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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Pollack A, Karrison T G, Balogh A G, et al. The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial. *Lancet* 2022; **399:** 1886–1901.

APPENDIX: The addition of androgen deprivation therapy and pelvic lymph node treatment to prostate bed salvage radiotherapy (NRG Oncology/RTOG 0534 SPPORT): an international, multicentre, randomised phase 3 trial, THELANCET-D-20-19617R2

Supplementary Tables and Methods

Supplementary Table S1: Endpoint Considerations From A Pooled Multi-Institutional Analysis of Patients Treated With Salvage Radiotherapy Only (No ADT; n=533) After Prostatectomy.

BECF Definition in mg/mL	% 5/8 yr. Failure	Specificity	Sensitivity	PPV
1. ≥ 0.2	59% / 72%	56%	95%	23%
2. ≥ 0.4	47% / 64%	66%	94%	27%
3. ≥ 1.0	35% / 52%	77%	92%	35%
4. ≥ 2.0	29% / 41%	84%	90%	43%
5. ≥ 0.2+2 rises	42% / 59%	72%	93%	31%
6. ≥ 0.4+2 rises	39% / 57%	74%	93%	32%
7. ≥ 1.0+2 rises	32% / 46%	80%	90%	39%
8. ≥ 2.0+2 rises	29% / 39%	85%	90%	45%
9. 3 consecutive rises (ASTRO)	33% / 36%	82%	90%	40%
10. Nadir+2 (Phoenix)	31% / 40%	83%	91%	43%

BECF = biochemical estimator of clinical failure based on PSA parameters after salvage radiotherapy; PPV = positive predictive value

The data used for this analysis is a subset of that reported by Stephenson AJ, Scardino PT, Kattan MW, et al: Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 25:2035-41, 2007

Supplementary Methods

Inclusion and Exclusion Criteria

Conditions for Patient Eligibility

1. Adenocarcinoma of the prostate treated primarily with radical prostatectomy, pathologically proven to be lymph node negative by pelvic lymphadenectomy (N0) or lymph node status pathologically unknown (undissected pelvic lymph nodes [Nx]), i.e. lymph node dissection is not required;
   - Any type of radical prostatectomy will be permitted, including retropubic, perineal, laparoscopic or robotically assisted. If performed, the number of lymph nodes removed per side of the pelvis and the extent of the pelvic lymph node dissection (obturator vs. extended lymph node dissection) should be noted. There is no time limit for the date of radical prostatectomy.
2. A post-radical prostatectomy entry PSA of ≥ 0.1 and < 2.0 ng/mL at least 6 weeks (45 days) after prostatectomy and within 30 days of registration;
3. One of the following pathologic classifications:
   - T3N0/Nx disease with or without a positive prostatectomy surgical margin; or
   - T2N0/Nx disease with or without a positive prostatectomy surgical margin;

4. Prostatectomy Gleason score of 9 or less;
5. Zubrod Performance Status of 0-1;
6. Age ≥ 18;
7. No distant metastases, based upon the following minimum diagnostic workup:
   - History/physical examination (including digital rectal exam) within 8 weeks (60 days) prior to registration;
   - A CT scan of the pelvis (with contrast if renal function is acceptable; a noncontrast CT is permitted if the patient is not a candidate for contrast) or MRI of the pelvis within 120 days prior to registration;
   - Bone scan within 120 days prior to registration; if the bone scan is suspicious, a plain x-ray and/or MRI must be obtained to rule out metastasis.
8. Adequate bone marrow function, within 90 days prior to registration, defined as follows:
   - Platelets ≥ 100,000 cells/mm^3 based upon CBC;
   - Hemoglobin ≥ 10.0 g/dl based upon CBC (Note: The use of transfusion or other intervention to achieve Hgb ≥ 10.0 g/dl is recommended).
9. AST or ALT < 2 x the upper limit of normal within 90 days prior to registration;
10. Serum total testosterone must be ≥ 40% of the lower limit of normal (LLN) of the assay used (testosterone ÷ LLN must be ≥ 0.40) within 90 days prior to registration (Note: Patients who have had a unilateral orchiectomy are eligible as long as this requirement is met);
11. Patients must sign a study-specific informed consent prior to study entry.

Conditions for Patient Ineligibility

1. A palpable prostatic fossa abnormality/mass suggestive of recurrence, unless shown by biopsy under ultrasound guidance not to contain cancer;
2. N1 patients are ineligible, as are those with pelvic lymph node enlargement ≥ 1.5 cm in greatest dimension by CT scan or MRI of the pelvis, unless the enlarged lymph node is sampled and is negative;
3. Androgen deprivation therapy started prior to prostatectomy for > 6 months (180 days) duration. Note: The use of finasteride or dutasteride (±tamsulosin) for longer periods prior to prostatectomy is acceptable;
4. Androgen deprivation therapy started after prostatectomy and prior to registration (Note: The use of finasteride or dutasteride (±tamsulosin) after prostatectomy is not acceptable - must be stopped within 3 months after prostatectomy. Androgen deprivation therapy must be stopped within 3 months after prostatectomy);
5. Neoadjuvant chemotherapy before or after prostatectomy;
6. Prior chemotherapy for any other disease site if given within 5 years prior to registration;
7. Prior cryosurgery or brachytherapy of the prostate; prostatectomy should be the primary treatment and not a salvage procedure;
8. Prior pelvic radiotherapy;
0. Prior invasive malignancy (except non-melanomatous skin cancer) or superficial bladder cancer unless disease free for a minimum of 5 years [for example, carcinoma *in situ* of the oral cavity is permissible];
9. Severe, active co-morbidity, defined as follows:
   - History of inflammatory bowel disease;
   - History of hepatitis B or C; Blood tests are not required to determine if the patient has had hepatitis B or C, unless the patient reports a history of hepatitis.
   - Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
   - Transmural myocardial infarction within the last 6 months;
   - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
   - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
   - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; AST or ALT are required; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.

- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; Note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may result in increased toxicity and immunosuppression.
- Prior allergic reaction to the study drug(s) involved in this protocol.

Prostatic Fossa Clinical Target Volume (CTVp)

1) Superiorly: The CTVp should extend superiorly to the level of the caudal vas deferens remnant. In some cases, the vas deferens remnant may be difficult to visualize. In the absence of gross disease or seminal vesicle remnants, the superior limit of the CTVp should extend at least 2 cm and need not extend more than 3-4 cm above the level of the pubic symphysis. The consensus definition calls for "inclusion of the seminal vesicle remnants, if present, in the CTVp if there is pathologic evidence of their involvement. However, inclusion of any seminal vesicle remnants seen is recommended.

2) Inferiorly: The CTVp should extend inferiorly to > 8-12 mm inferior to vesicourethral anastomosis (VUA). With axial CT imaging, the VUA can often be seen in the retropubic region as one slice below the most inferior urine-containing image (the bladder must be modestly full). Magnetic resonance (MR) imaging defines this landmark more clearly with the hyperintense urine signal on T2 images. Inferiorly, the border of the CTVp should be at least 8-12 mm below the VUA. A sagittal reconstruction facilitates identification of the position of the VUA and the inferior border of the CTVp below it. If visualization of the VUA is problematic due to image quality or surgical clip artifacts, the inferior limit of the CTVp can extend to a level just above the penile bulb (same border as described above). It should be noted that there was considerable discussion about this definition versus extending the inferior border of the CTVp to just above the penile bulb; both definitions were deemed acceptable.

3) Anteriorly: Below the superior border of the pubic symphysis, the anterior border is at the posterior aspect of the pubis. The CTVp extends posteriorly to the rectum where it may be concave at the level of the VUA. At this level the lateral border extends to the levator ani. Above the pubic symphysis the anterior border should encompass the posterior 1-2 cm of the bladder wall at the minimum and posteriorly it is bounded by the mesorectal fascia. At this level the lateral border is the sacrorectogenitopubic fascia. This is not well-defined in textbooks. If in question, the lateral border should extend to the obturator internus muscle.

4) Posteriorly: The CTVp extends posteriorly to the anterior rectal wall, but may be somewhat concave around the anterior-lateral aspect of the rectum to adequately encompass the prostate bed.

Planning Target Volumes (PTVs)

PTVp (prostate bed PTV)

The PTVp margins around the prostate bed Clinical Target Volume (CTVp) were defined to be a minimum of 0.8 cm and a maximum of 1.5 cm in all dimensions. A reduction of the PTVp margin from 0.8 cm to ≥ 0.6 cm to minimize rectal exposure was considered a variation acceptable. A posterior margin of < 0.6 cm was considered an unacceptable deviation. A margin for penumbra for 3D-CRT, usually 0.5–0.7 cm beyond the PTVp was added such that ≥ 95% of the PTVp received the prescribed dose (64.8-70.2 Gy); an acceptable variation was considered if < 95% to 90% of the PTVp received the prescribed dose, and an unacceptable deviation was noted if < 90% of the PTVp received the prescribed dose. At least 95% of the PTVp should have received the prescribed dose (64.8-70.2 Gy); a variation acceptable was noted if < 95% to 90% of the PTVp received the prescribed dose, and a deviation unacceptable was noted if < 90% of the PTVp received the prescribed dose. The planned dose, between 64.8 to 70.2, was declared after the patient was planned and all dosimetric parameters finalized.

PTVn (pelvic lymph node PTV)

The PTVn margin around the CTVn was the same as that described for the PTVp. The PTVn was to receive 45 Gy at 1.8 Gy per fraction during the first 25 fractions, along with the PTVp. A composite plan should be generated showing that at least 95% of the PTVn and PTVp receive the prescribed dose; a variation acceptable will be noted if < 95% to 90% of the PTV(s) receives the prescribed dose, and a deviation unacceptable will be noted if < 90% of the PTV(s) receives the prescribed dose.

Interim Analyses

A group sequential test with three planned interim analyses was specified. The interim analyses were to be carried out when cumulative accrual and follow-up targets (enrolled patients whose follow-up was at least 5 years from the randomization date) were met (Supplementary Table S2). At each planned interim analysis, the p-value from Z-test statistics for the difference between the five-year FFP rates assessing treatment efficacy or futility were compared to the nominal significance level. The nominal significance level of 0.001 (one-sided), which is similar to the Haybittle-Peto test (Peto et al., 1976), was chosen for efficacy testing. For the futility testing boundary, Rule C in Freidlin and Korn (2002) was used.

For efficacy testing, the following procedure was specified. Arm 3 is first compared with Arm 2 and the arm that has the higher observed FFP rate is chosen. Let p1, p2, and p3 equal the observed rate of 5-year FFP in Arm 1, Arm 2 and Arm 3, respectively.

1) If Arm 2 is better than Arm 3 ($p2 \geq p3$), Arm 2 is compared with Arm 1. The following hypothesis is tested:

$H_{01}: p2 \leq p1$ vs. $H_{A1}: p2 > p1$.

If H_{01} is rejected ($p \leq 0.001$), then we would conclude that the 5-year FFP of Arm 2 is better than Arm 1. We report that Arm 2 is better than arm 1 and stop accrual to arm 1 if applicable. If H_{01} is not rejected (p-value > 0.001), then we continue the trial and proceed to the next interim analysis without any results reporting. With respect to interim evaluation of Arm 2 vs. Arm 3, if H_{01} is rejected, the following hypothesis is tested:

$H_{02}: p2 \leq p3$ vs. $H_{A2}: p2 > p3$.

If H_{02} is rejected (p-value < 0.001), then Arm 2 is declared best and the complete trial results (superior arm identified) are reported. If H_{02} is not rejected (p-value > 0.001), then we continue the trial to the next interim analysis to evaluate Arm 2 vs. Arm 3.

2) If Arm 3 is better than Arm 2 ($p2 < p3$), then we compare Arm 3 with Arm 1. The following hypothesis is tested:

$H_{03}: p3 \leq p1$ vs. $H_{A3}: p3 > p1$.

If H_{03} is rejected (p-value $\leq$ 0.001), then we conclude that the 5-year FFP of Arm 3 is better than Arm 1. We report that Arm 3 is better than arm 1 and stop accrual to arm 1 if applicable. If H_{03} is not rejected (p-value > 0.001), then we continue the trial and proceed to the next interim analysis without any results reporting. With respect to interim evaluation of Arm 2 vs. Arm 3, if H_{03} is rejected, then the following hypothesis is tested.

$H_{04}: p3 \leq p2$ vs. $H_{A4}: p3 > p2$.

If H_{04} is rejected (p-value < 0.001), then Arm 3 is declared best and the complete trial results (superior arm identified) are reported. If H_{04} is not rejected (p-value > 0.001), then we continue the trial to the next interim analysis to evaluate Arm 2 vs. Arm 3.

For futility testing, we compare Arm 3 vs. Arm 1 and Arm 2 vs. Arm 1 if applicable. The following hypotheses are tested:

$H_{05}: p_1 \geq p_2$ vs. $H_{A5}: p_1 < p_2$ and $H_{06}: p_1 \geq p_3$ vs. $H_{A6}: p_1 < p_3$.

The alternative hypotheses, H_{A5} ($p2 = p1 + 0.1$) and H_{A6} ($p3 = p1 + 0.1$) will be tested at the 0.001 level (the futility nominal significance level). If the computed p-value is less than 0.001 then we consider stopping the trial in favor of H_{05} or H_{06} and report the results.

As described in the main text, the Arm 3 vs. Arm 1 efficacy boundary was crossed at the third interim analysis, and the DMC recommended reporting the full results of the trial.

Supplementary Table S2. Schedule for the Planned Interim Analysis

Information Time	Estimated Analysis Time*	Cumulative Accrual in the Three Arms**
0.25	7 years	397
0.50	9 years	794
0.75	11 years	1191
1.0	13 years	1587

* Time to the interim analysis from the first patient entry

**The number of eligible patients whose follow-up is at least 5 years from the randomization date

Secondary Endpoints and Post-Hoc Analyses

Secondary endpoints included local failure, regional failure, distant metastases, biochemical failure using an alternative definition (PSA $\geq$ 0.4 and a second rise above nadir or start of second salvage therapy), castrate resistant disease (three rises in PSA after the start of second salvage hormone therapy), prostate cancer cause-specific mortality, overall survival, and quality of life, and toxicity. Two post-hoc endpoints were also evaluated, namely, metastasis-free survival and time to initiation of ADT salvage therapy. While cumulative incidence curves are presented for the secondary endpoints (with the exception of overall survival), they were analyzed in terms of the cause-specific hazard rate (Freidlin and Korn, 2005*) using logrank tests and Cox regression modeling in which patients who died prior to the event of interest (or who died from non-prostate cancer in the case of cause-specific mortality) were censored as of the time of death. Of note, for the secondary endpoints patients who received salvage treatment prior to the event were not censored. Chi-square tests and logistic regression analyses were performed to compare the treatment groups with respect to acute (within 90 days of completion of RT) and late (more than 90 days) toxicity. As mentioned above, quality of life measures will be analyzed in a separate report. All patients are included in the analyses with the exception of those found to have been ineligible (modified intent-to-treat). To adjust for multiple comparisons, the protocol stipulated that the one-sided p-value for secondary endpoints (with the exception of toxicity) should be <0.0125 to declare statistical significance and that 97.5% confidence intervals be reported. The significance level for toxicity was 1p<0.025.

*Freidlin B, Korn EL. Testing treatment effects in the presence of competing risks. *Stat Med*. 24:1703-1712, 2005.

Supplementary Table S3: Treatment Compliance
A: Radiation Therapy Delivery, Central Review of All Eligible Patients

	PBRT Alone (n=564)		PBRT+STADT (n=578)		PLNRT+PBRT+STADT (n=574)		Total (n=1716)	
	n	%	n	%	n	%	n	%
Total Dose	(n=564)		(n=578)		(n=574)		(n=1716)	
N/A	1	0.2	3	0.5	3	0.5	7	0.4
Per Protocol	548	97.2	559	96.7	564	98.3	1671	97.4
Variation Acceptable	0	0.0	1	0.2	0	0.0	1	0.1
Deviation Unacceptable	0	0.0	2	0.3	0	0.0	2	0.1
Not evaluable	15	2.7	13	2.2	7	1.2	35	2.0
Fractionation	(n=564)		(n=578)		(n=574)		(n=1716)	
N/A	1	0.2	3	0.5	3	0.5	7	0.4
Per Protocol	541	95.9	556	96.2	557	97.0	1654	96.4
Variation Acceptable	4	0.7	2	0.3	3	0.5	9	0.5
Deviation Unacceptable	3	0.5	4	0.7	4	0.7	11	0.6
Not evaluable	15	2.7	13	2.2	7	1.2	35	2.0
Elapsed Days	(n=564)		(n=578)		(n=574)		(n=1716)	
N/A	1	0.2	3	0.5	3	0.5	7	0.4
Per Protocol	544	96.5	559	96.7	560	97.6	1663	96.9
Variation Acceptable	3	0.5	2	0.3	4	0.7	9	0.5
Deviation Unacceptable	1	0.2	1	0.2	0	0.0	2	0.1
Not evaluable	15	2.7	13	2.2	7	1.2	35	2.0
Target Volume / Organs at Risk	(n=564)		(n=578)		(n=574)		(n=1716)	
N/A	0	0.0	1	0.2	2	0.3	3	0.2
Per Protocol	198	35.1	197	34.1	153	26.7	548	31.9
Variation Acceptable	318	56.4	330	57.1	366	63.8	1014	59.1
Deviation Unacceptable	27	4.8	30	5.2	41	7.1	98	5.7
Not evaluable	21	3.7	20	3.5	12	2.1	53	3.1
Overall	(n=564)		(n=578)		(n=574)		(n=1716)	
Per Protocol	472	83.7	485	83.9	459	80.0	1416	82.5
Variation-Acceptable	60	10.6	59	10.2	82	14.3	201	11.7
Deviation-Unacceptable	12	2.1	12	2.1	18	3.1	42	2.4
Incomplete RT - Refused	0	0.0	2	0.3	1	0.2	3	0.2
No RT given	2	0.4	4	0.7	3	0.5	9	0.5

Supplementary Table S3: Treatment Compliance
A: Radiation Therapy Delivery, Central Review of All Eligible Patients

	PBRT Alone (n=564)		PBRT+STADT (n=578)		PLNRT+PBRT+STADT (n=574)		Total (n=1716)	
	n	%	n	%	n	%	n	%
Not Evaluable	18	3.2	16	2.8	11	1.9	45	2.6

STADT = Short Term Androgen Deprivation Therapy.

Supplementary Table S3: Treatment Compliance
B. Anti-Androgen Component of Androgen Deprivation Therapy, Central Review of Sampled Eligible Patients

	PBRT+STADT (n=258)		PLNRT+PBRT+STADT (n=255)		Total (n=513)	
	n	%	n	%	n	%
Dose						
80-120%	189	73.3	208	81.6	397	77.4
< 80%, due to protocol-specified reasons	7	2.7	12	4.7	19	3.7
< 80%, due to non-protocol-specified reasons*	15	5.8	13	5.1	28	5.5
> 120%*	38	14.7	15	5.9	53	10.3
No Treatment	9	3.5	7	2.7	16	3.1
Treatment delay						
No delays	246	95.3	247	96.9	493	96.1
< 2 weeks	1	0.4	1	0.4	2	0.4
> 2 weeks delay, due to non-protocol-specified reasons*	2	0.8	0	0.0	2	0.4
No Treatment	9	3.5	7	2.7	16	3.1
Overall score						
Per Protocol	195	75.6	220	86.3	415	80.9
Unacceptable Deviation	54	20.9	28	11.0	82	16.0
No Treatment	9	3.5	7	2.7	16	3.1

*Unacceptable Deviation
STADT = Short Term Androgen Deprivation Therapy.

Supplementary Table S3: Treatment Compliance
C. LHRH Targeted Component of Androgen Deprivation Therapy, Central Review of Sampled Eligible Patients

	PBRT+STADT (n=258)		PLNRT+PBRT+STADT (n=255)		Total (n=513)	
	n	%	n	%	n	%
Dose						
80-120%	223	86.4	225	88.2	448	87.3
< 80%, due to protocol-specified reasons	1	0.4	2	0.8	3	0.6
< 80%, due to non-protocol-specified reasons*	16	6.2	8	3.1	24	4.7
> 120%*	11	4.3	13	5.1	24	4.7
Wrong drug/agent given*	0	0.0	1	0.4	1	0.2
No Treatment	7	2.7	6	2.4	13	2.5
Treatment delay						
No delays	249	96.5	249	97.6	498	97.1
> 2 weeks delay, due to non-protocol-specified reasons*	2	0.8	0	0.0	2	0.4
No Treatment	7	2.7	6	2.4	13	2.5
Overall score						
Per Protocol	223	86.4	227	89.0	450	87.7
Unacceptable Deviation	28	10.9	22	8.6	50	9.7
No Treatment	7	2.7	6	2.4	13	2.5

*Unacceptable Deviation
STADT = Short Term Androgen Deprivation Therapy.

Supplementary Table S4: Treatment Delivery
A: Radiation Therapy Delivery, Site Reported for All Eligible Patients

	PBRTAlone (n=564)		PBRT+STADT (n=578)		PLNRT+PBRT+STADT (n=574)		Total (n=1716)	
	n	%	n	%	n	%	n	%
Type of RT Administered	(n=548)		(n=562)		(n=563)		(n=1673)	
3D Conformal	70	12.8	68	12.1	76	13.5	214	12.8
IMRT	478	87.2	494	87.9	487	86.5	1459	87.2
Number of Fractions	(n=548)		(n=562)		(n=563)		(n=1673)	
<36	10	1.8	8	1.4	8	1.4	26	1.6
36	105	19.2	95	16.9	138	24.5	338	20.2
37	142	25.9	153	27.2	147	26.1	442	26.4
38	134	24.5	135	24.0	132	23.4	401	24.0
39	157	28.6	171	30.4	138	24.5	466	27.9
Total Dose to 95% PTV (Gy)	(n=548)		(n=562)		(n=563)		(n=1673)	
Median	68.4		68.4		66.6		68.4	
Min - Max	62.8 - 70.8		5.4 - 70.2		1.8 - 70.2		1.8 - 70.8	
Q1 - Q3	66.6 - 70.2		66.6 - 70.2		66.0 - 68.4		66.6 - 70.2	
RT terminated early	(n=3)	0.5	(n=6)	1.0	(n=11)	1.9	(n=20)	1.2
Reason:								
Toxicity	0		1		0		1	
Patient refusal prior to beginning protocol therapy	1		1		0		2	
Patient withdrawal or refusal after beginning protocol therapy	0		2		1		3	
Alternative treatment given	0		0		1		1	
Other complicating disease	1		0		1		2	
Other*	1		2		8		11	

*Other reasons include machine problems, patient not feeling well, no shows, or transportation issues.

STADT = Short Term Androgen Deprivation Therapy.

Supplementary Table S4: Treatment Delivery
B: Anti-Androgen (AA) Delivery, Site Reported for All Eligible Patients on Androgen Deprivation Therapy Arms

	PBRT+STADT (n=578)		PLNRT+PBRT+STADT (n=574)		Total (n=1152)	
	n	%	n	%	n	%
Received AA	(n=578)		(n=574)		(n=1152)	
No	22	3.8	18	3.1	40	3.5
Yes	556	96.2	556	96.9	1112	96.5
Reason AA not received	(n=22)		(n=18)		(n=40)	
Patient refusal prior to Tx start	2	9.1	3	16.7	5	12.5
Other	1	4.5	1	5.6	2	5.0
Missing/Unknown	19	86.4	14	77.8	33	82.5
AA Duration* (months)	(n=548)		(n=550)		(n=1098)	
Median	3.9		3.9		3.9	
Min - Max	0.3 - 8.7		0.1 - 6.9		0.1 - 8.7	
Q1 - Q3	3.6 - 4.1		3.7 - 4.1		3.7 - 4.1	
Reason AA Terminated Early	(n=556)		(n=556)		(n=1112)	
Not applicable	491	88.3	492	88.5	983	88.4
Toxicity	27	4.9	25	4.5	52	4.7
Death	0	0.0	1	0.2	1	0.1
Patient withdrawal or refusal	3	0.5	2	0.4	5	0.4
Other complicating disease	2	0.4	1	0.2	3	0.3
Other	26	4.7	30	5.4	56	5.0
Missing/Unknown	7	1.3	5	0.9	12	1.1

*Patients who received drug but do not have a duration have incomplete treatment data.

STADT = Short Term Androgen Deprivation Therapy.

Supplementary Table S4: Treatment Delivery
C. LHRH Targeted Treatment Delivery Summary, Site Reported for All Eligible Patients on the Androgen Deprivation Therapy Arms

	PBRT+STADT (n=578)		PLNRT+PBRT+STADT (n=574)		Total (n=1152)	
	n	%	n	%	n	%
Received LHRH	(n=578)		(n=574)		(n=1152)	
No	18	3.1	18	3.1	36	3.1
Yes	560	96.9	556	96.9	1116	96.9
Reason LHRH not received	(n=18)		(n=18)		(n=36)	
Patient refusal prior to beginning protocol therapy	2	11.1	4	22.2	6	16.7
Missing/Unknown	16	88.9	14	77.8	30	83.3
LHRH duration* (months)	(n=555)		(n=549)		(n=1104)	
1-3	15	2.7	8	1.5	23	2.1
4	180	32.4	170	31.0	350	31.7
5	9	1.6	10	1.8	19	1.7
6	332	59.8	348	63.4	680	61.6
7-8	12	2.2	8	1.5	20	1.8
9-12	7	1.3	5	0.9	12	1.1
LHRH Termination Reason	(n=560)		(n=556)		(n=1116)	
Not applicable	534	95.4	529	95.1	1063	95.3
Toxicity	2	0.4	4	0.7	6	0.5
Death	0	0.0	1	0.2	1	0.1
Patient withdrawal or refusal after beginning protocol therapy	2	0.4	1	0.2	3	0.3
Alternative treatment given	1	0.2	0	0.0	1	0.1
Other	11	2.0	10	1.8	21	1.9
Missing/Unknown	10	1.8	11	2.0	21	1.9

*Patients who received drug but do not have a duration have incomplete treatment data.
STADT = Short Term Androgen Deprivation Therapy.

Supplementary Table S5: Cause of Death for All Eligible Patients

	PBRT Alone (n=69)	PBRT+STADT (n=63)	PLNRT+PBRT+STADT (n=69)	Total (n=201)
Death due to prostate cancer	36 (52.2%)	29 (46.0%)	21 (30.4%)	86 (42.8%)
Centrally certified	28 (40.6%)	21 (33.3%)	14 (20.3%)	63 (31.3%)
Following clinical or biochemical progression	8 (11.6%)	8 (12.7%)	7 (10.1%)	23 (11.4%)
Death due to other causes	33 (47.8%)	30 (47.6%)	47 (68.1%)	110 (54.7%)
Unknown	0 (0.0%)	4 (6.3%)	1 (1.4%)	5 (2.5%)

STADT = Short Term Androgen Deprivation Therapy.

Supplementary Table S6: Univariate and Multivariable Cox Regression Analyses – Time to Second Salvage Therapy by PSA at Entry

Endpoint	#Events/n	Comparison	Unadjusted HR and CI[1]	p-value[2]	Adjusted HR and CI[1]	p-value[3]
Time to 2nd Salvage ADT	Arm1: 62/293	Arm 3 vs. Arm 1	0.32 (0.18-0.55)	<0.001	0.29 (0.17, 0.51)	<0.001
PSA≤0.35	Arm2: 35/264	Arm 2 vs. Arm 1	0.58 (0.36-0.93)	0.005	0.60 (0.37, 0.96)	0.007
	Arm3: 23/301	Arm 3 vs. Arm 2	0.53 (0.29-0.96)	0.007	0.49 (0.27, 0.90)	0.004
Time to 2nd Salvage ADT	Arm1: 95/271	Arm 3 vs. Arm 1	0.38 (0.25-0.57)	<0.001	0.36 (0.24, 0.54)	<0.001
PSA>0.35	Arm2: 74/314	Arm 2 vs. Arm 1	0.59 (0.42-0.84)	<0.001	0.54 (0.38, 0.77)	<0.001
	Arm3: 45/273	Arm 3 vs. Arm 2	0.64 (0.42-0.98)	0.009	0.67 (0.44, 1.02)	0.016

Arm 1: PBRT Alone; Arm 2: PBRT+NC-STADT; Arm 3: PLNRT+PBRT+NC-STADT

[1] 97.5% confidence interval, adjusted for PSA, stage, SV involvement, Gleason score, age, and race.

[2] One-sided logrank test.

[3] One-sided Wald test.

Supplementary Table S7: Patterns of Failure by Treatment Arm

	PBRT Alone (n=103)		PBRT+STADT (n=71)		PLNRT+PBRT +STADT (n=49)		Total (n=223)	
Recurrence	**n**	**%**	**n**	**%**	**n**	**%**	**Total**	**%**
Local only	13	12.6	4	5.6	2	4.1	19	8.5
Regional only	19	18.4	11	15.5	6	12.2	36	16.1
Distant only	42	40.8	39	54.9	31	63.3	112	50.2
Local, Distant	7	6.8	6	8.5	3	6.1	16	7.2
Local, Regional	2	1.9	0	0.0	0	0.0	2	0.9
Regional, Distant	16	15.5	9	12.7	4	8.2	29	13.0
Local, Regional, Distant	4	3.9	2	2.8	3	6.1	9	4.0

STADT = Short Term Androgen Deprivation Therapy.

Supplementary Table S8: 5-Year Survival or Cumulative Incidence Rates for Primary and Secondary Endpoints

Endpoint	PBRT Alone	PBRT+STADT	PLNRT+PBRT+STADT
Freedom from Progression	70.9% (67.0%, 74.9%)	81.3% (78.0%, 84.6%)	87.4% (84.7%, 90.2%)
Distant Metastases	8.5% (6.3%, 11.1%)	6.1% (4.3%, 8.3%)	4.5% (3.0%, 6.5%)
Prostate Cancer Death	2.9% (1.7%, 4.6%)	0.9% (0.4%, 2.1%)	0.7% (0.2%, 1.8%)
Overall Survival	93.5% (91.4%, 95.6%)	96.1% (94.5%, 97.7%)	95.8% (94.2%, 97.5%)
Biochemical Failure (Phoenix)	20.3% (17.0%, 23.8%)	14.0% (11.2%, 17.0%)	8.3% (6.2%, 10.8%)
Alternative (Secondary) Biochemical Failure*	31.0% (27.1%, 34.9%)	21.0% (17.7%, 24.5%)	12.8% (10.2%, 15.8%)
Time to 2nd Salvage ADT	22.2% (18.7%, 25.8%)	14.5% (11.7%, 17.7%)	7.9% (5.9%, 10.4%)
Castrate Resistant Disease**	2.9% (1.7%, 4.6%)	2.1% (1.1%, 3.6%)	1.1% (0.5%, 2.3%)
Local Failure	3.2% (1.9%, 4.9%)	1.5% (0.7%, 2.8%)	0.4% (0.1%, 1.2%)
Regional Failure	4.7% (3.1%, 6.8%)	2.2% (1.2%, 3.7%)	0.7% (0.2%, 1.7%)
Distant Metastases-Free Survival	87.5% (84.7%, 90.3%)	91.4% (89.0%, 93.7%)	91.9% (89.6%, 94.1%)

* PSA > 0.4 and a second rise above nadir or start of second salvage therapy
**Three rises in PSA after institution of salvage hormone therapy
STADT = Short Term Androgen Deprivation Therapy

Supplementary Table S9: Acute* Adverse Events without Regard to Attribution
Adverse Event Categories of Interest
Distribution of Patients by Highest Grade Acute Adverse Event and by
Specific Adverse Event Term Within Blood/Bone Marrow, GI, Renal GU System Organ Class

Category/Term	PBRT Alone (n=547)†					PBRT+STADT (n=563)†					PLNRT+PBRT+STADT (n=563)†				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
BLOOD/BONE MARROW	16 (2.9)	9 (1.6)	3 (0.5)	0 (0.0)	0 (0.0)	49 (8.7)	9 (1.6)	1 (0.2)	0 (0.0)	0 (0.0)	35 (6.2)	14 (2.5)	15 (2.7)	0 (0.0)	0 (0.0)
Blood disorder	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	7 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CD4 lymphocytes decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin decreased	11 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	44 (7.8)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	39 (6.9)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hemolysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	13 (2.4)	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	12 (2.1)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	13 (2.3)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphopenia	2 (0.4)	7 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	7 (1.2)	12 (2.1)	15 (2.7)	0 (0.0)	0 (0.0)
Neutrophil count decreased	2 (0.4)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count decreased	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
GASTROINTESTINAL	78 (14.3)	10 (1.8)	1 (0.2)	0 (0.0)	0 (0.0)	92 (16.3)	17 (3.0)	5 (0.9)	0 (0.0)	0 (0.0)	144 (25.6)	34 (6.0)	4 (0.7)	0 (0.0)	0 (0.0)
Abdominal distension	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Anal exam abnormal	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anal fistula	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anal mucositis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	12	1	0	0	0	22	4	0	0	0	19	2	1	0	0

Supplementary Table S9: Acute* Adverse Events without Regard to Attribution
Adverse Event Categories of Interest
Distribution of Patients by Highest Grade Acute Adverse Event and by
Specific Adverse Event Term Within Blood/Bone Marrow, GI, Renal GU System Organ Class

Category/Term	PBRT Alone (n=547)†					PBRT+STADT (n=563)†					PLNRT+PBRT+STADT (n=563)†				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
	(2.2)	(0.2)	(0.0)	(0.0)	(0.0)	(3.9)	(0.7)	(0.0)	(0.0)	(0.0)	(3.4)	(0.4)	(0.2)	(0.0)	(0.0)
Dehydration	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	46 (8.4)	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	59 (10.5)	8 (1.4)	3 (0.5)	0 (0.0)	0 (0.0)	119 (21.1)	16 (2.8)	2 (0.4)	0 (0.0)	0 (0.0)
Dry mouth	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Enteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Esophageal mucositis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Esophagitis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fecal incontinence	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorder	8 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.4)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	15 (2.7)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hemorrhoids	3 (0.5)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.1)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.6)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Mucositis oral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.6)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	15 (2.7)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Proctitis	22 (4.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.6)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	18 (3.2)	6 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal anastomotic leak	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Category/Term	PBRT Alone (n=547)†					PBRT+STADT (n=563)†					PLNRT+PBRT+STADT (n=563)†				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Rectal mucositis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Small intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Taste alteration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
RENAL/GENITOURINARY	82 (15.0)	44 (8.0)	5 (0.9)	0 (0.0)	0 (0.0)	129 (22.9)	63 (11.2)	5 (0.9)	0 (0.0)	0 (0.0)	144 (25.6)	59 (10.5)	6 (1.1)	2 (0.4)	0 (0.0)
Bladder spasm	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cystitis	3 (0.5)	8 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.1)	7 (1.2)	1 (0.2)	0 (0.0)	0 (0.0)	6 (1.1)	7 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Prostatic disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Ureteric anastomotic leak	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ureteric obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ureteric perforation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urethral obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Urethral stricture	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary frequency	72 (13.2)	28 (5.1)	2 (0.4)	0 (0.0)	0 (0.0)	116 (20.6)	41 (7.3)	2 (0.4)	0 (0.0)	0 (0.0)	127 (22.6)	43 (7.6)	4 (0.7)	0 (0.0)	0 (0.0)
Urinary incontinence	13 (2.4)	15 (2.7)	1 (0.2)	0 (0.0)	0 (0.0)	27 (4.8)	26 (4.6)	0 (0.0)	0 (0.0)	0 (0.0)	31 (5.5)	11 (2.0)	1 (0.2)	2 (0.4)	0 (0.0)
Urinary retention	10	5	0	0	0	13	3	1	0	0	11	3	0	0	0

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Category/Term	PBRT Alone (n=547)†					PBRT+STADT (n=563)†					PLNRT+PBRT+STADT (n=563)†				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
	(1.8)	(0.9)	(0.0)	(0.0)	(0.0)	(2.3)	(0.5)	(0.2)	(0.0)	(0.0)	(2.0)	(0.5)	(0.0)	(0.0)	(0.0)
Urogenital disorder	18	4	1	0	0	17	1	1	0	0	22	7	1	0	0
	(3.3)	(0.7)	(0.2)	(0.0)	(0.0)	(3.0)	(0.2)	(0.2)	(0.0)	(0.0)	(3.9)	(1.2)	(0.2)	(0.0)	(0.0)

Adverse events were graded with CTCAE version 3.0.

*Acute: ≤ 90 days after End of Radiation Therapy or No Radiation Therapy Received

†17, 15, and 11 patients from PBRT Alone, PBRT+STADT, and PLNRT+PBRT+STADT arms, respectively, who received no treatment or for whom no acute AE information was provided are excluded.

Supplementary Table S10: Late* Adverse Events without Regard to Attribution
Adverse Event Categories of Interest
Distribution of Patients by Highest Grade Adverse Event and by Specific Adverse Event Term

Category/Term	PBRT Alone (n=545)[a]					PBRT+STADT (n=559)[b]					PLNRT+PBRT+STADT (n=562)[c]				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
BLOOD/BONE MARROW	39 (7.2)	17 (3.1)	1 (0.2)	2 (0.4)	0 (0.0)	51 (9.1)	8 (1.4)	2 (0.4)	0 (0.0)	0 (0.0)	48 (8.5)	18 (3.2)	5 (0.9)	2 (0.4)	0 (0.0)
Blood disorder	5 (0.9)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
CD4 lymphocytes decreased	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin decreased	20 (3.7)	4 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	43 (7.7)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	50 (8.9)	3 (0.5)	1 (0.2)	1 (0.2)	0 (0.0)
Hemolysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	19 (3.5)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	15 (2.7)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	19 (3.4)	8 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphopenia	10 (1.8)	11 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	14 (2.5)	5 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)	15 (2.7)	11 (2.0)	3 (0.5)	0 (0.0)	0 (0.0)
Neutrophil count decreased	3 (0.6)	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count decreased	14 (2.6)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	6 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)
GASTROINTESTINAL	119 (21.8)	52 (9.5)	4 (0.7)	0 (0.0)	0 (0.0)	110 (19.7)	52 (9.3)	5 (0.9)	0 (0.0)	0 (0.0)	136 (24.2)	43 (7.7)	8 (1.4)	0 (0.0)	0 (0.0)
Abdominal distension	3 (0.6)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.5)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Anal fistula	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Anal mucositis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anal ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Colonic obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)

Supplementary Table S10: Late* Adverse Events without Regard to Attribution
Adverse Event Categories of Interest
Distribution of Patients by Highest Grade Adverse Event and by Specific Adverse Event Term

Category/Term	PBRT Alone (n=545)[a]					PBRT+STADT (n=559)[b]					PLNRT+PBRT+STADT (n=562)[c]				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Constipation	40 (7.3)	7 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	23 (4.1)	12 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	36 (6.4)	7 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	67 (12.3)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	65 (11.6)	12 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	99 (17.6)	10 (1.8)	1 (0.2)	0 (0.0)	0 (0.0)
Dry mouth	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Enteritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Esophagitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fecal incontinence	13 (2.4)	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.3)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	13 (2.3)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	4 (0.7)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	10 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.2)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Gallbladder obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastric ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorder	20 (3.7)	9 (1.7)	1 (0.2)	0 (0.0)	0 (0.0)	29 (5.2)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	18 (3.2)	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
Hemorrhoids	16 (2.9)	8 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	17 (3.0)	6 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	22 (3.9)	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
Ileal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ileus	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Jejunal obstruction	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

Supplementary Table S10: Late* Adverse Events without Regard to Attribution
Adverse Event Categories of Interest
Distribution of Patients by Highest Grade Adverse Event and by Specific Adverse Event Term

Category/Term	PBRT Alone (n=545)[a]					PBRT+STADT (n=559)[b]					PLNRT+PBRT+STADT (n=562)[c]				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.2)	(0.0)	(0.0)
Mucositis oral	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	7 (1.3)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	11 (2.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	11 (2.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Proctitis	24 (4.4)	16 (2.9)	1 (0.2)	0 (0.0)	0 (0.0)	30 (5.4)	17 (3.0)	1 (0.2)	0 (0.0)	0 (0.0)	26 (4.6)	18 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)
Proctoscopy abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal anastomotic leak	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal mucositis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rectal stenosis	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Small intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
Taste alteration	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tooth disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
RENAL/GENITOURINARY	148 (27.2)	173 (31.7)	26 (4.8)	3 (0.6)	0 (0.0)	165 (29.5)	157 (28.1)	30 (5.4)	7 (1.3)	0 (0.0)	138 (24.6)	178 (31.7)	42 (7.5)	3 (0.5)	0 (0.0)
Bladder anastomotic leak	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder obstruction	0 (0.0)	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.5)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder perforation	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder spasm	3 (0.6)	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	4 (0.7)	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Bladder stenosis	0 (0.0)	3 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)

Supplementary Table S10: Late* Adverse Events without Regard to Attribution
Adverse Event Categories of Interest
Distribution of Patients by Highest Grade Adverse Event and by Specific Adverse Event Term

Category/Term	PBRT Alone (n=545)[a]					PBRT+STADT (n=559)[b]					PLNRT+PBRT+STADT (n=562)[c]				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Cystitis	18 (3.3)	39 (7.2)	5 (0.9)	1 (0.2)	0 (0.0)	20 (3.6)	45 (8.1)	8 (1.4)	0 (0.0)	0 (0.0)	12 (2.1)	46 (8.2)	12 (2.1)	0 (0.0)	0 (0.0)
Kidney perforation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Prostatic obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ureteric obstruction	3 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	4 (0.7)	2 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	3 (0.5)	2 (0.4)	0 (0.0)	0 (0.0)
Ureteric stenosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Urethral anastomotic leak	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Urethral fistula	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urethral obstruction	1 (0.2)	4 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	7 (1.3)	2 (0.4)	0 (0.0)	0 (0.0)	5 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Urethral stricture	1 (0.2)	8 (1.5)	3 (0.6)	0 (0.0)	0 (0.0)	2 (0.4)	5 (0.9)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary frequency	162 (29.7)	81 (14.9)	4 (0.7)	0 (0.0)	0 (0.0)	186 (33.3)	89 (15.9)	2 (0.4)	0 (0.0)	0 (0.0)	183 (32.6)	96 (17.1)	3 (0.5)	0 (0.0)	0 (0.0)
Urinary incontinence	109 (20.0)	116 (21.3)	9 (1.7)	2 (0.4)	0 (0.0)	103 (18.4)	90 (16.1)	12 (2.1)	4 (0.7)	0 (0.0)	96 (17.1)	111 (19.8)	23 (4.1)	2 (0.4)	0 (0.0)
Urinary retention	45 (8.3)	22 (4.0)	1 (0.2)	1 (0.2)	0 (0.0)	47 (8.4)	15 (2.7)	2 (0.4)	0 (0.0)	0 (0.0)	57 (10.1)	16 (2.8)	2 (0.4)	0 (0.0)	0 (0.0)
Urine discoloration	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urogenital disorder	52 (9.5)	13 (2.4)	7 (1.3)	1 (0.2)	0 (0.0)	43 (7.7)	12 (2.1)	4 (0.7)	1 (0.2)	0 (0.0)	40 (7.1)	11 (2.0)	9 (1.6)	0 (0.0)	0 (0.0)

Adverse events were graded with CTCAE version 3.0.

*Late: > 90 days after End of Radiation Therapy

†19, 19, and 12 patients from PBRT Alone, PBRT+STADT, and PLNRT+PBRT+STADT arms, respectively, who received no treatment or for whom no late AE information was provided are excluded.

Supplementary Table S11: All Reported Adverse Events without Regard to Attribution
Distribution of Patients by Highest Grade Adverse Event and by Category (System Organ Class)

Category	PBRT Alone (n=547)†					PBRT+STADT (n=563)†					PLNRT+PBRT+STADT (n=563)†				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Overall Highest Grade	110 (20.1)	257 (47.0)	70 (12.8)	9 (1.6)	0 (0.0)	120 (21.3)	273 (48.5)	100 (17.8)	15 (2.7)	0 (0.0)	96 (17.1)	275 (48.8)	131 (23.3)	14 (2.5)	0 (0.0)
Allergy/immunology	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Auditory/ear	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Blood/bone marrow	43 (7.9)	23 (4.2)	4 (0.7)	2 (0.4)	0 (0.0)	79 (14.0)	16 (2.8)	3 (0.5)	0 (0.0)	0 (0.0)	61 (10.8)	24 (4.3)	20 (3.6)	2 (0.4)	0 (0.0)
Cardiac arrhythmia	1 (0.2)	3 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	4 (0.7)	3 (0.5)	2 (0.4)	0 (0.0)
Cardiac general	4 (0.7)	5 (0.9)	5 (0.9)	2 (0.4)	0 (0.0)	6 (1.1)	11 (2.0)	6 (1.1)	4 (0.7)	0 (0.0)	3 (0.5)	14 (2.5)	7 (1.2)	1 (0.2)	0 (0.0)
Coagulation	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Constitutional symptoms	141 (25.8)	27 (4.9)	1 (0.2)	0 (0.0)	0 (0.0)	186 (33.0)	57 (10.1)	0 (0.0)	0 (0.0)	0 (0.0)	170 (30.2)	62 (11.0)	7 (1.2)	0 (0.0)	0 (0.0)
Dermatology/skin	30 (5.5)	9 (1.6)	1 (0.2)	0 (0.0)	0 (0.0)	36 (6.4)	19 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	48 (8.5)	18 (3.2)	2 (0.4)	0 (0.0)	0 (0.0)
Endocrine	31 (5.7)	11 (2.0)	2 (0.4)	0 (0.0)	0 (0.0)	228 (40.5)	97 (17.2)	6 (1.1)	0 (0.0)	0 (0.0)	209 (37.1)	117 (20.8)	5 (0.9)	0 (0.0)	0 (0.0)
Gastrointestinal	160 (29.3)	61 (11.2)	5 (0.9)	0 (0.0)	0 (0.0)	161 (28.6)	64 (11.4)	10 (1.8)	0 (0.0)	0 (0.0)	219 (38.9)	70 (12.4)	12 (2.1)	0 (0.0)	0 (0.0)
Hemorrhage/bleeding	61 (11.2)	33 (6.0)	5 (0.9)	1 (0.2)	0 (0.0)	74 (13.1)	25 (4.4)	4 (0.7)	0 (0.0)	0 (0.0)	79 (14.0)	31 (5.5)	8 (1.4)	0 (0.0)	0 (0.0)
Hepatobiliary/pancreas	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Infection	0 (0.0)	19 (3.5)	5 (0.9)	1 (0.2)	0 (0.0)	3 (0.5)	15 (2.7)	4 (0.7)	0 (0.0)	0 (0.0)	1 (0.2)	23 (4.1)	5 (0.9)	1 (0.2)	0 (0.0)
Lymphatics	6 (1.1)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	13 (2.3)	4 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)	15 (2.7)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Metabolic/laboratory	30 (5.5)	9 (1.6)	2 (0.4)	1 (0.2)	0 (0.0)	57 (10.1)	15 (2.7)	8 (1.4)	1 (0.2)	0 (0.0)	54 (9.6)	11 (2.0)	7 (1.2)	1 (0.2)	0 (0.0)
Musculoskeletal/soft tissue	20 (3.7)	4 (0.7)	2 (0.4)	0 (0.0)	0 (0.0)	22 (3.9)	12 (2.1)	1 (0.2)	0 (0.0)	0 (0.0)	35 (6.2)	21 (3.7)	2 (0.4)	0 (0.0)	0 (0.0)
Neurology	18 (3.3)	14 (2.6)	3 (0.5)	0 (0.0)	0 (0.0)	37 (6.6)	19 (3.4)	3 (0.5)	0 (0.0)	0 (0.0)	60 (10.7)	15 (2.7)	4 (0.7)	0 (0.0)	0 (0.0)

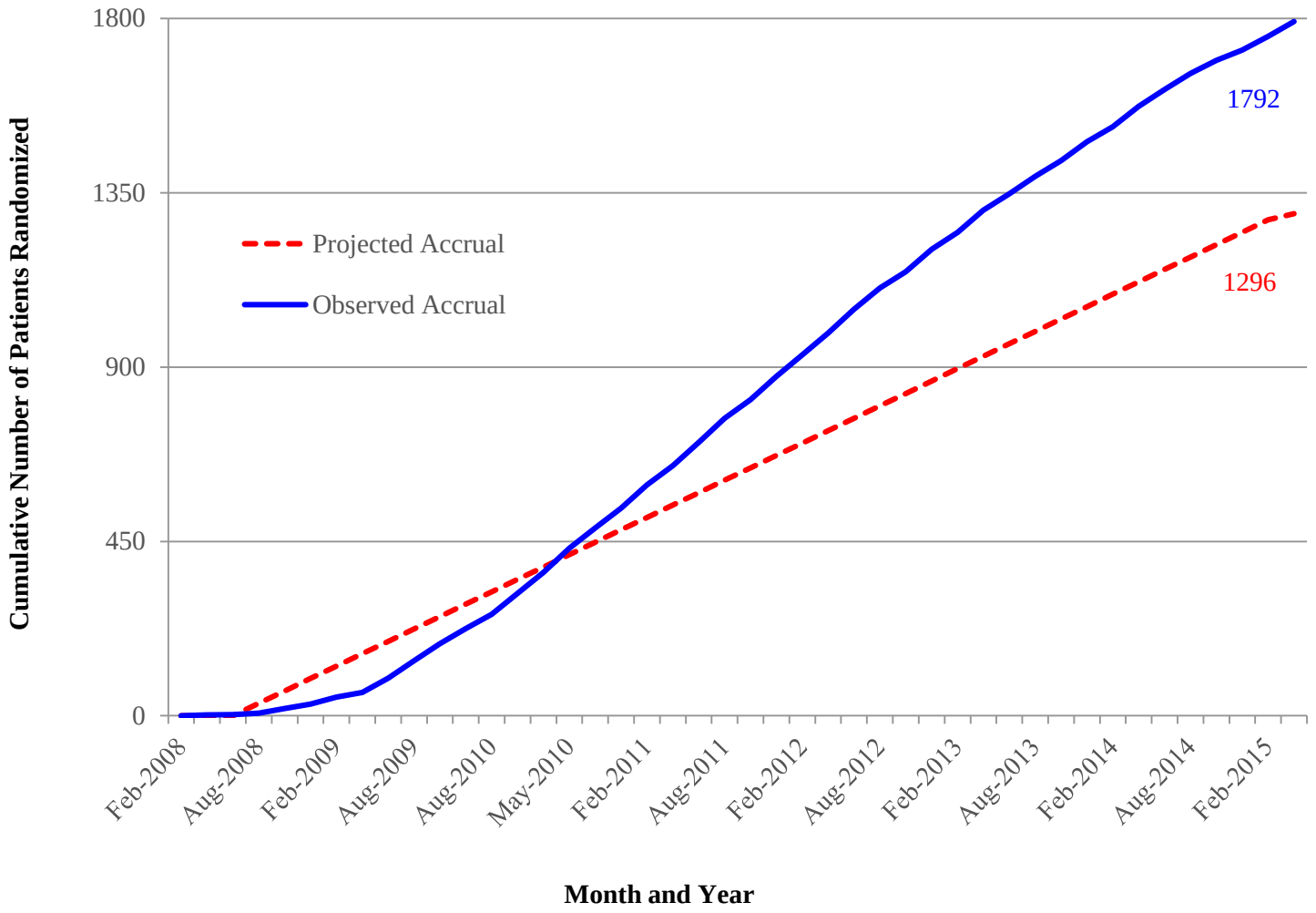
Supplementary Table S11: All Reported Adverse Events without Regard to Attribution
Distribution of Patients by Highest Grade Adverse Event and by Category (System Organ Class)

Category	PBRT Alone (n=547)†					PBRT+STADT (n=563)†					PLNRT+PBRT+STADT (n=563)†				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Ocular/visual	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	3 (0.5)	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)
Pain	85 (15.5)	38 (6.9)	6 (1.1)	0 (0.0)	0 (0.0)	102 (18.1)	42 (7.5)	9 (1.6)	0 (0.0)	0 (0.0)	108 (19.2)	49 (8.7)	6 (1.1)	0 (0.0)	0 (0.0)
Pulmonary/upper respiratory	16 (2.9)	8 (1.5)	1 (0.2)	0 (0.0)	0 (0.0)	29 (5.2)	6 (1.1)	3 (0.5)	0 (0.0)	0 (0.0)	18 (3.2)	8 (1.4)	0 (0.0)	2 (0.4)	0 (0.0)
Renal/genitourinary	158 (28.9)	189 (34.6)	29 (5.3)	3 (0.5)	0 (0.0)	189 (33.6)	185 (32.9)	31 (5.5)	7 (1.2)	0 (0.0)	169 (30.0)	202 (35.9)	44 (7.8)	5 (0.9)	0 (0.0)
Secondary malignancy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sexual/reproductive function	49 (9.0)	102 (18.6)	24 (4.4)	0 (0.0)	0 (0.0)	47 (8.3)	130 (23.1)	36 (6.4)	0 (0.0)	0 (0.0)	62 (11.0)	133 (23.6)	43 (7.6)	0 (0.0)	0 (0.0)
Surgery/intra-operative injury	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Syndromes	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular	2 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	8 (1.4)	3 (0.5)	2 (0.4)	2 (0.4)	0 (0.0)	8 (1.4)	3 (0.5)	2 (0.4)	0 (0.0)	0 (0.0)

Adverse events were graded with CTCAE version 3.0.

†17, 15, and 11 patients from PBRT Alone, PBRT+STADT, and PLNRT+PBRT+STADT arms, respectively, who received no treatment or for whom no acute AE information was provided are excluded.

Figure S1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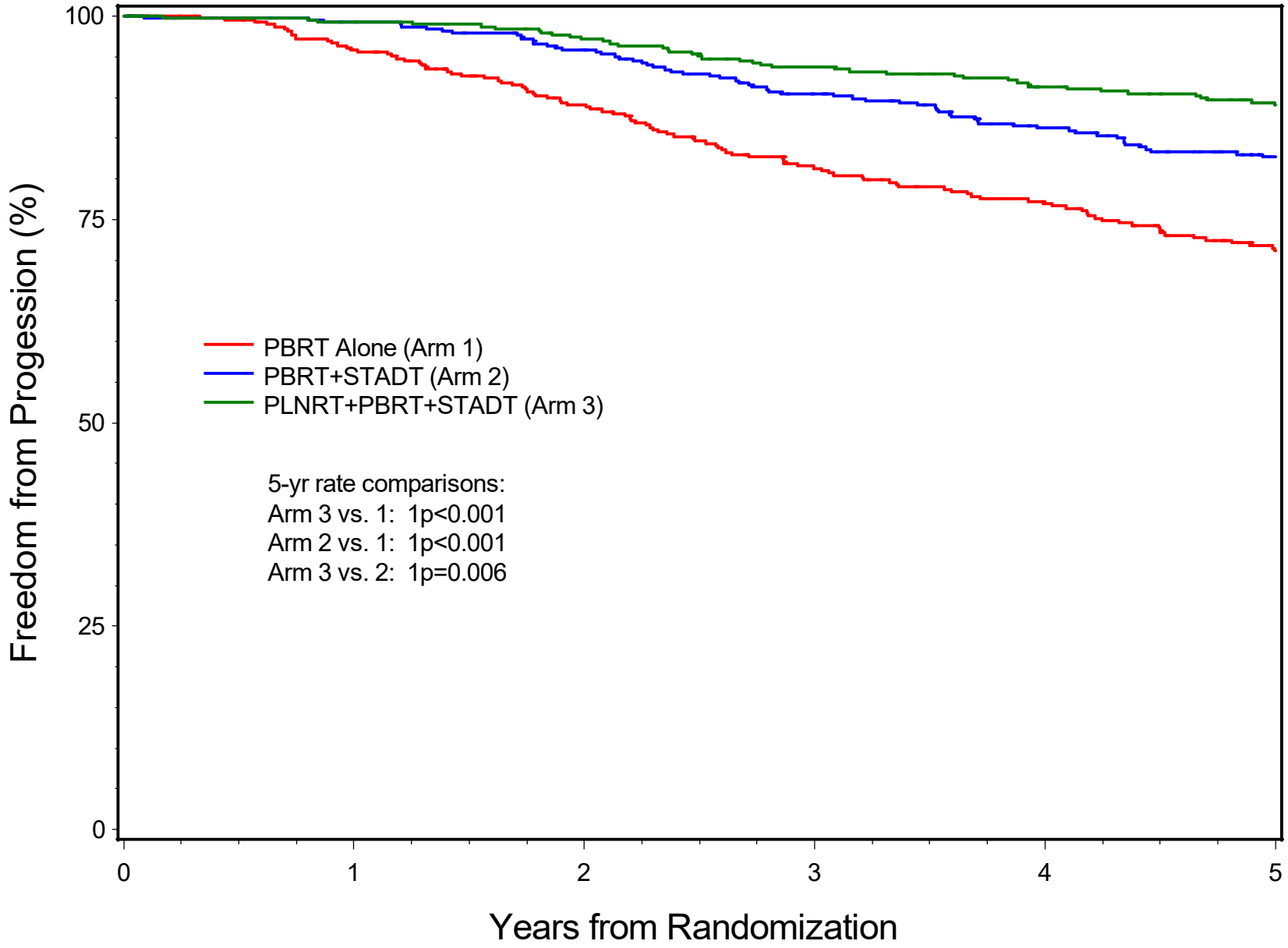
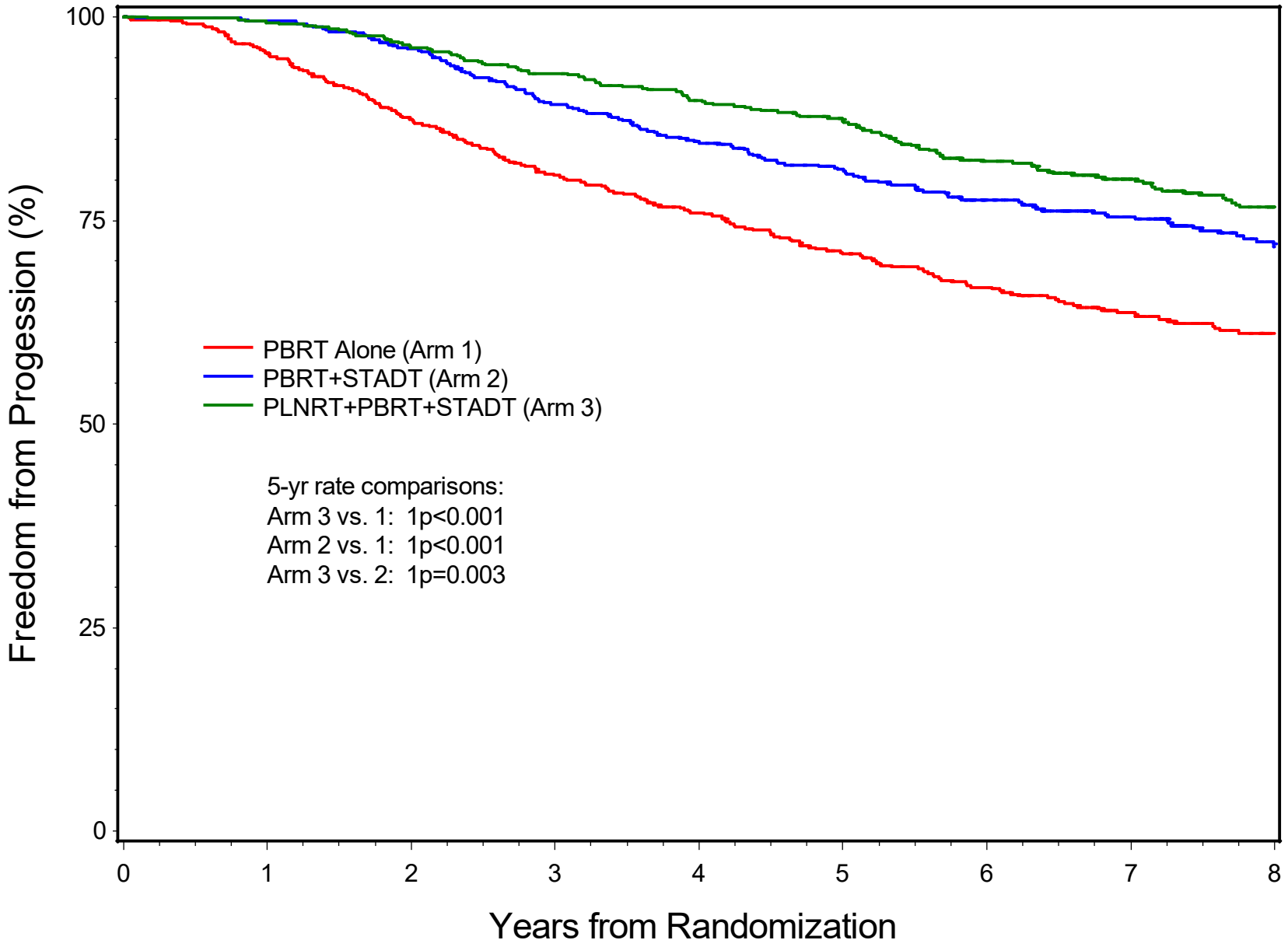
Month and Year



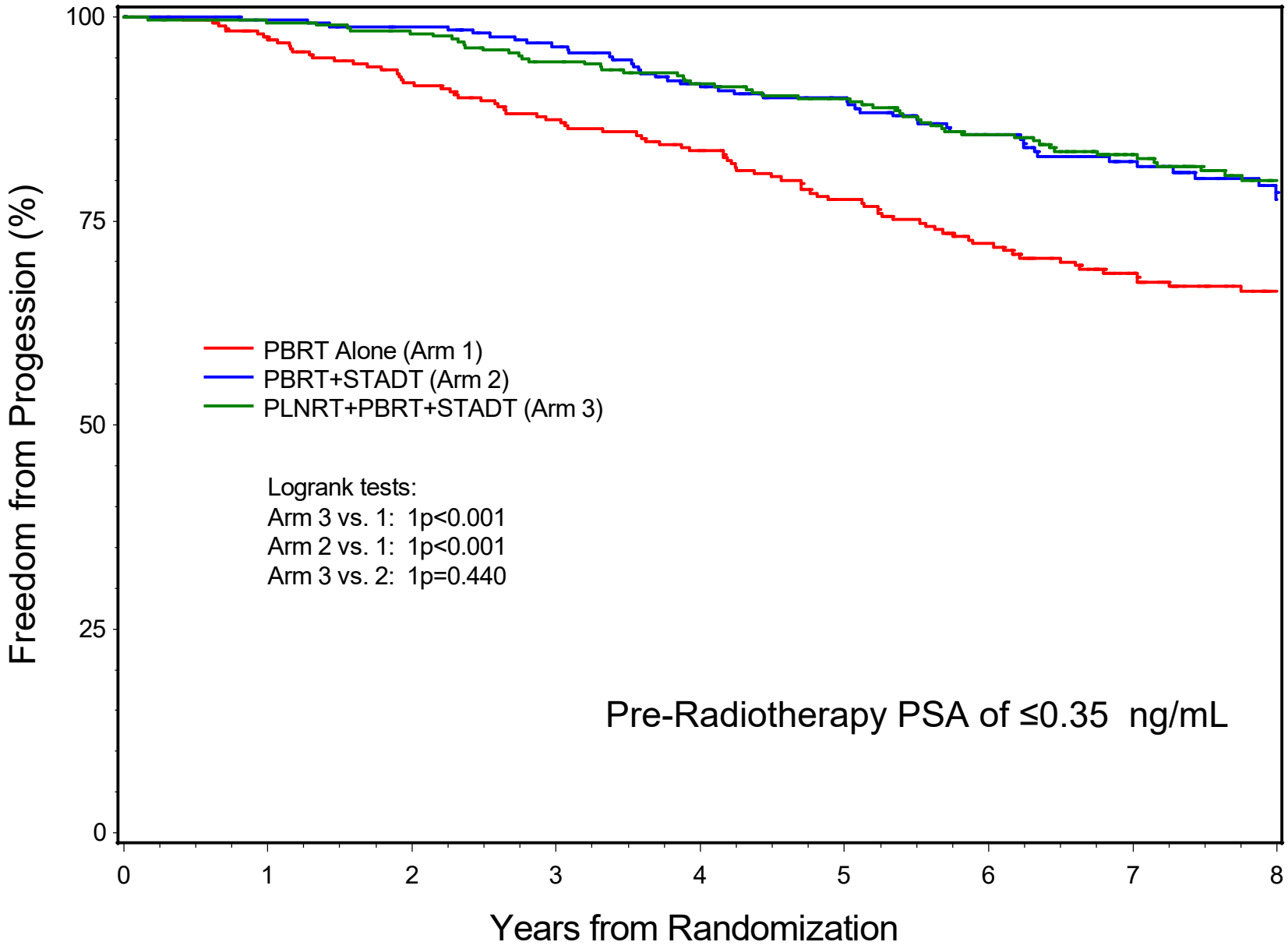
No. at Risk

PBRT Alone	399	363	324	286	259	223
PBRT+STADT	398	381	360	329	299	265
PLNRT+PBRT+STADT	394	385	371	352	334	311



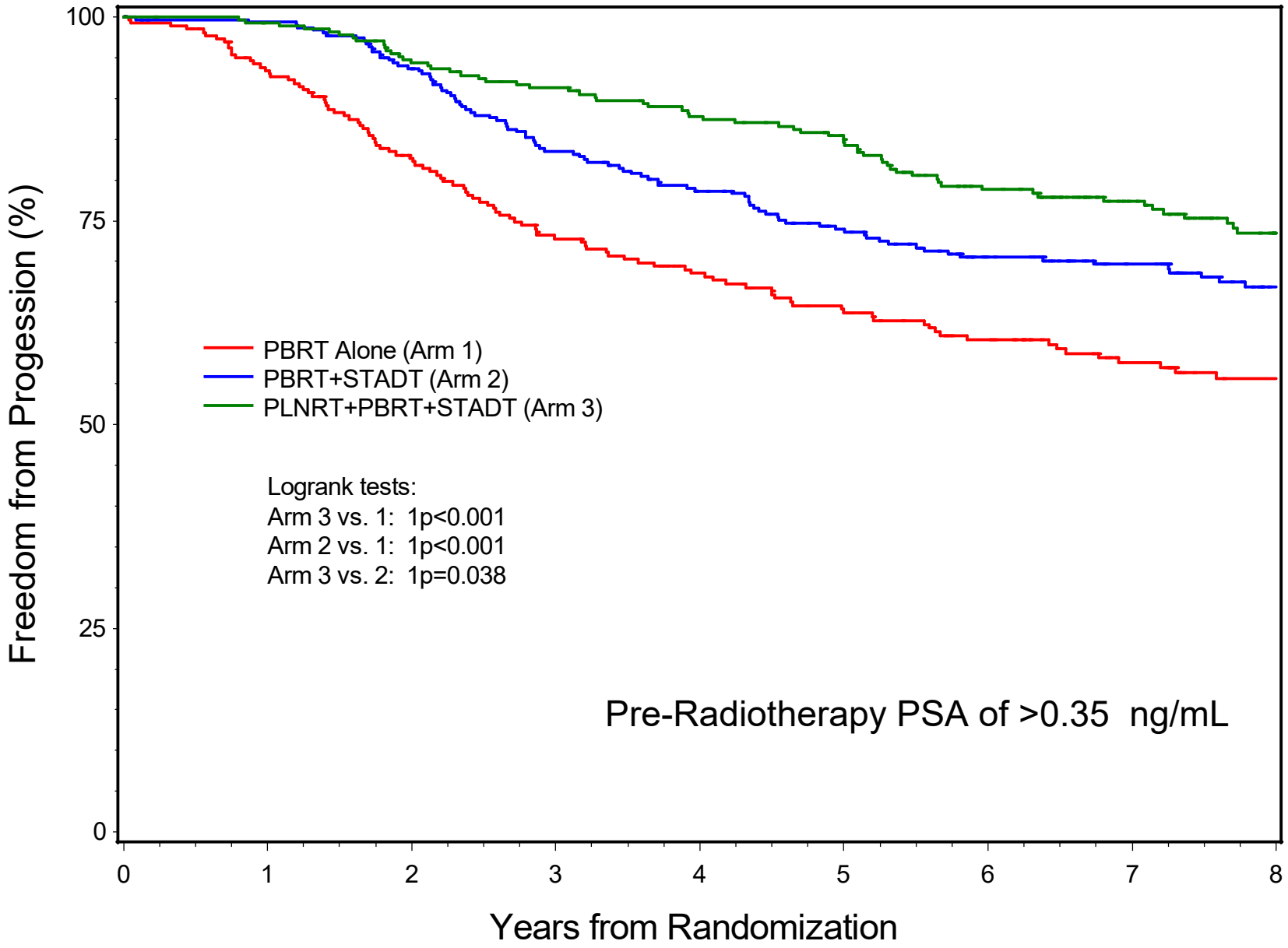
No. at Risk

PBRT Alone	564	517	469	426	393	358	317	257	197
PBRT+STADT	578	555	529	487	453	419	364	294	209
PLNRT+PBRT+STADT	574	559	538	516	491	466	404	328	254



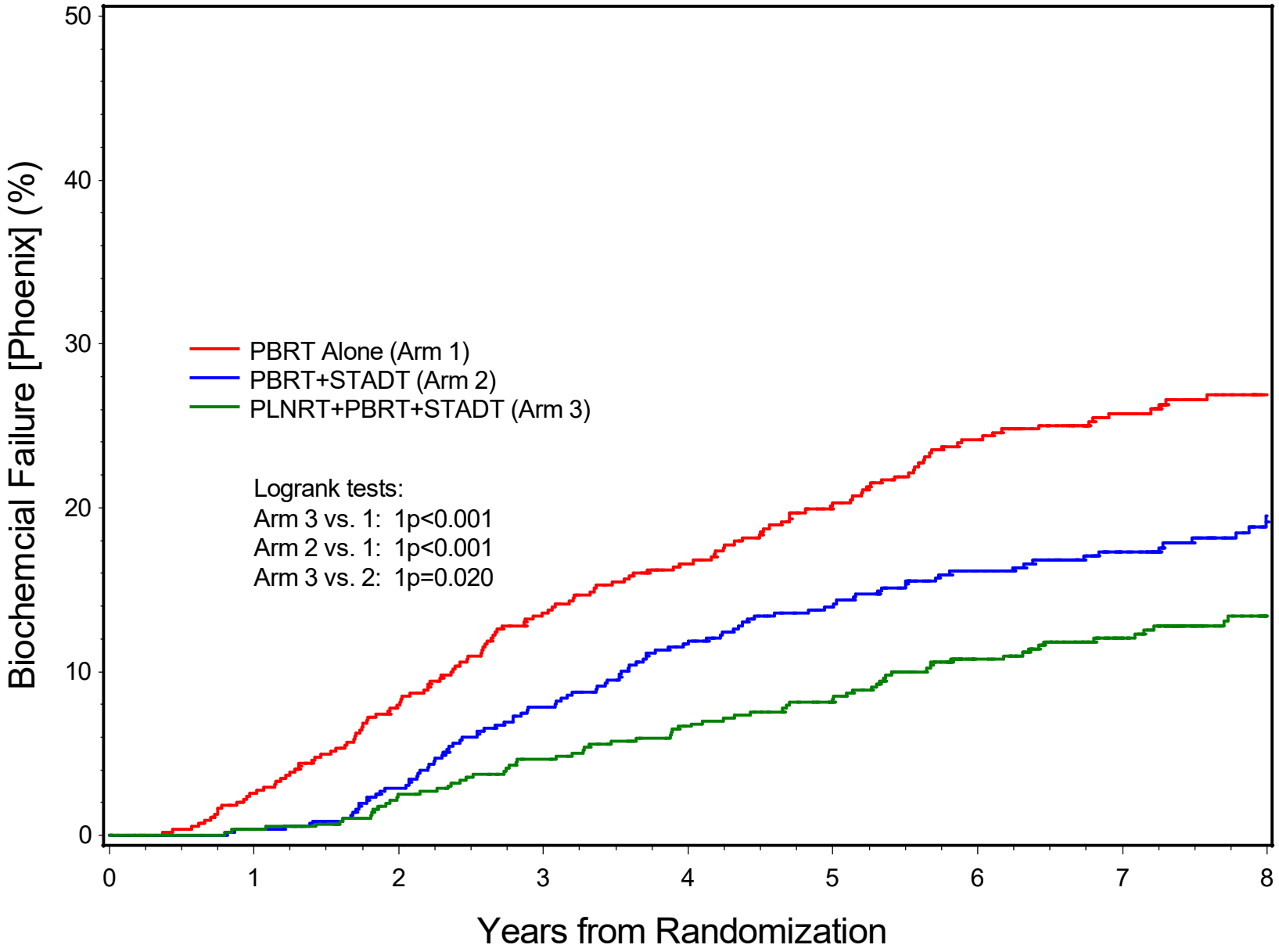
No. at Risk

PBRT Alone	293	268	246	228	213	191	167	134	100
PBRT+STADT	264	252	247	235	217	203	172	129	89
PLNRT+PBRT+STADT	301	294	288	275	261	250	215	176	133



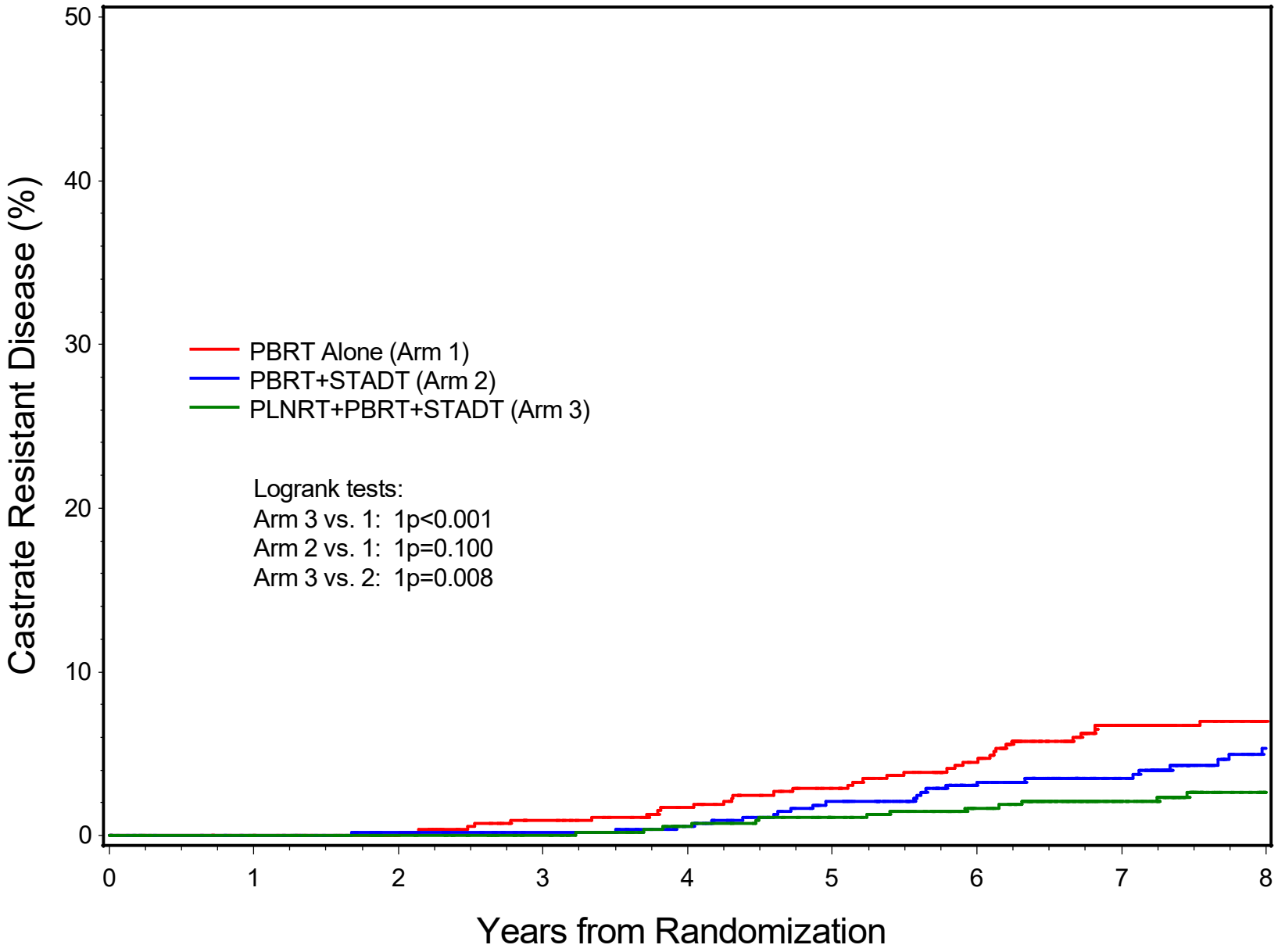
No. at Risk

PBRT Alone	271	238	203	175	158	142	123	100	80
PBRT+STADT	314	303	277	245	223	198	169	144	104
PLNRT+PBRT+STADT	273	265	248	236	223	209	181	148	117



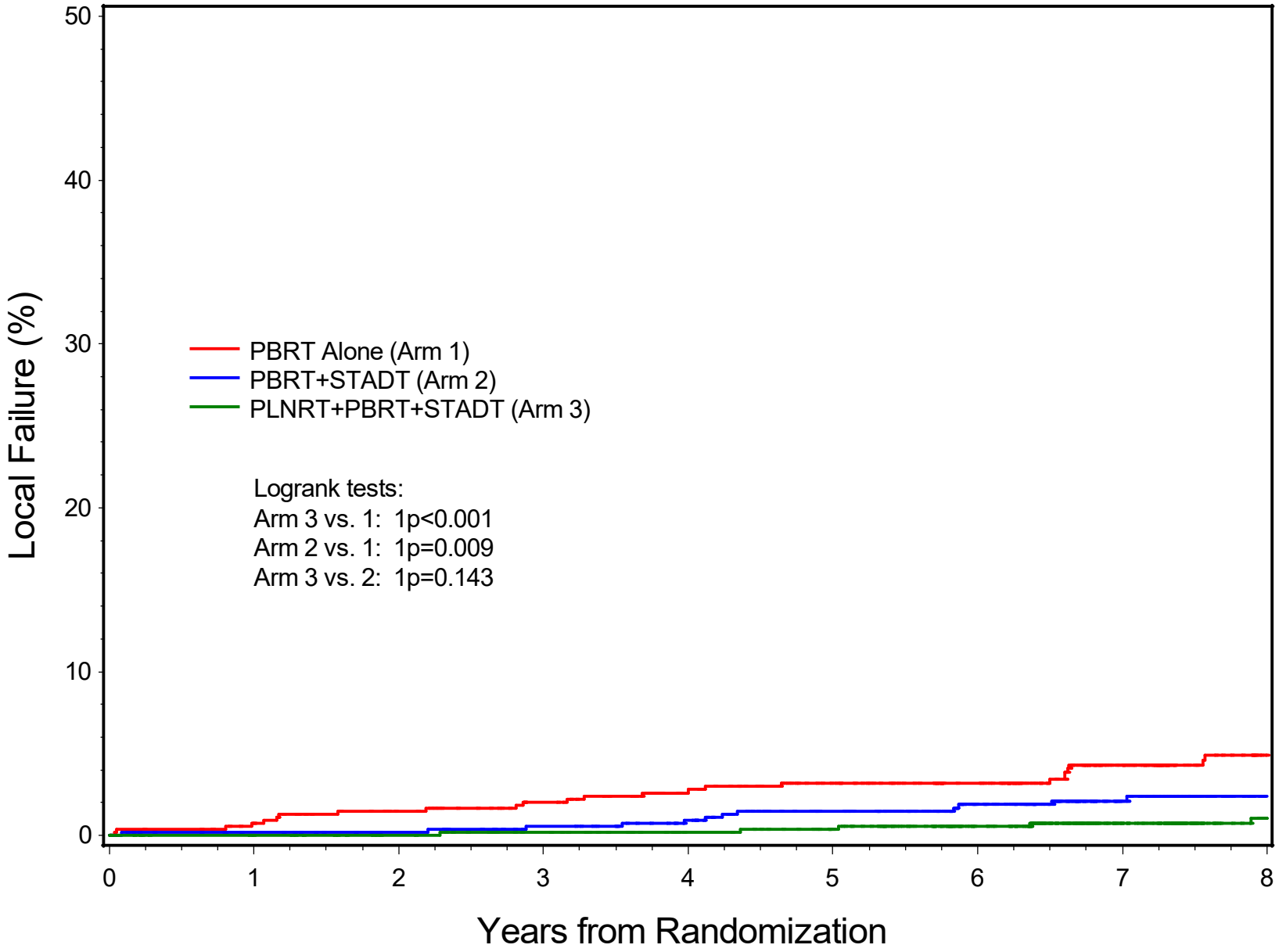
No. at Risk

PBRT Alone	564	526	486	445	415	379	335	267	205
PBRT+STADT	578	556	532	495	462	429	372	298	214
PLNRT+PBRT+STADT	574	559	539	519	495	473	413	336	258



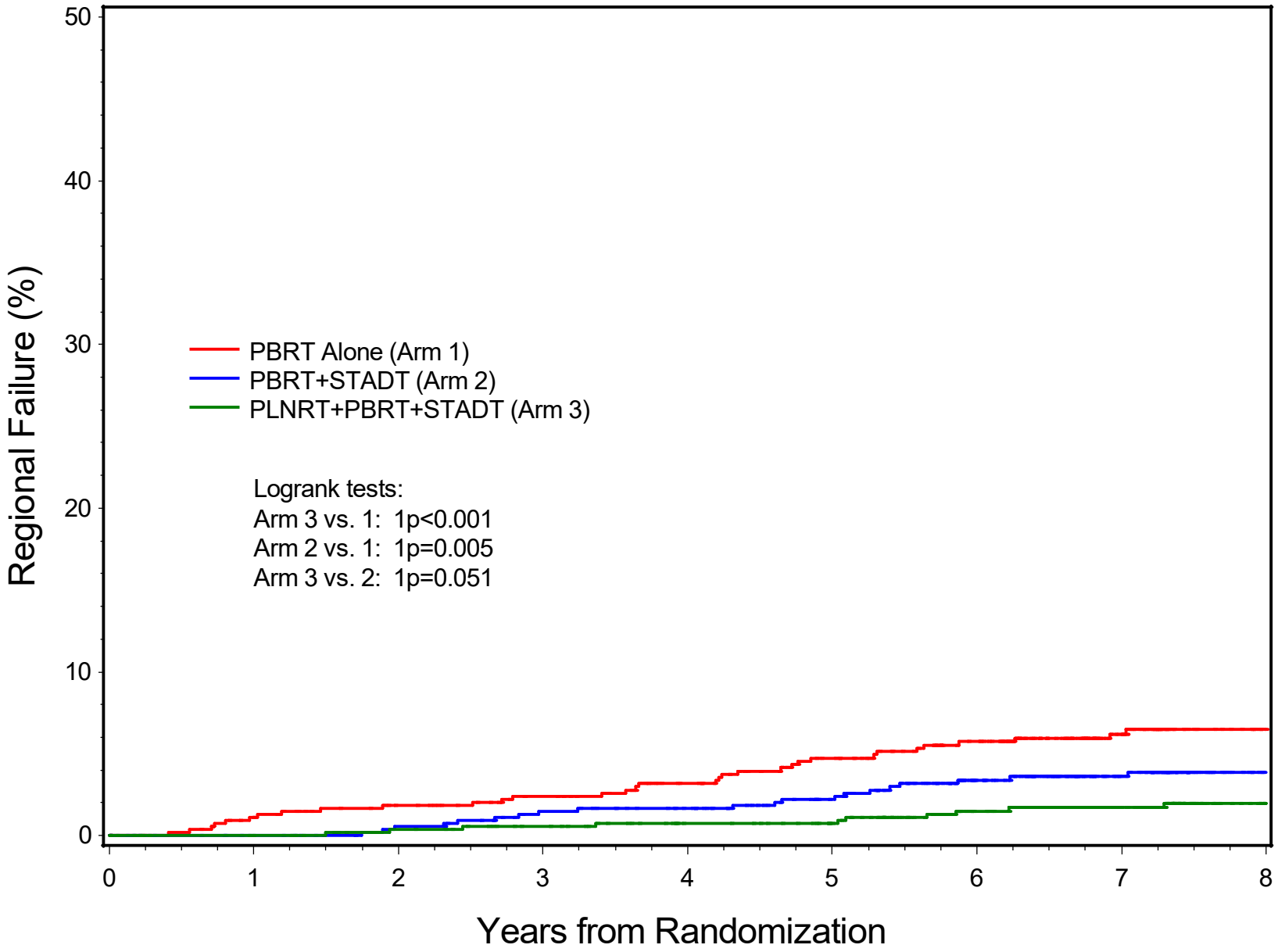
No. at Risk

PBRT Alone	564	540	529	512	490	466	430	346	274
PBRT+STADT	578	558	547	537	520	492	432	350	252
PLNRT+PBRT+STADT	574	561	552	543	525	507	449	366	286



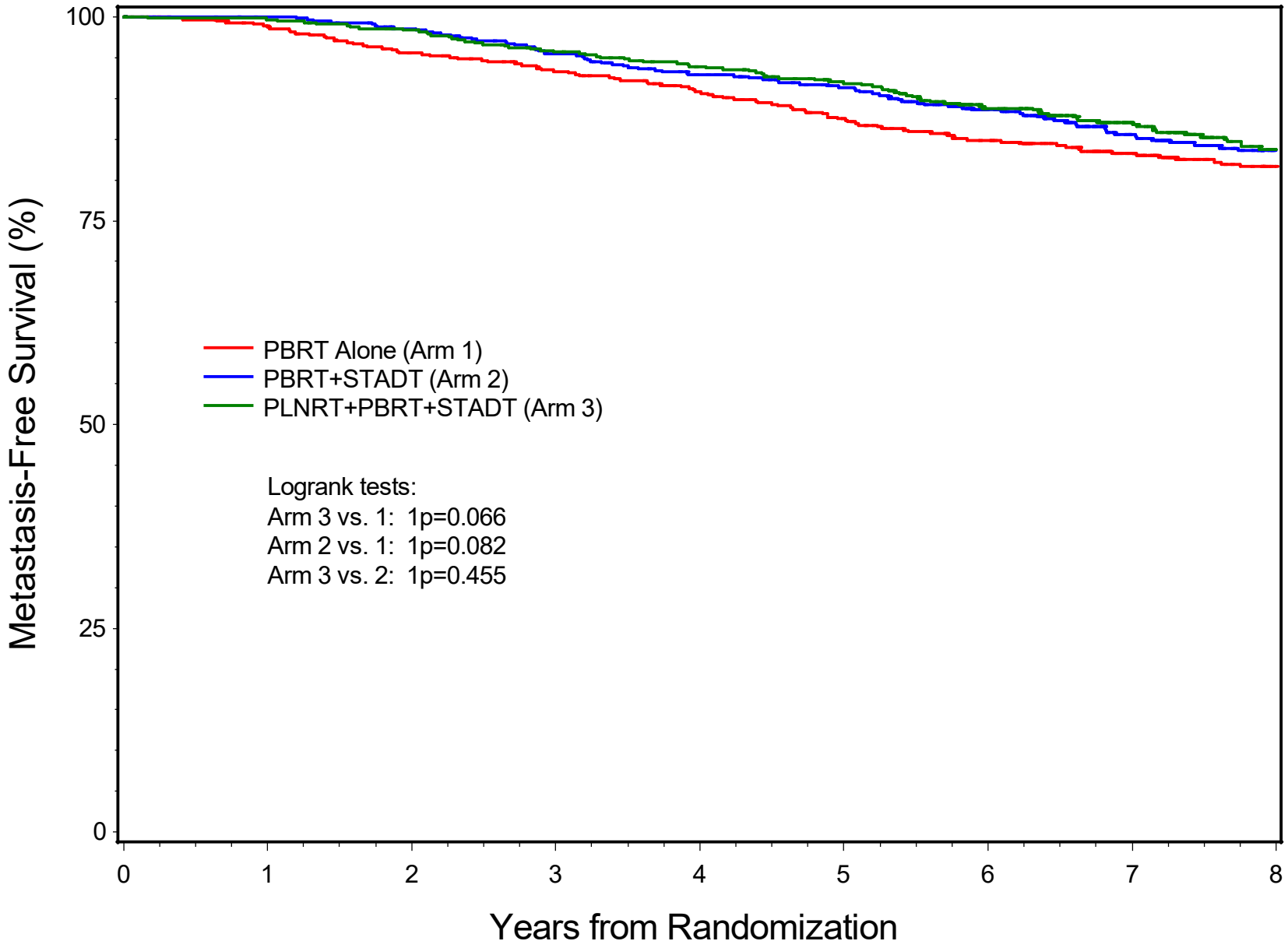
No. at Risk

PBRT Alone	564	536	521	505	481	456	426	348	274
PBRT+STADT	578	557	547	535	518	493	436	353	261
PLNRT+PBRT+STADT	574	561	552	542	526	510	453	366	285



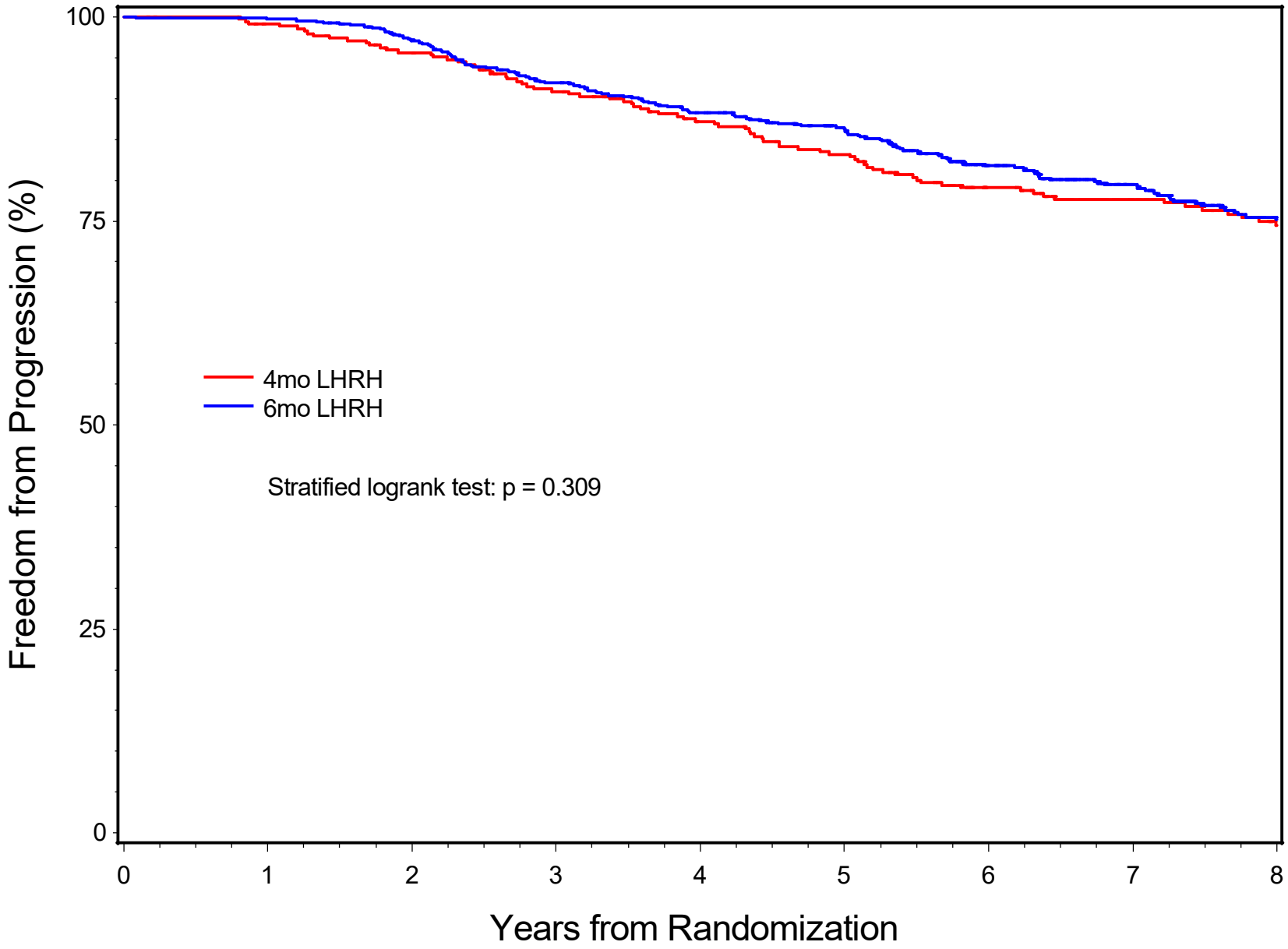
No. at Risk

PBRT Alone	564	534	519	503	480	453	420	345	274
PBRT+STADT	578	558	545	530	516	490	432	351	259
PLNRT+PBRT+STADT	574	561	550	540	523	508	451	366	287



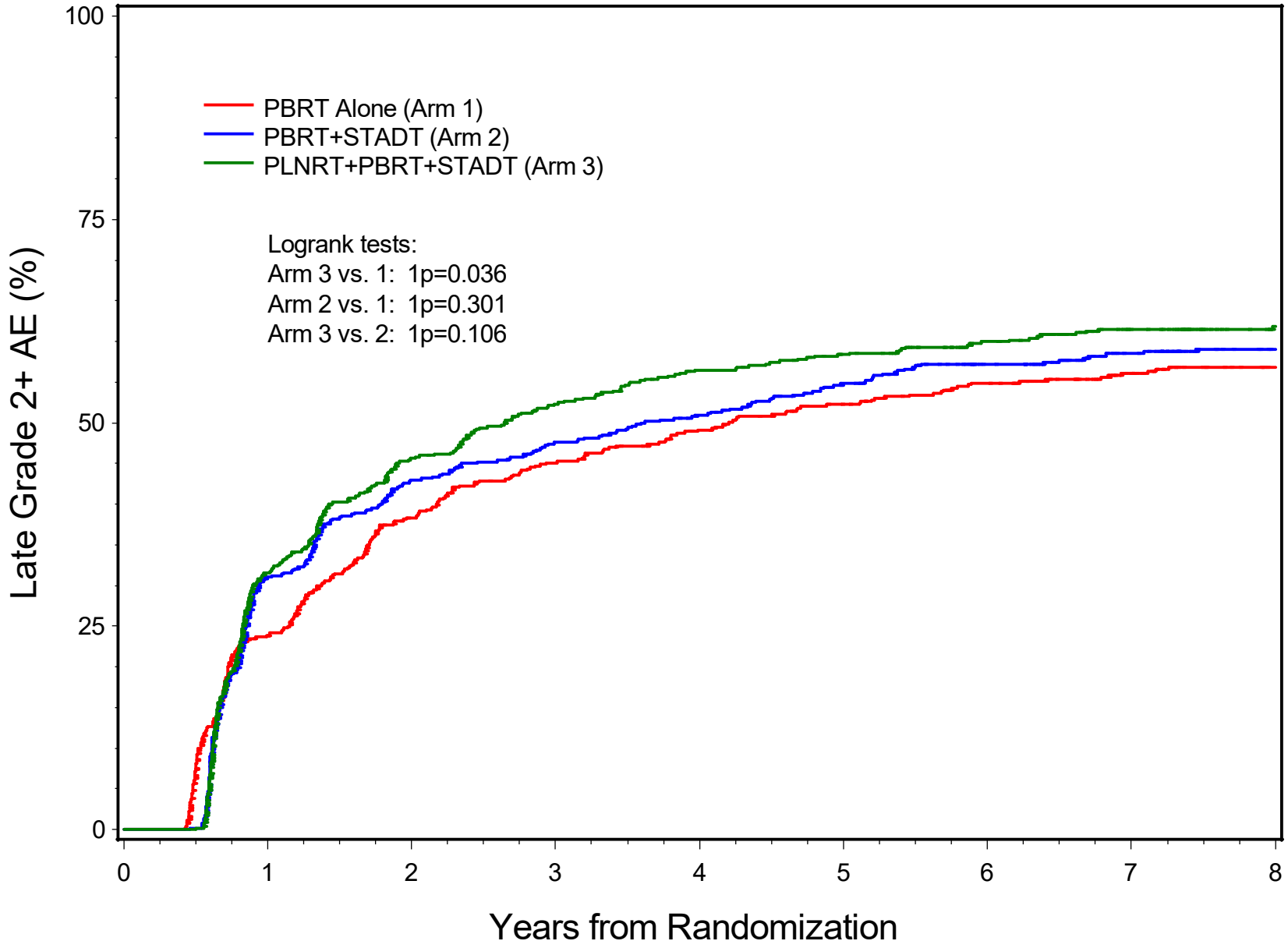
No. at Risk

PBRT Alone	564	535	513	494	470	441	404	337	268
PBRT+STADT	578	558	543	521	498	474	415	335	244
PLNRT+PBRT+STADT	574	561	550	531	513	491	436	354	275



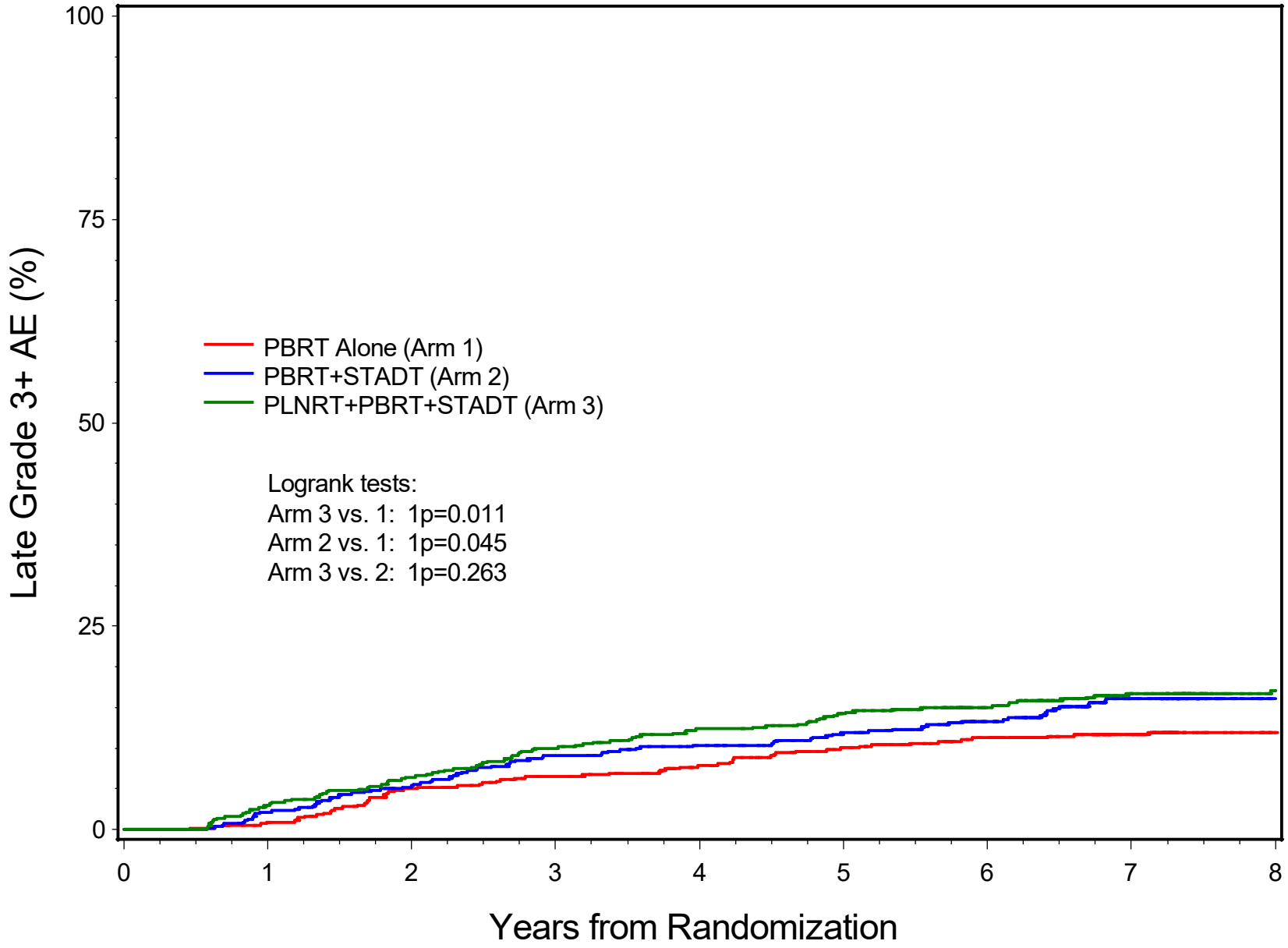
No. at Risk

4mo LHRH	350	342	324	302	282	266	232	187	151
6mo LHRH	680	676	647	605	566	525	449	364	259



No. at Risk

PBRT Alone	545	410	325	282	250	224	200	157	126
PBRT+STADT	559	383	309	278	250	217	176	136	101
PLNRT+PBRT+STADT	562	384	300	256	228	211	178	134	102



No. at Risk

PBRT Alone	545	532	503	482	456	426	392	321	256
PBRT+STADT	559	543	515	486	465	439	386	304	228
PLNRT+PBRT+STADT	562	543	517	490	463	439	383	299	233