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Duration of Androgen Deprivation Therapy Influences Outcomes for Patients Receiving Radiation Therapy Following Radical Prostatectomy

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Abstract

Background: Limited data exist to guide the use of androgen deprivation therapy (ADT) for men treated with radiation therapy (RT) after radical prostatectomy (RP). The optimal duration of ADT in this setting is unknown.
Objective: To determine if the duration of ADT influences clinical outcomes for men receiving post-RP RT.
Design, setting, and participants: A total of 680 men who received adjuvant radiation therapy (n = 105) or salvage radiation therapy (n = 575) between 1986 and 2010 at a single tertiary care institution were reviewed retrospectively. Median follow-up post-RT was 57.8 mo.
Intervention: RT was delivered using three-dimensional conformal or intensity-modulated RT in 1.8-Gy fractions. For patients treated with ADT, >80% were treated with a gonadotropin-releasing hormone agonist with or without a nonsteroidal antiandrogen.
Outcome measurements and statistical analysis: Biochemical failure (BF), distant metastasis (DM), prostate cancer–specific mortality (PCSM), and overall mortality were assessed using Kaplan-Meier analysis and propensity score analysis.
Results and limitations: Overall, 144 patients (21%) received ADT with post-RP RT, most of whom had high-risk disease features such as Gleason score 8–10, seminal vesicle invasion, or pre-RT prostate-specific antigen >1 ng/ml. Median ADT duration was 12 mo (interquartile range: 6.0–23.7). Patients who received <12 mo of ADT had an association with increased BF (hazard ratio [HR]: 2.27; p = 0.003) and DM (HR: 2.48; p = 0.03) compared with patients receiving ≥12 mo of ADT. The 5-yr rates of DM were 6.0% and 23% for ≥12 and <12 mo of ADT, respectively. On propensity score analysis controlling for pretreatment and treatment-related factors, each month of ADT was associated with a decreased risk for BF (HR: 0.95; p = 0.0004), DM (HR: 0.88; p = 0.0004), and PCSM (HR: 0.90; p = 0.037). These findings are limited by the retrospective nature of our analysis.
Conclusions: For men with high-risk disease features receiving ADT with post-RP RT, the duration of ADT is associated with clinical outcomes. Our findings suggest that for these men an extended course of ADT ≥12 mo may be preferable. Validation of our findings is needed.
Patient summary: We evaluated outcomes for men with high-risk disease features treated with androgen deprivation therapy (ADT) and radiotherapy after radical prostatectomy. Longer durations of ADT resulted in improved patient outcomes.

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1. Introduction

The addition of androgen deprivation therapy (ADT) to external-beam radiation therapy (EBRT) as definitive treatment for high-risk localized prostate cancer (PCa) has been demonstrated to improve patient outcomes in multiple randomized controlled trials [1–8]. An advantage in overall survival (OS) has been associated with both the use of short-term ADT (4–6 mo) [3,6,8] and long-term ADT (2–3 yr) [2] for men treated with definitive radiation therapy (RT). Both Radiation Therapy Oncology Group (RTOG) 9202 and European Organization for Research and Treatment of Cancer (EORTC) 22961 compared short-term ADT with long-term ADT and found improved outcomes among those randomized to long-term ADT [1,5].

Despite a significant amount of evidence suggesting that the addition of ADT to EBRT for the definitive treatment of localized PCa improves patient outcomes, little is known regarding the use of ADT for patients receiving RT after radical prostatectomy (RP). Several retrospective analyses identified an association between the use of ADT with post-RP RT and decreased rates of biochemical recurrence [9–14]. Early results from RTOG 9601, which randomized salvage RT patients to RT with or without the addition of 2 yr of ADT, found improved freedom from prostate-specific antigen (PSA) progression and a reduction in the development of metastases in those treated with the addition of ADT [15].

Although limited evidence suggests that there is indeed a role for the addition of ADT to RT for patients receiving RT post-RP, there are no data to guide the duration of ADT use in this setting. The ongoing Radiotherapy and Androgen Deprivation in Combination After Local Surgery (RADICALS) trial will hopefully shed light on this issue [16]; however, preliminary results are not expected in the near future because the trial plans to continue recruiting until at least mid-2016.

Given the lack of knowledge concerning the optimal duration of ADT when added to post-RP RT, we sought to assess retrospectively whether the duration of ADT in this setting had an impact on biochemical failure (BF), distant metastasis (DM), prostate cancer–specific mortality (PCSM), and overall mortality (OM) in a cohort of patients who were treated with RT and ADT after RP.

2. Patients and methods

2.1. Patient selection

A total of 680 patients who received either adjuvant (n = 105) or salvage RT (n = 575) post-RP at a single institution between 1986 and 2010 (with 75% treated after 1999) were reviewed retrospectively through an analysis approved by the institutional review board. Salvage radiation therapy (SRT) was defined as RT given for a persistently elevated PSA post-RP or for biochemical recurrence post-RP. All other RT was considered adjuvant radiation therapy (ART). Of the 680 patients treated with post-RP RT, 144 (21%) received ADT with RT and are the focus of this analysis.

2.2. Treatment and follow-up

RT was delivered using three-dimensional conformal RT or intensity-modulated RT typically in 1.8-Gy fractions, with >95% of patients receiving 64.0–70.2 Gy. Whole pelvis radiation therapy (WPRT) fields were treated in 17% of patients, typically in 1.8 Gy fractions to 45 Gy. For those patients treated with ADT, >80% were treated with a gonadotropin-releasing hormone (GnRH) agonist with or without the addition of a nonsteroidal antiandrogen. The remaining patients were treated with a nonsteroidal antiandrogen with or without a 5α-reductase inhibitor.

2.3. End points

Primary outcomes measured included BF, DM, PCSM, and OM. The time to all end points was determined from the start date of RT. ADT duration was calculated from the day of initiation of ADT to the last day of ADT effectiveness (i.e., a 3-mo injection of a GnRH agonist contributed 3 mo). Serum testosterone values were not routinely evaluated. BF was defined as a serum PSA value of at least 0.2 ng/ml greater than the post-SRT nadir followed by a second higher serum PSA value [17] or any PSA value of at least 0.5 ng/ml greater than the post-SRT nadir [18,17]. DM was defined as the presence of any clinical, pathologic, or radiologic evidence of metastasis. PCSM was defined as any death in a patient with metastatic or hormone-refractory PCa. OM was defined as any death, independent of the cause.

2.4. Statistical analysis

Patient characteristics were compared between treatment groups using one-way analysis of variance and chi-square methods for continuous and categorical variables, respectively. Survival outcomes were summarized with Kaplan-Meier methods. A propensity score analysis was performed to assess the impact of ADT use and ADT duration on patient outcomes while accounting for the nonrandomized nature of treatment assignment in these data. Specifically, the probability of treatment assignment (propensity score) was calculated using logistic regression. The inverse of this propensity was then used to fit weighted Cox models [19]. A robust sandwich variance estimator [20] was used to estimate the covariance matrix and calculate a p value for a score test of no treatment effect.

To calculate the propensity score, we used a stepwise logistic regression with outcome equal to treatment (ADT use vs no ADT use, ADT duration <12 mo vs ADT duration ≥12 mo). For the ADT use versus no use ADT propensity, we used a 0.2 level of significance to select variables for inclusion in the propensity score model. The identified model included Gleason score (2–6, 7, and 8–10), pre-RT PSA, and positive SMs. The same three variables were used to calculate the propensity of long-term ADT use (≥12 mo) even though in this case, pre-RT PSA was not significant at the 0.2 level (p = 0.7). This propensity score was then used to perform adjusted analyses of the impact of ADT duration (both as a long- vs short-term variable and as a continuous covariate) on patient outcomes.

We also performed sensitivity analyses in which the propensity score was built using all covariates regardless of statistical significance. The resulting estimates of treatment effect and statistical significance were similar and are not presented. All statistical analyses were performed using SAS v.9.3 (SAS Institute, Cary, NC, USA) and MedCalc v.12.3.0.0 (MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Patient characteristics

A total of 144 patients (21%) received concurrent ADT with post-RP RT. The median follow-up post-RT was 57 mo (interquartile range [IQR]: 32.7–86.5), with median follow-up of 57 mo (n = 114) for living patients, and 58 mo