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An age-corrected matched-pair study of erectile function in patients treated with dose-escalated adaptive image-guided intensity-modulated radiation therapy vs. high-dose-rate brachytherapy for prostate cancer

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ABSTRACT

PURPOSE: To compare erectile dysfunction (ED) after adaptive dose-escalated image-guided intensity-modulated radiotherapy (IG-IMRT) and high-dose-rate interstitial brachytherapy (HDR) monotherapy.

METHODS AND MATERIALS: Low- and intermediate-risk prostate cancer patients treated with IG-IMRT or HDR were matched on pretreatment ED, age, Gleason score, T-stage, and prostate specific antigen. Patients who received androgen deprivation therapy were excluded. ED was graded by Common Terminology Criteria for Adverse Events v4. Actuarial rates of ED were computed by the Kaplan−Meier method.

RESULTS: There were 384 patients with median followup of 2.0 years (0.5−6.1) for IG-IMRT and 2.0 years (0.5−8.7) for HDR. The median IG-IMRT dose was 75.6 Gy and HDR dose 38 Gy in four fractions. For patients with no pretreatment ED, actuarial rates of requiring intervention (Grade ≥2 ED) at 3 years were 31% for IG-IMRT and 19% for HDR ($p = 0.23$), and impotence despite medical intervention (Grade 3) were 0% for IG-IMRT and 6% for HDR ($p = 0.06$). For patients with Grade 1 pretreatment ED, Grade ≥2 ED at 3 years were 47% for IG-IMRT and 34% for HDR ($p = 0.79$), and Grade 3 ED were 15% in both groups ($p = 0.59$). For patients with Grade 2 pretreatment ED, Grade 3 ED at 3 years were 22% for IG-IMRT and 37% for HDR ($p = 0.70$). No variables were predictive of Grade ≥2 ED following treatment.

CONCLUSIONS: Rates of ED requiring medical intervention for both IG-IMRT and HDR are low and equivalent. Even patients with ED before treatment are likely to maintain potency with medication use at 3 years following treatment.

Keywords: Prostate cancer; Potency; Erectile function; Erectile dysfunction; Radiation therapy; Interstitial brachytherapy; Quality of life; IMRT; HDR

Introduction

Patients with low- or intermediate-risk prostate cancer can elect between prostatectomy, external beam radiation therapy (EBRT), or brachytherapy for definitive treatment. The effectiveness of these interventions seems to be similar (1). Treatment-related complications therefore become a major consideration in therapy selection. For patients with good erectile function before treatment, the risks of erectile dysfunction (ED) are not insignificant (2) and play a major role in the treatment selection process.

Radical prostatectomy has been associated with higher rates of ED compared with EBRT or brachytherapy in multiple retrospective reviews (1−4). These comparisons are fraught with difficulty, as outcomes are measured in different ways and are often not corrected for loss to followup, and the patient populations are imbalanced for factors that affect outcomes, in particular age (2). In addition,

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Conflicts of interest: None.

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studies describing brachytherapy outcomes generally include only data for low-dose-rate interstitial prostate brachytherapy (2, 5).

To address these limitations in the current literature, we performed a matched-pair analysis, using age as a criterion, to investigate post-radiotherapy ED in prostate cancer patients treated with two treatment options currently offered at our institution, adaptive dose-escalated image-guided intensity-modulated radiation therapy (IG-IMRT) and high-dose-rate interstitial brachytherapy (HDR) monotherapy.

Methods and materials

The charts of low- and intermediate-risk prostate cancer patients treated with definitive adaptive dose-escalated IG-IMRT or HDR monotherapy between January 2000 and December 2010, and with erectile function documented during followup, were evaluated. Exclusion criteria for this study included androgen deprivation therapy at any point before, during, or after treatment, undocumented pretreatment erectile function, ED not responsive to medical intervention (Grade 3) before treatment, and clinical followup less than half a year. IG-IMRT patients who were not treated with intensity-modulated radiotherapy or with a prescription dose less than 73.8 Gy were also excluded. This study was approved by our institutional review board, the human investigations committee (HIC #2011-312).

Our treatment techniques, pretreatment evaluations, and followup criteria have been previously reported for IG-IMRT (6, 7) and HDR (8–10). All IG-IMRT patients were treated using the adaptive radiation therapy protocol (6). In brief, patients received treatment with a four-field 3D-conformal treatment plan encompassing the prostate and proximal seminal vesicles for 1 week, while undergoing four daily CT scans. A confidence-limited planning target volume was constructed based on observed prostate motion on the CT scans and daily setup reproducibility, defining a margin generally in the range of 3–5 mm. An intensity-modulated radiotherapy treatment plan was then used for the remainder of treatment, with the dose prescribed to the confidence-limited planning target volume margin.

HDR was prescribed on a hypofractionation protocol, ranging from 38 Gy in four fractions to 27 Gy in two fractions, prescribed to the prostate volume without expansion (10). Brachytherapy was delivered in one or two implants, with multiple fractions in one implant separated by ≥6 h. Implants were performed under transrectal ultrasound guidance. Treatment was delivered using an ^{192}Ir source.

Patients are seen within 2–4 weeks following HDR to assess for acute toxicity. All prostate radiotherapy patients are seen every 3 months in our office or the urologist's office for the first 2 years, every 6 months until 5 years, and yearly thereafter. Since 2000, multiple post-treatment toxicities, including ED, were prospectively assessed at each followup visit in our clinic with a Common Terminology Criteria for Adverse Events (CTCAE, http://ctep.cancer.gov/reporting/ctc.html) v2.0, and subsequently v3.0, questionnaire. The radiation oncology patient charts were reviewed for questionnaires and followup notes to confirm appropriate conversion to CTCAE v4.0 ED grades (Table 1), with particular attention to the reported use of erectogenic medication.

Statistical evaluations

A matched-pair analysis was performed using a greedy matching algorithm. The pretreatment ED grade (0–2), Gleason score (6, 7), and clinical T-stage grouping (≤T2a, T2b-c) were matched exactly, and age at diagnosis and pretreatment prostate specific antigen (PSA) as continuous variables. Post-treatment ED rates as percentages were compared using Fisher's exact test, and actuarial rates were computed using the Kaplan–Meier method (log-rank test). For actuarial outcomes, the date the ED grade was first reached was used for statistical outcomes.

The Student unpaired 2-tailed *t* test was used to compare continuous variables, and Pearson's chi-square or Fischer's exact test to compare categorical variables. Cox regression analysis was used to estimate the hazard ratio and corresponding 95% confidence interval for univariate and multivariate analyses. Statistical analyses were performed using SPSS version 17 (IBM, Armonk, NY) and SAS version 9.1 (SAS Institute, Cary, NC).

Results

There were 441 HDR and 741 IG-IMRT low- and intermediate-risk prostate cancer patients retrieved from the database, of which 259 HDR and 353 IG-IMRT patients had adequate followup and met inclusion criteria to undergo matching. A total of 384 patients were matched (Table 2). The median followup was 2.0 years (0.5–6.1) for IG-IMRT and 2.0 years (0.5–8.7) for HDR. Pretreatment characteristics were balanced for all characteristics except for race. The median IG-IMRT dose was 75.6 Gy (73.8–82.28), with an equivalent biologically effective dose $(BED)_{\alpha/\beta=3}$ of 121 (118–134). The brachytherapy treatment was delivered as 24 Gy in two fractions ($n = 42$), 27 Gy in two fractions ($n = 46$), or 38 Gy in four fractions ($n = 104$), with an equivalent $BED_{\alpha/\beta=3}$ of 120, 149, and 158 Gy, respectively.

Table 1
Common Terminology Criteria for Adverse Events v4.0 grading

Grade	Description
0	Normal erectile function
1	Adequate function, with decreased frequency or rigidity of erections but no erectile aids needed
2	Decreased erectile function with erectile aids indicated
3	Decreased erectile function, erectile aids not helpful, penile prosthesis indicated