

# 6-Month Androgen Suppression Plus Radiation Therapy vs Radiation Therapy Alone for Patients With Clinically Localized Prostate Cancer

## A Randomized Controlled Trial

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**P**ROSTATE CANCER–SPECIFIC MORTALITY (PCSM) following external beam radiation therapy (RT) for patients with clinically localized prostate cancer has been shown to be associated with the Gleason score, serum prostate-specific antigen (PSA) level, and 1992 American Joint Commission on Cancer clinical tumor category at diagnosis.<sup>1,2</sup> Low-risk patients who have a PSA of 10 ng/mL or less, a Gleason score of 6 or less, and clinical category T1c or T2a disease have been reported to have PCSM estimates of less than 2% a decade following RT, whereas these estimates range from 12% to 30% for patients with higher PSA levels or Gleason scores at diagnosis.

Attempts at decreasing PCSM have included RT dose escalation<sup>3</sup> or the addition of androgen suppression therapy (AST) to 70 Gy RT. Although a single randomized trial<sup>3</sup> has shown a decrease in PSA progression for patients receiving RT dose escalation, survival data are not yet available. Given that PSA progression does not translate into PCSM for the vast majority of pa-

**Context** Survival benefit in the management of high-grade clinically localized prostate cancer has been shown for 70 Gy radiation therapy combined with 3 years of androgen suppression therapy (AST), but long-term AST is associated with many adverse events.

**Objective** To assess the survival benefit of 3-dimensional conformal radiation therapy (3D-CRT) alone or in combination with 6 months of AST in patients with clinically localized prostate cancer.

**Design, Setting, and Patients** A prospective randomized controlled trial of 206 patients with clinically localized prostate cancer who were randomized to receive 70 Gy 3D-CRT alone (n=104) or in combination with 6 months of AST (n=102) from December 1, 1995, to April 15, 2001. Eligible patients included those with a prostate-specific antigen (PSA) of at least 10 ng/mL, a Gleason score of at least 7, or radiographic evidence of extraprostatic disease.

**Main Outcome Measures** Time to PSA failure (PSA >1.0 ng/mL and increasing >0.2 ng/mL on 2 consecutive visits) and overall survival.

**Results** After a median follow-up of 4.52 years, patients randomized to receive 3D-CRT plus AST had a significantly higher survival ( $P=.04$ ), lower prostate cancer–specific mortality ( $P=.02$ ), and higher survival free of salvage AST ( $P=.002$ ). Kaplan-Meier estimates of 5-year survival rates were 88% (95% confidence interval [CI], 80%-95%) in the 3D-CRT plus AST group vs 78% (95% CI, 68%-88%) in the 3D-CRT group. Rates of survival free of salvage AST at 5 years were 82% (95% CI, 73%-90%) in the 3D-CRT plus AST group vs 57% (95% CI, 46%-69%) in the 3D-CRT group.

**Conclusion** The addition of 6 months of AST to 70 Gy 3D-CRT confers an overall survival benefit for patients with clinically localized prostate cancer.

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tients,<sup>4</sup> 70 Gy RT remains the standard of practice. Combining 3 years of AST with 70 Gy RT has been shown to improve survival for patients with locally advanced prostate cancer.<sup>5</sup> However, the toxicity of long-term AST can be significant, particularly in elderly patients.<sup>6</sup>

This prospective randomized controlled trial was performed to determine whether a survival benefit exists when adding 6 months of AST to 70 Gy 3-dimensional conformal RT (3D-CRT) in patients with clinically localized prostate cancer.

## METHODS

### Eligibility Criteria

Between December 1, 1995, and April 15, 2001, 206 patients from the Harvard outreach (Saint Anne's Hospital, Fall River, Mass; Metro West Medical

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Center, Framingham, Mass; Suburban Oncology Center, Quincy, Mass) and central hospitals (Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Beth Israel Deaconess Medical Center) with 1992 American Joint Commission on Cancer<sup>7</sup> category T1b to T2b, NX, M0 centrally reviewed adenocarcinoma of the prostate<sup>8</sup> were randomized to receive 70 Gy 3D-CRT alone or in combination with 2 months each of neoadjuvant, concurrent, and adjuvant AST. Eligible patients included those patients with a PSA of at least 10 ng/mL (maximum, 40 ng/mL) or a Gleason score of at least 7 (range, 5-10). Low-risk patients were ineligible unless they had radiographic evidence using endorectal coil magnetic resonance imaging (MRI) of extracapsular extension or seminal vesicle invasion. Patients were also considered ineligible if they had a prior history of malignancy except for nonmelanoma skin cancer or any history of hormone therapy use.

All patients were required to have a negative bone scan and pelvic lymph node assessment using MRI or computed tomography (CT) within 6 months of randomization. Eligible patients also needed to have an Eastern Cooperative Oncology Group performance status of 0 or 1 (range, 0-4), white blood cell count of at least 3000/ $\mu$ L, hematocrit of more than 30%, platelet count of more than  $100 \times 10^3/\mu$ L, and a life expectancy of at least 10 years, excluding death related to prostate cancer at study entry. All patients provided written informed consent; the study was approved by the institutional review boards at the Dana-Farber/Harvard Cancer Center, Saint Anne's Hospital, and the Metro West Medical Center.

### Randomization

Randomization was centralized at the Quality Assurance Center of the Dana-Farber/Harvard Cancer Center. A permuted blocks randomization algorithm was used with a block size of 4. Patients were assigned to the treatment groups with equal probability.

Prior to randomization, patients were stratified based on the baseline PSA level and centrally reviewed biopsy Gleason score<sup>8</sup> as follows: group 1, PSA of 20 to 40 ng/mL; group 2, biopsy Gleason score of at least 7; group 3, PSA of 10 to 20 ng/mL and a biopsy Gleason score of 6 or less; and group 4, low risk and extracapsular extension or seminal vesicle invasion on endorectal coil MRI.

### Treatment

**Radiation Therapy.** Photons of 10 MV or more were used. Patients were treated once daily and 5 days per week. The daily dose was 1.8 Gy for the initial 25 treatments, totaling 45 Gy, and 2.0 Gy for the final 11 treatments, totaling 22 Gy. Therefore, patients received a total dose of 70.35 Gy (67 Gy normalized to 95%) to the prostate plus a 1.5-cm margin using a 4-field 3D-CRT technique, which involved CT-based treatment planning and shaped conformal cerrobend blocks or a multileaf collimator. The prostate and the seminal vesicles were included in the initial radiation field using a 1.5-cm margin. Patients were simulated (radiation field mapped) before the start of neoadjuvant hormone therapy.

**Hormone Therapy.** AST consisted of a combination of a luteinizing hormone-releasing hormone (LHRH) agonist (leuprolide acetate) or goserelin and a nonsteroidal anti-androgen (flutamide). Leuprolide acetate (n=88) was delivered intramuscularly each month at a dose of 7.5 mg or 22.5 mg every 3 months. Goserelin (n=10) was administered subcutaneously each month at a dose of 3.6 mg or 10.8 mg every 3 months. Both LHRH agonists were permitted because they have been shown to have equivalent efficacy in the treatment of prostate cancer.<sup>9</sup> Flutamide (n=98) was taken orally at a dose of 250 mg every 8 hours and starting 1 to 3 days before the LHRH agonist to block the transient increase in testosterone caused by the LHRH agonist. Treating physicians and patients were not blinded to treatment groups because

the institutional review boards did not believe sham injections were justified.

At baseline and following the administration of the AST, a complete blood cell count and liver function tests, including aspartate aminotransferase, alanine aminotransferase, and total bilirubin, were obtained every 2 weeks during the first month of AST and then monthly until the 6-month course of AST was complete. Flutamide was discontinued if either aspartate aminotransferase or alanine aminotransferase exceeded 2 times the upper limit of normal or the patient developed drug-induced diarrhea or anemia causing clinical symptoms. The treating physician assessed toxicity at randomization.

### Follow-up Protocol

At each follow-up visit, a PSA level was obtained before performing the digital rectal examination. Follow-up visits were performed at the end of radiation treatment every 3 months for 2 years, every 6 months for an additional 3 years, and then annually thereafter. Genitourinary, gastrointestinal, dermatologic, and endocrinologic toxicities were assessed at each follow-up visit using common toxicity criteria.<sup>10</sup>

Patients were restaged with a bone scan and CT scan of the pelvis before the initiation of salvage AST and after PSA failure, defined as a PSA of more than 1.0 ng/mL and increasing by more than 0.2 ng/mL on 2 consecutive measurements. Salvage AST was started in both treatment groups following PSA failure, at a PSA level of approximately 10 ng/mL. Salvage therapy included an LHRH agonist dosed identically to initial therapy or a bilateral orchiectomy, which have been shown to be of equal efficacy.<sup>9</sup>

All patients were followed up directly by the site investigators (A.V.D. and P.W.K.) until death or until January 15, 2004, whichever came first. Patients who died with hormone refractory metastatic disease and an increasing PSA at the time of death were considered to have died from prostate cancer.

### Quality Assurance

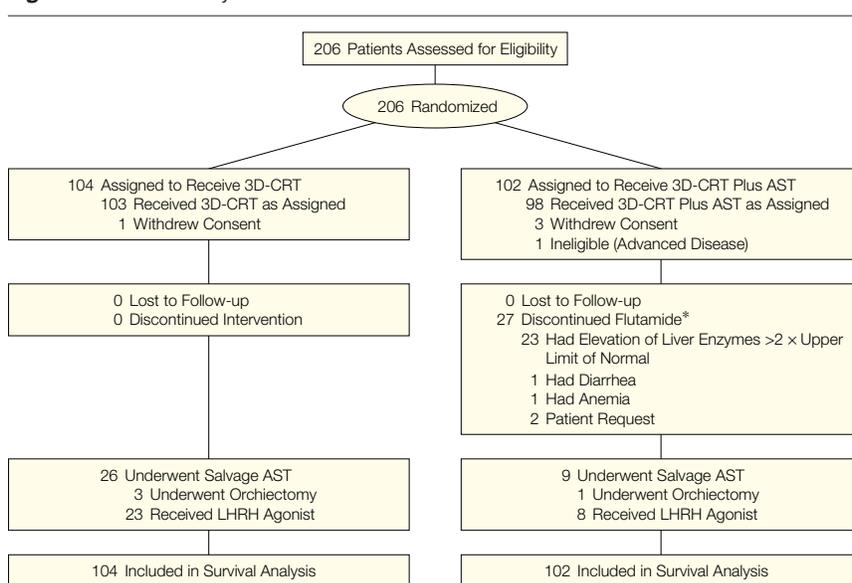
Before the start of RT, the principal investigator (A.V.D.) reviewed and modified as necessary the radiation prescription, simulation, and portal films. Patients who were randomized to receive 3D-CRT plus AST were required to keep a daily diary of flutamide usage, which was submitted monthly. The delivery of the LHRH agonist was recorded in the medical record and checked by the nurse protocol manager (M.L.).

### End Points and Statistical Analysis

The study was designed to detect a difference in freedom from biochemical progression between the 2 treatment groups, and assumed a true median time to failure of 2.7 years among patients treated with 3D-CRT and 4.8 years among patients treated with 3D-CRT plus AST, using a 2-sided log rank test with 80% power and type I error of 5%. Full power was projected to occur after 2.7 years of accrual at 100 patients per year and an additional 2 years of follow-up. An interim analysis for monitoring the primary end point was planned for 3 years following the end of accrual, using standard O'Brien-Fleming group sequential boundaries. Before the interim analysis, a publication<sup>5</sup> showed a much higher than expected (ie, 2-fold) reduction in death when AST was added to RT in patients with locally advanced prostate cancer. Therefore, follow-up was extended to allow assessment of the survival end point. Three months before the first planned analysis, the study statistician (J.M.) recommended an early analysis based on the number of deaths.

Descriptive statistics were used to characterize patients at study entry. The Wilcoxon rank sum test for ordered categorical data<sup>11</sup> was used to test for differences in toxicity rates of selected toxicities and the overall worst degree toxicity between treatment groups. The methods of Kaplan and Meier<sup>12</sup> and cumulative incidence<sup>13</sup> were used to estimate and characterize survival and mortality respectively over time. Overall survival was measured from the date

**Figure 1.** Flow of Study Patients



AST indicates androgen suppression therapy; 3D-CRT, 3-dimensional conformal radiation therapy; LHRH, luteinizing hormone-releasing hormone.  
\*Flutamide is the minor component of AST.

of randomization to the date of death or the date of last follow-up. Progression was defined on the date of institution of salvage AST. The log-rank test<sup>14</sup> was used to test for differences in survival between patients treated with 3D-CRT compared with 3D-CRT plus AST. Hazard ratios (HRs) and associated 95% confidence intervals (CIs) for death, death without progression, and PSA failure for patients receiving 3D-CRT compared with 3D-CRT plus AST were calculated before and after adjusting for the clinical tumor category, using a Cox proportional hazards regression model multivariable analysis.<sup>15</sup> Data were analyzed according to the intention-to-treat principle. SAS version 8.2 (SAS Institute, Cary, NC) was used for all statistical analyses.  $P < .05$  was considered statistically significant.

### RESULTS

From December 1, 1995, to April 15, 2001, 206 patients were randomized to the study ( $n = 104$  in the 3D-CRT group and  $n = 102$  in the 3D-CRT plus AST group) (FIGURE 1). The median duration of follow-up was 4.52 years. As of January 15, 2004, all but 5 patients had

been evaluated. For the survival analyses, these 5 patients were considered eligible. Four patients (1 in the 3D-CRT group and 3 in the 3D-CRT plus AST group) withdrew consent after randomization. After randomization, 1 patient in the 3D-CRT plus AST group was found to have clinical category T2c disease, which was considered locally advanced disease; therefore, that patient was considered ineligible. However, all patients regardless of eligibility were included in the survival analysis. Excluding these patients from the survival analyses did not affect the results. The 2 groups of patients were well balanced with regard to age, Eastern Cooperative Oncology Group performance status, Gleason score, percentage of positive prostate biopsies, prostate gland volume, and baseline PSA level, as shown in TABLE 1.

### Adherence

Information on treatment was available in 201 patients ( $n = 103$  in the 3D-CRT group and  $n = 98$  in the 3D-CRT plus AST group). The patients in the 3D-CRT group received 3D-CRT delivered per protocol guidelines. All pa-

tients in the 3D-CRT plus AST group completed 6 months of the LHRH agonist but 27 (28%) did not complete the 6-month course of flutamide because of adverse events: 23 patients (85%) had a liver function test result that was more than twice the upper limit of normal, 1 patient (4%) had diarrhea, 1 patient (4%) had anemia, and 2 (7%) patients requested to stop the drug (Figure 1).

**Toxicity**

TABLE 2 enumerates the genitourinary, gastrointestinal, dermatologic, and endocrinologic toxicity stratified by grade and treatment group. Patients receiving 3D-CRT plus AST therapy had a significant increase in grade 1 and 2 gynecomastia (18 vs 3,  $P = .002$ ) and, among men potent at baseline, grade 3 impotence increased significantly (26 vs 21,  $P = .02$ ). No other significant differences in late toxicity were noted and the results remained unchanged when estimates were performed by using an actuarial method.<sup>12</sup>

**Efficacy**

Estimates of overall survival were significantly higher for patients who were treated using 3D-CRT plus AST therapy compared with patients receiving only 3D-CRT ( $P = .04$ ), with Kaplan-Meier method estimates of 5-year survival of 88% (95% CI, 80%-95%) vs 78% (95% CI, 68%-88%), respectively (FIGURE 2). For patients receiving 3D-CRT (n=103), 6 deaths were due to prostate cancer and 17 were from other causes (5 from second cancers, 9 from cardiovascular disease, 1 from sepsis, and 2 from Alzheimer or liver disease), whereas, for patients who received 3D-CRT plus AST therapy (n=98), no deaths occurred due to prostate cancer and 12 were from other causes (3 from second cancers, 8 from cardiovascular disease, and 1 from sepsis).

**Table 1.** Baseline Clinical Characteristics of the Study Patients (N = 206)\*

Characteristic	3D-CRT (n = 104)	3D-CRT Plus AST (n = 102)
Clinical characteristics, median (range)		
Age, y	73 (51-81)	72 (49-82)
Baseline PSA level, ng/mL	11 (0.9-40)	11 (1.3-36)
Positive prostate biopsies, %	50 (17-100)	50 (17-100)
Gleason score†	7 (5-9)	7 (5-10)
5 or 6	27 (26)	30 (29)
3 + 4	37 (36)	35 (34)
4 + 3	24 (23)	23 (23)
8-10	16 (15)	14 (14)
Prostate gland volume, mL	41 (15-110)	37 (15-117)
Treatment stratification		
PSA of 20-40 ng/mL	13 (13)	12 (12)
Gleason score ≥7	64 (62)	64 (63)
PSA of 10-20 ng/mL and Gleason score ≤6	24 (23)	24 (24)
Low risk and endorectal MRI category T3	3 (3)	2 (2)
1992 AJCC clinical tumor category‡		
T1b	3 (3)	1 (1)
T1c	41 (40)	54 (53)
T2a	26 (25)	20 (20)
T2b	34 (33)	27 (27)
ECOG performance status§		
0	101 (97)	95 (93)
1	3 (3)	7 (7)
Potent at randomization	42 (40)	38 (37)

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; AJCC, American Joint Commission on Cancer; AST, androgen suppression therapy; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.

\*Data are No. (%) unless otherwise specified. Percentages may not sum to 100 due to rounding.

†Gleason score range is from 5 to 10. One patient among the 27 patients with a score of 5 or 6 in the 3D-CRT group who had a Gleason score of 3 + 3 disease was noted to have a tertiary grade of 4.

‡One patient in the combined therapy group had category T2c disease.

§ECOG performance status of 0 indicates asymptomatic and fully active; 1, restricted only in physically strenuous activity.

**Table 2.** Common Toxicity Criteria (Genitourinary, Gastrointestinal, Dermatologic, and Endocrinologic) by Grade and Treatment Group\*

Toxicity	3D-CRT (n = 103)				3D-CRT Plus AST (n = 98)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Urinary incontinence (complete)	3	1	1	0	2	1	1	0
Urinary incontinence (stress)	20	7	0	0	22	6	0	0
Hematuria	6	5	3	0	7	6	3	0
Diarrhea	19	8	3	0	18	9	1	0
Rectal bleeding	34	18	2	0	26	16	3	0
Anal fibrosis	1	0	0	0	1	0	0	0
Impotence†	4	7	21	0	1	6	26	0
Gynecomastia	1	2	0	0	14	4	0	0
Liver dysfunction	0	0	1‡	1‡	0	0	0	0

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; AST, androgen suppression therapy.

\*Toxicity grades are different for each type of adverse effect listed and are defined as 1, mild; 2, moderate; 3, severe; and 4, life-threatening (detailed explanation in Trotti et al<sup>10</sup>). Numbers are less than total number enrolled in each group because not all patients had toxicity.

†For men potent at baseline.

‡Not believed to be treatment related.

As shown in FIGURE 3, estimates of the cumulative incidence of PCSM significantly favored the 3D-CRT plus AST therapy ( $P=.02$ ), whereas estimates of the cumulative incidence of non-PCSM did not differ ( $P=.31$ ). The unadjusted and adjusted HRs for death were 2.07 (95% CI, 1.02-4.20;  $P=.04$ ) and 2.04 (95% CI, 1.01-4.20;  $P=.05$ ) for patients randomized to receive 3D-CRT compared with 3D-CRT plus AST (TABLE 3).

Median (interquartile range) time to initiation of salvage therapy following PSA failure was 8 months (3-13 months) in the 3D-CRT group vs 7 months (3-13 months) in the 3D-CRT plus AST group ( $P=.57$ ). At the initiation of salvage AST, patients randomized to receive 3D-CRT or 3D-CRT plus AST therapy had a negative bone scan and a median PSA level of 9.6 ng/mL. Survival without salvage AST was significantly higher for patients who were randomized to the 3D-CRT plus AST group vs 3D-CRT group ( $P=.002$ ). At 5 years, 82% of patients (95% CI, 73%-90%) in the 3D-CRT plus AST group vs 57% of patients (95% CI, 46%-69%) in the 3D-CRT group had not received salvage AST (FIGURE 4). Forty-three patients had disease progression in the 3D-CRT group compared with 21 patients in the 3D-CRT plus AST group. The unadjusted and adjusted HRs for survival without salvage AST were 2.30 (95% CI, 1.36-3.89;  $P=.002$ ) and 2.17 (95% CI, 1.28-3.69;  $P=.004$ ) for patients in the 3D-CRT group compared with the 3D-CRT plus AST group (Table 3).

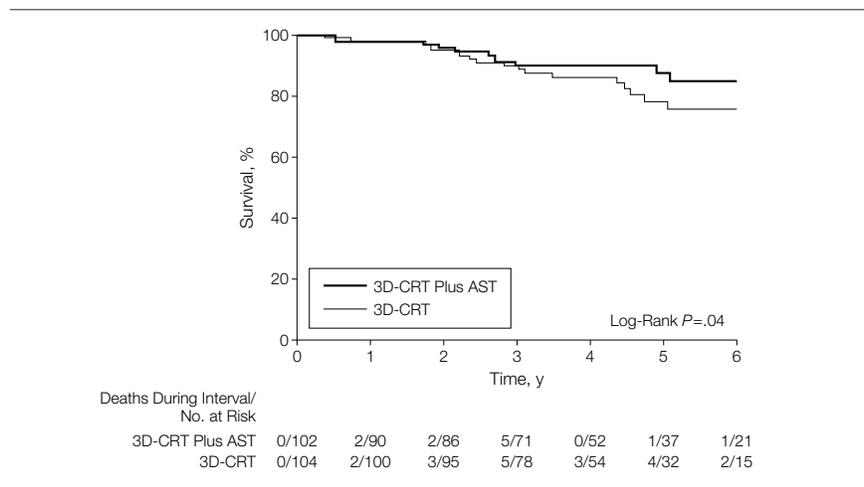
**COMMENT**

An overall survival benefit has been observed following 70 Gy RT plus 3 years of AST when compared with 70 Gy RT for patients with locally advanced and high-grade clinically localized prostate cancer.<sup>5</sup> This study found a similar 2-fold reduction in death before and after adjusting for clinical tumor category for patients with clinically localized disease and a PSA of at least 10 ng/mL or a Gleason score of at least 7 who were randomized to 70 Gy 3D-CRT plus 6 months of AST compared with 70 Gy 3D-CRT.

Given that many men treated for prostate cancer are often older and that AST use of more than 1 year has been shown to cause osteopenia,<sup>16</sup> impairment of memory, attention and executive functions,<sup>17</sup> and prolongation of the QT interval,<sup>18</sup> in addition to anemia,<sup>6</sup> muscle loss in exchange for body fat,<sup>19</sup> hot flashes,<sup>6</sup> and impo-

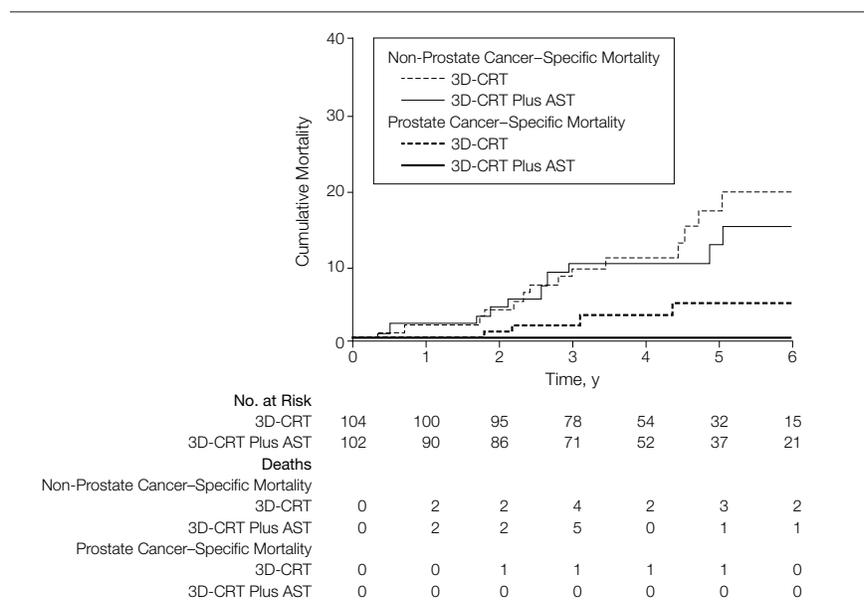
tence,<sup>6</sup> minimizing these effects by decreasing AST duration could profoundly impact a patient's quality of life. Therefore, the clinically significant implication of our study is that a 6-month course of AST in patients receiving RT who have clinically localized prostate cancer may be sufficient to reduce the risk of death.

**Figure 2.** Overall Survival for 3D-CRT vs 3D-CRT Plus AST



AST indicates androgen suppression therapy; 3D-CRT, 3-dimensional conformal radiation therapy.

**Figure 3.** Cumulative Incidence of Prostate Cancer and Non-Prostate Cancer-Specific Mortality for 3D-CRT vs 3D-CRT Plus AST



AST indicates androgen suppression therapy; 3D-CRT, 3-dimensional conformal radiation therapy. Log-rank  $P=.02$  for prostate cancer-specific mortality; log-rank  $P=.31$  for non-prostate cancer-specific mortality.

**Table 3.** Event Size and Hazard Ratio for Main Outcome Measures

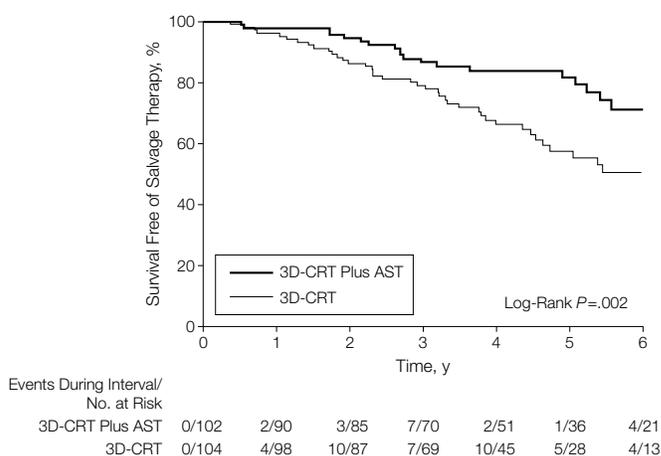
Outcome Measure	No. of Events		Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)*	P Value
	3D-CRT (n = 103)	3D-CRT Plus AST (n = 98)				
PSA failure	46	21	2.86 (1.69-4.86)	<.001	2.66 (1.56-4.55)	<.001
Survival free of salvage AST	43	21	2.30 (1.36-3.89)	.002	2.17 (1.28-3.69)	.004
Prostate cancer-specific mortality	6	0	NA	.02†	NA	.02†
Overall mortality	23	12	2.07 (1.02-4.20)	.04	2.04 (1.01-4.20)	.05

Abbreviations: 3D-CRT, 3-dimensional conformal radiation therapy; AST, androgen suppression therapy; CI, confidence interval; NA, not applicable due to no cancer-specific deaths in 3D-CRT plus AST group; PSA, prostate-specific antigen.

\*Adjusted for clinical tumor category.

†Log-rank P value comparing cumulative incidence.

**Figure 4.** Survival Without Progression for 3D-CRT vs 3D-CRT Plus AST



AST indicates androgen suppression therapy; 3D-CRT, 3-dimensional conformal radiation therapy. Progression was defined on the date of institution of salvage AST.

Several questions remain to be answered. First, the dose of radiation used is the current standard (ie, 70 Gy) and the pelvic lymph nodes were not treated. Whether a further increase in survival would have been observed if the pelvic lymph nodes were treated<sup>20</sup> remains to be answered by further follow-up of a completed study. In addition, to determine whether an RT dose of more than 70 Gy could improve survival over that measured in our study using 70 Gy and 6 months of AST would require a new randomized study. Second, patients received salvage AST when the bone scan was negative. Whether delaying initiation of salvage AST until the bone scan was positive would have further increased the survival benefit remains un-

answered. Third, the question of whether complete (LHRH agonist and nonsteroidal anti-androgen) compared with partial androgen blockade (LHRH agonist) is necessary to achieve the survival benefit noted in our study remains. Fourth, our study did not have a control group of AST alone; however, the Canadian Urologic Oncology Group has an ongoing study of AST with or without RT for patients with locally advanced prostate cancer that will address whether RT adds to overall survival when patients are androgen-suppressed.

Finally, whether long-term AST compared with short-term AST can provide an additional survival benefit for patients with locally advanced or high-

grade clinically localized prostate cancer requires further study and is the subject of a recently completed but not yet reported European randomized study in which a 3-year and a 6-month duration of AST were compared. In addition, the Radiation Therapy Oncology Group has completed and reported a randomized study<sup>21</sup> of men with locally advanced prostate cancer in which all patients received 70 Gy RT and were randomized to either 2 years and 4 months or 4 months of AST. Although a significant benefit of 3.4% in the 5-year estimates of PCSM was observed for patients who received long-term AST and RT, overall survival was not affected, likely the result of the competing causes of mortality in their study population.

In conclusion, the addition of 6 months of AST to 70 Gy 3D-CRT confers an overall survival benefit for patients with clinically localized prostate cancer.

**Author Contributions:** Dr D'Amico had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** D'Amico, Kantoff.  
**Acquisition of data:** D'Amico, Manola, Loffredo, Renshaw, DellaCroce.

**Analysis and interpretation of data:** D'Amico, Manola.  
**Drafting of the manuscript:** D'Amico, Manola, Loffredo, Renshaw, DellaCroce.

**Critical revision of the manuscript for important intellectual content:** D'Amico, Manola, Loffredo, Kantoff.  
**Statistical analysis:** Manola.

**Administrative, technical, or material support:** D'Amico, Loffredo, Renshaw, DellaCroce, Kantoff.

**Study supervision:** D'Amico.

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If any one faculty of our nature may be called more wonderful than the rest, I do think it is memory. There seems something more speakingly incomprehensible in the powers, the failures, the inequalities of memory, than in any other of our intelligences. The memory is sometimes so retentive, so serviceable, so obedient; at others, so bewildered and so weak; and at others again, so tyrannic, so beyond control! We are, to be sure, a miracle every way; but our powers of recollection and of forgetting do seem peculiarly past finding out.

—Jane Austen (1775-1817)