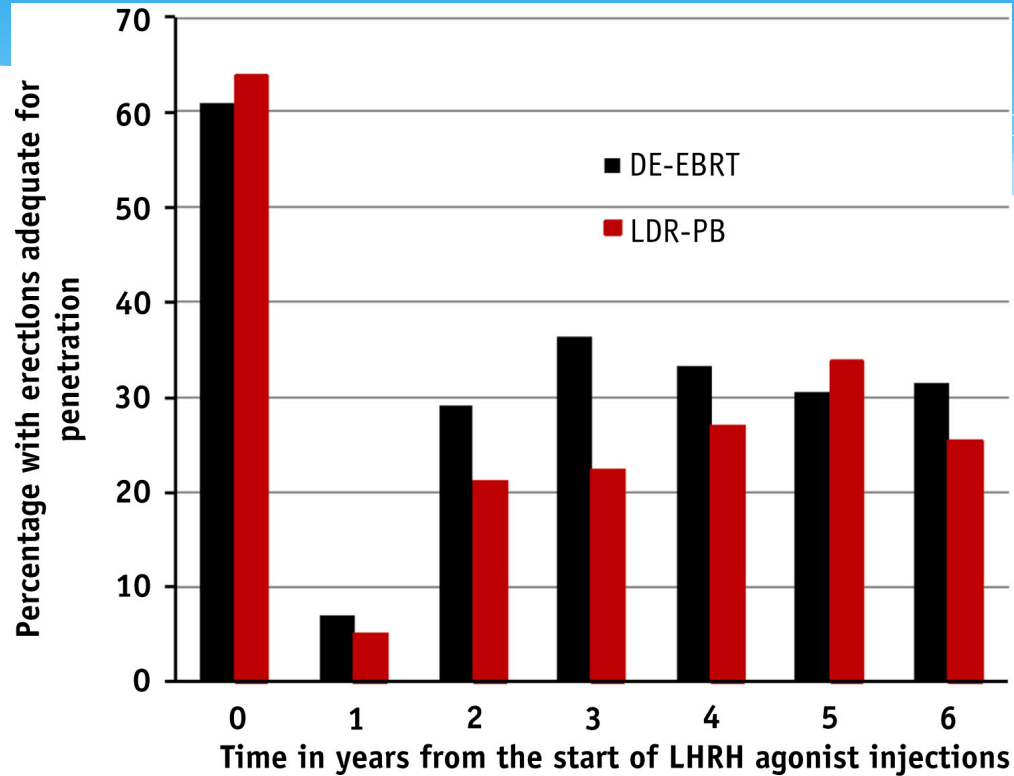
*Grade	1	2	3	4
GU	Nocturia twice baseline. Microscopic hematuria. Light atrophy and minor telangiectasia. Occasional (< weekly) use of incontinence pads.	Moderate frequency. Nocturia more than twice baseline. Generalized telangiectasia. Intermittent macroscopic hematuria. Two or fewer coagulations. Intermittent (< daily use of incontinence pads. Regular non-narcotic or occasional narcotic for pain.	Severe frequency and dysuria. Nocturia more frequent than once every hour. Minor surgical procedure (e.g. TURP, dilation). Reduction in bladder capacity (150 cc). Frequent hematuria requiring at least one transfusion. More than two coagulations for hematuria. Hyperbaric oxygen for bleeding/ulceration. Persistent use of incontinence pads/. Regular narcotic for pain.	Severe hemorrhagic cystitis or ulcerations with requirement for urinary diversion and/or cystectomy.
GI	Excess bowel movements at least twice baseline. Slight rectal discharge or blood.	More than 2 antidiarrheals/week. Two or fewer coagulations for bleeding. Occasional steroids for ulcerations. Occasional dilations. Intermittent use of incontinence pads. Regular non-narcotic or occasion narcotic for pain.	More than 2 antidiarrheals/day. At least one blood transfusion or more than two coagulations for bleeding. Prolonged steroids per enema. Minor surgical procedure. Hyperbaric oxygen for bleeding/ulceration. Regular dilation. Persistent use of incontinence pads. Regular narcotic for pain.	Dysfunction requiring surgery. Perforation. Life-threatening bleeding.

*Grade 0 = no adverse effects, Grade 5 corresponds to complications leading to death.





ED in ASCENDE-RT



Background RTOG 0526

- * **Local recurrence after beam radiotherapy for prostate cancer is common: 30-50%**
- * **Dose escalation studies suggest that this is rarely due to inherent radio-resistance but rather due to insufficient dose**
- * **Prior studies of salvage brachytherapy for recurrence after EBRT limited by retrospective reporting**
- * **For appropriately selected patients, single-institution studies report bNED rates of 85% at 3 years, 70% @ 4 years, 65% at 5 years, falling to 50% by 10 years**
- * **Complication rates vary widely but are reported up to 35% grade 3 GU and 12% grade 4 colostomy/urostomy**

Treatment Delivery

	Iodine 125	Palladium 103
# patients	85	7
# seeds	75 (32-120)	81 (62-98)
Activity per seed	0.34 (0.26-0.4)	1.6 (1.4-1.9)

- * Contour reviews per protocol (61%) or with acceptable variation (37%)
- * DVA reviews on tumor volume and organs at risk per protocol for 89%.
- * Median volume of ETV was 29.2 cc (range 6-54 cc)
- * Median D90 ETV 108% (range 46%-150%; IQR 101-116%)
- * Median V100 94% (range 61-100%; IQR 91-96%)

Conclusions 0526

- * **Salvage LDR brachytherapy for locally recurrent prostate cancer following EBRT is tolerated with grade 3 late GI/GU AE's seen in 13.8% of patients in a multi center phase 2 trial**
- * **Both occurrence of, and time to, late GI/GU AE's are related to dose as reflected by V100**
- * **Treatment efficacy will be reported when minimum 5 years follow up reached**

Major Randomized Trials Using HT & XRT:

- * RTOG 8307
 - * (DES vs Megestrol)
- * RTOG 8531 (-/+)
- * RTOG 8610 (+/-) ?
- * EORTC (+)
- * RTOG 9202 (+)
 - * Locally advanced PSA<150
 - * RT + Goserelin / Eulexin 2mos. prior and during
 - * +/- 2 years Goserelin

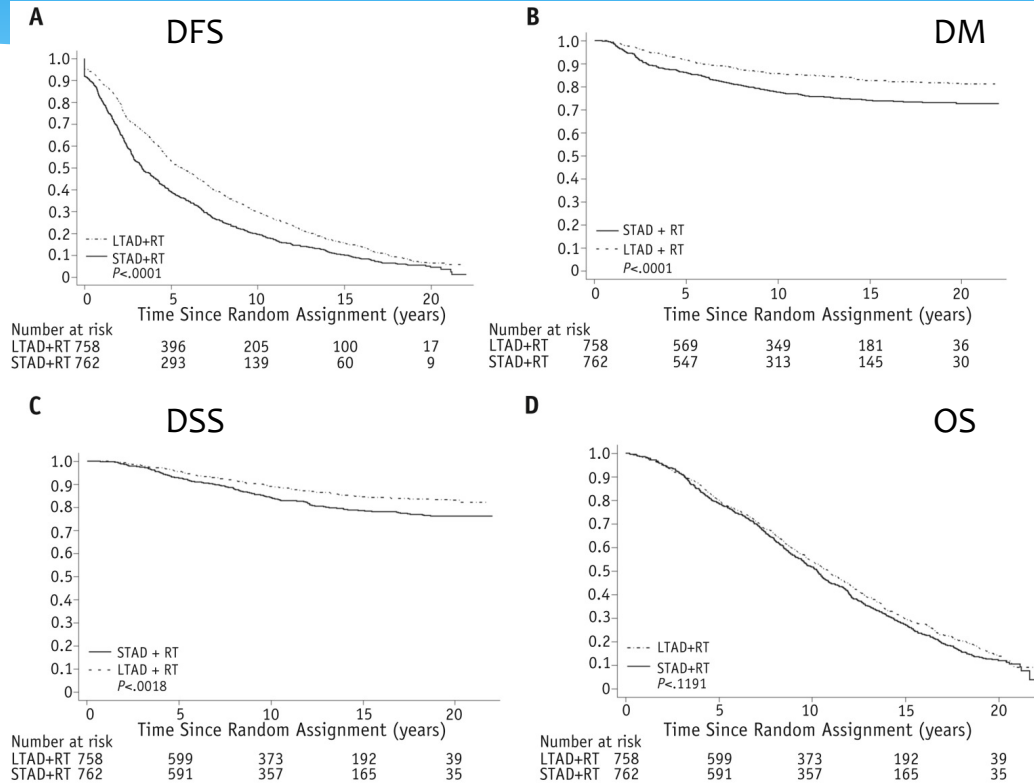
*Duration of Androgen Deprivation in Locally Advanced Prostate
Cancer: Long-Term Update of NRG Oncology RTOG 9202*

*Colleen A.F. Lawton, MD, Xiaolei Lin, MS, Gerald E. Hanks, MD,
Herbert Lepor, MD, David J. Grignon, MD, Harmar D. Brereton, MD,
Meena Bedi, MD, Seth A. Rosenthal, MD, Kenneth L. Zeitzer, MD,
Varagur M. Venkatesan, MD, Eric M. Horwitz, MD, Thomas M.
Pisansky, MD, Harold Kim, MD, Matthew B. Parliament, MD, Rachel
Rabinovitch, MD, Mack Roach, MD, Young Kwok, MD, James J.
Dignam, PhD, Howard M. Sandler, MD*

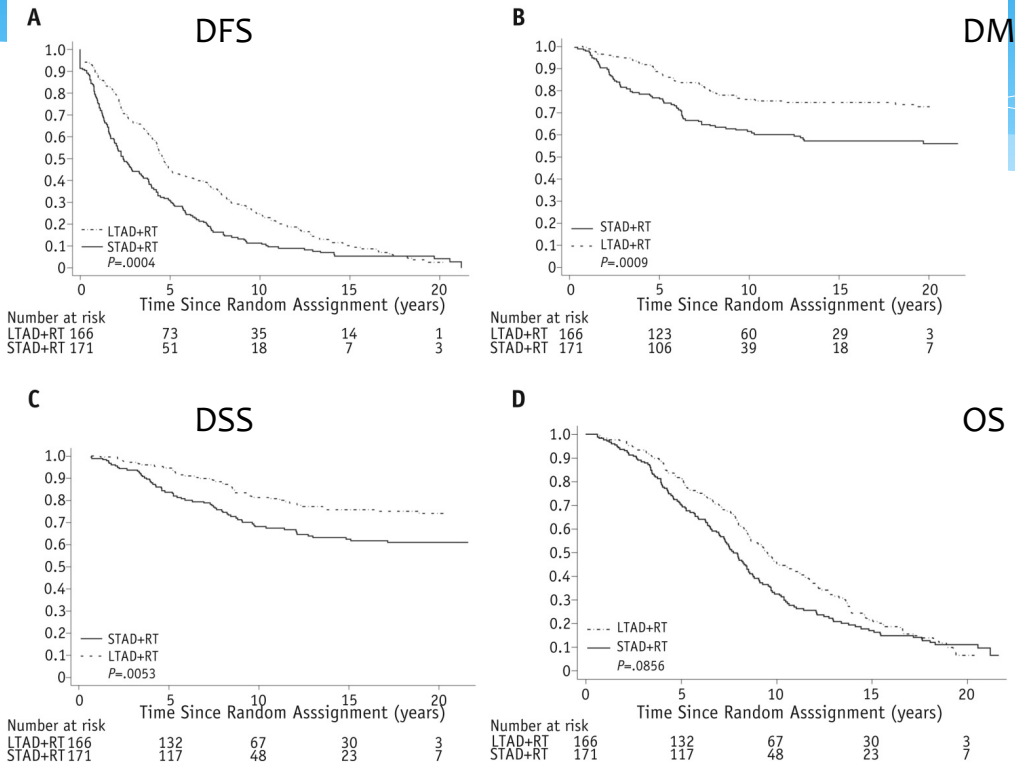
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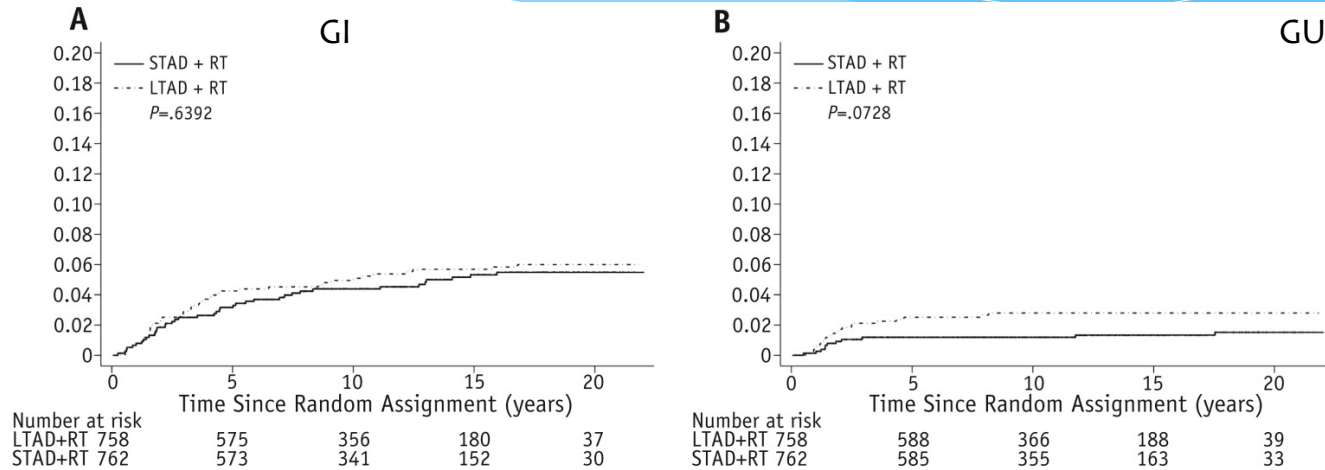
RTOG 92-02



92-02 Gleason 8-10



9202 Late Toxicity



External Beam Radiation Therapy or Brachytherapy With or Without Short-course Neoadjuvant Androgen Deprivation Therapy: Results of a Multicenter, Prospective Study of Quality of Life

Hiram A. Gay, MD, Martin G. Sanda, MD, Jingxia Liu, PhD, Ningying Wu, PhD, Daniel A. Hamstra, MD, PhD, John T. Wei, MD, Rodney L. Dunn, MS, Eric A. Klein, MD, Howard M. Sandler, MD, Christopher S. Saigal, MD, MPH, Mark S. Litwin, MD, MPH, Deborah A. Kuban, MD, Larry Hembroff, PhD, Meredith M. Regan, ScD, Peter Chang, MD Meredith Regan, Larry Hembroff, John T. Wei, Dan Hamstra, Rodney Dunn, Laurel Northouse, David Wood, Eric A. Klein, Jay Ciezki, Jeff Michalski, Gerald Andriole, Mark S. Litwin, Christopher Saigal, Thomas Greenfield, PhD, Louis Pisters, Deborah Kuban, Howard Sandler, Jim Hu, Adam Kibel, Douglas Dahl, Anthony Zietman, Peter Chang, Irving Kaplan, Andrew Wagner, Martin G. Sanda, Jeff M. Michalski, MD Hiram A. Gay, MD, Martin G. Sanda, MD, Jingxia Liu, PhD, Ningying Wu, PhD, Daniel A. Hamstra, MD, PhD, John T. Wei, MD, Rodney L. Dunn, MS, Eric A. Klein, MD, Howard M. Sandler, MD, Christopher S. Saigal, MD, MPH, Mark S. Litwin, MD, MPH, Deborah A. Kuban, MD, Larry Hembroff, PhD, Meredith M. Regan, ScD, Peter Chang, MD Meredith Regan, Larry Hembroff, John T. Wei, Dan Hamstra, Rodney Dunn, Laurel Northouse, David Wood, Eric A. Klein, Jay Ciezki, Jeff Michalski, Gerald Andriole, Mark S. Litwin, Christopher Saigal, Thomas Greenfield, PhD, Louis Pisters, Deborah Kuban, Howard Sandler, Jim Hu, Adam Kibel, Douglas Dahl, Anthony Zietman, Peter Chang, Irving Kaplan, Andrew Wagner, Martin G. Sanda, Jeff M. Michalski, MD

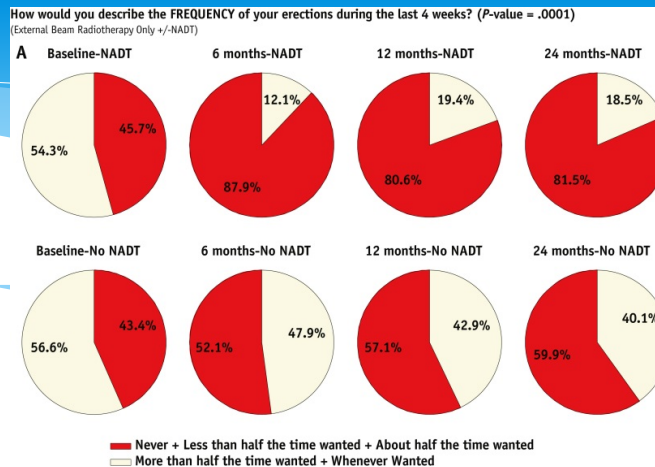
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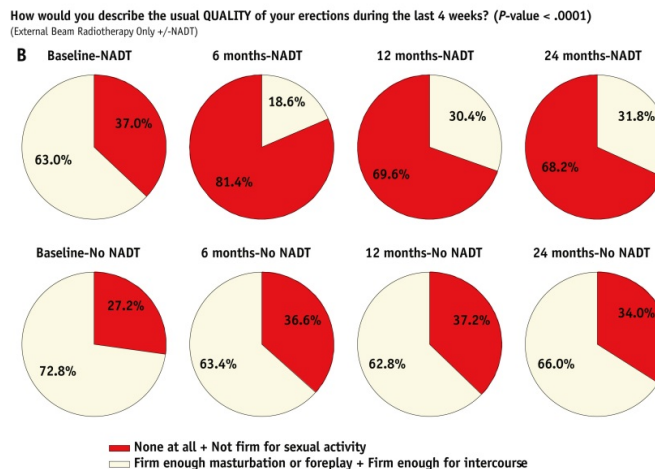
DOI: 10.1016/j.ijrobp.2017.02.019



Frequency of erections

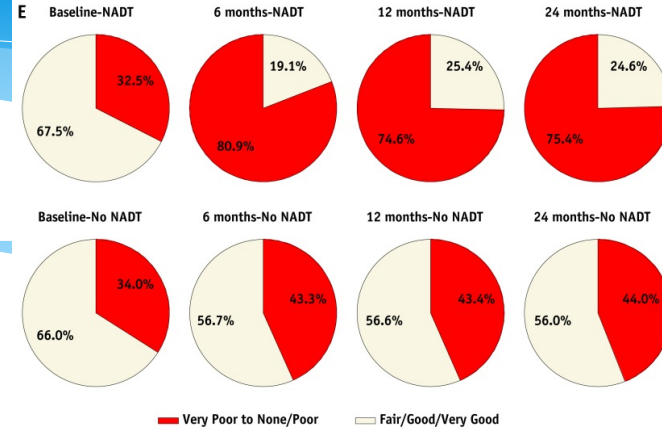


Quality of erections



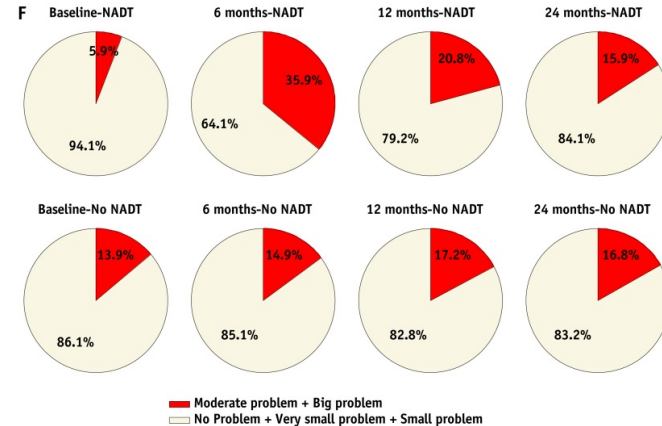
Ability to function sexually

Overall, how would you rate your ability to function sexually during the last 4 weeks? (*P*-value < .0001)
(External Beam Radiotherapy Only +/-NADT)



Problem with lack of energy

How big a problem has 'Lack of Energy' been for you during the last 4 weeks? (*P*-value = .0003)
(External Beam Radiotherapy Only +/-NADT)



Falcon Trial

^{18}F -fluciclovine PET/CT

- * **Pre-planned interim analysis of first**
 - * **85 new biochemical recurrences**
 - * **56 post prostatectomy**
 - * **PSA_m 0.63 ng/ml**
 - * **Scan + 40% in bed and 22% extraprostatic**
- * **Plan changed 61.2% post PET**
 - * **15.3% watch and wait**
 - * **21.2% systemic treatment**
 - * **23.5% Modified radiation fields**

RTOG Guidelines for Nodal Coverage

- * 54 C-11 PET positive patients
- * 47.2% within RTOG recommended WPRT fields

