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Urinary incontinence after high-dose-rate brachytherapy boost treatment for prostate cancer

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ABSTRACT

PURPOSE: To evaluate urinary incontinence (UI) and to elucidate potential risk factors important for the appearance or deterioration of pre-existing UI after high-dose-rate boost treatment of prostate cancer.

METHODS AND MATERIALS: The change in grade of UI regarding the state at the start of treatment was assessed in 88 patients, consecutively treated from October 2006 through April 2011 with high-dose-rate brachytherapy of 3 × 6−7 Gy to 50−50.4 Gy of external-beam radiation. Increase in UI grade was defined as deterioration of UI (DUI). The impact of patients and treatment characteristics on third year prevalence of DUI was analyzed by using binary logistic regression method.

RESULTS: At third year, DUI of followup was evidenced in 17/81 (20.9%) patients. It significantly impacted micturition quality ($p = 0.015$) and was associated with $D_{2cc_{\text{bladder volume}}}$ (odds ratio [OR]: 1.14; 95% confidence interval [CI]: 1.03−1.26; $p = 0.010$), diabetes (OR: 6.73; 95% CI: 1.17−38.56; $p = 0.032$), and initial nocturnal micturition frequency (OR: 3.72; 95% CI: 1.03−13.04; $p = 0.045$). Based on a multivariate model, a range of ''safe'' $D_{2cc_{\text{bladder volume (EQD2)}}}$ doses is suggested (no risk factor: 21.9 Gy, frequent initial nocturnal micturition only: 12.0 Gy, diabetes only: 7.6 Gy, both risk factors: no safe dose).

CONCLUSIONS: The study featured on urinary bladder base as a risk structure for UI. By taking account of the dose to urinary bladder base in conjunction with diabetes and initial nocturnal micturition frequency, the risk of UI could be reduced.

Keywords: Urinary incontinence; High-dose-rate brachytherapy; Prostate cancer

Introduction

Urinary incontinence (UI) is one of the adverse effects that may occur after various forms of radical local prostate cancer treatment. It may be a lifelong complication with significant impact on patients' outcome satisfaction (1).

UI can be expected also after the external-beam radiation (EBRT) and high-dose-rate brachytherapy (HDRB) boost treatment (2−9). The reported rates of UI after EBRT + HDRB are highly variable, and several factors may be implicated for this dispersity of data such as different definitions or different methods of assessment. In institutional series, the reported incidence of UI is up to 22% (3) with up to 4% rate of UI required the use of pads (4). Higher rates of more pronounced form of UI were reported if quality-of-life questionnaires were used to obtain data (7, 8).

In terms of UI, EBRT + HDRB is comparable to other modes of radiation treatment—sole EBRT and low-dose-rate brachytherapy (LDRPB) (5, 7) When compared to radical prostatectomy, EBRT + HDRB is as advantageous as other forms of radiation treatment (7). However, reported followup of patients after EBRT + HDRB is short and UI after EBRT + HDRB, unlike other treatments, seemed to increase with longer observation (7).

Clinical and dosimetric parameters as well as critical organs implicated in UI after EBRT + HDRB are largely unknown. Nevertheless, there exist some studies that provide valuable information. For example, Galalae *et al.* (10) have identified the relationship between the interval of less than

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6 months to transurethral resection with a significant increase of UI. However, in general, the rate of UI was very low. Aström *et al.* (11) and Luo *et al.* (12) showed basically identical very favorable outcomes of HDR brachytherapy for prostate cancer associated with very low rates of UI and significantly lower vs. EBRT alone. In consequence, the results of these three studies were perfectly in line demonstrating superiority of prostate HDR brachytherapy in terms of radiotherapy-related toxicity in comparison with alternative boost methods.

More is known about late-urinary toxicity (LUT) on general. Several dosimetric studies pointed at prostatic urethra as a critical organ (6, 8, 13, 14). LUT is related to either volumes of urethra that received doses higher than the prescribed dose (6, 14) or to high doses received by the small fragments of urethra (8, 13). Similar relation between LUT and the regions that received high doses was shown also for the whole prostate (3, 6, 9, 13). Critical are doses 10−100% higher than the prescribed dose with related volumes. However, generalization of these predictive factors for LUT on UI seems not to be absolutely reliable as at least in some of the aforementioned studies UI represented only a small part of LUT.

Aiming at individualizing treatment and improving safety of EBRT + HDRB, the objective of the study was to define patients' and treatment's characteristics that are related specifically to UI.

Methods and materials

Patients

In the followup study, 88 patients, consecutively treated by the author with EBRT + HDRB at the Institute of Oncology Ljubljana (IOL) in the period 2006−2011, were included.

EBRT + HDRB was primarily offered to patients with intermediate- or high-risk clinically localized or locally advanced prostate cancer (15) and to low-risk patients who refused to get radical prostatectomy, if feasible for brachytherapy. In general, patients were considered eligible for EBRT + HDRB if ultrasound showed no pubic arch interference, were eligible to undergo regional anesthesia with spinal block, and eligible to perform CT/MRI scan.

Treatment characteristics

Brachytherapy was performed with the patient in lithotomy position and consisted of TRUS-guided transperineal insertion of 20- or 30-cm-long closed-end plastic needles into the prostate and in selected patients also into the initial part of seminal vesicles, the use of the in-house made template that allows also needle fixation and aerated xylocaine gel in the Foley catheter to improve visibility of urethra. Needles were typically placed into prostate periphery and suburethraly. Finally, cystoscopy was performed with patient in recumbent position with extended legs for determining the final position of the tips of needles beneath bladder mucosa. After completion of the implant procedure, CT (slice thickness 1.6 mm) or MRI scan (T2-weighted fast-spin echo paratransversal sequence and fast recovery 3D fast-spin echo sequence with 1 mm isotropic voxels) was acquired for planning purposes. Brachyvision planning system was used for image registration, contouring, and dosimetry. Two planning target volumes (PTVs) were routinely defined: PTV1 encircled the prostate with additional 3-mm margin around the zone of suspected capsular invasion, whereas PTV2 encircled peripheral part of the prostate. When visible on the MRI images, also gross tumor volume was defined and included in the PTV2. Initially, prescribed dose was 21 Gy to PTV1 and 22.5 Gy to PTV2, with 7 Gy and 7.5 Gy per fraction, respectively. Later, the dose was reduced to 18 Gy to PTV1 and 19.5 Gy to PTV2, also given in three fractions. The biologically equivalent doses for PTV1 and accepting an $\alpha/\beta = 1.5$ were 119 Gy and 90 Gy respectively. Implanted fiducial markers (1.2×3−5 mm sized gold seeds) and in most patients CT scan were used to estimate needle shift before the third fraction. Interfraction interval was 6−8 hours. However, in case of excessive overnight needle shift that could not be compensated with extraplanning, an additional implantation was performed for the delivery of the third treatment fraction. Urethra was identified with the urinary catheter. The contour enclosed also the additional 1- to 2-mm margin around the catheter. Contouring of urethra started at bladder base and inferiorly extended to genitourinary diaphragm (always at least 0.5 cm caudally from the last slice of contoured apex of the prostate). The constraints for urethra recommended as ideal parameters relative to the prescribed doses were: urethra max $D90 < 110\%$, urethra max $D1<130\%$. Urinary bladder volume was defined by the outer surface of the bladder wall. Bladder contour encompassed bladder neck and extended minimally 2 cm above the prostate base. Contouring and treatment were performed with partially filled urinary bladder using 150 mL of 0.9% NaCl solution. The recommended constraint was to keep the maximal dose received by the most exposed 2ccm of urinary bladder bellow 10.5 Gy. Treatment was delivered with the Varian Gamamed plus stepping source device using ^{192}Ir with the activity of 0.7−1.4 Ci.

EBRT, that typically preceded HDRB, was delivered as three-dimensional conformal radiation. Clinical target volume included prostate, distal 1/3−2/3 of seminal vesicles with lymph nodes along external, internal, and common iliac vessels if the risk of positive lymph nodes exceeded 15% according to the equation of Roach *et al.* (16). Prescribed dose was 50−50.4 Gy in 25−28 fractions.

Study instrument for assessment of problems with UI

To detect late effects of treatment and to allow to grade LUT according to various grading systems (17−19), an in-house made questionnaire, used already for several years,