Comparison of Common Terminology Criteria for Adverse Events v3.0 and Radiation Therapy Oncology Group Toxicity Score System After High-dose-rate Interstitial Brachytherapy as Monotherapy for Prostate Cancer

KEN YOSHIDA[1], HIDEYA YAMAZAKI[2], SATOAKI NAKAMARA[2], KOJI MASUI[2], TADAYUKI KOTSUMA[3], HIRONORI AKIYAMA[3], EIICHI TANAKA[3] and YASUO YOSHIOKA[4]

[1]Department of Radiology, Osaka Medical College, Takatsuki-City, Osaka, Japan;
[2]Department of Radiology, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto, Japan;
[3]Department of Radiology, National Hospital Organization, Osaka National Hospital,Osaka City, Osaka, Japan;
[4]Department of Radiation Oncology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

Abstract. *Aim: The evaluation of toxicity after high-dose-rate interstitial brachytherapy (HDR-ISBT) as monotherapy for localized prostate cancer. Materials and Methods: We analyzed early and late toxicities in 100 patients treated by HDR-ISBT as monotherapy at the National Hospital Organization Osaka National Hospital using both Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) and Radiation Therapy Oncology Group (RTOG) score. The median follow-up was 72 (range=12-109) months. Results: Late-gastrointestinal (GI) toxicities were 4% grade 1 and 2% grade 2 in CTCAE v3.0 and 5% grade 1 in RTOG score. Late genitourinary (GU) toxicities grade 1: grade 2: grade 3 were 29%: 5%: 2% in RTOG and 47%: 10%: 2% in CTCAE v3.0. CTCAE v3.0 GU score identified more grade 1-2 adverse reactions than the RTOG score (p=0.01). Early RTOG GI toxicity-positive patients showed 13% of late RTOG GI toxicity, whereas early RTOG GI negative patients showed 0% of RTOG (p=0.0172) and CTCAE v3.0 late-GI toxicity (p=0.007). Conclusion: CTCAE v3.0 GU score identified more grade 1-2 adverse reactions than the RTOG score. Early RTOG GI toxicity is well-correlated to late GI toxicity and absence of RTOG acute GI toxicity is a safe surrogate for late GI toxicity after HDR-ISBT as monotherapy for prostate cancer.*

Correspondence to: Hideya Yamazaki, MD, Department of Radiology, Kyoto Prefectural University of Medicine, 465 Kajiicho Kawaramachi Hirokoji, Kamigyo-ku, Kyoto, Kyoto 602-8566 Japan. Tel: +81 752515618, Fax: +81 752515840, e-mail: hideya10@hotmail.com

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Radiotherapy is one of the standard treatment modalities for clinically-localized prostate cancer (1, 2). Interstitial brachytherapy (ISBT) can deliver a higher radiation dose to the prostate gland without avoiding surrounding normal tissues (3). Among ISBT, high-dose-rate ISBT (HDR-ISBT) monotherapy would definitely be the most efficient method of achieving a high degree of conformity even for seminal vesicle invasion or extracapsular invasion and dose escalation with short overall treatment time, therefore we have installed HDR-ISBT as a monotherapy and reported excellent outcomes (4, 5). Recently quality of life (QOL) has become an important outcome with improved prostate-specific antigen (PSA) control and survival especially for older patients (6, 7). Accordingly, we evaluated toxicity profiles after HDR-ISBT monotherapy both in Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0) (8) and Radiation Therapy Oncology Group (RTOG) score systems (9, 10) and examined prognostic factors for late toxicity.

Materials and Methods

Between July 2003 and May 2008, 100 patients were treated by HDR-ISBT as monotherapy at the National Hospital Organization Osaka National Hospital. Patients' characteristics are shown in Table I. The median patient age was 71 (range=48-86) years and median follow-up time was 72 (range=48-109) months. Using the UICC classification of 2002, 38 T1, 45 T2, and 17 T3 were identified (11). All patients were histologically-proven to have adenocarcinoma. Gleason scores were less than seven for 38 patients, seven for 42 patients, more than seven for 18 patients and unknown for two patients. The median pre-treatment prostate-specific antigen (PSA) was 19 (range=3.8-98.6) ng/ml. Using the risk group classification of National Comprehensive Cancer Network (NCCN) guidelines, 16, 40, 35 and 9 patients were classified as low-risk, intermediate-risk, high-risk and super high risk group (12). Androgen deprivation therapy (ADT) was performed in 91 patients as neoadjuvant and/ or

adjuvant treatment (median=7 months; range=3-25 months). The detailed method of applicator implantation was described elsewhere (5). All patients received a CT examination before the planning. The CT-based planning with or without MRI-assistance was performed by computer optimization (PLATO® and Oncentra® brachy, Elekta AB, Stockholm, Sweden) with or without manual modification. The prescribed dose was 38 Gy per 4 fractions, 40 Gy per five fractions, 54 Gy per 9 fractions in 5 days, and 49 Gy per 7 fractions. The treatment machine used was the microSelectron-HDR® (Elekta AB, Stockholm, Sweden). We analyzed early and late gastrointestinal (GI) and genitourinary (GU) toxicities using both CTCAE v3.0 and RTOG score systems. We analyzed influence of age, T factor, Gleason scores, PSA value, dose fractionation, ADT, and early toxicities on late GI and GU toxicities.

Statistical analysis. All statistical analyses were performed using the Statview 5.0 statistical software (SAS Institute, Inc., Cary, NC, USA). Frequencies were analyzed using the χ^2 test. Means were compared using the Student's t-test for normally-distributed data and the Mann-Whitney *U*-test for skewed data. Cut-off value was set at the average or the median value of each variable unless otherwise stated. All analyses used the conventional $p<0.05$ level of significance.

Results

Acute GI toxicities grade 1: grade 2 were 34%: 5% in RTOG and 29%: 1% in CTCAE v3.0 (Table I). Acute GU toxicities grade 1: grade 2: grade3 were 66%: 18%: 11% in RTOG and 65%: 22%: 9% in CTCAE v3.0. Late GI toxicities were 4% grade 1 and 2% grade 2 in CTCAE v3.0 and 5% grade 2 in RTOG score. Late GU toxicities grade 1: grade 2: grade 3 were 29%: 5%: 2% in RTOG and 47%: 10%: 2% in CTCAE v3.0. Comparison between RTOG and CTCAE v3.0 revealed that there are significant differences in late urinary toxicity between CTCAE v3.0 and RTOG ($p=0.01$) (Table II). RTOG underscored late urinary toxicity compared to CTCAE v3.0. Grade 4 or 5 late toxicity was not detected in any of the patients. CTCAE v3.0 GU score identified more grade 1-2 adverse reactions than RTOG score ($p=0.01$). We did not find any statistically significant predisposing factor for late toxicity except acute toxicities. Table III shows correlations between late toxicities and acute toxicities. Early RTOG GI toxicity is well-correlated to late GI toxicity both in RTOG and CTCAE v3.0 score and Early RTOG GI toxicity positive patients showed 13% of late RTOG GI toxicity, whereas early RTOG GI-negative patients showed 0% of RTOG ($p=0.0172$) and CTCAE v3.0 late GI toxicity ($p=0.007$). Therefore, absence of RTOG acute GI toxicity is a safe surrogate for late-GI toxicity after HDR-ISBT as monotherapy for prostate cancer.

Table I. *Patients' characteristics*.

Variable	
Age (years)	
Median (range)	71 (52-86)
Follow-up period (months)	
Median (range)	73 months (48-109)
Gleason score	
≤6	38
7	42
8≤	18
Unknown	2
T-stage	
T1	38
T2	45
T3	17
Initial prostate-specific antigen (ng/ml)	
Mean±SD	19±19 (3.8-98.6)
<10	39
10-20	31
>20	30
NCCN risk group classification	
Low	16
Intermediate	40
High	35
Super high risk	9
Dose/fraction (Gy/fractions)	
38 Gy/4 fractions	4
49 Gy/7 fractions	69
54 Gy/9 fractions	26
40 Gy/5 fractions	1
Androgen deprivation therapy	
Neoadjuvant only	81
Adjuvant only	0
Neoadjuvant + Adjuvant	10
No	9

NCCN; National Comprehensive Cancer Network.

Discussion

HDR monotherapy has been investigated in several Institutes (3). Yoshioka *et al*. reviewed the manuscripts and cited that reported toxicity levels were generally acceptable. Frequency of late-GU toxicity ≥grade 2 ranged from 0–59.0%, and for late-GI toxicity the rate was 0–13.0%. While late GI toxicity was ≤5% in most cases, several authors reported late-GU toxicity as high as 20-40% (3). For examples, Hoskin *et al*. reviewed that grade ≥2 late GU (and GI) complications using CTCAE v3 were 8-15% (0-7%) (13) and Zamboglou *et al*. also reported 19.9-32% (0.8-5.6%) (14). In the present study we presented 7% (RTOG), 12% (CTCAE v3.0) GI toxicities and 0% (RTOG), 2% (CTCAE v3.0) GU toxicities which is concurred to previously reported outcomes. Of note, the follow-up period of our study is the longest one among reported HDR-ISBT monotherapy series.

Association of early and late toxicities were reported in several external-beam radiotherapy studies. Zerlefsky *et al*., reported the presence of acute GI and GU symptoms during the course of treatment conferred a 7- and 3.5-fold increased risk of late GI and GU toxicities, respectively (15). Heemsbergen *et al*. noted such an association between acute-

Table II. *Toxicity assessed by RTOG and CTCAE v3.0 toxicity criteria*.

	Grade 0		Grade 1		Grade2		Grade 3	
RTOG								
Acute GI	61	(61%)	34	(34%)	5	(5%)	0	(0%)
Acute GU	5	(5%)	66	(66%)	18	(18%)	11	(11%)
Late GI	94	(95%)	5	(5%)	0	(0%)	0	(0%)
Late GU	62	(64%)	28	(29%)	5	(5%)	2	(2%)
CTCAE v3.0								
Acute GI	68	(70%)	28	(29%)	1	(1%)	0	(0%)
Acute GU	4	(4%)	63	(65%)	21	(22%)	9	(9%)
Late GI	93	(94%)	4	(4%)	2	(2%)	0	(0%)
Late GU	40	(40%)	47	(47%)	10	(10%)	2	(2%)

RTOG; Radiation Therapy Oncology Group, CTCAE v3.0; Common Terminology Criteria for Adverse Event 3.0; GI; gastrointestinal, GU; genitourinary.

Table III. *Correlation between late and other toxicities*.

RTOG late GI toxicity		Late RTOG GI toxicity				*p*-Value
		Negative		Positive		
Early GI (RTOG)	Negative	61	(62%)	0	(0%)	0.0164
	Positive	34	(34%)	5	(5%)	
Early GI (CTCAE v3.0)	Negative	65	(66%)	3	(3%)	>0.99
	Positive	27	(27%)	2	(2%)	
Late GI (CTCAE v3.0)	Negative	94	(95%)	0	(0%)	<0.0001
	Positive	1	(1%)	5	(5%)	
CTCAE late GI toxicity		Late CTCAE v3.0 GI toxicity				*p*-Value
		Negative		Positive		
Early GI (CTCAE v3.0)	Negative	65	(66%)	3	(3%)	
	Positive	26	(26%)	3	(3%)	0.51
Early GI (RTOG)	Negative	61	(62%)	0	(0%)	0.0071
	Positive	34	(34%)	6	(6%)	
RTOG late GU toxicity		Late RTOG GU toxicity				*p*-Value
		Negative		Positive		
Early GU (RTOG)	Negative	4	(4%)	1	(1%)	0.64
	Positive	58	(59%)	35	(35%)	
Early GU (CTCAE v3.0)	Negative	4	(4%)	0	(0%)	
	Positive	55	(56%)	36	(36%)	0.29
Late GU (CTCAE v3.0)	Negative	40	(40%)	0	(0%)	
	Positive	22	(22%)	35	(35%)	0.0002
CTCAE v3.0 late GU toxicity		Late CTCAE v3.0 GU toxicity				*p*-Value
		Negative		Positive		
Early GU (RTOG)	Negative	3	(3%)	2	(2%)	
	Positive	37	(37%)	57	(58%)	0.65
Early GU (CTCAE v3.0)	Negative	3	(3%)	1	(1%)	
	Positive	36	(36%)	57	(58%)	0.35

GI; Gastrointestinal, GU; genitourinary, RTOG; Radiation Therapy Oncology Group. CTCAE v3.0; Common Terminology Criteria for Adverse Event 3.0;

and late-GI toxicities and postulated that late effects are a direct consequence of the initial tissue injury, which is reflected in acute symptoms from normal tissue inflammation. In their reports presence of diarrhea during the course of treatment predicted for a higher risk of late Grade 2 and greater risk for late proctitis (16).

Several limitations exist in our study. At first, RTOG or CTCAE v3.0 score system was widely used for assessment of toxicity but was not enough to meet the requirement of recent radiotherapy outcome surveys for prostate cancer because in these score systems, compliance-related symptoms (such as stool frequency) and proctitis-related symptoms (such as rectal bleeding) are combined to one overall score, may result in loss of information and might obscure the relation between dose–volume parameters and complications (17). Therefore several trials added a patient self-assessment questionnaire to obtain detailed information on morbidity. Secondly, although DVH analysis for organs at-risk is an important predisposing factor for toxicity analysis, we could not add these data due to limitation of our equipment. New modern equipment are to be installed at our Institution during next year and those DNH analyses are warranted.

In conclusion, CTCAE v3.0 GU score identified more grade 1-2 adverse reactions than the RTOG score. Early-RTOG GI toxicity is well-correlated to late-GI toxicity and absence of RTOG acute GI toxicity is a safe surrogate for late-GI toxicity after HDR-ISBT as monotherapy for prostate cancer.

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