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ORIGINAL ARTICLE

Clinical effect of multileaf collimator width on the incidence of late rectal bleeding after high-dose intensity-modulated radiotherapy for localized prostate carcinoma

Haruo Inokuchi[1] · Takashi Mizowaki[1] · Yoshiki Norihisa[1] · Kenji Takayama[1] · Itaru Ikeda[1] · Kiyonao Nakamura[1] · Mitsuhiro Nakamura[1] · Masahiro Hiraoka[1]

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Abstract
Background Several studies have confirmed a dosimetric advantage associated with use of a smaller leaf in intensity-modulated radiation therapy (IMRT). However, no studies have identified any clinical benefits. We investigated the effect of a smaller multileaf collimator (MLC) width on the onset of late rectal bleeding after high-dose prostate IMRT.
Materials and methods Two hundred and five prostate cancer patients were treated with a total dose of 78 Gy in 39 fractions by use of a dynamic MLC technique; however, two different MLC were used: a 10-mm-wide device and a 5-mm-wide device. Gastrointestinal toxicity and several clinical factors were assessed.
Results The 5-year actuarial risk of grade 2 or higher rectal bleeding was 6.9 % for the 10-mm-wide group ($n = 132$) and 1.8 % for the 5-mm-wide group ($n = 73$) ($p = 0.04$). The median estimated rectal doses for the two groups were 55.1 and 50.6 Gy ($p < 0.001$), respectively. Univariate analysis showed that acute toxicity, rectal V30–60, median rectal dose, normal tissue complication probability (NTCP), and MLC type were significant predictive factors for late rectal toxicity. In multivariate analysis, acute toxicity and NTCP remained significant.
Conclusion In our planning approach for prostate IMRT, a decrease in MLC width from 10 to 5 mm contributed to further rectal dose reduction, which was the most important predictor of late rectal toxicity.

✉ Takashi Mizowaki
mizo@kuhp.kyoto-u.ac.jp

[1] Department of Radiation Oncology and Image-Applied Therapy, Kyoto University Graduate School of Medicine, 54 Shogoin Kawahara-cho, Sakyo-ku, Kyoto 606-8507, Japan

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Introduction

Intensity-modulated radiotherapy (IMRT) is now widely used as a standard radiotherapy procedure in routine clinical practice [1]. Many clinical studies have demonstrated the safety of the high-dose IMRT delivery system, especially for patients with prostate cancer, and shown that IMRT results in less gastrointestinal (GI) toxicity than conventional three-dimensional conformal radiation therapy (3D-CRT) [2–4]. The multileaf collimator (MLC) is an important component of IMRT delivery, because it facilitates delivery of irregularly shaped or intensity-modulated treatment fields. The development of treatment-planning software coupled with integration of MLC, a type of mechanized radiation beam-shaping device, has enabled the introduction of a more conformal intensity distribution [5, 6]. Several types of MLC offered by different vendors with different designs, leaf widths, and dosimetric characteristics are now commercially available. The literature contains large amounts of information about the potential advantages of novel smaller collimator leaf width in radiation beam delivery [7–9]. However, none of these studies has addressed clinical benefits of a smaller leaf width in the practical treatment of IMRT.

At our institution, IMRT has been clinically used for definitive treatment of all patients with prostate cancer since November 2000. Over time, two different MLC installed at the linear accelerator of the Clinac system have been continually refined with each update of the therapeutic instrument. The modern type of MLC was changed from a width of 10 to 5 mm in September 2006.

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In this study, we retrospectively evaluated the effect of MLC width on dose distribution by analyzing dose–volume histogram (DVH) curves and calculating the rectal normal tissue complication probability (NTCP). We focused on the clinical effect of MLC width on the onset of late rectal bleeding for patients with prostate cancer treated by IMRT in our institution during the past 10 years.

Materials and methods

Patient selection

Four hundred and forty Japanese men with T1-4N0M0 prostate cancer were treated by definitive IMRT to a prescribed dose of 70–78 Gy with neoadjuvant hormonal therapy (NAHT) at our institution from November 2000 to October 2010. NAHT consisting of maximum androgen blockade (MAB) for 5 months was planned. However, there were variations in the duration (range 3–16 months) and content of the NAHT, because many patients were referred from other institutions after beginning HT. Of these patients, 215 were excluded from the analysis because the prescribed dose was reduced from 78 to 70–74 Gy, because of the presence of risk factors for toxicity after radiotherapy (diabetes mellitus, antithrombotic therapy, previous irradiation adjacent to the prostate, history of transurethral resection of the prostate, age >80 years) or because the patient underwent whole-pelvis irradiation. Of the 225 patients, 205 received the same total dose of 78 Gy in 39 fractions, with delivery confined to the prostate and seminal vesicles, had available baseline clinical data with a minimum 2-year follow-up, and had available treatment-planning dosimetry data. Of the 205 patients, 132 were treated with a 10-mm-wide MLC (April 2003 to September 2006) and 73 were treated with a 5-mm-wide MLC (September 2006 to October 2010). The characteristics of the patients in the two groups are given in Table 1. Research authorization was provided by the internal review board of our institution (approval number: E-1806).

Table 1 Summary of patient characteristics and treatment conditions

Factor	10 mm MLC	5 mm MLC	*p* value
Patients (*n*)	132	73	
Median follow-up in months	102	66	<0.0001
Median age in years	72	70	
Clinical T stage			
T1–2	22	27	0.01
T3–4	110	46	
Gleason sum score			
≤6	9	3	0.24
7	68	31	
≥8	55	39	
Initial PSA			
≤10	16	11	0.12
10–20	35	28	
≥20	81	34	
NAHT (months)			
<5	12	5	0.57
≥5	120	68	
PTV (cc)	115	101	0.12
Rectal volume (cc)	36.1	31.2	0.23

NAHT neoadjuvant hormonal therapy, *PTV* planning target volume, *PSA* prostate-specific antigen

IMRT planning protocols

All of the patients were immobilized in the prone position by use of a thermoplastic shell in combination with a vacuum pillow and a leg support. All of the plans were performed by use of 15-MV photon beams delivered by a Clinac 2100C or 2300C/D (Varian Medical Systems) with a 40-leaf pair of MLC of 10 or 5 mm width. The same five-field beam arrangements and planning conditions, but with different MLC widths, were generated for each patient. A clinical target volume (CTV) was created on the basis of the prostate and seminal vesicles, which were contoured with reference to magnetic resonance images. With regard to the setup error-reduction strategy, errors were evaluated on the basis of the patient's pelvic bony structure, by use of film-based portal imaging. The margins for the planning target volume (PTV) were added to the CTV in accordance with the 3D settings 9 mm margins universally except for a 6 mm margin to the rectum side and a 10 mm margin in the caudal direction. Treatment plans were created by use of an Eclipse Helios system (Ver. 7; Varian Medical Systems). The final dose distributions were calculated by use of a pencil beam convolution algorithm with a calculation grid size of 2.5 mm. The modified Batho method was used for heterogeneity correction. The details of our IMRT protocol of treatment planning objectives to be achieved in the final dose distribution are provided in a previous report [10].

Clinical toxicity assessment

In general, follow-up examinations were initially performed 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; the RTOG late radiation morbidity scale and CTCAE ver 2.0 were used to grade late GI and genitourinary (GU) toxicity. 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 last follow-up.

An initial analysis of the obvious differences between follow-up periods suggested significant discordance between the two groups (median 102 months for 10-mm-wide group vs 66 months for 5-mm-wide group; $p < 0.0001$). The follow-up duration for each group may have been long enough to draw conclusions regarding late GI toxicity, which tends to occur within 3 years. However, because of loss to follow-up, censoring, and different follow-up in the two groups, late GI toxicity was evaluated as time to event outcome using Kaplan–Meier estimation and a Cox proportional hazard model.

Analysis of rectal dose statistics

Planning data were analyzed by using the outputs from the DVH generated by the treatment-planning system. For evaluation of the rectal dose, we used an inner rectal wall thickness of 4 mm, ranging from 10 mm below the apex of the prostate to 10 mm above the CTV end. We calculated the NTCP by using the Lyman–Kutcher–Burman model published by Tucker et al. [11] for grade 2 or higher rectal toxicity with the following values: TD50 = 76.9 Gy, $m = 0.13$, and $n = 0.09$.

Statistical analysis

We used GraphPad PRISM software 5.04 (GraphPad Software, La Jolla, CA, USA) and Stat View 5.0 (SAS Institute, Cary, NC, USA) for statistical analysis. We used Friedman's repeated-measures analysis of variance for nonparametric variables with Dunn's post-test to evaluate the statistical significance of the differences between DVH values and NTCP as calculated for the rectal wall dose. We performed univariate analysis for late GI toxicity, by use of the log-rank test, converting continuous prognostic variables into binary variables stratified by the median. Multivariate analysis by Cox proportional hazards was conducted for late toxicity, including only covariates associated with late toxicity in the univariate analysis ($p < 0.1$).

Results

One hundred and thirty-two and 73 patients were treated with the 10-mm-wide and 5-mm-wide MLC, respectively. The pretreatment characteristics stratified by both groups are listed in Table 1. The PTV, which was expected to result in a greater incidence of complications, was distributed equally between both groups ($p = 0.12$).

Thirty-three (16.1 %), 10 (4.8 %), and 2 (1.0 %) patients experienced grade 1, 2, and 3 late GI morbidity, respectively, according to the RTOG scale. The details of the other GI morbidity endpoints, including stool frequency, rectal incontinence, susceptibility to proctitis, and acute GI toxicity, are described in Table 2. The 5-year actuarial risk of grade 2 or higher rectal bleeding was 6.9 % for the 10-mm-wide group and 1.8 % for the 5-mm-wide group, by use of the Kaplan–Meier method ($p = 0.04$) (Fig. 1).

The dosimetric outcomes for the rectal doses for all the patients are summarized in Table 3. The median estimated rectal dose was 55.1 Gy in the 10-mm-wide group and 50.6 Gy in the 5-mm-wide group ($p < 0.001$). Compared with the plan with the 10-mm-wide MLC, the plan with the 5-mm-wide MLC was advantageous in terms of rectal volume receiving 30–70 Gy (V30–70) and the NTCP of the rectal wall ($p < 0.05$). In addition, delivery of monitor units in plans with the 10-mm-wide MLC was lower than that in plans with the 5-mm-wide MLC. The difference between PTV dose coverage in the two groups was not statistically significant.

Table 2 Cumulative incidence of all types of gastrointestinal toxicity by different MLC types

GI endpoint	10 mm MLC	%	5 mm MLC	%
Late toxicity (RTOG)				
Grade 1	29	22.0	4	5.5
Grade 2	9	6.8	1	1.4
Grade 3	2	1.5	0	0.0
Rectal bleeding (laser/transfusion)	5	3.8	1	1.4
Fecal incontinence (pads >2 days/week)	2	1.5	0	0.0
High stool frequency	2	1.5	1	1.4
Steroids for proctitis	6	7.6	1	1.4
Acute toxicity	22	16.7	4	5.5

MLC multileaf collimator

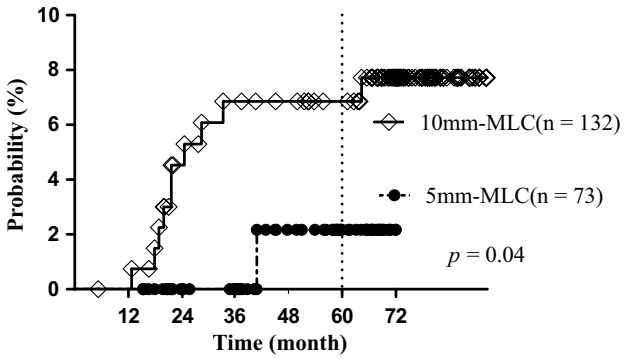

Fig. 1 Estimated cumulative probability of late grade 2 or higher gastrointestinal toxicity on the basis of different MLC types

Table 3 Comparison of dose–volume histogram results and standard errors for patients treated with different MLC widths

	10 mm MLC	5 mm MLC	*p* value
PTV D95	92.29 ± 0.47	91.40 ± 0.99	0.43
V90	97.01 ± 0.39	96.92 ± 0.60	0.89
Mean	100.4 ± 0.15	99.92 ± 0.21	0.09
Rectal wall V30	85.64 ± 0.86	67.47 ± 1.21	<0.0001
V40	56.51 ± 0.47	45.61 ± 0.88	<0.0001
V50	40.56 ± 0.41	33.66 ± 0.66	<0.0001
V60	28.96 ± 0.35	24.65 ± 0.49	<0.0001
V70	15.15 ± 0.30	13.25 ± 0.33	<0.0001
V78	0.084 ± 0.06	0.002 ± 0.001	0.18
Median dose (Gy)	55.1	50.6	<0.0001
NTCP	2.97 ± 0.07	1.93 ± 0.09	<0.0001
Total MU	534.0 ± 14.3	587.1 ± 9.2	0.001

MLC multileaf collimator, *PTV* planning target volume, *NTCP* normal tissue complication probability, *MU* monitor unit, *D95* percentage of the prescription dose covering 95 % of the volume, *V90* percentage of the volume receiving at least 90 % of the prescription dose

Clinical and dosimetric factors were assessed for univariate and multivariate correlations with the risk of grade 2 or higher rectal toxicity. In the univariate analysis, the rectal volume receiving 30–60 Gy (V30–60), median rectal dose, and NTCP were significant predictive factors for the development of late grade 2 or higher rectal toxicity; however, age, T-stage, Gleason sum, PSA, and PTV were not (Table 4). In the multivariate analysis, acute toxicity ($p = 0.04$; HR 7.3) and an NTCP <2 % ($p = 0.04$; HR 0.31) were significantly associated with rectal bleeding in our cohort. Because the rectal V30–60 and median rectal dose were highly correlated with each other, we did not use these factors in the multivariate analysis.

Figure 2 shows the mean DVH curves and standard deviations for patients with and without grade 2 late rectal bleeding (bleeder $n = 12$; non-bleeder $n = 193$). The V60, V50, V40, and V30 for bleeders and non-bleeders were 30.0 ± 2.1 vs 24.3 ± 4.6 % ($p = 0.05$), 40.8 ± 3.6 vs 32.9 ± 6.1 % ($p < 0.001$), 58.5 ± 3.0 vs 45.3 ± 8.3 % ($p < 0.001$), and 86.6 ± 5.2 vs 69.9 ± 8.8 % ($p < 0.001$), respectively. These results revealed a statistically significant dose–volume relationship for late GI toxicity.

Discussion

Although many published reports have addressed the dosimetric effect of MLC width on treatment planning [12–14], this is the first to compare the clinical advantages among different leaf widths for patients with localized prostate cancer treated with high-dose IMRT. This comparison was uniform in that both groups were treated with the same radiation dose, a unified protocol to ensure the delineation, and similar margins for the clinical target volume, which reflect consistent institutional policies. Smaller MLC width for delivery of IMRT have resulted in significantly improved dosimetric endpoints of critical rectal organ sparing, leading to a reduced incidence of late rectal bleeding. This report provides evidence that this novel form of dynamic MLC and inverse planning treatment software contributed to less gastrointestinal toxicity after IMRT for localized prostate cancer during the past 10 years.

In our study, univariate analysis showed that dosimetric conditions, acute toxicity, and MLC type were important predictors of late grade 2 or higher GI toxicity, irrespective of other clinical factors. Michalski et al. [15] recently reported toxicity outcomes for RTOG 0126 in a preliminary analysis comparing 3D-CRT and IMRT with regard to GI and GU toxicity in the high-dose group. In their multivariate analysis, IMRT was not significantly associated with toxicity, whereas the rectal volume receiving greater than a V70 >15 % was significantly associated with late grade 2 or higher rectal toxicity. In agreement with this result, our multivariate analysis revealed an association between the rectal dose and the development of late grade 2 or higher toxicity; however, the MLC type was not shown to be statistically significant ($p = 0.12$). These findings suggest that the individual rectal volume and dose data were the most important critical predictors of late toxicity for high doses of radiation therapy, irrespective of delivery modality. For clinical comparison of individual rectal doses, we used model data for prediction of rectal toxicity based on a review of DVH and toxicity data. The values obtained in our study differed only very slightly between individual plans. Tucker et al. [16] reported the efficacy of the Lyman model among 1,023 patients enrolled in the RTOG 94–06 dose-escalation trial. These results are characteristic of serial organs with marked sensitivity to high doses; therefore, we believe that the NTCP calculations may provide representative values of individual plans for comparison of late toxicity risk.

The most important clinical advantage of IMRT for prostate cancer is the possibility of avoiding severe GI toxicity for patients with a long life expectancy from the date of diagnosis. Zelefsky et al. [17] reported that the 3-year actuarial incidence of late grade 2 or higher GI toxicity for patients who received 81-Gy IMRT was only 2 % whereas that for patients who received the same dose of 3D-CRT was 14 % ($p = 0.005$). The incidence of late grade 2 or higher GI toxicity in this study was 4.8 % (8.3 % in the 10-mm-wide group and 1.4 % in the 5-mm-wide group), similar to other clinical reports for high-dose IMRT [18, 19]. Several important factors are associated with our lower risk of late GI toxicity. First, a more stringent rectal dose constraint should enable tighter normal tissue constraints

Table 4 Potential risk factors for late grade 2 or higher gastrointestinal toxicity by univariate and multivariate analysis

Factor	Variable	UVA		MVA	
		P value	HR (95 % CI)	*P* value	HR (95 % CI)
Age	<72	0.43	1.54 (0.52–4.57)		
T-stage	<T3	0.49	0.64 (0.18–2.31)		
Gleason sum	<7	0.25	1.89 (0.63–5.62)		
iPSA	<20	0.75	0.81 (0.27–2.43)		
PTV (cc)	<115	0.88	1.12 (0.25–5.00)		
Acute toxicity	YES	0.008	8.4 (3.66–54.6)	0.04	7.3 (2.44–50.2)
V30-RW (%)	<65	0.005	0.22 (0.08–0.62)		
V40-RW (%)	<55	0.003	0.19 (0.06–0.58)		
V50-RW (%)	<37	0.02	0.24 (0.07–0.80)		
V60-RW (%)	<27	0.01	0.26 (0.09–0.80)		
V70-RW (%)	<13	0.47	0.63 (0.17–2.25)		
Mean-RW (%)	<50	0.01	0.24 (0.07–0.78)		
NTCP (%)	<2	0.008	0.31 (0.07–0.76)	0.04	0.31 (0.12–0.92)
MLC type	5 mm	0.04	0.30 (0.09–0.96)	0.12	0.45 (0.16–1.10)

MLC multileaf collimator, *PSA* prostate-specific antigen, *PTV* planning target volume, *RW* rectal wall, *NTCP* normal tissue complication probability, *MU* monitor unit, *UVA* univariate analysis, *MVA* multivariate analysis

than the guidelines in the 3D-CRT era used at our institution prospectively for plan approval since 2000. Patient-based DVH recommendations involve a V60 of <35 % and a V70 of <20 % on the basis of a preliminary IMRT analysis [10]. As shown in Table 2, a smaller MLC enabled use of a lower rectal dose than that outlined in the rectal dose-restriction protocol of our high-dose IMRT cohort. Second, our eligibility criteria for receiving up to a prescribed dose of 78 Gy were relatively strict. The prescribed dose was reduced to 70–74 Gy if patients had risk factors for rectal bleeding with high-dose IMRT, for example anticoagulant therapy, severe diabetes mellitus, or cardio-cerebrovascular disease. We expected such risk factors to lead to more toxicity in the high-dose IMRT group; thus, a carefully designed modification of high prescribed dose is needed. Moreover,

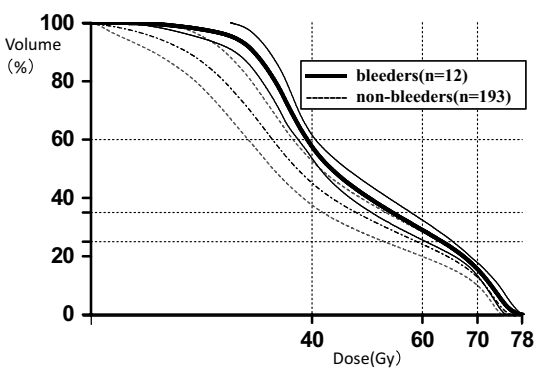

Fig. 2 The mean percentage dose–volume histogram curves and standard deviations for patients with and without late rectal bleeding

a recent retrospective report of prostate IMRT described a higher frequency of late GI toxicity in Japan than in Europe and the United States [20, 21]. Race-specific differences in tumor biology and obesity-mediated metabolic changes could be important in radiation-induced complications and comorbidity [22]. Additional studies assessing the association of race with toxicity are warranted.

There are some limitations to this retrospective study. First, The RTOG and CTC toxicity grades were assigned retrospectively, leading to a potential for inaccuracies in assigning grades. These values, however, have not been as carefully studied for health-related quality of life, which is a more sensitive and valid indicator of patients' satisfaction [23]. Second, our definition of PTV margins was based on our experience with bony structure-based correction in combination with our experience with the old 3D-CRT protocol. This definition of PTV margins can be justified by the very promising clinical outcomes achieved at the Memorial Sloan-Kettering Cancer Center [24]. For patients who undergo prostate-based image-guided radiotherapy at our institution, we have further reduced our PTV margins to 6 mm circumferentially around the prostate, including the prostate–rectal interface region. We believe that toxicity may be further reduced with the additional reduction of the PTV margin used for daily image guidance. Third, more recently, rotational IMRT approaches on a conventional linac system may provide more conformal dose distributions than segmental or dynamic MLC-IMRT approaches that only use a limited number of gantry directions [25]. More reports of the use of intensity-modulated arc therapy and additional studies to assess the optimum modality

among a variety of clinical delivery techniques are warranted over the next few years.

Finally, we believe that the recent implementation of the IMRT delivery technique with the development of highly sophisticated treatment-planning software and MLC will further enhance the accuracy and safety of dose delivery. However, radiation oncologists should interpret current results with caution, because these delivery systems do not simply promise a lower rate of radiation-induced complications, which are the most dose-limiting factors in prostate IMRT. We must perform careful treatment planning and make every effort to find the optimum balance between the patient's morbidity risk and most appropriate treatment.

In conclusion, we evaluated the clinical effect of MLC width on the onset of late rectal bleeding for patients with prostate cancer treated by IMRT at our institution during the past 10 years. In our planning approach and protocol for high-dose prostate IMRT, a change from a 10 to 5 mm MLC width contributed to further rectal dose reduction, which was the most important predictor of late rectal toxicity.

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

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