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Patient- and treatment-specific predictors of genitourinary function after high-dose-rate monotherapy for favorable prostate cancer

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ABSTRACT

PURPOSE: High-dose-rate (HDR) brachytherapy alone is an effective treatment option for patients with early-stage prostate cancer. The purpose of this study was to quantify patient-reported short- and long-term toxicity and quality of life (QOL) after HDR monotherapy.

METHODS AND MATERIALS: Thirty-nine consecutive men between May 2001 and January 2012 were identified for this analysis. All patients underwent definitive HDR monotherapy for favorable prostate cancer to a total dose of 3150 cGy in three fractions, 3800 cGy in four fractions, or 3850 in five fractions. Patient-reported genitourinary function was assessed before HDR, during an acute period after treatment (within 90 days of HDR), and on long-term followup using the American Urological Association International Prostate Symptom Score, a urinary QOL Likert questionnaire, and the Sexual Health Inventory for Men questionnaire. Regression analyses were performed using the ordinary least squares method.

RESULTS: With median followup of 57 months, biochemical progression-free survival was 100%. There were no grade ≥3 toxicities. Dose to the urethra and bladder, as well as prostate size and intraprostatic urethra length were predictive for short-term changes in QOL. Advanced patient age was predictive for worse sexual function on both acute and long-term followup.

CONCLUSIONS: Toxicity after HDR monotherapy for prostate cancer is acceptable. Patients with larger prostates, longer intraprostatic urethras, and greater doses to the bladder and urethra may experience worse acute urinary QOL. Older patients may experience greater impairment in sexual function in the short and long terms.

Keywords: Prostate cancer; Brachytherapy; High-dose-rate; Toxicity; Side effects; Quality of life

Introduction

With an estimated 240,000 new cases annually, prostate cancer is the most commonly diagnosed noncutaneous malignancy in the United States and the second most common cause of cancer-related mortality in American men (1). Curative options for early-stage prostate cancer include radical prostatectomy, brachytherapy, and external beam radiation. Low-dose-rate (LDR) brachytherapy has long been accepted as an effective monotherapeutic option for favorable prostate cancer, and a growing body of data suggests that high-dose-rate (HDR) brachytherapy monotherapy is similarly efficacious (2–8). HDR has several advantages over LDR. First, the low α/β ratio of prostate adenocarcinoma suggests that greater cancer cell death can be achieved through hypofractionated HDR than continuous LDR exposure (9, 10). Second, customization of radioactive source dwell times in HDR catheters allows for adaptive planning and optimal target volume coverage, whereas postimplantation seed migration may render LDR dosimetry suboptimal (11).

Despite the theoretic and logistic advantages of HDR, there have been no randomized comparisons of HDR to

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other treatment modalities for favorable prostate cancer. In the absence of high-grade evidence demonstrating superiority of one technique over another, quality of life (QOL) becomes the primary desired outcome for patients (12). Regardless of the technique, genitourinary and gastrointestinal toxicities are the most common side effects of treatment for localized prostate cancer (13). However, data are conflicting regarding the relative toxicities of each modality. On one hand, some studies suggest that radiation is associated with more irritative urinary symptoms and bowel problems, with prostatectomy leading to higher rates of urinary incontinence and erectile dysfunction despite the overall younger age of surgical patients (14–16). Other studies indicate that side effects are comparable among brachytherapy, external beam radiation, and prostatectomy (16–18).

These discrepancies illustrate the fact that toxicity and QOL studies in patients with prostate cancer are often limited by methodological challenges. Conflicts may arise between physician- and patient-reported symptoms, and many confounding factors have been identified, including disease burden, partnership status, patient anxiety, and supplemental interventions such as androgen deprivation therapy (19, 20). Given the relatively recent interest in HDR as monotherapy for favorable prostate cancer, most HDR tolerability studies typically pertain to boost treatment in conjunction with external beam radiation (21). The purpose of this study was to quantify both physician- and patient-reported toxicity and QOL after definitive HDR monotherapy for favorable prostate cancer in a cohort who did not receive either androgen deprivation therapy or external beam radiation. By doing so, our aim was to separate the side effects of prostate cancer treatment directly attributable to HDR from those potentially due to hormone deprivation or teletherapy. The data suggest that HDR monotherapy is associated with minimal acute and long-term toxicity. Moreover, we identify patient-specific and dosimetric factors that predict short- and long-term toxicity after HDR monotherapy that may be used to inform future treatment decisions.

Methods and Materials

Thirty-nine consecutive patients who underwent definitive HDR monotherapy for prostate cancer between May 2001 and January 2012 at our institution were identified from a prospectively maintained database for this analysis, which was approved by the Committee for Human Research. Most low-risk prostate cancer patients treated with brachytherapy during this period underwent permanent prostatic implantation per our institutional policy. As such, the patients included in this study were treated with HDR monotherapy due to personal preference, pubic arch interference, large prostate size, or poor pretreatment urinary symptom scores. All patients had transrectal ultrasound (TRUS)-guided, biopsy-proven malignancy with no evidence of either nodal or distant metastases. As described previously, HDR implants were performed under epidural anesthesia using 16 Flexi-guide catheters inserted by a free-hand method under TRUS guidance, and a urinary catheter filled with radio-opaque contrast was used to define the prostatic urethra (11). CT-based inverse planning simulated annealing optimization was used to treat the prostate and proximal seminal vesicles (22). Demographic data and disease characteristics were available for all subjects, and volumetric and dosimetric data were available for 35 patients.

Physician-reported side effects of treatment were prospectively assigned during clinical encounters according to the Common Terminology Criteria for Adverse Events v4.0 grading scale by one practitioner (ICH). Patient-reported urinary and sexual function were also collected prospectively at the time of clinical encounters and were quantified before and after treatment using three independent measures: (*1*) the American Urological Association International Prostate Symptom Score (AUA); (*2*) a urinary QOL Likert questionnaire, where higher scores are indicative of lower quality of life; and (*3*) the Sexual Health Inventory for Men (SHIM) questionnaire (23, 24). The acute period for side effects was defined up to 90 days from the end of HDR brachytherapy. For patients with more than one physician- or self-reported measurement during the acute period, the worst score was used for analysis. During long-term followup, the best score was reported when more than one was available, provided a trend to the contrary was not evident. Toxicity was graded, and patients were provided with a set of all questionnaires at each clinic visit, as well as by mail immediately before data analysis, for which the response rate was 62%.

All univariate and multivariate analyses were performed using ordinary least squares regression with STATA 13.1 software. A key assumption in interpreting our regression analyses is that there do not exist omitted independent variables that are both correlated with one or more of the included independent variables and the model's dependent variable. The presence of such variables could cause bias in our coefficient estimates. To partially test the robustness of this assumption against the possibility of omitting important independent variables, multivariate regression analyses were performed on the same dependent variables with additional independent variables and comparing coefficient estimates from the resulting extended models are compared with those from the baseline models. The inclusion of additional explanatory variables selected to reflect disease burden, such as Gleason score and pretreatment prostate-specific antigen (PSA), had little effect on the estimated coefficients for age, prostate volume or intraprostatic urethral length as measured on planning CT contours, urethral length, and other independent variables for all models. This leads us to conclude that these models sufficiently satisfy the aforementioned critical assumption. All data were tested as continuous variables. p-Values were calculated from t statistics with the appropriate degrees of freedom.