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Is supplemental external beam radiation therapy necessary for patients with higher risk prostate cancer treated with ^{103}Pd? Results of two prospective randomized trials

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ABSTRACT

PURPOSE: To determine the necessity and/or dose of supplemental external beam radiotherapy (EBRT) in conjunction with palladium-103 (^{103}Pd) brachytherapy for high-risk prostate cancer patients.

METHODS AND MATERIALS: Trial 44/20 randomized patients to 44 Gy plus 90 Gy ^{103}Pd vs. 20 Gy with 115 Gy ^{103}Pd, and the subsequent trial randomized patients to the 20 Gy arm vs. 125 Gy ^{103}Pd without EBRT (20/0 trial). Eligibility criteria included clinically organ-confined disease with Gleason scores 7–9 and/or a pretreatment prostate-specific antigen (PSA) 10–20 ng/mL. The brachytherapy prescription dose was prescribed to the prostate gland with generous periprostatic margins. Biochemical failure (BF) was defined as a PSA >0.40 ng/mL after nadir. Median Day 0 minimum dose covering 90% of the prostate volume (D_{90}) was >121.0% of the prescription dose. Multiple parameters were evaluated for effect on outcomes.

RESULTS: In 44/20 trial, 13-year BF, prostate cancer–specific mortality (PCSM), and overall mortality (OM) were 8.2%, 4.0%, and 42.8% vs. 8.0%, 1.0%. and 40.3% for the 44 and 20 Gy arms. In 20/0 trial, 8-year BF, PCSM, and OM were 2.1%, 0%, and 14.4% vs. 3.6%, 0%, and 16.1% in the 20 vs. 0 Gy arms. When stratified by either pretreatment PSA or by Gleason score, supplemental EBRT dose did not impact BF, PCSM, or OM. In multivariate analysis, BF was most closely related to percent positive biopsies and prostate volume. In both trials, patients with biochemically controlled disease had a median PSA of <0.02 ng/mL.

CONCLUSIONS: With high-quality brachytherapy dose distributions, supplemental EBRT did not influence BF or PCSM for patients with intermediate-risk disease. The number of patients with Gleason score 8–9 was too small to determine the role of supplemental EBRT in that cohort.
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Keywords: Brachytherapy; Higher risk; Supplemental external beam radiation therapy; Prospective randomized trial

Introduction

Brachytherapy represents an efficacious treatment modality for potentially curable prostate cancer with the caveat that high-quality implant dose distributions are essential for durable local control and favorable biochemical outcomes (1–3). Although low-risk patients are optimally managed with brachytherapy alone, patients with high-risk features harbor a substantial risk of extracapsular disease (4) and may require supplemental external beam radiotherapy (EBRT) to maximize tumoricidal radiation doses to the

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periprostatic, seminal vesicle, and nodal regions (5, 6). However, with appropriate monotherapeutic dosimetric planning to include the selective placement of extraprostatic seeds, the intraprostatic and periprostatic regions along with the proximal 1.0 cm of the seminal vesicles are routinely encompassed within the cancericidal dose distributions (6–8). Consequently, supplemental EBRT in high-risk patients may not be necessary.

Previously, we reported results of a prospective trial (44/20), which randomized patients with high-risk features to either a reduced dose of supplemental EBRT (20 Gy) with a corresponding increase in palladium-103 (^{103}Pd) boost dose (115 Gy) vs. standard dose supplemental EBRT (44 Gy) with a conventional ^{103}Pd boost (90 Gy) (9). This trial demonstrated that with high-quality brachytherapy, two markedly different supplemental EBRT dose regimens resulted in equivalent biochemical control in patients with high-risk features (9). In addition, the lower EBRT dose in the 44/20 trial significantly reduced the duration of treatment, patient inconvenience, and health care costs.

Because of the equivalence of biochemical control in the 44/20 trial, we embarked on a subsequent prospective trial, which randomized patients to the aforementioned 20 Gy arm vs. monotherapeutic full-dose ^{103}Pd (125 Gy American Brachytherapy Society 2000). Herein, we report biochemical failure (BF), prostate cancer–specific mortality (PCSM), and overall mortality (OM) in patients randomized to both clinical trials.

Methods and materials

From December 1999 to June 2004, 566 patients with clinically organ-confined disease and Gleason scores 7–9 and/or a pretreatment prostate-specific antigen (PSA) 10–20 ng/mL were randomized to either 20 Gy of supplemental EBRT in 2 Gy fractions followed by a ^{103}Pd boost (115 Gy) or 44 Gy of supplemental EBRT followed by a 90 Gy ^{103}Pd boost (44/20 trial). Subsequently, from November 2004 to September 2013, 471 patients with the same inclusion criteria were randomized to either the aforementioned 20 Gy arm or monotherapeutic ^{103}Pd (125 Gy) (20/0 trial). About 319 patients in 44/20 trial and 88 patients in 20/0 trial were implanted at the Puget Sound Veterans Administration Hospital and have been embargoed secondary to administrative (neither ethical nor scientific) institutional review board decisions. As such, the remaining 247 patients in 44/20 trial and 383 patients in 20/0 trial comprise this evaluation.

Both trials were designed to achieve a study power of 80% at an alpha value of 0.05 using the log-rank test for a 15% difference in time-to-event survival assuming proportional hazards. Thus, 172 subjects per treatment arm were required (total, 344 subjects) for each trial to meet statistical significance. Although in both studies, more patients were accrued than statistically necessary, the embargoed patients from the Puget Sound Veterans Administration Hospital resulted in the 44/20 trial current analysis being underpowered.

All evaluated patients in this study underwent implantation by a single brachytherapist (GSM). Before implantation, all slides underwent pathology review by a 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 (7, 8). This planning philosophy resulted in a planning target volume approximately 1.9 times the actual prostate volume. 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 completing supplemental EBRT in the 20 Gy arm and 10–14 days after 44 Gy arm.

When prescribed, androgen deprivation therapy (ADT) was initiated 3 months before implantation and consisted of a luteinizing hormone–releasing hormone agonist and an antiandrogen or a luteinizing hormone–releasing hormone antagonist. ADT was used for size reduction or secondary to adverse pathologic features. Most patients receiving ADT received short courses (<6 months) (Table 1).

Patients were monitored by physical examination including digital rectal examination and PSA determinations at 3- and 6-month intervals. The endpoint of the analysis was BF. BF was defined as a PSA >0.40 ng/mL after nadir, which has been demonstrated to be a particularly sensitive definition by indentifying patients for whom treatment has failed (10). Patients who failed to achieve a nadir <0.40 ng/mL were categorized as BFs. PCSM and OM were also evaluated. The cause of death was determined for each deceased patient. Patients with metastatic prostate cancer and or nonmetastatic castrate–resistant disease who died of any cause were classified as dead of prostate cancer. All other deaths were attributed to the immediate cause of death. Multiple clinical, treatment, and dosimetric parameters were evaluated for their effect on survival.

Differences in the clinical, treatment, and dosimetric parameters across the two groups for both trials (44/20 and 20/0) in which continuous data were collected were determined using a one-way analysis of variance. Planned contrasts were made between the two arms when a significant difference was identified. When data were categorical, comparisons were used using χ^2 analysis. Competing risk analysis was used to determine differences in overall

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