Risk Factors and Time to Occurrence of Genitourinary Toxicity After External Beam Radiotherapy for Prostate Cancer

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Abstract. *Aim: To retrospectively investigate the risk factors and time to occurrence of genitourinary (GU) toxicity after radiotherapy for localized prostate cancer. Patients and Methods: The study included 320 patients. The radiotherapy planning target volume encompassed the prostate with a 1-cm margin in the transverse plane and a 1-cm margin (Group A) or a 1.5-cm margin (Group B) in the longitudinal plane. Incidence rates, risk factors and time to occurrence of GU toxicity were evaluated. Results: After a median follow-up of 38.2 months, the rate of late grade 2-3 GU toxicity was 5.9% and the median interval was 18.3 months. The wider longitudinal margin was the single significant independent factor. The 2-year cumulative incidence rates of late grade ≥2 GU toxicity were 2.8% and 7.5% in Group A and B patients. Conclusion: A wider radiotherapy margin increased the risk of GU toxicity and led to earlier occurrence.*

External beam radiotherapy (EBRT) is a key modality for the definitive treatment of localized prostate cancer (1). High-dose advanced EBRT with three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) for patients with localized prostate cancer has obtained excellent local control with a low rate of late severe adverse events (2, 3). The cumulative incidence rate of late grade ≥2 toxicity was reported to range from 9% to 33% (4). Gastrointestinal (GI) and genitourinary (GU) toxicities are common late treatment-related events. There have been few studies on the risks of late GU toxicity, although the rates of GU toxicity are reported to range from 3% to 41% and affect more patients than GI toxicity (3, 5-8). In addition, the late development of GU toxicity showed a trend toward significant correlation with quality changes of physical life, such as working or activity (9). The aim of this retrospective study was to investigate the occurrence of GU toxicity in patients with localized prostate cancer who underwent 3D-CRT.

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Patients and Methods

Patients' and tumor's characteristics. From May 2007 to December 2013, 320 patients with T1c-4aN0M0 prostate cancer underwent 3D-CRT at Niigata Cancer Center Hospital in Japan and were followed for at least 6 months after treatment. There were 314 patients who received radiotherapy combined with hormonal therapy and 6 were treated with radiotherapy alone. These patients were evaluated retrospectively and patients' characteristics are summarized in Table I. The median age at treatment was 72 years. Sixty-three patients had other cancers. TNM staging was performed according to the 2009 classification of the International Union Against Cancer and the patients were classified into risk groups according to the guidelines of the National Comprehensive Cancer Network (10). Of these patients, 39, 168 and 113 were classified as low-, intermediate- and high-risk, respectively.

Three-dimensional conformal radiotherapy (3D-CRT). 3D-CRT was administered for a total of 70 Gy in 35 daily fractions. The clinical target volume (CTV), which was defined as the prostate alone, was based on computed tomography with a 5-mm slice thickness under free-breathing conditions. The planning target volume (PTV) encompassed the CTV with a 1-cm margin in the transverse plane and a 1-cm margin (Group A patients) or 1.5-cm margin (Group B patients) in the longitudinal plane. The edges of the multileaf collimator were directly fitted to the PTV. Five 15-MV photon beams were used. The 70-Gy dose was prescribed for the isocenter point in the center of the PTV.

Follow-up and evaluation. Follow-up, including measurement of tumor marker levels, was performed periodically at intervals of 3 months. Late treatment-related toxicity was assessed at follow-up visits using

Table I. *Patients' characteristics*.

	Patients' characteristics
Age (years)	55-83 (median=72)
T stage (UICC 2009)	
T1c	190
T2a	39
T2b	28
T2c	47
T3a	14
T3b	0
T4a	2
Gleason score	
≤6	92
7	154
≥8	74
Initial PSA value (ng/ml)	2.14-307 (median=10.3)
Treatment method	
RT alone	6
RT and HT	314

UICC, Classification of the International Union Against Cancer; PSA, prostate-specific antigen; RT, radiotherapy; HT, hormonal therapy.

the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Prostate-specific antigen (PSA) failure was defined by an increase in the PSA level of greater than 2 ng/ml over the lowest level (nadir) (11).

Statistical analysis. Data were collected and analyzed retrospectively. The cumulative incidence rates of late toxicities were estimated using the Kaplan-Meier method. To analyze the risk factors of late GU toxicity, univariate and multivariate analyses were performed using a Cox proportional hazards model for the following factors: age at time of treatment; prostate risk groups (low- *vs*. intermediate- *vs*. high-risk); hormonal therapy (yes *vs*. no); past history of holmium laser enucleation of the prostate (HoLEP) or transurethral resection of the prostate (TUR-P) (yes *vs*. no); PSA failure (yes *vs*. no); 3D-CRT margin (Group A *vs*. Group B). Data analysis was performed using the Ekuseru-Toukei software package (version 2010; Social Survey Research Information Co., Ltd., Tokyo, Japan); *p*-values <0.05 were considered significant.

Results

The median follow-up periods from the end of 3D-CRT and from the end of all treatments were 38.2 months (range=7.4-86.2 months) and 31.4 months (range=6.0-86.2 months), respectively. At the final follow-up, 318 of 320 patients were alive and 2 had died of another disease. The 3-year PSA-failure-free survival rates after the end of all treatments and after the end of 3D-CRT were 93.7% and 95.0%, respectively. Regarding toxicity, 10 (3.1%) and 19 patients (5.9%) had late grade 2 or 3 GI and GU toxicities, respectively. No grade 4-5 toxicity was observed.

With respect to late urinary toxicity, 3 had macrohematuria, 11 had frequent urination and 5 patients had urinary retention. The 2- and 3-year cumulative incidence rates of grade ≥2 late GU toxicities after the end of 3D-CRT were 4.1% and 5.5%, respectively. The median interval from the end of 3D-CRT to the date of observation of toxicity was 18.3 months (range=0.6-66.2 months). At the final follow-up, 12 of 19 patients still had grade 2 or 3 GU toxicity with a median duration from the date of toxicity to final follow-up of 7.0 months (range=0-46.8 months). The GU toxicity improved to grade 1 in 7 patients, for whom the median duration from the date of grade 2 or 3 toxicity to the date of the improvement to grade 1 was observed 6.0 months later (range=3.0-13.1 months). Univariate analysis revealed that a history of HoLEP or TUR-P and a wider longitudinal 3D-CRT margin were significant risk factors for GU toxicity (Table II). Multivariate analysis of these factors revealed that a wider longitudinal 3D-CRT margin was a significant (p=0.028) independent risk factor.

The 2-year cumulative incidence rates of late grade ≥2 GU toxicity after the end of 3D-CRT in Group A (PTV 1-cm margin in longitudinal plane) and Group B (PTV 1.5-cm margin) patients were 2.8% and 7.5%, respectively (log-rank test, p=0.013) (Figure 1). On the other hand, the 2-year PSA-failure-free survival rates after the end of all treatments were 98.5% and 99.0% in Group A and Group B patients, respectively (log-rank test, p=0.85).

Discussion

This was a retrospective study that evaluated the incidence and risk factors of late GU toxicities in a large number of patients with localized prostate cancer who underwent high-dose advanced EBRT with 3D-CRT. Nineteen patients (5.9%) had late grade 2 or 3 GU toxicities, whereas no grade 4 toxicity was observed. The median interval from the end of 3D-CRT to the occurrence of toxicity was 18.3 months, while the 2-year cumulative incidence rate of late grade ≥2 GU toxicity was 4.1%. These findings are consistent with the results of previous studies (3, 5-8). GU toxicity incidence rates ranging from 3% to 41% have been reported previously (3, 5-8). The duration from radiotherapy until the first development of GU toxicity has been reported to range from 19 to 30 months (6, 7).

Univariate analysis of our study patients found that a history of HoLEP or TUR-P and a wider 3D-CRT longitudinal margin were significant risk factors of GU toxicity. Multivariate analysis revealed a wider 3D-CRT longitudinal margin as the only significant independent factor. This finding is similar to that of previous studies. Among clinical factors, baseline symptoms, age, type 2 diabetes mellitus, history of TUR-P and acute toxicity were reported to be significant risk factors of GU toxicity (4, 6, 12). About the dosimetric factors, Zelefsky *et al*. reported that a radiation dose >81 Gy was a risk factor when compared to a dose <81 Gy (6), whereas Peeters *et al*.

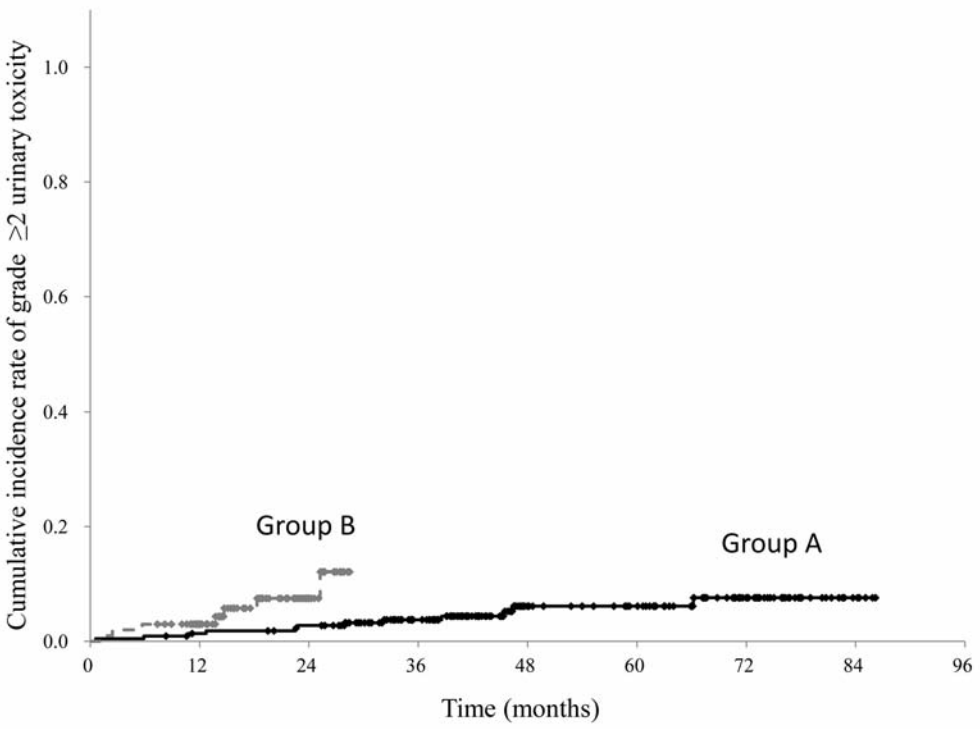

Figure 1. *Cumulative incidence rates of late grade ≥2 genitourinary toxicity. For external beam radiotherapy administered to patients with localized prostate cancer, the planning target volume encompassed the prostate with a 1-cm margin in the transverse plane and a 1-cm margin (Group A patients) or 1.5-cm margin (Group B patients) in the longitudinal plane. The 2-year cumulative incidence rates of late grade ≥2 genitourinary toxicity after external-beam radiotherapy in Group A and B patients were 2.8% and 7.5%, respectively (log-rank test, p=0.013).*

Table II. *Univariate and multivariate analysis of risk factors for incidence of urinary toxicity.*

Characteristic	Grade 0-1 (N=301)	Grade 2-3 (N=19)	Univariate analysis *p*-Value	Multivariate analysis *p*-Value
Age at time of treatment			0.22	-
Median, years old	72 (range=55-83)	72 (range=66-81)		
History of HoLEP or TUR-P			0.038	0.067
yes *vs*. no	8:293	2:17		
Hormonal therapy			0.50	-
yes *vs*. no	295:6	19:0		
PSA failure			0.11	-
yes *vs*. no	25:276	0:19		
Prostate risk group			0.79	-
high- *vs*. intermediate- *vs*. low-risk	106:158:37	7:10:2		
3D-CRT margin			0.020	0.028
Group A *vs*. Group B	208:93	12:7		

HoLEP, Holmium Lasor enuculation of prostate; TUR-P, transurethral resection of prostate; 3D-CRT, three-dimensional conformal radiotherapy; PSA, prostate-specific antigen. Group A: The planning target volume encompassed the prostate with a 1-cm margin in the transverse plane and in the longitudinal plane. Group B: The planning target volume encompassed the prostate with a 1-cm margin in the transverse plane and a 1.5-cm margin in the longitudinal plane.

compared 68 Gy to 78 Gy and did not find any differences (5). Nakamura *et al*. reported radiation dose over 70 Gy on 30% of initial bladder volume was a risk factor (4). Cheung *et al*. reported the hottest volume of bladder was a risk factor, which recognized that the best fit hottest volume was 2.9% of bladder (13). According to their study, about 50% of patients who received ≥78 Gy to the hottest 2.9% of bladder experience GU toxicity at 8 years. Shimizu *et al*.

also reported a very low rate of GU toxicity; only 3 patients (2.7%) developed late grade 2 GU toxicity. They thought that their results might have been attributable to the small PTV margin and the reduced radiation dose to the urethra (14). In our study, the wider 3D-CRT longitudinal margin was the single significant independent factor. With a wider 3D-CRT margin in the longitudinal plane, the volume of irradiated bladder and urethra increases. The results of our study and these previous studies (13, 14) suggest that the irradiated volume is important. Regardless of whether the margin in the longitudinal plane was 1.5 or 1 cm, the PSA-failure-free survival rate was the same, although the follow-up period of our study was short.

The 2-year cumulative incidence rates of late grade ≥2 GU toxicities were 2.8% and 7.5% in Group A and Group B patients, respectively. According to this result, GU toxicity occurred earlier in Group B than in Group A patients, which means that GU toxicity occurred earlier with a wider irradiation margin in the longitudinal plane.

In conclusion, the significant independent risk factor of late grade ≥2 GU toxicity was a wider radiotherapy margin in the longitudinal plane, which led to the earlier occurrence of GU toxicity.

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