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Brachytherapy ■ (2017) ■

BRACHYTHERAPY

External beam radiation therapy with or without low-dose-rate brachytherapy: Analysis of favorable and unfavorable intermediate-risk prostate cancer patients

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ABSTRACT

PURPOSE: To compare the tumor control and toxicity in men with intermediate-risk prostate cancer treated with either external beam radiation therapy (EBRT) or EBRT plus low-dose-rate brachytherapy (combo-RT).

METHODS AND MATERIALS: Between 1995 and 2012, 579 men with intermediate-risk prostate cancer were treated with either EBRT (n = 388) or combo-RT (n = 191). Outcomes assessed included biochemical recurrence−free survival (bRFS), distant metastasis−free survival (DMFS), and cumulative incidence of genitourinary (GU) and gastrointestinal toxicity. Favorable and unfavorable intermediate-risk subgroups were analyzed.

RESULTS: Median followup was 7.5 years. Combo-RT group had improved 10-year bRFS compared with EBRT (91.7% vs. 75.4%, p = 0.014). On multivariable analysis, combo-RT (hazard ratio, 0.48; 95% confidence interval: 0.25, 0.92; p = 0.03) was associated with improved bRFS. Combo-RT had significantly improved bRFS compared with EBRT in the unfavorable subgroup (p = 0.02) but not in the favorable subgroup (p = 0.37). DMFS was similar within the entire cohort and by risk group. Combo-RT was associated with an increased rate in the 6-year cumulative incidence of Grade 3 GU toxicity (hazard ratio, 3.48; 95% confidence interval: 1.1, 11.1; p = 0.026); however, 57% of Grade 3 GU toxicity was resolved, 29% had partial improvement, and only 1 patient had persistent Grade 3 GU toxicity.

CONCLUSIONS: In intermediate-risk prostate cancer, combo-RT improved bRFS but not DMFS and increased Grade 3 GU toxicity. The bRFS benefit was limited to unfavorable intermediate-risk patients. © 2017 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Combination therapy; Intermediate-risk; Prostate cancer; Brachytherapy; Dose escalation; PSA

Introduction

There have been three randomized controlled trials comparing external beam radiation therapy (EBRT) with EBRT plus brachytherapy in men with localized intermediate- and high-risk prostate cancer (1−3). All three trials have demonstrated an improvement in biochemical recurrence−free survival (bRFS) with EBRT plus brachytherapy treatment, but the combination did not demonstrate an improvement in distant metastasis or overall survival. The recently reported a multicenter, randomized trial of dose-escalated external beam radiation therapy (EBRT-B) versus

Received 7 March 2017; received in revised form 3 April 2017; accepted 4 April 2017.

Conflict of interest: Daniel E. Spratt has served on an advisory board for Dendreon. Felix Y. Feng has served on the following advisory boards: Medivation/Astellas, GenomeDx, Nanostring, Celgene, and Dendreon.

Financial disclosure: Felix Y. Feng received funding from Varian, Medivation/Astellas, and Celgene.

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http://dx.doi.org/10.1016/j.brachy.2017.04.001

low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer (ASCENDE-RT) trial was unique in that it used dose-escalated EBRT (78 Gy) in the standard arm in contrast to the prior two trials. Thirty-one percent of patients in the ASCENTDE-RT trial were at intermediate risk as per the National Comprehensive Cancer Network classification, and both the intermediate-risk and the high-risk subgroups demonstrated a bRFS benefit with combination therapy.

Intermediate-risk prostate cancer, however, remains a heterogeneous disease classification and is treated with a variety of strategies (4). Zumsteg *et al.* (5) have further stratified intermediate-risk patients into favorable and unfavorable risk subgroups. Those with primary Gleason pattern 4, percentage of positive biopsy cores ≥50%, or multiple intermediate-risk factors (clinical T-stage T2b/T2c; prostate-specific antigen [PSA], 10−20, or Gleason 7) are considered unfavorable. Little is known about the relative benefit of adding a brachytherapy boost to EBRT compared with dose-escalated EBRT in men with favorable vs. unfavorable intermediate-risk disease. Previous work from Spratt *et al.* (6) demonstrated that EBRT plus low-dose-rate brachytherapy (combo-RT) may have a small but statistically significant improvement in distant metastasis−free survival (DMFS); however, analysis by favorable and unfavorable intermediate risk was not performed.

In this study, we analyzed a large cohort of men with intermediate-risk prostate cancer treated with dose-escalated EBRT or EBRT plus low-dose-rate (LDR) brachytherapy and hypothesized that the greatest improvement in bRFS would be evident in men with unfavorable intermediate-risk disease. We also evaluated the impact of EBRT plus brachytherapy on local progression−free survival (LPFS), DMFS, and genitourinary (GU) and gastrointestinal (GI) toxicity. In doing so, we aimed to elucidate the therapeutic ratio of tumor control to toxicity to identify which intermediate-risk patients are best suited for consideration of escalated local therapy.

Methods and materials

Patients

Between May 1995 and March 2012, 579 consecutive patients with localized biopsy-proven prostate cancer were treated at two institutions (University of Michigan [UM], Ann Arbor, MI, and Providence Hospital [Providence], Novi, MI) with either EBRT (n = 388, all at UM) or EBRT + LDR brachytherapy (combo-RT, n = 191, all at Providence). Eligible patients included those characterized as intermediate risk as per the National Comprehensive Cancer Network: clinical T-stage T2b/T2c or Gleason score = 7 or PSA 10−20 ng/mL. Before the treatment commencement, all patients had complete physical examination and blood tests including complete blood count and PSA. Staging with CT of the chest, abdomen, and pelvis and/or bone scan was completed at the treating physicians' discretion, generally only for select unfavorable intermediate-risk patients.

Treatment

For patients treated with EBRT, CT-based simulation was used for target delineation, which included the prostate and seminal vesicles. Median dose prescribed to the planning target volume was 77.5 Gy in 1.8−2.0 Gy daily fractions. EBRT was planned using three-dimensional conformal techniques (n = 238 of 388) or intensity-modulated radiation therapy (IMRT, n = 150 of 388). Image guidance was used in 45% of patients (n = 173 of 388) using either Calypso markers (7) (n = 68) or gold seeds (8) (n = 105).

The patient treated with combo-RT underwent permanent interstitial LDR brachytherapy implant. The LDR implant technique used at our institution has been described previously (9). Briefly, the clinical target volume (prostate plus proximal seminal vesicles) was identified using transrectal ultrasound guidance under general anesthesia. A template-based transperineal catheter approach was used to implant iodine-125 seeds (90−108 Gy). Postimplant dosimetry was performed approximately 3 weeks after the treatment with goals of $D_{90} \geq 90\%$ and $V_{100} \geq 90\%$. Approximately 6 weeks after implant, patients received IMRT in 25−30 fractions over 5−6 weeks using three-dimensional conformal technique or IMRT with gold seed image guidance. Brachytherapy dose was imported into the IMRT calculation as background, and the final dose was a full integration of IMRT beam and brachytherapy to deliver 90 Gy external equivalent to the 3−5 mm expansion of the prostate. This amounted to a 90−108 Gy implant, plus EBRT doses of 45−55.8 Gy in 1.8−2.0 Gy per fraction.

For both EBRT and combo-RT, androgen deprivation therapy (ADT) was administered at the treating physicians' discretion for a total of 6 months' duration.

Covariables

Candidate binary variables for our analysis included treatment type (EBRT vs. combo-RT), T-stage (T1c/T2a vs. T2b/T2c), baseline PSA (<10 vs. 10−20 ng/mL), percent positive cores (≤50% vs. >50%), and treatment era (1995−2004 vs. 2005−2012). Treatment era was analyzed to account for potential grade migration with Gleason scoring (10). ADT was also analyzed as a binary variable (yes vs. no) as only short-term ADT was administered. Grade group (1 [≤6], 2 [3 + 4], or 3 [4 + 3]) was analyzed as a categorical variable.

Endpoints

After treatment, patients were evaluated with physical examination and PSA level every 3 months for the first

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