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The impact of timing of salvage hormonal therapy on survival after brachytherapy for prostate cancer

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ABSTRACT

PURPOSE: We aimed to evaluate the impact of timing of androgen deprivation therapy (ADT) on survival in a cohort of patients with biochemical recurrence (BCR) after brachytherapy treatment for prostate cancer.

METHODS AND MATERIALS: We retrospectively identified 2366 men receiving permanent prostate brachytherapy with or without external beam radiation therapy. Patients experiencing BCR were stratified by receipt of immediate or delayed (≥3 months) ADT and prostate-specific antigen (PSA) failure threshold of 10 ng/mL. Prostate cancer–specific mortality (PCSM) and all-cause mortality (ACM) were evaluated using Fine–Gray's competing risks regression and Cox proportional hazard model, respectively.

RESULTS: We identified 109 patients in the study cohort treated with ADT for BCR, followed for a median of 11.4 years. Competing risk regression revealed that there was no difference in PCSM for patients receiving delayed vs. immediate ADT (hazard ratio [HR], 0.94; 95% confidence interval [CI]: 0.44–2.00: $p = 0.871$) or for those initiating hormonal therapy at PSA threshold of 10 vs. <10 ng/mL (HR, 0.85; 95% CI: 0.41–1.75; $p = 0.649$); similarly, there was no difference in ACM. PSA doubling time <6 months (HR, 2.52; 95% CI: 1.22–5.23; $p = 0.013$), time to BCR <3 years (HR, 3.27; 95% CI: 1.67–6.42; $p = 0.003$), and permanent prostate brachytherapy with external beam radiation therapy (HR, 5.21; 95% CI: 2.05–13.26; $p = 0.001$) were significantly associated with PCSM, as well as ACM.

CONCLUSIONS: Among a cohort of brachytherapy patients, we identified no significant difference in survival for delayed salvage hormonal therapy. Shorter PSA doubling time and time to BCR are significantly associated with adverse outcomes, and these patients should be considered for immediate salvage therapy.

Keywords: Brachytherapy; Androgen deprivation; Prostate cancer; Salvage treatment; Survival

Introduction

The use of androgen deprivation therapy (ADT) with pelvic radiation therapy (RT) has been accepted as the standard of care for patients with intermediate- and high-risk prostate cancer (PCa) opting for treatment with radiation. This recommendation has emerged from randomized evidence demonstrating a benefit in both cancer-specific and overall survival in high clinical-risk men receiving ADT with RT, compared to RT alone (1, 2). For patients who experience biochemical failure after RT, however, the optimal timing and modality of salvage therapy remains unclear.

Despite the prevalent use of salvage hormonal therapy, no consensus exists regarding the optimal timing of ADT after primary RT. Moreover, given the detriment to health-related quality of life, metabolic syndrome, and cardiovascular outcomes, there is a growing interest in minimizing duration of androgen blockage without compromising oncologic control. In this context, we aimed to evaluate the impact of salvage ADT timing on survival in a cohort of patients

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treated with permanent prostate brachytherapy (PPB) with or without external beam radiation therapy (EBRT). To our knowledge, this is the first study to address this question in a PPB cohort. We additionally evaluated clinical factors associated with prostate cancer–specific mortality (PCSM) and all-cause mortality (ACM) in this cohort.

Methods

Under institutional review board approval, we retrospectively identified men receiving PPB ± EBRT for cT1-T3 PCa at a single institution between 1990 and 2012. Study participants were further refined to those experiencing biochemical recurrence (BCR) as defined by Phoenix criteria as a rise of 2 ng/mL or more of the prostate-specific antigen (PSA) nadir. Patients who had received local salvage treatment (i.e., salvage prostatectomy, cryotherapy) or neoadjuvant ADT in the 12-month period before BCR were excluded, along with those patients missing data on precise timing of salvage ADT.

Prostate biopsy was not routinely performed in patients with BCR. Testosterone recovery was assumed present 12 months from last administration of neoadjuvant ADT. Patients experiencing BCR were stratified by: receipt of immediate vs. delayed ADT (≥3 months), receipt of ADT at PSA threshold of 10, PSA doubling time (PSA-DT) at hormone initiation (<6 months vs. ≥6 months), and time to BCR (<3 years vs. ≥3 years from completion of RT). The cutoffs for these variables were chosen near the median of their respective distributions to maximize statistical power. Patients who initiated ADT up to 3 months after the date of BCR were included in the immediate group as they likely had a PSA confirmation before initiation of hormones. PSA-DT was calculated using the last two to three PSA values before the initiation of hormonal therapy, each separated in time by a minimum of 3 months. The slope of the regression line of log2 (PSA) vs. time was used to calculate the number of doublings per unit time and 1/slope defined the PSA-DT (3).

Additional clinical variables included Gleason score, clinical stage, baseline (pretreatment) PSA, age, biologic effective dose, receipt of neoadjuvant ADT, and combined EBRT with PPB. Survival was calculated from the completion of PPB ± EBRT to the date of death. The primary and secondary outcomes were PCSM and ACM, respectively. PCSM was defined as death with evidence of metastatic PCa. Distant metastases were documented by cross-sectional imaging (chest/abdomen or pelvis) and/or radionuclide bone scans. Imaging studies were obtained at the treating physician's discretion based on symptoms or PSA findings.

PPB was performed using a real-time transrectal ultrasound-guided technique as described previously (4). Patients were stratified into three risk groups as per the National Comprehensive Cancer Network (NCCN) guidelines (5) and treated with: ^{125}I or ^{103}Pd implant alone (NCCN low risk); ADT and a full dose implant or a partial ^{103}Pd implant followed by EBRT to 45 Gy (NCCN intermediate risk); trimodal therapy including ADT, partial ^{103}Pd implant, and 45 Gy of EBRT (NCCN high risk). Iodine-125 implants were generally prescribed to 160 Gy, full ^{103}Pd implants to 124 Gy, and partial ^{103}Pd implant to 100 Gy. EBRT was delivered with three-dimensional conformal radiation before 2003 and intensity-modulated RT or image-guided RT with gold fiducials thereafter. Fields were six fields for three-dimensional conformal. Intensity-modulated RT was on the Novalis with exact tract image-guided RT. Dose per fraction was 180 cGy. Median EBRT dose was 4500 cGy.

Postimplant dosimetry was performed for all patients using CT-based dosimetric analysis. ADT consisted of a gonadotropin-releasing hormone agonist with or without an antiandrogen. In general, neoadjuvant ADT was given for 3–6 months for low-risk cases with prostate volume greater than 50 cc. For intermediate-risk patients, ADT was given for 6-month duration, including 3-month neoadjuvant. For high-risk patients, ADT was given for the duration between 9 months and 2 years with most patients treated for 9 months (6). After treatment, patients were followed at least every 6 months prospectively.

Baseline clinical and pathologic characteristics were analyzed using χ^2 tests and t-statistics. Cumulative incidence curves were generated, and Gray's test was used to test differences between the groups. Fine–Gray's competing risk regression model was used to adjust for multiple covariates for PCSM; Cox proportional hazard model was used for ACM. Statistical significance was defined as an alpha level of <0.05. All analyses were performed using SPSS version 19 (Armonk, NY).

Results

Of 2366 patients receiving treatment for clinically localized PCa, 246 (10.4%) experienced failure, and 109 met inclusion criteria. Immediate ADT was pursued in 38 patients, delayed in 71. Six of the patients in the delayed ADT group had not yet received ADT at the time of this study but were included in the analysis. Thirteen of 137 patients (9.5%) were excluded from the study population as they received local salvage therapies. The median followup was 11.4 years (interquartile range [IQR]: 8.0–14.3). Fifty-three patients died during followup, 35 of PCa. Mean age at treatment was 67 years (IQR: 62–72), and median initial PSA was 9.5 ng/mL (IQR: 6.7–20).

The baseline clinical and tumor characteristics were matched between the immediate and delayed ADT groups; however, the immediate group had a significantly higher population of patients receiving neoadjuvant ADT (73.7% vs. 52.1%, $p = 0.01$) along with combined EBRT/PPB (72.1% vs. 47.9%, $p = 0.02$) (Table 1). The baseline characteristics were similar for patients initiating ADT at a PSA