

Supplementary Appendix

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

Supplement to: Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without antiandrogen therapy in recurrent prostate cancer. *N Engl J Med* 2017;376:417-28. DOI: [10.1056/NEJMoa1607529](https://doi.org/10.1056/NEJMoa1607529)

Supplementary Appendix

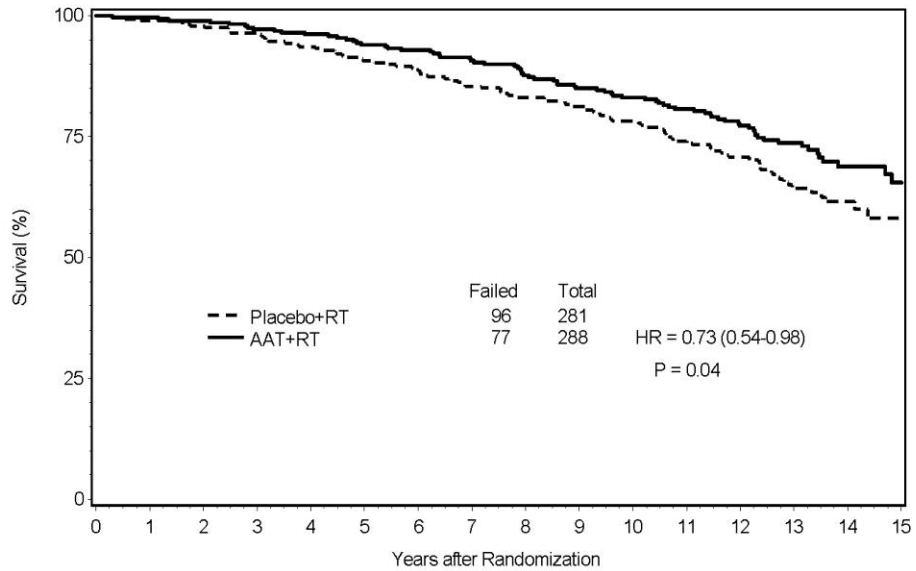
Supplement to: Shipley WU, Seiferheld W, Lukka HR, et al. NRG Oncology RTOG 9601: A randomized trial of salvage radiotherapy with or without anti-androgen therapy in prostate cancer patients with recurrence following radical prostatectomy

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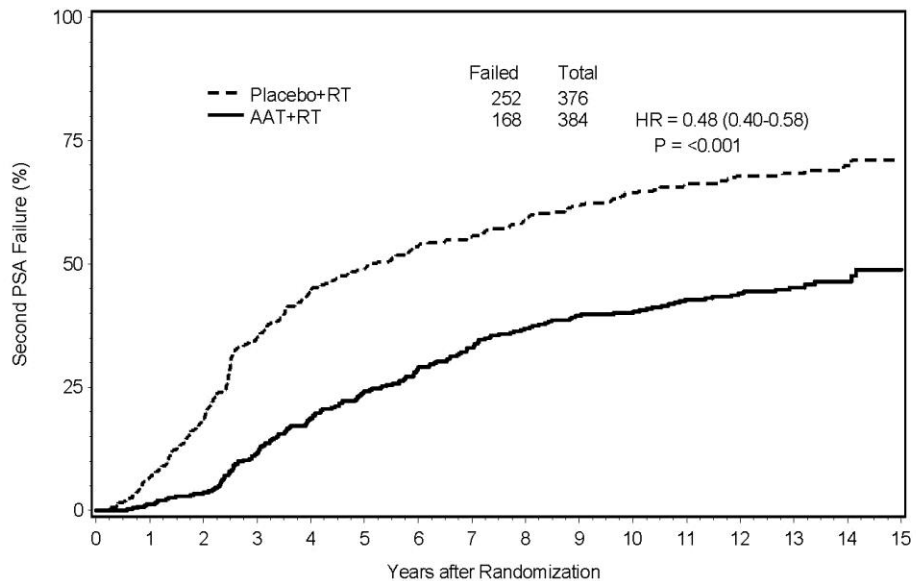
Figure S1. Kaplan-Meier estimates of overall survival (Panel A) and Cumulative-incidence estimates of disease-specific biochemical (PSA) recurrence (Panel B). AAT denotes anti-androgen therapy and panel A shows a *post hoc* analysis.

A: Overall Survival - Positive Margins



No. at Risk	0	5	10	15
Placebo+RT	281	268	237	16
AAT+RT	288	277	254	25

B: Time to 2nd PSA Failure



No. at Risk	0	5	10	15
Placebo+RT	376	236	156	5
AAT+RT	384	324	236	13

Figure S2. Effect of anti-androgen therapy (AAT) on the 12 year metastatic PC rate.

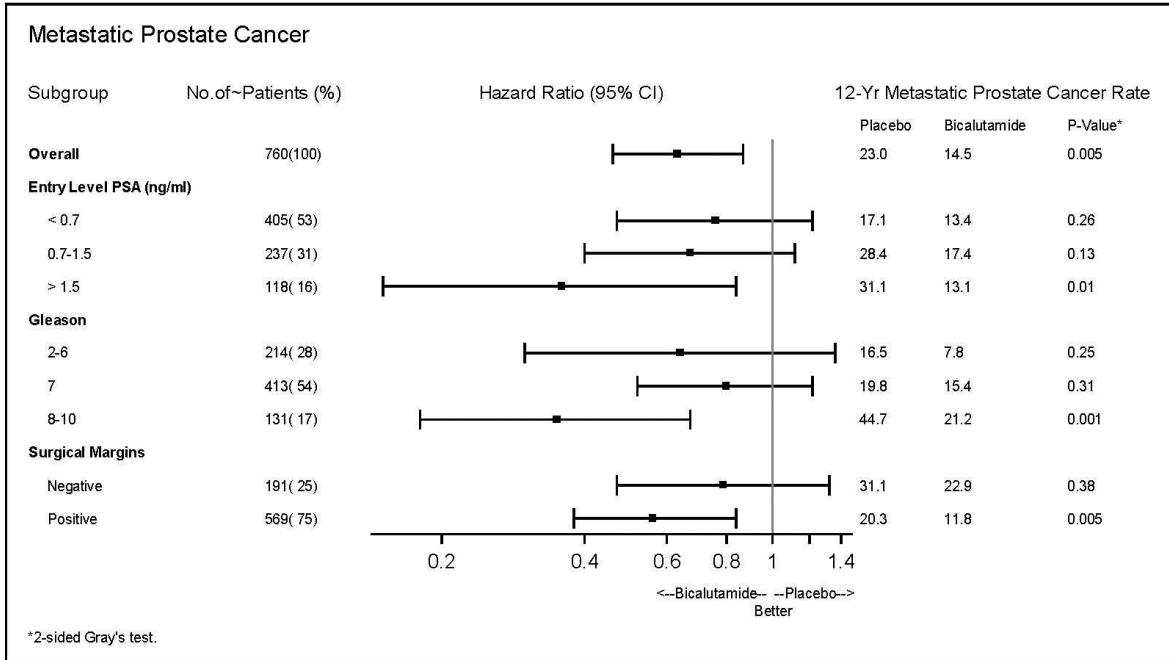


Table S1. Definition of Second Biochemical Recurrence

Biochemical (PSA) recurrence is defined as the first occurrence of one of the following events:

- Increase in PSA following protocol treatment according to the following criteria met during protocol treatment:
 - If PSA decreased to undetectable level (<0.2 ng/mL) during protocol treatment
 - Recurrence = increase in PSA after protocol treatment to 0.5 ng/mL or more after protocol treatment
 - If PSA decreased to a detectable level (≥ 0.2 ng/mL) during protocol treatment
 - Recurrence= increase in PSA after protocol treatment of 0.3 ng/mL or more above the lowest detectable level
 - If PSA did not decrease during protocol treatment
 - Recurrence= increase in PSA after protocol treatment of 0.5 ng/mL or more above entry PSA level
 - The start of salvage hormone therapy
-

Table S2. Cause of Death (Centrally Reviewed)

	RT+Placebo (n=131)	RT+ AAT* (n=108)
Centrally reviewed cause of death		
Treated cancer	46 (35.1%)	21 (19.4%)
Second Primary	21 (16.0%)	30 (27.8%)
Other cause	47 (35.9%)	49 (45.4%)
Unknown	17 (13.0%)	8 (7.4%)
Other cause of death specification reported by institution	(n=47)	(n=49)
Blood/lymph disease	1 (2.1%)	0 (0.0%)
Cardiovascular (MI, CHF)	21 (44.7%)	15 (30.6%)
Cerebrovascular (stroke, CVA)	1 (2.1%)	5 (10.2%)
Decompensated cirrhosis	1 (2.1%)	0 (0.0%)
Diabetes	1 (2.1%)	0 (0.0%)
Fell off trampoline and hit head on rock	0 (0.0%)	1 (2.0%)
Hemoptysis	0 (0.0%)	1 (2.0%)
Infectious disease	3 (6.4%)	7 (14.3%)
Interstitial lung disease	1 (2.1%)	0 (0.0%)
Metastatic cancer	1 (2.1%)	0 (0.0%)
Multiple comorbid disease	0 (0.0%)	1 (2.0%)
Neurological (dementia, Alzheimer's)	3 (6.4%)	3 (6.1%)
Pulmonary (respiratory failure/COPD)	0 (0.0%)	1 (2.0%)
Pulmonary, aspiration	1 (2.1%)	0 (0.0%)
Renal failure	1 (2.1%)	0 (0.0%)
Respiratory Failure	1 (2.1%)	0 (0.0%)
Site reported cause of death: Complications of other treatment	0 (0.0%)	1 (2.0%)
Site reported cause of death: Second Primary	0 (0.0%)	1 (2.0%)
Site reported cause of death: Unknown	8 (17.0%)	13 (26.5%)
Trauma (accidental)	2 (4.3%)	0 (0.0%)

* AAT: Anti-Androgen Therapy

Salvage radiation and anti-androgen therapy in prostate cancer

Table S3. Overall Survival Multivariate Cox Model

Covariate	Comparison	HR (95% CI)	p-value*
Treatment Arm	AAT** vs. Placebo	0.75 (0.58, 0.96)	0.025
Entry PSA Level(1)	1.6-4.0 vs. 0.2-1.5	1.59 (1.17, 2.17)	0.003
Age	>=65 vs. <65	2.18 (1.66, 2.85)	<.001
KPS	100 vs. 80,90	0.78 (0.59, 1.04)	0.096
Gleason Score	7 vs. 2-6	1.23 (0.90, 1.68)	0.196
	8-10 vs. 2-6	1.89 (1.30, 2.74)	<.001

HR = hazard ratio, CI = confidence interval

*Two-sided log-rank p-value

** AAT: Anti-Androgen Therapy

Initial variables: treatment group, prior hormone therapy, entry PSA level, PSA nadir after surgery, positive surgical margins, age, KPS, Gleason score, race

Final models were determined using a stepwise method with entry and exit significant levels of 0.10 and 0.15, respectively.

(1) Stratification variables

Table S4. Study Endpoints

Event Type	12-Year Rate (%)		Hazard Ratio	P-value
	RT+Placebo (n=376)	RT+ AAT** (n=384)		
Overall survival	71.3	76.3	0.77 (0.59-0.99)	0.04
Distant recurrence	23.0	14.5	0.63 (0.46-0.87)	0.005
Local progression	4.7	1.8	0.36 (0.15-0.85)	0.02
Second biochemical recurrence	67.9	44.0	0.48 (0.40-0.58)	<0.001
Third biochemical recurrence	80.7	84.2	1.11 (0.85-1.46)	0.43
Disease progression	69.2	47.1	0.51 (0.42-0.61)	<0.001
Prostate cancer death	13.4	5.4	0.49 (0.32-0.74)	<0.001
Non-prostate cancer death	15.3	17.9	1.10 (0.79-1.53)	0.58

*Third biochemical recurrence only includes patients who started salvage hormone therapy, n=128 and 90 for the two groups respectively.

** AAT: Anti-Androgen Therapy

Table S5. Non-Disease Specific Survival (Centrally Reviewed)

Year	RT+Placebo				RT+AAT*			
	Estimate (%)	95% CI (%)	Cumulative Failures	At Risk	Estimate (%)	95% CI (%)	Cumulative Failures	At Risk
0	0.0	--	0	376	0.0	--	0	384
1	0.8	0.2-2.2	4	372	0.5	0.1-1.8	2	382
2	1.9	0.8-3.6	7	368	1.0	0.4-2.5	4	376
3	3.2	1.7-5.4	12	359	2.9	1.5-4.9	11	368
4	4.5	2.8-7.0	17	350	3.9	2.3-6.3	15	362
5	5.6	3.6-8.3	21	332	5.6	3.6-8.2	21	347
6	6.8	4.5-9.6	25	319	6.4	4.2-9.2	24	337
7	7.9	5.4-10.9	29	307	8.1	5.6-11.1	30	326
8	9.0	6.3-12.2	33	294	10.0	7.2-13.4	37	308
9	9.9	7.1-13.2	36	280	12.0	8.9-15.6	44	294
10	11.9	8.8-15.5	43	262	13.5	10.2-17.2	49	280
11	13.1	9.9-16.9	47	240	15.0	11.5-18.9	54	259
12	15.3	11.8-19.3	54	203	17.9	14.0-22.1	63	223
13	17.7	13.8-22.0	60	130	19.7	15.7-24.1	68	151
14	20.3	15.8-25.1	64	71	20.8	16.6-25.4	70	78
15	21.5	16.5-26.9	65	25	23.9	18.1-30.2	72	32
Total			67				74	

* AAT: Anti-Androgen Therapy

CI = confidence interval.

Univariate analysis

hazard ratio (95% CI) [AAT* /Placebo]:	1.10 (0.79-1.53)
p-value (1-sided log-rank test):	0.289
p-value (2-sided log-rank test):	0.578

Cumulative incidence is used to estimate failure rates.

A failure is defined as any death that does not fall into the following categories: death due to prostate cancer or complications of protocol treatment (centrally reviewed), death with known progressive metastatic disease while on salvage hormone therapy, or death with a known rising PSA while on salvage hormone therapy. All other deaths are considered competing risks.

Table S6. Distribution of Patients by Highest Grade Toxicity Acute Radiotherapy

	RT+placebo (n=374)					RT+AAT* (n=382)				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Overall Highest Grade	160 (41.9)	120 (31.4)	16 (4.2)	1 (0.3)	0 (0.0)	191 (51.1)	112 (29.9)	8 (2.1)	0 (0.0)	0 (0.0)
Bladder	120 (31.4)	45 (11.8)	11 (2.9)	0 (0.0)	0 (0.0)	143 (38.2)	45 (12.0)	4 (1.1)	0 (0.0)	0 (0.0)
Bowel	156 (40.8)	79 (20.7)	3 (0.8)	0 (0.0)	0 (0.0)	158 (42.2)	74 (19.8)	1 (0.3)	0 (0.0)	0 (0.0)
Hematologic	21 (5.5)	7 (1.8)	2 (0.5)	0 (0.0)	0 (0.0)	27 (7.2)	7 (1.9)	3 (0.8)	0 (0.0)	0 (0.0)
Skin	79 (20.7)	9 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	73 (19.5)	14 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
Other	37 (9.7)	13 (3.4)	0 (0.0)	1 (0.3)	0 (0.0)	57 (15.2)	11 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)

* AAT: Anti-Androgen Therapy

Table S7. Distribution of Patients by Highest Grade Toxicity Hormone Therapy and Late Radiotherapy

	RT+Placebo (n=374)					RT+AAT* (n=382)				
	n and (%) of Patients by Grade					n and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Overall Highest Grade	108 (28.3)	131 (34.3)	58 (15.2)	14 (3.7)	1 (0.3)	94 (25.1)	170 (45.5)	88 (23.5)	9 (2.4)	3 (0.8)
Bladder/GU	106 (27.7)	93 (24.3)	23 (6.0)	3 (0.8)	0 (0.0)	109 (29.1)	96 (25.7)	26 (7.0)	1 (0.3)	0 (0.0)
Bowel/GI	111 (29.1)	52 (13.6)	5 (1.3)	1 (0.3)	0 (0.0)	118 (31.6)	67 (17.9)	9 (2.4)	1 (0.3)	0 (0.0)
Cardiac	4 (1.0)	5 (1.3)	1 (0.3)	5 (1.3)	0 (0.0)	9 (2.4)	6 (1.6)	10 (2.7)	5 (1.3)	2 (0.5)
Dyspnea	6 (1.6)	6 (1.6)	1 (0.3)	0 (0.0)	0 (0.0)	3 (0.8)	8 (2.1)	2 (0.5)	1 (0.3)	0 (0.0)
Fluid Retention	6 (1.6)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gynecomastia	33 (8.6)	8 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	162 (43.3)	90 (24.1)	14 (3.7)	0 (0.0)	0 (0.0)
Headache	10 (2.6)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	13 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematologic	23 (6.0)	9 (2.4)	2 (0.5)	2 (0.5)	0 (0.0)	44 (11.8)	9 (2.4)	6 (1.6)	0 (0.0)	0 (0.0)
Hot flashes	54 (14.1)	11 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	62 (16.6)	17 (4.5)	3 (0.8)	0 (0.0)	0 (0.0)
Impotence	9 (2.4)	20 (5.2)	16 (4.2)	0 (0.0)	0 (0.0)	10 (2.7)	24 (6.4)	28 (7.5)	0 (0.0)	0 (0.0)
Liver	12 (3.1)	3 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)	8 (2.1)	6 (1.6)	3 (0.8)	0 (0.0)	0 (0.0)
Nausea/vomiting	9 (2.4)	3 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)	16 (4.3)	2 (0.5)	1 (0.3)	0 (0.0)	0 (0.0)
Neurologic	15 (3.9)	9 (2.4)	3 (0.8)	1 (0.3)	0 (0.0)	7 (1.9)	11 (2.9)	6 (1.6)	2 (0.5)	0 (0.0)
Pain	28 (7.3)	31 (8.1)	6 (1.6)	0 (0.0)	0 (0.0)	24 (6.4)	27 (7.2)	2 (0.5)	0 (0.0)	0 (0.0)
Pending	4 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.9)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Skin-general	6 (1.6)	9 (2.4)	2 (0.5)	0 (0.0)	0 (0.0)	35 (9.4)	13 (3.5)	1 (0.3)	0 (0.0)	0 (0.0)
Skin-within XRT field	28 (7.3)	6 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	32 (8.6)	13 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Other	52 (13.6)	36 (9.4)	9 (2.4)	3 (0.8)	1 (0.3)	77 (20.6)	42 (11.2)	12 (3.2)	0 (0.0)	1 (0.3)
Unknown	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* AAT: Anti-Androgen Therapy

Table S8. List of Investigators

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