Adjuvant Versus Neoadjuvant Androgen Deprivation With Radiotherapy for Prostate Cancer: Does Sequencing Matter?

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Abstract

Androgen deprivation therapy (ADT) with external-beam radiotherapy is the standard of care for patients with high-risk prostate cancer, but the optimal sequencing of ADT is not well established. In a retrospective review of 515 patients, we found no differences in outcomes between patients who received adjuvant ADT versus those who received a neoadjuvant and concurrent regimen.

Introduction/Background: Androgen deprivation therapy (ADT) is typically provided neoadjuvantly and concurrently with radiotherapy (RT) in the management of intermediate and high-risk prostate cancer. Our objective was to compare outcomes between patients who received adjuvant ADT (ADJ), ie, immediately after the completion of RT, to those who received a neoadjuvant and concurrent regimen (NEO). **Materials and Methods:** From 1995 to 2002, 515 patients with prostate cancer were definitively treated with RT and ADT. NEO was provided 2 to 3 months before the start of RT (n = 311). ADJ was initiated immediately after the completion of RT (n = 204). Kaplan-Meier analysis was used to calculate biochemical relapse-free survival (bRFS), distant metastasis-free survival (DMFS), and overall survival (OS). Cox proportional hazards regression was used to examine the impact of ADT timing on outcomes. **Results:** Ten-year bRFS, DMFS, and OS rates were 61%, 80%, and 66%, respectively. Ten-year bRFS rates for ADJ versus NEO were 63% versus 60% ($P = .98$). Ten-year DMFS rates for ADJ versus NEO were both 80% ($P = .60$). Ten-year OS rates for ADJ versus NEO were 65% versus 67% ($P = .98$). **Conclusion:** There was no significant difference in bRFS, DMFS, or OS between neoadjuvant versus adjuvant ADT in the setting of dose-escalated RT for localized prostate cancer. This suggests that the synergy between RT and androgen deprivation is independent of the sequencing of both modalities and that the initiation of RT does not need to be delayed for a course of neoadjuvant ADT.

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Introduction

Prostate cancer is an androgen-dependent malignancy, and androgen deprivation therapy (ADT) in combination with external-beam radiotherapy (EBRT) is a standard of care for patients with high-risk or locally advanced prostate cancer, as well as for select patients with intermediate-risk disease. The benefit of ADT with EBRT has been established in multiple randomized trials[1-3] that showed improvements in overall and/or cause-specific survival with concomitant utilization of ADT.

Long-term (at least 2 years) hormone therapy has been shown to be beneficial in men with high-risk, clinically localized prostate cancer. Two large randomized trials[4,5] compared short-term (4 to 6 months) with long-term (28 to 36 months) ADT. Both trials demonstrated that prolonged androgen blockade improved disease-free and disease-specific survival rates, and the European Organisation for Research and Treatment of Cancer (EORTC) 22961 trial showed a benefit in overall survival (OS).

Although the use of ADT is well established in the treatment of high-risk, clinically localized prostate cancer, the optimal sequencing of ADT is not. The majority of clinical trials have used the neoadjuvant/concurrent/adjuvant paradigm, with most studies initiating radiotherapy (RT) approximately 2 months after the initiation

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of ADT. To our knowledge, Radiation Therapy Oncology Group (RTOG) 9413 is the only major prospective study to examine ADT sequencing, and there has been significant controversy regarding the interpretation of the results from the trial.[6]

In this study, we retrospectively reviewed a series of 515 patients with prostate cancer treated at Cleveland Clinic between 1995 and 2002 who received definitive EBRT with either neoadjuvant and concurrent (NEO) or adjuvant (ADJ) hormone therapy for a total of 6 months.

Materials and Methods

Using our institutional review board–approved, prospectively maintained prostate cancer registry, we identified 515 patients who were treated with definitive, high-dose EBRT and 6 months of hormone therapy at Cleveland Clinic from 1995 to 2002.

Routine workup included history and physical examination, digital rectal examination, serum prostate-specific antigen (PSA), and transrectal ultrasound-guided core needle biopsies of the prostate gland, with histologic grading of Gleason score. Patients with distant or nodal metastatic disease as identified on bone scans or computed tomographic scans of the abdomen and pelvis were excluded from this study. Patients were clinically staged in accordance with the sixth edition of the American Joint Committee on Cancer, as recorded by the digital rectal examination. Magnetic resonance imaging was not used for staging. For patients initially diagnosed outside of our institution, we

Table 1 Patient and Treatment Characteristics

Characteristic	All Patients	Adjuvant AD	Neoadjuvant AD	*P*
No. of Patients	515 (100)	204 (39.6)	311 (60.4)	
Age (years)				.32
Median	69	68.5	69	
Range	45-85	45-85	49-85	
Clinical T Stage				.6
T1-T2a	346 (67.2)	134 (65.7)	212 (68.2)	
T2b-c	105 (20.4)	46 (22.5)	59 (19)	
T3	64 (12.4)	24 (11.8)	40 (12.9)	
Prostate-Specific Antigen				.31
Median (ng/mL)	13	12.9	13.1	
Mean (ng/mL)	16.9	16.1	17.4	
Range	2.2-111.1	2.3-90	2.2-111.1	
<4 ng/mL	10 (1.9)	2 (1)	8 (2.6)	
4-10 ng/mL	173 (33.6)	70 (34.3)	103 (33.1)	
10.1-20 ng/mL	200 (38.8)	83 (40.7)	117 (37.6)	
>20 ng/mL	132 (25.6)	49 (24)	83 (26.7)	
Bx Gleason Score				.003
<6	133 (25.8)	44 (21.6)	89 (28.6)	
7	268 (52)	125 (61.3)	143 (46)	
>8	114 (22.1)	35 (17.2)	79 (25.4)	
Risk Group (a)				<.001
High	240 (46.6)	86 (42.2)	154 (49.5)	
2 Intermediate RF	109 (21.2)	55 (27)	54 (17.4)	
Intermediate	144 (28)	63 (30.9)	81 (26)	
Low	22 (4.3)	0 (0)	22 (7.1)	
Risk Group (b)				.6
High	349 (67.8)	141 (69.1)	208 (66.9)	
Low/intermediate	166 (32.2)	63 (30.9)	103 (33.1)	
Dose				.1
78 Gy at 2 Gy/Fx	168 (32.6)	75 (36.8)	93 (29.9)	
70 Gy at 2.5 Gy/Fx	347 (67.4)	129 (63.2)	218 (70.1)	
Radiotherapy Technique				.1
CRT	168 (32.6)	75 (36.8)	93 (29.9)	
IMRT	347 (67.4)	129 (63.2)	218 (70.1)	

Data are presented as n (%) unless otherwise indicated.
Abbreviations: Adjuvant AD = adjuvant androgen deprivation after radiotherapy; CRT = 3-dimensional conformal radiotherapy; Fx = fraction; IMRT = intensity-modulated radiotherapy; Neoadjuvant AD = neoadjuvant and concurrent androgen deprivation therapy; RF = risk factor.