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Boost brachytherapy in prostate cancer

Expert: **Dr Alfonso Gomez Iturriaga**, Cruces University Hospital, Baracaldo, Spain

Discussant: **Dr Berardino De Bari**, Réseau Hospitalier Neuchâtelois, La Chaux-de-Fonds, Switzerland

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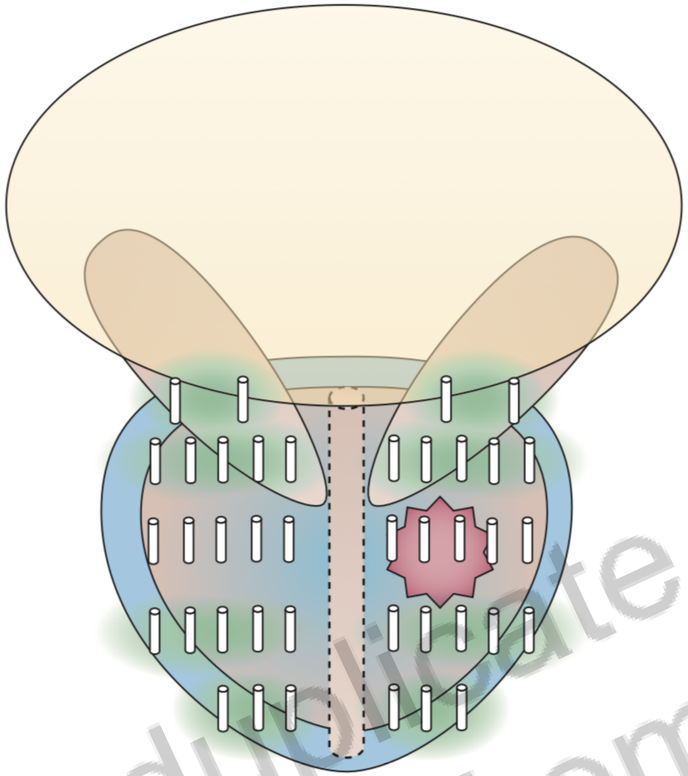
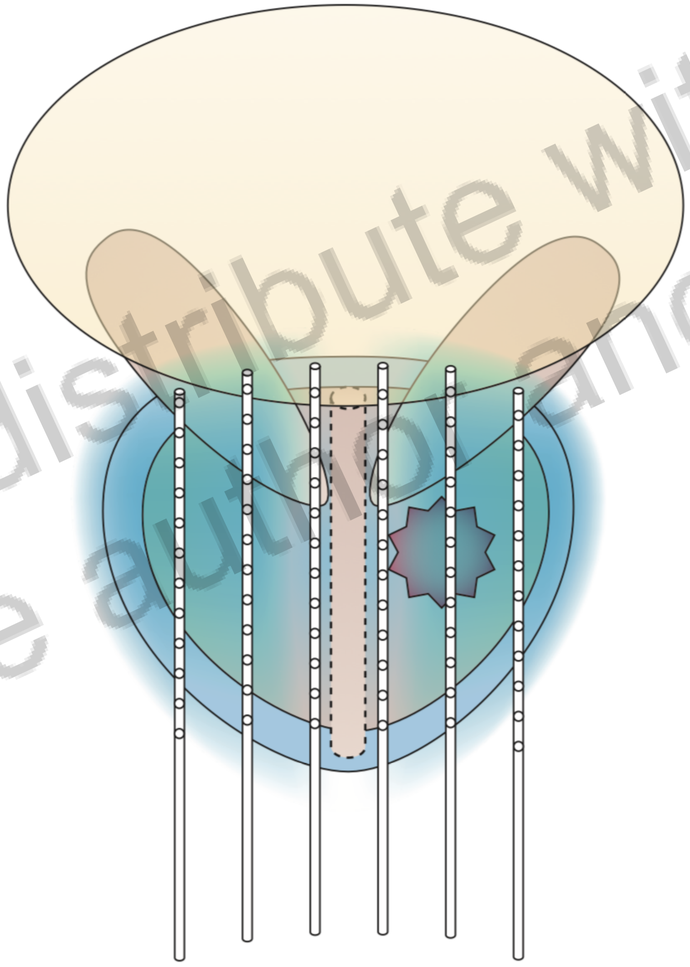
HDR prostate brachytherapy

Alfonso Gomez Iturriaga
Cruces University Hospital
Biocruces Bizkaia Health Research Institute
Barakaldo, SPAIN



LDR-BT
A needle deposits ^{125}I seeds with a dose cloud that covers the CTV

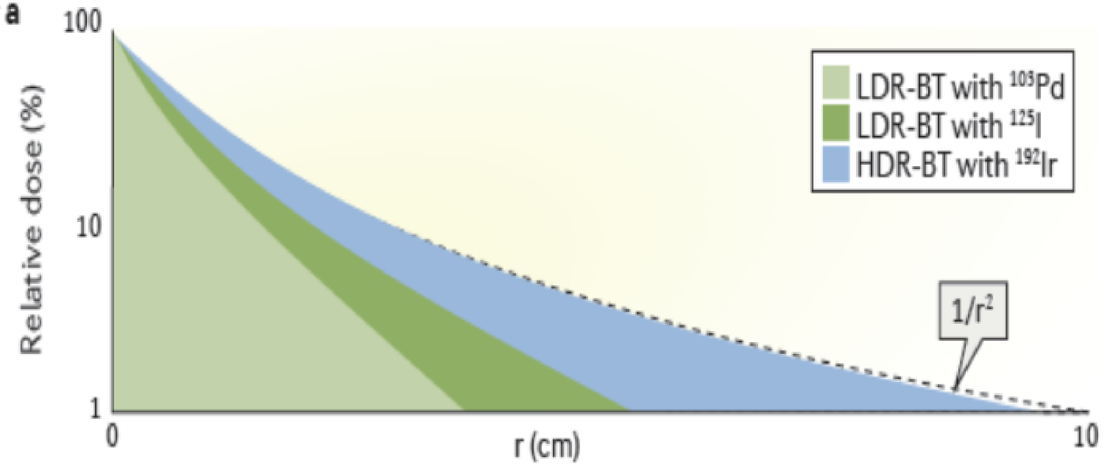


HDR-BT
^{192}Ir dwell positions and dwell times create a dose cloud to cover the CTV

Source Characteristics

- LDR
  - Most commonly uses ^{125}I or ^{103}Pd
  - Relatively lower energy
    - Source placement critical
    - No room shielding required
- HDR
  - Significantly higher energy source
    - Dosimetry more forgiving
    - Requires shielded room for treatment delivery

Radio-nuclide	Half-life (days)	Average Energy (keV)
^{125}I	59.4	28.4
^{103}Pd	17.0	20.7
^{131}Cs	9.7	30.4
^{192}Ir	73.8	380



Prostate Brachytherapy

- Superior form of conformal radiotherapy
- Tightest achievable dose distribution of any modern radiotherapy treatment
- Allows dose escalation far beyond what is safe with EBRT alone

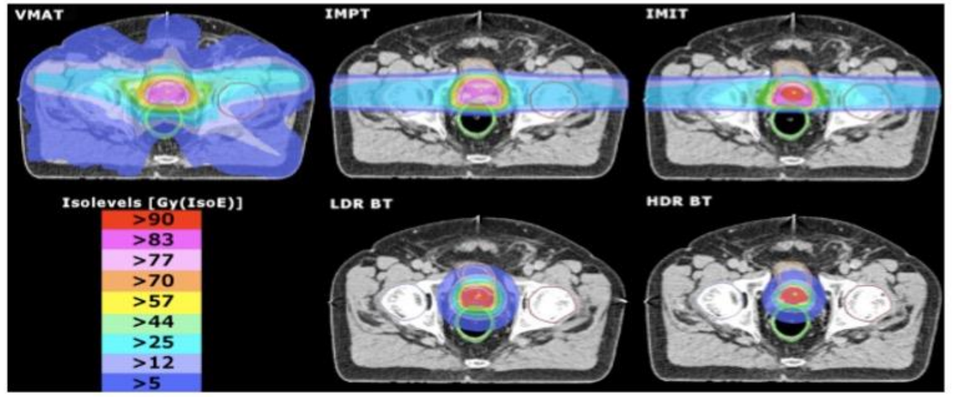
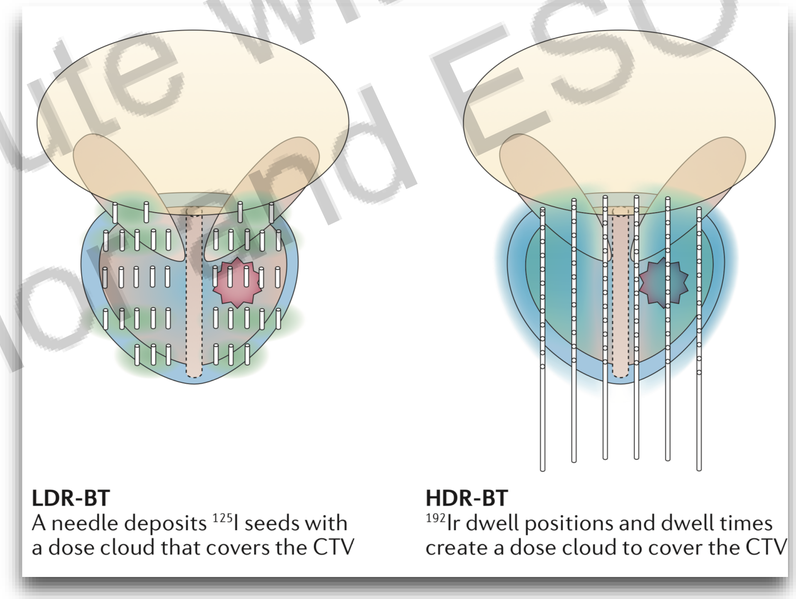


Fig. 2. Representative dose distributions for a selected patient for all 5 treatment techniques after radiobiological conversion.

IJROBP. Volume 88, Issue 3 , Pages 715-722, 1 March 2014

Treatment delivery

- HDR dose optimization:
  - Needle insertion (geometry)
  - Dwell position
  - Dwell times
- Compared to LDR, HDR is “high density”:
  - HDR implant has 2x the number of dwell positions vs LDR seeds
  - Seeds usually the same strength, but in HDR dwell times vary at each position
- Most Brachytherapists or Physicist experienced in both modalities agree that with HDR gets consistently more robust dose coverage and better normal tissue sparing



LDR-BT
A needle deposits ^{125}I seeds with a dose cloud that covers the CTV

HDR-BT
^{192}Ir dwell positions and dwell times create a dose cloud to cover the CTV

Radiation Oncologists

- All in the same team
- All want to use the most effective treatment
- Increase the chances of CURE

Low dose rate prostate brachytherapy

Bradley J. Stish[1], Brian J. Davis[1], Lance A. Mynderse[2], Robert H. McLaren[2], Christopher L. Deufel[1], Richard Choo[1]

Transl Androl Urol 2018;7(3):341-356

Study	Number of patients	Risk group (%)			Supplemental EBRT (%)	Biochemical control (%)				CSS (%)	OS (%)
		Low	Intermediate	High		Overall (years follow-up)	Low risk	Intermediate risk	High risk		
Blasko *et al.* 2000 (68)	230	45	46	9	0	83.5 (9 years)	87	79	68	100	–
Zelefsky *et al.* 2007 (69)	2,693	55	40	5	0	N/A (8 years)	82	70	40	–	–
Henry *et al.* 2010 (70)	1,298	44	33	14	0	N/A (10 years)	86	77	61	–	–
Taira *et al.* 2011 (71)	1,656	35	37	28	49.8	95.6 (12 years)	99	97	91	98.2	72.6
Crook *et al.* 2011 (72)	1,111	86.9	13.1	13.1	4.1	95.2 (4 years)	–	–	–	99	95
Marshall *et al.* 2014 (10)	2,495	44	39	17	38	83 (12 years)	90	84	64	95	70
Morris *et al.* 2013 (73)	1,006	58	42	0	0	94.1 (10 years)	–	–	–	99	83.5
Funk *et al.* 2015 (74)	966	71	29	0	0	85 (10 years)	90	74	–	98	74
Kittel *et al.* 2015 (67)	1,989	61	30	5	0	81.5 (10 years)	87	79	68	97	76
Fellin *et al.* 2016 (75)	2,237	66	26	2	0	88.5 (7 years)	93	78	73	98	89

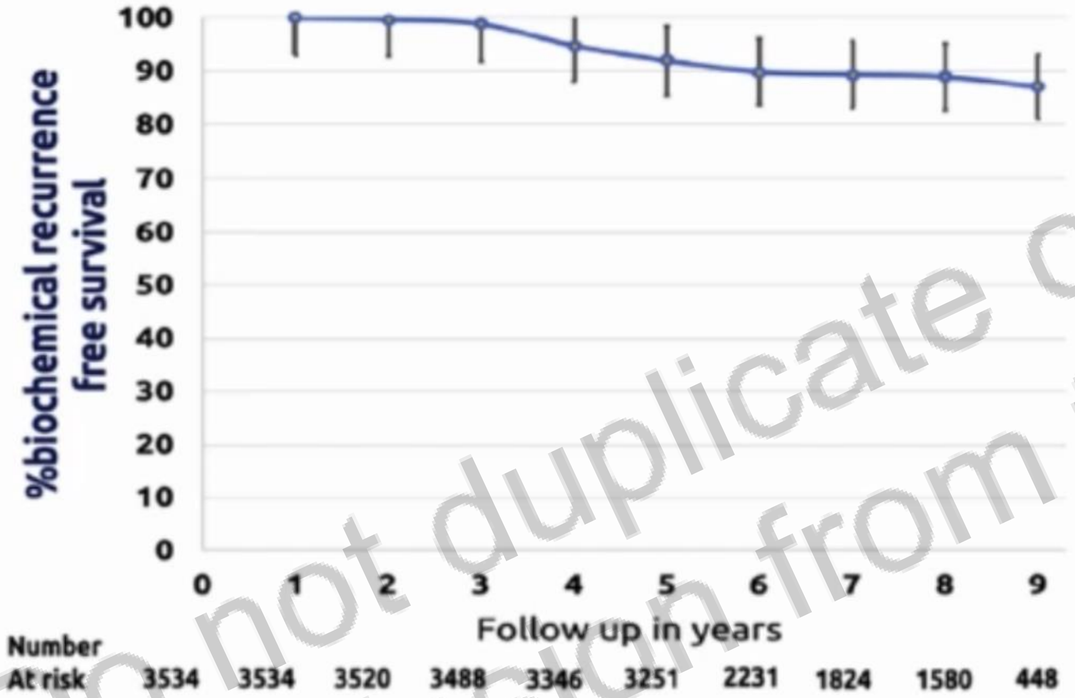
LDR, low dose rate; EBRT, external beam radiation therapy; CSS, cause-specific survival; OS, overall survival.

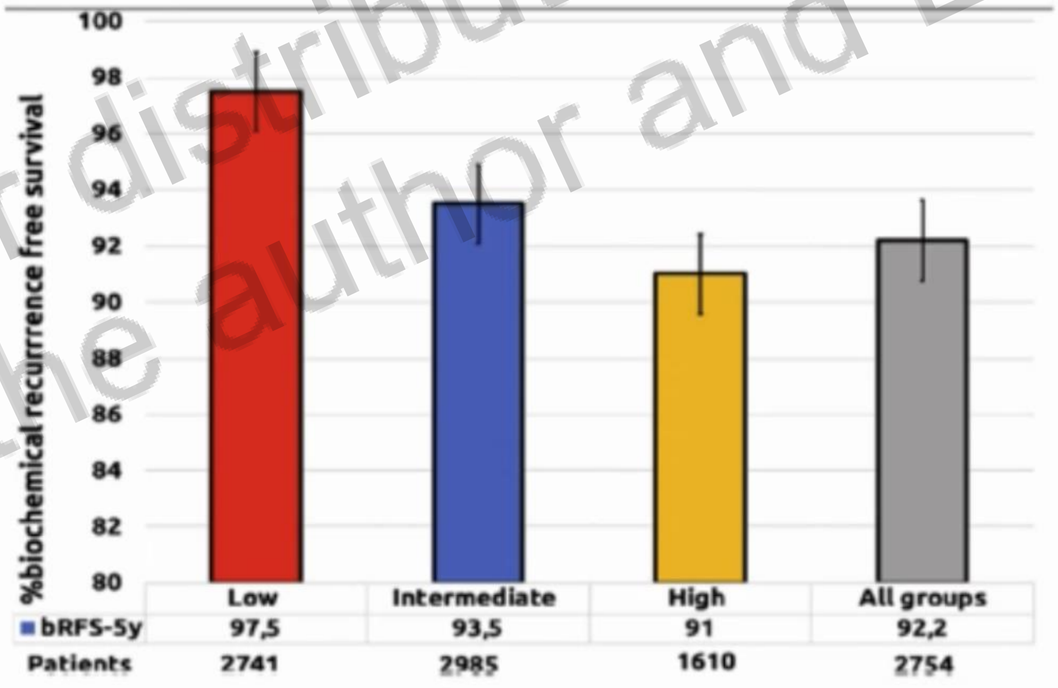
Adapted from Hoskin P. ESTRO 2021

HDR brachytherapy as monotherapy for prostate cancer: A systematic review with meta-analysis

Gustavo Arruda Viani[1,*], Caio Viani Arruda[2], Antonio Cassio Assis Pellizzon[3], Ligia Issa De Fendi[1]

ESTRO 2021





14 studies: 3534 patients

Brachytherapy 20 (2021) 307–314

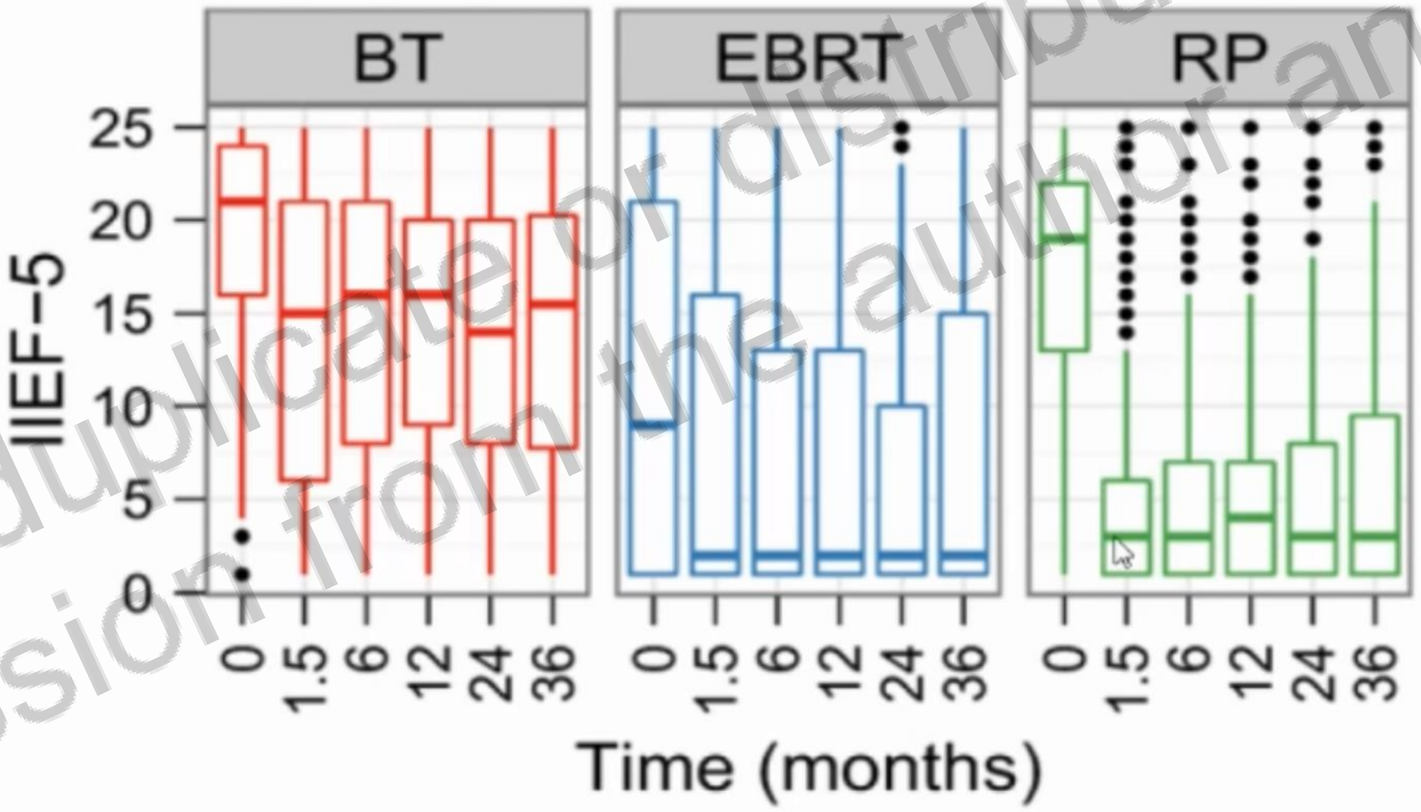
Adapted from Hoskin P. ESTRO 2021

Erectile function following brachytherapy, external beam radiotherapy, or radical prostatectomy in prostate cancer patients

P. M. Putora · D. Engeler · S. R. Haile · N. Graf · K. Buchauer · H. P. Schmid · L. Plasswilm

Strahlenther Onkol (2016) 192:182–189

ESTRO 2021



Adapted from Hoskin P. ESTRO 2021

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Published at jco.org on March 27, 2017.

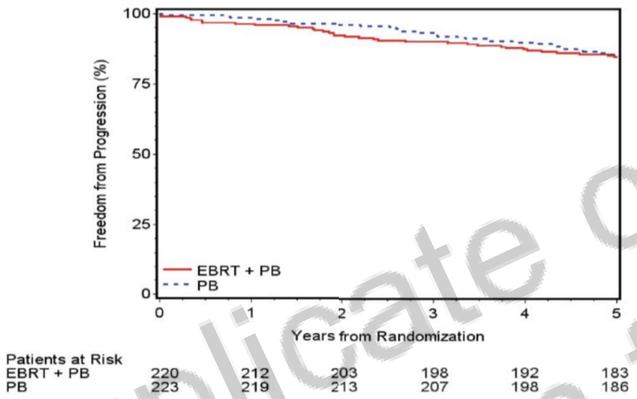
Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update

Joseph Chin, R. Bryan Rumble, Marisa Kollmeier, Elisabeth Heath, Jason Efstathiou, Tanya Dorff, Barry Berman, Andrew Feifer, Arthur Jacques,† and D. Andrew Loblaw

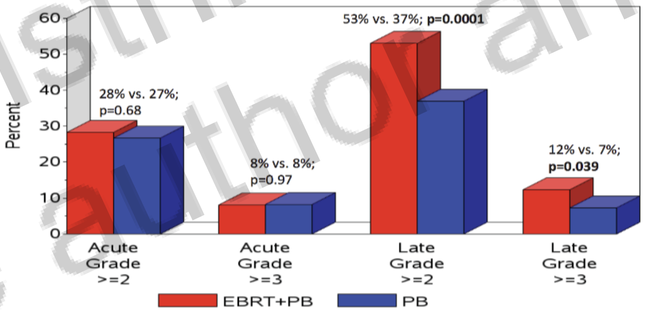
- For patients with intermediate-risk prostate cancer choosing EBRT with or without androgen-deprivation therapy (ADT), brachytherapy boost (LDR or high–dose rate [HDR]) should be offered to eligible patients. For low-intermediate risk prostate cancer (Gleason 7, prostate-specific antigen < 10 ng/mL or Gleason 6, prostate-specific antigen, 10 to 20 ng/mL) LDR brachytherapy alone may be offered as monotherapy. For patients with high-risk prostate cancer receiving EBRT and ADT, brachytherapy boost (LDR or HDR) should be offered to eligible patients.

RTOG 0232

RTOG 0232: intermediate-risk



Results: Adverse Events



Predstige et al. ASTRO 2016

	24 mos Δ mean ± SD			
Domain/ Subscale	**EBT+B**	**B**	**p-value ($\|\mu_B - \mu_{EBT+B}\| > 0$)**	**Effect Size**
Urinary	-11.2 ± 15.7	-5.6 ± 13.6	0.0002	0.38
Urinary-irritative	-11.9 ± 17.4	-4.8 ± 14.3	<0.0001	0.44
Bowel	-7.1 ± 12.6	-2.4 ± 9.9	<0.0001	0.42
Sexual	-16.7 ± 23.4	-10.6 ± 21.0	0.0072	0.27

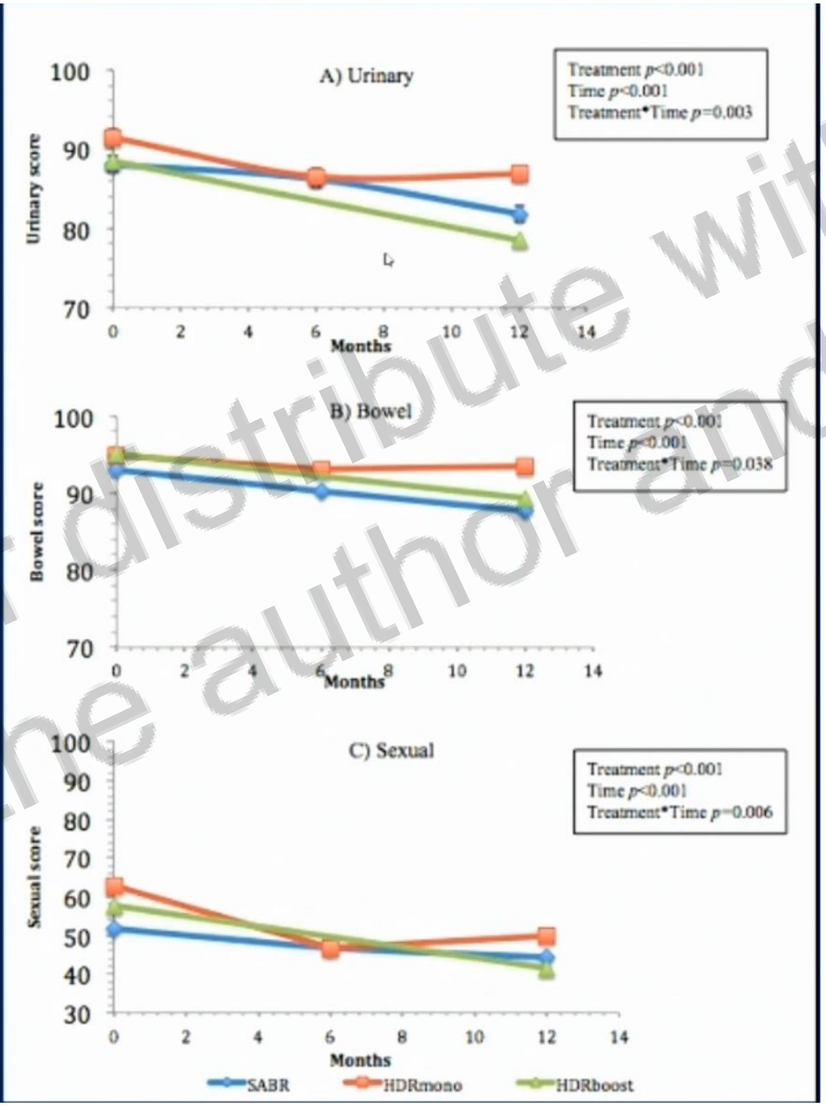
Moughan et al. ASTRO 2018

BT mono has better QOL

648 patients were included from 7 prospective trials:

- SBRT n=288
- HDR monotherapy n=173
- HDR boost group n=187

Helou J et al., submitted to Radioth & Oncol

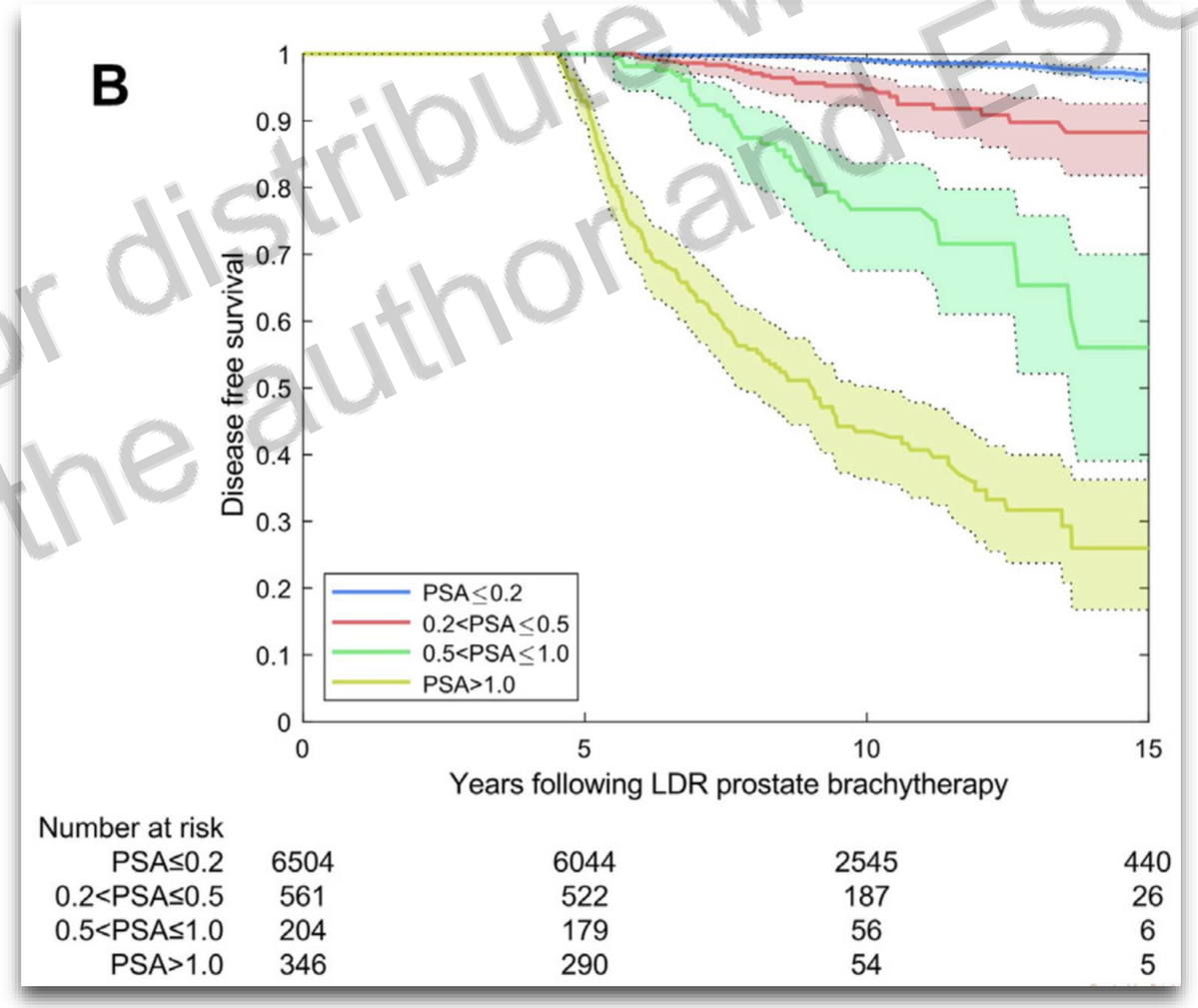


Adapted from Loblaw A. ESTRO 2021

Definition of CURE

- Definitive cure vs Functional cure
- Definitive LOCAL CONTROL
- Definitive BIOCHEMICAL CONTROL

By 4 years after LDR brachytherapy, most patients will achieve a PSA level of 0.2 ng/mL. Regardless of risk group, this is associated with rates of freedom from prostate cancer recurrence of 97% to 99% at 10 years

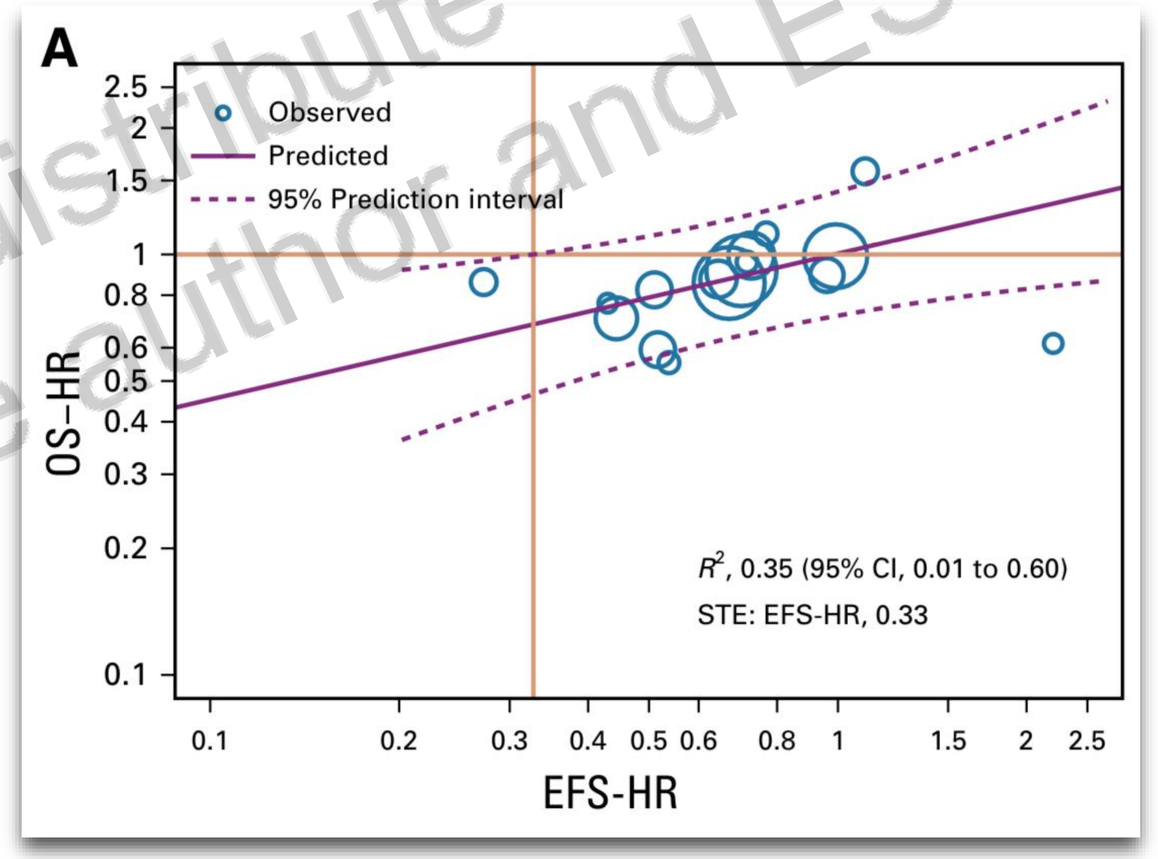


J. Crook Radiother & Oncol 2020

Failure after definitive local radiotherapy

- EFS: weak surrogate for OS in clinically localized PCa in a patient population treated with RT with approximately a 10% chance of dying of PCa over 10 years despite potentially curative local therapy.

- EFS cannot be used as a surrogate for OS and replace it as the primary end point to accelerate (neo)adjuvant prostate cancer phase III trials



Xie W. JCO 2020

Failure after definitive local radiotherapy

- High risk population, at risk of **rapidly rising PSA at relapse** are **more likely to die** as a result of prostate cancer
- Nowadays, **NGI (PSMA PET)** finds nodal or distant disease in a important % patients with PSA relapse
- PSA relapse means: more staging studies, salvage local treatments and salvage systemic therapies

PATIENT PERSPECTIVE

Anxiety

Recurrence and adverse effects of salvage treatments

Protracted testosterone suppression

Comorbidities associated with ADT

Glucose intolerance

Cardiovascular events

Bone loss

If patient progresses to M1 disease

Cancer Related Events

Bone pain

Fatigue

Costs

Toxicity of novel ADT and chemo

Failure after definitive local radiotherapy

- MSKCC retrospective study
- 2694 patients
- Treated with EBRT alone (75.9-81.4Gy)

- Most common pattern of Failure specially in Interm and High-risk PCa: LOCAL!

- **89% (393/442) of patients received ADT**

Table 3

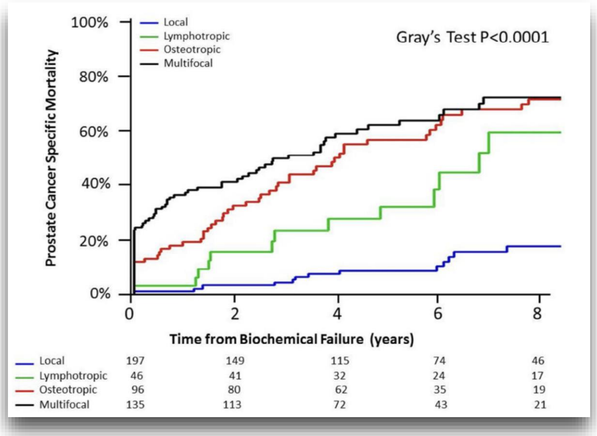
Number (and percentage) of patients in each risk group having a given anatomic location as a first recurrence site among the 474 patients with clinically detected recurrence

	Low Risk	Intermediate Risk	High Risk	All Patients
Local	25 (73.5%)	117 (67.6%)	120 (44.9%)	262 (55.3%)
Pelvic lymph nodes	0 (0%)	33 (19.1%)	68 (25.4%)	101 (21.3%)
Abdominal lymph nodes	2 (5.9%)	16 (9.2%)	25 (9.4%)	43 (9.1%)
Thoracic lymph nodes	0 (0%)	7 (4.0%)	3 (1.1%)	10 (2.1%)
Bone	8 (23.5%)	43 (24.9%)	108 (40.4%)	159 (33.5%)
Visceral	0 (0%)	1 (0.6%)	8 (3.0%)	9 (1.9%)
Total clinically detected recurrences	34	173	267	474

Note: Patients could have multiple first recurrence sites, so percentages may not sum to 100%.

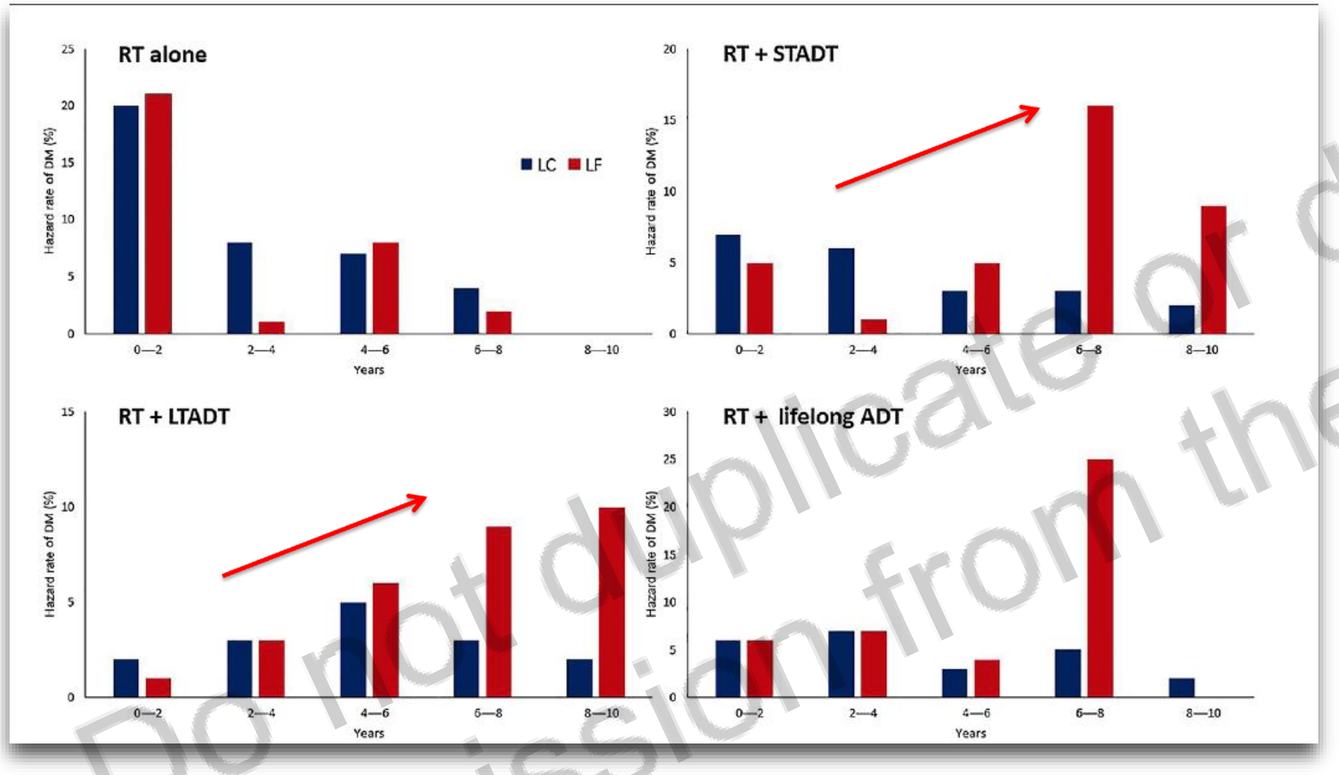
Supplementary Table 1. Salvage therapies administered following recurrence

Salvage Treatment	N (%)
Any salvage treatment	442
Androgen-deprivation therapy	393
Brachytherapy	39
Radical prostatectomy	43
Cryotherapy	5
Pelvic lymph node dissection	3
Stereotactic body radiation therapy	7
Taxol	88



Zumsteg et al. J. Urol 2016

Importance of the local failure



- Individual patient meta-analysis of 992 patients (593 GG 4 and 399 GG 5) enrolled in six randomized clinical trials.
- Local Failure is an important prognostic endpoint in high-grade PCa
- The development of LF temporally precedes the development of DMs in a subset of patients.

Trial & period	Total patients	Included (%)	Arms
RTOG 8531 [1987–1992]	977	216 (21.8)	RT
			RT + LL-ADT
RTOG 8610 [1987–1991]	456	128 (12.8)	RT
			RT + STADT
RTOG 9202 [1992–1995]	1,554	337 (34)	RT + ST-ADT
			RT + LT-ADT
EORTC 22863 [1987–1995]	415	43 (4.3)	RT
			RT +LT-ADT
EORTC 22961 [1997–2001]	970	186 (18.8)	RT + STADT
			RT + LTADT
EORTC 22991 [2001–2008]	819	82 (8.3)	RT
			RT + STADT

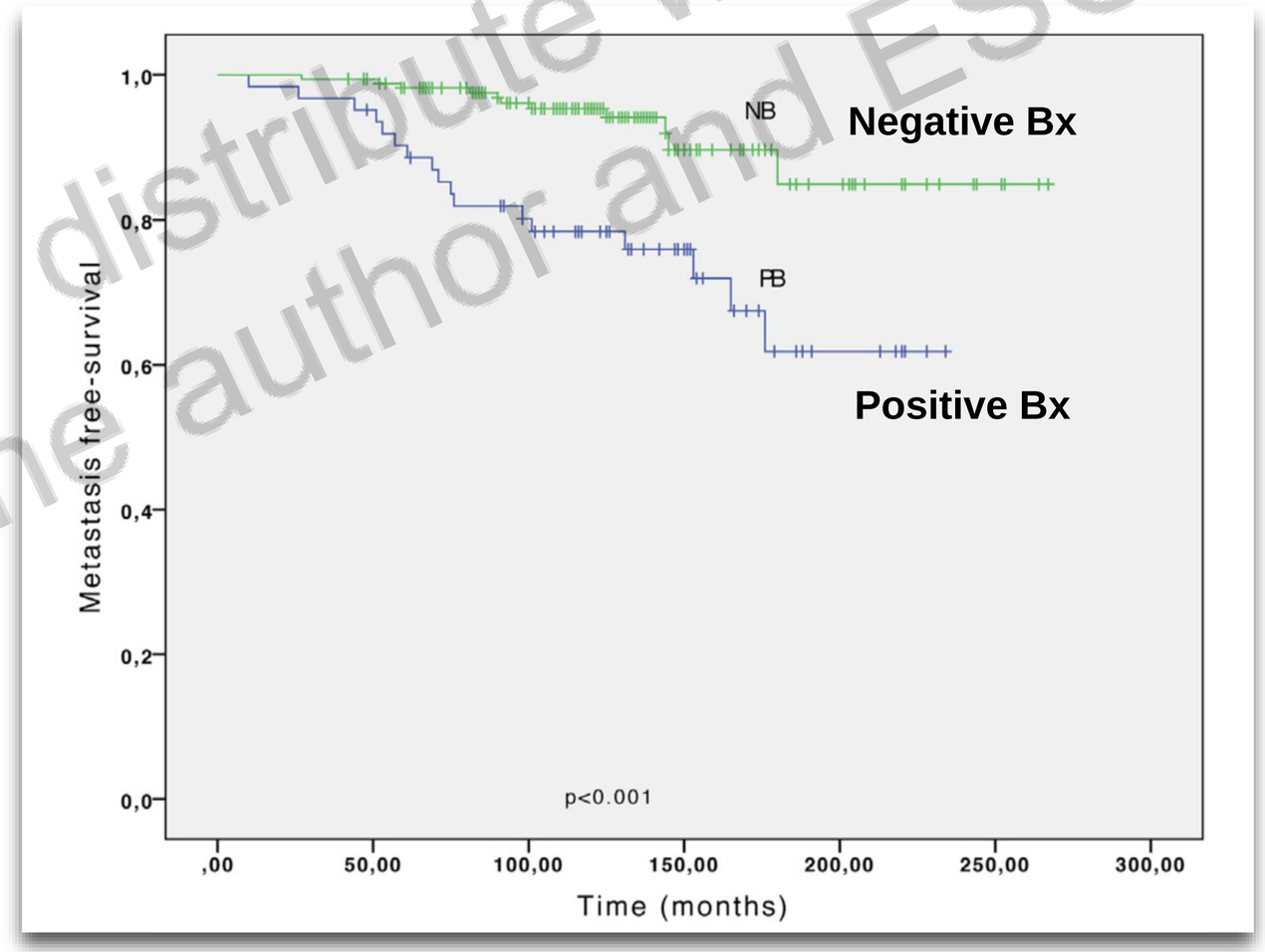
LT-ADT, long-term ADT; ST-ADT, short-term ADT; LL-ADT: lifelong ADT.

Kishan A. Eur Urol 2020

Importance of the local failure

- As part of 2 sequential studies of Biomarkers
- **232 patients** T1c-T3b N0M0 PCa, planned **TRUS- guided biopsy** after RT
- Median follow-up was 124 months (range 26–267)
- 73% patients high-risk PCa
- Median RT dose was 77 Gy. LTAD was administered in 143 (62%) patients

- **<u>Multivariate Analysis:</u>**
  - **Gleason >7** (p =0.002; HR 2.24 (1.33–3.79)
  - **+ Biopsy** (p <0.001; HR 5.4 (2.26–12.85)



Zapatero A. Rep Pract Oncol Radiot. 2020

Dose escalation

Randomized EBRT trials

	bDFS		
Author	**Standard**	**High Dose**	**Time**
MD Anderson	59%	78%	8 years
GETUG	68%	77%	5 years
Dutch Multicenter	45%	56%	7 years
Royal Marsden	59%	71%	5 years
MGH/ Loma Linda	79%	91%	5 years
MRC RT01	60%	71%	5 years

10% increase in EBRT dose is associated with a 10% in bDFS

Kuban DA, Int J Radiat Oncol Biol Phys. 2008 Jan 1;70(1):67-74
Beckendorf V, Int J Radiat Oncol Biol Phys. 2004 Nov 15;60(4):1056-65
Peeters ST, J Clin Oncol. 2006 May 1;24(13):1990-6
Dearnaley DP, Lancet Oncol. 2007 Jun;8(6):475-87
Zietman AL. J Clin Oncol. 2010 Mar 1;28(7):1106-11

UCLA Consortium: 12 centres, >2100 pts

Institution or Trial	Years Treated	# of patients	Median Follow-up (Years)	Dose/Fraction	Risk Group
Virginia Mason	2000-2004	40	5·9 (0·7-15·0)	6·7 Gy x 5	100% Low
Stanford	2003-2009	67	9·5 (3·3-13·3)	7·25 Gy x 5	73% Low 15% Fav Int, 2% Unfav Int
Flushing	2006-2010	477	7·9 (0·5-9·9)	7 Gy x 5 (32%) 7·25 Gy x 5 (68%)	68% Low 22% Fav Int, 9·8% Unfav Int
21st Century Oncology	2007-2012	415	7·7 (5·0-10·4)	8 Gy x 5	68·2% Low 27% Fav Int, 5% Unfav Int
NCT00643994	2008-2011	141	5·0 (0·1-8·2)	7·25 Gy x 5	35% Low 33% Fav Int, 31% Unfav Int
NCT00643617	2007-2012	206	5·0 (0·1-9·6)	9·5 Gy x 4	43% Low 35% Fav Int, 21% Unfav Int
Sunnybrook pHART3	2006-2008	84	9·6 (1-10·8)	7 Gy x 5	100% Low
Sunnybrook pHART6	2010	30	6·8 (5·7-7·2)	8 Gy x 5	60% Low 30% Fav Int, 10% Unfav Int
Beth Israel Deaconess Medical Center	2006-2011	135	6·3 (0·1-10·3)	7·25 Gy x 5	35% Low 31% Fav Int, 34% Unfav Int
University of California, Los Angeles	2010-2012	95	6·0 (0·3-8·1)	8 Gy x 5	91% Low 5% Fav Int, 4% Unfav Int
Genesis Healthcare	2006-2012	51	6·0 (1·7-10·1)	9·5 Gy x 4	1% Low 71% Fav Int, 28% Unfav Int
Georgetown	2007-2012	402	4·3 (1·8-9·1)	7 Gy x 5 (33%) 7·25 Gy x 5 (67%)	36% Low 48% Fav Int, 16% Unfav Int
Total	2000-2012	2142	6·9 (0·1-15)		65% Low 25% Fav Int, 9·9% Unfav Int

Kishan A et al., JAMA Open 2019

Radiation Oncology UNIVERSITY OF TORONTO Sunnybrook

Adapted from Loblaw A. ESTRO 2021

Ultra Hypofractionation RCTs

Trial	Planned accrual	Population	Primary Endpoint	Ultrahypofractionated Regimen	Comparator Regimen	Current Status
HEAT NCT01794403	456	LR and IR	BF or CF	36.25 Gy / 5f	70.2 Gy / 26f	Accruing 1/3 accrued Nov 2020
HYPO-RT-PC ISRCTN45905321	1200	IR	BF or CF	42.7 Gy / 7f	78 Gy / 39f	Efficacy Published
NRG-GU005 NCT03367702	606	IR	HRQOL Toxicity	36.25 Gy / 5f	70 Gy / 28f	Closed July 2018
PACE B NCT01584258	871	LR and IR (GG1-2)	BF or CF	36.25 Gy / 5f	78 Gy / 39f or 62 Gy / 20f	Acute Toxicity / QOL Published

Morgan SC et al., JCO 2018

Radiation Oncology UNIVERSITY OF TORONTO Sunnybrook

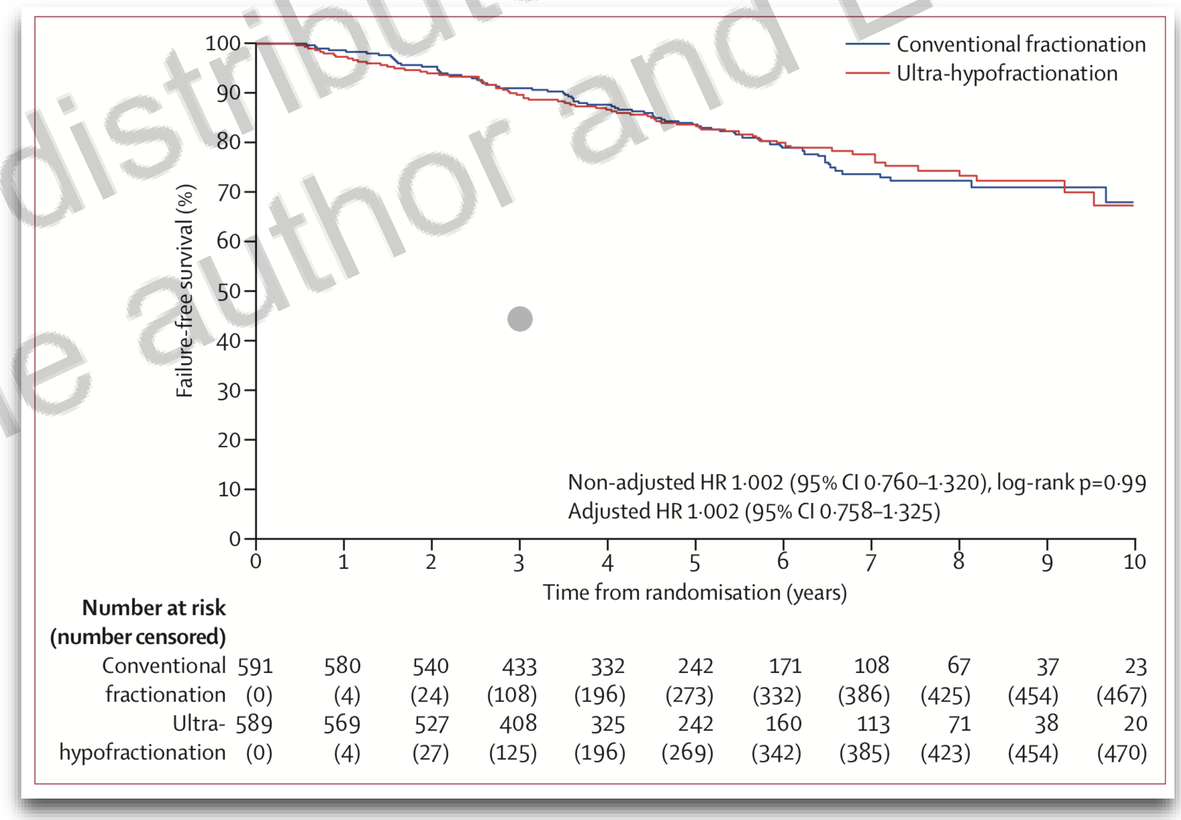
Adapted from Loblaw A. ESTRO 2021

SABR vs EBRT

HYPO-RT-PC TRIAL

- 1180 patients
- EBRT 78 Gy (39 fx) vs SABR 42.7Gy (7 fractions)
- Intermediate (89%) and High-Risk (11%)

- Median F-up: 5 years (3.1-7)
- 102 failures in Conv. and 100 failures with SABR



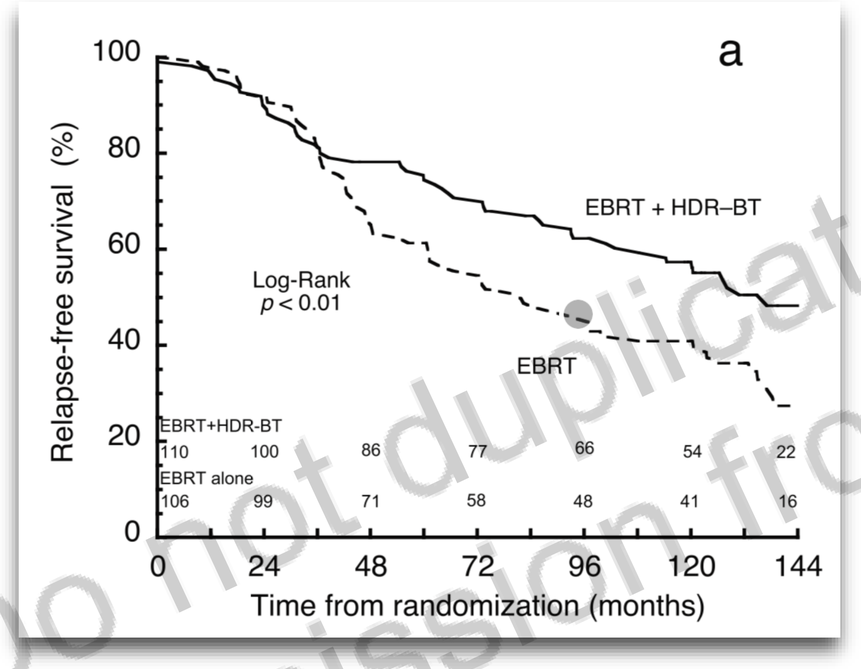
Widmark A. Lancet 2019

Published evidence on BT boost

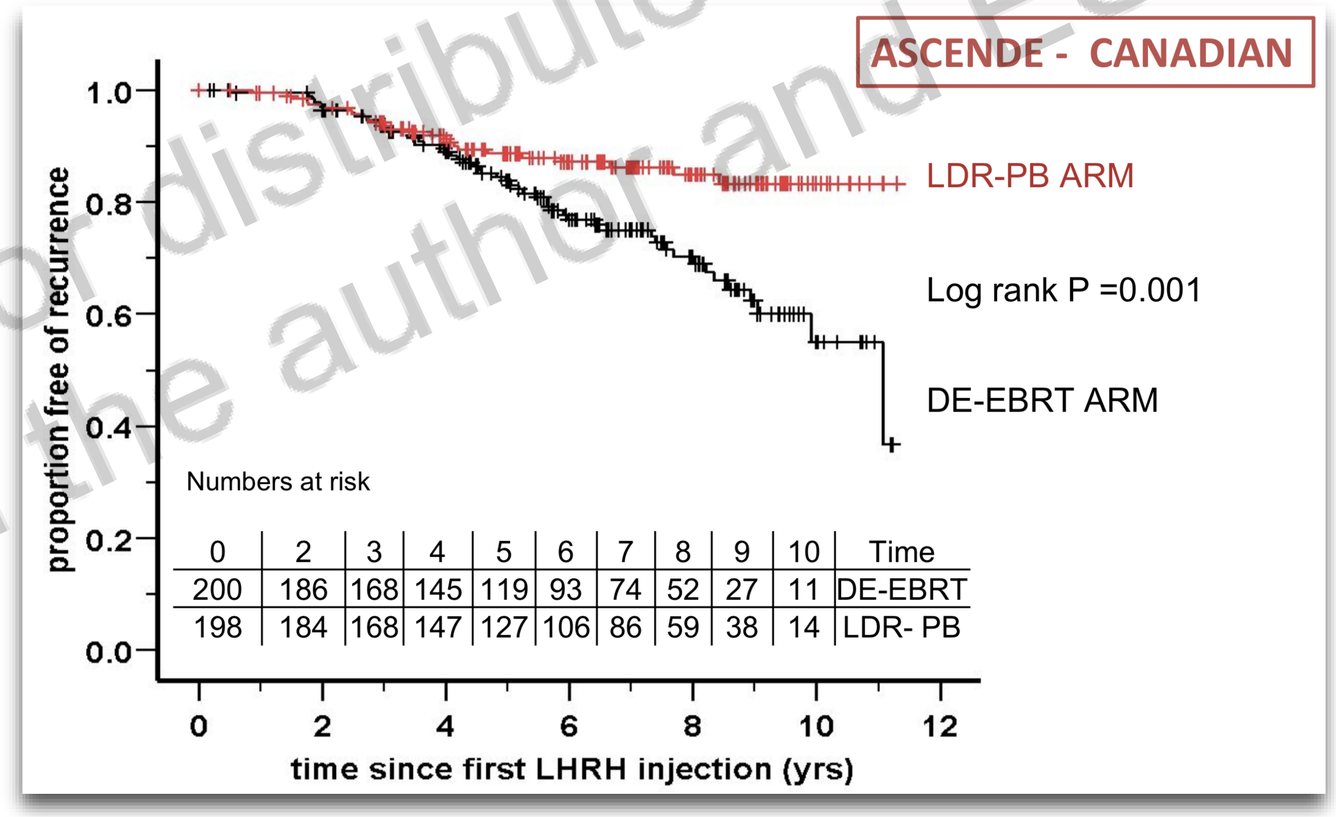
- Important to consider this issue...
- Almost every single published study (retrospective, prospective and Randomized) comparing BT boost vs EBRT alone in unfav-intermediate and high-risk disease, have demonstrated better tumor control outcomes with the combo strategy!

Dose escalation: Brachy boost

UK - Hoskin



Hoskin P et al. Radiother & Oncol 2021



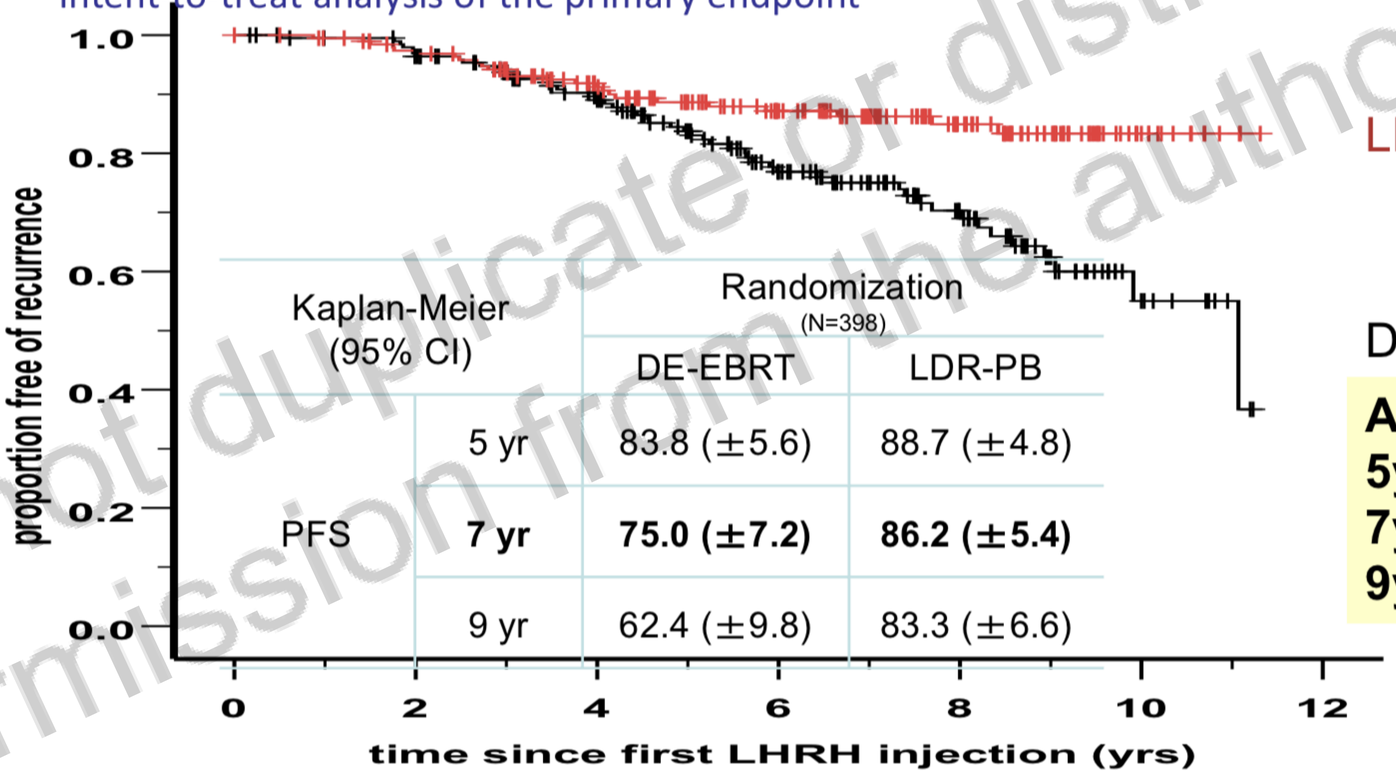
Morris et al IJROBP 2017

ASCENDE-RT

ASCENDE RT - CANADIAN

Results: Biochemical PFS

Intent-to-treat analysis of the primary endpoint



Kaplan-Meier (95% CI)		Randomization (N=398) DE-EBRT	LDR-PB
PFS	5 yr	83.8 (±5.6)	88.7 (±4.8)
	7 yr	**75.0 (±7.2)**	**86.2 (±5.4)**
	9 yr	62.4 (±9.8)	83.3 (±6.6)

LDR-PB ARM

DE-EBRT ARM

Absolute difference
5y – 4.9%
7y – 11.2%
9y – 20.95%

ASCENDE-RT

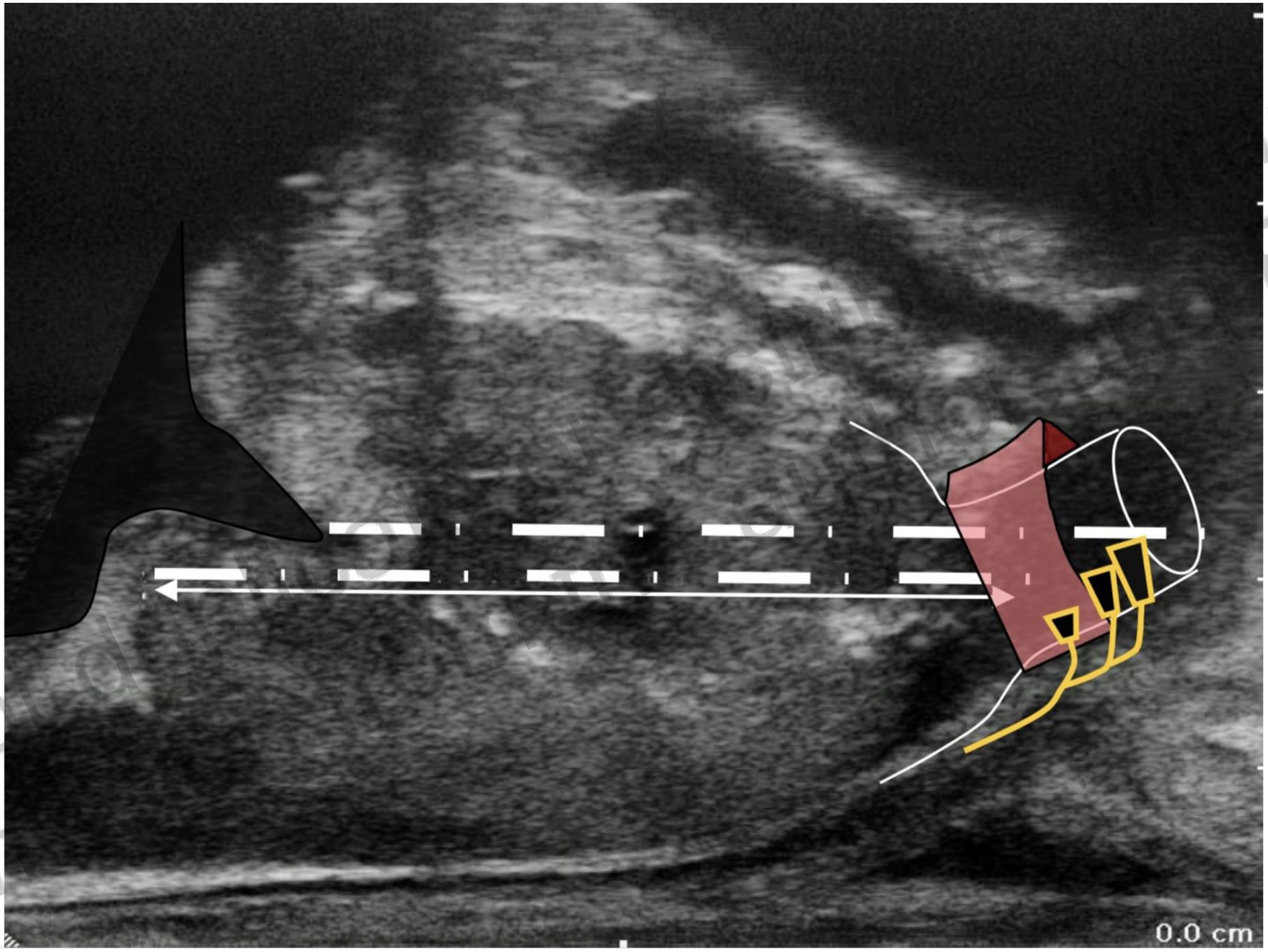
5y Cumulative Incidence of Late G3+ Toxicity

(worst grade ever recorded) in 383 pts (ASCENDE-RT)

	Toxicity	LDR-PB	DE-EBRT	P-Value
GU	Grade 3	19%	5%	<0.001
	Grade 4	1%	1%	0.547
GI	Grade 3	9%	4%	0.120
	Grade 4	1%	0%	NA

GU gr3 - 50% urethral strictures

Rodda IJROBP 2017



Urethral Strictures

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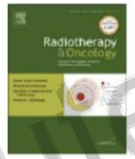
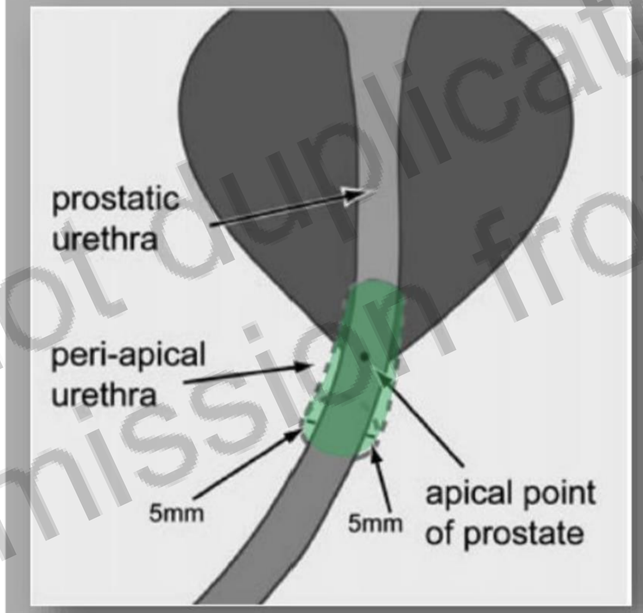


Prostate brachytherapy

Correlation between prostate brachytherapy-related urethral stricture and peri-apical urethral dosimetry: A matched case–control study

James J. Earley [a,*], Ather M. Abdelbaky [b], Melanie J. Cunningham [a], Eliot Chadwick [c], Stephen E.M. Langley [b], Robert W. Laing [c]

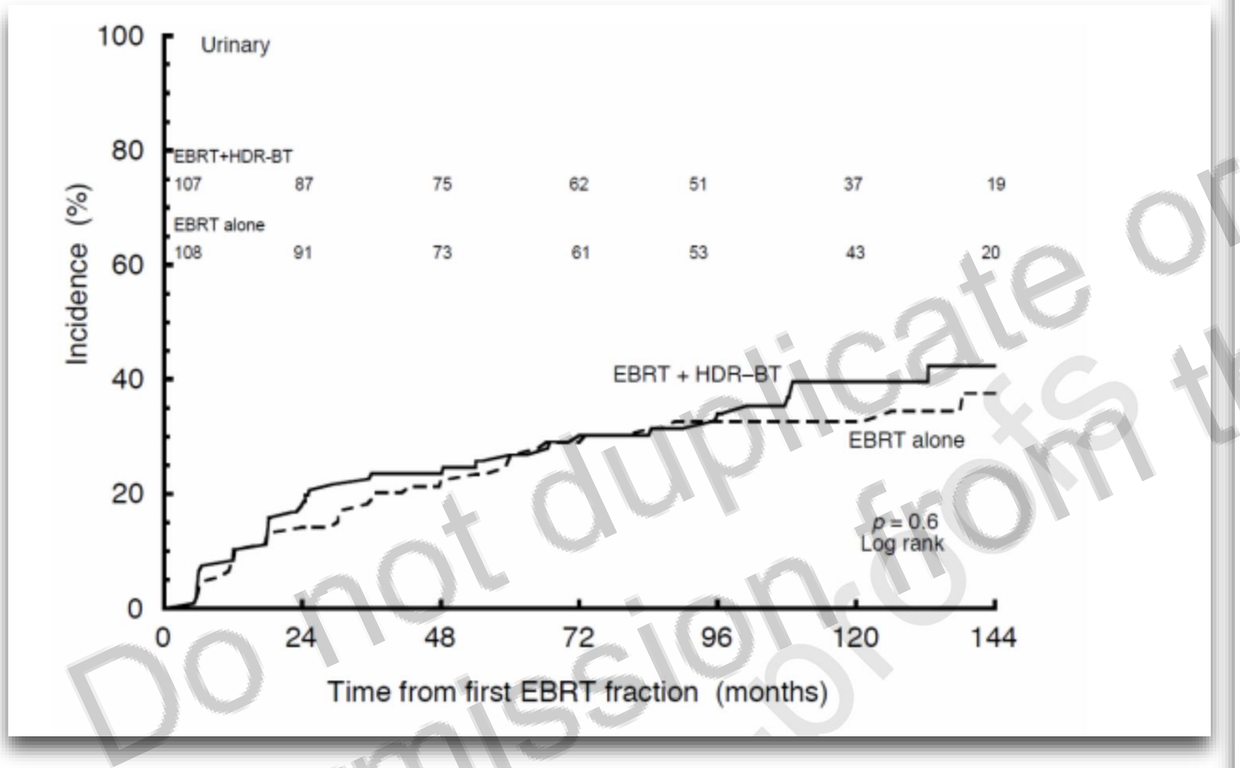


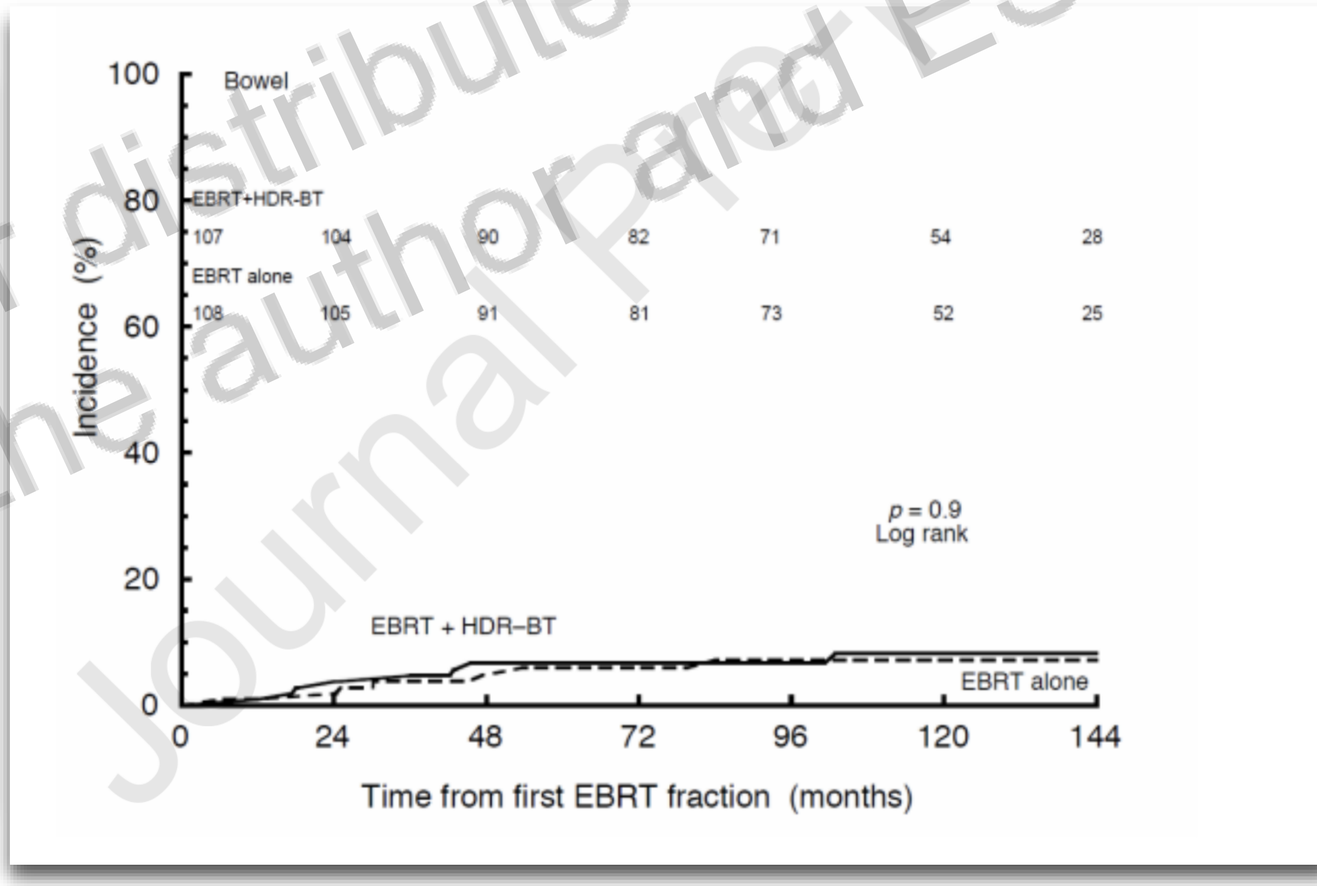
Urethral Strictures

- *Peri- urethral dose significant*
- *D90, V150, V100 not important*

V_{150} (cc)	Stricture group	Control group	*p* Value
No margin	0.08 (0.13 ± 0.03)	0.02 (0.07 ± 0.02)	0.13
0.1 cm margin	0.2 (0.3 ± 0.1)	0.1 (0.13 ± 0.03)	0.06
0.5 cm margin	0.9 (1.1 ± 0.2)	0.6 (0.8 ± 0.1)	0.02*
1.0 cm margin	3.5 (3.5 ± 0.3)	2.4 (2.7 ± 0.2)	0.56

HOSKIN -UK TRIAL



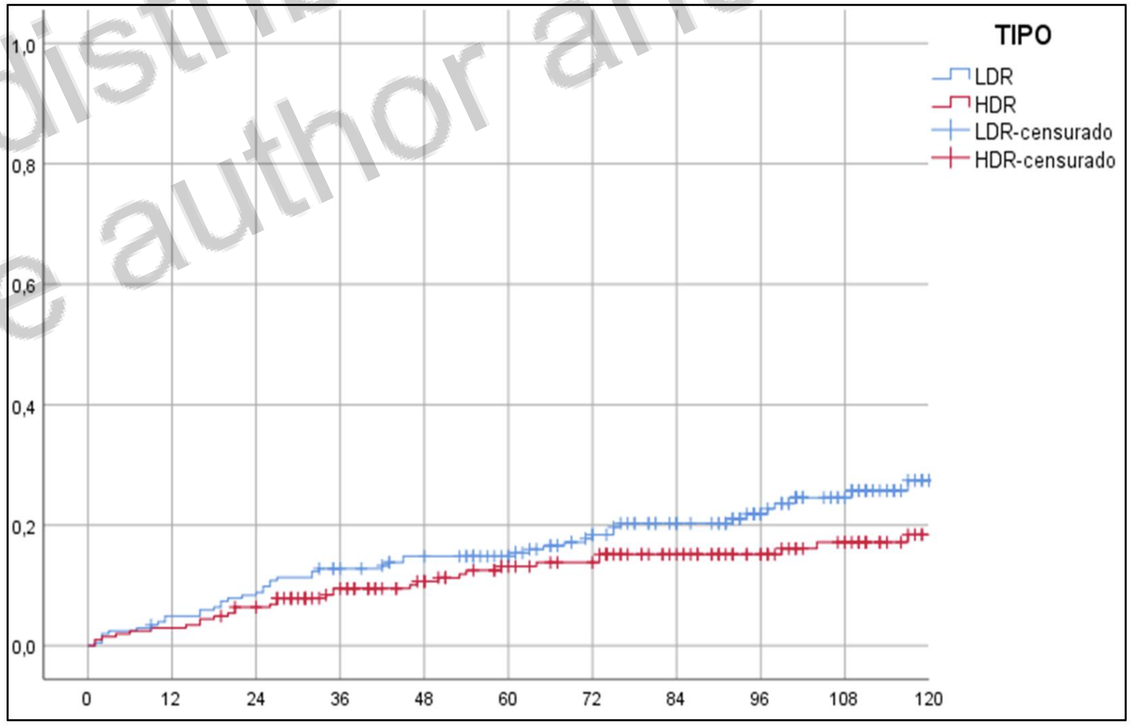


Hoskin P. Radiother & Oncol 2021

Match Cohort analysis HDR (CT-based) vs LDR boost. One center with high volume of Prostate Brachy

Median f-up: 7 years for both groups

	TOXICIDAD ACUMULADA GU ≥ G3 GU				TOXICIDAD ACUMULADA GI ≥ G3 GU			
n (%)	LDR N=204	HDR N=204	χ^2	P	LDR N=204	HDR N=204	χ^2	p
6 Meses	6 (2,9%)	4 (2%)	0,41	0,522	0	0	N/A	N/A
24M	25 (12,3%)	17 (8,3%)	1,7	0,192	8 (3,9%)	3 (1,5%)	2,34	0.126
60M	39 (19,1%)	28 (13,7%)	2,16	0,142	10 (4,9%)	5 (2,5%)	1,73	0,188
90M	46 (22,5%)	29 (14,2%)	4,72	**0,030**	11 (5,4%)	5 (2,5%)	2,34	0,126
120M	50 (24,5%)	32 (15,7%)	4,95	**0,026**	11 (5,4%)	5 (2,5%)	2,34	0,126

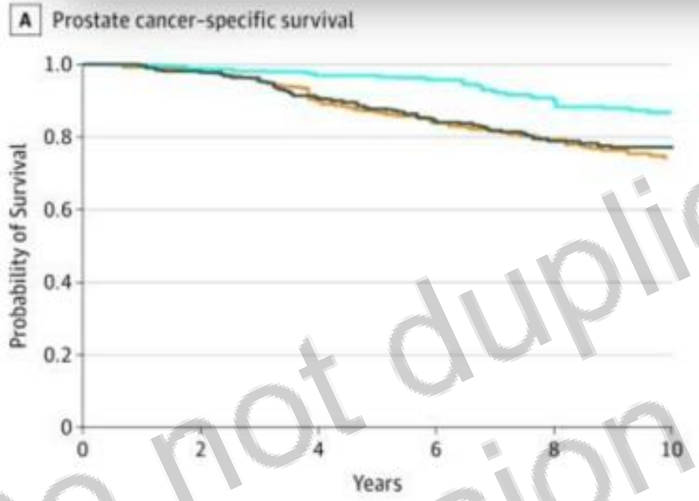


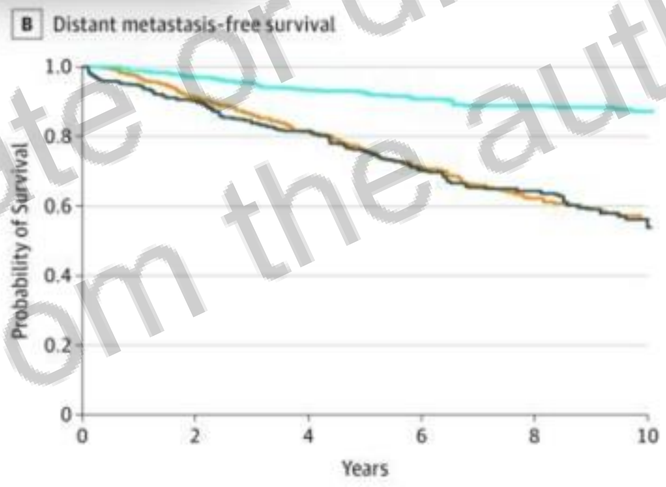
Alai Goñi, ESTRO 2021, Doctoral Thesis not published

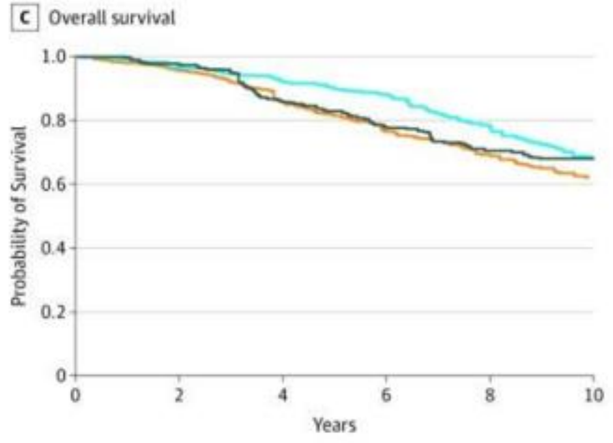
March 6, 2018

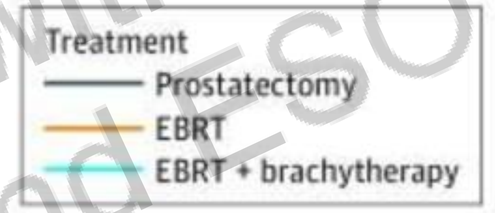
Radical Prostatectomy, External Beam Radiotherapy, or External Beam Radiotherapy With Brachytherapy Boost and Disease Progression and Mortality in Patients With Gleason Score 9-10 Prostate Cancer

Amar U. Kishan, MD[1]; Ryan R. Cook, MSPH[2]; Jay P. Ciezki, MD[3]; et al









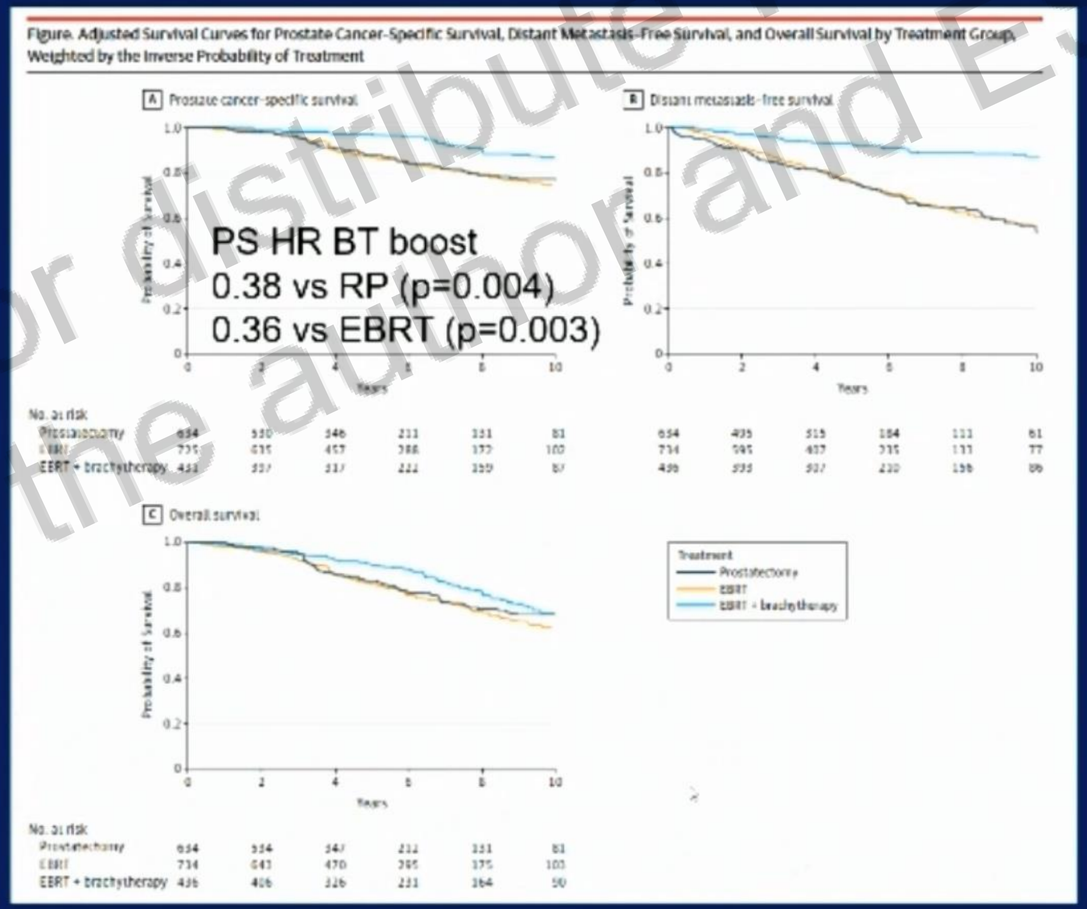
No. at risk						
Prostatectomy	634	530	346	211	131	81
EBRT	725	635	457	288	172	102
EBRT + brachytherapy	431	397	317	222	159	87

	634	495	315	184	111	61
	734	595	407	235	133	77
	436	393	307	210	156	86

No. at risk						
Prostatectomy	634	534	347	212	131	81
EBRT	734	643	470	295	175	103
EBRT + brachytherapy	436	406	326	231	164	90

Brachy Boost Best for G9-10

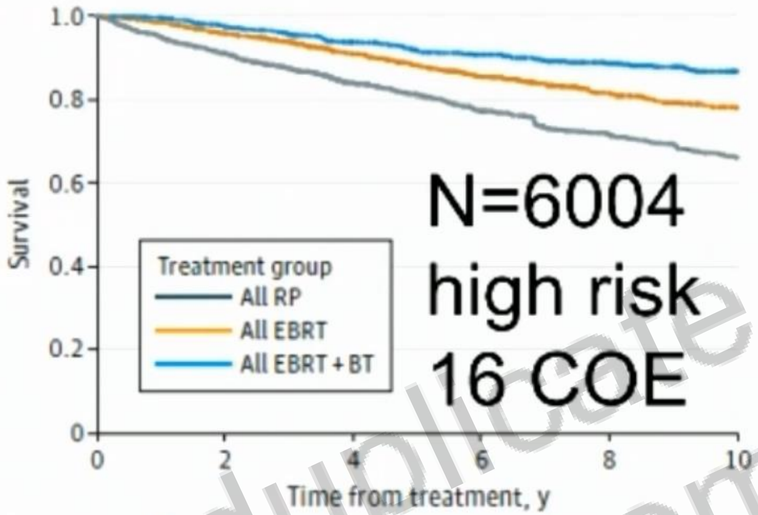
- N=1809 pts
- 12 US centres of excellence
- RP (n=634)
  EBRT + ADT (n=725)
  BT, EBRT, ADT (n=436)
- RP pts younger, less G10
- EBRT cohort had more ADT



Kishan AU et al., JAMA 2018

BT Boost improves MFS (vs RP or EBRT)

B Distant metastasis-free survival among all treatment groups



N=6004
high risk
16 COE

No. at risk (No. censored):

All RP	3111 (10)	2279 (593)	1303 (1436)	734 (1943)	393 (2250)	220 (2629)
All EBRT	1676 (1)	1498 (120)	1186 (380)	888 (640)	604 (910)	411 (1506)
All EBRT + BT	947 (3)	827 (94)	697 (195)	557 (317)	382 (495)	217 (882)

Table 4. Competing Risk Models of Time Until Prostate Cancer-Specific Mortality and Distant Metastasis Among Patients With Greater Than 4.5 Years of Follow-up

Comparison	Subdistribution hazard ratio (95% CI)[a]	*P* value
All patients (n = 3187)		
Prostate cancer specific mortality		
All EBRT vs all RP	0.74 (0.55-0.99)	.045
All EBRT+BT vs all RP	0.75 (0.52-1.07)	.12
All EBRT+BT vs all EBRT	1.02 (0.71-1.45)	.92
Distant metastasis		
All EBRT vs all RP	0.53 (0.44-0.63)	<.001
All EBRT+BT vs all RP	0.28 (0.21-0.36)	<.001
All EBRT+BT vs all EBRT	0.52 (0.39-0.69)	<.001
Optimal treatment (n = 1673)		
Prostate cancer specific mortality		
Optimal EBRT vs optimal RP	0.63 (0.38-1.04)	.07
Optimal EBRT+BT vs optimal RP	0.99 (0.58-1.69)	.97
Optimal EBRT+BT vs optimal EBRT	1.56 (0.87-2.79)	.13
Distant metastasis		
Optimal EBRT vs optimal RP	0.47 (0.35-0.63)	<.001
Optimal EBRT+BT vs optimal RP	0.28 (0.18-0.44)	<.001
Optimal EBRT+BT vs optimal EBRT	0.59 (0.36-0.95)	.03

Kishan AU et al., JAMA Open 2021

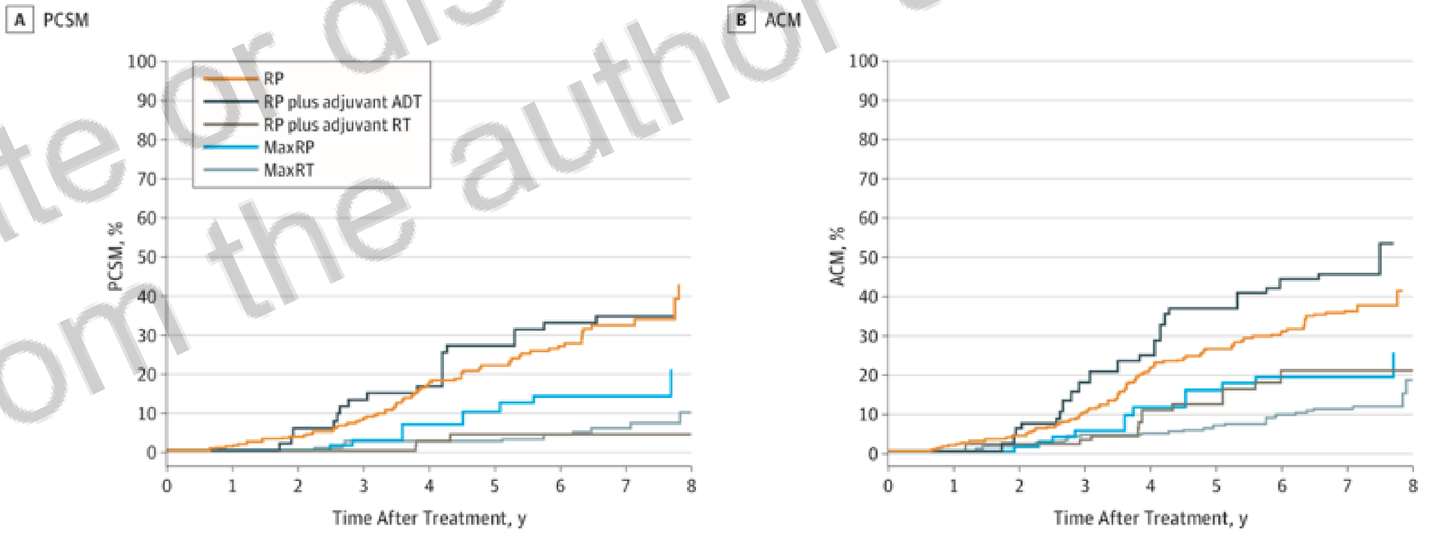
Research

JAMA Oncology | Original Investigation

Surgery vs Radiotherapy in the Management of Biopsy Gleason Score 9-10 Prostate Cancer and the Risk of Mortality

Derya Tilki, MD; Ming-Hui Chen, PhD; Jing Wu, PhD; Hartwig Huland, MD; Markus Graefen, MD, PhD; Michelle Braccioforte, MPH; Brian J. Moran, MD; Anthony V. D'Amico, MD, PhD

Figure. Adjusted Estimates of Prostate Cancer–Specific Mortality (PCSM) and All-Cause Mortality (ACM)



No. at risk

RP	557	359	332	289	225	136	70	22	0
RP plus adjuvant ADT	2	49	45	38	29	16	9	4	0
RP plus adjuvant RT	0	86	78	70	58	31	13	6	1
MaxRP	0	49	49	44	40	27	18	12	0
MaxRT	80	74	61	48	45	35	23	11	1

No. at risk

RP	557	359	332	289	225	136	70	22	0
RP plus adjuvant ADT	2	49	45	38	29	16	9	4	0
RP plus adjuvant RT	0	86	78	70	58	31	13	6	1
MaxRP	0	49	49	44	40	27	18	12	0
MaxRT	80	74	61	48	45	35	23	11	1

FLAME trial

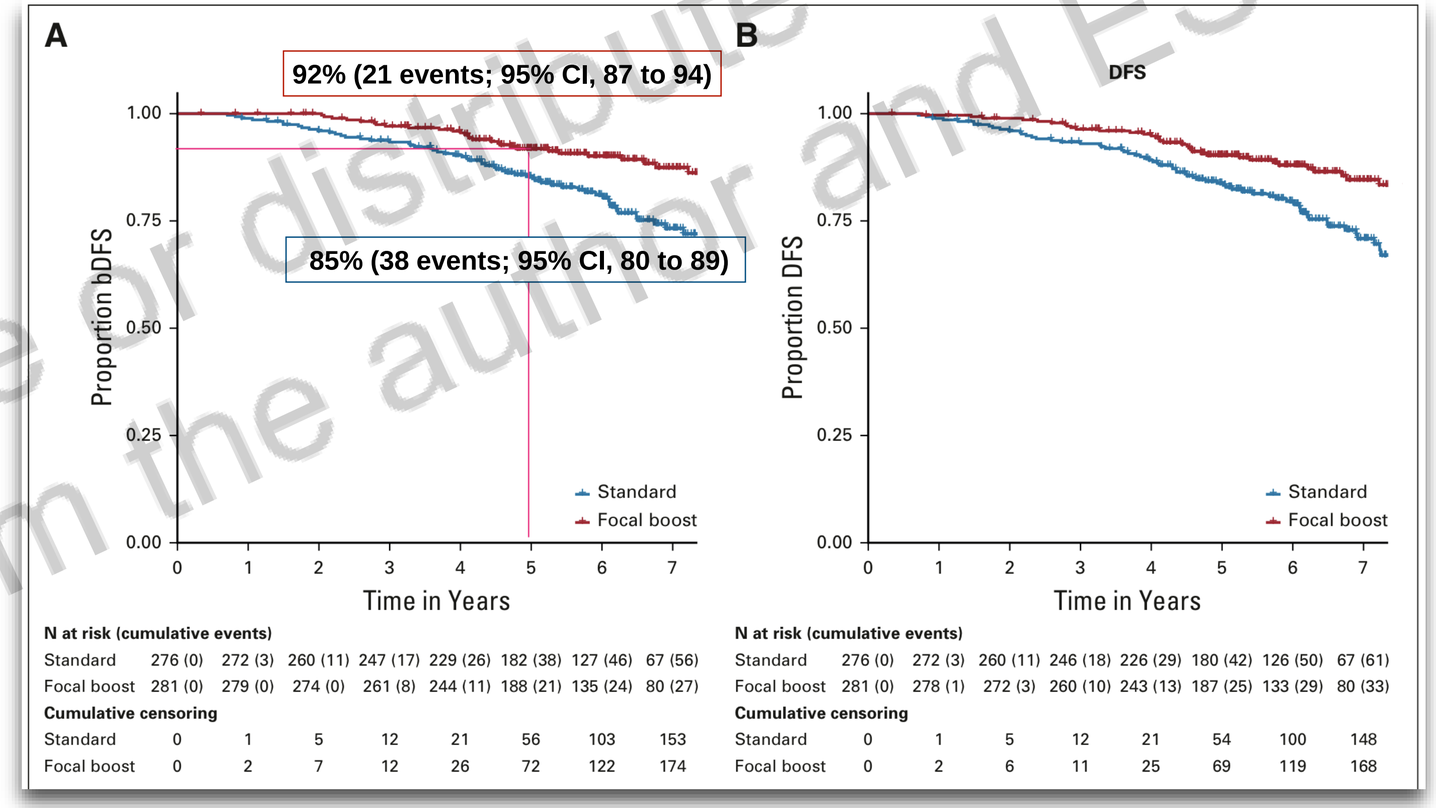
- 77Gy in 35 fx (2.2 Gy/fx) and focal boost DIL to 95Gy (2.7Gy/fx)
- 571 patients, median F-up: 72mo

Patients Characteristics

84% High Risk
62% >/= T3
48% Gleason 7
32% Gleason >/= 8

ADT

20% 6 months
11% 6-18 mo
29% 18-36 mo
35% No ADT



Kerkmeijer L. JCO 2021

FLAME trial

- Few comments on FLAME trial

1. This is the first study demonstrating better outcomes with focal dose escalation

2. Most of high risk PCa are multi focal, which may difficult the dose escalation to several DILs

3. 35 fractions in the era of moderate hypofractionation may not be very well accepted

Brachy Boost

1. High amount evidence demonstrating that is a very effective option

2. Allows for whole prostate dose escalation

3. Reduces the length of the treatment

Better HDR for Salvage in terms of toxicity?

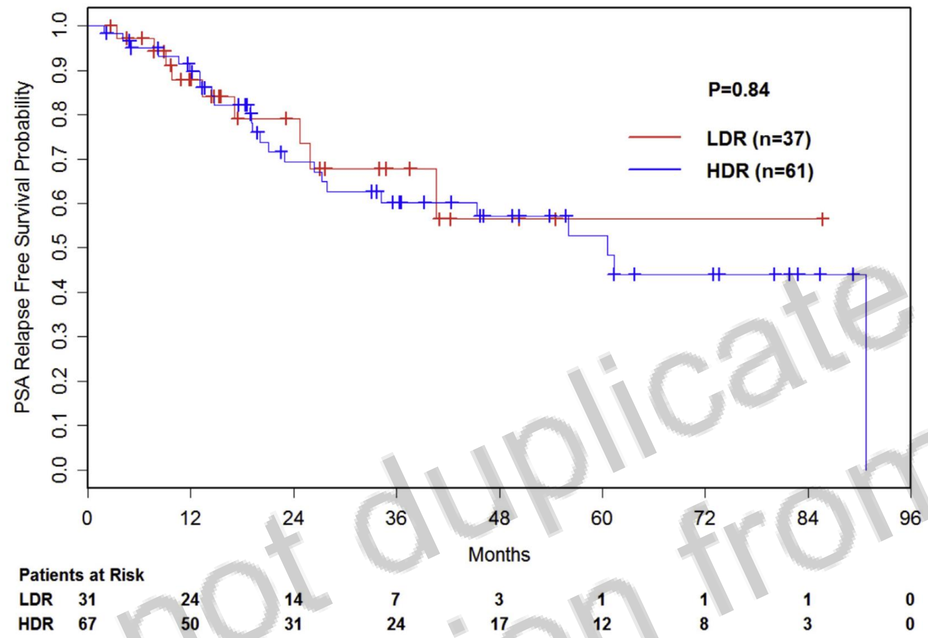


Fig. 2. Comparison of PSA relapse-free survival for HDR and LDR salvage brachytherapy. PSA = prostate-specific antigen; LDR = low-dose-rate; HDR = high-dose-rate.

Kollmeier M. Brachytherapy 2017

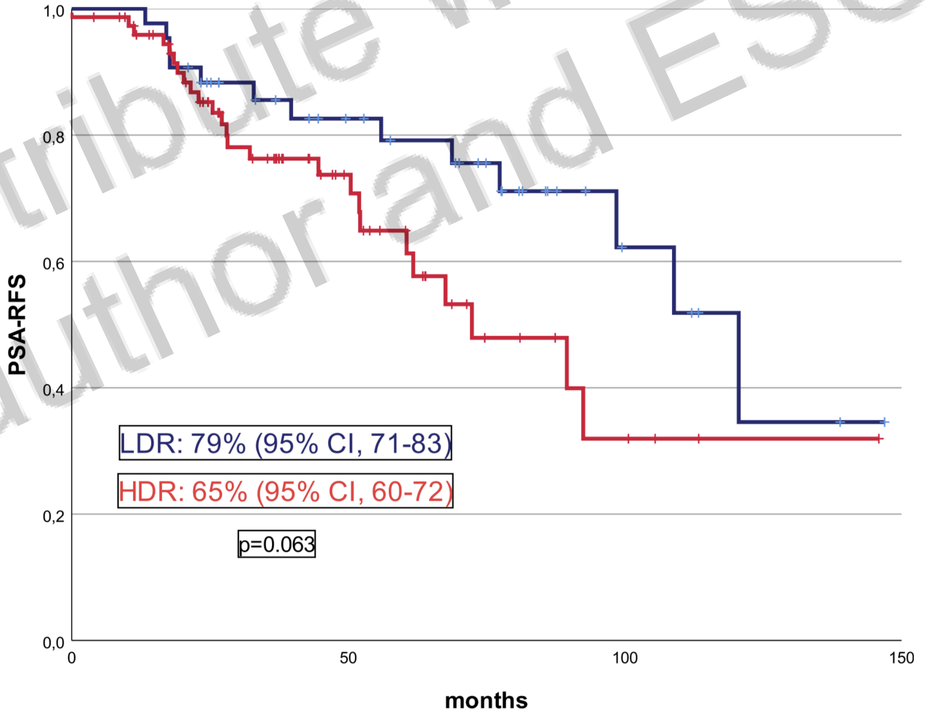


Fig. 2. Prostate-specific antigen relapse-free survival (PSA-RFS) for high-dose rate (HDR) and low-dose rate (LDR) salvage brachytherapy.

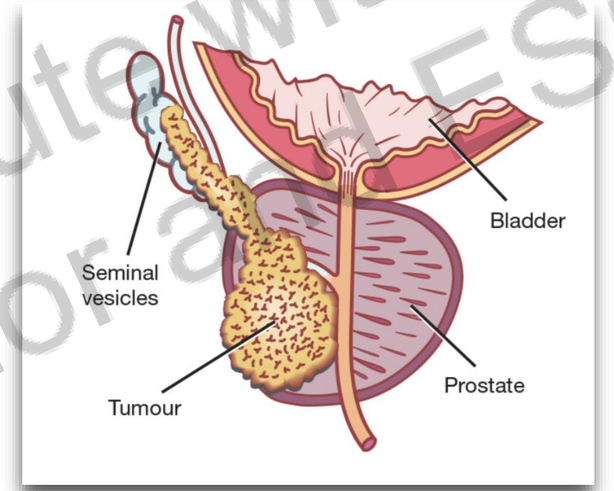
Henriquez I. Radiother &

Relative contraindications and difficulties in OR

- More difficult implant and increased risk of side effects
  - **Very large** (>60cc) or **very small** prostate (<15cc)
  - Urinary symptoms (**IPSS**): more imp if **obstructive**
  - Prior **TURP**: urethral defect
- Neoadyuvant ADT may be used for prostate volume reduction
  - Higher toxicity can be expected

T-stage considerations

- **HDR catheters safely implanted outside** the prostate capsule and into the seminal vesicles without risk of seed migration
- HDR has potential for significantly improve dose coverage in **T3 disease**
- LDR potential **migration of seeds** if implanted outside the prostate or SV



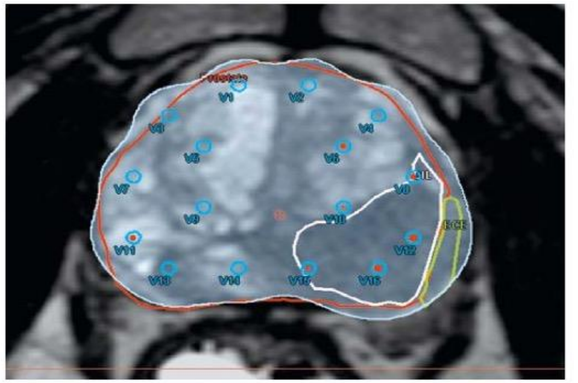
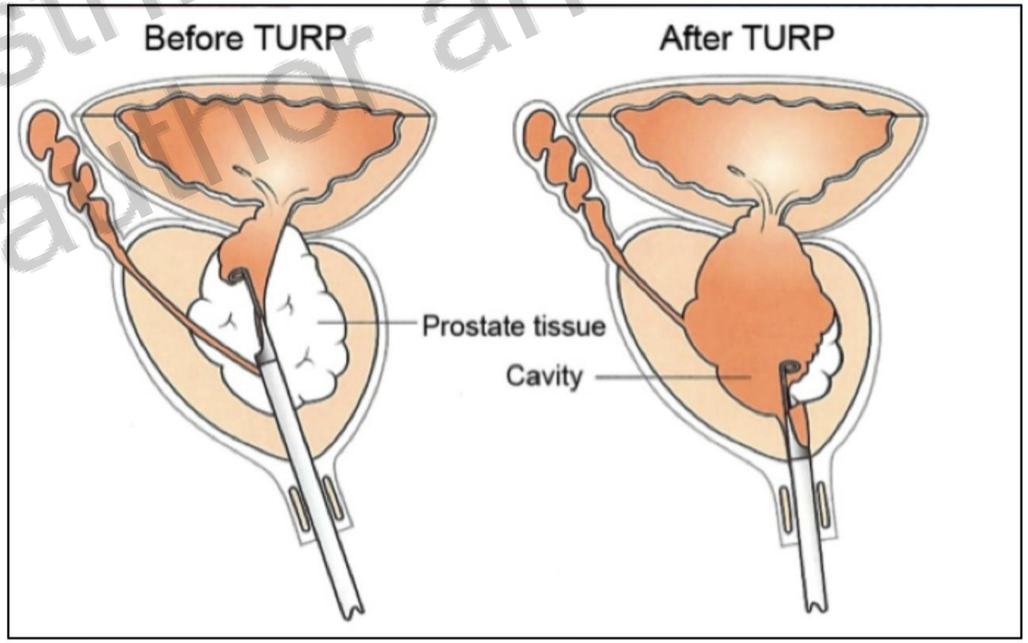


Fig. 2. Fused MR data set. Volumes delineated: prostate (red), dominant intraprostatic lesion (pink), extracapsular extension (green). V_{100} isodose distribution (blue color wash)

Gomez Iturriaga A. J. Contem Brachytherapy 2014

Anatomic Issues: TURP defects

- Irregular or big urethral defect after TURP may be an issue for LDR
- No tissue (missing) where seeds should be implanted for optimal dose distribution
- HDR is a more stable implant, higher energy of the source and more capability to “play” with dwell positions and dwell times

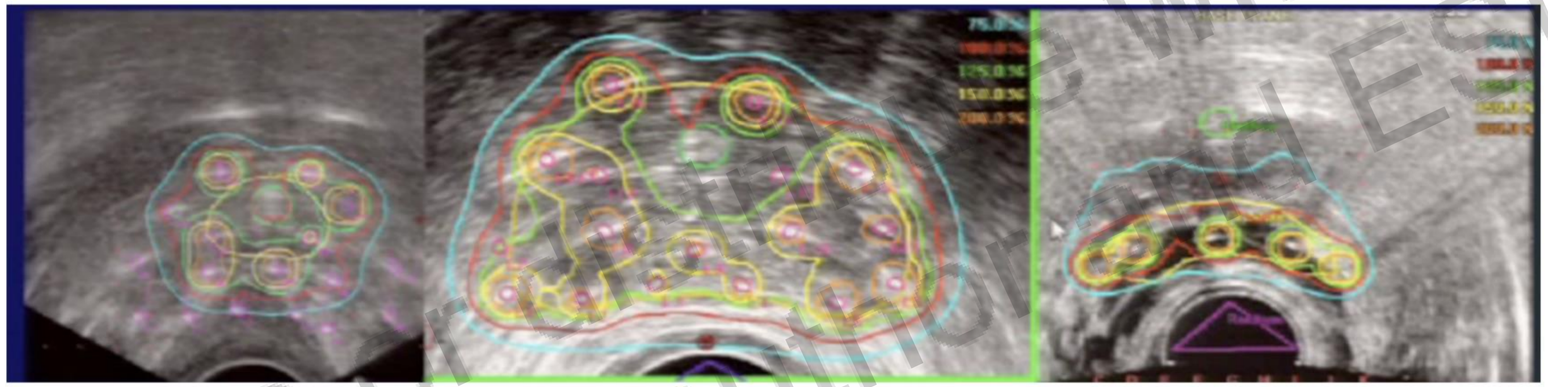


Anatomic Issues: volume changes over time

- **LDR**: during the lifetime of dose delivery anatomic changes can occur
  - **Edema** after implant and first weeks of radiation dose
  - **Shrinkage** of the prostate (when ADT is used in high-risk PCa)
- **HDR**: full dose delivered within minutes to hours of planning
  - Confidence higher with real time HDR

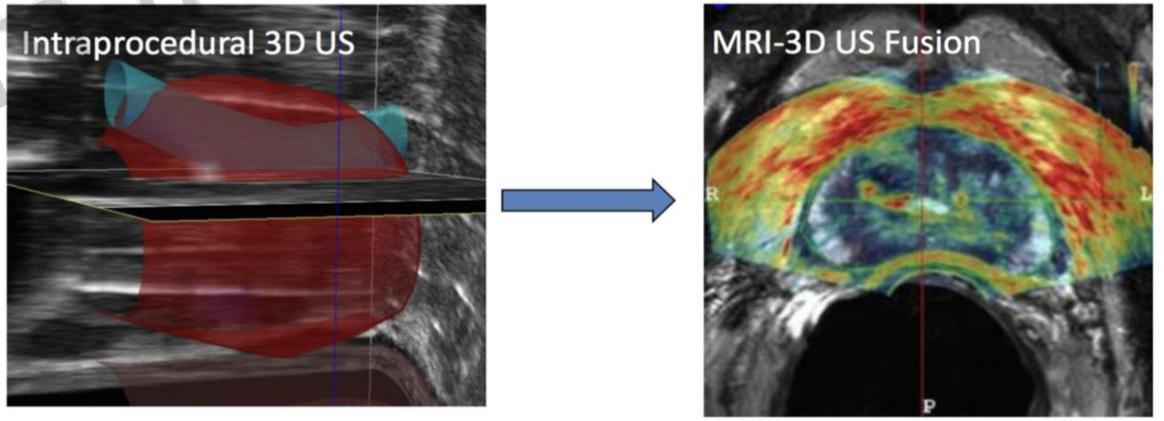
HDR brachytherapy

Dose painting



APEX MID-GLAND SEMINAL VESICLES

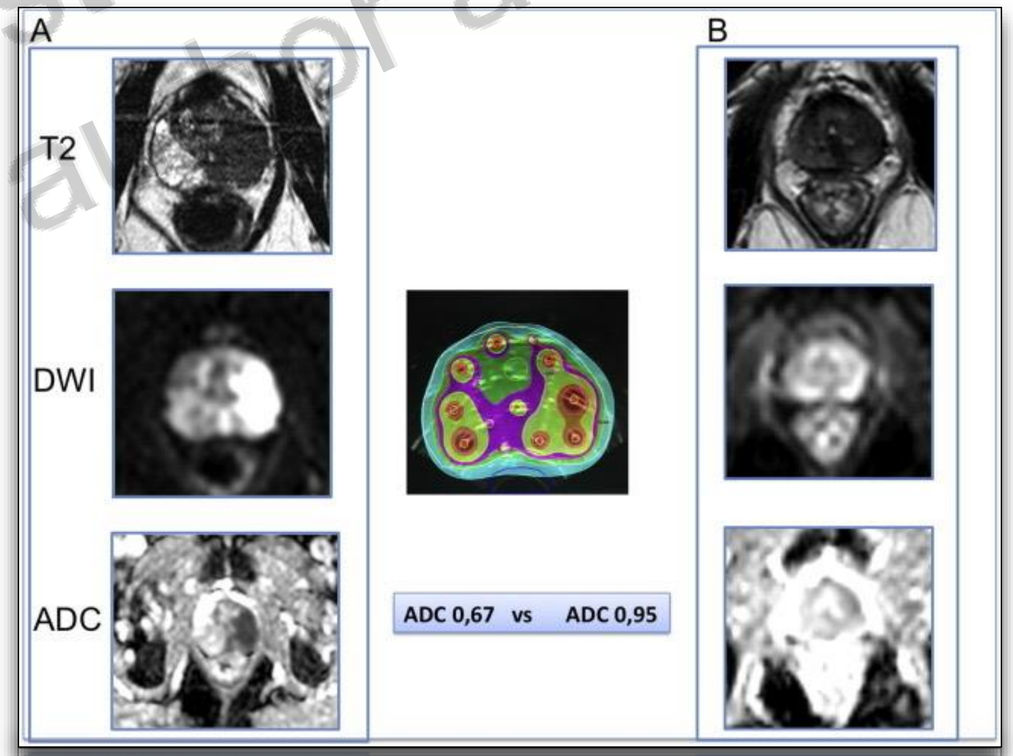
TRUS-MRI fusion



Further innovation

- ✔ **Multiparametric MRI**: morphological and functional information (ECE, SVI, location of DIL)

- ✔ **Individualized** treatment plan:
  - ✔ Dose painting to DIL
  - ✔ Broader margin (ECE)…



Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

CCTG-Led Trial Proposal

Androgen Suppression Combined with Elective Nodal and a Dose Escalated Boost. A Non-Inferiority, Phase 3 Randomized Controlled Trial of Stereotactic Body Radiation Therapy versus Brachytherapy Boost (ASCENDE-SBRT)

Andrew Loblaw

March 9, 2021

Previous Work Shows SBRT Boost Not Worse

Brachy Boost

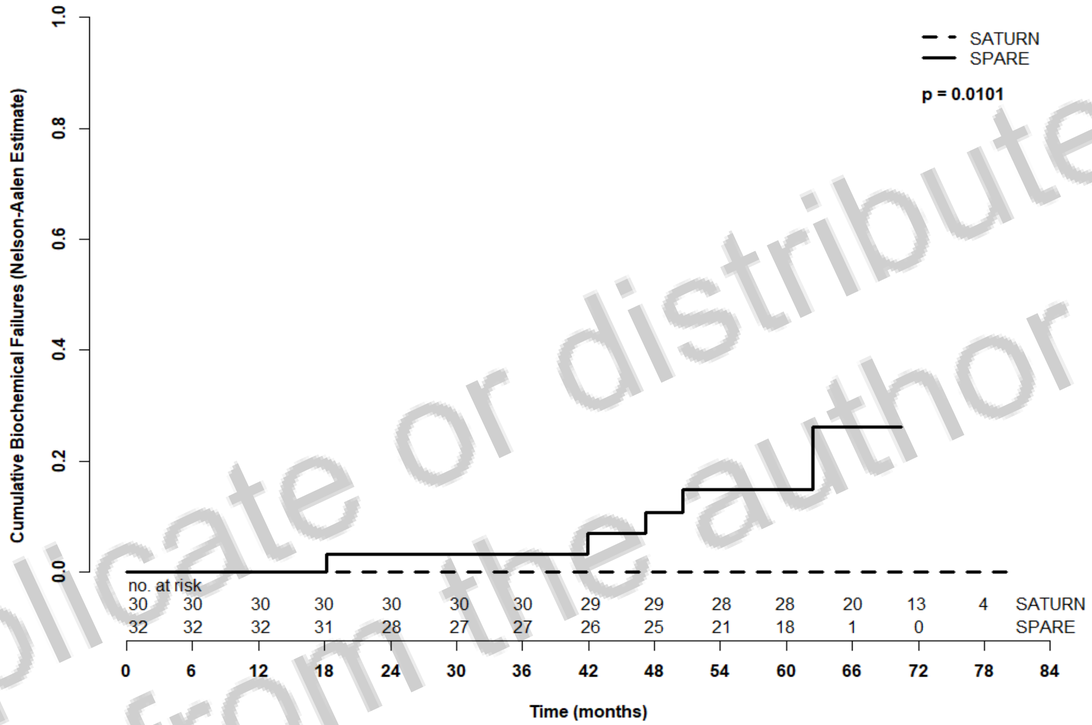
SPARE

50% HR

SBRT 25/5 ENI

HDR 15Gy prostate

6-18 mo ADT



SBRT Boost

SATURN

93% HR

SBRT 25/5 ENI

40/5 prostate

12-18 mo ADT

Domain	Timing	SPARE (HDR boost)	SATURN (SBRT)	p-value
Late GU	Grade 2*	23%	50%	0.13
	Grade 3*	3%	0%	
Late GI	Grade 2*	7%	23%	0.15
	Grade 3*	0%	0%	
BF	5-year	14.8%	0%	0.010
MFS	5-year	89.5%	100%	0.022

Loblaw DA

GU ASCO 2020

Canadian Cancer Trials Group | Groupe canadien des essais sur le c

Trial Proposal

To compare SBRT boost to brachytherapy boost for men with unfavorable risk prostate cancer in context of whole pelvic radiotherapy and androgen deprivation therapy

Priority of study question:

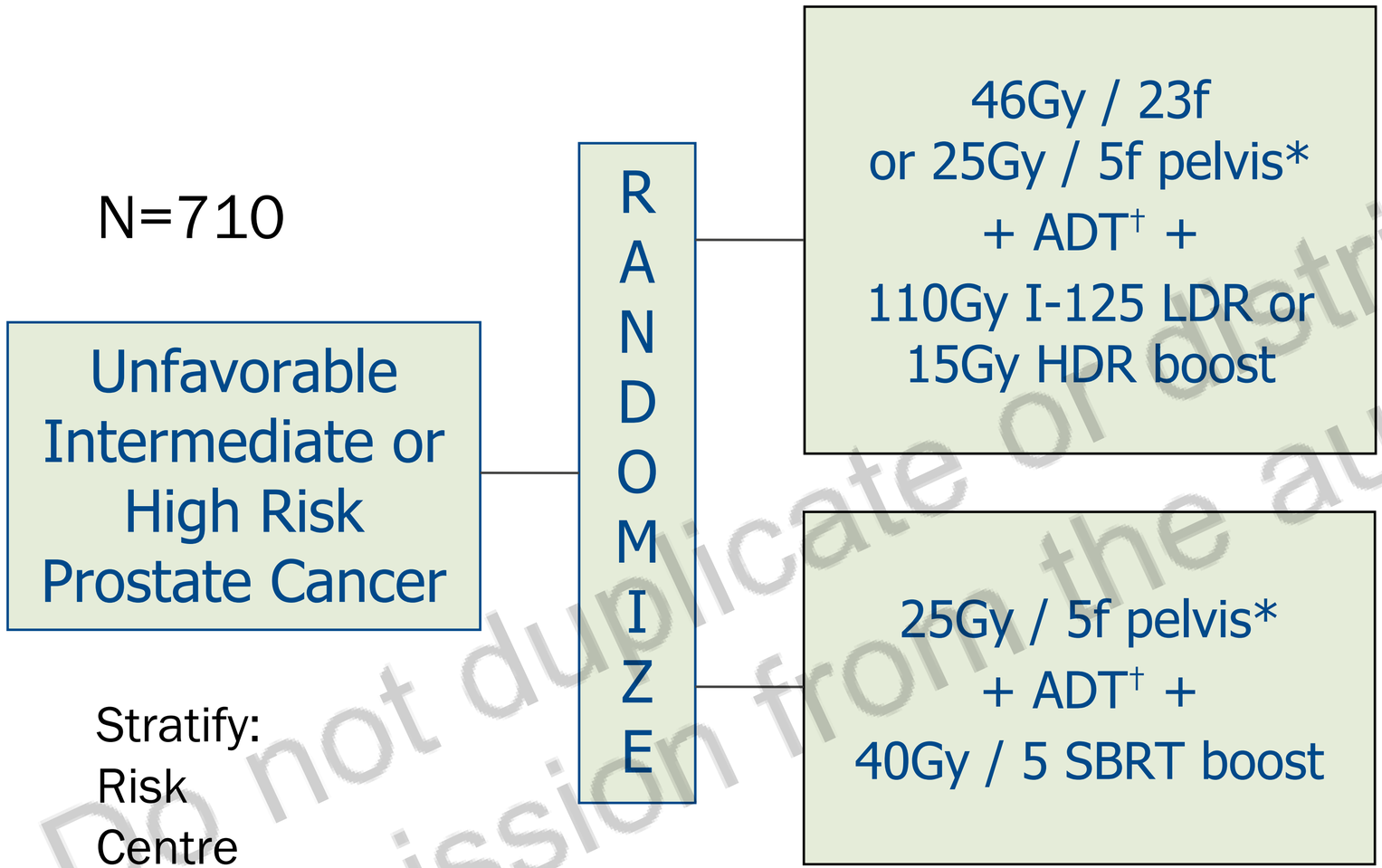
- Highest priority study from GU Disease Site Group
- Very important study question among experts in UK, US, and Australia
  - UK and US expressed a desire to participate

Trial Proposal

Practice Changing Potential

- If SBRT boost is non-inferior to brachytherapy boost, SBRT would become a global standard of care option for unfavorable risk patients.
- If SBRT was inferior to brachytherapy, then this trial would provide important data to support an informed decision-making process but also allow health systems to plan for greater brachytherapy capacity
- The trial will increase SBRT use across Canada for favorable risk patients

Trial Schema



*NRG pelvic LN, SVs, prostate
†UIR: 4 – 6 mo ADT
HR: 18 – 36 mo ADT

Outcomes

- Progression-free survival‡
- Safety, tolerability
- RT quality
- Quality of Life
- 4yPSARR
- MFS, CSS, OS
- Financial Burden

‡biochemical failure, local salvage, metastasis or death

The FUTURE is Collaboration

- Time to define and individualize:
  - The best Radiation technique (Brachy, SABR, EBRT)
  - The best treatment strategy (Total or focal boost)
  - Single technique or combination
  - Use NGI (MRI, PSMA PET) for staging and volume definition
  - Combination with Chemo or Novel antiandrogens

For the moment...

If you want :

- Extremely low PSA values after treatment
- Higher biochemical and local control
- Allows for dose escalation to the whole prostate

Brachytherapy +/- EBRT