60 134 patients who received radiation therapy with 25 904 who underwent observation.

High-dose irradiation and/or hormonal therapy result in excellent outcomes, not only in PSA control, but also in overall survival. Nguyen *et al.* reported good 5- and 10-year actuarial overall survival rates (no ADT plus 75.6 Gy, 87.3% and 72.0% respectively; and ADT plus 75.6 Gy, 92.3% and 72% respectively; $P = 0.0035$) [4]. We also obtained similar results: 70 Gy plus ADT achieve 91–93% of overall survival after 5 years [7, 93]. Therefore, we should pay attention to adverse effects and quality of life (QOL) rather than disease control because almost 90% of the patients after EBRT live longer than 5 (or 10) years.

Multiple health-related QOL studies have been conducted using the IPSS, IIEF, and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Prostate Cancer 25 items (QLQ-PR25) etc. Such comparison between radical prostatectomy, EBRT, BT, and combined approaches uncovers a link between observed toxicity and QOL. For example, Sanda *et al.* prospectively measured outcomes reported by 1201 patients and 625 spouses or partners at multiple centers before and after radical prostatectomy, BT or EBRT [94]. Adjuvant ADT is associated with worse outcomes across multiple QOL domains among patients receiving BT or radiotherapy. Patients in the BT group report long-lasting urinary irritation, bowel and sexual symptoms, and transient problems with vitality or hormonal function. Adverse effects of prostatectomy on sexual function are mitigated by nerve-sparing procedures. After prostatectomy, urinary incontinence is frequent, but urinary irritation and obstruction are improved, particularly in patients with a large prostate. No treatment-related deaths occurred in that study; serious adverse events were rare. Their results suggest that treatment-related symptoms are exacerbated by obesity, large prostate size, high PSA score and older age. Black patients report a lower degree of satisfaction with the overall treatment outcomes. Changes in QOL are significantly associated with the degree of outcome satisfaction among patients and their spouses or partners. However, there are several problems with the use of QOL questionnaires. For example, the IPSS is considered a major QOL questionnaire in the treatment of prostate cancer, but IPSS was constructed mainly for prostate hypertrophy symptoms. Thus, this questionnaire cannot evaluate adverse effects after prostatectomy (the IPSS of most patients improves after prostatectomy). Therefore, when it comes to comparison of different treatment methods, accurate QOL evaluation is a challenge.

The impact of age on prostate cancer outcomes was found not only in PSA control and survival but also in QOL in less aggressive prostate cancers in older men [95], independent of other clinical features. When adjusted for other covariates, age >70 years still correlates with decreased OS (HR, 1.56 [95% CI] 1.43–1.70 $P < 0.0001$) and with a decreased incidence of metastasis (HR, 0.72 [95% CI, 0.63–0.83], $P < 0.0001$) and prostate cancer-specific death (HR, 0.78 [95% CI, 0.66–0.92], $P < 0.0001$). Although the biological underpinnings of this finding remain unknown, stratification by age in future trials is warranted. Several reports show that adverse reactions occur more frequently in older patients [32, 33, 77]. In this context, major data provided by a clinical trial (i.e. a large randomized controlled trial) were based on the data from patients younger than 80 years of age.

There are several limitations to our study. First, we did not analyze BT (although there are plenty of data in the literature) because we focused on the changes in adverse effects as a result of the advancement of EBRT from 2D to IMRT and IGRT. Second, as a result of this we did not analyze particle therapy because of the limited use of this therapy (both proton and carbon ion) in patients with prostate cancer except for clinical studies. Finally, hypofractionated radiotherapy was also excluded from this analysis, even though there is a hypothesis that hypofractionation has a radiobiological advantage in prostate carcinoma because of the low α/β ratio. This topic—the influence of fractionation—is beyond the scope of this study and will be explored in future studies.

In conclusion, the focus of toxicity analysis following radiotherapy for prostate cancer patients is changing from rectal bleeding to total elaborate QOL assessment.

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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

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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.*

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Key Words: High dose rate brachytherapy, prostate cancer, early toxicity, late toxicity, interstitial brachytherapy, radiation therapy.

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

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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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Role of Novel Risk Classification Method, Prostate Cancer Risk Index (PRIX) for Clinically Localized Prostate Cancer After High-dose-rate Interstitial Brachytherapy as Monotherapy

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Abstract. *Aim: To examine the role of the new grading system Prostate Cancer Risk Index (PRIX) with existing risk-grouping after high-dose-rate interstitial brachytherapy (HDR-ISBT) as monotherapy for localized prostate cancer. Patients and Methods: We analyzed outcome in 100 patients treated by HDR-ISBT as monotherapy using PRIX and compared this with D'Amico, the National Comprehensive Cancer Network (NCCN), and Seattle classifications. The median follow-up was 74 (range=48-109) months. Results: Five-year prostate-specific antigen control and overall survival rates were 94% and 98%, respectively. PRIX separated the risks statistically significantly (p=0.004), while D'Amico (p=0.319), NCCN 2002 (p=0.126), NCCN 2012 (p=0.052) and Seattle (p=0.112) classifications failed to show a statistically significant separation. Conclusion: PRIX is a more useful risk classification system in high-risk patient selection than existing risk classification system in clinically localized prostate cancer after HDR-ISBT as monotherapy.*

Prostate cancer is one of the major malignancies of men in Western countries. Interstitial brachytherapy (ISBT) can deliver a higher radiation dose to the prostate gland avoiding surrounding normal tissue and is, therefore, regarded as an effective treatment option among different types of radiotherapy (1-3). High-dose-rate ISBT (HDR-ISBT) monotherapy would definitely be the most efficient method of achieving good dose distribution with a high degree of conformity, even for adjacent tissue invasion (seminal vesicle or extracapsular extension), with short overall treatment time. We have implemented HDR-ISBT as monotherapy and reported excellent outcome (4, 5).

For risk factor classification, a simplified categorization with three risk groups is widely used, known as low-, intermediate-, and high-risk groups. This grouping is very simple and usable, but entails problem. With the advent of modern treatment modalities, dose escalation and hormonal therapy have improved biochemical control and overall survival rate of patients with localized prostate cancer. Generally, the high-risk groups of conventional groupings include cases so heterogeneous that it often makes it difficult to choose the most appropriate treatment from many alternatives. Yoshioka *et al.* proposed a new grouping method, namely Prostate Cancer Risk Index (PRIX), with an additional number of risk categories, which should be fully compatible with the existing data such as the Partin Table (6). The aim of the current study was to examine the role of PRIX by comparison with the existing risk-grouping methods such as D'Amico (7), the National Comprehensive Cancer Network (NCCN) 2005 (8), NCCN 2012 (9), and Seattle (10) classifications in assessment of outcome after HDR-ISBT monotherapy.

Patients 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=52-86) years and median follow-up time was 74 (range=48-109) months. Using the UICC classification of 2002, most patients had stage T2 disease or higher (11). All patients were histologically-proven to have adenocarcinoma. Gleason scores were 7 or more in most patients (62%). The median pre-treatment

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Key Words: High-dose-rate brachytherapy, prostate cancer, risk classification.

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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	34
T2	49
T3	16
T4	1
Initial prostate-specific antigen (ng/ml)	
Mean±SD	19±19 (3.8-98.6)
<10	39
10-20	31
>20	30
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

Table II. *Patients' distribution among risk classification systems.*

Variable	
NCCN 2002	
Low	21
Intermediate	35
High	44
NCCN 2012	
Low	21
Intermediate	35
High	38
Super high risk	6
D' Amico	
Low	15
Intermediate	33
High	52
Siatle	
Low	21
Intermediate	27
High	52
PRIX	
0	15
1	20
2	14
3	20
4	16
5	10
6	3

NCCN; National Comprehensive Cancer Network, PRIX: Prostate Cancer Risk Index.

prostate-specific antigen (PSA) was 19 (range=3.8-98.6) ng/ml. Androgen deprivation therapy (ADT) was performed in 91 patients as neoadjuvant or adjuvant treatment (median=7 months; range=3-25 months). The detailed method of applicator implantation was described elsewhere (5). All patients underwent a computed tomographic (CT) examination before planning. The CT-based planning with or without magnetic resonance imaging (MRI) assistance was performed by computer optimization (Nucletron an Elekta Company, Veenendaal, the Netherlands; PLATO® and Oncentra® brachy, Elekta AB, Stockholm, Sweden) with or without manual modification. The prescribed dose was 38 Gy in four fractions, 40 Gy in five fractions, 54 Gy in nine fractions in five days, and 49 Gy in seven fractions. The treatment machine used was the microSelectron-HDR® (Nucletron).

The new grading system consists of three factors (6). The first factor is for PSA of 4.1-10.0 ng/ml (score 0), 10.1-20.0 ng/ml (score 1), and >20.0 ng/ml (score 2). The second is for Gleason score (GS) of 6 (score 0), 7 (score 1), and 8-10 (score 2). The third is T classifications (UICC 2002) of T1c–T2a (score 0), T2b–T2c (score 1), and T3a (score 2). The sum of the three scores derives the PRIX. Definition of the following three risk-grouping systems, which seemed the most widely accepted currently, were examined in this study.

D'Amico defines low-risk patients as having disease stage T1c, 2a, PSA level ≤10 ng/ml and GS ≤6; intermediate-risk as T2b or GS 7 or PSA level >10 and ≤20 ng/ml; and high-risk as T2c or PSA level >20 ng/ml or GS ≥8 (7).

The NCCN defines recurrence risk as follows: low: T1-T2a and GS 2-6 and PSA <10 ng/ml; intermediate: T2b-T2c or GS 7 or PSA 10-20 ng/ml; high: T3a or GS 8-10 or PSA >20 ng/ml (8); and very high: T3–T4 (9).

The Seattle group defines risk categories as follows: low: PSA ≤10 ng/ml, GS <7, and stage <T2c; intermediate: PSA >10 ng/ml or GS ≥7 or stage ≥T2c (one intermediate risk factor); and high: two or more intermediate risk factors (10). Table II shows the patient distribution by each risk classifications.

Statistical analysis. All statistical analyses were performed using Statview 5.0 (SAS Institute, Inc., Cary, NC, USA) and IBM SPSS statistics 20 software (IBM, Armonk, NY, USA). Frequencies were analyzed using the χ^2 test. Means were compared using Student's *t*-test for normally-distributed data and the Mann–Whitney *U*-test for skewed data. Survival data and cumulative incidences were estimated by the Kaplan–Meier method and examined for significance using the log-rank test. The 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

All ISBT was finished without skipping treatment sessions or reducing planned doses. The 5-year PSA control rate was 94%. No PSA failure was found among low-risk patients by any risk classification system. Nine PSA failures occurred

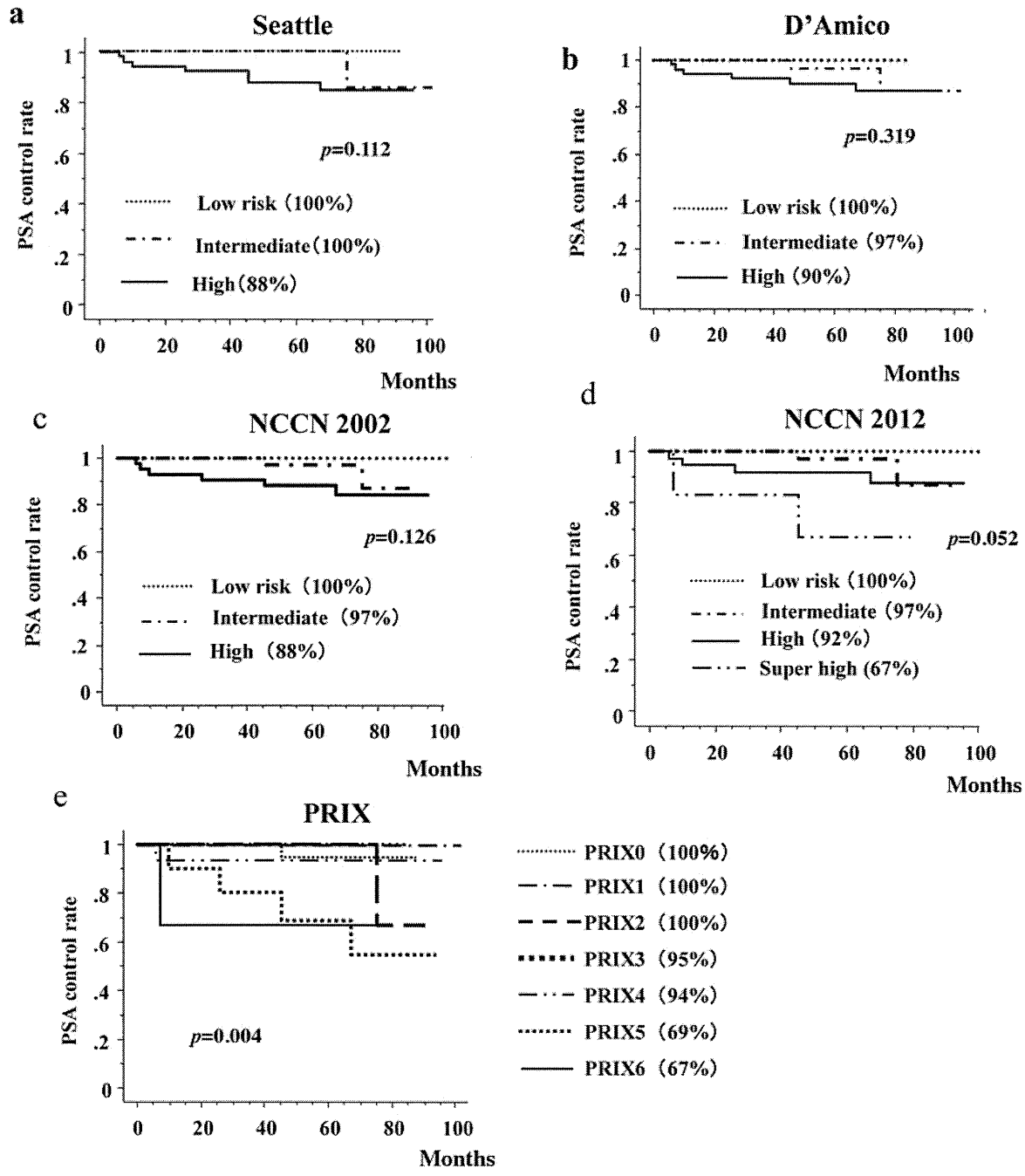

Figure 1. *PSA control rates according to Seattle (a), D'Amico (b), NCCN 2002 (c) NCCN 2012 (d) and PRIX (e) risk classification systems. Five-year PSA control rates are given in parentheses. PRIX separated the risks statistically significantly (p=0.004), while the D'Amico (p=0.319), NCCN 2002 (p=0.126), NCCN 2012 (p=0.052) and Seattle (p=0.112) risk classifications failed to show statistically significant separation.*

and seven of those were observed within 48 months. The 5-year biochemical control rate was 100%, 93% and 82% for T1-2a, T2b and 2c and T3-4 (p=0.015). The 5-year biochemical control rate was 100%, 95% and 78% for Gleason score <7, 7 and >7, respectively (p=0.037). The 5-year biochemical control rate was 100%, 90% and 90% for PSA<10, PSA=10-20 and PSA >20 ng/ml (p=0.074). The 5-year biochemical control rate was 100%, 100%, 100% , 95%, 94%, 69% and 67% for PRIX 0-6 (Figure 1, p=0.004), whereas the other risk classification systems (D'Amico:

p=0.319, NCCN 2002: p=0.126, NCCN 2012: p=0.052 and Seattle: p=0.112 classifications failed to show a statistically significant separation.

The 5-year overall survival rate was 98%; six patients died 40 to 76 months after HDR-ISBT. Only one patient was dead due to prostate cancer. The other five patients died due to concurrent disease (second cancer: 4, brain vascular disease: 1).

Grade 2 late gastrointestinal complications (rectal bleeding) occurred in two patients (2%). No grade 3 or more late gastrointestinal complication was observed.

Discussion

Until recently, HDR-ISBT as monotherapy was mainly used for low-intermediate risk patients (1, 2). The Osaka University Group initiated clinical investigation to expand eligibility criteria to all risk groups in 1995 (4). The recent treatment results (5-year PSA control rates) were 85%, 93% and 79% for low-, intermediate- and high-risk patients (NCCN 2002) (3) data which concur with our data.

Several other groups also reported good outcomes. Challapalli *et al.* reviewed the treatment results of combined HDR-ISBT and external-beam radiotherapy and showed that 4-10 year biochemical control rates were 82-100% for low-intermediate risk and 62-97% for high-risk patients (NCCN 2002) (11). Zamboglou *et al.* investigated HDR-ISBT monotherapy in over 700 patients and obtained 5-year biochemical control rate 95%, 95% and 93% for low-risk, intermediate-risk and high-risk groups (D'Amico) (12). Therefore, HDR brachytherapy is now one of the highly curative potential treatments, not only for low- and intermediate-risk patients, but also for high-risk patients. In addition, some phase III trials demonstrated that neoadjuvant or adjuvant hormone therapy for 'locally advanced prostate cancer' is associated with a significant improvement in cause-specific survival or overall survival, compared to radiotherapy alone (13-15). The definitions of 'locally advanced prostate cancer' in these trials are different. We should decide which patients really benefit from the addition of hormone therapy or intensive treatment such as HDR-ISBT, in future experimental clinical trials. PRIX may contribute to finding more consistent answers by specifying that patients with, for example, a given PRIX or greater would benefit, and others not (6).

However, several limitations remain. Firstly, this was a retrospective single-Institute analysis dealing with a rather small number of patients. To confirm reliability and potential for PRIX, longer follow-up with a larger number of patients is required before reaching concrete conclusions.

In conclusion, PRIX is a useful risk classification system after HDR-ISBT as monotherapy for prostate cancer patients.

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Longitudinal Analysis of Late Vaginal Mucosal Reactions After High-dose-rate Brachytherapy in Patients with Gynecological Cancer

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Abstract. *Aim: To longitudinally examine the late vaginal mucosal reactions in patients following high-dose-rate brachytherapy (BT). Patients and Methods: We examined late vaginal mucosal reactions in 100 patients using the modified Dische score at 6, 12, 18, 24, 36, and 60 months after treatment, which consisted of 37 interstitial BTs and 63 conventional intracavitary BTs, with a median follow-up of 41 months (range=6-144 months). Results: There were no cases of lethal toxicity or severe toxicity requiring surgery. Bleeding or discharge grade 1 or more was exhibited by fewer than 2-4% of patients, and in most cases only until 1.5 years following treatment. Erythema was detected in approximately 30% (mainly grade 1) of the patients up to five years. With regard to ulceration, four patients (7%) developed superficial ulceration; however, no patient had ulceration lasting six months or longer. Telangiectasia increased gradually over time in approximately 91% of patients (grades 1 and 2=73% and 18%, respectively) in the five years following treatment. The pallor reaction also increased over time in 100% of patients (grades 1, 2, and 3=30%, 48%, and 22%, respectively) in the five years after treatment. Stenosis also increased with time in approximately 97% of patients (grades 1, 2, and 3=29%, 61%, and 7%, respectively) over five years. There was a close correlation between pallor reaction and stenosis. Conclusion: High-dose-rate BT caused mild-to-moderate toxicities. Almost all patients showed pallor reaction, telangiectasia, and stenosis up to five years after treatment, and pallor reaction correlated with stenosis.*

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Key Words: Brachytherapy, gynecological cancer, high dose rate, late vaginal mucosal reaction.

Radiotherapy plays an important role in the management of gynecological cancer. Because vaginal mucosa is located adjacent to the tumor lesion, doses nearly as high as the prescribed dose are irradiated to the proximal vagina. Fortunately, the vaginal mucosa is reasonably tolerant to radiation, and severe adverse grade 3 reactions or higher are rarely reported (1). However, late injuries to the vagina should not be ignored because they may potentially be serious complications resulting from radiotherapy of gynecological cancer (2). Furthermore, mild-to-moderate toxicity (grade 1 or 2) analyses are often poorly- and ambiguously-reported in the literature. Several scoring systems, such as those of the Radiation Therapy Oncology Group (RTOG) and the French–Italian glossary of complications, have been introduced, but no standard system has been yet established (3). We have introduced a modified Dische scoring system and validated its usefulness (4). However, although we reported the maximum reaction scores, we did not present longitudinal data. In the quality-of-life (QOL) analysis, some authors suggest that longitudinal data are important because toxicity is otherwise negligible and because they provide valuable information not only for the physician but also for the patient (5). Therefore the purpose of the present study was to present the longitudinal outcomes of late vaginal sequelae observed in patients after high-dose-rate brachytherapy (HDR-BT).

Patients and Methods

We retrospectively examined 100 patients with gynecological cancer (median age=61 years; range=33-88 years) who were treated between 1993 and 2011. The patient characteristics are listed in

Table I. Out of the 100 patients, 90 were diagnosed with cervical cancer (79 newly-diagnosed, 11 recurrent), six with endometrial cancer, one with ovarian cancer, and three with vaginal cancer. The data of 63 patients after intracavitary BT and 37 patients after interstitial BT were collected. The median follow-up was 41 months (range=6-144 months). The intracavitary BT group included only patients with newly diagnosed cervical cancer, whereas the interstitial BT group included 17 patients with recurrent cancer (including one of ovarian cancer that recurred at the distal vagina) and 20 with newly diagnosed cancer.

According to previously reported methods, intra-cavitary BT was performed with a combination of external radiotherapy (6). In brief, 30 Gy in 2-Gy fractions (0-50.4; 0 Gy for two patients with stage Ib; 1.8-2 Gy fractionations) of external irradiation was administered to the entire pelvic field (WP), and 20 Gy (10-40 Gy; 40 Gy for stage Ib) to the center-shielded field (CS; entire pelvis plus midline block). Source loading corresponded to the Manchester system for cervical cancer. Furthermore, an average of 30 Gy (range=16.5-47 Gy) was administered to a patient in intracavitary BT on an average of four (range=2-5 Gy fractions) fractions once a week over an average time period of four (range=2-5) weeks. Interstitial BT for previously untreated cervical cancer was administered at 30-36 Gy (6 Gy per fraction, twice per day) combined with external beam radiotherapy (7). They received a median prescribed dose of 30 Gy (range=0-50 Gy; 0 Gy for two patients aged ≥80 years) to the WP and 20 Gy (range=0-30 Gy) to the CS. We performed interstitial BT between the WP and CS. HDR-interstitial BT for patients with recurrent tumors was performed using a range of 42-51 Gy/7-8 fractions over 2-5 days (twice per day) without external irradiation for re-irradiation cases. The eligibility criteria for undergoing interstitial BT were determined on the basis of the recommendations of the American Brachytherapy Society (bulky lesion, narrow vagina, inability to enter the cervical os, extension to the lateral parametrium or pelvic side wall, and lower vaginal extension) (8). The treatment planning was performed using the planning system PLATO (software version 14.2; Nucletron, Veenendaal, the Netherlands) with manual modification after computer optimization. For recurrent cancer and clinical treatment volume (CTV)-based dose prescription, the PLATO planning system was used with manual modification to cover the CTV by the 100% isodose line on each slice after computer optimization using a geometrical optimization algorithm (9). We used microSelectron-HDR (Elekta Ab, Stockholm, Sweden) with ^{192}iridium as the treatment source for BT. All patients received the prescribed doses or more (BT and WP doses) with the proximal vagina (4). We assessed at 6, 12, and, 18 months and 2, 3, and 5 years after radiotherapy using modified Dische score (4). These assessments were conducted by the same physician (KY) throughout the examination period and were later confirmed by another physician (HY) including a photograph assessment.

Concurrent or neoadjuvant chemotherapy were administered to 39 patients (27 intracavitary BT and 12 interstitial BT). Chemotherapy consisted of the following: cisplatin in 23, carboplatin in one, pepleomycin, ifomide, and cisplatin in four, paclitaxel, ifosfamide, and cisplatin in four, and intra-arterial infusion (cisplatin plus mytomycin C) in seven.

For statistical analyses, Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for skewed data were used. The percentages were analyzed using the chi-square test. Results with $p<0.05$ were considered statistically significant (two-sided).

Table I. *Patients' characteristics.*

Variables	Strata	
Age, years	Median (range)	65 (33-88)
Disease	Cervix	90
	Endometrial	6
	Ovary	1
	Vagina	3
Modality	ICBT	63 new case
	ISBT	20 new +17 rec
Histology	Adenocarcinoma	15
	Squamous cell carcinoma	85
T Category		
Cervix	0	2
	1a	0
	1b	5
	2a	6
	2b	28
	3a	6
	3b	42
	4a	1
Endometrium	2a	1
	2b	1
	3b	2
Ovary	1	1
Vagina	2	1
	3	2

ICBT; Intracavitary brachytherapy, ISBT; interstitial brachytherapy.

Results

There were no cases of lethal toxicity or severe toxicity requiring for surgery. Results from the bleeding and discharge analyses are shown in Table II. The assessments of bleeding (type and severity) and discharge (frequency and type) showed that fewer than 5% of patients experienced grade 1 reactions, without any reactions of greater severity, until 1.5 years after BT, except one patient with mild grade 1 bleeding seen after five years. Table III shows the results from the assessments of erythema, ulcer, telangiectasia, stenosis, and pallor score. Erythema was observed in approximately 30% of patients (mainly grade 1, only 4-5% with grade 2) after BT, which peaked at three years and gradually improved over time. Ulceration was relatively rare, and 7% of patients exhibited superficial ulceration after BT. Only one patient had grade 2 ulceration; however, none had ulcerations lasting six months or more. The frequencies of telangiectasias, pallor reactions, and stenosis reactions

Table II. *Results of assessment for late vaginal reactions: bleeding and discharge.*

(a) Bleeding Type

Grade	0	1
6M	87 (98%)	2 (2%)
12M	78 (98%)	2 (3%)
1.5Y	54 (98%)	1 (2%)
2Y	56 (100%)	0
3Y	38 (100%)	0
5Y	30 (100%)	0

(b) Bleeding Severity

Grade	0	1
6M	87 (96%)	4 (4%)
12M	78 (98%)	2 (3%)
1.5Y	53 (96%)	2 (4%)
2Y	55 (96%)	2 (4%)
3Y	38 (100%)	0
5Y	29 (97%)	1 (4%)

(C) Discharge Frequency

Grade	0	1
6M	86 (97%)	3 (3%)
12M	78 (100%)	0
1.5Y	54 (98%)	1 (2%)
2Y	57 (100%)	0
3Y	38 (100%)	0
5Y	30 (100%)	0

(d) Discharge Type

Grade	0	1
6M	86 (97%)	3 (3%)
12M	79 (99%)	1 (1%)
1.5Y	54 (98%)	1 (2%)
2Y	57 (100%)	0
3Y	38 (100%)	0
5Y	30 (100%)	0

increased gradually up until five years after BT, and nearly all patients experienced grade 1 or more reactions. Telangiectasia increased gradually over time in approximately 91% of patients (grades 1 and 2 at 73% and 18%, respectively) five years after BT. The pallor reaction also increased over time in approximately 100% of patients (grades 1, 2, and 3=32%, 48%, and 20%, respectively) five years after treatment. The pale areas, defined by the distance between the external os and the pallor reaction, ranged from 2.4 to 2.7 cm (Table III). Stenosis also increased with time in approximately 97% of patients (grades 1, 2, and 3=29%,

Table III. *Results of assessment for late vaginal reactions of erythema, ulcer, telangiectasia, stenosis and pale score.*

(a) Erythema

Grade	0	1	2
6M	55 (68%)	18 (27%)	2 (3%)
12M	51 (69%)	17 (31%)	0
1.5Y	35 (69%)	10 (27%)	2 (4%)
2Y	37 (73%)	12 (24%)	2 (4%)
3Y	23 (68%)	10 (32%)	0
5Y	24 (83%)	4 (17%)	0

(b) Ulcer

Grade	0	1	2
6M	75 (99%)	1 (1%)	0
12M	67 (96%)	0 (4%)	0
1.5Y	46 (96%)	1 (2%)	0
2Y	69 (93%)	2 (5%)	0
3Y	33 (95%)	1 (3%)	0
5Y	27 (97%)	1 (3%)	0

(c) Telangiectasia

Grade	0	1	2
6M	46 (61%)	26 (35%)	4 (5%)
12M	30 (41%)	34 (54%)	4 (6%)
1.5Y	18 (38%)	26 (55%)	3 (6%)
2Y	16 (31%)	30 (60%)	4 (8%)
3Y	10 (27%)	20 (65%)	3 (9%)
5Y	3 (10%)	20 (73%)	5 (18%)

(d) Stenosis

Grade	0	1	2	3
6M	33 (43%)	37 (49%)	6 (8%)	0
12M	14 (21%)	40 (59%)	14 (21%)	0
1.5Y	6 (13%)	28 (60%)	13 (28%)	0
2Y	6 (12%)	22 (43%)	23 (45%)	0
3Y	2 (6%)	13 (38%)	18 (53%)	1 (3%)
5Y	1 (4%)	8 (29%)	17 (61%)	2 (7%)

(e) Pale score

Grade	0	1	2	3
6M	31 (42%)	32 (43%)	9 (12%)	2 (3%)
12M	7 (10%)	39 (58%)	15 (22%)	6 (9%)
1.5Y	2 (4%)	21 (45%)	16 (34%)	8 (17%)
2Y	2 (4%)	20 (40%)	24 (48%)	4 (8%)
3Y	0	12 (38%)	17 (53%)	3 (9%)
5Y	0	7 (30%)	11 (48%)	5 (22%)

d) Pale area	(cm)
6M	2.7±0.7
12M	2.8±0.4
1.5Y	2.9±0.7
2Y	2.6±1.0
3Y	2.6±0.5
5Y	2.4±0.9

Table IV. *Correlation between stenosis and pallor reaction.*

Stenosis	Pale										
	0		1		2		3		Not available		*p*-value
a) 6 months											
0	17	(52%)	14	(42%)	1	(3%)	1	(3%)			0.05
1	12	(34%)	17	(49%)	5	(14%)	1	(3%)			
2	2	(33%)	1	(17%)	3	(50%)	0				
b) 12 months											
0	4	(29%)	9	(64%)	1	(7%)	0				0.017
1	2	(5%)	25	(63%)	10	(25%)	3	(8%)			
2	1	(7%)	5	(36%)	4	(29%)	4	(29%)			
c) 1.5 years											
0	1	(17%)	4	(67%)	1	(17%)	0				0.32
1	1	(4%)	12	(43%)	11	(39%)	4	(14%)			
2	0		5	(38%)	4	(31%)	4	(31%)			
d) 2 years											
0	1	(17%)	5	(83%)	0	(0%)	0				0.01
1	1	(5%)	10	(45%)	11	(50%)	0				
2	0		5	(23%)	13	(59%)	4	(18%)			
e) 3 years											
0	0		1	(50%)	1	(50%)	0				0.0037
1	0		8	(62%)	5	(38%)	0				
2	0		3	(16%)	11	(61%)	3	(17%)	1	(6%)	
3	0		0		0		0		1	(100%)	
f) 5years											
0	0		0		1		0				0.0256
1	0		3	(43%)	3	(43%)	1	(14%)			
2	0		4	(24%)	7	(44%)	4	(25%)	1	(6%)	
3	0		0		0		0		2	(100%)	

Not available; cases impossible to assess pale reaction due to stenosis.

61%, and 7%) after five years. There were statistically significant correlations between stenosis and pallor reaction at 12 months, 2 years, 3 years and 5 years after treatment (Table IV). Grade 3 stenosis was found in two patients who had a grade 2 or 3 pallor reaction in previous examinations.

Discussion

Several authors have reported serious vaginal complications, such as mucosal necrosis or fistula formation (10, 11); however, we did not experience such severe adverse reactions, probably because of the lower irradiation dose used in Japan. The recommended dose for a T3 tumor in Japan is 30 Gy/15 fractions (WP) + 20 Gy/10 fractions (CS) + 24 Gy/4 (BT) fractions (EQD2=58 Gy, α/β=10) (12), whereas the recommended dose in the U.S. is 45 Gy/25 fractions (WP) + 30 Gy/5 (BT) fractions (EQD2=88 Gy, α/β=10) (8). Therefore the tolerance dose reported in the Western study ranged from 140 to 175 Gy for the vaginal surface dose (EQD2 of 470-640 Gy, α/β=3) (11), which is higher than our prescribed dose of 50-60 Gy (EQD2=80-90 Gy, α/β=3). In a U.S. study, Gondi *et al.* reported that the probabilities of severe late toxicity of the vagina three years after treatment were 20.2% for radiotherapy alone and 35.1% for concomitant chemoradiotherapy (1). In a U.K. study, Güth *et al.* reported that 8.2% of patients experienced severe late toxicities, including total vaginal necrosis in 3.1% (three patients) of 98 patients with cervical cancer who received chemoradiation (2). In a Japanese prospective trial, Toita *et al.* (12) did not report moderate to severe vaginal toxicity grade 2 or more using the National Cancer Institute Common Toxicity Criteria version 3.0 (6).

To date, no standard system of recording and reporting late radiation morbidity from gynecological malignancies has been

established. The The Radiation Therapy Oncology Group (RTOG)'s late-toxicity scoring system for the vagina is not detailed sufficiently with regard to vaginal stenosis and telangiectasia (3). Although the RTOG defines severe telangiectasia as grade 3 morbidity, multiple telangiectasias are less severe than grade 3. We concur with those opinions because nearly all patients who displayed telangiectasias had no serious complaints during the follow-up period. Ultimately, asymptomatic telangiectasia scored as grade 2 would cause an increase in false-positive grade 2 vaginal toxicities. In the same manner, mucosal pallor reaction does not seem to be a serious phenomenon, because few patients complained of inconvenience. On the other hand, pallor reaction and telangiectasias are phenomena related to mucosal thinning and dryness, atrophy, and/or fibrosis in patients, and pallor reaction was found to correlate with vaginal stenosis. Therefore, those mild-to-moderate toxicities may be a surrogate to severe toxicities. A study documented the decrease in vaginal length after intracavitary radiation therapy (13) in patients with cervical or endometrial cancer; the authors noted a mean vaginal shortening of 1.5 cm in patients compared to the pre-treatment values. In another study, patients were asked to document vaginal changes for one year following radiation, and 48% of the patients reported that their vaginal dimensions had decreased following radiation for cervical cancer (14). Our results were consistent with a report that 21% of patients required a smaller speculum (grade 2) after one year, and this figure increased to 61% after five years, with 7% of cases being grade 3 reactions. As those moderate toxicities may influence patients' QOL, physicians should pay attention to these high incidences of telangiectasia, pallor reaction, and stenosis in order to enhance patients' QOL. The three-dimensional dose distribution scheme for conventional intracavitary BT. The distance between the external os and the 100% prescribed dose area was ~2.8 cm, and we speculated that the pallor reaction appeared within at least the area irradiated by the prescribed dose. To the best of our knowledge, this is the first study to present the longitudinal frequencies and characteristics of mild-to-moderate toxicities after HDR-BT.

There are several limitations to our study. Firstly, this was a single. Institutional retrospective analysis of a relatively small number of patients with a limited follow-up period. A larger number of patients with longer follow-up and preferably in a prospective fashion is required for more concrete conclusions. Secondly, three-dimensional meticulous assessment using dose volume histogram analysis is required in this modern radiotherapy era, as proposed by Fidarova *et al.* (15). Because we used our conventional two-dimensional treatment plan until 2008, it is difficult to draw dose–volume histogram data. However, it is warranted for future assessments.

In conclusion, HBR–BT caused mild-to-moderate toxicities. Almost all patients showed pallor reaction, telangiectasia, and stenosis. Pallor reaction correlated with stenosis.

Conflicts of Interest

None.

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Hypofractionated Stereotactic Radiotherapy Using CyberKnife as a Boost Treatment for Head and Neck Cancer, a Multi-institutional Survey: Impact of Planning Target Volume

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Abstract. *Aim: To evaluate the role of hypofractionated stereotactic radiotherapy (hSRT) as a boost treatment for head and neck cancer. Patients and Methods: We conducted a multi-institutional retrospective review for the outcome of boost irradiation using CyberKnife for head and neck cancer patients from the charts of four Institutes. Twenty-five patients were treated with hSRT boost for primary site with a median follow-up of 28 months. Treatment sites were 11 nasopharynx, 7 oropharynx, one hypopharynx, 3 nasal cavity or paranasal sinus and three oral cancers. All patients underwent preceding conventional radiotherapy of 35 to 72 Gy (median, 50 Gy) in 1.2- to 2Gy-fractions. The dose and fractionation scheme of the Cyberknife SRT boost was individualized and the prescribed dose ranged from 12 Gy to 35 Gy in 1 to 5 fractions (median, 15 Gy in 3 fractions). Results: There were 18 complete responses, 6 partial responses and one progressive disease, resulting in 96% (24/25) response rate. Local control (LC) rates at 2- and 5-years were 89% and 71%, respectively. Progression-free survival (PFS) and overall survival (OS) at 2- and 5-years were 70%/ 83% and 70%/ 70%, respectively. Planning target volume (PTV) at boost treatment planning and initial response were predisposing factors for PFS and OS. Patients with PTV ≤20 cm^3 showed better PFS (92%) and OS (100%) than those with a PTV > 20 cm^3 (PFS, 61% and OS, 47%). Good initial response predicts better outcome in LC, PFS and OS. Conclusion: The results of the present study showed potential benefits of the CyberKnife hSRT boost. Smaller PTV and good initial response predict good outcome.*

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External-beam radiotherapy with or without concurrent chemotherapy is generally considered a standard treatment method for head and neck cancer (1). However, close proximity of several critical organs, such as optic pathways, brain stem and spinal cord, sometimes limit high-dose delivery from conventional radiotherapy techniques. Recently, development of the image-guided stereotactic radiotherapy devices make it possible to deliver highly conformal radiotherapy for head and neck cancers, as is the case in central nervous system tumors (2, 3). The CyberKnife system was specifically developed to perform frameless stereotactic radiosurgery for intracranial lesions and the technique can now be applied to deliver conformal doses of radiation to tumors throughout the entire body including the head and neck region (2, 3). Although the effects of normal tissue sparing can theoretically allow the use of hypofractionation, necessity of therapeutic and prophylactic nodal irradiation make it difficult to use large dose per fractionation for relatively large target volume in the head and neck region. Thus, at first, hypofractionated stereotactic radiotherapy (hSRT) is mainly used for salvage treatment of locally-recurrent tumors (4). It has been

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