Late Rectal Toxicity from Image-guided Intensity Modulated Radiotherapy for Prostate Cancer

SAYO MAKI[1], YOSHIYUKI ITOH[1], SEIJI KUBOTA[1], TOHRU OKADA[1], RIE NAKAHARA[1], JUNJI ITO[1], MARIKO KAWAMURA[1], TAKESHI KAMOMAE[1], SHINJI NAGANAWA[1], YASUSHI YOSHINO[2], MOMOKAZU GOTOH[2] and MITSURU IKEDA[3]

[1]*Department of Radiology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan;*
[2]*Department of Urology, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan;*
[3]*Department of Radiological Sciences, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan*

Abstract. *Aim: Late rectal toxicity (LRT) was retrospectively evaluated in men with prostate cancer treated with image-guided intensity modulated radiotherapy (IG-IMRT). Patients and Methods: Between May 2008 and December 2009, 47 men with prostate adenocarcinoma were treated with IG-IMRT using in-room computed tomography (CT). Results: The median time to grade 2 LRT was 12 months (range=1–24 months). Two of 3 men who developed grade 2 LRT had received treatment for diabetes, and the other was receiving anticoagulant/antiplatelet therapy (AC therapy). Their rectal wall V70 (the volume of rectal wall receiving 70 Gy) values were 12.6%, 13.0%, and 13.3%. Univariate analysis revealed that V70 of the rectal wall was the only significant risk factor for LRT (p=0.0073). Conclusion: No man with V70 ≤12.0% experienced grade 2 LRT. Strict rectal wall V70 ≤12% dose constraints should be considered when treating prostate cancer patients who are also receiving diabetic or AC therapy.*

According to a recent report, prostate cancer incidence in Japan is increasing (1). During the last 10 years, nearly 60% of the increase in male cancer incidence was due to increased prostate cancer incidence. Currently, the most frequently chosen treatment for initial therapy in Japan (2) is androgen deprivation therapy (ADT; 40.2%), followed by radical prostatectomy (32.0%), radiation therapy (21.0%), and prostate-specific antigen (PSA) surveillance (6.4%).

Regarding external-beam radiotherapy (EBRT) for prostate cancer, conventional radiotherapy by two-dimensional planning was performed until the 1990s. Although three-dimensional conformal radiation therapy (3D-CRT) was developed in the 1990s, intensity modulated radiation therapy (IMRT), a further advancement in radiotherapy techniques, facilitates precise dose delivery. IMRT minimizes the volume of normal tissue that is irradiated. Conventional EBRT doses in the range of 70 Gy are not sufficient to eradicate local prostate disease (3, 4), but higher EBRT doses require greater accuracy and precision to avoid increasing the risk of marginal misses. Thus, various effective position verification methods, including image-guided radiotherapy (IGRT), have been developed (5-8). IGRT is important in combination with highly conformal techniques.

An in-room on rails-LINAC system CT was installed in 2003 in the Nagoya University Hospital. The system consists of a LINAC system and a moveable CT scanner that can slide along a pair of rails. This in-room CT can be used not only to acquire planning CT images but also to compare planning CT images on physician-drawn contours with target structures based on anatomy captured just before the treatment. At our hospital, prostate cancer treatment using IG-IMRT with daily in-room CT imaging on this system (9, 10) was initiated in May 2008. However, in current clinical practice, IG-IMRT is performed using a kilovoltage cone beam CT (CBCT) due to a machine renewal.

In this study, we retrospectively analyzed late rectal toxicity (LRT) in men who were diagnosed with prostate cancer and treated with IG-IMRT using in-room CT.

Patients and Methods

Patient population. We retrospectively analyzed 47 men treated in the Nagoya University Hospital between May 2008 and December 2009 who received IG-IMRT with in-room CT imaging for prostate cancer. This study was approved by the Institutional Review Board of the Nagoya University Hospital, and all patients provided written informed consent.

Correspondence to: Yoshiyuki Itoh, MD. Professor, Department of Radiology, Nagoya University Graduate School of Medicine 65 Tsurumai-cho, Shouwa-ku, Nagoya, Aichi 466-8550, Japan. Tel: +81 527442328, Fax: +81 527442335, e-mail: rin01291823@gmail.com

Key Words: Prostate cancer, IGRT, IMRT, late rectal bleeding.

The median age of patients was 68 years (range=55-80 years). Patients' characteristics are shown in Table I. All men had a biopsy-confirmed adenocarcinoma of the prostate, that was proven pathologically in our hospital. The median initial PSA level was 11.6 ng/ml (range=4.2–363.0 ng/ml). Men were classified into low-, intermediate-, and high-risk groups based on the National Comprehensive Cancer Network (NCCN) risk group classification. Five men (10.6%) had low-risk disease, 18 men (38.3%) had intermediate risk disease, and 24 men (51.1%) had high-risk disease. The 24 men in the high-risk group included 4 men with lymph node metastases at diagnosis and 1 with a distant metastasis to the para-aortic lymph nodes.

Androgen deprivation therapy (ADT). Forty-three men (91.5%) received hormonal therapy. Most men had high- or intermediate-risk disease. As per our hospital protocol, hormonal therapy was not administered to patients with low-risk disease in principle, and courses were usually short (<6 months) for those with intermediate-risk disease and longer (>24 months) for those with high-risk disease. With long-term hormonal therapy, PSA values were very low, and lymph node metastases were remarkably reduced or had disappeared on diagnostic imaging by CT/MRI. Therefore, radiation therapy to a prostate region was judged to provide significant clinical benefit, and IMRT was performed.

Concomitant disease. Nine men (19.1%) were being treated for diabetes and 6 (12.8%) were being treated with anticoagulant therapy or antiplatelet therapy (AC therapy) before, during, and after RT for cardiovascular or cerebrovascular disease.

Pre-treatment procedure. The most important normal organs near the prostate target are the rectum and bladder. Each organ exhibits significant day-to-day shape variations if uncontrolled during routine treatment (11). Therefore, we implemented the following measures. Simethicone was prescribed to reduce gas and feces in the rectum, beginning 1 week before the patients underwent CT scans. In the absence of daily defecation, hydrated magnesium sulfate was used as a laxative, and a purgative medication was added on a case-by-case basis. No patient was implanted with gold fiducial markers in the prostate gland before the treatment-planning CT scan was acquired. All men were instructed to empty their rectums using the medication described above and fill their bladders by drinking 250–500 ml of water 30 min to 1 h before the treatment-planning CT. Planning CT images were obtained at 2-mm slice thickness continuously for 3 days, and the best images obtained are shown in Figure 1, from patients with full bladders and rectums empty of gas and contents, were transferred to the treatment-planning system. Treatment planning and verification lasted 7 to 10 days.

Radiation therapy. Of the 47 men, 5 began treatment in the prone position, and the other 42 in the supine position. All men underwent CT scans using the in-room CT system (GE HiSpeed NX/i, General Electric Medical Systems, Waukesha, WI, USA) that was installed in the treatment room. Prostate position was assessed before administration of each fraction through in-room CT image guidance. Men were positioned first using lasers and skin marks. Then, an in-room CT was acquired. To quantify setup error, we first performed a pelvic bone match using the in-room CT. Then, matching was manually adjusted by a radiation therapist to overlap the prostate on the planning CT and in-room CT scans. Feces and gas in the rectum, change in bladder volume, and deviation of adjacent intestines (large and small intestines) from the planning CT images were checked. When feces and gas and were noted in the rectum, we encouraged defecation or passage of gas. However, if the situation did not improve, deaeration was performed by inserting a catheter into the rectum through the anus. In addition, patients were encouraged to drink water when they had insufficient bladder volumes. CT images were acquired once again after some time. After there was enough geometric verification, irradiation was performed.

Target volume definitions and organs at risk. The clinical target volume (CTV) included the prostate and the base of the seminal vesicles in low-risk men, but the CTV included the prostate and proximal two-thirds of seminal vesicles for intermediate- and high-risk men. The planning target volume (PTV) was obtained using automatic expansions of the CTV, adding 9 mm in the left, right, and anterior directions, 6 mm in the posterior direction, 10 mm in the superior direction, and 9 mm in the inferior direction.

Dose volume histograms (DVHs) are widely used in conformal radiotherapy to evaluate normal tissue complication probabilities (NTCPs). The DVH is an effective tool to evaluate 3D dose distributions of the rectum wall and to estimate the complication probability of the rectum in high-dose conformal radiotherapy (12). The rectum was defined as a cylindrical structure around the outer rectal wall. The thickness of the rectal wall was defined with a 4-mm internal wall extraction, and to determine PTV, 10 mm was added to the superior and inferior directions of the rectal wall craniocaudal length. In a similar way, the bladder was entirely contoured, and a 4-mm inner wall defined the bladder wall volume (Figure 1).

To plan treatment and delivery, an isocentric five-field technique was used. The beam angles used were posterior (0˚), right posterior oblique (75˚), right anterior oblique (135˚), left anterior oblique (225˚), and left posterior oblique field (285˚) in the prone position. Meanwhile, in the supine position, the beam angles were 35˚, 105˚, 180˚, 225˚, and 325˚, respectively. Treatments were planned using an inverse optimization algorithm. All men were treated to a prescribed dose of 74 Gy in 37 daily fractions of 2.0 Gy using 10-MV photons.

We present the dose distribution information of a typical case treated with IMRT. The isodose distributions, superimposed on the PTV, rectum, and bladder are shown in Figure 1 in the transverse and sagittal planes. The DVH parameters evaluated included the volume of normal tissue receiving: 70 Gy (V70); 65 Gy (V65); 60 Gy (V60); 50 Gy (V50); 45 Gy (V45); and 30 Gy (V30) expressed as absolute percentages in the rectal wall volume and the overall volume of the rectum. Dose-volume constraints for surrounding normal tissues were as follows: V40 ≤65% (ideal constraint (IC): ≤60%),V60 ≤35% (IC: ≤30%), V70 ≤25% (IC: ≤20%), and V78 <1% for the rectal wall; V40 ≤65% (IC: ≤60%) and V70 ≤35% for the bladder wall; V65 ≤1.0 mL (IC: ≤0.5 mL) for the colon; and V60 ≤1.0 mL (IC: ≤0.3 mL) for the small intestine. Meanwhile, dose-volume constrains for PTV were as follows: D90 ≥90% (IC: ≥95%), V90 ≥96% (IC: ≥98%), max ≤110%, and mean ≥99% and ≤103% (Table II).

Follow-up. Follow-up evaluations after treatment were performed at intervals of 3-6 months for 5 years. The median follow-up time was 33 months (range=24-46 months). During the follow-up study, we performed a physical interview, physical examination, and serum

Table I. *Patients' characteristics (n=47).*

Characteristic	
Age (y)	Median 58 {range, 55-80)
Initial PSA (ng/mL)	Median 11.6 (range, 4.2-363.0)
Risk group (NCCN)	
Low	5 (10.6%)
Intermediate	18 (38.3%)
High	24 (51.1%)
Gleason score	
≤6	14 (29.8%)
7	21 (44.7%)
≥8	12 (25.5%)
T stage	
T1	19 (40.4%)
T2	12 (25.5%)
T3	14 (29.8%)
T4	2 (4.8%)
Hormone therapy	
Yes	43 (91.5%)
None	4 (8.5%)
Diabetes	
Yes	9 (19.1%)
None	38 (80.9%)
Antiplatelet /Anticoagulant	
Yes	6 (12.8%)
None	41 (87.2%)

NCCN: National Comprehensive Cancer Network.

PSA measurement. Additionally, on an as-needed basis, residual urine measurements were performed. When PSA relapse was suspected because of increased PSA levels, we performed bone scintigraphy and whole body CT.

Late toxicity. Late toxicity was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (13). In brief, grade 1 toxicity is mild, and intervention is not required. Grade 2 toxicity indicates that there are moderate symptoms, and medical intervention or minor cauterization should be performed for the indicated symptoms. Grade 3 toxicity indicates severe or medically significant, but not immediately life-threatening, symptoms. Transfusions or radiologic, endoscopic, or elective operative interventions are indicated. Grade 4 indicates life-threatening consequences, and urgent intervention is required.

Statistical analysis. The rate of grade 2 LRT was calculated using the Kaplan-Meier method. In this study, the following were analyzed as possible risk factors for LRT: hormone use, hemorrhoid diagnosis, diabetes, AC therapy, age, and DVH parameters of the rectal wall and rectum (V30, V45, V50, V60, V65, and V70). Categorical and continuous variables were analyzed using Fisher's exact tests and unpaired t-tests, respectively, for univariate analysis, and all variables were evaluated using logistic regression for multivariate analysis. A two-sided probability value of less than 0.05 was considered to indicate statistical significance.

Table II. *Dose constraints of PTV and OARs.*

Structure	Constraint (preferable)
PTV	
D95	≥90% (≥95%)
V90	≥96% (≥98%)
Max	≤110%
mean	≥99%, ≤103%
Rectal wall	
V40Gy	≤65% (≤60%)
V60Gy	≤35% (≤30%)
V70Gy	≤25% (≤20%)
V78Gy	<1%
Bladder wall	
V40Gy	≤65% (≤60%)
V70Gy	≤35%
Bowel_L	
V65Gy	≤1.0 ml (≤0.5 mL)
Bowel_S	
V60Gy	≤1.0 ml (≤0.5 mL)

PTV: Planning target volume; OARs: organ at risk.

Results

Late toxicity. A Kaplan-Meier curve of grade 2 LRT is shown in Figure 2. The 3-year rate of grade 2 LRT was 6.4%. For other rectal toxicity, 38 men (80.8%) experienced grade 0 toxicity, 6 men (12.8%) experienced grade 1 toxicity, and no men experienced grade 3 toxicity. The median time to grade 2 LRT development was 12 months (range=1-24 months). The three men who developed grade 2 LRT included 2 men being treated for diabetes and 1 man being treated with AC therapy. Of the two diabetic men, one was treated with insulin, and the other was treated using oral therapies. Each man was given a suppository. Because the rectal bleeding of the man receiving AC therapy continued after treatment using the suppository, endoscopic hemostatic therapy was performed using argon plasma coagulation (APC). This was the only case that required endoscopic hemostatic therapy.

Univariate and multivariate analysis of late rectal toxicity. The LRT results are shown in Table III. Only V70 of the rectal wall was a significant risk factor by univariate analysis (p=0.0073), and no significant risk factor was identified by multivariate analysis.

Analysis of DVH dose groupings with respect to late toxicity. In Figure 3, rectal wall V70 values are shown on the vertical axis, and each patient is plotted horizontally. The three men with grade 2 LRT are represented in red. The V70 values of the rectal walls of the three men who developed grade 2 late

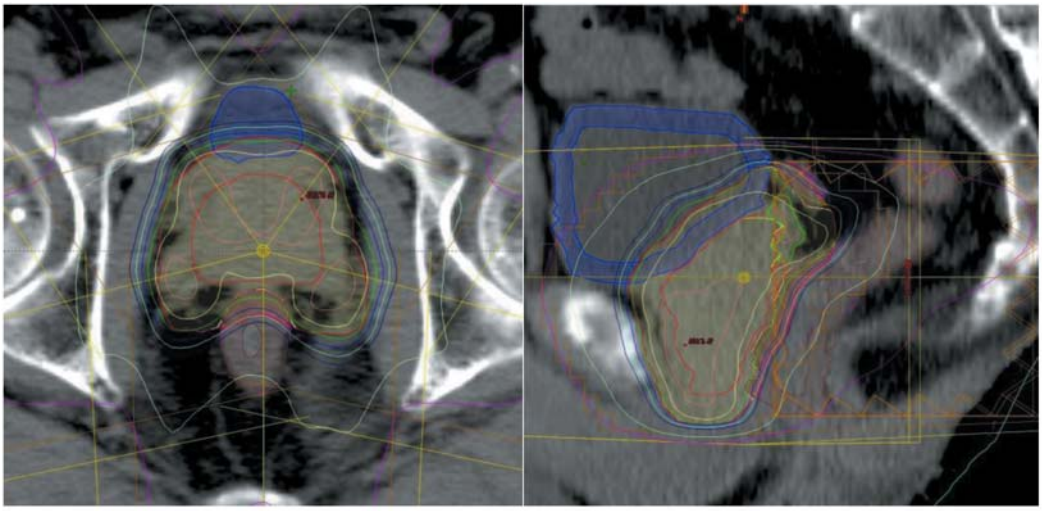

Figure 1. *Radiation fields and dose distribution. (a) Axial (Transverse) Image. (b) Sagittal Image.*

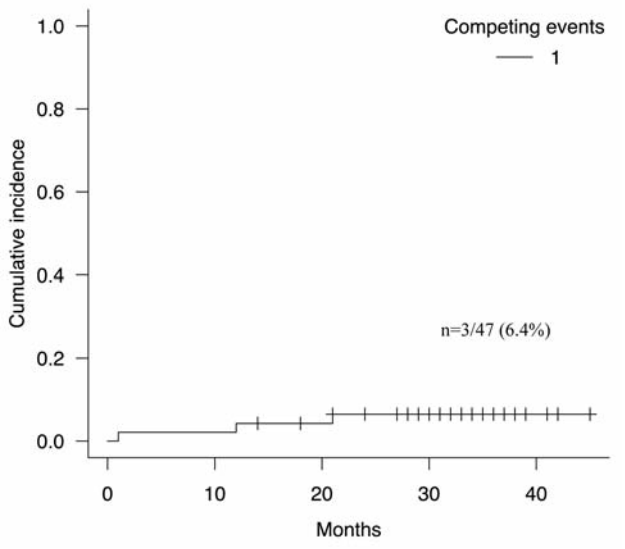

Figure 2. *Incidence of grade 2 rectal bleeding.*

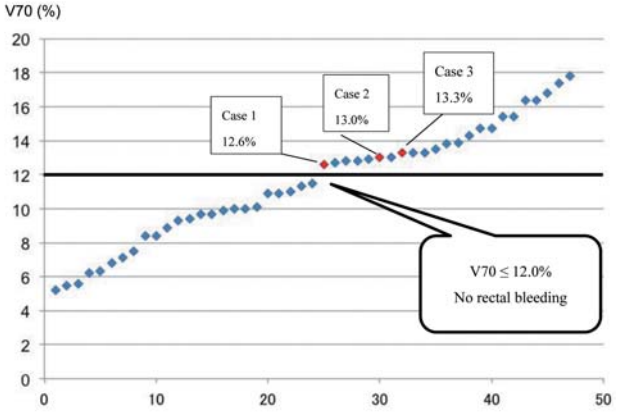

Figure 3. *Rectal wall V70.*

rectal bleeding were 12.6%, 13.0%, and 13.3%. No man with a rectal wall V70 ≤12.0% experienced grade 2 LRT.

Discussion

In the era of highly precise radiotherapy, accurate patient set-up and target localization are essential. The in-room CT on rails-LINAC system is an IGRT system. We began to treat prostate cancer with IG-IMRT using daily in-room CT imaging in May 2008 at our Institution. As stated in the Patients and Methods section, in the treatment-planning CT we made efforts to obtain reproducible CT images as often as possible by filling bladders and clearing bowels in each patient. Moreover, after enough geometric verification by in-room CT images was confirmed, irradiation was performed. Here, we retrospectively analyzed LRT of an initial group of men with prostate cancer who were treated using this radiotherapy system. In patients treated with 74-Gy IG-IMRT using in-room CT, the 3-year rate of grade 2 LRT was 6.4% (Figure 2). Regarding the rate of grade 2 or higher LRT, several reports of adverse rectal events after IMRT or IG-IMRT are shown in Table IV (5, 14-19). The results of this study were not inferior, compared to the reports of the other Institutions. In this study, rectal wall V70 was the only significant risk factor for grade 2 rectal bleeding by univariate analysis, and no significant risk factor was shown by multivariate analysis. In a report on the relationship between LRT and the rectal DVH parameter, Peterson *et al.* (20) stated

Table III. *Risk factors for Grade 2 late rectal bleeding*.

Factor	*p*-Value	Exp(B) (95% CI)	
Hormone therapy	1	0.0321-Inf	Fisher's Exact Test
Hemorrhoid	0.4364	0.0392-56.0536	
Diabetes	0.0895	0.4541-636.5542	
Anti platelet/Anticoagulant	0.3426	0.0551-84.8252	
Age	0.1226	–12.9895-1.595571	Two-sample *t*-test
Rectal Wall V30	0.2241	–4.8610-20.2004	
Rectal Wall V40	0.7099	–7.4460-10.8460	
Rectal Wall V50	0.7342	–7.3387-5.2099	
Rectal Wall V65	0.4131	–7.1677-2.9980	
Rectal Wall V70*	0.0073*	–2.7146- –0.4504	
Rectal Outer V30	0.2842	–6.0237-20.0586	
Rectal Outer V40	0.777	–7.1398-9.4928	
Rectal Outer V50	0.8506	–7.6071-6.2995	
Rectal Outer V65	0.5662	–5.5990-3.1020	
Rectal Outer V70	0.493	–4.0592-1.9849	

CI: Confidence interval.

Table IV. *Rates of late Grade 2 and/or higher GI toxicity.*

Author	Reference	N	Study period	Median follow-up	Modality dose	Toxicity scoring	Grade 2-3 late GI toxicity rate
Takeda K *et al*.	15	141	2003-2008	60 mo	IG-IMRT 76 Gy/38 F or 80 Gy/40 F	CTCAEv4.0	Grade 2-3 6% (5 y)
Guckenberger M *et al*.	16	100	2005-	26 mo	IG-IMRT (SIB) 73.91 Gy/32 F or 76.23 Gy/33 F	CTCAEv3.0	Grade 2 1.5% (2 y) Grade 3 1%
Martin JM *et al*.	17	259	2001-2003	67.8 mo	3D-CRT(non-IGRT) vs. IG-IMRT 79.8 Gy/42 F	RTOG	Grade 2-3 13.7% (3D-CRT) Grade 2-3 3.5% (IG-IMRT) (5y)
Lips IM *et al*.	18	331	2001-2004	47 mo	IG-IMRT 76 Gy/35 F	CTCAEv2.0	Grade 3 1% Grade 4 0.3%
Zelefsky MJ *et al*.	26	561	1996-2000	84 mo	IMRT (non-IGRT) 81 Gy/45 F	RTOG	Grade 2 1.6% (8 y) Grade 3 0.1%
Cahlon O *et al*.	5	478	1997-2004	53 mo	IMRT 86.4 Gy/48 F	CTCAEv3.0	Grade 2 3% Grade 3 <1%
Pederson AW	19	296	2000-2007	41 mo	IMRT 76 Gy/38 F	CTCAEv3.0	Grade 2 6% Grade 3 1%
Present study	Nagoya University	47	2008-2009	33 mo	IG-IMRT 74 Gy/37 F	CTCAEv4.0	Grade 2 6.4% Grade 3 0%

Mo: Months; CTCAE: Common Terminology Criteria for Adverse Events, 3D-CRT: three-dimensional conformal radiation therapy, GI: gastrointestinal, IG-IMRT: image-guided intensity-modulated radiotherapy, IMRT: intensity-modulated radiotherapy, SIB: simultaneous integrated boost, F: fraction.

that from the evaluation of the rectal toxicity in 111 men who received IG-IMRT for prostate cancer, dose constraints of the anterior wall of the rectum are important. A recent report also mentioned that rectal bleeding was associated with the anorectum (V70) and anticoagulant use in the multivariable model (21).

Next, we considered other risk factors. By univariate analysis, hormonal therapy, presence or absence of hemorrhoids, diabetes, AC therapy, and age were not found to be significant risk factors in this study. Two men who were diabetics and one man who was receiving AC therapy experienced grade 2 rectal bleeding. They were two (22.2%) of nine total diabetics, and one (16.7%) of 6 total patients receiving AC therapy (Table I). Choe *et al*. (22) investigated the risk of bleeding in prostate cancer patients treated with EBRT who were receiving AC therapy. The 4-year risk of grade 3 bleeding toxicity was shown to be 15.5% for those receiving AC therapy, compared with 3.6% among those not receiving AC therapy ($p<0.0001$) (23). Additionally, AC therapy was indicated to be the only significant factor associated with grade 3 bleeding ($p<0.0001$) (19). In the present study, there were no instances of grade 2 rectal bleeding in men without diabetes or without AC therapy. Furthermore, these three men had been receiving androgen deprivation therapy (ADT). ADT use has been reported to significantly increase the risk of GI morbidity for patients treated with 3D-CRT (24). Long-term ADT in men with diabetes has been reported to increase grade 2 rectal bleeding incidence. Additionally, in another report, by multivariate analysis, a history of diabetes was the most statistically significant risk factor for the incidence of grade 2 rectal bleeding after hypofractionated radiotherapy for prostate cancer (25–27).

Although a dose constraint of V70 even less than 12.0% has been recommended by other reports, no man meeting the V70 ≤12% criteria experienced late rectal bleeding even if they had concomitant disease. There have been few reports of IMRT using IGRT as in this study, but there are still not enough to provide definitive results. However, grade 2 or higher late rectal bleeding may be suppressed if the strict dose constraint of rectal wall V70 ≤12.0% is set.

Conclusion

The 3-year rate of grade 2 LRT was 6.4%. All three men with late grade 2 rectal bleeding were receiving diabetic or AC therapy. However, no man with a rectal wall V70 ≤12.0% experienced grade 2 late toxicity. It may be necessary to set strict dose constraints of rectal wall V70 ≤12.0% when planning to treat men with prostate cancer who are receiving diabetic or AC therapy.

Conflicts of Interest

None declared.

References

1 Katanoda K, Hori M, Matsuda T, Shibata A, Nishino Y, Hattori M, Soda M, Ioka A, Sobue T and Nishimoto H: An updated report on the trends in cancer incidence and mortality in Japan, 1958–2013. Jpn J Clin Oncol *45*: 390-401, 2015.

2 Onozawa M, Hinotsu S, Tsukamoto T, Oya M, Ogawa O, Kitamura T, Suzuki K, Naito S, Namiki M, Nishimura K, Hirao Y and Akaza H: Recent trends in the initial therapy for newly diagnosed prostate cancer in Japan. Jpn J Clin Oncol *44*: 969-981, 2014.

3 Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr., Miller DW, Adams JA and Shipley WU: Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA *294*: 1233-1239, 2005.

4 Peters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, Dielwart MF, Bonfrer JM, Incrocci L and Lebesque JV: Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78Gy. J Clin Oncol *24*: 1990-1996, 2006.

5 Cahlon O, Zelefsky MJ, Shippy A, Chan H, Fuks Z, Yamada Y, Hunt M, Greenstein S and Amols H: Ultra-high dose (86.4 Gy) IMRT for localized prostate cancer: toxicity and biochemical outcomes. Int J Radiat Oncol Biol Phys *71*: 330-337, 2008.

6 Zelefsky MJ, Fuks Z, Hunt M, Yamada Y, Marion C, Ling CC, Amols H, Venkatraman ES and Leibel SA: High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys *53*: 1111-1116, 2002.

7 Zelefsky MJ, Kollmeier M, Cox B, Fidaleo A, Sperling D, Pei X, Carver B, Coleman J, Lovelock M and Hunt M: 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 *84*: 125-129, 2012.

8 Wortel RC, Incrocci L, Pos FJ, van der Heide UA, Lebesque JV, Aluwini S, Witte MG and Heemsbergen WD: Late side effects after image guided intensity modulated radiation therapy compared to 3D-conformal radiation therapy for prostate cancer: results from 2 prospective cohorts. Int J Radiat Oncol Biol Phys *95*: 680-689, 2016.

9 Kuriyama K, Onishi H, Sano N, Komiyama T, Aikawa Y, Tateda Y, Araki T and Uematsu MA: New irradiation unit constructed of self-moving gantry-CT and linac. Int J Radiat Oncol Biol Phys *55*: 428-435, 2003.

10 Ikushima H, Balter P, Komaki R, Hunjun S, Bucci MK, Liao Z, McAleer MF, Yu ZH, Zhang Y, Chang JY and Dong L: Daily alignment results of in-room computed tomography-guided stereotactic body radiation therapy for lung cancer. *79*: 473-480, 2011.

11 Frank SJ, Dong L, Kudchadker RJ, De Crevoisier R, Lee AK, Cheung R, Choi S, O'Daniel J, Tucker SL, Wang H and Kuban DA: Quantification of prostate and seminal vesicle interfraction variation during IMRT. Int J Radiat Oncol Biol Phys *71*: 813-820, 2008.

12 Meijer GJ, van den Brink M, Hoogeman MS, Meinders J and Lebesque JV: Dose-wall histograms and normalized dose-surface histograms for the rectum: a new method to analyze the dose distribution over the rectum in conformal radiotherapy. Int J Radiat Oncol Biol Phys *45*: 1073-1080, 1999.

13 Common Terminology Criteria for Adverse Events: CTCAE v4.0http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
14 Zelefsky MJ, Cowen D, Fuks Z, Shike M, Burman C, Jackson A, Venkatramen ES and Leibel SA: Long term tolerance of high dose three-dimensional conformal radiotherapy in patients with localized prostate carcinoma. Cancer *85*: 2460-2468, 1999.
15 Takeda K, Takai Y, Narazaki K, Mitsuya M, Umezawa R, Kadoya N, Fujita Y, Sugawara T, Kubozono M, Shimizu E, Abe K, Shirata Y, Ishikawa Y, Yamamoto T, Kozumi M, Dobashi S, Matsushita H, Chida K, Ishidoya S, Arai S, Jingu K and Yamada S: Treatment outcome of high-dose image-guided intensity-modulated radiotherapy using intra-prostate fiducial markers for localized prostate cancer at a single institute in Japan. Radiat Oncol *7*: 105, 2012.
16 Guckenberger M, Ok S, Polat B, Sweeney RA and Flentje M: Toxicity after intensity-modulated,image-guided radiotherapy for prostate cancer. Strahlenther Onkol *186*: 535-543, 2010.
17 Martin JM, Barley A, Bristow R, Chung P, Gospodarowicz M, Menard C, Milosevic M, Rosewall T, Warde PR and Catton CN: Image guided dose escalated prostate radiotherapy: still room to improve. Radiat Oncol *4*: 50, 2009.
18 Lips IM, Dehnad H, van Gils CH, Boeken Kruger AE, van der Heide UA and van Vulpen M: High-dose intensity-modulated radiotherapy for prostate cancer using daily fiducial marker-based position verification: acute and late toxicity in 331 patients. Radiat Oncol *3*: 15, 2008.
19 Pederson AW, Fricano J, Correa D, Pelizzari CA and Liauw SL: Late toxicity after intensity-modulated radiation therapy for localized prostate cancer: an exploration of dose-volume histogram parameters to limit genitourinary and gastrointestinal toxicity. Int J Radiat Oncol Biol Phys *82*: 235-241, 2012.
20 Peterson JL, Buskirk SJ, Heckman MG, Diehl NN, Bernard JR Jr, Tzou KS, Casale HE, Bellefontaine LP, Serago C, Kim S, Vallow LA, Daugherty LC and Ko SJ: Image-guided intensity-modulated radiotherapy for prostate cancer: Dose constraints for the anterior rectal wall to minimize rectal toxicity. Med Dosim *39*: 12-17, 2014.
21 Schaake W, van der Schaaf A, van Dijk LV, Bongaerts AH, van den Bergh AC and Langendijk JA: Normal tissue complication probability (NTCP) models for late rectal bleeding, stool frequency and fecal incontinence after radiotherapy in prostate cancer patients. Radiother Oncol, 2016. doi: 10.1016/j.radonc.2016.04.005. [Epub ahead of print]
22 Choe KS, Jani AB and Liauw SL: External beam radiotherapy for prostate cancer patients on anticoagulation therapy: how significant is the bleeding toxicity? Int J Radiat Oncol Biol Phys *76*: 755-760, 2010.
23 Sveistrup J, af Rosenschöld PM, Deasy JO, Oh JH, Pommer T, Petersen PM and Engelholm AS: Improvement in toxicity in high risk prostate cancer patients treated with image-guided intensity-modulated radiotherapy compared to 3D conformal radiotherapy without daily image guidance. Radiat Oncol *9*: 44, 2014.
24 Feigenberg SJ, Hanlon AL, Horwtz EM, Uzzo RG, Eisenberg D and Pollack A: Long-term androgen deprivation increases Grade 2 and higher late morbidity in prostate cancer patients treated with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys *62*: 397-405, 2005.
25 Akimoto T, Muramatsu H, Takahashi M, Saito J, Kitamoto Y, Harashima K, Miyazawa Y, Yamada M, Ito K, Kurokawa K, Yamanaka H, Nakano T, Mitsuhashi N and Niibe H: Rectal bleeding after hypofractionated radiotherapy for prostate cancer: correlation between clinical and dosimetric parameters and the incidence of grade 2 or worse rectal bleeding. Int J Radiat Oncol Biol Phys *60*: 1033-1039, 2004.
26 Zelefsky MJ, Chan H, Hunt M, Yamada Y, Shippy AM and Amols H: Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. J Urol 176: 1415-1419. 2006.
27 Herold DM, Hanlon AL and Hanks GE: Diabetes mellitus: a predictor for late radiation morbidity. Int J Radiat Oncol Biol Phys *43*: 475-479, 1999.

Received April 2, 2016
Revised May 12, 2016
Accepted May 17, 2016