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Original Research Article

Correlation between urinary dose and delayed radiation cystitis after 78 Gy intensity-modulated radiotherapy for high-risk prostate cancer: A 10-year follow-up study of genitourinary toxicity in clinical practice

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ABSTRACT

Purpose: To investigate the factors associated with the risk of long-term genitourinary (GU) toxicity among high-risk prostate cancer (PC) patients treated with high-dose intensity-modulated radiotherapy (IMRT).

Methods and materials: Between 2000 and 2011, PC patients treated with 78 Gy in 39 fractions delivered by IMRT combined with neo-adjuvant hormonal therapy were selected from among our database. GU toxicities and clinical factors, as well as separate anatomical urinary structures, were evaluated in terms of their associations.

Results: A total of 309 patients was included in this study. The median follow-up was 104 months (range: 24–143 months). The most frequently observed late grade ≥2 GU toxicity was hematuria (11.2%: 10-year actuarial risk) with radiation cystitis observed in the majority of patients. In univariate analysis, late grade ≥2 hematuria was associated with the exposure to doses >75 Gy (V75) of the bladder neck and V70 of the bladder wall, as well as with T stage. V75 of the bladder neck remained significant in multivariate analysis ($p = 0.049$).

Conclusions: At the 10-year follow up of high-dose IMRT, a major concern was proved to be delayed cystitis related to the higher volume of bladder neck dose exposed excess over 75 Gy.

Introduction

Intensity-modulated radiotherapy (IMRT) is now applied worldwide in routine clinical practice as a standard radiotherapy procedure. Many clinical studies have demonstrated the efficacy and safety of the clinical use of high-dose IMRT, particularly for intermediate- and high-risk prostate cancer (PC) patients, who show a better progression-free rate and fewer complications than those patients treated using conventional three-dimensional conformal radiotherapy (3D-CRT) [1–3]. Many studies have reported on the potential advantages of rectal dose reduction after PC IMRT, with respect to gastrointestinal (GI) toxicity [4–6]. PC patients undergoing conformal radiotherapy, including IMRT as unavoidable consequence have several urinary tract structures, i.e., the entire bladder, or to the bladder neck or the urethra, all being organs at risk from which genitourinary (GU) symptoms may originate. Currently, there is already evidence of a likely dose response relationship for late GU toxicity in PC, however limited knowledge about dose relationship of the urinary sub-structures, adjacent to the prostate and detailed GU toxicity reported [7].

Recently, a preliminary study by the Radiation Therapy Oncology Group (RTOG), which was the largest of its kind, revealed detailed 5-year toxicity profiles associated with high-dose IMRT [8], but more long-term follow-up data are needed, especially on chronic GU toxicity. At our institution, IMRT has been used clinically for the definitive treatment of all PC patients since November 2000; it has been approximately 15 years since the first clinical application of IMRT [9], such that a sufficient follow-up period (i.e., >10 years) has passed to enable conclusions to be drawn regarding late GU toxicity. In the present study, we retrospectively evaluated the prevalence and course of urinary late toxicity and identified factors predictive of severe late urinary toxicity. We focused on urinary-related organs at risk of late GU toxicity after

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high-dose IMRT, using data gathered during the past 15 years of our clinical practice.

Material and methods

Patient selection

From November 2000 to October 2011, 652 Japanese men with T1-4N0M0 PC were treated at our institution by definitive IMRT, at a prescribed dose of 70–78 Gy, with neoadjuvant hormonal therapy (NAHT). Among these patients, 378 (57.9%) with at least one high-risk factor, according to D'Amico's classification [10] or with stage C disease, as defined by the Jewett staging system, were eligible for a total dose of 78 Gy, delivered in 39 fractions, according to the protocol of our institutional review board. In total, 69 patients were excluded from the analysis, because their prescribed dose was reduced from 78 to 70–74 Gy due to the presence of the following unfavorable morbidity risk factors: diabetes mellitus, cardiovascular disease receiving antithrombotic treatment, previous irradiation adjacent to the prostate, collagen disease, past history of trans-urethral resection of the prostate (TURP), and age > 80 years. Consequently, patients with unfavorable risk factors for increased urinary toxicities were not treated with dose-escalated IMRT.

All patients received the same total dose 78 Gy in 39 fractions, with delivery confined to the prostate and seminal vesicles; furthermore, baseline clinical data, with a minimum of 2 years of follow-up data and treatment-planning dosimetry data, were available for all patients. This research was approved by the internal review board of our institution (approval number: E-1806).

IMRT planning protocols

Patients were immobilized in the prone position using a thermoplastic shell in combination with a vacuum pillow and a leg support. All of the planning protocols used 5–7 field beam arrangements and 6–15 MV photon beams, delivered by the Clinac 2100C or Clinac 2300C/D unit (Varian Medical Systems, Crawley, UK). A clinical target volume (CTV) was created based on the prostate and seminal vesicles, which were contoured by referring to magnetic resonance imaging data. Regarding the setup error reduction strategy, errors were evaluated based on the patient's pelvic bony structure using film-based portal imaging. The margins for the planning target volume (PTV) were added to the CTV, according to the following 3D settings: 9-mm margins applied universally, except for a 6-mm margin on the rectum side and a 10-mm margin in the caudal direction. Patients in the very high-risk group were treated using the simultaneous integrated boost method, which simultaneously delivers a high-dose (78 Gy) to the prostate and seminal vesicles and a relatively lower-dose (58.5 Gy) to the regional pelvic nodes. Treatment plans were created using the Eclipse Helios system (ver. 6.3 –8.2, Varian Associates, Palo Alto, CA, USA). The isodose distributions and dose–volume histograms (DVH) were evaluated according to the clinical criteria described in previous reports [11].

Clinical toxicity assessment

Generally, follow-up examinations were performed initially at 3- to 4-month intervals after completion of IMRT during the first 2 years, and every 6 months thereafter. A patient symptom questionnaire was completed at each visit to assess toxicity, and the RTOG Late Radiation Morbidity Scale and Common Terminology Criteria for Adverse Events (ver. 3.0; National Institutes of Health, Bethesda, MD, USA) were used to grade acute and late GU toxicity. In total, five different GU symptoms were recorded: frequency/urgency, dysuria, retention, incontinence, and hematuria. Grade 1 hematuria was recorded as an incidental finding of a routine urine test. In cases of macrohematuria or continuous severe microhematuria on urine tests during the follow-up, examination of cystoscope and urine cytology allowed for distinguishing between early metachronal bladder cancer and late Grade 2 hematuria. Acute toxicity was defined as that occurring within 3 months of treatment completion, and late toxicity was defined as that occurring at any point thereafter. Outcomes were measured from the initiation of IMRT to the date of onset of complications or the last follow-up. All time intervals were measured from the completion of radiotherapy to the onset of toxicity events. Because of loss to follow-up, censoring, and different follow-up times among groups, comparison of late GU toxicity was evaluated as the time to event outcome using the Kaplan–Meier estimation.

Analyses of urinary dose statistics

Planning data were analyzed using the outputs from the DVH generated by the treatment planning system. To evaluate the dose distribution within the urinary tract, we characterized the anatomical urinary structure of the PTV as follows: inner bladder wall (thickness, 4 mm), bladder neck wall of the prostatic base, urethra of the central 5-mm round structure (from below the apex to above the base of the prostate), and sphincter overlying the penile bulb. Fig. 1 shows a representative sagittal view of a planning CTV with a segmented urinary tract (1A) and the overlying radiation dose distribution (1B). The DVH planning data for the bladder wall, bladder neck, urethra, and sphincter were obtained.

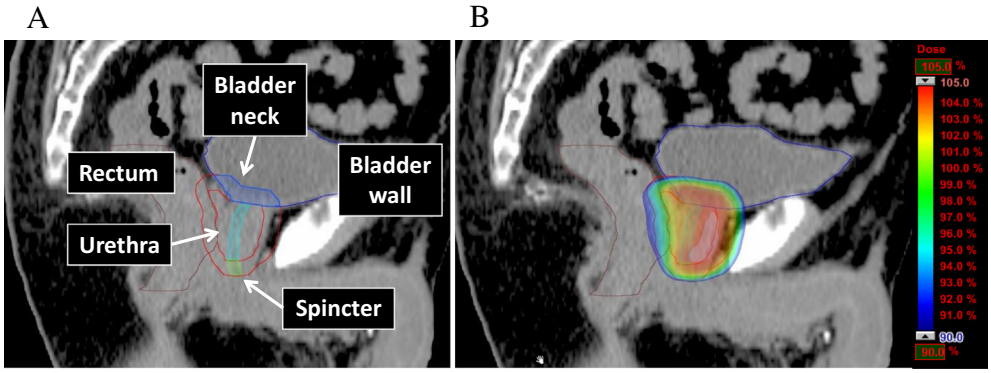

Fig. 1. Anatomical relationships among at-risk organs in the segmented urinary tract (1A) and absorbed dose distributions in the sagittal view (1B).