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Comparison of dose-escalated, image-guided radiotherapy vs. dose-escalated, high-dose-rate brachytherapy boost in a modern cohort of intermediate-risk prostate cancer patients

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ABSTRACT

PURPOSE: We compared outcomes in intermediate-risk prostate cancer patients treated with dose-escalated adaptive image-guided radiation therapy (IGRT) or dose-escalated high-dose-rate brachytherapy boost (HDR-B).

METHODS AND MATERIALS: Patients with intermediate-risk prostate cancer by National Comprehensive Cancer Network criteria were treated with either CT-based off-line adaptive IGRT ($n = 734$) or HDR-B ($n = 282$). IGRT was delivered with 3D-conformal or intensity-modulated radiation therapy with a median dose of 77.4 Gy. For HDR-B, the whole pelvis received a median 46 Gy, and the prostate 2 implants of 9.5 Gy ($n = 71$), 10.5 Gy ($n = 155$), or 11.5 Gy ($n = 56$).

RESULTS: Median followup was 3.7 years for IGRT and 8.0 years for HDR-B ($p < 0.001$). Eight-year biochemical control was 86% for IGRT and 91% for HDR-B ($p = 0.22$), disease-free survival 67% for IGRT and 79% for HDR-B ($p = 0.006$), and overall survival 75% for IGRT and 86% for HDR-B ($p = 0.009$). Cause-specific survival (8-year, 100% vs. 99%), freedom from distant metastases (98% vs. 97%), and freedom from local recurrence (98% vs. 98%) did not differ ($p > 0.50$ each). A worse prognosis group was defined by percent positive prostate biopsy cores >50%, perineural invasion, or stage T2b–c, encompassing 260 (35%) IGRT and 171 (61%) HDR-B patients. These patients evidenced a 5-year biochemical control of 96% for HDR-B and 87% for IGRT ($p = 0.002$).

CONCLUSIONS: Dose-escalated IGRT and HDR-B both yield excellent clinical outcomes for patients with intermediate-risk prostate cancer. Improved biochemical control with HDR-B for patients with worse pretreatment characteristics suggests that a subgroup of intermediate-risk prostate cancer patients may benefit from dual-modality treatment.

Keywords: Prostate cancer; High-dose-rate brachytherapy; Image-guided radiation therapy; Comparative outcomes; IMRT

Options for patients undergoing definitive radiation therapy for organ-confined, intermediate-risk prostate cancer include brachytherapy, dose-escalated image-guided radiation therapy (IGRT), and external beam radiation therapy (EBRT) in combination with interstitial brachytherapy as a boost. Hypofractionated radiotherapy via high-dose-rate brachytherapy boost (HDR-B) was developed for conformal dose escalation, allowing more accurate dose delivery than was possible with EBRT (1). HDR-B for dose escalation is also supported by evidence of a low α/β for prostate cancer as low as 1.2 Gy (2).

Prior studies, including two randomized phase III studies, have compared EBRT with brachytherapy boost and have shown a benefit to combined modality treatment in patients with intermediate- and high-risk prostate cancer (3–6). These studies, however, either used conventional dose EBRT or, when delivering dose-escalated EBRT, did

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not employ image guidance (7). Conventional EBRT is no longer used in the definitive setting because multiple randomized dose escalation trials have shown improved outcomes with increased radiation dose in prostate cancer (8). For intermediate-risk prostate cancer, a retrospective review of dose-escalation to 86.4 Gy (9) and a randomized study of 68 Gy vs. 78 Gy (10) have reported a benefit in disease control for patients receiving higher radiotherapy doses.

With the advent of adaptive radiotherapy and image guidance (11), the advantage derived from the brachytherapy component of HDR-B in terms of improved dose conformality to the planning target volume has been minimized. However, HDR-B treatment continues to offer an increased, biologically effective dose (BED) delivered to the prostate. We therefore reviewed our experience with dose-escalated IGRT and HDR-B to determine whether further dose escalation with HDR-B leads to improved outcomes for patients with intermediate-risk prostate cancer.

Methods and materials

The charts of intermediate-risk prostate cancer patients treated at our institution and entered into a prospective database were reviewed. Intermediate-risk prostate cancer was defined per National Comprehensive Cancer Network guidelines: Prostate-specific antigen (PSA) $\geq$10 and $<$20 ng/mL, Gleason score 7, or clinical stage T2b–c. Only patients treated with dose-escalated IGRT ($\geq$73.8 Gy) or HDR-B ($BED_{\alpha/\beta=1.2} \geq 268$ Gy) were selected for analysis. The dose criteria were selected to match current treatment patterns at our institution, and for HDR-B based on a publication showing improved outcomes with dose escalation (12). This study was approved by our institutional review board (HIC #2011-067).

All IGRT patients were treated using our off-line adaptive radiation therapy protocol (11, 13). In brief, patients received treatment with a four-field 3D-conformal plan encompassing the prostate and proximal seminal vesicles for 1 week, while undergoing 4 additional daily helical CT scans. A confidence-limited planning target volume was constructed based on observed variation in prostate position and setup reproducibility during the first week of treatment. A new treatment plan was then generated. Patients were treated with 3D-conformal or intensity-modulated radiation therapy (IMRT) for the remainder of their treatment.

HDR-B was prescribed based on a dose-escalation protocol (1, 12). In brief, this included whole pelvis radiotherapy to 46 Gy in 23 fractions, with EBRT held on days that HDR implants were performed. The first HDR treatment was given either immediately before or during the first week of EBRT, and the second implant typically 2 weeks thereafter. Implants were performed under transrectal ultrasound guidance through a transperineal template, treatment planning was ultrasound-based, and treatment was delivered using an ^{192}Ir source.

Statistical evaluations

Biochemical failure (BF) was defined by the Phoenix criteria, of PSA nadir+2, or initiation of salvage therapy (14). A rise to PSA nadir+2 with a subsequent sustained decrease in PSA without intervention was classified as a PSA bounce and excluded from BF (15). Biochemical control (BC) was defined as lack of BF. Distant metastasis (DM) was defined by imaging findings or biopsy-proven disease, and locoregional recurrence as biopsy-proven disease. Cause-specific survival was defined as death attributed to prostate cancer in our institutional cancer registry, or death with DM. Disease-free survival (DFS) was censored at the time of death or the first event of BF, DM, or locoregional recurrence. All endpoints were calculated from the date of radiation therapy completion. The percent positive prostate biopsy cores (PPC) was defined as the number of positive cores divided by the total number of biopsy cores (16).

The Student unpaired two-tailed t test was used to compare continuous variables, and Pearson's χ^2 to compare categorical variables. Survival curves for OS and DFS were calculated using the Kaplan–Meier method, and compared using the log-rank test. Cumulative incidence curves for events with a competing risk of death were compared with Gray's test. Cox regression analysis was used to estimate the hazard ratio and corresponding 95% confidence intervals for univariate and multivariate analyses of OS and DFS. Competing risk regression accounting for the competing risk of death was performed for the other events (17). Statistical analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC) and R 2.15.1 (R-project.org).

Results

Patient characteristics

All consecutive patients treated at our facility who met the selection criteria were selected for inclusion, yielding 734 IGRT and 287 HDR-B patients (Table 1). Among these, there were 116 IGRT and 141 HDR-B patients with $\geq$8-year clinical followup, and 50 IGRT and 94 HDR-B patients with $\geq$8-year biochemical followup. There were 29 (4%) IGRT and 45 (16%) HDR-B patients lost to follow-up, defined as alive but without followup during the 2 years before data extraction in August 2012. IGRT was delivered with IMRT in 75% of patients. HDR-B patients received whole pelvis irradiation to a median dose of 46 Gy in 23 fractions, with only 16 patients receiving a different fractionation (range, 40–50 Gy), and brachytherapy in two fractions of 9.5 Gy (n = 71), 10.5 Gy (n = 155), or 11.5 Gy (n = 56).