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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.

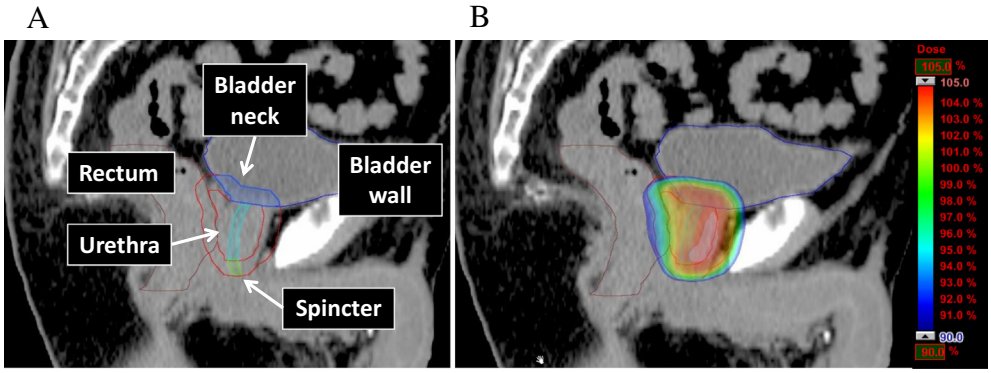

Fig. 1. Anatomical relationships among at-risk organs in the segmented urinary tract (1A) and absorbed dose distributions in the sagittal view (1B).

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 late toxicity in the univariate analysis ($p < 0.1$).

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 dysuria ($n = 14$, 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 neck (>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.

Table 1
Summary of patient characteristics and treatment parameters.

	Number 10r ($n = 178$)	%
Patients (n)	309	
Median follow-up in months	104	
Median age in years	70	
Clinical T stage		
T1–2	84	27
T3a	151	49
T3b	64	21
T4	10	3
Gleason sum score		
≤6	16	5
7	130	42
≥8	163	53
Initial PSA		
≤10	42	14
10–20	81	26
≥20	186	60
ADT		
Yes	49	16
No	260	84
Pelvic lymph nodes irradiation		
Yes	45	15
No	264	85
Prostate mean volume (cc)	24.8	
Bladder mean volume (cc)	126.2	

Abbreviations: PSA, prostate-specific antigen; ADT, androgen deprivation therapy.

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 homogenous 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 GU 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

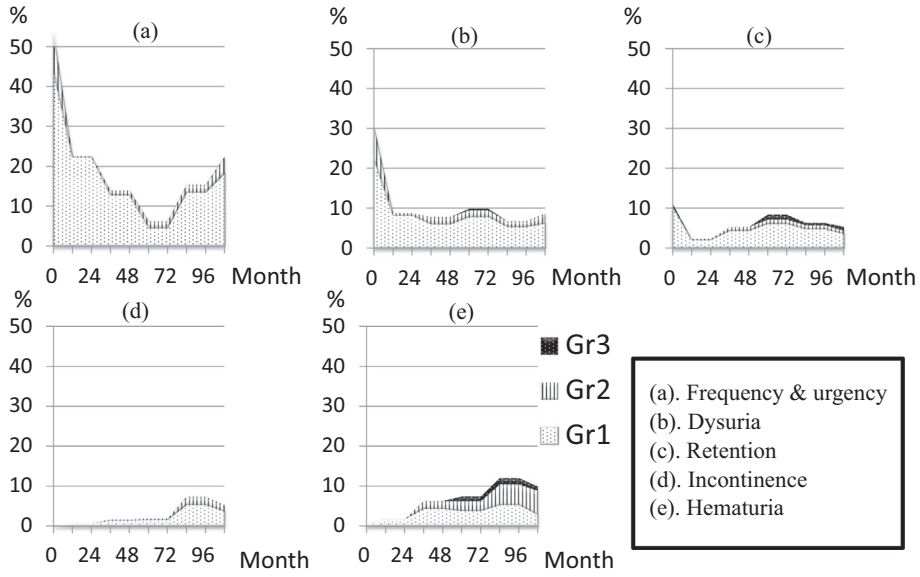

Fig. 2. Line chart showing changes in the Common Terminology Criteria for Adverse Events grading score from baseline to follow-up in all patients: (a) frequency and urgency, (b) dysuria, (c) retention, (d) incontinence, and (e) hematuria.

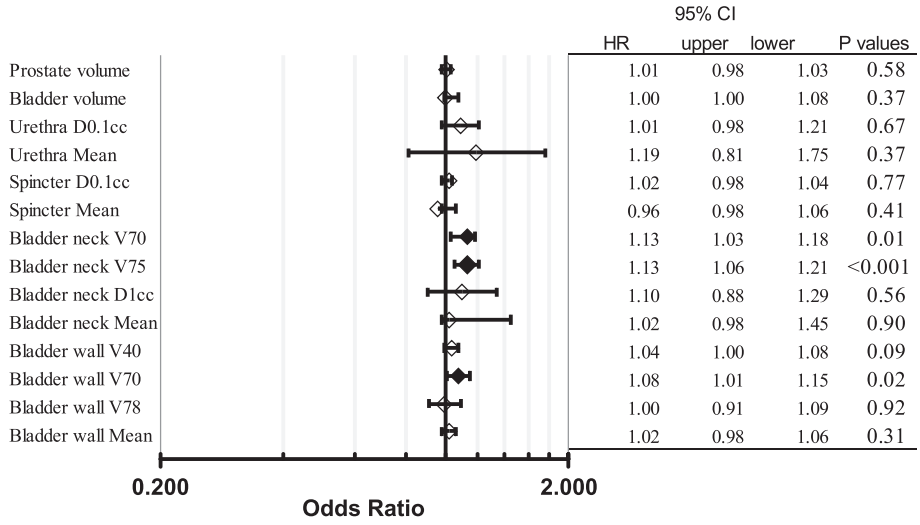

Fig. 3. Odds ratios (95% CI) for each dose–volume histogram parameter with respect to the incidence of late grade 2 or higher hematuria (◆; $p < 0.05$).

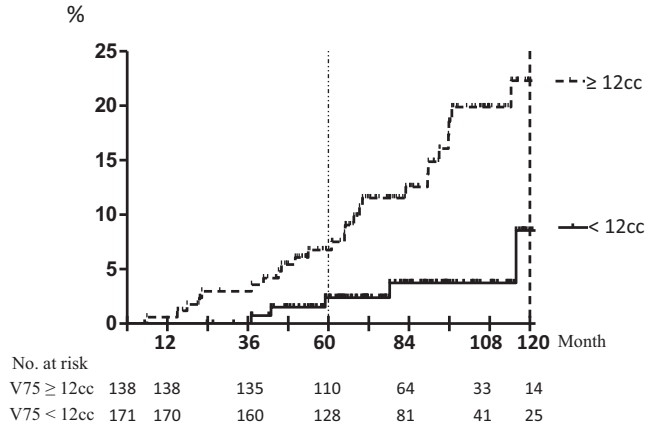

Fig. 4. Kaplan–Meier curves for actuarial incidence of late grade 2 or higher hematuria according to V75 of the bladder neck volume using an optimal cutoff of 12 cc.

of late GU toxicity. 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

Table 2
Potential risk factors for late grade 2 or higher toxicity of hematuria by univariate and multivariate analysis.

Factor	Variable	UVA		MVA	
		p Value	HR (95% CI)	*p* Value	HR (95% CI)
Age	>71	0.69	0.74 (0.36–1.52)		
Clinical T stage	>T3b	0.04	2.13 (1.01–5.00)	0.27	1.17 (0.88–1.56)
Gleason sum score	>8	0.39	0.73 (0.36–1.49)		
Initial PSA	>20	0.61	1.20 (0.40–1.72)		
Prostate volume (cc)	>25	0.16	1.67 (0.81–3.45)		
Pelvic nodes RT	YES	0.23	1.30 (0.26–2.27)		
Bladder wall volume (cc)	>126	0.64	1.19 (0.58–2.44)		
Bladder wall V40 (%)	>38	0.08	1.92 (0.90–4.00)		
Bladder wall V70 (%)	>20	0.04	2.08 (1.02–4.34)	0.37	1.11 (0.87–1.41)
Bladder wall V78 (%)	>6.4	0.09	1.85 (0.90–3.84)		
Bladder neck V70 (cc)	>20	0.056	2.08 (0.96–5.00)		
Bladder neck V75 (cc)	>12	0.0025	3.13 (1.45–6.67)	0.049	1.27 (1.01–1.60)
Bladder neck V80 (cc)	>1.33	0.17	1.92 (0.85–4.35)		
Bladder neck D1 (%)	>103	0.23	1.27 (0.78–2.62)		
Acute GU Grade	>2	0.19	2.02 (0.84–4.82)		

Abbreviations: HR, hazard ratio; CI, confidence interval; PSA, prostate-specific antigen; UVA, univariate analysis; MVA, multivariate analysis; GU, genitourinary.

for determining optimum beam intensity profiles using the Eclipse Helios inverse planning software demonstrated that a slightly modified algorithm can be achieved using separate beamlets and monitor units [17,18]. This allows heterogeneous treatment planning to be performed with equal or improved dose conformity for delivery of higher peripheral doses to peri-prostatic bladder neck lesions. Under the current planning system, we found that by using additional segmental structures, we could control the dose distribution and maintain homogeneity of the PTV during the optimization process. Additionally, regarding the evaluation and optimization of bladder dose constraint curves, dose–volume parameters of the entire bladder, including the superior part locating out of the field, do not appear to be the best predictors of GU toxicity. As a segmented, sensitive organ related to late cystitis, the bladder neck dose–volume must be evaluated carefully to strike the optimum balance between GU morbidity risk and the most appropriate treatment. Specific urinary tumor control probability/normal tissue complication probability data for computer-aided optimization and evaluation will be a topic of further investigation [19].

Early-stage PC cases have increased in the Western countries, while the prevalence of advanced (T3–4) cases has decreased dramatically due to increased PSA screening. Our Japanese cohort included a higher proportion of high-risk cases compared with Western studies. In fact, in our clinical cohort, approximately 58% of the patients were included in the high-risk group. In T3b or T4 stage cases, the overlap between the PTV interface and bladder neck tends to be greater. According to our findings, these problems may be additional risk factors for greater GU toxicity in advanced T stage patients in univariate analysis. More recently, stereotactic body radiation therapy has been tested on PC patients [20]. However, the long term results of using hypo-fractionation regimens favoring large doses per fraction have yet to be reported, and their application in advanced stage patients should be carefully considered from the viewpoint of long-term GU toxicity.

There are certain limitations of this retrospective study. First, each symptom was registered as maximal toxicity. Cumulative incidence was reported in Fig. 2 which does not cover relevant patient numbers with symptom improvement. Our data confirm that fifty-three patients (17%) have developed grade 2 or higher toxicity; however, 58.5% of these patients experienced resolution of 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 on 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 addition, our study was that not all of the cases included were treated using an image-guided radiotherapy (IGRT) system. Currently, for patients undergoing prostate-based IGRT at our institution, we have further reduced our PTV margins to 6 mm circumferentially around the prostate, including the prostate–bladder neck interface region. We believe that toxicity may be further reduced by limiting the dose of these inferior parts of the bladder. Further studies to assess the validity of the proposed bladder neck dose response on independent clinical datasets are warranted as an important next step [21].

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.

Acknowledgments

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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.

References

[1] Zelefsky MJ, Fuks Z, Hunt M, Lee HJ, Lombardi D, Ling CC. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. J Urol 2001;166:876–81.

[2] Vora SA, Wong WW, Schild SE, Ezzell GA, Halyard MY. Analysis of biochemical control and prognostic factors in patients treated with either low-dose three-dimensional conformal radiation therapy or high-dose intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2007;68:1053–8.

[3] Zelefsky MJ, Yamada Y, Fuks Z, Zhang Z, Hunt M, Cahlon O. Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. Int J Radiat Oncol Biol Phys 2008;71:1028–33.

[4] Spratt DE, Pei X, Yamada J, Kollmeier MA, Cox B, Zelefsky MJ. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2013;85:686–92.

[5] Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:1124–9.

[6] Sharma NK, Li T, Chen DY, Pollack A, Horwitz EM, Buyyounouski MK. Intensity-modulated radiotherapy reduces gastrointestinal toxicity in patients treated with androgen deprivation therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2011;80:437–44.

[7] Ghadjar P, Zelefsky MJ, Spratt DE, Munck af Rosenschold P, Oh JH, Hunt M. Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2014;88:339–44.

[8] Michalski JM, Yan Y, Watkins-Bruner D, Bosch WR, Winter K, Galvin JM. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 Prostate Cancer Trial. Int J Radiat Oncol Biol Phys 2013;87:932–8.

[9] Mizowaki T, Norihisa Y, Takayama K, Ikeda I, Inokuchi H, Nakamura K. Long-term outcomes of intensity-modulated radiation therapy combined with neoadjuvant androgen deprivation therapy under an early salvage policy for patients with T3-T4N0M0 prostate cancer. Int J Clin Oncol 2015;21:148–55.

[10] D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969–74.

[11] Norihisa Y, Mizowaki T, Takayama K, Miyabe Y, Matsugi K, Matsuo Y. Detailed dosimetric evaluation of intensity-modulated radiation therapy plans created for stage C prostate cancer based on a planning protocol. Int J Clin Oncol 2012;17:505–11.

[12] Fonteyne V, Villeirs G, Lumen N, De Meerleer G. Urinary toxicity after high dose intensity modulated radiotherapy as primary therapy for prostate cancer. Radiother Oncol 2009;92:42–7.

[13] Alicikus ZA, Yamada Y, Zhang Z, Pei X, Hunt M, Kollmeier M. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. Cancer 2011;117:1429–37.

[14] Peeters ST, Heemsbergen WD, van Putten WL, Slot A, Tabak H, Mens JW. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. Int J Radiat Oncol Biol Phys 2005;61:1019–34.

[15] Harsolia A, Vargas C, Yan D, Brabbins D, Lockman D, Liang J. Predictors for chronic urinary toxicity after the treatment of prostate cancer with adaptive three-dimensional conformal radiotherapy: dose–volume analysis of a phase II dose-escalation study. Int J Radiat Oncol Biol Phys 2007;69:1100–9.

[16] Cahlon O, Zelefsky MJ, Shippy A, Chan H, Fuks Z, Yamada Y. Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes. Int J Radiat Oncol Biol Phys 2008;71:330–7.

[17] Cho PS, Marks 2nd RJ. Hardware-sensitive optimization for intensity modulated radiotherapy. Phys Med Biol 2000;45:429–40.

[18] Zhang X, Liu H, Wang X, Dong L, Wu Q, Mohan R. Speed and convergence properties of gradient algorithms for optimization of IMRT. Med Phys 2004;31:1141–52.

[19] Azzeroni R, Maggio A, Fiorino C, Mangili P, Cozzarini C, De Cobelli F. Biological optimization of simultaneous boost on intra-prostatic lesions (DILs): sensitivity to TCP parameters. Phys Med 2013;29:592–8.

[20] Kim DW, Straka C, Cho LC, Timmerman RD. Stereotactic body radiation therapy for prostate cancer: review of experience of a multicenter phase I/II dose-escalation study. Front Oncol 2014;4:319.

[21] Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 2012;84:125–9.