Exceptionally High Incidence of Grade 2-3 Late Rectal Toxicity in Patients with Prostate Cancer Receiving Hypofractionated (*2.2 Gy*) Soft Tissue-matched Image-guided Intensity-modulated Radiotherapy

TAKUYA NISHIMURA[1], HIDEYA YAMAZAKI[2], NORIHIRO AIBE[2], SATOAKI NAKAMURA[2], KEN YOSHIDA[3] and HARUUMI OKABE[1]

[1]*Department of Radiology, Ujitakeda Hospital, Uji-city, Kyoto, Japan;*
[2]*Department of Radiology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto, Japan;*
[3]*Department of Radiology, Osaka Medical College, Takatsuki-City, Osaka, Japan*

Abstract. *Aim: To evaluate the incidence of rectal toxicity in patients undergoing hypofractionated (2.2 Gy) image-guided intensity-modulated radiotherapy (IG-IMRT) for prostate cancer. Patients and Methods: We examined 117 consecutive patients with prostate cancer who underwent IG-IMRT from June 2007 to July 2009. The median follow-up time was 32 months (range 20-42 months). The clinical target volume (CTV) consisted of the prostate and seminal vesicles, and the planning target volume (PTV) consisted of the CTV plus a 5-mm expansion, not avoiding the rectum. The PTV received a dose of 72.6-74.8 Gy in 33-34 fractions (2.2 Gy/fraction). Megavoltage computed tomographic (MVCT) scans were performed before each treatment and corrected to the registered position for planning CT scans using prostate soft tissue matching. Results: Late rectal bleeding of grades 1, 2, and 3 (Common Terminology Criteria for Adverse Events v3.0) occurred in 19 (16%), five (4%), and four (3%) patients, respectively. Late urinary toxicities of grades 1 and 2 occurred in five (4.3%) and eight (6.8%) patients, respectively. We found a paradoxically increased risk of rectal bleeding with more accurate irradiation of the rectum using soft tissue matching, whereas only a small percentage was reported in other IMRT series. Conclusion: IG-IMRT using daily MVCT scans allowed for exact dose delivery, which resulted in an increased rectal dose and exceptionally high incidence of rectal toxicity. Therefore, careful PTV contouring and dose schedule settings are important for safe administration of IG-IMRT.*

Ccorrespondence to: Takuya Nishimura, MD, Ujitakeda Hospital, 465 Ujisatojiri, Uji, Kyoto 602-8566, Japan. Tel: +81 775252500, Fax: +81 752515840, e-mail: t-nishi@koto.kpu-m.ac.jp

Key Words: Tomotherapy, prostate cancer, image-guided intensity-modulated radiotherapy.

In order to achieve a good outcome without many adverse events, for prostate cancer, intensity-modulated radiotherapy (IMRT) is preferred (1, 2); it causes fewer adverse events than three-dimensional conformal radiotherapy (2-9). Image-guided (IG) radiotherapy is a promising technique for achieving a more precise dose delivery, which we believe results in a higher control rate, with reduced incidence of adverse events. Chen *et al*. evaluated patients with anal cancer undergoing IG radiotherapy and reported that it reduced the planning target volume (PTV) margin and had a favorable toxicity profile, except for acute hematological toxicity (10).

Helical tomotherapy (HT) permits for delivery of IG-IMRT using megavoltage computed tomography (MVCT). These techniques enable the accurate and precise delivery of radiotherapy; therefore, we hypothesized that this advantage of HT would reduce toxicity. HT approach was installed at our institution in 2006 and we began hypofractionated IG-IMRT for the treatment of prostate cancer. However, we observed a relatively higher incidence of late rectal bleeding than that reported in other studies. This prompted us to explore the characteristics and factors influencing toxicities in patients treated with IG-IMRT.

Patients and Methods

Patients. We examined 117 consecutive patients with stage T1-T3 prostate cancer treated with IG-IMRT from June 2007 to July 2009. All patients had biopsy-proven adenocarcinoma. Patients were staged according to the 2002 Union for International Cancer Control (International Union Against Cancer; UICC version 6) staging classification system. The clinical characteristics of patients are shown in Table I.

Table I. *Patients' characteristics.*

Patients' demographics	(n=117) n	%
Pretreatment PSA (ng/ml)		
<10	51	44%
10-20	31	26%
>20	34	29%
NA	1	1%
Total Gleason score		
<7	43	37%
7	30	26%
>7	38	32%
NA	6	5%
T-stage		
T1c-T2a	58	50%
T2b	25	21%
>T2b	30	26%
NA	4	3%
Total dose (Gy)		
72.6	18	15%
74.8	99	85%
Age(years)		
<70	47	40%
>=70	70	60%

PSA: Prostate-specific antigen; NA: not applicable.

Table II. *Late rectal and urinary toxicity*

Late toxicity	(n=117) n	%
Late rectal toxicity		
Grade 0	89	76.1%
Grade 1	19	16.2%
Grade 2	5	4.3%
Grade 3	4	3.4%
Late urinary toxicity		
Grade 0	104	88.9%
Grade 1	5	4.3%
Grade 2	8	6.8%
Grade 3	0	0%

Common Toxicity Criteria, note grade 0 stands for lack of toxicity.

Table III. *The effects of patient characteristics and DVH parameters on Grade 2 or more late rectal toxicity.*

Characteristic	≤Grade 1	≥Grade 2	*p*-Value
Age (years)	69.8±6.8	70.1±2.5	n.s.
Tumor stage (≤T3)	27.20%	12.50%	n.s.
PTV volume (cc)	98.0±32.5	84.1±15.5	n.s.
Rectum volume (cc)	44.3±13.3	51.9±12.5	n.s.
Prescribed dose (Gy)	74.5±0.79	74.3±0.97	n.s.
Rectum median (Gy)	30.8±5.4	27.4±6.1	n.s.
Rectum max dose(Gy)	78.3±1.3	78.3±0.85	n.s.
V70 (%)	5.5±2.2	5±2.4	n.s.
V60 (%)	13.4±2.9	13±1.8	n.s.
V50 (%)	22.1±2.9	21±3.6	n.s.
V40 (%)	34.1±4.4	32±3.9	n.s.
V30 (%)	55.0±12.2	47.6±10.8	n.s.
V20 (%)	79.7±14.7	66.9±17.2	n.s.
V10 (%)	94.98	88.143	n.s.

The median follow-up time was 32 months (range: 20-42 months). Prostate specific antigen (PSA) failure was defined using the Phoenix definition (nadir +2 ng/ml). Toxicity was classified and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Treatment planning. Approximately one week before treatment initiation, we obtained CT and magnetic resonance images for treatment planning. At this time, each patient followed instructions for rectal emptying and bladder filling to minimize interfraction motion. Patients were placed in the supine position, and CT was performed with 2-mm slice thickness.

The clinical target volume (CTV) was defined as the prostate and proximal seminal vesicles. The CTV-to-PTV expansion margin was 5 mm in all directions, not avoiding the rectum. Pelvic nodal irradiation was not used. Ninety-five percent of the PTV (D95) received at least the prescribed dose of 74.8 Gy in 34 fractions (2.2 Gy/fraction), unless the tumor was of low risk (stage T1c, Gleason <7, PSA <10 ng/ml), in which case a dose of 72.6 Gy in 33 fractions was used. We defined the bladder and rectum as the organs at risk. The rectal volumes were contoured on axial slices 10 mm above and below the PTV. Planning constraints were set for the rectum and bladder: 35% of the rectal volume received <40 Gy; 18% of the rectal volume received <60 Gy; 35% of the bladder volume received <40 Gy; and 25% of the bladder volume received <65 Gy.

Daily treatment. All patients were treated with HT. MVCT scan was performed before each treatment to confirm the PTV location and verify that the rectum and bladder conditions were met. We then corrected the registered position to the simulated CT using soft tissue matching (pitch and yaw were not adjusted because rotational corrections were not implemented at the time of this study). The accuracy and reproducibility of these methods have been reported elsewhere (14). Late rectal toxicity was defined as any toxicity experienced three months after the completion of radiotherapy. We then determined whether volumes 10-70 Gy received in the rectum and bladder, prostate volume, and rectal volume correlated with adverse events.

Statistical analysis. StatView 5.0 statistical software was used for statistical analyses. Percentages were analyzed using the Chi-square test, and the Student's *t*-test was used for normally distributed data. The Mann–Whitney *U*-test for skewed data was used to compare means or medians, and the Kaplan–Meier method was used to analyze PSA control. For all analyses, $p<0.05$ was considered statistically significance.

Table IV. *Summary of studies comparing late rectal and urinary toxicity after intensity-modulated (IMRT) and three-dimensional conformal (CRT). radiotherapy.*

Study	Median Follow-up (months)	Definition	IMRT n	IMRT Dose	CRT n	CRT Dose	Late rectal toxicity IMRT	Late rectal toxicity CRT	Late rectal toxicity *p*-value	Late urinary toxicity IMRT	Late urinary toxicity CRT	Late urinary toxicity *p*-value	Posterior margin for defining PTV IMRT	Posterior margin for defining PTV CRT
Kupelian *et al*.	25/30	RTOG Gr ≥2	166	70 Gy/2.5 Gy	116	78 Gy	5%	12%	0.24	0	0	NA	4 mm	10 mm
Sanguineti *et al*.	26/24	RTOG Gr ≥2	45	76 Gy	68	76 Gy	6%	21%	0.06	NR	NR	NR		
Vora *et al*.	60/60	RTOG Gr 3	145	75.6 Gy	271	68.4 Gy	1%	2%	0.24	6%	5%	0.33		
Zelefsky *et al*.	96/120	CTC ≥Gr 2	472	81 Gy	358	≤75.6 Gy	5%	13%	0.001	20%	12%	0.01	6 mm	6 mm
Odrazka *et al*.	53/36	RTOG Gr 3	112	78 Gy	228	70 Gy	2%	5%	0.20	5%	16%	0.01		
Bekelman *et al*.	36/24	Medicare claims	5,845	NA	6,753	NA	3.5%	4.5%	0.01	7.7%	8.3%	0.19		
Alicikus *et al*.	99	CTC ≥Gr 2	170	81Gy	NR	NR	3.5%	NR	NR	13.5%	NR	NR	6 mm	NR
			IG-IMRT				IG-IMRT			IG-IMRT			IG-IMRT	
Present study	32	CTC ≥Gr 1	117	74.8 Gy/2.2 Gy	NR	NR	23.9%	NR	NR	11.1%	NR	NR	5 mm	NR
		CTC ≥Gr 2					7.7%			6.8%				
		CTC Gr 3					3.4%			0.0%				

CTC: Common Toxicity Criteria; Gr: grade; NA: not applicable; NR: not reported; RTOG: Radiation Therapy Oncology Group; PTV: planning target volume. Note: 70 Gy/2.5 Gy and 74.8 Gy/2.2 Gy are equialent to 77 Gy and 77.8 Gy in 2 Gy fractions, respectively.

Results

All patients completed radiotherapy without interruption. Table II shows the incidence of late rectal and urinary toxicities. Late rectal bleeding of grades 1, 2, and 3 occurred in 19 (16%), five (4%), and four (3%) patients, respectively. Grade 1 and 2 late urinary toxicities occurred in five (4.3%) and eight (6.8%) patients, respectively. No correlations of V10-70 with adverse events of the rectum or bladder were detected (Table III). In addition, prostate and rectal volumes, and doses were not related to adverse events. Biochemical failure was observed in seven patients, and the PSA control rate at three years was 95%.

Discussion

For higher-dose irradiation of the tumor while maintaining normal tissues within the endurable dose range, IG-IMRT is regarded as a promising technique; its use has increased in recent years. Furthermore, the number of publications related to IG-IMRT is also increasing. Results of MEDLINE searches for the number of articles on IG-IMRT gave 10 articles in 2001-2004, 109 in 2005-2008, and 216 in 2009-2012 (Table IV).

IMRT has already reduced the incidence of gastrointestinal (GI) adverse events; nevertheless, recent reports have found a small amount of late rectal bleeding to be common (11) (Table III). Furthermore, the IGRT technique enables for precise radiation exposure of the prostate, in contrast to the uncertain exposure with non-IGRT methods. Guckenberger *et al*. reported a lower rate (1.5%) of rectal bleeding by IG-IMRT using bone matching after treatment with 73.91 Gy in 32 fractions (12). However, we observed an increased risk of rectal bleeding using IG-IMRT and HT. This discrepancy may be caused by several factors. The use of soft-tissue matching may have led to more accurate irradiation delivery to the anterior rectal wall compared with conventional bone matching. In addition, the high incidence of rectal toxicity may be due to the use of hypo-fractionation. Based on the assumption that $\alpha/\beta=3$ Gy for normal tissues, the total doses of 72.6-74.8 Gy at 2.2 Gy/fraction equates to 2 Gy-equivalent doses of 75.5-77.8 Gy which is comparable to these of other studies. Our observations of urinary toxicity are consistent with the findings of Zelefsky *et al*. (11), who noted a low rate of urinary toxicity after IG-IMRT.

A dose–volume analysis did not reveal any significant correlation between V10-70 and rectal or bladder toxicities in our population. Pederson *et al*. (13) reported that the freedom from GI toxicity of grade 2 or more at few years was 100% for males with rectal V70 ≤10%, V65 ≤20%, and V40 ≤40% using IMRT. Although our data satisfied their requirement, we encountered 7% of cases of GI toxicity of grade 2 or more. Therefore, the DVH analysis itself did not confirm the safety of IG-IMRT. Finally, the margin status is an issue that must be discussed. Chen *et al*. reported that the application of IG-IMRT could reduce the PTV margin in patients with anal cancer, and caused for favorable toxicities (10). We, therefore, tried to assess the required margin at our institution.

We reduced the margin from 5 to 3 mm posterior of the prostate and reduced the fraction dose from 2.2 to 2 Gy (14).

In conclusion, IGRT using daily MVCT scans allowed for delivery of an exact dose, which resulted in increased rectal doses and an exceptionally high incidence of rectal toxicity. Therefore, careful PTV contouring and dose schedule settings are important for the safety of IG-IMRT.

References

1 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(4 Pt 1)*: 1415-1419, 2006.

2 Alicikus ZA, Yamada Y, Zhang Z, Pei P, Hunt M, Kollmeier M, Cox B and Zelefsky MJ: Ten year outcomes of high dose, intensity modulated radiotherapy for localized prostate cancer. Cancer *117*: 1429-1437, 2011.

3 Shu HG, Lee TT, Vigneault E, Xia P, Pickett B, Phillips TL and Roach M III: Toxicity following high-dose three-dimensional conformal and intensity-modulated radiation therapy for clinically localized prostate cancer. Urology *57*: 102-107, 2001.

4 Kuplian PA, Reddy CA, Carlson TP, Altsman KA and Willoughby TR: Preliminary observations on biochemical relapse-free survival rates after short-course intensity-modulated radiotherapy (70 Gy at 2.5 Gy/fraction) for localized prostate cancer. Int J Radiat Oncol Biol Phys *53*: 904-912, 2002.

5 Sanguineti G, Cavey ML, Endres EJ, Franzone P, Barra S, Parker BC, Marcenaro M, Colman M, Agostinelli S, Foppiano F and Vitale V: Dose treatment of the pelvic nodes with IMRT increase late rectal toxicity over conformal prostate-only radiotherapy to 76 Gy? Strahlenther Onkol *182*: 543-549, 2006.

6 Vora SA, Wong WW, Schild SE, Ezzell GA and 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 *68*: 1053-1058, 2007.

7 Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A and Amols HI: 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 *70*: 1124-1129, 2008.

8 Odrazka K, Dolezel M, Vanasek J, Vaculikova M, Zouhar M, Sefrova J, Paluska P, Vosmik M, Kohlova T, Kolarova I, Navratil P, Brodak M, Prosvic P and Hoffmann P: Late toxicity after conformal and intensity-modulated radiation therapy for prostate cancer: Impact of previous surgery for benign prostatic hyperplasia. Int J Urol *17*: 784-790, 2010.

9 Bekelman JE, Nitra N, Efstathiou J, Liao K, Sunderland R, Yeboa DN and Armstrong K: Outcome after intensity-modulated versus conformal radiotherapy in older men with nonmetastatic prostate cancer. Int J Radiat Oncol Biol Phys *81*: e325-e334, 2011.

10 Chen YJ, Suh S, Nelson RA, Liu A, Pezner RD and Wong JY: Setup Variations in Radiotherapy of Anal Cancer: Advantages of Target Volume Reduction Using Image-Guided Radiation Treatment: Int J Radiat Oncol Biol Phys *84*: 289-295, 2012.

11 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 Clnically Localized Prostate Cancer. Int J Radiat Oncol Biol Phys *84*: 125-129, 2012.

12 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.

13 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*: 235-41, 2012.

14 Nishimura T, Yamazaki H, Iwama K, Kotani T, Oota Y, Aibe H, Nakamura S, Ikeno H, Yoshida K, Isohashi F and Okabe H: Assessment of planning target volume margin for a small number of vertebral metastatic lesions using image-guided intensity-modulated radiation therapy by helical tomotherapy. Anticancer Res *33*: 2453-2456, 2013.

Received September 27, 2013
Revised November 3, 2013
Accepted November 4, 2013