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Is supplemental external beam radiation therapy essential to maximize brachytherapy outcomes in patients with unfavorable intermediate-risk disease?

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ABSTRACT

PURPOSE: To evaluate whether supplemental external beam radiotherapy (EBRT) is essential to maximize Pd-103 brachytherapy outcomes in patients with unfavorable intermediate-risk (IR) disease.
METHODS AND MATERIALS: A total of 630 patients were assessed from two prospective randomized brachytherapy trials evaluating the role of supplemental EBRT in patients with higher risk features. Patients were stratified into unfavorable IR (primary Gleason pattern 4, ≥50% positive biopsies, or ≥2 IR features), favorable IR, and high-risk (HR) cohorts. Median follow-up was 7.5 years. The brachytherapy prescription dose was prescribed to the prostate gland with generous periprostatic margins. Biochemical failure (BF) was defined as a prostate-specific antigen >0.40 ng/mL after nadir. Patients with metastatic prostate cancer or nonmetastatic castrate–resistant disease who died of any cause were classified as dead of prostate cancer. Multiple parameters were evaluated for effect on outcomes.
RESULTS: The 10-year BF for favorable IR, unfavorable IR, and HR was 1.7%, 6.6%, and 15.5% ($p < 0.001$). At 10 years, prostate cancer–specific mortality (PCSM) and overall mortality (OM) were 0% and 20.4%, 2.1% and 23.2%, and 4.3% and 42.4% for favorable IR, unfavorable IR, and HR. Although unfavorable IR patients had a greater incidence of BF, PCSM, and OM when compared with favorable IR, neither the addition nor dose of supplemental EBRT influenced outcome.
CONCLUSIONS: Outcomes for favorable IR were superior to those with unfavorable IR. Within the confines of this study, neither the addition nor dose of supplemental EBRT influenced BF, PCSM, or OM in patients with IR disease.

Keywords: Prostate cancer; Brachytherapy; Biochemical outcome; Prostate cancer–specific mortality; Intermediate risk disease

Introduction

Intermediate-risk (IR) prostate cancer has been defined by the NCCN as "T2b or T2c, Gleason score ≤7 or prostate-specific antigen (PSA) 10-20 ng/mL"(1). Recently, Zumsteg *et al.* (2) divided IR patients into favorable and unfavorable categories with the conclusion that patients with unfavorable IR disease (primary Gleason pattern 4, ≥50% positive biopsies, or ≥2 IR features) had a statistically increased risk of biochemical failure (BF), prostate cancer–specific mortality (PCSM), and distant metastases when compared with favorable IR prostate cancer patients who were treated with dose-escalated intensity-modulated external beam radiation therapy with or without 6 months of androgen deprivation therapy (ADT). Unfortunately, the National Comprehensive Cancer Network risk-group stratification does not account for a multitude of additional prognosticators including multiple IR factors (3, 4), fewer

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diagnostic biopsy cores (5), and percent positive biopsies ≥50% (6–8) which result in PSA recurrence rates and PCSM consistent with high-risk (HR) disease.

Brachytherapy compares favorably with radical prostatectomy (RP) and dose-escalated intensity-modulated external beam radiation therapy for all risk groups including those with IR disease with the caveat that durable biochemical control is dependent on high-quality implant dose distributions (9–14). Recently, our group reported BF, PCSM, and overall mortality (OM) in IR patients stratified to 44 Gy of supplemental external beam radiotherapy (EBRT), followed by a 90-Gy Pd-103 boost, 20-Gy EBRT with a 115-Gy Pd-103 boost, or monotherapeutic Pd-103 (125 Gy) with the conclusion that supplemental EBRT did not impact BF, PCSM, or OM in IR patients (15). To date, although favorable and unfavorable IR prostate cancer outcomes have been reported for patients receiving dose-escalated EBRT and RP with better outcomes in favorable IR patients (2, 16), the impact of such stratification on brachytherapy outcomes remains unknown. In the present study, we evaluate whether the addition and/or dose of EBRT influences the outcome of favorable and unfavorable IR patients randomized to one of two prospective randomized brachytherapy trials evaluating the role of EBRT.

Methods and materials

From December 1999 to September 2013, 1037 patients with clinically organ–confined disease and Gleason score 7–9 and/or a pretreatment PSA 10–20 ng/mL were randomized to one of two prospective randomized trials evaluating the role of supplemental EBRT. The first trial (44/20) randomized patients to either 20 Gy supplement EBRT in 2-Gy fractions, followed by a Pd-103 boost (115 Gy) or 44 Gy supplemental EBRT with a 90-Gy Pd-103 boost. The subsequent trial using the same inclusion criteria randomized patients to either the aforementioned 20-Gy arm or monotherapeutic Pd-103 (125 Gy; trial 20/0). A total of 319 patients on 44/20 and 88 patients on 20/0 were implanted at the Puget Sound Veterans Adminstration Hospital and have been embargoed secondary to administrative (neither ethical nor scientific) institutional review board decisions. The remaining 630 patients implanted at the Schiffler Cancer comprise this evaluation. For this study, patients were stratified into the following three cohorts: unfavorable IR (primary Gleason pattern 4, ≥50% positive biopsies, or ≥2 IR factors), favorable IR (<50% positive biopsies and only one IR criteria–Gleason score 3 + 4 or PSA 10–20 ng/mL or clinical stage T2b), and HR (Gleason score≥ 8).

All patients underwent implantation by a single brachytherapist (GSM). Before implantation, all slides were reviewed by a single pathologist with significant expertise in prostate pathology (EA). Patients were clinically staged using medical history and physical examination including digital rectal examination and serum PSA. Bone scans and computed tomography of the abdomen/pelvis were obtained at the discretion of either the referring or treating physician.

The brachytherapy planning target volume consisted of the prostate gland with a 5-mm periprostatic margin and the proximal 1.0 cm of the seminal vesicles with a resultant planning target volume of approximately 1.9 times the actual prostate volume (17, 18). All postimplant dosimetric calculations were based on Day 0 evaluation. The target volume for supplemental EBRT consisted of the prostate gland and seminal vesicles with a 2.0-cm margin in all dimensions except for a 1.0-cm posterior margin. Patients were treated with a three-dimensional conformal technique using anterior–posterior/posterior–anterior and opposed lateral portals with 18-mv photons and custom treatment devices to spare as much normal tissue as possible. Patients underwent brachytherapy within 4 days of completion of 20 Gy and within 14 days following 44 Gy. When prescribed, ADT was initiated 3 months before implantation and consisted of a leuteinizing hormone–releasing agonist and an anti-androgen or an LHRH antagonist. ADT was used for size reduction or adverse pathologic features. Most ADT-treated patients received a short-course regimen (≤6 months; Table 1).

Patients were monitored by physical examination including digital rectal examination and PSA determinations at 3- and 6-month intervals. The end point of the analysis was BF, PCSM, and OM. BF was defined as PSA >0.40 ng/mL after nadir. Patients who failed to achieve a nadir of ≤0.40 ng/mL were categorized as BFs (19). The cause of death was determined for each deceased patient. Patients with metastatic prostate cancer or nonmetastatic castrate–resistant disease who died of any cause were classified as dead of prostate cancer. All other deaths were attributable to the immediate cause of death. Multiple clinical, treatment, and dosimetric parameters were evaluated for effect on survival.

Clinical and treatment variables that were continuous were compared across groups using a one-way analysis of variance. Categorical variables were compared using a χ^2 analysis or a Fisher exact test. Competing risk analysis was used to compare BF and PCSM with the population stratified by favorable IR, unfavorable IR, and HR. All-cause mortality across the three levels of risk was determined using a Cox proportional hazards model. All analyses were completed using STATA version 12.0 software (StataCorp, College Station, TX).

Results

Table 1 summarizes the clinical, treatment, and dosimetric parameters for the 630 evaluated patients. The mean and median follow-up for the entire group was 7.7 and 7.5 years, respectively (range, 0.1–14.8 years). Favorable