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...
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 cystoscopy 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.
Statistical analysis

We used GraphPad PRISM (ver. 5.04; GraphPad Software, Inc., La Jolla, CA, USA) and Stat View software (ver. 5.0; SAS Institute, Inc., Cary, NC, USA) for the statistical analyses. Linear regression modeling of the incidence of grade 2 or higher toxicity was performed, with differences between DVH parameters, prostate volume and bladder volume used as continuous variables. Dose volumes were assessed via receiver operating characteristic (ROC) curves to determine the optimal cut-off values at 0.5-Gy dose-volume intervals, and toxicity probability values for each cut-off value were produced. Only dose volumes with a sensitivity and specificity >0.65 were included in the analysis of GU toxicity. We performed univariate analyses for late GU toxicity using the log-rank test, converting continuous prognostic variables into binary variables stratified by the optimal cut-off value. Multivariate analysis by Cox’s proportional hazards model was performed for late toxicity, including only covariates that were associated with any outcome.

Results

In total, 309 patients met the inclusion criteria for the analysis, and the median follow-up period was 104 months (range: 24–143 months). The pretreatment characteristics and treatment parameters are listed in Table 1. Using the Jewett staging system, most patients were classified as stage C (n = 225; 73%), with the remaining patients classified as stage B (n = 84; 27%).

The details of acute and late GU toxicity – i.e., cumulative incidence rates, frequency and urgency, dysuria, retention, incontinence, hematuria, and highest all-toxicity grade are provided in Supplementary data. Two cases of late macrohematuria were found to be metachronous microinvasive bladder cancer, as confirmed by cytology, and thus were not counted as grade 2 hematuria. The most frequently observed late grade 2 or higher GU toxicities were hematuria (n = 30, 9.7%; 10-year actuarial risk, 11.2%), with radiation cystitis observed endoscopically in the majority of patients. Other grade 2 symptoms were increased urgency and frequency (n = 14, 4.5%; 10-year actuarial risk, 5.6%), frequency/urgency (n = 17, 5.5%; 10-year actuarial risk, 3.4%) and incontinence (n = 6, 1.9%; 10-year actuarial risk, 1.8%). At the last follow-up, late grade 2 or higher GU toxicity was observed in 31 patients (10.0%), but no late grade 4 GU toxicity was observed during the follow-up. Fig. 2 shows a line chart of the changes in the various GU grading scores, from baseline to follow-up, in all patients. It is clear that the incidence rates of incontinence and hematuria increased gradually over time after 60 months, while the other symptoms decreased during the first 60 months of follow-up.

Concerning the effect of the DVH factors on GU toxicity, the incidence of late grade 2 or higher hematuria was significantly associated with V70 (p = 0.01, 95% confidence interval [CI], 1.03–1.18) and V75 (p < 0.0001, 95% CI, 1.06–1.21) of the bladder neck and V70 of the bladder wall (p = 0.02, 95% CI, 1.01–1.15). The hazard ratios [HRs] associated with these factors are shown in Fig. 3. In addition, no DVH factors were associated with the other symptoms of GU toxicity.

ROC analysis was conducted to identify the optimal cut-off dose–volume values of the urinary-related organs with respect to late grade 2 or higher GU toxicity. V75 of the bladder wall (>12 cc) was the strongest predictor of grade 2 or higher hematuria (area under the curve [AUC], 0.72; p < 0.0001; Supplementary data) No other GU toxicity symptoms were significantly associated with any of the other urinary bladder volume cut-off values. By dividing the V75 of the bladder neck volume using an optimal cutoff of 12 cc, the higher-volume group showed a significantly higher 10-year actuarial incidence rate of late hematuria (19.2% vs. 5.2%; 95% CI: p = 0.002; Fig. 4). The median incidence time of grade 2 or higher hematuria was 61 months (range: 6–108 months), indicating that more than half of the cystitis cases continued to occur more than five years after irradiation.

Fifteen clinical and dosimetric factors were correlated with the risk of grade 2 or higher hematuria in univariate and multivariate correlation analyses. In the univariate analysis, T-stage (>stage T3b), V70 of the bladder wall >20%, and V75 of the bladder neck volume >12 cc were significant predictive factors for the development of late grade 2 or higher hematuria. In the multivariate analysis, only V75 of the bladder neck volume >12 cc was significantly associated with late hematuria (p = 0.049; HR = 1.27, 95% CI, 1.01–1.60) The HRs associated with these factors are listed in Table 2. None of the other late GU toxicity symptoms were correlated with any outcome.

Discussion

Many published reports have addressed the clinical effectiveness of IMRT for PC, especially with respect to its ability to prevent severe late GI toxicity, but less data on urinary toxicity from large institutional series are available [5,7,12]. To the best of our knowledge, the present report used the longest longitudinal observational period (>10 years) of any study conducted in this area to provide detailed data on late toxicity in patients with high-risk localized PC treated with high-dose IMRT. The treatment received by our patients was homogeneous in terms of the radiation dose, planning policy, and similar margins for the CTV. The present report provides evidence that a higher volume of the bladder neck exposed to >75 Gy is related to delayed cystitis, which has been a major concern – in terms of late toxicity among PC patients after high-dose IMRT – over the past 15 years of clinical practice.

Several other PC IMRT studies reported late GU toxicity related to various important clinical factors. Prior to this study, the longest follow-up was conducted by Alicikus et al., who reported a 10-year actuarial risk of developing late grade 2 GI toxicity of 17%, which is similar to our study [13]. These authors reported that acute grade 2 or higher GU toxicity was predictive of the development...
However, detailed toxicity data were not presented. Several other studies have confirmed that ADT, a history of TURP [14], the bladder wall V30 and V82 [15], and medication use [16] are risk factors for 3- to 5-year urinary morbidity. However, few studies have shown an association between the dose delivered to the bladder and GU toxicity after ≥5 years. Our study shows that the actuarial incidence rate of late cystitis becomes a major GU toxicity about 10 years of median follow-up. Furthermore, an impact on the dose–volume response of the urinary bladder neck was apparent approximately 5 years after high-dose IMRT (Fig. 4). Therefore, we emphasize that a sufficiently long follow-up period, of >5 years, is required to assess the actual incidence rate of late GU toxicity.

Interestingly, in this study, univariate and multivariate analyses showed that V75 of the bladder neck >12 cc was an independent predictor of late grade 2 or higher GU toxicity. The dose–volume toxicity relationships investigated herein provide several useful indicators for IMRT planning, with respect to optimizing and evaluating urinary-related organ doses. A recent update to the methods.

Fig. 2. Line chart showing changes in the Common Terminology Criteria for Adverse Events grading score from baseline to follow-up in all patients: (a) frequency and urgency, (b) dysuria, (c) retention, (d) incontinence, and (e) hematuria.

Fig. 3. Odds ratios (95% CI) for each dose–volume histogram parameter with respect to the incidence of late grade 2 or higher hematuria (●, p < 0.05).
Body radiation therapy has been tested on PC patients [20]. How may be additional risk factors for greater GU toxicity in advanced T neck tends to be greater. According to our findings, these problems of the patients were included in the high-risk group. In T3b or T4 matically due to increased PSA screening. Our Japanese cohort while the prevalence of advanced (T3–4) cases has decreased dra-

mented with delayed cystitis and the possibility of major, long-term toxicity; however, 58.5% of these patients experienced resolution of the symptoms at the last follow up time. An obvious decreased change of the symptoms can be seen in Fig. 2 except incontinence and hematuria. There is a need for correctly report scoring system of GU toxicity which is a more sensitive and valid indicator of patient satisfaction.

Another limitation is uncertainties in the GU dose calculations and actual delivery. We contoured the virtual GU structures with reference to MRI findings, nevertheless uncertainties of indication existed in their narrow urethral position. Additionally, the daily filling and the positioning of the bladder may not be uniform and this may impact actual radiation dose and volume of the bladder and urethra. In our cohort, no other GU structure except the bladder neck were associated with the other symptoms of GU toxicity; however, we cannot exclude that these concerns may contribute to our results.

In conclusion, we demonstrated that high-dose IMRT was well tolerated, with <10% of our high-risk PC patients developing grade 2 or higher GU late toxicities during long-term follow-up over the past 15 years. We should be careful when planning treatment, by taking into account the bladder neck dose–volume effects associated with delayed cystitis and the possibility of major, long-term GU toxicity in high-dose IMRT.

**Conflict of interest statement**

The authors report no conflict of interest with regard to this manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ctro.2017.09.005.

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