EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on

Prostate Cancer

P. Cornford (Chair), D. Tilki (Vice-chair), R.C.N. van den Bergh, E. Briers, Patient Advocate (European Prostate Cancer Coalition/Europa UOMO), D. Eberli, G. De Meerleer, M. De Santis, S. Gillessen, A.M. Henry, G.J.L.H. van Leenders, J. Oldenburg, I.M. van Oort, D.E. Oprea-Lager, G. Ploussard, M. Roberts, O. Rouvière, I.G. Schoots, J. Stranne, T. Wiegel

Update on Prostate Brachytherapy Guidelines from the EAU

Prof Philip Cornford

Bon Secours Hospital, Cork

Chair EAU Prostate Cancer Guidelines

BON SECOURS HOSPITAL CORK

Disclosures

Honoraria: Accord, Astellas, AstraZeneca, Bayer, Ferring Pharmaceuticals, Ipsen, Janssen and Novartis

Scientific advisory board meetings: Accord, AstraZeneca, Bayer, Bristol Myers Squibb, Ferring Pharmaceuticals and Janssen

I don’t do brachytherapy but I am involved in guidelines production

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Avoid Over Treatment

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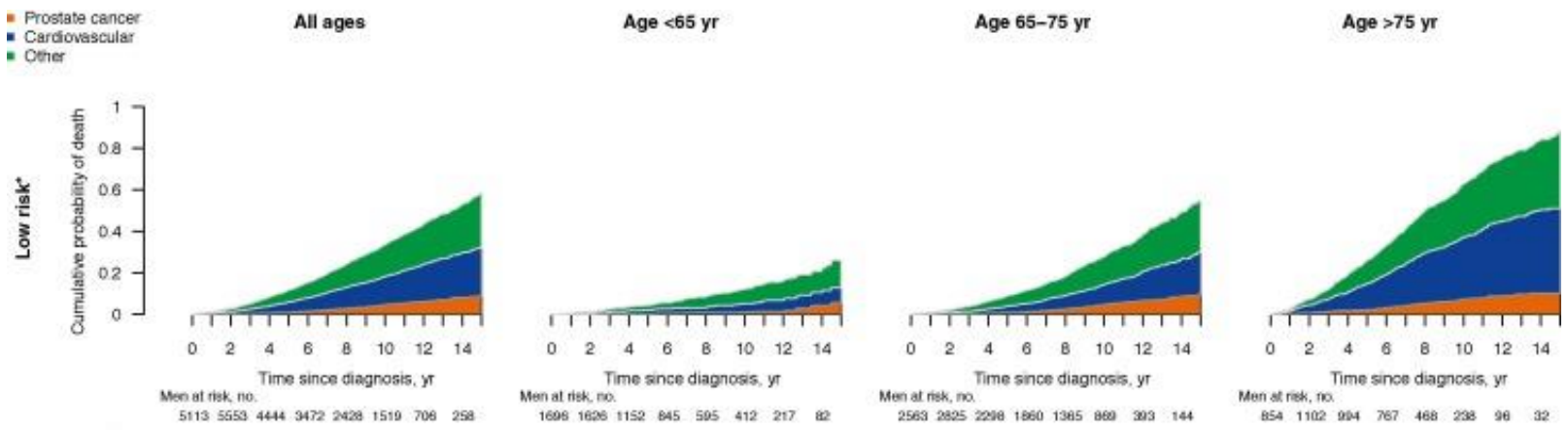
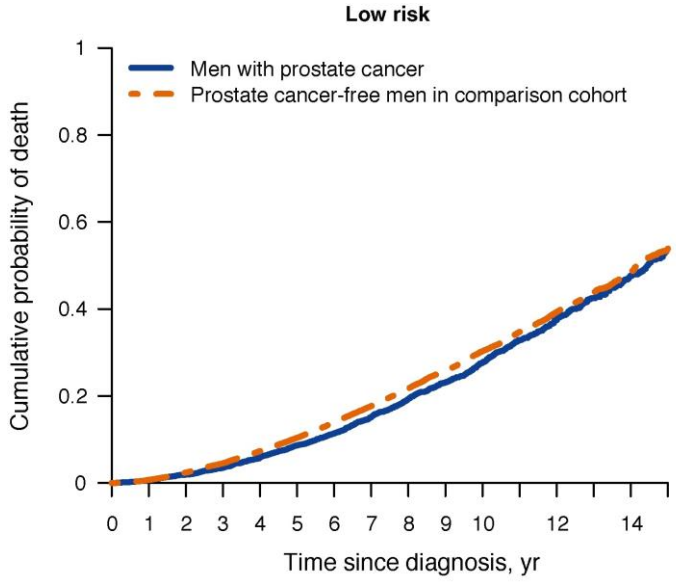
Recommendations	Strength rating
Watchful Waiting	
Manage patients with a life expectancy < 10 years by watchful waiting.	Strong

You need to live >10 years to gain any benefit from treating low risk prostate cancer





Risk of dying from Ca P at 10 yrs 4.5% (3.8-5.2%) other causes 29% (27.5-30.5%)
at 15 yrs 8.9% (7.4-10.5) and other causes 49.5(46.5-52.4)

Rider JR et al Euro Urol 2013; 63(1): 88-96

Lead Times and Overdetection Due to Prostate-Specific Antigen Screening: Estimates From the European Randomized Study of Screening for Prostate Cancer

Gerrit Draisma, Rob Boer, Suzie J. Otto, Ingrid W. van der Cruijsen, Ronald A. M. Damhuis, Fritz H. Schröder, Harry J. de Koning

Table 3. Predictions of mean lead time and overdetection rates associated with screening from the basic model*

		Type of cancer		
		Any	Relevant	Irrelevant
Lifetime risk per 1000 men†		151‡ (145 to 166)‡	64	87 (80 to 103)
Mean sojourn time§, y† (range)		12.7 (12.1–14.2)	15.4	10.8 (10.0–12.5)

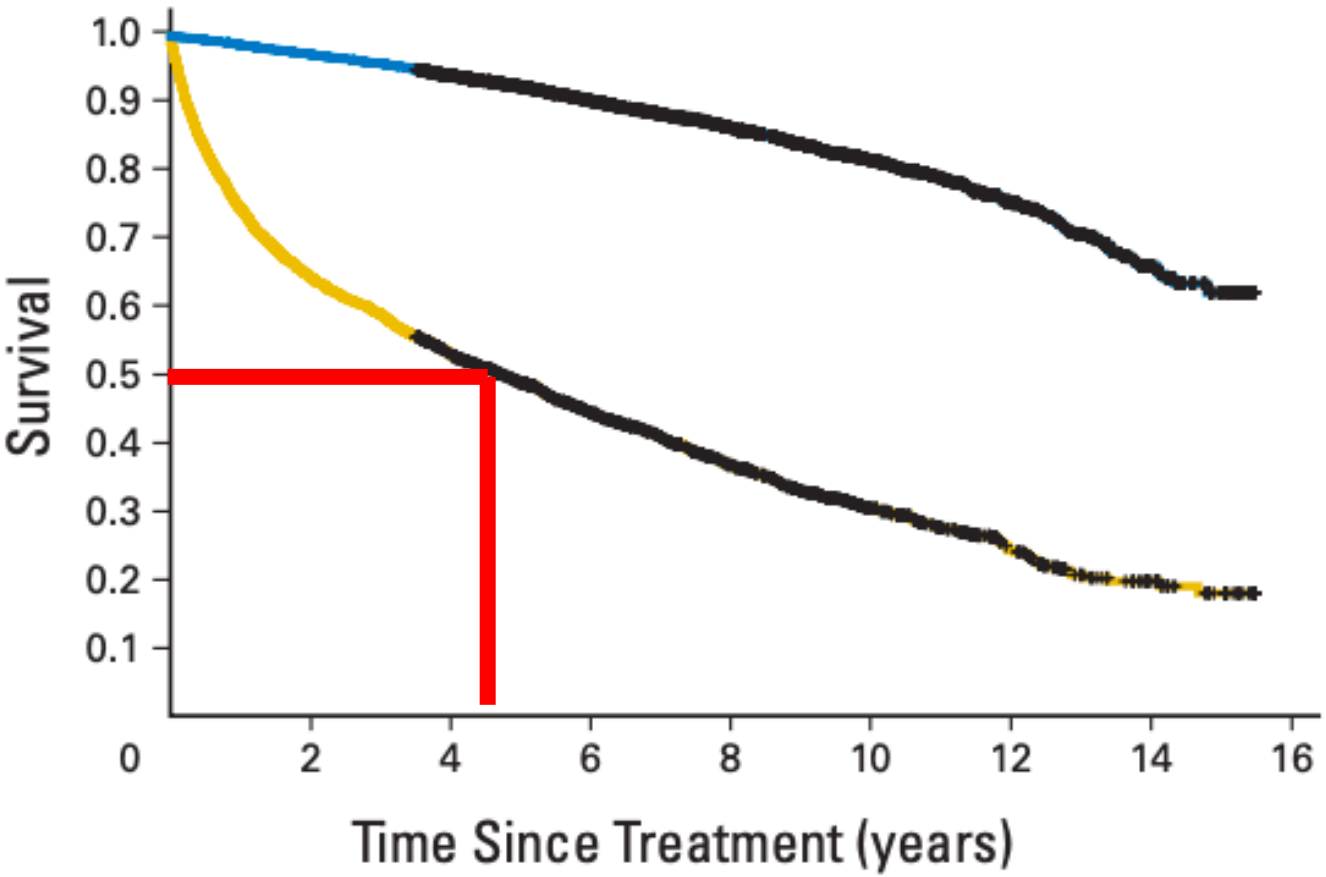
		Mean lead time‖, y (range)		Detection per 1000 men			Overdetection (range)	
Screening program	Age, y	All cases	Relevant cases	All cases	Relevant cases	Irrelevant cases	% of detection	% increase lifetime risk
Single	55	12.3 (11.6–14.1)	12.8 (12.0–14.6)	15	11	4	27 (24–37)	6 (5–9)
	60	11.0 (10.4–12.4)	11.5 (11.0–13.0)	31	19	12	38 (34–47)	18 (15–25)
	65	9.5 (9.0–10.5)	10.0 (9.6–11.0)	52	28	24	47 (43–55)	38 (33–49)
	70	7.7 (7.4–8.3)	8.1 (7.9–8.7)	64	30	34	53 (50–60)	54 (49–60)
	75	6.0 (5.8–6.3)	6.2 (6.0–6.6)	54	24	30	56 (53–61)	47‡
Interval	Every y, 55–67	12.3 (11.8–13.3)	13.7 (13.3–14.7)	103	52	51	50 (46–57)	80 (69–116)
	Every y, 55–75	11.6 (11.1–12.6)	13.4 (13.0–14.4)	140	61	79	56 (54–61)	124 (111–153)
	Every 4 y, 55–67	11.2 (10.8–12.1)‡	12.3 (11.9–13.2)	87	45	41	48 (44–55)	65 (56–87)
	Every 4 y, 55–75	10.3 (9.9–11.2)	11.7 (11.3–12.5)	123	57	66	54 (51–59)	105 (95–124)

For a screening programme with a 4-year screening interval from age 55-67 the estimated mean lead time was 11.2 years

JNCI 2003; 95(12): 868-78

Overall Survival in men who did not receive secondary therapy

Walz J et al J Clin Oncol 2007; 25:3576-81



N=9,131

Between 1989 and 2000, 9,131 men were treated with either RP (n 5,955) or EBRT (n 3,176), without any secondary therapy and all deaths were considered unrelated to PCa

Median age was 66 years, median CCI was 1, median follow-up was 5.9 years and median actuarial survival was 13.8 years. Advanced age (*P* .001), elevated CCI score (*P* .001) and treatment type (EBRT *v* RP, *P* .001) were independent predictors of poor 10 year LE

Table 2. Univariable and Multivariable Cox Regression Analyses of the Effect of Age, CCI, and Treatment Type on Overall Mortality in Men Who Did Not Receive Secondary Therapy After RP or EBRT (N = 9,131)

	Univariable			Multivariable		
Variable	Rate ratio	95% CI	*P*	Rate ratio	95% CI	*P*
Age at treatment						
Continuously coded	1.13	1.12 to 1.14	< .001	1.07	1.06 to 1.07	< .001
CCI						
Continuously coded	1.35	1.33 to 1.38	< .001	1.16	1.13 to 1.20	< .001
Treatment type						
EBRT *v* RP	6.56	6.06 to 7.11	< .001	3.80	3.47 to 4.12	< .001

Abbreviations: RP, radical prostatectomy; EBRT, external-beam radiation therapy; CCI, Charlson comorbidity index.

Low dose rate brachytherapy for localised prostate cancer

NICE National Institute for Health and Care Excellence

2.1.1 Treatment options for prostate cancer depend on whether the disease is localised to the prostate gland. Current management options for localised prostate cancer include radiotherapy, radical prostatectomy and 'watchful waiting'.

2.1.2 Radiation therapy can take the form of external-beam radiotherapy or brachytherapy. Brachytherapy may be given at either low or high dose rates. Low dose rate brachytherapy may be used alone (monotherapy) or in combination with external-beam radiotherapy.

2.3.5 The Specialist Advisors considered low dose rate brachytherapy to be an established procedure and stated that the results are comparable with those achieved with surgery or external-beam radiotherapy in well-selected patients.

www.nice.org.uk/guidance/ipg132

Prostate cancer: diagnosis and management

NICE National Institute for Health and Care Excellence

1.3.24 Consider brachytherapy in combination with external beam radiotherapy for people with CPG 2, 3, 4 and 5 localised or locally advanced prostate cancer. **[2019, amended 2021]**

1.3.25 Do not offer brachytherapy alone to people with CPG 4 and 5 localised or locally advanced prostate cancer. **[2008, amended 2021]**

www.nice.org.uk/guidance/ng131

Guidelines

GEC-ESTRO ACROP prostate brachytherapy guidelines

Ann Henry [a], Bradley R. Pieters [b], Frank André Siebert [c], Peter Hoskin [d,e,*],
on behalf of the UROGEC group of GEC ESTRO with endorsement by the European Association of Urology [1]

[a] *St James University Hospital, Leeds, UK;* [b] *Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands;* [c] *University of Kiel/University Hospital Schleswig-Holstein Campus Kiel, Germany;* [d] *Mount Vernon Cancer Centre, Northwood; and* [e] *University of Manchester, Manchester, UK*

Prostate brachytherapy is a highly effective treatment for localised prostate cancer in patients who have no evidence of metastases. It is indicated:

Alone as sole modality for low and selected intermediate risk prostate cancer.

Radiotherapy and Oncology 2022; 167: 244-51

Clinically Localized Prostate Cancer: AUA/ASTRO Guideline. Part III: Principles of Radiation and Future Directions

In patients with low- or favorable intermediate-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT (moderate or ultra), permanent low-dose rate (LDR) seed implant, or temporary high-dose rate (HDR) prostate implant as equivalent forms of treatment. (Strong Recommendation; Evidence Level: Grade B)

Eastham JA et al J Urol 2022; 208(1): 26-33

Avoid Over Treatment

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Recommendations	Strength rating
Watchful Waiting	
Manage patients with a life expectancy < 10 years by watchful waiting.	Strong
Active surveillance (AS)	
Manage patients with a life expectancy > 10 years and low-risk disease by AS.	Strong

Low-risk : PSA <10 ng/ml, and ISUP 1 and cT1-T2a

Brachytherapy

EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on **Prostate Cancer**

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Recommendations	**Strength rating**
Offer low-dose rate (LDR) brachytherapy monotherapy to patients with good urinary function and NCCN favourable intermediate-risk disease.	Strong

IPSS <12 and Qmax >15 ml/sec

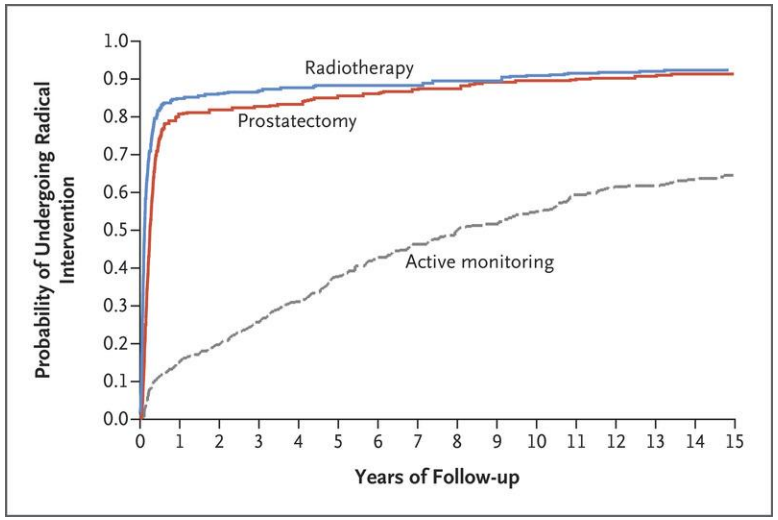
Martens C et al Brachytherapy 2006; 5(1): 9-13

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

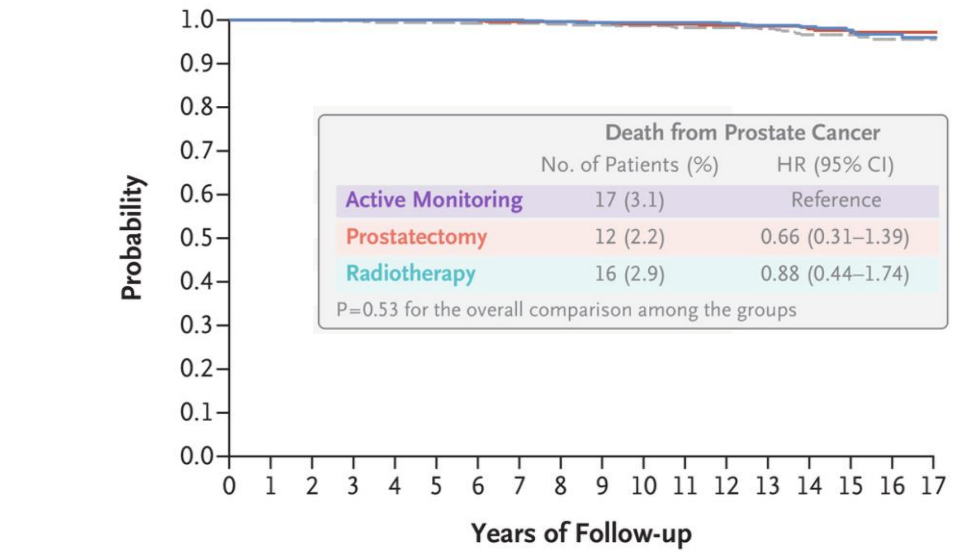
Fifteen-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, C. Metcalfe, M. Davis, E.L. Turner, R.M. Martin, G.J. Young, E.I. Walsh, R.J. Bryant, P. Bollina, A. Doble, A. Doherty, D. Gillatt, V. Gnanapragasam, O. Hughes, R. Kockelbergh, H. Kynaston, A. Paul, E. Paez, P. Powell, D.J. Rosario, E. Rowe, M. Mason, J.W.F. Catto, T.J. Peters, J. Oxley, N.J. Williams, J. Staffurth, and D.E. Neal, for the ProtecT Study Group*



Prostatectomy — Radiotherapy — Active monitoring

Prostate Cancer–Specific Survival

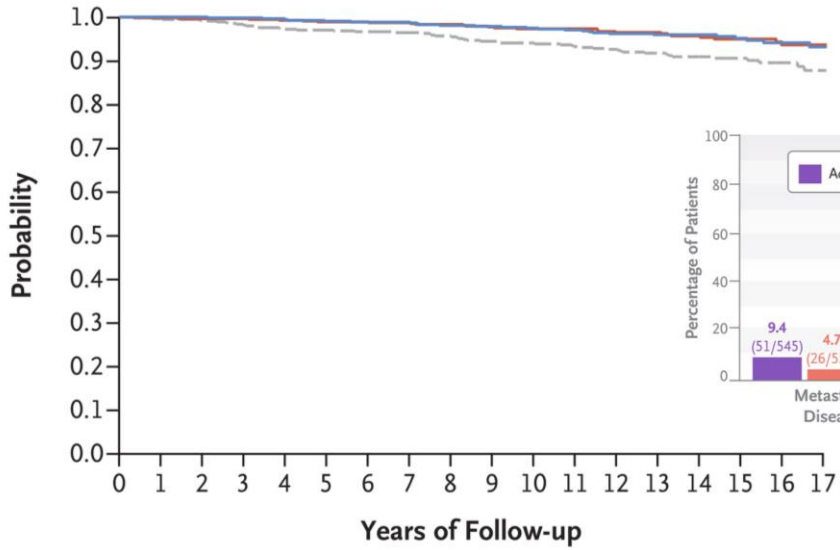


Death from Prostate Cancer	No. of Patients (%)	HR (95% CI)
Active Monitoring	17 (3.1)	Reference
Prostatectomy	12 (2.2)	0.66 (0.31–1.39)
Radiotherapy	16 (2.9)	0.88 (0.44–1.74)

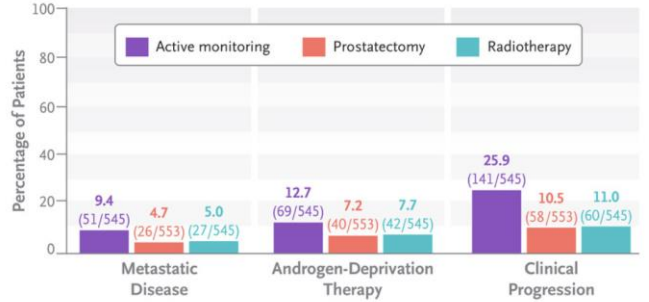
P=0.53 for the overall comparison among the groups

No. at Risk					
	1643	1589	1490	654	282

Metastasis-free Survival



Secondary Outcomes



No. at Risk					
	1643	1569	1456	636	274

Of the 488 men who had RP within 12 months 138 (28.5%) had pT3 or T4 disease; 155 (32%) had an increase in tumour grade and 245 (50.5%) had a Gleason score of 7 or higher)

Hamdy FC et al NEJM 2023;338:1547-58

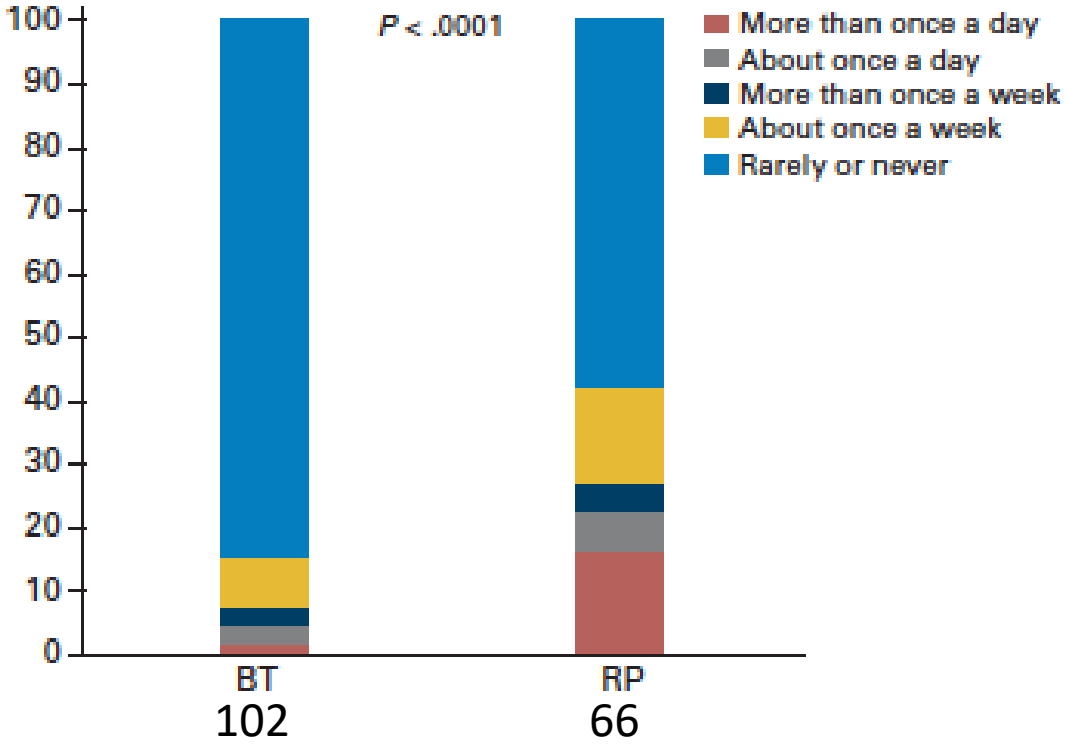
VOLUME 29 · NUMBER 4 · FEBRUARY 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comparison of Health-Related Quality of Life 5 Years After SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial

Juanita Mary Crook, Alfonso Gomez-Iturriaga, Kris Wallace, Clement Ma, Sharon Fung, Shabbir Alibhai, Michael Jewett, and Neil Fleshner



102 66

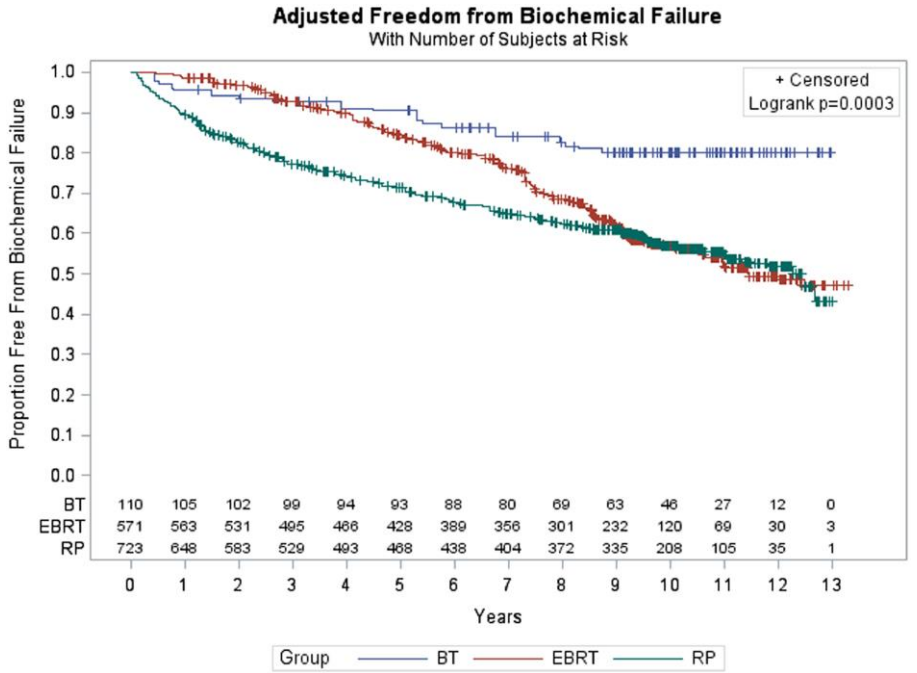
Urinary Leakage

The ability to have erections

Ten-Year Treatment Outcomes of Radical Prostatectomy Vs External Beam Radiation Therapy Vs Brachytherapy for 1503 Patients with Intermediate-risk Prostate Cancer

Barry W. Goy [a], Raoul Burchette [b], Margaret S. Soper [a], Tangel Chang [c], Harry A. Cosmatos [a]

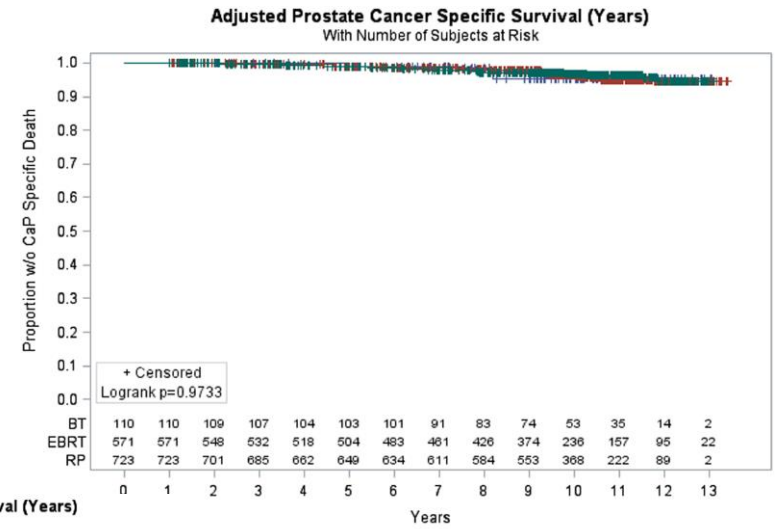
	RP	RT	BT	
Gleason score				.0001
6 (3 + 3)	194 (23.7%)	156 (27.2%)	47 (42.7%)	
7 (3 + 4)	483 (59.0%)	279 (48.6%)	51 (46.4%)	
7 (4 + 3)	142 (17.3%)	139 (24.2%)	12 (10.9%)	
Risk				<.0001
Favorable	507 (61.9%)	297 (51.7%)	75 (68.2%)	
Unfavorable	312 (38.1%)	277 (48.3%)	35 (31.8%)	
NADT	5 (0.6%)	338 (58.9%)	14 (12.7%)	<.0001

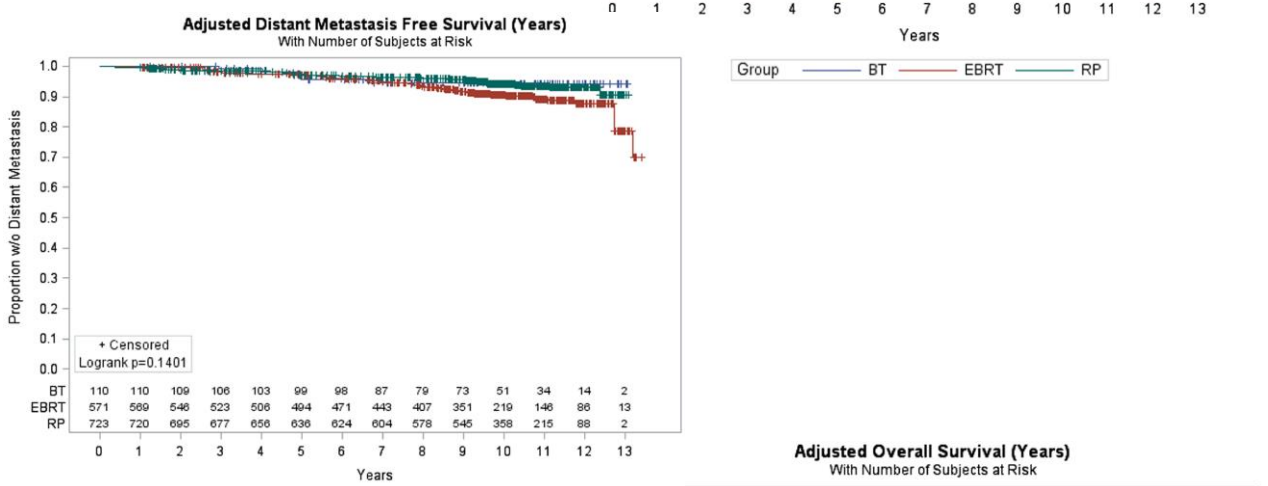


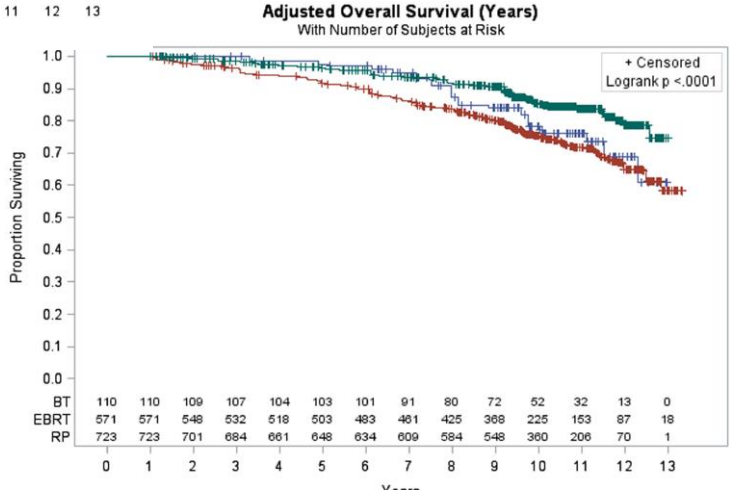
Urology 2020; 136: 180-9

Oncological Outcomes

Metastases-free survival					
BT	110	7	97.1%	92.5% (87.3, 98.1%)	.10
RP	819	38	97.2%	94.6% (92.9, 96.3%)	
EBRT	574	41	97.8%	91.2% (88.6, 93.8%)	
Prostate cancer-specific survival					
BT	110	3	99.0%	96.7% (93.1, 100%)	.78
RP	819	21	99.0%	96.9% (95.6, 98.2%)	
EBRT	574	16	99.2%	96.1% (94.2, 98.0%)	
Overall survival					
BT	110	13	98.1%	85.7% (78.7, 93.3%)	<.0001
RP	819	76	96.6%	88.8% (86.4, 91.3%)	
EBRT	574	150	90.6%	71.2% (67.3, 75.2%)	







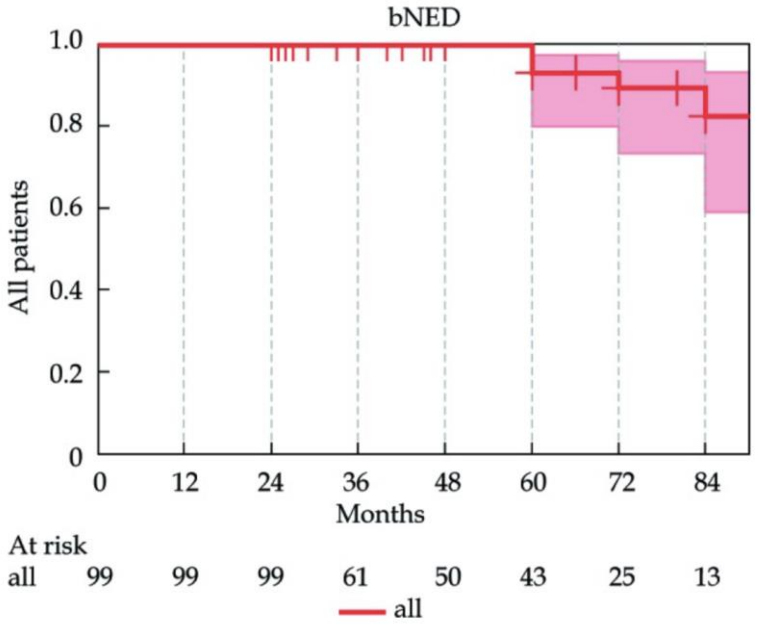
Goy BW et al Urology 2020; 136: 180-9

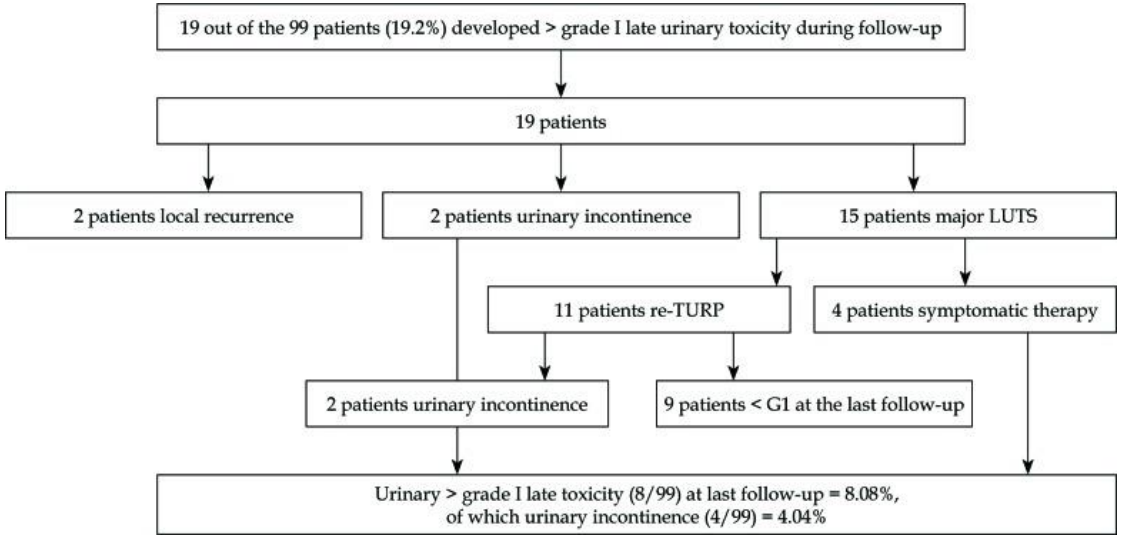
A history of transurethral resection of the prostate should not be a contra-indication for low-dose-rate ^{125}I prostate brachytherapy: results of a prospective Uro-GEC phase-II trial

Journal of Contemporary BRACHYTHERAPY
Journal of Polish Brachytherapy Society /// Published by Termedia sp. z o.o.

Salembier C et al J Contemp Brachytherapy 2020; 12(1): 1-5

Characteristics	Number of patients (%)
T-classification	
T1a-b-c	51 (52%)
T2a-b	49 (48%)
ISUP grade group / Gleason score	
Grade group 1 / VI (3 + 3)	67 (67%)
Grade group 2 / VII (3 + 4)	26 (26%)
Grade group 3 / VII (4 + 3)	6 (6%)
Pretreatment PSA (ng/ml)	Median 6.9 (min. 1.2, max. 16)
Risk level	
Low-risk	54 (55%)
Intermediate-risk	45 (45%)
Androgen deprivation therapy	0 (0%)
Median follow-up time	49 months (min. 24, max. 96)





Patients having had a previous TURP can undergo BT without an increase in risk of urinary toxicity with due attention to dose distribution. A minimal channel TURP is recommended, leaving at least 1 cm rim of prostate tissue around the post-TURP urethral defect at the postero-lateral sides of the prostate and there should be at least a 3-month interval between TURP and BT to allow for adequate healing

Brachytherapy

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Recommendations	**Strength rating**
Offer LDR or high-dose rate (HDR) brachytherapy boost combined with IMRT/VMAT plus IGRT to patients with good urinary function and NCCN unfavourable intermediate-risk or high-risk disease and/or locally-advanced disease.	Weak

ADT should be given as appropriate for the risk of disease

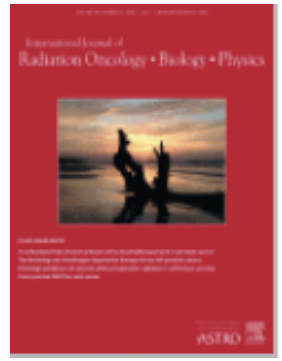
Clinically Localized Prostate Cancer: AUA/ASTRO Guideline. Part III: Principles of Radiation and Future Directions

In patients with unfavorable intermediate- or high-risk prostate cancer electing radiation therapy, clinicians should offer dose-escalated hypofractionated EBRT or combined EBRT+brachytherapy (LDR, HDR) along with a risk-appropriate course of ADT. (Strong Recommendation; Evidence Level: Grade A/B)

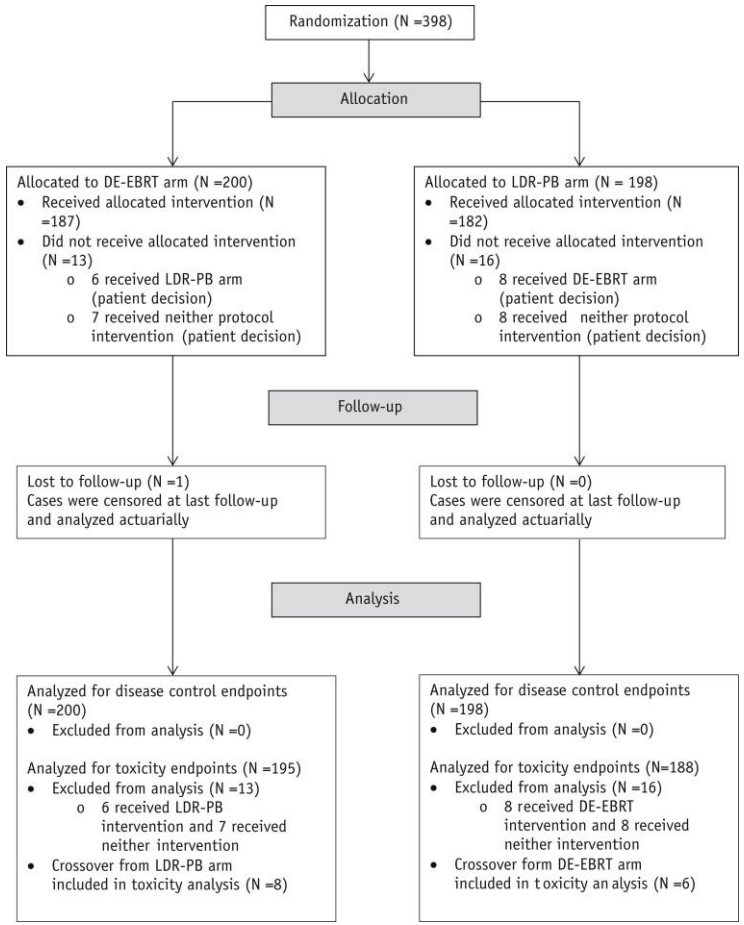
Trials have demonstrated a benefit in clinical control for unfavorable intermediate- or high-risk prostate cancer patients who receive either dose-escalated moderately hypofractionated IMRT or EBRT plus a brachytherapy boost (HDR temporary prostate implant or LDR permanent prostate implant).[1–6] Combining EBRT and brachytherapy has demonstrated improved biochemical control over EBRT plus ADT alone in randomized trials.[1–4]

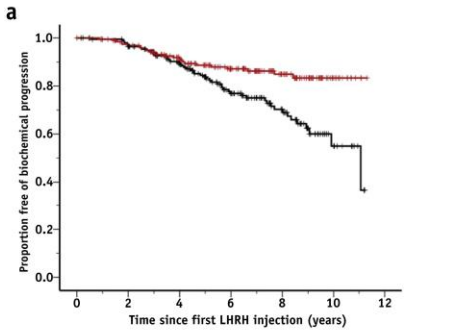
Eastham JA et al J Urol 2022; 208(1): 26-33

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



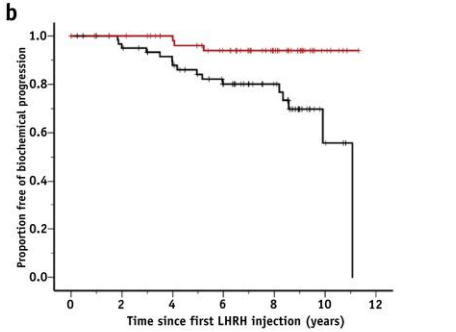
Morris WJ et al Int J Radiat Oncol Biol Phys 2017; 98(2): 275-85.





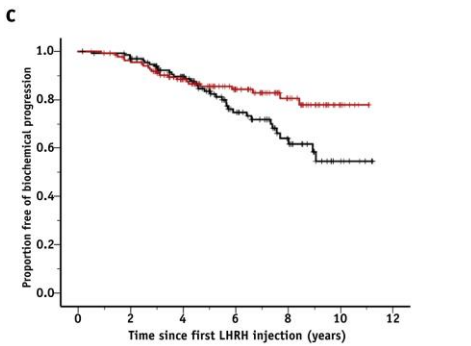
Numbers at risk:

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



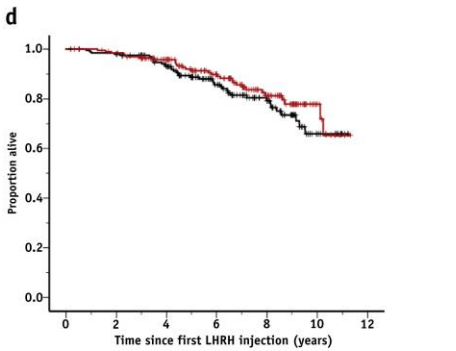
Numbers at risk:

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

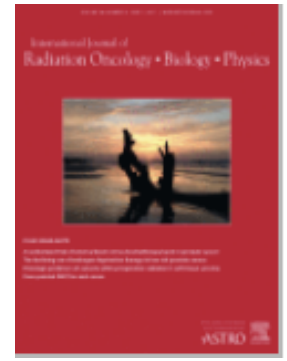


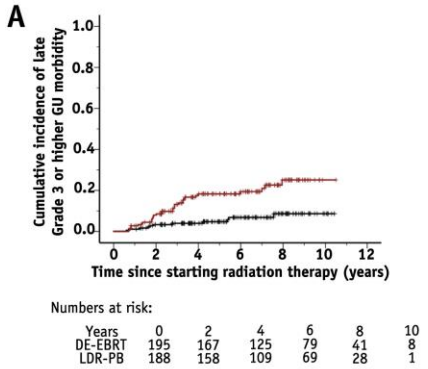
Numbers at risk:

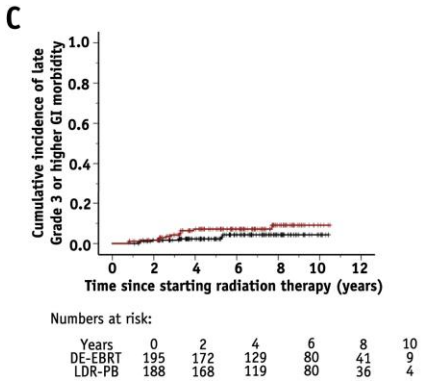
Time (yrs)	0	2	3	4	5	6	7	8	9	10
DE-EBRT	200	192	184	161	134	109	85	66	40	16
LDR-PB	198	191	182	160	137	116	94	65	41	15

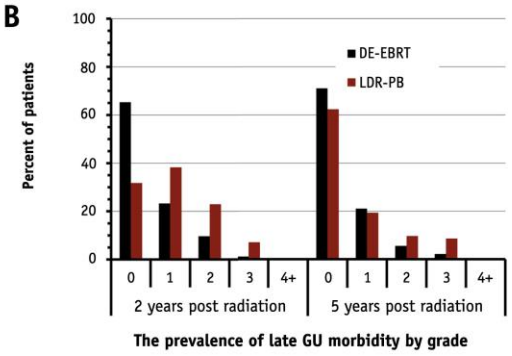
ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer

Rodda S et al al Int J Radiat Oncol Biol Phys 2017; 98(2): 286-95.









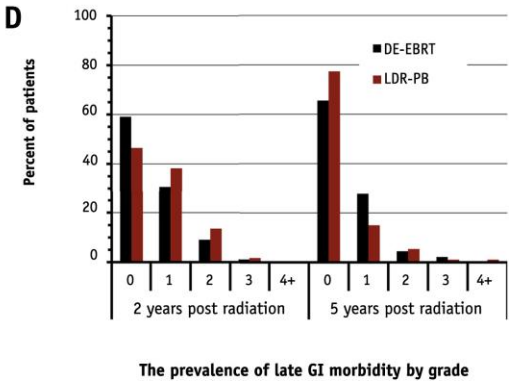
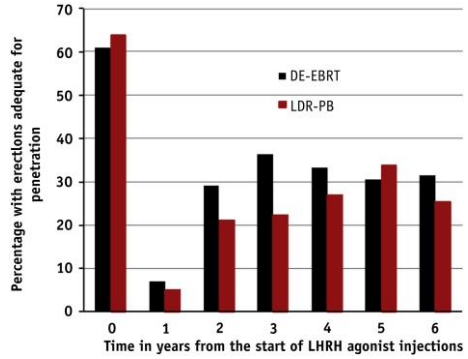


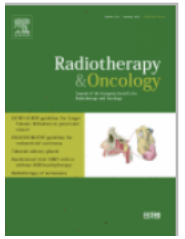
Table 3. Worst grade of late GU and GI toxicity experienced (5-year actuarial cumulative incidence and hazard ratios)

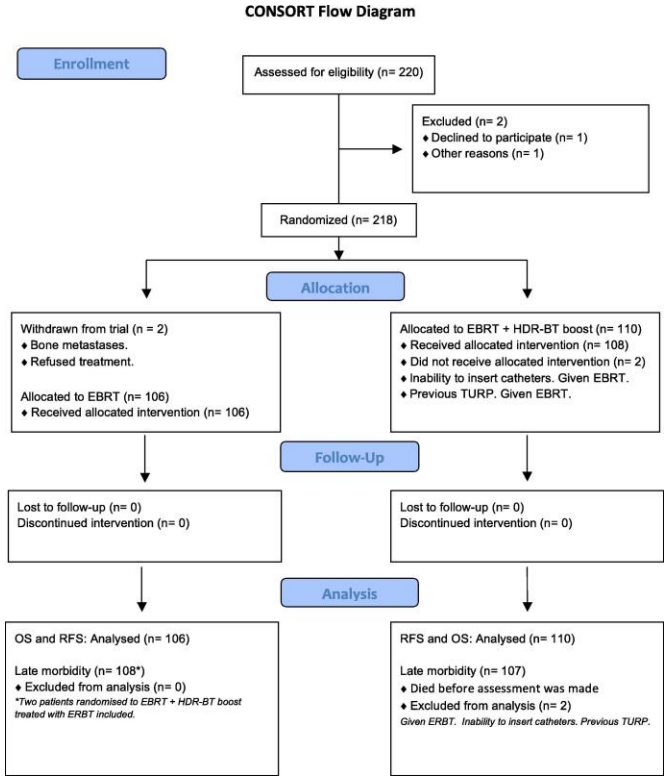
Maximum grade	DE-EBRT (%) (n=195)	LDR-PB (%) (n=188)	Hazard ratio: LDR-PB vs DE-EBRT	*P*
Cumulative incidence of late GU side effects at 5 y				
0	29.6 (23-36)	20.6 (9-32)	0.51 (0.32-0.80)	.003*
1	43.8 (36-51)	33.7 (27-41)	0.75 (0.54-1.04)	.088
2	20.6 (14-27)	32.8 (26-40)	1.97 (1.3-3.00)	.002*
3	5.2 (1-8)	18.4 (12-25)	3.46 (1.7-7.07)	<.001 *
4/5	0.6 (0-2)	2.1 (0-6)	2.05 (0.19-22.6)	.559
Cumulative incidence of late GI side effects at 5 y				
0	35.8 (28-42)	31.3 (23-38)	0.83 (0.56-1.23)	.343
1	48.2 (41-56)	42.0 (35-49)	0.86 (0.63-1.16)	.322
2	20.2 (14-26)	31.3 (17-45)	1.33 (0.86-2.08)	.205
3	3.2 (0-6)	8.1 (3-13)	2.16 (0.81-5.75)	.124
4/5	0	1.0	N/A	N/A

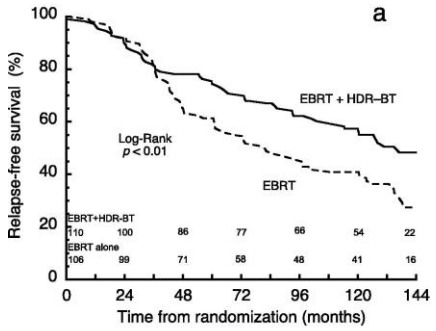


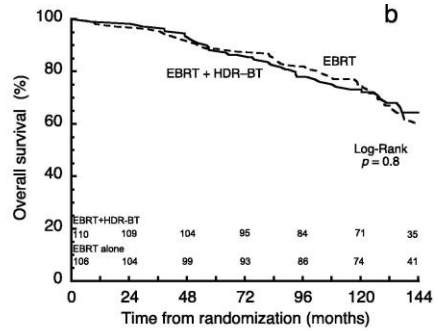
Randomised trial of external-beam radiotherapy alone or with high-dose-rate brachytherapy for prostate cancer: Mature 12-year results

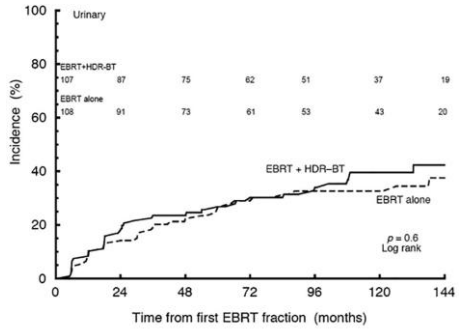
Hoskin PJ et al Radiotherapy and Oncology 2021; 154: 214-9

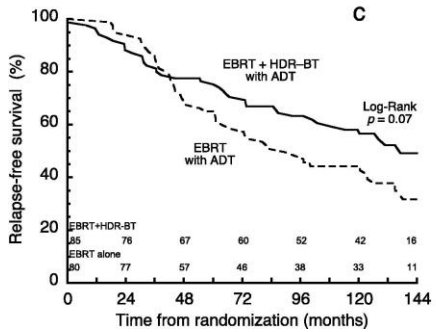


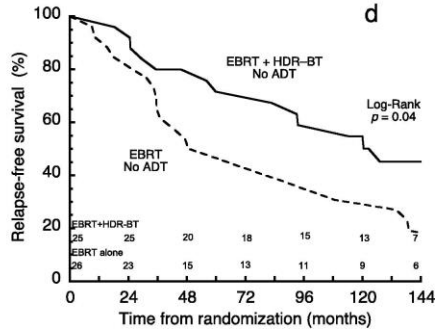


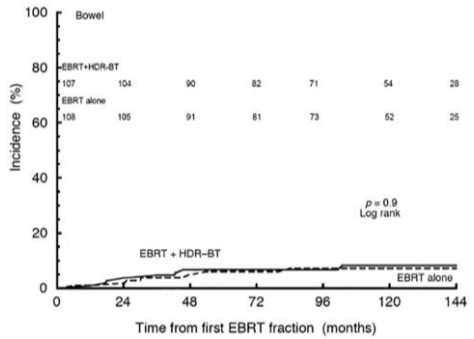








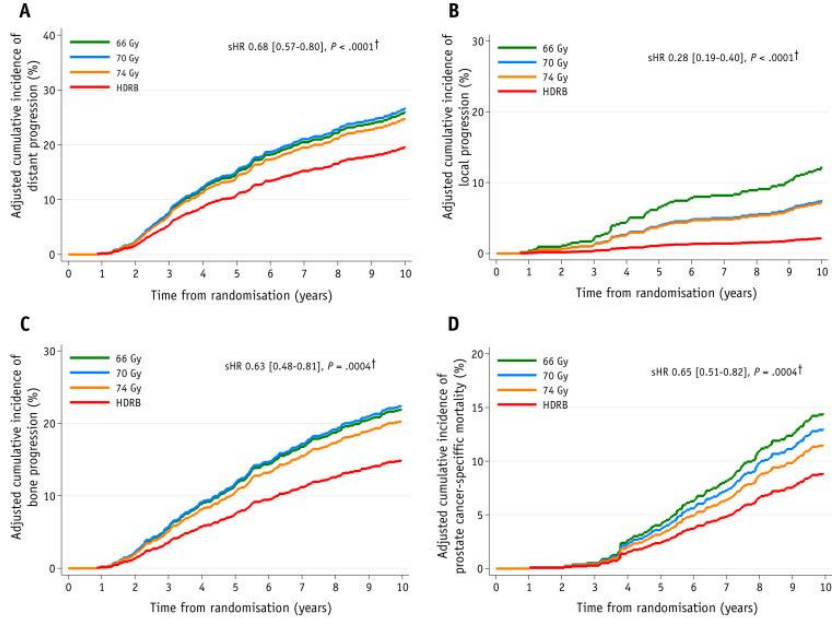




Improved relapsed free survival with no added toxicity but no obvious improvement in overall survival

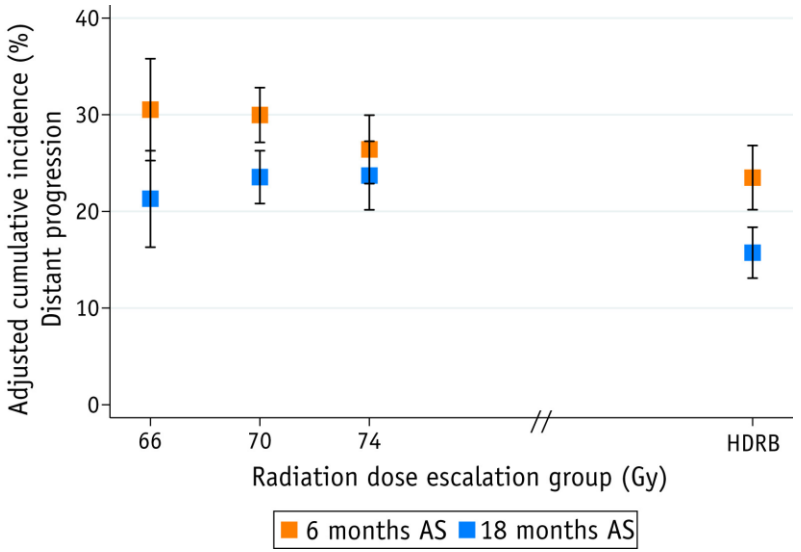
Radiation Dose Escalation or Longer Androgen Suppression to Prevent Distant Progression in Men With Locally Advanced Prostate Cancer: 10-Year Data From the TROG 03.04 RADAR Trial

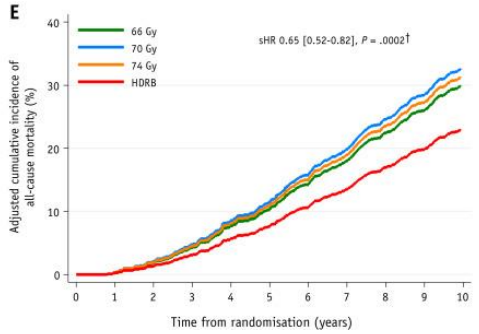
David Joseph, FRANZCR • James W. Denham, MD, FRANZCR • Allison Steigler, BMath • ...
Brett Delahunt, MD • Christopher Oldmeadow, PhD • John Attia, MD, PhD • Show all authors



1051 patients were randomized to 6 or 18 months of androgen suppression and were stratified at randomization between 66, 70, or 74 Gy external beam radiation therapy (EBRT), or 46 Gy EBRT plus high-dose-rate brachytherapy boost (HDRB).

Primary endpoint distant progression

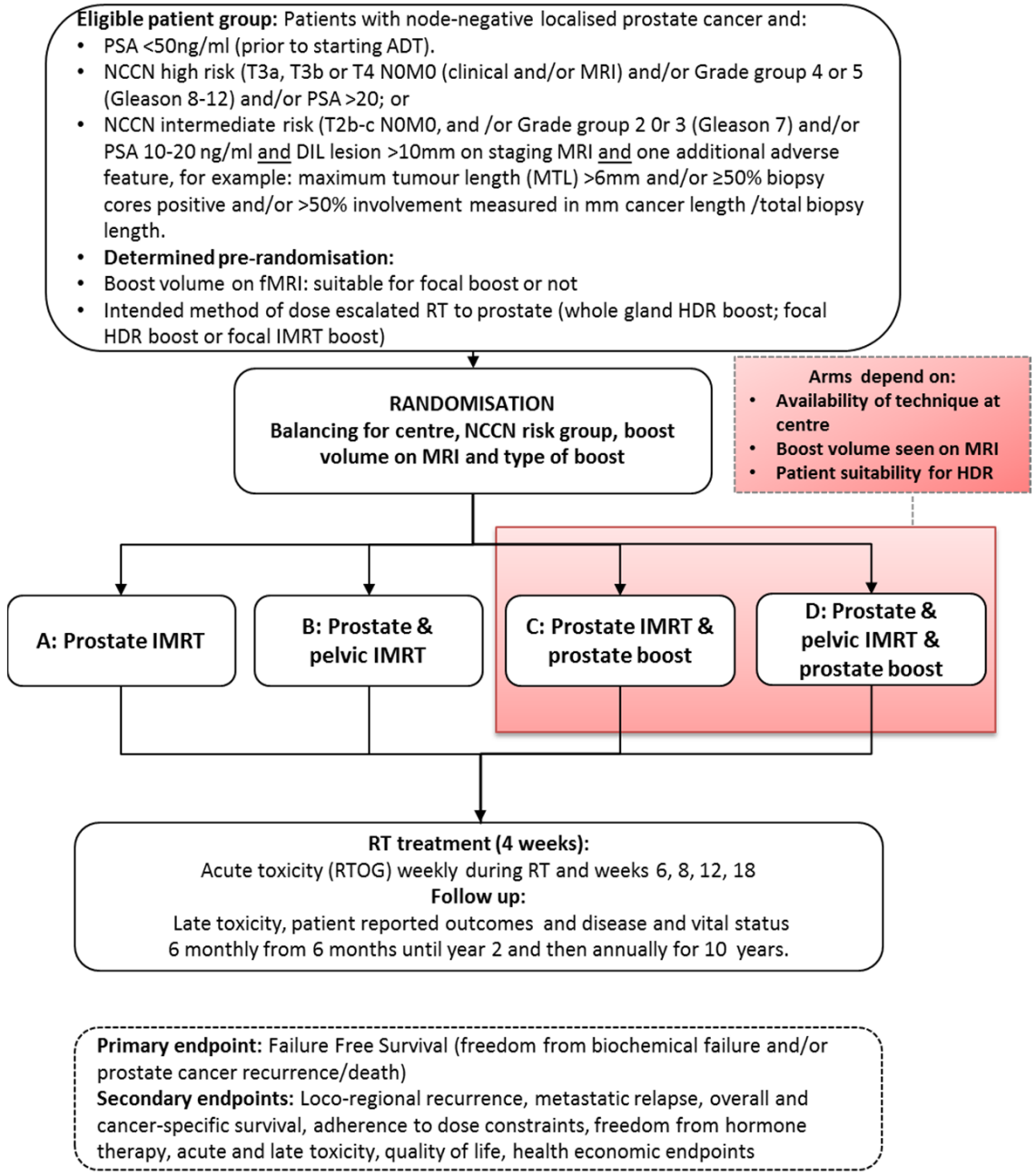




18 months of AS together with EBRT plus HDR boost should be considered an effective option for men with locally advanced, high-risk PC

Int J Rad Oncol Biol Physic 2020; 106(4): 693-702

PIVOTALboost: A phase III randomised controlled trial of prostate and pelvis versus prostate alone radiotherapy with or without prostate boost (CRUK/16/018)



Syndikus I et al Clin Transl Radiat Oncol 2020; 25: 22-28

Guidelines

GEC-ESTRO ACROP prostate brachytherapy guidelines

Ann Henry [a], Bradley R. Pieters [b], Frank André Siebert [c], Peter Hoskin [d,e,*],
on behalf of the UROGEC group of GEC ESTRO with endorsement by the European Association of Urology [1]

[a] *St James University Hospital, Leeds, UK;* [b] *Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands;* [c] *University of Kiel/University Hospital Schleswig-Holstein Campus Kiel, Germany;* [d] *Mount Vernon Cancer Centre, Northwood; and* [e] *University of Manchester, Manchester, UK*

Prostate brachytherapy is a highly effective treatment for localised prostate cancer in patients who have no evidence of metastases. It is indicated in two settings:

Alone as sole modality for low and selected intermediate risk prostate cancer.

Combined to dose escalate with external beam radiotherapy for intermediate and high-risk prostate cancer

Brachytherapy boosts may be delivered before or after EBRT

ADT should be used in addition to brachytherapy in line with that used when delivering EBRT alone for unfavourable intermediate risk and high-risk patients

Focal, focal boost and salvage brachytherapy are only recommended within the context of a clinical trial.

Radiotherapy and Oncology 2022; 167: 244-51

Summary of the role of Brachytherapy in the management of Localised disease