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BRACHYTHERAPY

Predictive factors for urinary toxicity after iodine-125 prostate brachytherapy with or without supplemental external beam radiotherapy

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ABSTRACT

PURPOSE: We examined the factors associated with urinary toxicities because of brachytherapy with iodine-125 with or without supplemental external beam radiotherapy (EBRT) for prostate cancer.

METHODS AND MATERIALS: We investigated 1313 patients with localized prostate cancer treated with iodine-125 brachytherapy with or without supplemental EBRT between 2003 and 2009. The International Prostate Symptom Score (IPSS) and Common Terminology Criteria for Adverse Events data were prospectively determined. Patients, treatment, and implant factors were investigated for their association with urinary toxicity or symptoms.

RESULTS: IPSS resolution was not associated with biologically effective dose (BED). Baseline IPSS, total needles, and the minimal dose received by 30% of the urethra had the greatest effect according to multivariate analysis (MVA). Urinary symptom flare was associated with baseline IPSS, age, BED, and EBRT on MVA. Urinary symptom flare and urinary Grade 2 or higher (G2+) toxicity occurred in 51%, 58%, and 67% ($p = 0.025$) and 16%, 22%, and 20% ($p = 0.497$) of the <180, 180−220, and >220 Gy BED groups, respectively. Urinary G2+ toxicity was associated with baseline IPSS, neoadjuvant androgen deprivation therapy (NADT), and seed density on MVA. When we divided patients into four groups according to prostate volume (< 30 cc or ≥30 cc) and NADT use, urinary G2+ toxicity was most commonly observed in those patients with larger prostates who received NADT, and least in the patients with smaller prostates and no NADT.

CONCLUSIONS: NADT was associated with urinary G2+ toxicity. Higher dose and supplemental EBRT did not appear to increase moderate to severe urinary toxicities or time to IPSS resolution; however, it influenced urinary symptom flare.

Keywords: Brachytherapy; ^{125}I; Prostate cancer; Urinary toxicity; Neoadjuvant androgen deprivation therapy; Higher biological effective dose; Supplemental external beam radiotherapy

Introduction

Permanent prostate brachytherapy with iodine-125 (^{125}I) is a standard treatment for localized prostate cancer along with radical prostatectomy and external beam radiotherapy (EBRT) (1). In EBRT for prostate cancer, several randomized controlled trials (2, 3) have demonstrated a relationship between dose escalation and a better biochemical control rate. In terms of comparison between EBRT and brachytherapy, the results of a multicenter randomized trial of EBRT boost vs. low-dose-rate brachytherapy boost for unfavorable-risk localized prostate cancer (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy [ASCENDE-RT]: NCT00175396) were reported at the Genitourinary Cancers Symposium in

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Conflict of interest: None of the authors have any conflicts of interest to declare.

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2015 (4). In this trial, an ^{125}I low-dose-rate boost was much more effective than an EBRT boost in rendering unfavorable-risk prostate cancer patients biochemically disease free but was associated with greater cumulative incidences of late Grade 3 genitourinary (GU) toxicity compared with EBRT boost. Another Phase III study comparing combined EBRT and brachytherapy with brachytherapy alone for select patients with intermediate-risk prostatic carcinoma (Radiation Therapy Oncology Group 0232 [RTOG 0232]) is ongoing.

Although treatment-related toxicity is considered to be relatively low in brachytherapy (5), almost all patients experience urinary symptoms to varying degrees. In recent years, several predictive factors for urinary toxicities such as urinary symptom flare, which is a late transient worsening of urinary symptoms described by Cesaretti *et al.* (6), have been reported. In some large series (7, 8), baseline International Prostate Symptom Score (IPSS), larger prostate volumes, lack of androgen deprivation therapy (ADT), and higher radiation doses were revealed as factors associated with late urinary toxicity. As urinary toxicities are strongly influenced by patient-related factors, such as baseline IPSS and prostate volume, they can be difficult to interpret. However, whether treatment-related factors, such as higher dose, ADT, and supplemental EBRT, are associated with urinary toxicities is still controversial. Thus, in the present study, we aimed to examine factors associated with urinary toxicities in brachytherapy patients, including those who were treated with higher biologically effective doses (BEDs).

Methods and materials

A total of 1313 consecutive patients with localized prostate cancer were treated with ^{125}I brachytherapy between 2003 and 2009 at our institution. The median followup for the entire cohort was 7 years (range, 4−11 years). Patients with low risk (T1−T2a, prostate-specific antigen [PSA] $<$ 10 ng/mL and Gleason score $\leq$6) were treated with seed implantation alone (monotherapy) with a prescribed dose of 145 Gy; patients with intermediate (T2b−T2c, PSA of 10−20 ng/mL, or Gleason score 7) and high risks (T3a, PSA $>$20 ng/mL or Gleason score $\geq$8) were treated with seed implantation with a prescribed dose of 100 Gy followed by EBRT using a three-dimensional conformal technique of 45 Gy in 25 fractions (combined therapy). Intermediate-risk group patients with PSA $<$ 10 ng/mL, Gleason score 3 + 4 = 7, and positive core needle biopsy rates $<$33% received monotherapy. Neoadjuvant androgen deprivation therapy (NADT) was administered to 40% of the patients with the aim of reducing prostate volume or because some patients had already been treated with ADT when they appeared for brachytherapy as ADT alone was a common treatment option in Japan for any stage of the disease in the early study period. ADT comprises a luteinizing hormone-releasing hormone agonist with or without an antiandrogen agent. Adjuvant ADT was not administered.

We performed the implant procedure as described previously (9). In intraoperative planning dosimetry, we aimed for 99% of the prostate volume to receive 100% of the prescribed dose (V_{100}) and for the dose to 90% of the prostate (D_{90}) to be 110−130% of the prescribed dose. The urethral volume receiving 150% of the prescribed dose (uV_{150}) was $<$0.1 cc, and the rectal volume receiving 100% of the prescribed dose (rV_{100}) was $<$0.1 cc. In particular, a urethral D_{30} (uD_{30}) of $<$130% of the prescribed dose was strictly applied. On the next day, a CT scan was obtained while the patient had a urinary catheter inserted; a contoured circle 7 mm in diameter acted as a surrogate for the urethra. Therefore, only the urethral dose was acquired on the day after the implant. For postimplant dosimetric analysis, a CT scan was obtained 1 month after implantation.

IPSS and Common Terminology Criteria for Adverse Events (CTCAE, version 4) data were prospectively collected. The IPSS was recorded before treatment, at 3, 6, and 12 months after treatment, and annually thereafter for 5 years. Urinary symptoms were assessed every 3 months for the first 2 years, every 4 months for the next 3 years, and every 6 months for 5 years. Prophylactic α-blockers were prescribed for a minimum of 3 months after implantation. Administration of α-blockers after the first 3 months was at the urologists' discretion according to symptoms.

The patient, treatment, and implant factors were examined for an association with urinary toxicity or associated symptoms. IPSS resolution was defined as a return of the total IPSS to within two points of the baseline score. Late transient worsening of urinary symptom flare was defined as an increase in IPSS to $\geq$5 points greater than the post-treatment nadir. Postimplant edema was defined as postimplant CT volume on Day 30 divided by ultrasound volume at preimplant volume study. Seed density was defined as the number of seeds divided by ultrasound volume at preimplant volume study. The times to IPSS resolution, urinary symptom flare occurrence, urinary G2+ toxicity, and urinary retention requiring catheterization were calculated by the Kaplan-Meier method. The BEDs were calculated from the prostate D_{90} and the EBRT dose using an a/b ratio of 2 (Gy2), applying the formulas described previously by Stock *et al.* (10). The BED groups were stratified to $<$180, 180−220, and $>$220 Gy.

Comparisons were made by the log-rank test, and the Cox proportional hazards model was used for univariate analysis and multivariate analysis (MVA). MVA was performed for all factors shown to be statistically significant on univariate analysis. Analyses were carried out using SPSS 22.0 (IBM Corp., Armonk, NY). Differences were regarded as statistically significant for p-values $<$0.05.

Results

Patient and treatment characteristics are shown in Table 1.