Supplementary Online Content

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eTable 11. Unadjusted general health related quality of life outcomes of unfavorable-risk patients by treatment and time point; Adjusted differences between treatment groups in general health related quality of life domain scores by treatment and time point

eFigure 2. Adjusted general health related quality of life outcomes of favorable-risk patients by treatment and time point

eFigure 3. Adjusted general health related quality of life outcomes of unfavorable-risk patients by treatment and time point

eTables 12-15 and eFigures 4-6. Exploratory Analyses of Effect Modification of Covariates

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplemental Material

eMethods

Handling of Missing Data and Imputation

From the CEASAR analysis cohort, among those with the relevant treatments for this analysis, patients with no post-baseline outcome measures (EPIC domains scores) were excluded. The resulting data set is referred to as the analytic cohort (n=2,005).

According to the EPIC scoring algorithm, patients who answered at least 80% of questions within a particular domain received a score for that domain (computed as an average of the scores on questions that were answered, scaled from 0 to 100). Those who answered less than 80% of questions on a particular domain were considered to have missing data for that domain.[1]

Multiple Imputation

Missing values of regression model covariates, including the values of the baseline EPIC domain score or individual EPIC item, were imputed using the MICE (Multiple imputation using chained equations) multiple imputation procedure.[2,3] No outcome variables were imputed. In this procedure, missing values of covariates are imputed by modeling each covariate as an outcome in a regression model, using all other model covariates as predictors. In this case, only baseline data (excluding treatment) were used. This is described by Harrell and implemented using the rms package in R.[4,5,6]

Multiple imputation was used to avoid case-wise deletion of all observations with at least one missing value of the independent variables. The imputation and regression model fitting with imputed data involve the following three steps: imputing the data using the imputation models, estimating coefficient parameters and their standard errors in the *analysis* regression models, and adjusting the standard error estimates to account for the variability associated with the imputation procedure.

To impute missing data on a covariate (X), we first imputed the missing data using a random sample of non-missing X. Then a flexible additive model was fit on a bootstrap resampled dataset using X as the outcome. Using this model, we obtained fitted values for the variable. To impute a missing value, we found non-missing X whose fitted value was closest to the fitted value of the missing observation, and imputed the missing value with the matching non-missing X. This approach is referred to as predictive mean matching.[4]

This resample-model-impute step was repeated 15 times after a burn-in period of 10 iterations with the missing values updated with the imputed values after each step. Then the final model was fit using the complete data set using the values imputed at the last iteration, and the standard error estimates were adjusted to account for additional uncertainty associated with the imputation as described in Harrell.[4]

References:

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4. Harrell FE, Jr. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. New York (NY): Springer-Verlag; 2001.
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eTable 1. Number of Non-missing Expanded Prostate Index Composite Questionnaires By Time Point and Treatment Group

Time Point	EPIC Domain	Favorable-risk disease cohort					Unfavorable-risk disease cohort		
		All (N=1,386)	Nerve-Sparing Radical Prostatectomy (N=675)	External Beam Radiation Therapy (N=261)	LDR Brachy-therapy (N=87)	Active Surveillance (N=363)	All (N=619)	External Beam Radiation Therapy with Androgen Deprivation Therapy (N=217)	Radical Prostatectomy (N=402)
Baseline		1386 (100%)	675 (100%)	261 (100%)	87 (100%)	363 (100%)	619 (100%)	217 (100%)	402 (100%)
	Sexual	1322 (95%)	648 (96%)	248 (95%)	85 (98%)	341 (94%)	580 (94%)	199 (92%)	381 (95%)
	Urinary Incontinence	1339 (97%)	658 (97%)	251 (96%)	84 (97%)	346 (95%)	597 (96%)	211 (97%)	386 (96%)
	Urinary Irritative	1331 (96%)	649 (96%)	250 (96%)	84 (97%)	348 (96%)	595 (96%)	210 (97%)	385 (96%)
	Bowel	1355 (98%)	662 (98%)	256 (98%)	86 (99%)	351 (97%)	606 (98%)	212 (98%)	394 (98%)
	Hormone	1331 (96%)	651 (96%)	246 (94%)	84 (97%)	350 (96%)	592 (96%)	203 (94%)	389 (97%)
6 month		1356 (98%)	665 (99%)	252 (97%)	85 (98%)	354 (98%)	589 (95%)	208 (96%)	381 (95%)
	Sexual	1310 (95%)	655 (97%)	237 (91%)	83 (95%)	335 (92%)	562 (91%)	191 (88%)	371 (92%)
	Urinary Incontinence	1344 (97%)	659 (98%)	252 (97%)	82 (94%)	351 (97%)	583 (94%)	205 (94%)	378 (94%)
	Urinary Irritative	1329 (96%)	651 (96%)	249 (95%)	82 (94%)	347 (96%)	577 (93%)	203 (94%)	374 (93%)
	Bowel	1348 (97%)	662 (98%)	250 (96%)	82 (94%)	354 (98%)	585 (95%)	206 (95%)	379 (94%)
	Hormone	1329 (96%)	654 (97%)	240 (92%)	85 (98%)	350 (96%)	573 (93%)	202 (93%)	371 (92%)
12 month		1318 (95%)	651 (96%)	248 (95%)	84 (97%)	335 (92%)	570 (92%)	198 (91%)	372 (93%)
	Sexual	1274 (92%)	643 (95%)	238 (91%)	82 (94%)	311 (86%)	556 (90%)	190 (88%)	366 (91%)
	Urinary Incontinence	1266 (91%)	621 (92%)	238 (91%)	80 (92%)	327 (90%)	545 (88%)	184 (85%)	361 (90%)
	Urinary Irritative	1297 (94%)	641 (95%)	245 (94%)	81 (93%)	330 (91%)	556 (90%)	191 (88%)	365 (91%)
	Bowel	1309 (94%)	645 (96%)	247 (95%)	83 (95%)	334 (92%)	567 (92%)	197 (91%)	370 (92%)
	Hormone	1293 (93%)	643 (95%)	236 (90%)	82 (94%)	332 (91%)	558 (90%)	194 (89%)	364 (91%)

Time Point / EPIC Domain	Favorable-risk disease cohort					Unfavorable-risk disease cohort		
	All (N=1,386)	Nerve-Sparing Radical Prostatectomy (N=675)	External Beam Radiation Therapy (N=261)	LDR Brachy-therapy (N=87)	Active Surveillance (N=363)	All (N=619)	External Beam Radiation Therapy with Androgen Deprivation Therapy (N=217)	Radical Prostatectomy (N=402)
36 month	1195 (86%)	602 (89%)	222 (85%)	72 (83%)	299 (82%)	511 (83%)	170 (78%)	341 (85%)
Sexual	1158 (84%)	592 (88%)	214 (82%)	70 (80%)	282 (78%)	487 (79%)	160 (74%)	327 (81%)
Urinary Incontinence	1172 (85%)	592 (88%)	218 (84%)	71 (82%)	291 (80%)	494 (80%)	162 (75%)	332 (83%)
Urinary Irritative	1163 (84%)	590 (87%)	214 (82%)	69 (79%)	290 (80%)	500 (81%)	164 (76%)	336 (84%)
Bowel	1190 (86%)	600 (89%)	219 (84%)	72 (83%)	299 (82%)	505 (82%)	167 (77%)	338 (84%)
Hormone	1174 (85%)	592 (88%)	216 (83%)	71 (82%)	295 (81%)	495 (80%)	163 (75%)	332 (83%)
60 month	1092 (79%)	556 (82%)	203 (78%)	64 (74%)	269 (74%)	450 (73%)	144 (66%)	306 (76%)
Sexual	1046 (75%)	543 (80%)	192 (74%)	62 (71%)	249 (69%)	429 (69%)	130 (60%)	299 (74%)
Urinary Incontinence	1072 (77%)	544 (81%)	199 (76%)	64 (74%)	265 (73%)	437 (71%)	138 (64%)	299 (74%)
Urinary Irritative	1062 (77%)	540 (80%)	198 (76%)	63 (72%)	261 (72%)	442 (71%)	139 (64%)	303 (75%)
Bowel	1078 (78%)	550 (81%)	200 (77%)	64 (74%)	264 (73%)	445 (72%)	141 (65%)	304 (76%)
Hormone	1063 (77%)	545 (81%)	193 (74%)	63 (72%)	262 (72%)	438 (71%)	139 (64%)	299 (74%)

eTable 2. Number Missing Covariates for Multivariable Models

	Favorable-risk disease cohort N=1,386	Unfavorable-risk disease cohort N=619
Age at diagnosis	0 (0%)	0 (0%)
Race/ethnicity	5 (0%)	7 (1%)
Education	33 (2%)	33 (5%)
Marital status	36 (3%)	35 (6%)
Comorbidity score	30 (2%)	30 (5%)
Prostate cancer risk category	0 (0%)	0 (0%)
PSA at diagnosis	0 (0%)	0 (0%)
Clinical tumor stage	6 (0%)	2 (0%)
Biopsy Gleason Group	0 (0%)	1 (0%)
Accrual Site	0 (0%)	0 (0%)
Baseline Survey Scores		
Sexual function	64 (5%)	39 (6%)
Urinary incontinence function	47 (3%)	22 (4%)
Urinary irritative function	55 (4%)	24 (4%)
Bowel function	31 (2%)	13 (2%)
Hormonal function	55 (4%)	27 (4%)
Short-form 36		
Physical function scale	48 (3%)	18 (3%)
General health scale	5 (0%)	1 (0%)
Emotional well-being	33 (2%)	9 (1%)
Energy/fatigue	5 (0%)	1 (0%)
Social support scale	6 (0%)	8 (1%)
Depression scale	35 (3%)	10 (2%)
Participatory decision-making	20 (1%)	16 (3%)

eTable 3. Probability of overall survival and disease-specific survival by treatment[a]

	Favorable risk disease					Unfavorable risk disease		
	Nerve-sparing radical prostatectomy (N=671)	**External beam radiation therapy** (N=258)	**Low-dose-rate brachytherapy** (N=85)	**Active Surveillance** (N=359)	**P[c]**	**Radical prostatectomy** (N=399)	**External beam radiation therapy with androgen deprivation therapy** (N=214)	**P[c]**
Median follow-up time in months (25th, 75th percentile)[b]	72 (63,79)	71 (63,78)	74 (64,78)	73 (62,78)		73 (63,79)	73 (63,78)	
All-cause deaths (n)	8	21	10	23	<0.001	12	31	<0.001
Estimated 5-year overall survival[c]	99.2% (98.6, 99.9)	94.0% (91.1, 97.0)	92.6% (87.0, 98.5)	94.7% (92.3, 97.1)		97.7% (96.2, 99.2)	91.8% (88.2, 95.6)	
Prostate cancer deaths (n)	0	0	0	1	0.40	3	5	0.10
Estimated 5-year disease specific survival [d]	100% (100, 100)	100% (100, 100)	100% (100, 100)	100% (100, 100)		99.5% (98.8, 100)	99.0% (97.7, 100)	

a. Vital status, cause of death and follow-up time were determined by each registry through their internal processes. The most recent registry linkage dates for each site are: Atlanta, August 2018; CaPSURE, December 2017; Los Angeles September 2018; Louisiana, August 2018; New Jersey, July 2018; Utah, August 2018
b. Median (25th, 75th percentile) follow-up time since diagnosis in months
c. P value of the log-rank test
d. The estimated survival probability was calculated using the Kaplan-Meier method

eTable 4. Selected Clinical Treatment Details

	Favorable-risk	Unfavorable-Risk
Prostatectomy Cohort	n=675	n=402
Surgical volume		
Median (lower quartile, upper quartile)	10 (3, 16)	7 (3, 15)
Robotic approach		
Yes	542 (81%)	257 (66%)
No	130 (19%)	132 (34%)
Prostate gland volume		
Median (lower quartile, upper quartile)	36 (27, 46)	32 (26, 44)
External Beam Radiation Therapy Cohort	n=261	n=217
Intensity-modulated radiation therapy		
Yes	198 (76%)	188 (87%)
No	63 (24%)	29 (13%)
Proton beam radiation therapy		
Yes	16 (7%)	3 (1%)
No	222 (93%)	198 (99%)
Image-guided radiation therapy		
Yes	200 (85%)	181 (89%)
No	35 (15%)	22 (11%)
Radiation dose		
Median (lower quartile, upper quartile)	7800 (7560, 7920)	7800 (7600, 7920)
Radiation dose >= 7500		
Yes	204 (81%)	196 (94%)
No	47 (19%)	13 (6%)
Radiation dose per fraction		
Median (lower quartile, upper quartile)	180 (180, 192)	180 (180, 200)
Radiation dose per fraction greater than 200?		
Yes	22 (9%)	4 (2%)
No	225 (91%)	199 (98%)
Treatment of pelvic lymph nodes?		
Yes	14 (6%)	74 (35%)
No	239 (94%)	137 (65%)
Prostate gland volume		
Median (lower quartile, upper quartile)	38 (27, 51)	36 (26, 51)
Low-dose-rate Brachytherapy Cohort	n=87	
Radioisotope		
I125	69 (80%)	n/a
Pd103	15 (17%)	n/a
Cs131	2 (2%)	n/a
Radiation dose		
Median (lower quartile, upper quartile)	145 (125, 145)	n/a
Prostate gland volume		
Median (lower quartile, upper quartile)	32 (26, 40)	n/a
Active surveillance cohort	n=363	
Prostate gland volume		
Median (lower quartile, upper quartile)	40 (30, 58)	n/a

eTable 5. Unadjusted functional outcomes of favorable risk patients on the Expanded Prostate Cancer Index Composite (EPIC) domain scores and selected individual item responses by treatment and time point; Adjusted differences between treatment groups and active surveillance patients in Expanded Prostate Cancer Index Composite domain scores and selected individual item responses by treatment and time point

Time	N	Nerve-sparing radical prostatectomy (N=675)	External beam radiation therapy (N=261)	Low-dose-rate brachytherapy (N=87)	Active surveillance (N=363)	Nerve-sparing radical prostatectomy vs. Active surveillance			External beam radiation therapy vs. Active surveillance			Low-dose-rate brachytherapy vs. Active surveillance		
						Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value
Sexual Function Domain[a]														
Sexual function score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups[d]								
Baseline	1322	80 (53, 100)	60 (28, 85)	75 (38, 85)	75 (42, 88)									
6 month	1310	28 (10, 60)	53 (22, 78)	60 (22, 80)	70 (38, 85)	-36.7[b]	[-40.1, -33.4]	<0.001	-7.8	[-11.6, -4.0]	<0.001	-11.0[b]	[-15.9, -6.0]	<0.001
1 year	1274	38 (12, 70)	47 (21, 75)	60 (19, 80)	75 (41, 86)	-30.7[b]	[-33.6, -27.8]	<0.001	-6.8	[-10.1, -3.5]	<0.001	-10.1[b]	[-14.6, -5.7]	<0.001
3 year	1158	48 (14, 79)	43 (12, 75)	59 (17, 80)	63 (20, 85)	-15.2[b]	[-18.8, -11.5]	<0.001	-4.8	[-9.0, -0.6]	0.03	-6.1	[-12.1, -0.2]	0.04
5 year	1046	48 (15, 80)	28 (9, 69)	53 (24, 78)	55 (22, 85)	-9.8	[-13.8, -5.8]	<0.001	-5.1	[-10.0, -0.2]	0.04	-1.4	[-8.3, 5.4]	0.69
Sexual Function Individual Items[c]														
Sexual function bother		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1321	144 (22%)	71 (29%)	16 (19%)	80 (23%)									
6 month	1327	366 (56%)	75 (31%)	20 (24%)	66 (19%)	8.4	[5.7, 12.5]	<0.001	1.7	[1.1, 2.7]	0.02	1.4	[0.7, 2.6]	0.29
1 year	1282	317 (49%)	76 (32%)	18 (22%)	63 (20%)	6.0	[4.4, 8.1]	<0.001	1.5	[1.1, 2.1]	0.02	1.5	[0.9, 2.5]	0.12
3 year	1164	240 (40%)	69 (32%)	20 (29%)	74 (26%)	2.5	[1.7, 3.6]	<0.001	1.2	[0.8, 1.9]	0.33	1.5	[0.8, 2.7]	0.18
5 year	1058	193 (35%)	69 (35%)	16 (25%)	60 (24%)	1.9	[1.3, 2.8]	<0.001	1.4	[0.9, 2.2]	0.15	1.1	[0.6, 2.3]	0.73
Erection insufficient for penetration		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of insufficient erection								
Baseline	1331	216 (33%)	140 (56%)	38 (45%)	135 (39%)									
6 month	1320	498 (76%)	152 (63%)	45 (54%)	141 (42%)	14.0	[9.4, 20.8]	<0.001	2.0	[1.3, 3.0]	0.001	1.9	[1.1, 3.3]	0.03
1 year	1280	442 (69%)	157 (65%)	42 (52%)	126 (39%)	9.9	[7.1, 13.9]	<0.001	1.9	[1.4, 2.7]	<0.001	1.9	[1.2, 3.1]	0.01
3 year	1164	376 (63%)	146 (68%)	38 (54%)	140 (49%)	3.6	[2.5, 5.2]	<0.001	1.7	[1.1, 2.6]	0.02	1.7	[0.9, 3.0]	0.10
5 year	1056	332 (61%)	145 (74%)	39 (61%)	143 (57%)	1.9	[1.3, 2.9]	<0.001	1.5	[0.9, 2.4]	0.11	1.3	[0.6, 2.6]	0.48
Urinary Function Domains														
Urinary Incontinence score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups								
Baseline	1339	100 (81, 100)	100 (79, 100)	100 (92, 100)	100 (85, 100)									
6 month	1344	73 (49, 100)	100 (79, 100)	94 (73, 100)	100 (84, 100)	-23.9 [b]	[-27.0, -20.9]	<0.001	-0.1	[-2.8, 2.6]	0.96	-7.0[b]	[-11.2, -2.8]	<0.001
1 year	1266	79 (54, 100)	100 (79, 100)	97 (79, 100)	100 (84, 100)	-19.8 [b]	[-22.3, -17.3]	<0.001	0.7	[-1.6, 3.0]	0.54	-5.2	[-8.7, -1.6]	0.004
3 year	1172	79 (58, 100)	100 (77, 100)	100 (79, 100)	94 (77, 100)	-10.9 [b]	[-13.8, -8.0]	<0.001	3.2	[0.3, 6.1]	0.03	-0.6	[-5.1, 3.8]	0.78
5 year	1072	79 (58, 100)	100 (79, 100)	100 (81, 100)	92 (73, 100)	-10.9 [b]	[-14.2, -7.6]	<0.001	4.9	[1.3, 8.5]	0.007	0.7	[-5.2, 6.6]	0.82

Time	N	Nerve-sparing radical prostatectomy (N=675)	External beam radiation therapy (N=261)	Low-dose-rate brachytherapy (N=87)	Active surveillance (N=363)	Nerve-sparing radical prostatectomy vs. Active surveillance Effect	95% Confidence Interval	p-value	External beam radiation therapy vs. Active surveillance Effect	95% Confidence Interval	p-value	Low-dose-rate brachytherapy vs. Active surveillance Effect	95% Confidence Interval	p-value
Urinary Irritative score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups								
Baseline	1331	88 (75, 100)	88 (75, 94)	94 (80, 100)	88 (75, 100)									
6 month	1329	94 (88, 100)	94 (81, 100)	81 (62, 88)	94 (81, 100)	3.3	[1.6, 5.1]	<0.001	0.5	[-1.7, 2.7]	0.66	-11.8 [b]	[-16.1, -7.6]	<0.001
1 year	1297	94 (88, 100)	88 (81, 94)	88 (69, 94)	88 (81, 100)	4.2	[2.7, 5.6]	<0.001	1.0	[-0.8, 2.7]	0.28	-7.0 [b]	[-10.1, -3.9]	<0.001
3 year	1163	94 (88, 100)	88 (77, 100)	94 (88, 94)	88 (81, 100)	5.8 [b]	[4.1, 7.6]	<0.001	2.0	[-0.1, 4.0]	0.06	2.3	[-0.8, 5.5]	0.15
5 year	1062	94 (88, 100)	94 (81, 100)	94 (84, 100)	88 (81, 100)	5.7 [b]	[3.9, 7.4]	<0.001	1.9	[-0.4, 4.1]	0.11	0.2	[-3.6, 4.0]	0.91
Urinary Function Individual Items														
Urinary function bother		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1332	82 (13%)	31 (12%)	9 (11%)	44 (13%)									
6 month	1345	94 (14%)	25 (10%)	17 (20%)	33 (9%)	2.1	[1.3, 3.4]	0.004	0.9	[0.5, 1.7]	0.81	2.3	[1.2, 4.4]	0.02
1 year	1284	65 (10%)	16 (7%)	8 (10%)	28 (9%)	1.5	[1.0, 2.2]	0.05	0.8	[0.5, 1.4]	0.47	1.5	[0.8, 2.8]	0.19
3 year	1190	56 (9%)	21 (10%)	6 (8%)	26 (9%)	0.9	[0.5, 1.5]	0.69	0.7	[0.4, 1.3]	0.28	0.7	[0.3, 1.8]	0.47
5 year	1084	55 (10%)	17 (8%)	6 (9%)	24 (9%)	1.3	[0.8, 2.2]	0.31	0.8	[0.4, 1.5]	0.42	0.9	[0.4, 2.4]	0.91
Urinary leakage		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1353	41 (6%)	11 (4%)	3 (4%)	16 (5%)									
6 month	1351	120 (18%)	11 (4%)	9 (11%)	12 (3%)	11.7	[5.5, 24.9]	<0.001	1.3	[0.5, 3.2]	0.62	3.6	[1.4, 9.4]	0.01
1 year	1307	86 (13%)	9 (4%)	2 (2%)	12 (4%)	7.5	[4.1, 13.8]	<0.001	1.1	[0.5, 2.3]	0.87	1.6	[0.6, 4.2]	0.33
3 year	1187	72 (12%)	9 (4%)	2 (3%)	16 (5%)	2.5	[1.4, 4.8]	0.003	0.7	[0.3, 1.6]	0.43	0.4	[0.1, 1.8]	0.23
5 year	1083	56 (10%)	12 (6%)	3 (5%)	19 (7%)	1.9	[1.0, 3.4]	0.04	0.7	[0.3, 1.4]	0.29	0.8	[0.2, 3.0]	0.77
Burning on urination		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1351	21 (3%)	14 (5%)	3 (4%)	12 (3%)									
6 month	1348	7 (1%)	8 (3%)	7 (8%)	5 (1%)	1.0	[0.3, 3.6]	0.97	3.1	[0.8, 12.0]	0.10	15.8	[4.5, 55.8]	<0.001
1 year	1308	7 (1%)	7 (3%)	11 (13%)	4 (1%)	1.1	[0.4, 2.8]	0.87	2.0	[0.7, 5.3]	0.17	8.2	[2.8, 23.8]	<0.001
3 year	1189	6 (1%)	4 (2%)	1 (1%)	5 (2%)	0.8	[0.2, 3.4]	0.79	0.9	[0.2, 5.1]	0.89	2.9	[0.7, 12.7]	0.16
5 year	1081	1 (0%)	1 (0%)	2 (3%)	2 (1%)	0.3	[0.0, 3.5]	0.33	1.2	[0.2, 9.3]	0.87	6.7	[0.9, 53.5]	0.07
Frequent urination		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1353	117 (18%)	52 (20%)	12 (14%)	72 (20%)									
6 month	1353	97 (15%)	35 (14%)	26 (31%)	59 (17%)	1.2	[0.8, 1.9]	0.36	0.8	[0.4, 1.3]	0.31	3.5	[1.8, 6.7]	<0.001
1 year	1308	85 (13%)	24 (10%)	15 (18%)	51 (15%)	0.9	[0.6, 1.2]	0.41	0.6	[0.4, 0.9]	0.01	1.8	[1.1, 3.2]	0.03
3 year	1186	64 (11%)	32 (15%)	8 (11%)	53 (18%)	0.5	[0.3, 0.8]	0.002	0.4	[0.3, 0.7]	0.002	0.6	[0.3, 1.5]	0.32
5 year	1085	68 (12%)	27 (13%)	9 (14%)	40 (15%)	0.8	[0.5, 1.2]	0.25	0.7	[0.4, 1.3]	0.32	1.3	[0.5, 3.2]	0.54

Time	N	Nerve-sparing radical prostatectomy (N=675)	External beam radiation therapy (N=261)	Low-dose-rate brachytherapy (N=87)	Active surveillance (N=363)	Nerve-sparing radical prostatectomy vs. Active surveillance Effect	95% Confidence Interval	p-value	External beam radiation therapy vs. Active surveillance Effect	95% Confidence Interval	p-value	Low-dose-rate brachytherapy vs. Active surveillance Effect	95% Confidence Interval	p-value
Bowel Function Domain														
Bowel function score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups								
Baseline	1355	100 (96, 100)	100 (96, 100)	100 (96, 100)	100 (96, 100)									
6 month	1348	100 (96, 100)	96 (88, 100)	96 (83, 100)	100 (92, 100)	-0.4	[-1.7, 0.9]	0.52	-3.7	[-5.8, -1.7]	<0.001	-5.9 [b]	[-9.0, -2.9]	<0.001
1 year	1309	100 (96, 100)	96 (88, 100)	96 (83, 100)	100 (92, 100)	0.0	[-1.0, 1.0]	0.95	-3.5	[-5.1, -1.8]	<0.001	-5.0 [b]	[-7.6, -2.4]	<0.001
3 year	1190	100 (96, 100)	96 (88, 100)	100 (88, 100)	100 (92, 100)	0.7	[-0.7, 2.1]	0.32	-2.9	[-4.9, -0.9]	0.005	-2.7	[-5.5, 0.1]	0.06
5 year	1078	100 (96, 100)	96 (88, 100)	100 (88, 100)	100 (92, 100)	0.4	[-1.0, 1.9]	0.55	-2.7	[-5.0, -0.5]	0.02	-2.3	[-5.1, 0.6]	0.13
Bowel Function Individual Items														
Bowel function bother		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1346	12 (2%)	6 (2%)	3 (3%)	16 (5%)									
6 month	1347	20 (3%)	11 (4%)	7 (8%)	12 (3%)	1.7	[0.7, 4.2]	0.22	2.4	[1, 5.8]	0.05	3.6	[1.3, 10.4]	0.02
1 year	1294	11 (2%)	17 (7%)	4 (5%)	10 (3%)	1.1	[0.6, 2.2]	0.77	1.8	[0.9, 3.4]	0.08	2	[0.9, 4.8]	0.11
3 year	1191	10 (2%)	9 (4%)	2 (3%)	13 (4%)	0.6	[0.2, 1.6]	0.27	1.0	[0.4, 2.8]	0.98	0.7	[0.1, 3.4]	0.67
5 year	1081	13 (2%)	9 (4%)	3 (5%)	11 (4%)	1.1	[0.4, 2.5]	0.90	1.2	[0.5, 3.2]	0.68	1.1	[0.2, 5]	0.89
Bloody stools		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1353	2 (0%)	2 (1%)	0 (0%)	4 (1%)									
6 month	1348	2 (0%)	2 (1%)	0 (0%)	3 (1%)	0.9	[0.1, 7.6]	0.96	0.8	[0.1, 8.4]	0.88	0.1	[0, 8.2]	0.28
1 year	1307	3 (0%)	2 (1%)	1 (1%)	3 (1%)	0.4	[0.1, 1.9]	0.25	0.9	[0.2, 3.5]	0.90	1.3	[0.1, 12.3]	0.84
3 year	1190	1 (0%)	5 (2%)	1 (1%)	2 (1%)	0.1	[0.0, 4.7]	0.28	2.6	[0.3, 21.9]	0.39	0.7	[0, 13.6]	0.83
5 year	1079	0 (0%)	1 (0%)	0 (0%)	0 (0%)	[e]			[e]			[e]		
Bowel urgency		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1356	16 (2%)	5 (2%)	5 (6%)	12 (3%)									
6 month	1350	14 (2%)	10 (4%)	9 (11%)	14 (4%)	1.0	[0.5, 2.2]	0.98	1.7	[0.7, 3.9]	0.23	4	[1.5, 10.4]	0.005
1 year	1309	13 (2%)	18 (7%)	8 (10%)	10 (3%)	0.7	[0.4, 1.4]	0.36	1.8	[0.9, 3.5]	0.09	2.4	[1.0, 5.7]	0.05
3 year	1191	8 (1%)	16 (7%)	3 (4%)	14 (5%)	0.4	[0.2, 1.0]	0.06	1.8	[0.8, 4.3]	0.18	1.1	[0.4, 3.3]	0.86
5 year	1079	10 (2%)	15 (8%)	6 (9%)	13 (5%)	0.5	[0.2, 1.1]	0.08	1.4	[0.6, 3.2]	0.42	2.0	[0.7, 6.0]	0.20
Hormone Function Domain														
Hormone function score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups								
Baseline	1331	95 (90, 100)	95 (85, 100)	100 (81, 100)	95 (85, 100)									
6 month	1329	95 (85, 100)	95 (85, 100)	95 (85, 100)	95 (85, 100)	-1.2	[-2.7, 0.4]	0.14	-1.7	[-3.6, 0.1]	0.07	-0.9	[-3.4, 1.6]	0.48
1 year	1293	95 (85, 100)	95 (84, 100)	95 (81, 100)	95 (85, 100)	-0.8	[-2.1, 0.4]	0.19	-1.2	[-2.7, 0.4]	0.14	0.0	[-1.8, 1.8]	0.99

Time	N	Nerve-sparing radical prostatectomy (N=675)	External beam radiation therapy (N=261)	Low-dose-rate brachytherapy (N=87)	Active surveillance (N=363)	Nerve-sparing radical prostatectomy vs. Active surveillance Effect	95% Confidence Interval	p-value	External beam radiation therapy vs. Active surveillance Effect	95% Confidence Interval	p-value	Low-dose-rate brachytherapy vs. Active surveillance Effect	95% Confidence Interval	p-value
3 year	1174	95 (85, 100)	95 (85, 100)	100 (90, 100)	95 (86, 100)	0.4	[0.2, 1.0]	0.06	1.8	[0.8, 4.3]	0.18	1.1	[0.4, 3.3]	0.86
5 year	1063	95 (85, 100)	95 (80, 100)	95 (85, 100)	95 (85, 100)	0.4	[-1.3, 2]	0.65	-1.1	[-3.2, 0.9]	0.28	-0.5	[-3.4, 2.5]	0.76

a. Domain scores are from the Expanded Prostate Cancer Index Composite (EPIC-26). Domain scores are scaled from 0 to 100, with higher score indicating better function. The left side of the table shows unadjusted median domain score and interquartile range (25th percentile, 75th percentile). The right side shows multivariable model results. The effect size in the multivariable model for domain score indicates the adjusted mean point difference between groups at each time point. A minimally important difference in score is 10-12 points on the sexual function domain; 6-9 points on the urinary incontinence domain; 5-7 points on the urinary irritative domain; 4-6 points on the bowel domain; and 4-6 points on the hormonal domain 4-6. The primary outcome was the difference in domain score at 5 years.

b. Signifies that the difference between groups exceeds the minimally important difference for clinical significance.

c. Individual items are clinically important components of the domain, scored on a Likert scale and then dichotomized for group comparisons. The left side of the table shows the unadjusted number (%) of patients reporting a moderate or big problem. The right side shows the adjusted odds ratio of reporting a moderate or big problem comparing treatment groups.

d. All regression models are adjusted for baseline domain score, age, race, comorbidity, disease risk group, physical function, social support, depression, medical decision-making style and accrual site.

e. Analysis not performed because the limited number of events did not permit computation of reliable estimates

eTable 6. Adjusted pairwise differences between treatment groups among favorable risk patients in Expanded Prostate Cancer Index Composite domain scores and selected individual item responses by treatment and time point

Time	Nerve-sparing radical prostatectomy vs. External beam radiation therapy			Nerve-sparing radical prostatectomy vs. Low-dose-rate brachytherapy			External beam radiation therapy vs. Low-dose-rate brachytherapy		
	Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value
Domain [a]									
Sexual function score	Adjusted linear model; effect size = point difference between groups[d]								
6 month	-29.0 [b]	[-32.6, -25.3]	<0.001	-25.8 [b]	[-30.9, -20.7]	<0.001	3.2	[-2.2, 8.5]	0.25
1 year	-23.9 [b]	[-27.2, -20.6]	<0.001	-20.6 [b]	[-25.2, -15.9]	<0.001	3.3	[-1.6, 8.2]	0.19
3 year	-10.4 [b]	[-14.4, -6.4]	<0.001	-9.0	[-14.9, -3.2]	0.002	1.3	[-4.9, 7.6]	0.68
5 year	-4.8	[-9.3, -0.2]	0.04	-8.4	[-15.1, -1.8]	0.01	-3.7	[-10.8, 3.5]	0.32
Individual Items [c]									
Sexual function bother	Adjusted logistic model; effect size = odds ratio of moderate or big problem								
6 month	4.9	[3.5, 7.1]	<0.001	6.0	[3.4, 10.8]	<0.001	1.2	[0.7, 2.3]	0.53
1 year	3.9	[2.9, 5.4]	<0.001	4.0	[2.5, 6.6]	<0.001	1.0	[0.6, 1.7]	0.94
3 year	2.0	[1.4, 2.9]	<0.001	1.7	[1.0, 2.9]	0.06	0.8	[0.5, 1.5]	0.54
5 year	1.4	[0.9, 2.1]	0.14	1.7	[0.8, 3.4]	0.14	1.2	[0.6, 2.6]	0.58
Erection insufficient for penetration	Adjusted logistic model; effect size = odds ratio of insufficient erection								
6 month	7.1	[4.7, 10.7]	<0.001	7.4	[4.3, 12.9]	<0.001	1.0	[0.6, 1.9]	0.88
1 year	5.2	[3.6, 7.5]	<0.001	5.3	[3.2, 8.7]	<0.001	1.0	[0.6, 1.7]	0.96
3 year	2.1	[1.4, 3.3]	<0.001	2.2	[1.2, 3.9]	0.01	1.0	[0.5, 1.9]	0.98
5 year	1.3	[0.8, 2.1]	0.24	1.5	[0.8, 3.0]	0.24	1.1	[0.5, 2.4]	0.72
Domains									
Incontinence score	Adjusted linear model; effect size = point difference between groups								
6 month	-23.9 [b]	[-27.0, -20.8]	<0.001	-16.9 [b]	[-21.4, -12.5]	<0.001	6.9 [b]	[2.7, 11.2]	0.001
1 year	-20.5 [b]	[-23.3, -17.7]	<0.001	-14.6 [b]	[-18.6, -10.7]	<0.001	5.9	[2.1, 9.6]	0.002
3 year	-14.1 [b]	[-17.1, -11.1]	<0.001	-10.3 [b]	[-14.8, -5.7]	<0.001	3.8	[-0.7, 8.3]	0.10
5 year	-15.9 [b]	[-19.5, -12.3]	<0.001	-11.6 [b]	[-17.5, -5.7]	<0.001	4.3	[-1.8, 10.3]	0.17
Urinary Irritative score	Adjusted linear model; effect size = point difference between groups								
6 month	2.8	[0.9, 4.8]	0.005	15.2 [b]	[11, 19.3]	<0.001	12.3 [b]	[7.9, 16.7]	<0.001
1 year	3.2	[1.6, 4.8]	<0.001	11.2 [b]	[8.1, 14.2]	<0.001	8	[4.7, 11.3]	<0.001
3 year	3.9	[2.1, 5.7]	<0.001	3.5	[0.5, 6.5]	0.02	-0.4	[-3.6, 2.9]	0.82
5 year	3.8	[1.8, 5.8]	<0.001	5.4 [b]	[1.7, 9.1]	0.004	1.6	[-2.4, 5.7]	0.42

Time	Nerve-sparing radical prostatectomy vs. External beam radiation therapy			Nerve-sparing radical prostatectomy vs. Low-dose-rate brachytherapy			External beam radiation therapy vs. Low-dose-rate brachytherapy		
	Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value
Individual Items									
Urinary function bother	Adjusted logistic model; effect size = odds ratio of moderate or big problem								
6 month	2.2	[1.3, 3.7]	0.003	0.9	[0.5, 1.7]	0.76	0.4	[0.2, 0.8]	0.01
1 year	1.8	[1.1, 2.8]	0.01	1.0	[0.5, 1.8]	0.98	0.6	[0.3, 1.1]	0.08
3 year	1.3	[0.7, 2.3]	0.41	1.2	[0.5, 3.0]	0.62	1.0	[0.4, 2.5]	0.96
5 year	1.7	[0.9, 3.2]	0.09	1.4	[0.6, 3.3]	0.48	0.8	[0.3, 2.1]	0.66
Urinary leakage	Adjusted logistic model; effect size = odds ratio of moderate or big problem								
6 month	9.3	[4.6, 18.5]	<0.001	3.3	[1.6, 6.9]	0.002	0.4	[0.1, 0.9]	0.03
1 year	7.1	[3.8, 13.0]	<0.001	4.7	[2.0, 10.9]	<0.001	0.7	[0.2, 1.8]	0.41
3 year	3.6	[1.7, 7.3]	<0.001	6.3	[1.5, 25.7]	0.01	1.8	[0.4, 8.0]	0.46
5 year	2.9	[1.4, 6.0]	0.005	2.3	[0.7, 7.7]	0.19	0.8	[0.2, 3.1]	0.74
Burning on urination	Adjusted logistic model; effect size = odds ratio of moderate or big problem								
6 month	0.3	[0.1, 1.0]	0.04	0.1	[0.0, 0.2]	<0.001	0.2	[0.1, 0.6]	0.004
1 year	0.5	[0.2, 1.2]	0.14	0.1	[0.0, 0.4]	<0.001	0.2	[0.1, 0.7]	0.009
3 year	0.9	[0.2, 4.5]	0.93	0.3	[0.1, 1.2]	0.09	0.3	[0.1, 1.8]	0.19
5 year	0.2	[0.0, 3.6]	0.31	0.0	[0.0, 0.8]	0.03	0.2	[0, 2.1.0]	0.17
Frequent urination	Adjusted logistic model; effect size = odds ratio of moderate or big problem								
6 month	1.6	[1.0, 2.6]	0.04	0.4	[0.2, 0.7]	<0.001	0.2	[0.1, 0.4]	<0.001
1 year	1.5	[1.0, 2.1]	0.05	0.5	[0.3, 0.8]	0.005	0.3	[0.2, 0.6]	<0.001
3 year	1.1	[0.7, 1.9]	0.67	0.8	[0.3, 1.8]	0.53	0.7	[0.3, 1.7]	0.40
5 year	1.0	[0.6, 1.8]	0.96	0.6	[0.2, 1.4]	0.21	0.6	[0.2, 1.4]	0.23
Domain									
Bowel function score	Adjusted linear model; effect size = point difference between groups								
6 month	3.3	[1.4, 5.2]	<0.001	5.5 [b]	[2.5, 8.5]	<0.001	2.2	[-1.2, 5.7]	0.20
1 year	3.4	[1.9, 4.9]	<0.001	5.0 [b]	[2.4, 7.5]	<0.001	1.5	[-1.3, 4.4]	0.29
3 year	3.5	[1.8, 5.3]	<0.001	3.4	[0.8, 6.0]	0.01	-0.1	[-3.1, 2.9]	0.94
5 year	3.2	[1.2, 5.2]	0.002	2.7	[0, 5.4]	0.05	-0.5	[-3.7, 2.7]	0.76
Individual Items									
Bowel function bother	Adjusted logistic model; effect size = odds ratio of moderate or big problem								
6 month	0.7	[0.3, 1.6]	0.43	0.5	[0.2, 1.3]	0.16	0.7	[0.2, 1.9]	0.44
1 year	0.6	[0.3, 1.2]	0.18	0.6	[0.2, 1.3]	0.19	0.9	[0.4, 2.1]	0.78
3 year	0.6	[0.2, 1.6]	0.28	0.8	[0.2, 4]	0.78	1.4	[0.3, 7.1]	0.67
5 year	0.9	[0.3, 2.3]	0.77	1	[0.2, 4.2]	0.95	1.1	[0.2, 5.4]	0.90

Time	Nerve-sparing radical prostatectomy vs. External beam radiation therapy			Nerve-sparing radical prostatectomy vs. Low-dose-rate brachytherapy			External beam radiation therapy vs. Low-dose-rate brachytherapy		
	Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value
Bloody stools	Adjusted logistic model; effect size = odds ratio of moderate or big problem								
6 month[e]									
1 year	0.4	[0.1, 2.0]	0.28	0.3	[0, 3.7]	0.36	0.7	[0.1, 6.9]	0.78
3 year	0.1	[0, 1.2]	0.07	0.2	[0, 6.6]	0.37	3.6	[0.3, 45]	0.33
5 year[e]	[e]			[e]			[e]		
Bowel urgency	Adjusted logistic model; effect size = odds ratio of moderate or big problem								
6 month	0.6	[0.3, 1.4]	0.23	0.3	[0.1, 0.7]	0.005	0.4	[0.2, 1.2]	0.10
1 year	0.4	[0.2, 0.8]	0.008	0.3	[0.1, 0.7]	0.008	0.7	[0.3, 1.8]	0.50
3 year	0.2	[0.1, 0.6]	0.001	0.4	[0.1, 1.1]	0.08	1.6	[0.5, 4.9]	0.38
5 year	0.3	[0.1, 0.8]	0.02	0.2	[0.1, 0.7]	0.01	0.7	[0.2, 2.1]	0.51
Domain									
Hormone function score	Adjusted linear model; effect size = point difference between groups								
6 month	0.6	[-1.2, 2.4]	0.52	-0.2	[-2.7, 2.2]	0.842	-0.8	[-3.5, 1.9]	0.55
1 year	0.3	[-1.2, 1.9]	0.67	-0.8	[-2.6, 1.0]	0.39	-1.1	[-3.2, 0.9]	0.28
3 year	0.3	[-1.4, 2.0]	0.71	-1.1	[-3.2, 0.9]	0.29	-1.5	[-3.7, 0.8]	0.21
5 year	1.5	[-0.4, 3.4]	0.12	0.8	[-2.0, 3.7]	0.56	-0.7	[-3.8, 2.4]	0.66

a. Domain scores are from the Expanded Prostate Cancer Index Composite (EPIC-26). Domain scores are scaled from 0 to 100, with higher score indicating better function. The effect size in the multivariable model for domain score indicates the adjusted mean point difference between groups at each time point. A minimally important difference in score is 10-12 points on the sexual function domain; 6-9 points on the urinary incontinence domain; 5-7 points on the urinary irritative domain; 4-6 points on the bowel domain; and 4-6 points on the hormonal domain 4-6. The primary outcome was the difference in domain score at 5 years.

b. Signifies that the difference between groups exceeds the minimally important difference for clinical significance.

c. Individual items are clinically important components of the domain, scored on a Likert scale and then dichotomized for group comparisons. The effect size of the logistic regression models indicates the adjusted odds ratio of reporting a moderate or big problem comparing treatment groups.

d. All regression models are adjusted for baseline domain score, age, race, comorbidity, disease risk group, physical function, social support, depression, medical decision-making style and accrual site.

e. Analysis not performed because the limited number of events did not permit computation of reliable estimates.

eTable 7: Proportion of patients with erections firm enough for intercourse at baseline who retained or regained erections firm enough for intercourse at 5 years by treatment group

	Favorable Risk				Unfavorable Risk	
# of patients	Nerve-sparing radical prostatectomy	External beam radiation therapy	Low-dose-rate brachy-therapy	Active Surveillance	Radical Prostatectomy	External beam radiation therapy with androgen deprivation therapy
Reported erections firm enough for intercourse at baseline	428	109	46	200	204	80
Retained or regained erections firm enough for intercourse at 5 years (%)	205 (48%)	53 (49%)	25 (54%)	133 (66%)	63 (31%)	37 (46%)

eTable 8. Unadjusted functional outcomes of favorable risk patients on the Expanded Prostate Cancer Index Composite (EPIC) domain scores and selected individual item responses by treatment and time point; Adjusted differences between treatment groups and untreated active surveillance patients in Expanded Prostate Cancer Index Composite domain scores and selected individual item responses by treatment and time point

Time	N	Nerve-sparing radical prostatectomy (N=675)	External beam radiation therapy (N=261)	Low-dose-rate brachytherapy (N=87)	Untreated active surveillance (N=274)	Nerve-sparing radical prostatectomy vs. Untreated active surveillance			External beam radiation therapy vs. Untreated active surveillance			Low-dose-rate brachytherapy vs. Untreated active surveillance		
						Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value	Effect	95% Confidence Interval	p-value
Domain[a]														
Sexual function score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups[d]								
Baseline	1239	80 (53, 100)	60 (28, 85)	75 (38, 85)	75 (43, 90)									
6 month	1230	28 (10, 60)	53 (22, 78)	60 (22, 80)	73 (39, 90)	-35.6 [b]	[-39.2, -31.9]	<0.001	-6.7	[-10.8, -2.6]	0.001	-9.7	[-14.9, -4.6]	<0.001
1 year	1193	38 (12, 70)	47 (21, 75)	60 (19, 80)	75 (43, 90)	-30.7 [b]	[-33.8, -27.6]	<0.001	-6.8	[-10.4, -3.3]	<0.001	-10.1 [b]	[-14.7, -5.6]	<0.001
3 year	1073	48 (14, 79)	43 (12, 75)	59 (17, 80)	70 (27, 90)	-18.5 [b]	[-22.4, -14.6]	<0.001	-8.1	[-12.6, -3.6]	<0.001	-9.5	[-15.7, -3.4]	0.002
5 year	968	48 (15, 80)	28 (9, 69)	53 (24, 78)	65 (32, 85)	-14.8 [b]	[-19.0, -10.7]	<0.001	-10.2 [b]	[-15.2, -5.1]	<0.001	-6.4	[-13.4, 0.7]	0.08
Individual Items[c]														
Sexual function bother		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1238	144 (22%)	71 (29%)	16 (19%)	58 (22%)									
6 month	1244	366 (56%)	75 (31%)	20 (24%)	49 (19%)	8.3	[5.3, 12.9]	<0.001	1.6	[1.0, 2.7]	0.04	1.4	[0.7, 2.6]	0.37
1 year	1199	317 (49%)	76 (32%)	18 (22%)	41 (18%)	6.2	[4.4, 8.7]	<0.001	1.5	[1.1, 2.3]	0.02	1.5	[0.9, 2.6]	0.12
3 year	1079	240 (40%)	69 (32%)	20 (29%)	46 (23%)	3.0	[2.0, 4.7]	<0.001	1.5	[0.9, 2.4]	0.12	1.8	[1.0, 3.4]	0.07
5 year	980	193 (35%)	69 (35%)	16 (25%)	33 (19%)	2.5	[1.6, 3.9]	<0.001	1.8	[1.0, 3.0]	0.04	1.5	[0.7, 3.1]	0.34
Erection insufficient for penetration		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of insufficient erection								
Baseline	1247	216 (33%)	140 (56%)	38 (45%)	100 (39%)									
6 month	1240	498 (76%)	152 (63%)	45 (54%)	102 (40%)	13.7	[9, 20.7]	<0.001	2.0	[1.3, 3.0]	0.002	1.9	[1.1, 3.3]	0.03
1 year	1197	442 (69%)	157 (65%)	42 (52%)	90 (38%)	10.4	[7.3, 14.8]	<0.001	2.1	[1.4, 2.9]	<0.001	2.0	[1.2, 3.3]	0.005
3 year	1079	376 (63%)	146 (68%)	38 (54%)	84 (42%)	4.6	[3.1, 7.0]	<0.001	2.2	[1.4, 3.5]	<0.001	2.2	[1.2, 4.1]	0.01
5 year	978	332 (61%)	145 (74%)	39 (61%)	85 (49%)	2.9	[1.9, 4.4]	<0.001	2.2	[1.3, 3.6]	0.002	1.9	[0.9, 3.9]	0.07
Domains														
Urinary Incontinence score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups								
Baseline	1252	100 (81, 100)	100 (79, 100)	100 (92, 100)	100 (83, 100)									
6 month	1259	73 (49, 100)	100 (79, 100)	94 (73, 100)	100 (79, 100)	-23.2 [b]	[-26.5, -19.9]	<0.001	1.0	[-2.0, 4.0]	0.50	-5.8	[-10.2, -1.5]	0.009
1 year	1181	79 (54, 100)	100 (79, 100)	97 (79, 100)	100 (85, 100)	-19.7 [b]	[-22.4, -17.0]	<0.001	1.1	[-1.4, 3.6]	0.38	-4.8	[-8.4, -1.1]	0.01
3 year	1087	79 (58, 100)	100 (77, 100)	100 (79, 100)	100 (79, 100)	-13.0 [b]	[-16.0, -9.9]	<0.001	1.4	[-1.7, 4.5]	0.37	-2.6	[-7.1, 2.0]	0.26
5 year	992	79 (58, 100)	100 (79, 100)	100 (81, 100)	100 (77, 100)	-14.5 [b]	[-17.7, -11.3]	<0.001	1.7	[-1.9, 5.2]	0.36	-2.8	[-8.6, 3.1]	0.35

Time	N	Nerve-sparing radical prostatectomy (N=675)	External beam radiation therapy (N=261)	Low-dose-rate brachytherapy (N=87)	Untreated active surveillance (N=274)	Nerve-sparing radical prostatectomy vs. Untreated active surveillance Effect	95% Confidence Interval	p-value	External beam radiation therapy vs. Untreated active surveillance Effect	95% Confidence Interval	p-value	Low-dose-rate brachytherapy vs. Untreated active surveillance Effect	95% Confidence Interval	p-value
Urinary Irritative score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups								
Baseline	1244	88 (75, 100)	88 (75, 94)	94 (80, 100)	88 (75, 94)									
6 month	1244	94 (88, 100)	94 (81, 100)	81 (62, 88)	88 (77, 100)	3.4	[1.5, 5.4]	<0.001	0.8	[-1.6, 3.1]	0.51	-11.6 [b]	[-15.9, -7.3]	<0.001
1 year	1211	94 (88, 100)	88 (81, 94)	88 (69, 94)	88 (81, 100)	4.1	[2.5, 5.6]	<0.001	1.1	[-0.8, 3.0]	0.25	-7.0 [b]	[-10.1, -3.8]	<0.001
3 year	1080	94 (88, 100)	88 (77, 100)	94 (88, 94)	88 (81, 100)	5.6 [b]	[3.6, 7.5]	<0.001	1.9	[-0.3, 4.1]	0.10	2.1	[-1.2, 5.4]	0.21
5 year	984	94 (88, 100)	94 (81, 100)	94 (84, 100)	88 (81, 100)	5.8 [b]	[3.9, 7.7]	<0.001	2.1	[-0.3, 4.5]	0.08	0.4	[-3.5, 4.3]	0.83
Individual Items														
Urinary function bother		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1245	82 (13%)	31 (12%)	9 (11%)	36 (14%)									
6 month	1260	94 (14%)	25 (10%)	17 (20%)	27 (10%)	2.0	[1.2, 3.3]	0.01	0.8	[0.5, 1.6]	0.58	2.1	[1.0, 4.1]	0.04
1 year	1200	65 (10%)	16 (7%)	8 (10%)	20 (8%)	1.6	[1.0, 2.4]	0.05	0.8	[0.5, 1.4]	0.47	1.5	[0.8, 2.9]	0.21
3 year	1107	56 (9%)	21 (10%)	6 (8%)	16 (8%)	1.1	[0.6, 2.1]	0.68	0.8	[0.4, 1.7]	0.65	0.9	[0.3, 2.3]	0.80
5 year	1003	55 (10%)	17 (8%)	6 (9%)	14 (8%)	1.7	[0.9, 3.1]	0.09	0.9	[0.4, 2.0]	0.85	1.2	[0.4, 3.2]	0.73
Urinary leakage		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1266	41 (6%)	11 (4%)	3 (4%)	15 (6%)									
6 month	1266	120 (18%)	11 (4%)	9 (11%)	11 (4%)	10.3	[4.5, 23.6]	<0.001	1.0	[0.4, 2.8]	0.94	3.0	[1.1, 8.2]	0.03
1 year	1221	86 (13%)	9 (4%)	2 (2%)	10 (4%)	7.2	[3.7, 13.7]	<0.001	0.9	[0.4, 2.1]	0.89	1.5	[0.5, 3.9]	0.45
3 year	1102	72 (12%)	9 (4%)	2 (3%)	9 (4%)	3.5	[1.7, 7.3]	<0.001	0.9	[0.4, 2.3]	0.84	0.5	[0.1, 2.4]	0.41
5 year	1002	56 (10%)	12 (6%)	3 (5%)	7 (4%)	4.0	[1.7, 9.2]	0.001	1.3	[0.5, 3.4]	0.61	1.6	[0.4, 6.8]	0.49
Burning on urination		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1264	21 (3%)	14 (5%)	3 (4%)	8 (3%)									
6 month	1263	7 (1%)	8 (3%)	7 (8%)	3 (1%)	1.2	[0.1, 12.5]	0.88	3.8	[0.4, 41.2]	0.27	19.6	[1.9, 207.8]	0.01
1 year	1222	7 (1%)	7 (3%)	11 (13%)	1 (0%)	2.0	[0.6, 6.6]	0.27	3.7	[1, 13.5]	0.04	14.9	[4, 55.1]	<0.001
3 year	1104	6 (1%)	4 (2%)	1 (1%)	2 (1%)	3.8	[0.2, 74]	0.38	4.3	[0.2, 96.2]	0.36	13	[0.7, 247.6]	0.09
5 year	1000	1 (0%)	1 (0%)	2 (3%)	1 (1%)	[e]			[e]			[e]		
Frequent urination		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1266	117 (18%)	52 (20%)	12 (14%)	58 (22%)									
6 month	1268	97 (15%)	35 (14%)	26 (31%)	51 (19%)	1.1	[0.7, 1.8]	0.72	0.6	[0.4, 1.1]	0.11	3.0	[1.5, 5.9]	0.001
1 year	1222	85 (13%)	24 (10%)	15 (18%)	39 (16%)	0.8	[0.6, 1.2]	0.30	0.5	[0.3, 0.8]	0.003	1.7	[1.0, 3.0]	0.06
3 year	1101	64 (11%)	32 (15%)	8 (11%)	37 (17%)	0.5	[0.3, 0.9]	0.01	0.5	[0.3, 0.8]	0.007	0.7	[0.3, 1.7]	0.44
5 year	1004	68 (12%)	27 (13%)	9 (14%)	28 (15%)	0.8	[0.5, 1.4]	0.50	0.8	[0.4, 1.4]	0.42	1.4	[0.6, 3.5]	0.44
Domain														

Time	N	Nerve-sparing radical prostatectomy (N=675)	External beam radiation therapy (N=261)	Low-dose-rate brachytherapy (N=87)	Untreated active surveillance (N=274)	Nerve-sparing radical prostatectomy vs. Untreated active surveillance Effect	95% Confidence Interval	p-value	External beam radiation therapy vs. Untreated active surveillance Effect	95% Confidence Interval	p-value	Low-dose-rate brachytherapy vs. Untreated active surveillance Effect	95% Confidence Interval	p-value
Bowel function score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups								
Baseline	1269	100 (96, 100)	100 (96, 100)	100 (96, 100)	100 (96, 100)									
6 month	1263	100 (96, 100)	96 (88, 100)	96 (83, 100)	100 (96, 100)	-0.1	[-1.5, 1.4]	0.93	-3.4	[-5.5, -1.2]	0.002	-5.6 [b]	[-8.8, -2.5]	<0.001
1 year	1222	100 (96, 100)	96 (88, 100)	96 (83, 100)	100 (92, 100)	-0.2	[-1.3, 1.0]	0.79	-3.6	[-5.2, -1.9]	<0.001	-5.2 [b]	[-7.8, -2.6]	<0.001
3 year	1104	100 (96, 100)	96 (88, 100)	100 (88, 100)	100 (96, 100)	-0.4	[-1.7, 1.0]	0.61	-3.9	[-5.9, -1.9]	<0.001	-3.9	[-6.7, -1.1]	0.006
5 year	997	100 (96, 100)	96 (88, 100)	100 (88, 100)	100 (96, 100)	-0.4	[-2.0, 1.2]	0.62	-3.6	[-5.9, -1.3]	0.002	-3.2	[-6.1, -0.2]	0.04
Individual Items														
Bowel function bother		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1260	12 (2%)	6 (2%)	3 (3%)	11 (4%)									
6 month	1263	20 (3%)	11 (4%)	7 (8%)	9 (3%)	1.6	[0.6, 4.0]	0.34	2.1	[0.8, 5.2]	0.11	3.3	[1.1, 10.1]	0.03
1 year	1207	11 (2%)	17 (7%)	4 (5%)	8 (3%)	1.1	[0.5, 2.3]	0.84	1.7	[0.8, 3.5]	0.16	2.0	[0.8, 5.2]	0.14
3 year	1105	10 (2%)	9 (4%)	2 (3%)	8 (4%)	0.6	[0.2, 1.9]	0.39	1.1	[0.4, 3.1]	0.91	0.8	[0.2, 4.0]	0.82
5 year	1000	13 (2%)	9 (4%)	3 (5%)	8 (4%)	1.0	[0.4, 2.8]	0.97	1.1	[0.4, 3.3]	0.83	1.1	[0.2, 5.4]	0.87
Bloody stools		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem [e]								
Baseline	1267	2 (0%)	2 (1%)	0 (0%)	4 (2%)									
6 month	1263	2 (0%)	2 (1%)	0 (0%)	2 (1%)	[e]			[e]			[e]		
1 year	1220	3 (0%)	2 (1%)	1 (1%)	1 (0%)	[e]			[e]			[e]		
3 year	1104	1 (0%)	5 (2%)	1 (1%)	0 (0%)	[e]			[e]			[e]		
5 year	998	0 (0%)	1 (0%)	0 (0%)	0 (0%)	[e]			[e]			[e]		
Bowel urgency		Unadjusted frequency (%)				Adjusted logistic model; effect size = odds ratio of moderate or big problem								
Baseline	1270	16 (2%)	5 (2%)	5 (6%)	9 (3%)									
6 month	1265	14 (2%)	10 (4%)	9 (11%)	11 (4%)	0.9	[0.4, 2.1]	0.75	1.4	[0.6, 3.5]	0.48	3.4	[1.2, 9.4]	0.02
1 year	1222	13 (2%)	18 (7%)	8 (10%)	7 (3%)	0.7	[0.4, 1.5]	0.41	1.7	[0.8, 3.6]	0.14	2.4	[1.0, 6.0]	0.05
3 year	1105	8 (1%)	16 (7%)	3 (4%)	7 (3%)	0.5	[0.2, 1.5]	0.24	2.3	[0.8, 6.3]	0.11	1.5	[0.5, 4.8]	0.51
5 year	998	10 (2%)	15 (8%)	6 (9%)	8 (4%)	0.5	[0.2, 1.4]	0.19	1.6	[0.6, 3.9]	0.34	2.3	[0.7, 7.1]	0.16
Domain														
Hormone function score		Unadjusted median (IQR) domain score				Adjusted linear model; effect size = point difference between groups								
Baseline	1245	95 (90, 100)	95 (85, 100)	100 (81, 100)	95 (85, 100)									
6 month	1245	95 (85, 100)	95 (85, 100)	95 (85, 100)	95 (85, 100)	-1.3	[-3.0, 0.4]	0.14	-1.9	[-3.9, 0.1]	0.07	-0.9	[-3.5, 1.7]	0.49
1 year	1206	95 (85, 100)	95 (84, 100)	95 (81, 100)	95 (85, 100)	-1.1	[-2.4, 0.3]	0.11	-1.4	[-3.0, 0.2]	0.10	-0.2	[-2.0, 1.7]	0.85
3 year	1089	95 (85, 100)	95 (85, 100)	100 (90, 100)	95 (88, 100)	-0.6	[-2.3, 1.0]	0.46	-0.9	[-2.8, 1.1]	0.37	0.5	[-1.7, 2.8]	0.64
5 year	984	95 (85, 100)	95 (80, 100)	95 (85, 100)	95 (90, 100)	-0.6	[-2.3, 1.2]	0.52	-2.1	[-4.2, 0.0]	0.06	-1.3	[-4.4, 1.7]	0.39

a. Domain scores are from the Expanded Prostate Cancer Index Composite (EPIC-26). Domain scores are scaled from 0 to 100, with higher score indicating better function. The left side of the table shows unadjusted median domain score and interquartile range (25th percentile, 75th percentile). The right side shows multivariable model results. The effect size in the multivariable model for domain score indicates the adjusted mean point difference between groups at each time point. A minimally important difference in score is 10-12 points on the sexual function domain; 6-9 points on the urinary incontinence domain; 5-7 points on the urinary irritative domain; 4-6 points on the bowel domain; and 4-6 points on the hormonal domain 4-6. The primary outcome was the difference in domain score at 5 years.

b. Signifies that the difference between groups exceeds the minimally important difference for clinical significance.

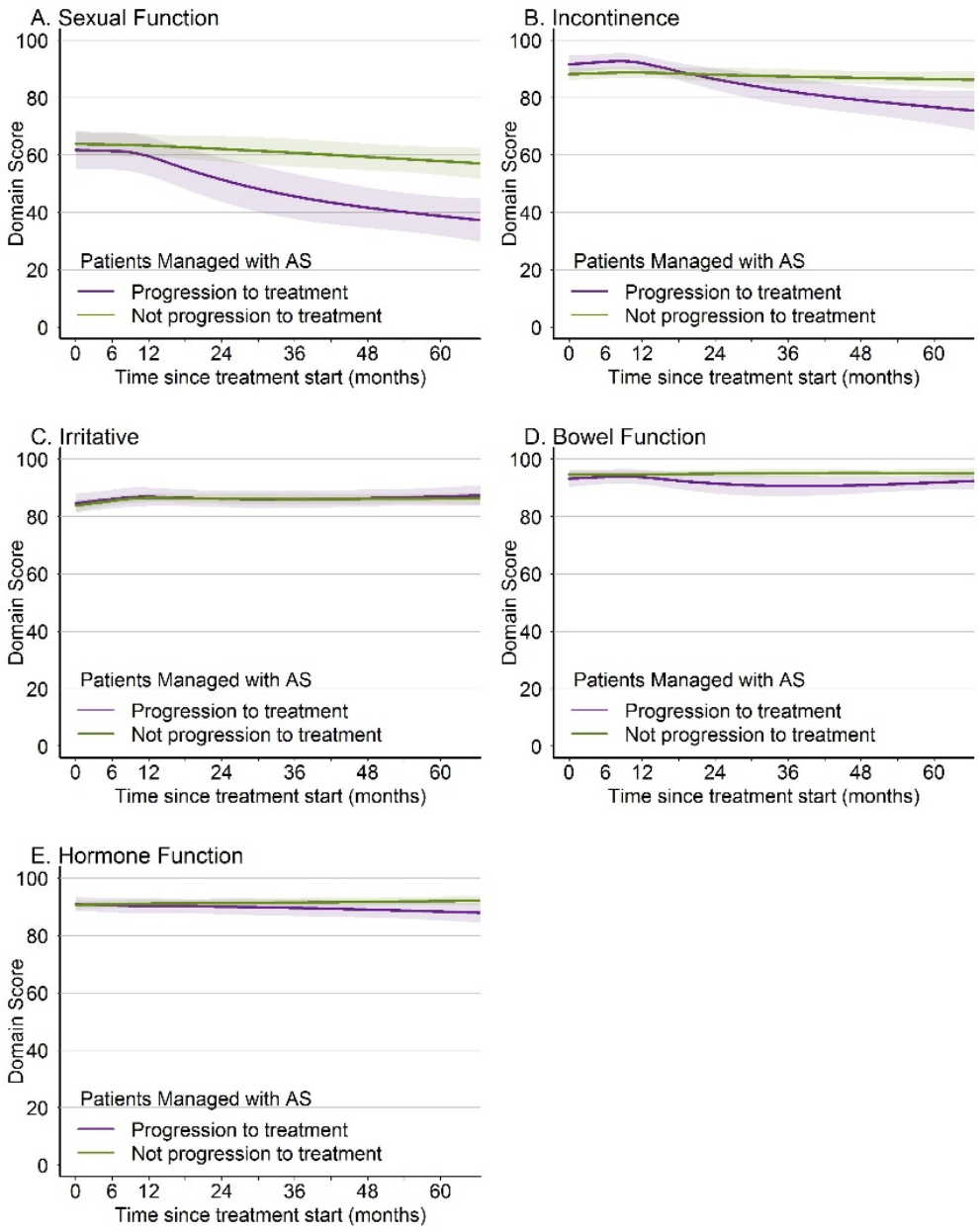
c. Individual items are clinically important components of the domain, scored on a Likert scale and then dichotomized for group comparisons. The left side of the table shows the unadjusted number (%) of patients reporting a moderate or big problem. The right side shows the adjusted odds ratio of reporting a moderate or big problem comparing treatment groups.

d. All regression models are adjusted for baseline domain score, age, race, comorbidity, disease risk group, physical function, social support, depression, medical decision-making style and accrual site.

e. Analysis not performed because the limited number of events did not permit computation of reliable estimates.

eFigure 1: Unadjusted disease-specific function by time among Active Surveillance patients who remained untreated and those who progressed to treatment.

Unadjusted mean sexual (panel A) urinary incontinence (panel B), urinary irritative (panel C), bowel (panel D), and hormonal (panel E) function over time reported by men with low and favorable-intermediate risk prostate cancer managed with Active Surveillance who remained untreated and those who progressed to treatment.



eTable 9. Unadjusted functional outcomes of unfavorable-risk patients on the Expanded Prostate Cancer Index Composite (EPIC) domain scores and selected individual item responses by treatment and time point; Adjusted differences between treatment groups in Expanded Prostate Cancer Index Composite domain scores and selected individual item responses by treatment and time point.

Time	N	External beam radiation therapy with androgen deprivation (N=217)	Radical prostatectomy (N=402)	External beam radiation therapy with androgen deprivation vs. Radical prostatectomy Effect	95% Confidence interval	p-value
Sexual Function Domain[a]						
Sexual function score		Unadjusted median (IQR) domain score		Adjusted linear model effect size = point difference between groups[d]		
Baseline	580	48 (12, 80)	70 (33, 85)			
6 month	562	5 (0, 42)	15 (0, 38)	10.9[b]	[6.0, 15.8]	<0.001
1 year	556	17 (0, 52)	17 (0, 50)	9.8	[5.1, 14.5]	<0.001
3 year	487	20 (0, 60)	20 (0, 53)	9.1	[3.5, 14.8]	0.002
5 year	429	27 (0, 65)	15 (0, 57)	12.5[b]	[6.2, 18.7]	<0.001
Sexual Function Individual Items[c]						
Sexual function bother		Unadjusted frequency (%)		Adjusted logistic model effect size = odds ratio of moderate or big problem		
Baseline	591	70 (34%)	122 (32%)			
6 month	569	85 (43%)	207 (56%)	0.5	[0.3, 0.7]	<0.001
1 year	555	85 (45%)	195 (53%)	0.5	[0.4, 0.8]	<0.001
3 year	493	64 (40%)	155 (47%)	0.7	[0.4, 1.1]	0.11
5 year	433	58 (44%)	145 (48%)	0.6	[0.4, 1.0]	0.08
Erection insufficient for penetration		Unadjusted frequency (%)		Adjusted logistic model effect size = odds ratio of insufficient erection		
Baseline	589	120 (59%)	175 (45%)			
6 month	567	158 (81%)	322 (87%)	0.3	[0.2, 0.5]	<0.001
1 year	557	155 (81%)	303 (83%)	0.4	[0.2, 0.7]	<0.001
3 year	492	126 (79%)	264 (80%)	0.6	[0.3, 1.1]	0.13
5 year	434	99 (75%)	243 (80%)	0.4	[0.2, 0.8]	0.01
Urinary Function Domains						
Urinary Incontinence score		Unadjusted median (IQR) domain score		Adjusted linear model effect size = point difference between groups		
Baseline	597	100 (75, 100)	100 (79, 100)			
6 month	583	88 (67, 100)	60 (40, 85)	27.7[b]	[23.3, 32.1]	<0.001
1 year	545	92 (73, 100)	67 (46, 100)	25.6[b]	[21.5, 29.7]	<0.001
3 year	494	92 (75, 100)	67 (48, 92)	21.8[b]	[17.1, 26.6]	<0.001
5 year	437	92 (73, 100)	69 (46, 92)	23.2[b]	[17.7, 28.7]	<0.001
Urinary Irritative score		Unadjusted median (IQR) domain score		Adjusted linear model effect size = point difference between groups		
Baseline	595	88 (75, 94)	88 (69, 100)			
6 month	577	88 (75, 94)	88 (81, 100)	-1.8	[-4.4, 0.8]	0.18
1 year	556	88 (75, 94)	94 (81, 100)	-0.9	[-3.1, 1.3]	0.44
3 year	500	88 (81, 100)	94 (81, 100)	1.1	[-1.6, 3.7]	0.48
5 year	442	88 (81, 94)	94 (81, 100)	1.2	[-2.2, 4.5]	0.50

Time	N	External beam radiation therapy with androgen deprivation (N=217)	Radical prostatectomy (N=402)	External beam radiation therapy with androgen deprivation vs. Radical prostatectomy: Effect	95% Confidence interval	p-value
Urinary Function Individual Items						
Urinary function bother		Unadjusted frequency (%)		Adjusted logistic model effect size = odds ratio of moderate or big problem		
Baseline	600	23 (11%)	70 (18%)			
6 month	584	35 (17%)	78 (21%)	0.5	[0.3, 0.8]	0.004
1 year	558	24 (12%)	56 (15%)	0.4	[0.3, 0.7]	0.001
3 year	507	18 (11%)	54 (16%)	0.4	[0.2, 0.7]	0.005
5 year	444	18 (13%)	52 (17%)	0.4	[0.2, 0.8]	0.005
Urinary leakage		Unadjusted frequency (%)		Adjusted logistic model effect size = odds ratio of moderate or big problem		
Baseline	605	7 (3%)	39 (10%)			
6 month	586	16 (8%)	81 (21%)	0.2	[0.1, 0.4]	<0.001
1 year	560	16 (8%)	71 (19%)	0.2	[0.1, 0.3]	<0.001
3 year	501	11 (7%)	55 (16%)	0.2	[0.1, 0.4]	<0.001
5 year	447	10 (7%)	49 (16%)	0.2	[0.1, 0.5]	<0.001
Burning on urination		Unadjusted frequency (%)		Adjusted logistic model effect size = odds ratio of moderate or big problem		
Baseline	603	6 (3%)	13 (3%)			
6 month	585	16 (8%)	8 (2%)	2.5	[0.9, 6.9]	0.07
1 year	561	5 (3%)	7 (2%)	1	[0.4, 2.7]	0.97
3 year	505	3 (2%)	11 (3%)	0.2	[0, 0.8]	0.03
5 year	447	2 (1%)	10 (3%)	0.3	[0.1, 1.4]	0.14
Frequent urination		Unadjusted frequency (%)		Adjusted logistic model effect size = odds ratio of moderate or big problem		
Baseline	604	49 (23%)	97 (25%)			
6 month	582	45 (22%)	85 (23%)	0.7	[0.4, 1.1]	0.15
1 year	562	35 (18%)	74 (20%)	0.8	[0.5, 1.2]	0.21
3 year	510	26 (15%)	49 (14%)	0.7	[0.4, 1.3]	0.25
5 year	447	20 (14%)	55 (18%)	0.5	[0.2, 0.9]	0.02
Bowel Function Domain						
Bowel function score		Unadjusted median (IQR) domain score		Adjusted linear model effect size = point difference between groups		
Baseline	606	100 (92, 100)	100 (88, 100)			
6 month	585	96 (79, 100)	100 (92, 100)	-5.4 [b]	[-8, -2.9]	<0.001
1 year	567	92 (83, 100)	100 (92, 100)	-4.1 [b]	[-6.3, -1.9]	<0.001
3 year	505	96 (83, 100)	100 (92, 100)	-1.6	[-4.3, 1.2]	0.26
5 year	445	96 (83, 100)	100 (88, 100)	-2.0	[-5.1, 1.1]	0.21
Bowel Function Individual Items						
Bowel function bother		Unadjusted frequency (%)		Adjusted logistic model effect size = odds ratio of moderate or big problem		
Baseline	602	11 (5%)	17 (4%)			
6 month	584	20 (10%)	23 (6%)	1.1	[0.5, 2.3]	0.80
1 year	567	18 (9%)	15 (4%)	1.3	[0.7, 2.5]	0.39
3 year	508	13 (8%)	14 (4%)	1.4	[0.5, 3.4]	0.53
5 year	446	9 (6%)	18 (6%)	0.6	[0.2, 1.6]	0.34

Time	N	External beam radiation therapy with androgen deprivation (N=217)	Radical prostatectomy (N=402)	External beam radiation therapy with androgen deprivation vs. Radical prostatectomy Effect	95% Confidence interval	p-value
Bloody stools		Unadjusted frequency (%)		Adjusted logistic model effect size = odds ratio of moderate or big problem		
Baseline	605	1 (0%)	0 (0%)			
6 month	586	5 (2%)	2 (1%)	3.6	[0.6, 21.3]	0.15
1 year	568	6 (3%)	3 (1%)	2.0	[0.5, 9.2]	0.35
3 year	507	1 (1%)	6 (2%)	0.7	[0.1, 3.8]	0.68
5 year	446	2 (1%)	3 (1%)	0.9	[0.1, 8.4]	0.95
Bowel urgency		Unadjusted frequency (%)		Adjusted logistic model effect size = odds ratio of moderate or big problem		
Baseline	607	11 (5%)	27 (7%)			
6 month	587	22 (11%)	19 (5%)	1.8	[0.9, 3.9]	0.12
1 year	568	16 (8%)	20 (5%)	1.7	[0.9, 3.4]	0.12
3 year	507	10 (6%)	11 (3%)	1.5	[0.6, 4.1]	0.41
5 year	446	13 (9%)	18 (6%)	1.5	[0.6, 3.7]	0.44
Hormone Function Domain						
Hormone function score		Unadjusted median (IQR) domain score		Adjusted linear model effect size = point difference between groups		
Baseline	592	90 (80, 95)	90 (80, 100)			
6 month	573	81 (70, 95)	90 (80, 100)	-5.3	[-8.2, -2.4]	<0.001
1 year	558	85 (70, 95)	90 (80, 100)	-3.9	[-6.5, -1.4]	0.002
3 year	495	90 (75, 95)	95 (80, 100)	-0.2	[-3.0, 2.6]	0.90
5 year	438	90 (80, 100)	90 (80, 100)	1.7	[-1.4, 4.9]	0.28

a. Domain scores are from the Expanded Prostate Cancer Index Composite (EPIC-26). Domain scores are scaled from 0 to 100, with higher score indicating better function. The left side of the table shows unadjusted median domain score and interquartile range (25th percentile, 75th percentile). The right side shows multivariable model results. The effect size in the multivariable model for domain score indicates the adjusted mean point difference between groups at each time point. A minimally important difference in score is 10-12 points on the sexual function domain; 6-9 points on the urinary incontinence domain; 5-7 points on the urinary irritative domain; 4-6 points on the bowel domain; and 4-6 points on the hormonal domain 4-6. The primary outcome was the difference in domain score at 5 years.

b. Signifies that the difference between groups exceeds the minimally important difference for clinical significance.

eTable 10. Unadjusted general health related quality of life outcomes of favorable-risk patients by treatment and time point; Adjusted differences between treatment groups in general health related quality of life domain scores by treatment and time point.

Time	N	Nerve-sparing radical prostatectomy (N=675)	External beam radiation therapy (N=261)	Low-dose-rate brachytherapy (N=87)	Active surveillance (N=363)	Nerve-sparing radical prostatectomy vs. Active surveillance Effect	95% Confidence Interval	p-value	External beam radiation therapy vs. Active surveillance Effect	95% Confidence Interval	p-value	Low-dose-rate brachytherapy vs. Active surveillance Effect	95% Confidence Interval	p-value
Physical Function Score[a]														
		Unadjusted median (IQR)				Adjusted linear model[b]; effect size = mean point difference between groups								
6 month	1350	95 (85, 100)	90 (70, 100)	95 (75, 100)	95 (80, 100)	-1.0	[-3.0, 0.9]	0.30	-2.1	[-4.6, 0.4]	0.10	-3.4	[-6.9, 0.1]	0.05
1 year	1315	100 (95, 100)	93 (75, 100)	95 (80, 100)	95 (85, 100)	-0.5	[-2.1, 1.1]	0.54	-1.8	[-3.9, 0.3]	0.09	-3.6	[-6.8, -0.5]	0.02
3 year	1190	95 (85, 100)	90 (67, 95)	90 (60, 100)	95 (80, 100)	0.5	[-1.6, 2.5]	0.67	-2.3	[-5.0, 0.4]	0.10	-4.6	[-8.7, -0.5]	0.03
5 year	1083	95 (85, 100)	85 (65, 95)	90 (74, 100)	90 (80, 100)	0.0	[-2.4, 2.4]	0.99	-4.8	[-8.2, -1.4]	0.006	-5.8	[-11.0, -0.6]	0.03
Emotional Well Being Score[a]														
6 month	1352	88 (76, 92)	88 (72, 92)	88 (79, 92)	88 (76, 92)	0.3	[-1.5, 2.0]	0.78	-1.0	[-3.2, 1.1]	0.36	1.2	[-1.5, 3.9]	0.38
1 year	1304	88 (76, 92)	88 (72, 92)	92 (75, 96)	88 (76, 92)	0.7	[-0.8, 2.1]	0.39	-0.3	[-2.1, 1.5]	0.76	1.6	[-0.9, 4.1]	0.21
3 year	1186	88 (76, 92)	88 (72, 92)	88 (76, 92)	88 (76, 92)	1.2	[-0.6, 3.0]	0.18	1.0	[-1.1, 3.1]	0.37	2.0	[-1.2, 5.1]	0.22
5 year	1082	88 (76, 92)	88 (76, 92)	88 (74, 96)	88 (76, 92)	0.5	[-1.4, 2.5]	0.60	0.3	[-2.1, 2.7]	0.81	0.9	[-3.6, 5.3]	0.71
Energy/Fatigue Score[a]														
6 month	1351	80 (60, 85)	70 (55, 80)	75 (55, 85)	75 (60, 85)	0.1	[-2.0, 2.2]	0.95	-2.7	[-5.3, -0.2]	0.04	-1.7	[-5.4, 1.9]	0.36
1 year	1304	80 (65, 85)	70 (55, 80)	75 (54, 85)	75 (60, 85)	0.1	[-1.6, 1.8]	0.92	-1.6	[-3.7, 0.5]	0.13	-0.7	[-3.9, 2.5]	0.67
3 year	1186	75 (60, 85)	70 (55, 81)	75 (55, 85)	75 (60, 85)	0.3	[-1.6, 2.3]	0.75	0.0	[-2.5, 2.4]	0.97	1.4	[-2.2, 5.0]	0.45
5 year	1082	75 (60, 85)	70 (54, 80)	70 (60, 85)	75 (55, 85)	0.7	[-1.5, 2.9]	0.51	-1.8	[-4.7, 1.1]	0.22	1.2	[-3.7, 6.0]	0.64

Footnote:

[a]. Domain scores are from the Medical Outcomes Study – Short Form-36 general quality of life instrument. Domain scores are scaled from 0 to 100, with higher score indicating better function or less disability. The left side of the table shows unadjusted median score and Interquartile range (IQR). The right side shows multivariable model results.

[b]. The effect size in the multivariable model for domain score indicates the adjusted mean point difference between groups at each time point. A minimally important difference in score is estimated as 7 for Physical Function Score, 6 for Emotional Well-Being Score, and 9 for Energy/Fatigue Score. The primary outcome was the difference in domain score at 5 years. All regression models are adjusted for baseline domain score, age, race, comorbidity, prostate cancer risk group, social support, depression, medical decision-making style and accrual site.

eTable 11. Unadjusted general health related quality of life outcomes of unfavorable-risk patients by treatment and time point; Adjusted differences between treatment groups in general health related quality of life domain scores by treatment and time point.

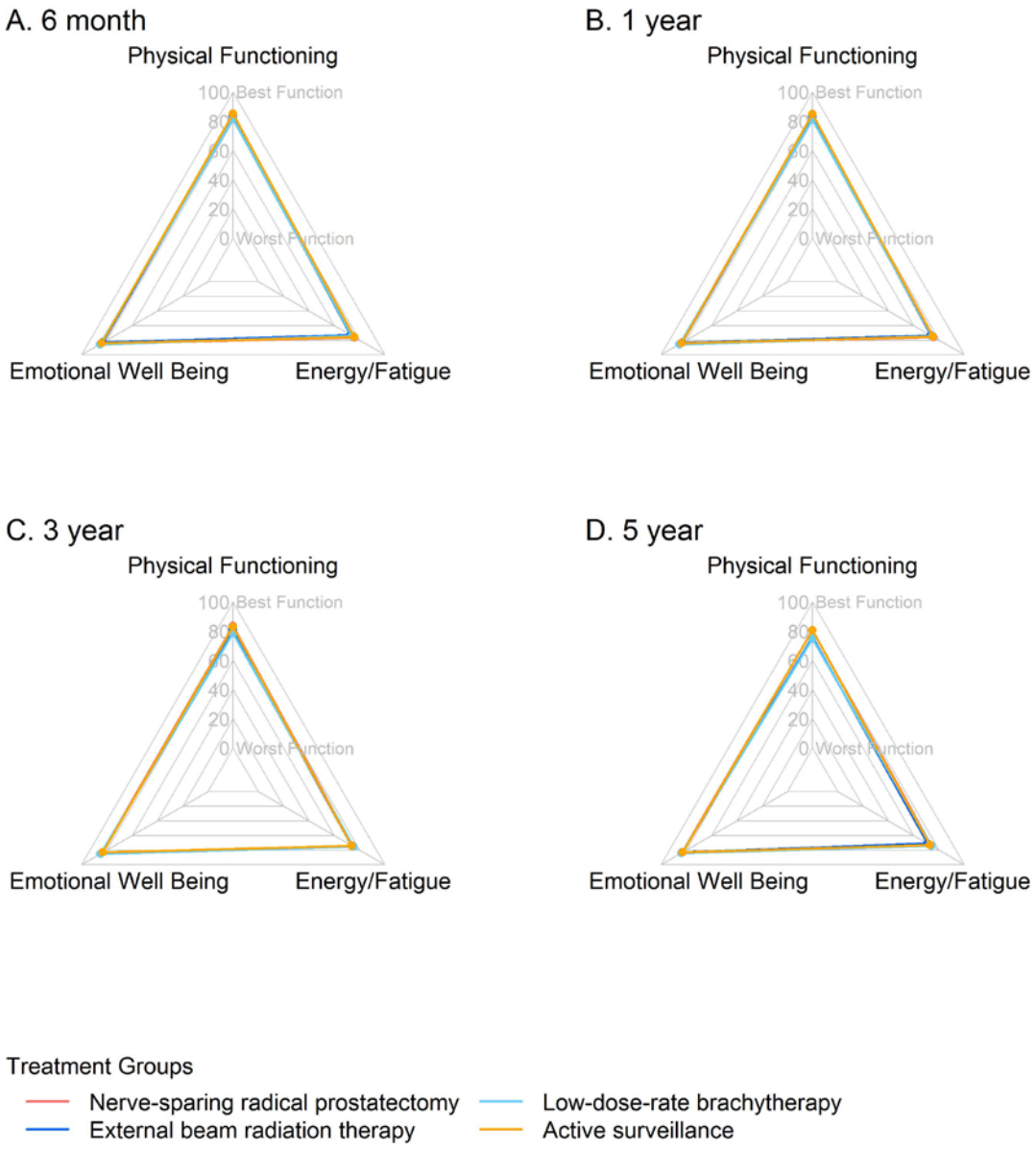
Time	N	External beam radiation therapy with androgen deprivation (N=217)	Radical prostatectomy (N=402)	External beam radiation therapy with androgen deprivation vs. Radical prostatectomy Effect	95% Confidence interval	p-value
Physical Function Score[a]						
		Unadjusted median (IQR)		Adjusted linear model[b] effect size = mean point difference between groups		
6 month	586	75 (48, 94)	90 (80, 100)	-4.7	[-8.2, -1.1]	0.01
1 year	567	85 (55, 95)	95 (80, 100)	-4.2	[-7.6, -0.8]	0.01
3 year	508	80 (50, 95)	95 (80, 100)	-4.8	[-9.0, -0.7]	0.02
5 year	448	80 (40, 95)	90 (75, 100)	-8.1	[-13.3, -2.9]	0.002
Emotional Well Being Score[a]						
6 month	583	86 (72, 92)	84 (76, 92)	-0.7	[-3.1, 1.6]	0.54
1 year	568	84 (68, 92)	84 (72, 92)	-1.1	[-3.3, 1.1]	0.35
3 year	504	84 (72, 92)	84 (72, 92)	-1.7	[-4.4, 1.1]	0.24
5 year	448	84 (68, 92)	88 (72, 92)	-1.5	[-4.7, 1.6]	0.34
Energy/Fatigue Score[a]						
6 month	583	65 (50, 80)	75 (60, 80)	-2.4	[-5.4, 0.6]	0.12
1 year	568	65 (50, 76)	75 (60, 85)	-3.3	[-6.0, -0.7]	0.01
3 year	504	65 (55, 80)	70 (60, 85)	-3.4	[-6.7, -0.2]	0.04
5 year	448	65 (50, 80)	70 (55, 80)	0.2	[-3.4, 3.8]	0.91

Footnote:

[a]. Domain scores are from the Medical Outcomes Study – Short Form-36 general quality of life instrument. Domain scores are scaled from 0 to 100, with higher score indicating better function or less disability. The left side of the table shows unadjusted median score and Interquartile range (IQR). The right side shows multivariable model results.

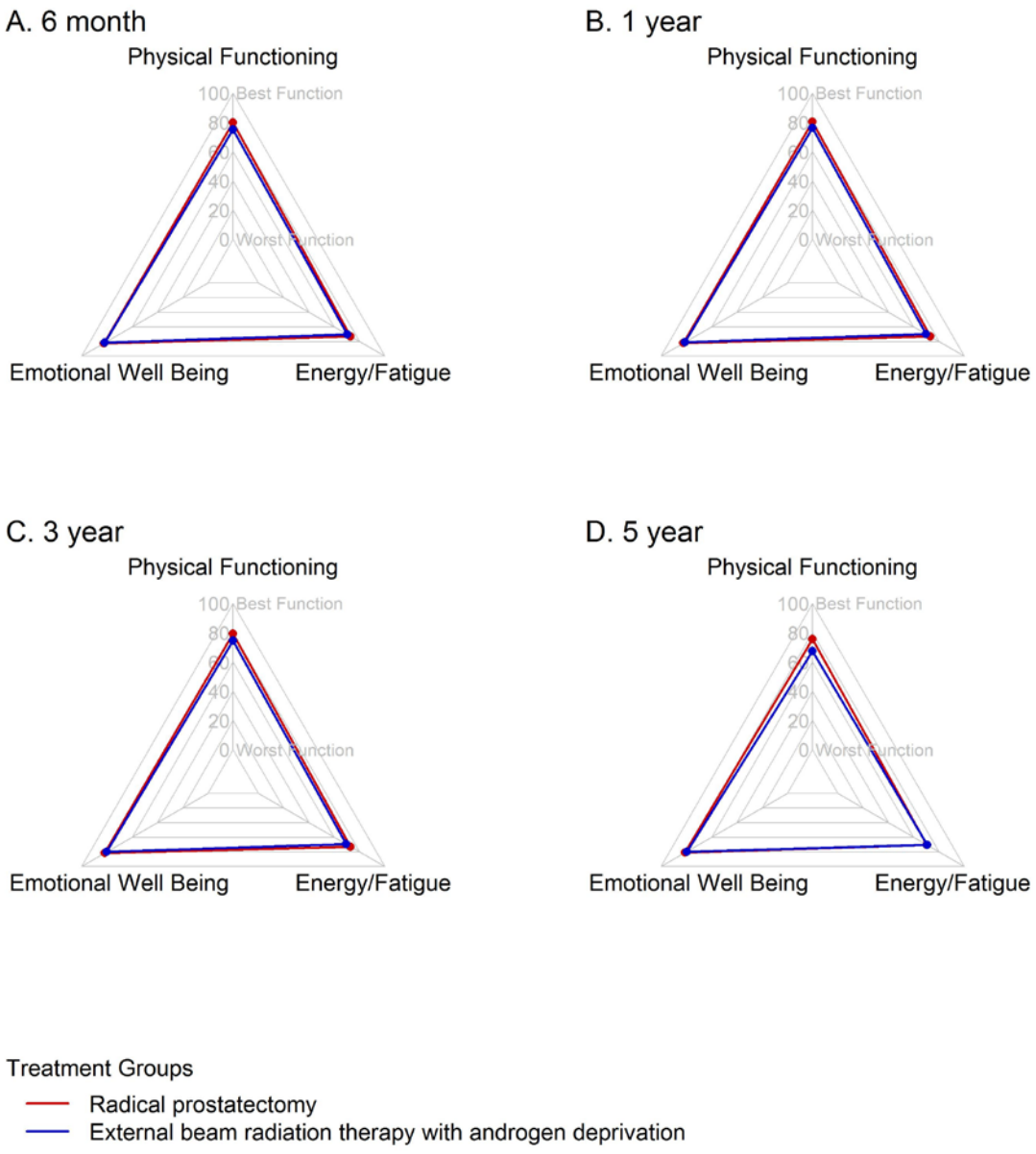
[b]. The effect size in the multivariable model for domain score indicates the adjusted mean point difference between groups at each time point. A minimally important difference in score is estimated as 7 for Physical Function Score, 6 for Emotional Well-Being Score, and 9 for Energy/Fatigue Score. The primary outcome was the difference in domain score at 5 years. All regression models are adjusted for baseline domain score, age, race, comorbidity, prostate cancer risk group, social support, depression, medical decision-making style and accrual site.

eFigure 2. Adjusted general health related quality of life outcomes of favorable-risk patients by treatment and time point.



Legend: Adjusted mean scores on the Medical Outcomes Study Short Form-36 are plotted for each treatment group at (A) 6 months, (B) 1 year, (C) 3 years and (D) 5 years after treatment among men with favorable-risk disease. The center of each figure represents worst function (score of zero), while the outermost line represents best function (score of 100.) The regression models are adjusted for baseline domain score, age, race, comorbidity, cancer characteristics, social support, depression, medical decision-making style and accrual site.

eFigure 3. Adjusted general health related quality of life outcomes of unfavorable-risk patients by treatment and time point.



Legend: Adjusted mean scores on the Medical Outcomes Study Short Form-36 are plotted for each treatment group at (A) 6 months, (B) 1 year, (C) 3 years and (D) 5 years after treatment among men with unfavorable-risk disease. The center of each figure represents worst function (score of zero), while the outermost line represents best function (score of 100.) The regression models are adjusted for baseline domain score, age, race, comorbidity, cancer characteristics, social support, depression, medical decision-making style and accrual site.

Exploratory Analyses of Effect Modification of Covariates

Section 1: Interaction term for Treatment X Baseline Function

For each EPIC-26 domain score multivariable model, we tested the interaction term between treatment and baseline function domain score on the EPIC-26 (excellent vs. less than excellent, defined as baseline domain score >=90 vs. <90 for sexual function and 100 vs <100 for all other domains).

The proportion of patients with excellent baseline function in the sexual function domain was 29.7% in the favorable risk group and 19.0% in the unfavorable risk group; in the urinary incontinence domain was 69.3% in the favorable risk group and 62.6% in the unfavorable risk group; in the urinary irritative domain was 44.9% in the favorable risk group and 39.5% in the unfavorable risk group; in the bowel function domain was 83.6% in the favorable risk group and 74.6% in the unfavorable risk group; and in the hormone function domain was 73.4% in the favorable risk group and 59.3% in the unfavorable risk group.

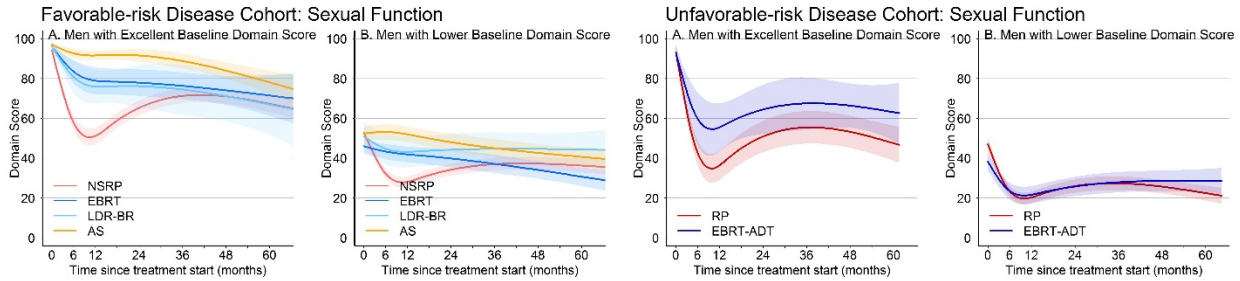
eTable 12. P value for the interaction term (Treatment X Baseline function [excellent vs. lower])

EPIC-26 Domain	Favorable-risk disease cohort	Unfavorable-risk disease cohort
Sexual function	0.008	0.007
Urinary incontinence	0.009	p<.001
Urinary irritative	p<.001	0.03
Bowel function	0.40	0.55
Hormone function	0.64	0.12

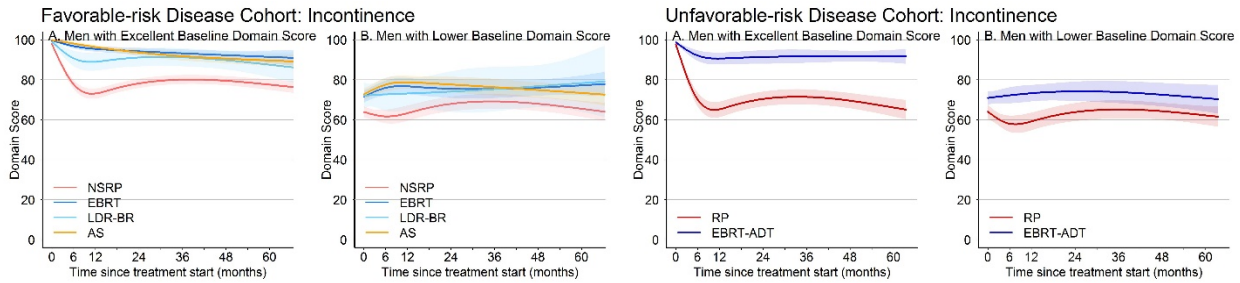
In these exploratory analyses, the interaction term was significant in the models for sexual function, urinary incontinence and urinary irritative function in both favorable-risk and unfavorable risk men (eTable 12). Therefore, we went on to show plots of unadjusted mean disease-specific function over time, stratified by baseline function (eFigure 4). Each figure shows, on the left, unadjusted mean disease-specific function over time reported by men with low and favorable-intermediate risk prostate cancer managed with nerve-sparing radical prostatectomy (NS-RP), external beam radiation therapy (EBRT), brachytherapy (BT), and active surveillance (AS), stratified by baseline function. Shaded regions indicate 95% confidence interval. The right side panels show unadjusted mean disease-specific function over time reported by men with high and unfavorable-intermediate risk prostate cancer managed with radical prostatectomy (RP) and external beam radiation therapy with androgen deprivation therapy (EBRT-ADT), stratified by baseline function. Shaded regions indicate 95% confidence interval.

In general, the figures demonstrate larger differences between groups in men who start with higher baseline function. The exception is in the urinary irritative domain in the favorable risk cohort, in which men treated with prostatectomy experience improvement and men undergoing brachytherapy experience exacerbation of symptoms, and the difference appears larger in the group with poor baseline function.

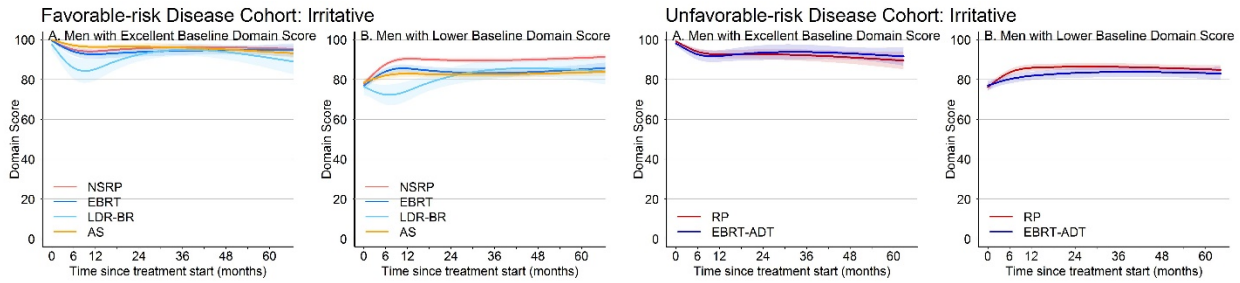
eFigure 4A. Sexual Function Domain Score By Treatment in Men with Favorable-Risk Disease and Unfavorable Risk Disease According to Baseline Sexual Function Domain Score (Excellent >= 90; or Lower < 90)



eFigure 4B. Urinary Incontinence Function Domain Score By Treatment in Men with Favorable-Risk Disease and Unfavorable Risk Disease According to Baseline Urinary Incontinence Function Domain Score (Excellent = 100; or Lower < 100)



eFigure 4C. Urinary Irritative Function Domain Score By Treatment in Men with Favorable-Risk Disease and Unfavorable Risk Disease According to Baseline Urinary Irritative Function Domain Score (Excellent = 100; or Lower < 100)



Section 2: Interaction term for Treatment X Comorbidity Score

For each EPIC-26 domain score multivariable model, we tested the interaction term between treatment and comorbidity score from the Total Illness Burden Index for Prostate Cancer (TIBI-Cap). Scores were categorized as low (0-2, 30.0% favorable risk and 24.3% unfavorable risk), intermediate (3-4, 42.7% favorable risk and 40.0% unfavorable risk) or high (5 or more, 27.3% favorable risk and 35.7% unfavorable risk).

eTable 13. P value for the interaction term (Treatment X Comorbidity score [low, intermediate or high])

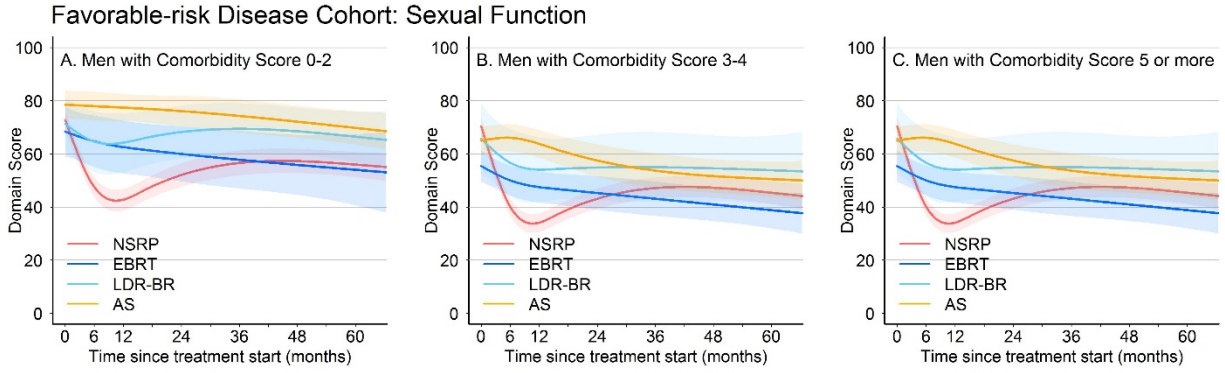
EPIC-26 Domain	Favorable-risk disease cohort	Unfavorable-risk disease cohort
Sexual function	0.04	0.69
Urinary incontinence	0.36	0.90
Urinary irritative	0.27	0.48
Bowel function	0.96	0.28
Hormone function	0.68	0.03

In these exploratory analyses, the interaction term was significant in the models for sexual function in the favorable risk cohort and for hormonal function in the unfavorable risk cohort (eTable 13). Therefore, we went on to show plots of unadjusted mean disease-specific function for these domains over time, stratified by comorbidity level (eFigure 5A, 5B).

eFigure 5A shows unadjusted mean disease-specific sexual function over time reported by men with favorable-risk prostate cancer managed with nerve-sparing radical prostatectomy (NS-RP), external beam radiation therapy (EBRT), brachytherapy (BT), and active surveillance (AS), stratified by comorbidity level. Shaded regions indicate 95% confidence interval.

The figure demonstrates that the relationship between treatment and sexual function outcome is modified by comorbidity level.

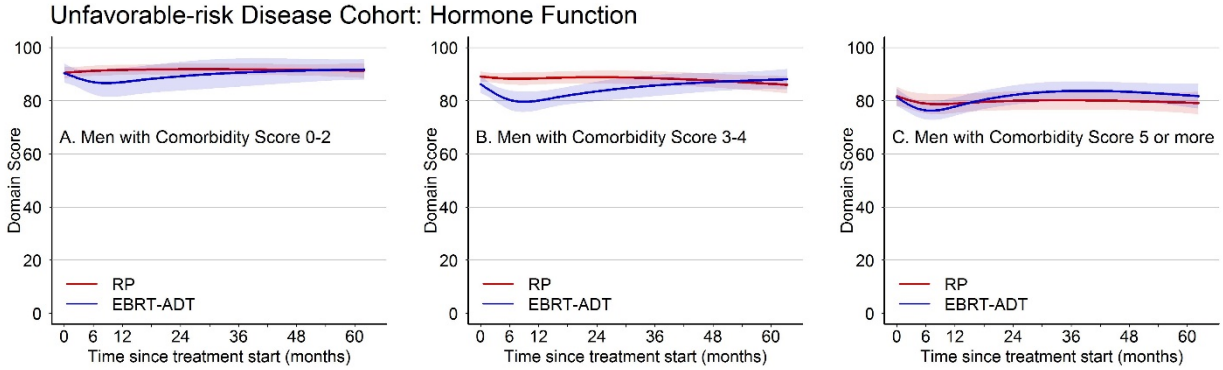
eFigure 5A. Sexual Function Domain Score By Treatment in Men with Favorable-Risk Disease According to Comorbidity Level (Low 0-2, Intermediate 3-4, High >= 5)



eFigure 5B shows unadjusted mean disease-specific hormone function over time reported by men with unfavorable-risk prostate cancer managed with radical prostatectomy (RP) and external beam radiation therapy with androgen deprivation therapy (EBRT-ADT), stratified by comorbidity. Shaded regions indicate 95% confidence interval.

The figure demonstrates that the relationship between treatment and hormone function outcome is modified by comorbidity level.

eFigure 5B. Hormonal Function Domain Score By Treatment in Men with Unfavorable-Risk Disease According to Comorbidity Level (Low 0-2, Intermediate 3-4, High >= 5)



Section 3: Interaction term for Treatment X Disease Risk Stratum

For each EPIC-26 domain score multivariable model, we tested the interaction term between treatment and National Comprehensive Care Network (NCCN) disease risk stratum. The favorable risk disease cohort was comprised of 66% low-risk (PSA < 10 and cT1c or T2a and Biopsy Grade Group 1) and 34% favorable intermediate risk patients (PSA 10-19.9 or cT2b or Biopsy Grade Group 2). The unfavorable risk disease cohort was comprised of 35% unfavorable intermediate-risk (PSA 10-19.9 or cT2b or Biopsy Grade Group 3) and 65% high-risk patients (PSA ≥ 20 or cT2c or higher or Biopsy Grade Group 4 or 5).

eTable 14. P value for the interaction term (Treatment X Disease risk stratum [low or favorable intermediate in the favorable risk disease cohort; unfavorable intermediate or high in the unfavorable disease risk cohort])

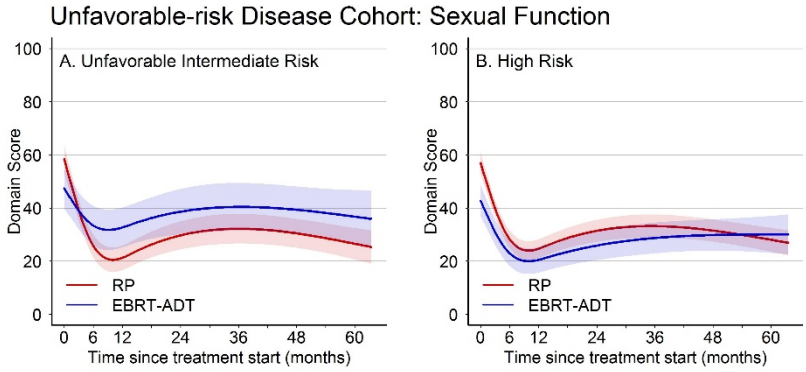
EPIC-26 Domain	Favorable-risk disease cohort	Unfavorable-risk disease cohort
Sexual function	0.64	0.03
Urinary incontinence	0.30	0.66
Urinary irritative	0.15	0.74
Bowel function	0.77	0.12
Hormone function	0.41	0.50

In these exploratory analyses, the interaction term was significant in the model for sexual function in the unfavorable risk cohort (eTable 14). Therefore, we went on to show plots of unadjusted mean disease-specific function for these domains over time, stratified by disease risk stratum (eFigure 6).

eFigure 6 shows unadjusted mean disease-specific function over time reported by men in the unfavorable risk disease cohort managed with radical prostatectomy (RP) and external beam radiation therapy with androgen deprivation therapy (EBRT-ADT), stratified by disease risk stratum (unfavorable intermediate risk and high risk). Shaded regions indicate 95% confidence interval.

eFigure 6 demonstrates that the relationship between treatment and sexual function outcome is modified by NCCN disease risk stratum. Further analysis, controlling for all covariates, showed that radical prostatectomy was associated with clinically significantly worse sexual function compared to patients treated with external beam radiation therapy with androgen deprivation therapy throughout the five-year period for the unfavorable intermediate-risk patients (AMD at 5 years -20.3 [-30.0, -10.5], p<0.001). There was no clinically meaningful difference between radical prostatectomy and external beam radiation therapy with androgen deprivation therapy throughout the five-year period for the high-risk patients (AMD at 5 years -8.4 [-16.5, -0.3], p=0.041).

eFigure 6. Sexual Function Domain Score By Treatment in Men with Unfavorable-Risk Disease According to National Comprehensive Care Network Disease Risk Stratum



Section 4: Interaction term for Treatment X Race

For each EPIC-26 domain score multivariable model, we tested the interaction term between treatment and race (Black vs. non-Black). The favorable risk group was 11% Black and 89% non-Black. The unfavorable risk group was 15% Black and 85% non-Black.

eTable 15. P value for the interaction term (Treatment X Race)

EPIC-26 Domain	Favorable-risk disease cohort	Unfavorable-risk disease cohort
Sexual function	0.47	0.96
Urinary incontinence	0.86	0.72
Urinary irritative	0.50	0.95
Bowel function	0.48	0.07
Hormone function	0.30	0.88

In these exploratory analyses, the interaction term was not significant in any of the models, so no further analyses were performed.