

## Phase II Study of Neoadjuvant Androgen Deprivation Followed by External-Beam Radiotherapy With 9 Months of Androgen Deprivation for Intermediate- to High-Risk Localized Prostate Cancer

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### A B S T R A C T

#### Purpose

To evaluate the toxicity and efficacy of individualized neoadjuvant androgen deprivation (AD) to maximal response followed by external beam radiotherapy (RT) with continued AD for a total of 9 months in a prospective phase II trial.

#### Patients and Methods

One hundred twenty-three patients received a total of 9 months of flutamide and luprolipe combined with RT. RT initiation was individualized to begin after maximum response to AD as assessed by monthly digital rectal examination and prostate-specific antigen (PSA). The neoadjuvant phase was restricted to no more than 6 months.

#### Results

Median time to initiation of RT was 4.7 months. Indications to begin RT (and their rates) were undetectable PSA (28%), PSA unchanged from one month to the next (46%), PSA rising from one month to the next (10%), 6 months of AD (14%), and other (2%). Five-year outcomes were biochemical disease-free survival, (DFS)  $63\% \pm 7\%$ ; clinical DFS,  $75\% \pm 5\%$ ; cancer-specific survival,  $99\% \pm 1\%$ ; and overall survival,  $89\% \pm 3\%$ . Patients initiating RT after 6 months of AD had significantly lower biochemical and clinical DFS. Those patients whose testosterone recovered to normal after completion of AD had a significantly superior survival rate. Of those patients potent before treatment, 65% remained so at last follow-up.

#### Conclusion

The combination of 9 months of AD and RT, with initiation of RT individualized on the basis of maximum response to AD, achieves disease control rates comparable with past studies, while preserving potency in many patients. Further studies are warranted to determine the optimal combination of AD and RT in this patient population.

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### INTRODUCTION

Attempts at decreasing prostate cancer-related morbidity and mortality through the addition of androgen deprivation therapy (AD) to treatment with external beam radiotherapy (RT) have been successful. Emerging data suggest that longer periods of AD are even more beneficial.<sup>1-4</sup> The drawback of extended AD is that patients are potentially subject to significant deleterious adverse effects including impotence, loss of libido, and osteoporosis.<sup>5-7</sup>

In addition to the extent of AD, the timing of RT and AD has varied across studies with strategies ranging from simultaneous initiation to

treatment with AD for anywhere from 2 to 8 months before RT initiation.<sup>1-4,8</sup> Zietman et al have demonstrated in a mouse androgen-responsive mammary adenocarcinoma model that delivering RT after maximal response to AD is superior to delivering RT on the day AD is given.<sup>9,10</sup> In addition, using a rat model, Kaminski et al demonstrated a significant advantage to a longer course of neoadjuvant AD compared with RT administered shortly after beginning AD.<sup>11</sup>

These models give strong preclinical support to the notion of neoadjuvant AD in combination with RT. Here, they are directly applied and individualized to patients by delivering RT after maximal response of the tumor to AD.

## PATIENTS AND METHODS

**Study Design**

This is a phase II trial evaluating the toxicity and efficacy of individualized neoadjuvant AD administered to maximal response followed by RT with continued AD for a total of 9 months for clinically localized prostate cancer. Between July 1997 and September 2002, 123 patients were enrolled at the Columbia University Medical Center (CUMC; New York, NY).

**Patients**

Patients had to have a biopsy-proven adenocarcinoma of the prostate graded by a CUMC pathologist. Patients had to have a serum prostate-specific antigen (PSA) greater than 4 ng/mL or a Gleason score (GS) greater than or equal to 8 at study entry. Bone scan and either computed tomography or magnetic resonance imaging of the pelvis were required. Patients with serum PSA greater than 50 ng/mL ( $n = 18$ ) were required to undergo pelvic lymphadenectomy. Patients with evidence of metastasis were deemed ineligible. All CUMC patients meeting eligibility criteria were offered enrollment in the study. Those who accepted had baseline characteristics generally representative of all CUMC patients, including approximately equal numbers of black, white, and Hispanic patients, although the exact numbers and characteristics of those offered enrollment were not tracked (Table 1).

**Table 1.** Patient Characteristics at Baseline

Characteristic	No.	%
Age, years		
Median	71	
Range	52-84	
Race/ethnicity		
Black	38	31
Hispanic	41	33
White	43	35
Other	1	1
Clinical stage		
T1a-T2a	60	49
T2b-T4	63	51
Gleason score		
$\leq 6$	16	13
7	42	34
8-10	65	53
Baseline PSA, ng/mL		
$\leq 30$	91	74
$> 30$	32	26
Baseline PSA ng/mL		
Median	16	
Range	1-163	
Risk group		
Low	1	1
Intermediate	20	16
High	102	83
RT technique		
CRT	97	79
IMRT	26	21
RT daily dose, Gy		
$< 1.80$	0	0
1.80	121	98
$> 1.80$	2	2
RT total dose, Gy		
$< 70.2$	3	2
70.2	108	88
$> 70.2$	12	10

Abbreviations: PSA, prostate-specific antigen; CRT, conformal radiotherapy; IMRT, intensity-modulated radiotherapy; RT, external beam radiotherapy.

**Treatment**

**RT.** Patients were treated with either conformal or intensity-modulated (IMRT) radiation therapy. Either a four-field or a six-field technique was used. The four-field technique consisted of 1.8 Gy daily to 45 Gy followed by a three-field technique to 70.2 Gy. The six-field technique utilized this beam arrangement throughout the treatment. The dose per fraction and total dose were the same with either technique. The planning target volume (PTV) was defined as the prostate and seminal vesicles with 1-cm margins. Dose was prescribed to the isodose volume encompassing the PTV. Two patients were treated with a cone-down off the seminal vesicles after 45 Gy.

On the basis of preliminary data from Royal Marsden Hospital<sup>12</sup> and M.D. Anderson Cancer Center (The University of Texas, Houston, TX),<sup>13</sup> beginning in February 2003, the target total dose of radiation per patient was raised to 75.6 Gy. For these high-dose IMRT patients ( $n = 6$ ), 100% of the prostate and seminal vesicles and at least 95% of the PTV were enclosed by the prescription isodose volume. Analysis revealed that exclusion of these patients did not alter any results (data not shown). Therefore, results are presented for the entire patient population only.

One patient did not receive radiation, and one patient discontinued radiation after receiving only 5.4 Gy. The five other noncompliant doses were due to miscellaneous factors such as machine malfunction, extra set-up x-rays, or physician preference.

**Hormonal therapy.** Patients received intramuscular luteal acetate 7.5 mg/mo injected monthly or once every 3 months and oral flutamide 250 mg tid for a total of 9 months. One patient received goserelin acetate instead of luteal acetate. Five percent of patients ( $n = 6$ ) did not receive flutamide at study entry because they did not meet predefined eligibility criteria for taking the medication. Ten percent ( $n = 13$ ) discontinued flutamide for other than protocol-defined reasons.

**Determination of time to start RT.** Starting at initiation of AD, tumors were monitored monthly by digital rectal examination (DRE) and serum PSA until they reached maximal response by both methods of assessment, at which time patients began RT. A patient was defined as having reached maximal PSA response if his serum PSA became undetectable ("undetectable") or was unchanged ("nadir") or rising ("rising") from one month to the next. A patient was defined as having reached maximal DRE response if his DRE findings stabilized from one month to the next or completely resolved ("complete response"). In order to avoid excessive delay, patients began RT no later than 6 months after initiation of AD ("6 months"), even if the criteria for maximal response were not met.

**Efficacy Assessments**

Protocol efficacy was determined post-therapy by determination of serum PSA, DRE, imaging (if serum PSA were found to be rising), biopsy, and mortality. Although biopsies were required by the protocol 18 months after completion of treatment, few were performed because of patient and physician reluctance. Consequently, treatment failure determinations were based on serum PSA or DRE in most cases. In addition, because failure to recover testosterone after AD may effectively prolong the therapeutic effects of AD, serum testosterone concentrations were determined. Patients were assessed 1 month after completion of RT, at completion of AD, every 3 months after completion of treatment during the first 2 years, every 6 months through the fifth year, and then annually for the remainder of the patient's life.

The primary end point of this study was biochemical disease-free survival (BDFS). Although the American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Conference produced guidelines for defining BDFS,<sup>14</sup> these guidelines were based on data obtained from clinical studies involving patients treated with radiotherapy alone. BDFS remains difficult to define for patients treated with both radiotherapy and hormonal therapy. Therefore, failure of BDFS was defined according to the definition used by Bolla et al<sup>3</sup>: serum PSA greater than 1.5 ng/mL and increasing on two consecutive measurements separated by at least 3 months. Death from any cause subsequent to two consecutive measurements demonstrating rising PSA was also considered a failure of BDFS.

Clinical disease-free survival (CDFS) was a secondary end point. Failure of local tumor control (defined by prostate biopsy or DRE), failure of

metastasis-free survival, and reinitiation of therapy were each defined as a failure of CDFS.

Another secondary end point was overall survival, with failure defined as death as a result of any cause. Cause-specific survival, with failure defined as either death during treatment for cancer recurrence or recurrence resulting in death, was additionally considered.

Freedom from hormone-refractory prostate cancer (HRPC) was considered as well, because it is a good surrogate end point for survival.<sup>15</sup> Failure of HRPC-free survival was defined for patients receiving AD as three consecutive rises in serum PSA, evidence of progressive metastases by imaging, or initiation of new treatment.

### Toxicity Assessments

Adverse events were assessed in detail during and after treatment by patient interview or laboratory measurement where appropriate. Acute adverse effects—those that manifest themselves during RT and within 6 months of completion of RT—associated with genitourinary and GI systems were considered separately from chronic adverse effects—those that manifest themselves 6 months after completion of RT and later. All adverse effects (except dysuria) were graded according to the National Cancer Institute's Common Terminology Criteria (CTC), version 3.0, with the following caveats. Grade 2 hot flashes/flushes were defined as those for which intervention was indicated. Erectile dysfunction for which erectile aids were indicated but not used was scored as "grade 2, 3." For patients with no documented rate of bowel movements at baseline, a rate of one per day was assumed. Grade 1 and grade 2 urinary frequency/urgency were not differentiated from one another, and patients with such toxicity were scored as "grade 1, 2." Rectal bleeding was evaluated on the basis of both the CTC (GI hemorrhage) and the Fox Chase-Late Effects Normal Tissue (FC-LENT) Task Force Criteria.<sup>16</sup> Secondary malignancies were recorded even if they were not related to cancer treatment. Dysuria was evaluated based on the Radiation Therapy Oncology Group (RTOG) toxicity system<sup>17</sup> because it is not scored in the CTC.

### Statistical Analysis

All data were analyzed in SPSS (SPSS Inc, Chicago, IL). Median follow-up time from initiation of treatment was 45 months (range, 0 to 81 months). All time-related end points were estimated by the Kaplan-Meier method with the log-rank statistic and the Bonferroni adjustment used to test for differences and correct for multiple comparisons, respectively. The multivariate prognostic-factor analysis used the Cox proportional hazards regression model. All data were analyzed according to the intention-to-treat principle.

### Conduct of Study

The institutional review board of CUMC approved the solicitation of subjects to participate in the study. All patients provided written informed consent.

## RESULTS

### Efficacy

Patient characteristics at initiation of RT are displayed in Table 2. Measures of disease control and mortality are reported in Table 3.

**Predictors of biochemical failure.** Patients with baseline serum PSA more than 30 ng/mL were significantly more likely to have a failure of BDFS at 5 years ( $54\% \pm 13\%$ ) than were those with baseline serum PSA  $\leq 30$  ng/mL ( $30\% \pm 7\%$ ;  $P = .045$ ). Similarly, patients who began RT after 6 months were significantly more likely to have a failure of BDFS at 5 years ( $82\% \pm 15\%$ ) than were patients who began RT with an undetectable ( $33\% \pm 12\%$ ), nadir ( $29\% \pm 8\%$ ), or rising ( $18\% \pm 11\%$ ) serum PSA (pooled comparison  $P = .002$ ). Pair-wise comparisons of the 6-month group with the undetectable ( $P = .005$ ) and nadir ( $P = .001$ ) serum PSA

**Table 2.** Patient Characteristics at Initiation of RT

Characteristic	No.	%
Time to initiation of RT		
Median		4.7
Range		2.0-24.5
PSA, ng/mL		
< 0.2	69	56
$\geq 0.2$	54	44
DRE		
Complete response	83	67
Incomplete response	40	33
Reason for initiation of RT		
Serum PSA undetectable	35	28
Serum PSA unchanged from one month to the next	56	46
Serum PSA rising from one month to the next	12	10
6 months since initiation of AD	17	14
Other	3	2

Abbreviations: RT, external beam radiotherapy; PSA, prostate-specific antigen; DRE, digital rectal examination; AD, androgen deprivation.

groups were also significant, even after Bonferroni adjustment (required significance of  $P < .0083$ ). Comparison with the rising serum PSA group was significant by standard criteria ( $P = .043$ ), but not after Bonferroni adjustment. Clinical stage, GS, risk group, race, age, serum PSA at initiation of RT, and complete response to DRE at initiation of RT failed to predict for biochemical failure. On multivariate analysis, only indication to begin RT independently predicted BDFS (Table 4).

**Predictors of clinical failure.** Patients with tumors of GS greater than 7 were significantly more likely to have a failure of CDFS at 5 years ( $40\% \pm 9\%$ ) than were patients with tumors of GS 7 ( $19\% \pm 8\%$ ) or less than 7 ( $0\%$ ;  $P = .024$ ). Patients who began RT after 6 months were also significantly more likely to have a failure of CDFS at 5 years ( $75\% \pm 15\%$ ) than were patients who began RT with an undetectable ( $27\% \pm 10\%$ ), nadir ( $15\% \pm 6\%$ ), or rising ( $0\%$ ) serum PSA (pooled comparison  $P = .001$ ; Fig 1). Pair-wise comparisons of the 6-month group with the nadir ( $P < .001$ ) and rising ( $P = .008$ ) serum PSA groups were also significant, even after Bonferroni adjustment. Comparison with the undetectable serum PSA group was significant by standard criteria ( $P = .043$ ), but not after Bonferroni adjustment.

**Table 3.** Study End Points and 5-Year Treatment Outcomes

Study End Point	Estimated 5 Years (%)
Biochemical DFS	$63 \pm 7$
Local tumor control	$84 \pm 4$
Metastasis-free survival	$96 \pm 3$
Freedom from re-initiation of therapy	$79 \pm 6$
Clinical DFS	$75 \pm 5$
Freedom from hormone refractory prostate cancer	$99 \pm 1$
Prostate cancer-specific survival	$99 \pm 1$
Overall survival	$89 \pm 3$

Abbreviation: DFS, disease-free survival.

**Table 4.** Multivariate Prognostic-Factors Model for BDFS

Variable	Relative-Risk Estimate	95% CI	P
Baseline PSA, ng/mL			
> 30*	1.00		
≤ 30	0.61	0.26 to 1.42	.25
Reason for initiation of RT			
6 months since initiation of AD*	1.00		
Serum PSA undetectable	0.30	0.10 to 0.89	.03
Serum PSA unchanged from one month to the next	0.23	0.08 to 0.67	.01
Serum PSA rising from one month to the next	0.21	0.04 to 0.99	.05
Other	0.00	NA	.99

Abbreviations: BDFS, biochemical disease-free survival; RT, external beam radiotherapy; AD, androgen deprivation; PSA, prostate-specific antigen; NA, not applicable.  
\*Reference category.

**Table 5.** Multivariate Prognostic-Factors Model for CDFS

Variable	Relative-Risk Estimate	95% CI	P
Gleason score			
8-10*	1.00		
7	0.33	0.12 to 0.92	.03
≤ 6	0.11	0.01 to 0.83	.03
Reason for initiation of RT			
6 months since initiation of AD*	1.00		
Serum PSA undetectable	0.29	0.10 to 0.88	.03
Serum PSA unchanged from one month to the next	0.12	0.04 to 0.39	< .01
Serum PSA rising from one month to the next	0.00	NA	.98
Other	19.20	1.14 to 323.89	.04

Abbreviations: CDFS, clinical disease-free survival; RT, external beam radiotherapy; AD, androgen deprivation; PSA, prostate-specific antigen; NA, not applicable.  
\*Reference category.

Clinical stage, risk group, race, age, baseline serum PSA, serum PSA at initiation of RT, and complete response to DRE at initiation of RT failed to predict for clinical failure. Multivariate analysis demonstrated that both GS and indication to begin RT independently predicted CDFS (Table 5).

*Further analysis of the group beginning RT after 6 months of AD.* There were no significant differences in age, race, clinical stage, GS, or risk group between this subgroup at study entry and the other response groups (PSA undetectable, nadir, and rising). There were also no significant differences in serum PSA at study entry, immediately

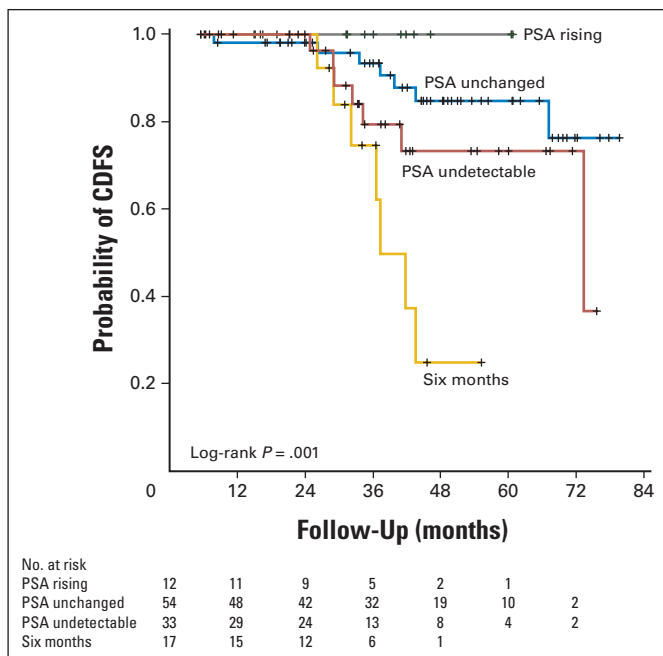
before RT, or at 3 months after initiation of AD. Furthermore, patients who initiated RT after 3 months of AD had elapsed were not more likely to have a failure of any study end point at 5 years compared with those who reached maximal response within 3 months (data not shown).

*Testosterone recovery.* Serum testosterone concentration returned to normal ( $\geq 270$  ng/dL) in 69% of patients ( $n = 85$ ). Median time to recovery was 9 months (range, 0 to 54 months). Pretreatment serum testosterone concentrations were determined in 86 patients. Serum testosterone returned to its baseline concentration after completion of AD in 37% ( $n = 32$ ) of those patients. Median time to recovery was 11 months (range, 0 to 52 months).

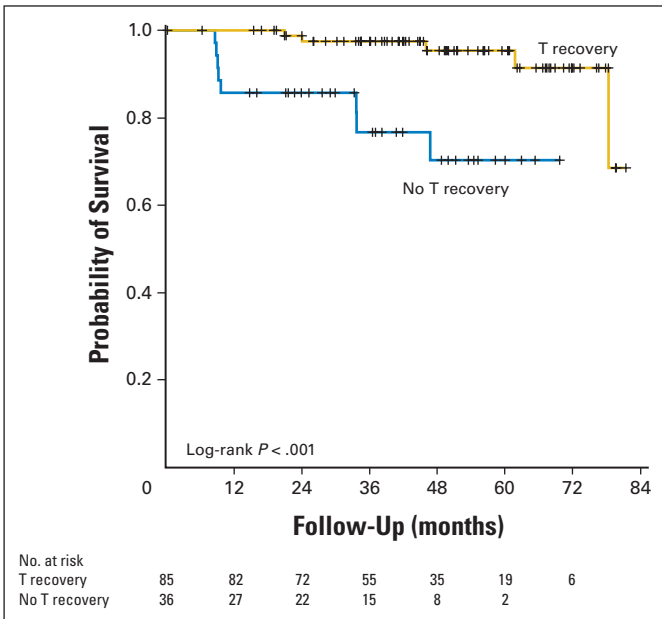
Patients who recovered serum testosterone to normal levels after completion of AD were not more likely to have a failure of BDFS or CDFS at 5 years compared with those who did not recover serum testosterone to normal levels (BDFS,  $40\% \pm 7\%$  v  $26\% \pm 14\%$ ,  $P = .176$ ; CDFS,  $25\% \pm 6\%$  v  $25\% \pm 12\%$ ,  $P = .840$ ). Interestingly, patients who recovered serum testosterone to normal levels after completion of AD were significantly more likely to survive for 5 years ( $95\% \pm 3\%$ ) than were those who did not recover serum testosterone to normal levels ( $70\% \pm 10\%$ ;  $P < .001$ ; Fig 2). Clinical stage, GS, risk group, race, age, serum PSA at study entry, serum PSA at initiation of RT, reason for initiation of RT, and complete response to DRE at initiation of RT failed to predict for overall mortality. Because of the small numbers of deaths, cause-of-death analysis was limited, but there was no statistically significant difference in cause of death between those who did and did not recover serum testosterone to normal levels.

**Toxicity**

*Erectile dysfunction.* The majority of patients lost potency during treatment (Table 6). At study entry, 69% ( $n = 85$ ) of patients had some potency (erectile dysfunction of grades 0, 1, or 2). During treatment, only 16% of patients ( $n = 25$ ) maintained some potency. Fortunately, many patients recovered potency after treatment (Table 7). Of the 85 patients with some potency at baseline, 65% ( $n = 55$ ; 45% of total) had some potency at last follow-up. Median time to recovery of potency was 10 months (range, 0 to 57 months). Age, race,



**Fig 1.** Actuarial rates of clinical disease-free survival (CDFS) comparing patients initiating external beam radiotherapy (RT) 6 months after initiation of androgen deprivation (AD) with patients initiating RT with undetectable serum prostate-specific antigen (PSA), serum PSA unchanged from one month to the next, and serum PSA rising from one month to the next with the number of patients at risk annually for each group listed.



**Fig 2.** Actuarial survival rates comparing patients who recovered serum testosterone (T) to normal levels with those who did not (normal, T concentration  $\geq$  270 ng/dL) with the number of patients at risk annually for each group listed.

and return to normal of serum testosterone concentration failed to predict for return of potency (data not shown).

**Other adverse events.** Most toxicities were mild, and patients often recovered quickly (Tables 8, 9, and 10). Less than 5% of patients experienced grade 3 toxicity except for anemia and acute urinary frequency/urgency. Ninety percent of patients with grade 3 anemia recovered, and they did so with a median recovery time of less than 1 month. Twenty percent of patients (n = 24) discontinued flutamide due to elevated liver function tests (n = 18) or diarrhea (n = 6), as required by the protocol.

Baseline		During AD						
Grade	No.	%	Stratified			Totals		
			Grade	No.	%	Grade	No.	%
0 or 1	81	66	0 or 1	16	20	0 or 1	16	13
			2	8	10			
			2 or 3	55	68			
			3	2	2			
2	4	3	0 or 1	0	0	2	9	7
			2	2	50			
			2, 3	1	25			
			3	1	25			
2, 3	38	31	0 or 1	0	0	2, 3	89	72
			2	0	0			
			2, 3	33	87			
			3	5	13			
						3	8	7

Abbreviation: AD, androgen deprivation.

Baseline		At Last Follow-Up						
Grade	No.	%	Stratified			Totals		
			Grade	No.	%	Grade	No.	%
0 or 1	81	66	0 or 1	29	36	0 or 1	30	25
			2	23	28			
			2, 3	20	25			
			3	9	11			
2	4	3	0 or 1	0	0	2	33	27
			2	3	75			
			2, 3	0	0			
			3	1	25			
2, 3	38	31	0 or 1	1	3	2, 3	45	37
			2	7	18			
			2, 3	25	66			
			3	5	13			
						3	15	12

**DISCUSSION**

Several randomized clinical trials have indicated improvement in the efficacy of treatment for clinically localized prostate cancer when RT is combined with AD, and some indicate that an extended course of AD may add benefit.<sup>1-4</sup> Here, the toxicity and efficacy of a protocol utilizing AD with RT in a novel way have been considered. Tables 11 and 12 put this protocol in the context of previously published prospective AD-with-RT trials.

Toxicity	Worst Grade (%)		
	1	2	3
Urinary frequency/urgency	NA	72*	12
Urinary retention	7	46	3
Dysuria	16	54	0
Hemorrhage, GU	13	1	0
Infection with unknown ANC, GU	NA	7	0
Urinary incontinence	11	1	0
Diarrhea	62	7	1
Hemorrhage, GI (CTC)	28	2	0
Hemorrhage, GI (FC-LENT)	NA	0	0
Proctitis	9	17	0
Abdominal distension/bloating	2	1	0
Anal incontinence	10	0	0
Flatulence	11	0	NA
Infection with unknown ANC, GI	NA	2	0
Mucositis/stomatitis (clinical examination)	2	0	0
Nausea	10	0	0
Obstruction, GI	0	1	1

NOTE. Radiation toxicities are considered to be acute if they manifest themselves during RT or within 6 months of completion of RT. Toxicity grades refer to those in the National Cancer Institute's Common Toxicity Criteria (CTC) for Adverse Events, version 3.0, except where noted.  
Abbreviations: NA, not applicable; GU, genitourinary; ANC, absolute neutrophil count; FC-LENT, Fox Chase-Late Effects Normal Tissue Task Force Criteria.  
\*Grade 1, 2 urinary frequency/urgency.

**Table 9.** Chronic Radiation Toxicities

Toxicity	Grade 1			Grade 2			Grade 3		
	%	Recovery Rate (%)	Median Recovery Time (months)	%	Recovery Rate (%)	Median Recovery Time (months)	%	Recovery Rate (%)	Median Recovery Time (months)
Urinary frequency/urgency	NA	—	—	53*	63	12	4	80	4
Urinary retention	21	73	4	18	73	7	2	100	4
Dysuria	28	76	7	19	74	6	0	0	0
Hemorrhage, GU	17	86	3	0	0	0	0	0	0
Infection, GU	NA	—	—	3	75	4	0	0	0
Urinary incontinence	11	79	6	2	67	13	0	0	0
Diarrhea	23	82	7	2	100	3	0	0	0
Hemorrhage, GI (CTC)	37	69	6	3	75	13	2	100	10
Hemorrhage, GI (FC-LENT)	NA	—	—	2	67	28	1	100	41
Proctitis	7	100	5	4	100	3	0	0	0
Abdominal distension/bloating	2	100	3	2	100	3	1	100	2
Anal incontinence	10	100	6	0	0	0	0	0	0
Flatulence	7	100	3	1	100	13	NA	—	—
Infection, GI	NA	—	—	0	0	0	0	0	0
Mucositis/stomatitis	1	0	0	0	0	0	0	0	0
Nausea	2	100	1	0	0	0	0	0	0
Obstruction, GI	0	0	0	0	0	0	0	0	0

NOTE. Radiation toxicities are considered to be chronic if they manifest themselves six months after completion of RT and later. Toxicity grades refer to those in the National Cancer Institute's Common Toxicity Criteria (CTC) for Adverse Events, version 3.0, except where noted. The percentage of patients in each grade refers to the percentage of patients who developed at least that toxicity grade. Median recovery time is calculated from the initial manifestation of the given toxicity grade. Abbreviations: NA, not applicable; GU, genitourinary; ANC, absolute neutrophil count; FC-LENT, Fox Chase-Late Effects Normal Tissue Task Force Criteria.

\*Grade 1, 2 urinary frequency/urgency.

The suggestion that extending the neoadjuvant phase is advantageous appears to conflict with data from Crook et al,<sup>8</sup> who reported no statistically significant differences in 5-year outcomes between patients receiving 3 months and 8 months of neoadjuvant AD. However, in their trial, patients were not monitored during their neoadjuvant phase. Therefore, it is possible that some patients on the 8-month arm were already progressing at initiation of RT. Furthermore, subgroup analysis of the Crook et al trial did show a benefit to 8 months of AD in their high-risk group. The vast majority of patients in the trial reported here were at high risk.

To assess different approaches in treating patients with clinically localized prostate cancer, it is useful to compare their treatment toxicities. Such toxicities may be assessed using a patient-reported validated quality-of-life instrument. However, given a multilingual patient population, the robust, clinician-driven CTC toxicity scale, which superbly details all toxicities and their grades, was chosen.

Of note in the study presented here is the relatively high rate of preservation of sexual potency after completion of AD. Unfortunately, with the exception of the trial conducted by D'Amico et al in 2004,<sup>1</sup> trials that combine AD with RT have not reported impotence rates

**Table 10.** Other Toxicities

Toxicity	Grade 1			Grade 2			Grade 3			Grade 4			Grade 5		
	%	Recovery (%)	Median Recovery Time (months)	%	Recovery (%)	Median Recovery Time (months)	%	Recovery (%)	Median Recovery Time (months)	%	Recovery (%)	Median Recovery Time (months)	%	Recovery (%)	Median Recovery Time (months)
Secondary malignancy	NA			NA			3	50	3	3	50	3	2	0	0
Ejaculatory dysfunction	11	8	3	3	25	3	NA			NA			NA		
Gynecomastia	NA			14	94	4	0	0	0	NA			NA		
Orgasmic dysfunction	4*	20	3	NA			NA			NA			NA		
Fatigue	72	100	1	23	100	1	1	100	1	0	0	0	NA		
Weight gain	52	63	5	19	65	13	2	100	40	NA			NA		
Hot flashes	90	96	3	10	100	1	3	100	1	NA			NA		
Alkaline phosphatase	31	74	6	2	100	2	1	100	1	0	0	0	NA		
ALT	37	84	2	11	100	1	6	100	1	1	100	0	NA		
AST	34	86	2	8	90	1	3	100	1	1	100	0	NA		
Hemoglobin	66	65	10	21	81	1	8	90	0	3	100	0	0	0	

NOTE. Toxicity grades refer to those in the National Cancer Institute's Common Toxicity Criteria (CTC) for Adverse Events, version 3.0, except where noted. The percentage of patients in each grade refers to the percentage of patients who developed at least that toxicity grade. Median recovery time is calculated from the initial manifestation of the given toxicity.

\*Orgasmic dysfunction is scored as present or absent.

Phase II Trial of AD and RT

**Table 11.** Comparison of Patient Characteristics at Baseline Among Studies of Combination AD and RT for Treatment of Clinically Localized Prostate Cancer

Study	No. of Patients	Follow-Up (months)		Gleason Score (%)			Clinical Stage (%)		Baseline PSA (%)			Age (years)		Race (%)		
		Median	Range	≤ 6	7	≥ 8	T1-T2	T3-T4	< 10 ng/mL	10- ≤ 20 ng/mL	> 20 ng/mL	Median	Range	White	African American	Other
D'Amico et al <sup>1</sup>	102	54		29	57	14	100	0	*	*	*	72	49-82			
Pilepich et al <sup>4</sup>	226	80		33	41	26	30	70				70	50-88			
Bolla et al <sup>3</sup>	203	66	1-126	29			8	92	21	15	64	71	54-80			
Hanks et al <sup>2</sup>																
ST	761	70	0-107	41	32	27	45	55	†	†	†	70	43-87	84	12	4
LT	753	70	0-107	40	35	25	45	55	‡	‡	‡	70	43-88	84	14	2
Crook et al <sup>8</sup>																
3-month	184	44	10-84	51	37	12	87	13	57	27	16	72	55-85			
8-month	184	44	10-84	50	39	11	86	14	50	32	18	72	50-81			
Heymann et al	123	44	0-81	13	34	53	73	27	34	23	43	71	52-84	35	31	34

Abbreviations: AD, androgen deprivation; RT, external beam radiotherapy; ST, short term; LT, long term; PSA, prostate-specific antigen.

\*Median PSA at baseline is 11 ng/mL (range, 1 to 36 ng/mL).

†Median PSA at baseline is 21 ng/mL.

‡Median PSA at baseline is 20 ng/mL.

after treatment. It is certain that patients in those trials that delivered hormone therapy for 2 to 3 years had a longer period of impotence than those treated with our approach. It is not known, however, whether the rates of sexual recovery after completion of AD are as good as those reported in this study.

A striking result obtained after analysis of patient outcomes was the high prevalence of biochemical and clinical failure among patients who initiated RT without first reaching maximal response (ie, after 6

months). The mechanism for the recurrence of biochemical and clinical disease in patients who initiate therapy without first reaching maximal response warrants further investigation. These patients might represent a subset of the population requiring more aggressive treatment than administered in this study. Thus, monitoring patient response, as demonstrated here, may be advantageous not only in delivering a more favorable sequence of AD and RT, but also in identifying a high-risk subgroup.

**Table 12.** Comparison of 5-Year Outcomes Among Studies of Combination AD and RT for Treatment of Clinically Localized Prostate Cancer

	Duration of Neoadjuvant AD (months)	Total Duration of AD (months)	Failure of BDFS (definition)	5-Year BDFS (%)	5-Year Local Tumor Control (%)	5-Year Metastasis-Free Survival (%)	5-Year Clinical Disease Free Survival (%)	5-Year Survival (%)	5-Year Cause-Specific Survival (%)
D'Amico et al <sup>1</sup>	2	6	PSA > 1.0 ng/mL and increasing > 0.2 ng/mL on two consecutive visits				82	88	100
Pilepich et al <sup>4</sup>	2	4	PSA ≥ 1.5 ng/mL	28	78	71	49	72	85
Bolla et al <sup>3</sup>	0	36	PSA > 1.5 µg/L and increasing on two consecutive measurements	76	98	90	74	78	94
Hanks et al <sup>2</sup>			Three consecutive increases in PSA, the administration of hormone treatment for an increasing PSA, or a post-treatment PSA nadir > 4.0 ng/mL						
ST	2	4		45	88	83	28	79	91
LT	2	28		72	94	89	46	80	95
Crook et al <sup>8</sup>			A rising PSA according to ASTRO consensus guidelines, DRE negative, and post-treatment biopsy negative if completed						
Intermediate risk, 3-month	3	3		65*					
Intermediate risk, 8-month	8	8		50*					
High risk, 3-month	3	3		39					
High risk, 8-month	8	8		52					
Heymann et al	Individualized	9	PSA > 1.5 ng/mL and increasing on two consecutive measurements	63	84	96	75	89	99

Abbreviations: AD, androgen deprivation; RT, external beam radiotherapy; BDFS, biochemical disease-free survival; PSA, prostate-specific antigen; ST, short term; LT, long term; ASTRO, American Society for Therapeutic Radiology and Oncology; DRE, digital rectal examination.

\*Estimated from visual inspection of Kaplan-Meier curves.

The finding of an improved survival in those patients whose testosterone recovered compared with those whose testosterone remained suppressed is surprising. Whether this reflects unseen and unappreciated overall benefits to health of having normal serum testosterone levels or whether lack of testosterone recovery is a marker for overall poor health is uncertain. Of note, those whose testosterone recovered did not have significantly higher rates of biochemical or clinical failure. These findings suggest that testosterone recovery may be beneficial to overall health without having deleterious effects on prostate cancer control, and further support the notion of limiting the length of time AD is administered to the minimum necessary.

In summary, the results of this study provide evidence that individualization of neoadjuvant AD to maximal response followed by RT with continued AD for a total of 9 months can safely be used to treat patients with intermediate- to high-risk clinically localized prostate cancer and preserve potency in many patients. Additional studies are needed to determine the optimal combination of AD and RT in this patient population.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author or immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being*

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#### REFERENCES

- D'Amico AV, Manola J, Loffredo M, et al: 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. *JAMA* 292:821-827, 2004
- Hanks GE, Pajak TF, Porter A, et al: Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytorreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 21:3972-3978, 2003
- Bolla M, Collette L, Blank L, et al: Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. *Lancet* 360:103-106, 2002
- Pilepich MV, Winter K, John MJ, et al: Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 50:1243-1252, 2001
- Denis LJ, Carneiro de Moura JL, Bono A, et al: Goserelin acetate and flutamide versus bilateral orchiectomy: A phase III EORTC trial (30853). EORTC GU Group and EORTC Data Center. *Urology* 42:119-130, 1993
- Crawford ED, Eisenberger MA, McLeod DG, et al: A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 321:419-424, 1989
- Fowler FJ Jr, Barry MJ, Lu-Yao G, et al: Outcomes of external-beam radiation therapy for prostate cancer: A study of Medicare beneficiaries in three surveillance, epidemiology, and end results areas. *J Clin Oncol* 14:2258-2265, 1996
- Crook J, Ludgate C, Malone S, et al: Report of a multicenter Canadian phase III randomized trial of 3 months vs 8 months neoadjuvant androgen deprivation before standard-dose radiotherapy for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 60:15-23, 2004
- Zietman AL, Nakfoor BM, Prince EA, et al: The effect of androgen deprivation and radiation therapy on an androgen-sensitive murine tumor: An in vitro and in vivo study. *Cancer J Sci Am* 3:31-36, 1997
- Zietman AL, Prince EA, Nakfoor BM, et al: Androgen deprivation and radiation therapy: Sequencing studies using the Shionogi in vivo tumor system. *Int J Radiat Oncol Biol Phys* 38:1067-1070, 1997
- Kaminski JM, Hanlon AL, Joon DL, et al: Effect of sequencing of androgen deprivation and radiotherapy on prostate cancer growth. *Int J Radiat Oncol Biol Phys* 57:24-28, 2003
- Dearnaley D, Hall E, Jackson C, et al: Phase III trial of conformal radiotherapy following neoadjuvant hormone treatment in early prostate cancer. *Int J Radiat Oncol Biol Phys* 54:134-135, 2002 (suppl)
- Pollack A, Zagars GK, Starkschall G, et al: Prostate cancer radiation dose response: Results of the MD Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 53:1097-1105, 2002
- Consensus statement: Guidelines for PSA following radiation therapy—American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys* 37:1035-1041, 1997
- Zietman AL, Dallow KC, McManus PA, et al: Time to second prostate-specific antigen failure is a surrogate endpoint for prostate cancer death in a prospective trial of therapy for localized disease. *Urology* 47:236-239, 1996
- Teshima T, Hanks GE, Hanlon AL, et al: Rectal bleeding after conformal 3D treatment of prostate cancer: Time to occurrence, response to treatment and duration of morbidity. *Int J Radiat Oncol Biol Phys* 39:77-83, 1997
- Cox JD, Stetz J, Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 31:1341-1346, 1995

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