Original paper

Correlations of post-implant regional dosimetric parameters at 24 hours and one month, with clinical results of low-dose-rate brachytherapy for localized prostate cancer

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Abstract

Purpose: To evaluate the correlations of post-implant regional dosimetrics at 24 hours (24 h) and 1 month after implant procedures, with clinical outcomes of low-dose-rate (LDR) brachytherapy for localized prostate cancer.

Material and methods: Between January 2008 and December 2014, 130 consecutive patients treated for localized prostate cancer, receiving definitive iodine-125 (^{125}I) brachytherapy treatment were retrospectively analyzed. All patients underwent post-implant CT imaging for dosimetric analysis at 24 h and 1 month after implantation procedure. Prostate contours were divided into quadrants: anterior-superior (ASQ), posterior-superior (PSQ), anterior-inferior (AIQ), and posterior-inferior (PIQ). Predictive factors and cut-off values of biochemical failure-free survival (BFFS) and toxicities of LDR brachytherapy were analyzed.

Results: The median follow-up time was 69.5 months. Seven patients (5.4%) had biochemical failure. The 3-year and 5-year BFFS rates were 96.7% and 93.1%, respectively. On multivariate analysis, prostate-specific antigen and Gleason score were significant prognostic factors for biochemical failure. D_{90} (the minimal dose received by 90% of the volume) of PSQ and PIQ at 24 h, and D_{90} of PSQ at 1 month were also significant factors. The cut-off values of PSQ D_{90} were 145 Gy at 24 h and 160 Gy at 1 month. D_{90} of the whole prostate was not significant at 24 h and at 1 month. D_{90} of PSQ at 1 month was a significant factor for rectal hemorrhage.

Conclusions: Post-implant D_{90} of PSQ is significantly associated with BFFS for localized prostate cancer not only at 1 month, but also at 24 hours. D_{90} of PSQ at 1 month is also a significant factor for rectal hemorrhage.

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Key words: brachytherapy, low-dose-rate, prostate cancer, seeds.

Purpose

Prostate cancer is one of the most common malignancies in men and a major cause of cancer death [1]. Prostate-specific antigen (PSA) screening enables the detection of early and localized prostate cancer. There are many therapeutic options for patients with localized prostate cancer, including androgen deprivation therapy (ADT), radical prostatectomy, external beam radiation therapy, and brachytherapy. Permanent seed brachytherapy, also known as low-dose-rate (LDR) brachytherapy, allows for a higher dose of radiation to the prostate with a steep dose gradient to surrounding normal tissues. Previous reviews have shown that outcomes with brachytherapy for localized prostate cancer are comparable to those with other therapeutic modalities, including radical prostatectomy and external beam radiation therapy [2,3,4]. Furthermore, brachytherapy is less invasive than surgery and can be performed in a shorter period than external beam radiation therapy.

The implant quality of LDR brachytherapy can be assessed by performing a dosimetric evaluation based on post-implant computed tomography (CT) and/or magnetic

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resonance imaging (MRI) [5,6], and dosimetric parameters such as D90 (the minimum dose received by 90% of the volume) and V100 (the percentage of the volume receiving 100% of prescribed dose) of the whole prostate are mainly used for analysis [5]. Several reports have shown that these dosimetric parameters are significant factors in predicting biochemical failure [7,8,9,10,11], although there is a controversy about the usefulness of the dosimetric parameters in predicting biochemical failure [12,13,14]. Many of these reports have mentioned dosimetric parameters of the whole prostate, and there is a small number of reports evaluating dose distribution in different regions of the prostate [15,16,17,18,19]. It is known that there are dose deviations from prescribed dose in different regions of the prostate; in particular, the anterior and basal regions tend to be underdosed compared to other regions [17,20]. There are few reports assessing the relationships between regional dose distribution of the prostate and therapeutic outcomes, including biochemical failure and radiation toxicities [19, 20].

The optimal timing for obtaining post-implant CT and/or MRI also remains a debated issue. Prostatic edema arises in the first 24 h after implantation, and post-implant imaging obtained within 24 h results in lower calculated doses [6,21]. Some studies suggest an interval of 2 to 6 weeks after implantation for the effect of prostatic edema to decrease [22,23], while other reports recommends dosimetric evaluation within 24 h, because this allows for immediate correction of a dose deficiency, if necessary [24,25,26]. To the best of our knowledge, there have been no reports about the correlations between therapeutic outcomes and regional dosimetry of the prostate using images obtained at 24 h after the procedure.

The purposes of this study were to evaluate the correlations between post-implant regional dosimetrics and the outcomes of LDR brachytherapy, and to assess the effectiveness of post-implant CT obtained early, at 24 hours, compared with that obtained later, at 1 month after implantation.

Material and methods

Patients' characteristics

This study was approved by institutional review board, and was conducted in accordance with the principles of the Declaration of Helsinki. From January 2008 to December 2014, outcome data of consecutive patients treated with LDR brachytherapy for localized prostate cancer at Osaka City University Hospital were retrospectively analyzed. Patients were staged according to the guidelines of the American Joint Committee on Cancer, and they were classified into prognostic risk groups according to the National Comprehensive Cancer Network (NCCN: www.nccn.org) guidelines. Low- and intermediate-risk patients who received LDR brachytherapy as monotherapy were included in this study. Patients treated with combined external beam radiation therapy or those who missed the post-implant CT examination were excluded. Neoadjuvant ADT was generally administered to patients with prostate volumes > 40 cc to reduce the volumes.

Pre-implant planning

MRI-based pre-implant volume studies were performed with a patient in supine position using 1.5T Avanto scanner (Siemens Medical Solutions, Erlangen, Germany) at a median of 7 weeks (range, 2-42 weeks) before implantation. T2-weighted 3D MR images of 2.5 mm thickness were imported into the treatment planning system (TPS). Through March 2014, an Interplant (version 3.4.0, Computerized Medical Systems, Champaign, IL, USA) TPS was used for pre-implant and real-time planning, and from April 2014, an Oncentra (version 4.2.2, Nucletron, Veenendaal, The Netherlands) TPS was used. The dosimetry of pre-implant planning aimed for a prostate V100 of > 95%, a prostate D90 of > 110% and < 130% of the prescribed dose, a prostate V150 (the volume receiving 150% of the prescribed dose) of < 60%, a urethral D30 (the minimum dose received by 30% of the volume) of < 150%, and a rectal V100 of < 0.2 cc.

Implant procedure

The implant procedure was performed under spinal anesthesia in dorsal lithotomy position. For all patients, iodine-125-free seeds (BARD, BrachySource model, Covington, GA, USA) with an apparent activity of 0.342 mCi and an air kerma strength of 0.432 U (μGym^2h^{-1}) were used, and the prescribed brachytherapy dose was 145 Gy. The seeds were implanted transperineally with a Mick applicator (Mick Radio-Nuclear Instruments, New York, NY, USA) using real-time transrectal ultrasonography. A modified peripheral loading technique was used to deliver the dose to the prostate, avoiding placement of seeds close to the urethra [27]. Dose-volume constraints for the prostate, urethra, and rectum were the same as the pre-implant planning.

Post-implant dosimetry

Post-implant axial CT images of the pelvis with the patient in supine position using an Asteion (Toshiba Medical Systems, Tokyo, Japan) at 2.0 mm thickness were taken 24 h and 1 month (median, 34 days) after the implant procedure. Post-implant dosimetry was re-analyzed with Oncentra TPS, including what was previously calculated with Interplant (before April 2014) by a single radiation oncologist (EO). To mitigate the influence of metal artifacts of the seeds and variation of contouring related practitioner on CT images, CT-MRI image fusion for delineation of volumes was done for all patients on Oncentra TPS, using MRI images obtained at pre-implant volume studies. The prostate volume was divided into four quadrants: anterior-superior quadrant (ASQ), posterior-superior quadrant (PSQ), anterior-inferior quadrant (AIQ), and posterior-inferior quadrant (PIQ). The superior-inferior and anterior-posterior segments were divided by the midpoint of the prostate on reconstructed images (Figure 1).

Patient follow-up

The date of implantation was considered day 0 for the analysis of follow-up duration. Patients were assessed every 2 or 3 months during the first to third year, and every

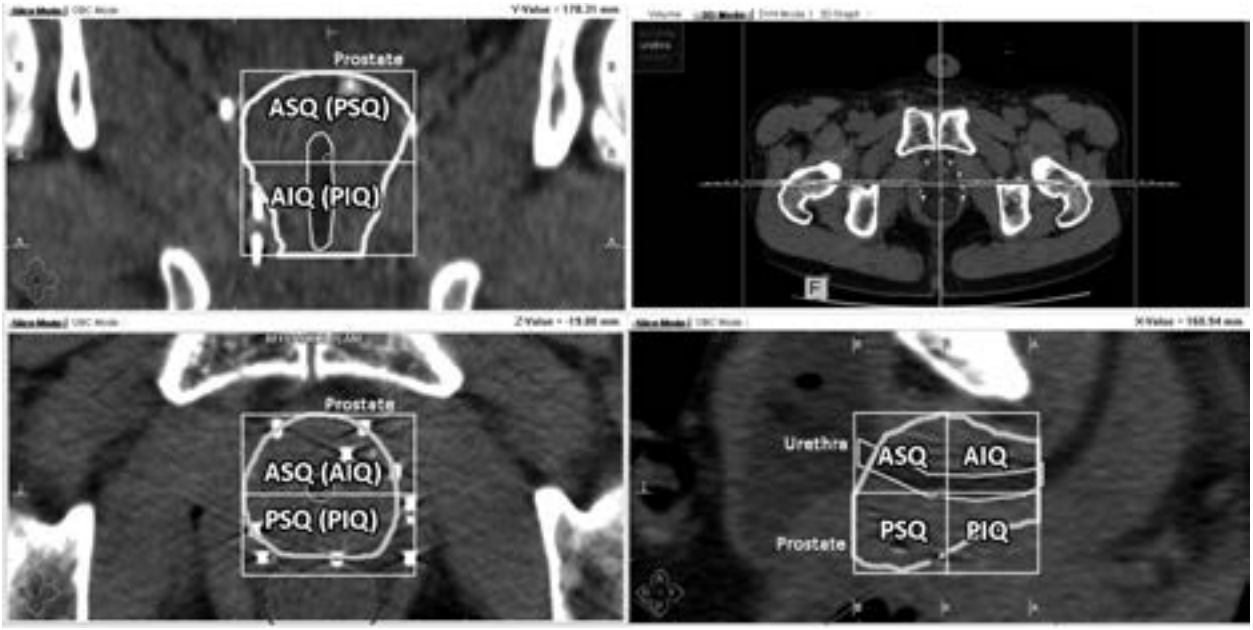

Fig. 1. Separation of the prostate into four quadrants

ASQ – anterior-superior quadrant, PSQ – posterior-superior quadrant, AIQ – anterior-inferior quadrant, PIQ – posterior-inferior quadrant

3 to 6 months at 3-10 years after brachytherapy. During clinical follow-up visits, serum PSA levels and toxicity data were collected. Biochemical failure was determined according to the Phoenix definition [28]. Genitourinary (GU) and gastrointestinal (GI) toxicities were documented using the Common Terminology Criteria for Adverse Events version 4.0. Acute toxicity was defined as that occurring within the first 12 months after implantation, and late toxicity was defined as that developing after 12 months.

Statistical analyses

Statistical analysis was performed to compare continuous variables using paired or unpaired *t*-tests and one-way ANOVA with Tukey's honest significant difference (HSD) for post-hoc testing. Univariate and multivariate analyses were performed using Cox proportional hazards models with corresponding 95% confidence intervals. Variables with a p value < 0.2 on univariate analyses were incorporated into multivariate analysis. To avoid multicollinearity, univariate and multivariate analyses were performed separately by the post-implant dosimetric parameters at 24 h or 1 month. Coordinate points of a receiver operating characteristic (ROC) curve were used to identify significant dosimetric parameters for predicting biochemical failure and toxicities. Survival curves were estimated using Kaplan-Meier method to determine biochemical failure-free survival (BFFS), and the log-rank test was used to evaluate differences between groups. Statistical analyses were performed using R environment (version 3.2.2) available from http://www.R-project.org.

Results

From January 2008 to December 2014, 132 consecutive patients with low- and intermediate-risk prostate cancer underwent LDR brachytherapy as monotherapy at our institution. Two patients were excluded for not undergoing post-implant CT, and a total of 130 patients were eligible for this study. Median age was 69 years (range, 42-82 years), and median follow-up time was 69.5 months (range, 10.6-112.9 months). Patients' characteristics are listed in Table 1. Sixty patients received neoadjuvant ADT approximately 3-6 months before brachytherapy (34 patients with luteinizing hormone-releasing hormone agonist, 18 with maximum androgen blockade, and 8 with anti-androgen). No deaths occurred during the follow-up period. Seven patients (5.4%) had biochemical failure. The 3-year and 5-year BFFS rates for all patients were 96.7% and 93.1%, respectively. The 5-year BFFS rates for low- and intermediate-risk patients were 97.5% and 88.5%, respectively (p = 0.087 with log-rank test).

Dosimetric analysis

Post-implant dosimetric data are shown in Table 2A and 2B. The prostate D90 at 1 month was significantly higher than that at 24 h for all quadrants (p < 0.001 for all quadrants). D90 of each quadrant at 24 h were strongly correlated with those at 1month (r = 0.63-0.71, and p < 0.001 for all with Pearson's correlation). With multiple comparisons of dosimetric parameters for each quadrant, D90 of PIQ was significantly lower than that of the other quadrants at 24 h (p < 0.001 with Tukey HSD). At 1 month, D90 of ASQ was significantly lower than that of the other quadrants, and D90 of AIQ was significantly higher than that of the others (p < 0.001).

Dosimetry and therapeutic outcomes

The results of univariate and multivariate analyses of prognostic factors for predicting biochemical failure at 24 h and 1 month are shown in Table 3A and 3B, respec-

Table 1. Patients' characteristics

Variable	*n* (%)
Age (years)	
Median	69
Range	42-82
Pretreatment PSA (ng/ml)	
Median	6.6
Range	3.6-15.1
Gleason score	
≤ 6	97 (74.6)
7	33 (25.4)
Clinical T stage	
T1c	64 (49.2)
T2a	48 (36.9)
T2b	8 (6.2)
T2c	10 (7.7)
NCCN risk group	
Low	68 (52.3)
Intermediate	62 (47.7)
Neoadjuvant ADT	
No	70 (53.8)
Yes	60 (46.2)
Pre-implant MRI prostate volume (cc)	
Median	23.2
Range	8.0-68.7
Number of seeds	
Median	67
Range	43-100
Follow-up (months)	
Median	69.5
Range	10.6-112.9

PSA – prostate specific antigen, NCCN – National Comprehensive Cancer Network, ADT – androgen deprivation therapy, MRI – magnetic resonance imaging

tively. On multivariate analysis, PSA and Gleason score were significant prognostic factors for biochemical failure, while T stage and risk group were not significant, both at 24 hours and at 1 month. For dosimetric parameters, D90 of PSQ (PSQ $D90_{24h}$), PIQ at 24 hours, and D90 of PSQ at 1 month (PSQ $D90_{1m}$) were significant factors on multivariate analysis (p = 0.002, 0.048, and 0.014, respectively), while D90 of the whole prostate was not significant (p = 0.15 at 24 h and 0.77 at 1 month, respectively). D90 of PSQ was a significant prognostic factor in both analyses at 24 hours and 1 month. Therefore, a ROC analysis to identify the best cut-off value of PSQ D90 was performed. The cut-off values of PSQ D90 were 101.7% (area under the curve [AUC] = 0.80, sensitivity = 100%, specificity = 72.4%) at 24 hours, and 112.3% (AUC = 0.74, sensitivity = 85.7%, specificity = 65.9%) at 1 month. These cut-off values of PSQ D90 was simplified as 145 Gy (100.0%) at 24 h, and 160 Gy (110.3%) at 1 month. Kaplan-Meier Curves with these cut-off values of PSQ D90 are shown in Figures 2a and 2b, and the log-rank tests of these curves were significant (145 Gy at 24 h: p = 0.033; 160 Gy at 1 month: p = 0.037).

No grade 3 acute and chronic GU toxicity was observed. Twenty-nine patients (22.3%) experienced late grade 2 GU toxicities (mainly urinary urgency and retention). During the follow-up period, 20 patients (15.4%) experienced at least one episode of hematuria (median, 36.6 months; range, 2.6-75.4 months). There was no significant relationship between an episode of hematuria and post-implant dosimetric parameters. No grade 3 acute GI toxicity was observed. Eight patients (6.0%) experienced rectal hemorrhage (median, 17.1 months; range, 10.3-38.7 months). One patient received argon plasma coagulation. Comparing dosimetric parameters between patients who experienced rectal hemorrhage and others, there were significant differences in PSQ $D90_{1m}$ (137.1% [198.8 Gy] vs. 117.8% [170.8 Gy], p = 0.037), and V100 of the rectum at 24 hours (0.64 cc vs. 0.31 cc, p = 0.038) and at 1 month (1.51 cc vs. 0.83 cc, p = 0.008) with the t-test. Cut-off values of each parameter on ROC curve analysis were 134.4% (194.9 Gy, AUC = 0.69, sensitivity = 71.4%, specificity = 76.2%) for PSQ $D90_{1m}$, 0.88 cc (AUC = 0.64, sensitivity = 50.0%, specificity = 90.2%) for rectal V100 at 24 h, and 1.36 cc (AUC = 0.75, sensitivity = 71.4%, specificity = 80.3%) for rectal V100 at 1 month. Kaplan-Meier curve for the cumulative risk of rectal hemorrhage with a simplified cut-off value of PSQ $D90_{1m}$ (195 Gy) and rectal V100 at 1 month are shown in Figures 3a and 3b (p = 0.016 and 0.048 with the log-rank test, respectively). Unlike PSQ $D90_{1m}$, PSQ $D90_{24h}$ was not a significant factor for rectal hemorrhage (p = 0.33).

Discussion

The results of this study indicate that there is a significant relationship between D90 of PSQ and BFFS, and this correlation is significant not only at 1 month after the implant procedure, but also at 24 h. D90 of PSQ is also correlated with rectal hemorrhage as a late complication of brachytherapy.

In this study, D90 of PSQ was found to be a significant predictive factor of BFFS, and D90 of the whole prostate was not significant at 24 h and 1 month. In a cohort of consecutive patients, Spadinger *et al.* [19,20] confirmed that the dosimetrics of the whole prostate did not predict BFFS, and that dosimetrics of AIQ were predictors on multivariate analysis. The difference by prostatic region, PSQ, or AIQ can be affected by the different methods of prostate separation. The process of dividing the superior and inferior segments was the same in the present study, but the processes of dividing the anterior and posterior

Table 2A. Post-implant dosimetric data for the prostate, urethra, and rectum (24 h and 1 month)

		Prostate				Urethra		Rectum
		Volume (cc)	D_{90} (%)	V_{100} (%)	V_{150} (%)	D_{30} (%)	V_{150} (%)	V_{100} (cc)
24 h	Median	28.4	99.1	89.3	44.7	124.5	0	0.18
	Range	11.9-51.7	52.9-125.2	62-98.8	19.8-76.8	93.4-191.3	0-75.43	0-0.24
1 month	Median	22.1	112.6	94.6	67.4	159.0	43.9	0.75
	Range	9.6-46.7	66.4-163.2	74.0-100	29.8-99.8	113.2-250	0-81.5	0-3.5

D_{90} – minimal dose received by 90% of volume, V_{100} – volume receiving 100% of prescribed dose, V_{150} – volume receiving 150% of prescribed dose, D_{30} – minimal dose received by 30% of volume

Table 2B. Post-implant dosimetric data for the quadrants of prostate (24 h and 1 month)

		Prostate			
		ASQ D_{90} (%)	PSQ D_{90} (%)	AIQ D_{90} (%)	PIQ D_{90} (%)
24 h	Median	100.1	111.4	106.7	92.7
	Range	54.3-191.7	50.4-145.3	39.3-165.4	38.9-147.5
1 month	Median	107.4	118.5	133.4	120.2
	Range	50.4-181.8	56.6-184.7	72.4-195.7	61.4-186.6

D_{90} – minimal dose received by 90% of volume, ASQ – anterior-superior quadrant, PSQ – posterior-superior quadrant, AIQ – anterior-inferior quadrant, PIQ – posterior-inferior quadrant

Table 3A. Univariate and multivariate analyses of prognostic factors using variables obtained from post-implant CT at 24 h

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	0.977	0.881-1.084	0.67			
PSA	1.287	1.015-1.633	0.037	1.638	1.159-2.315	0.005
Gleason score (≤ 6 vs. 7)	4.492	1.003-20.12	0.050	39.080	3.264-467.800	0.004
T stage (T1 vs. T2)	0.751	0.168-3.357	0.71			
Risk group (low vs. intermediate)	0.158	0.019-1.311	0.087	0.433	0.017-11.010	0.61
Neoadjuvant ADT (no vs. yes)	2.244	0.434-11.62	0.34			
Number of seeds	0.963	0.907-1.023	0.22			
Prostate volume (24 h)	0.987	0.910-1.070	0.92			
Prostate D90 (24 h)	0.934	0.886-0.985	0.012	1.255	0.923-1.706	0.15
ASQ D90 (24 h)	0.956	0.918-0.997	0.034	0.968	0.916-1.023	0.25
PSQ D90 (24 h)	0.952	0.916-0.990	0.014	0.904	0.848-0.964	0.002
AIQ D90 (24 h)	0.995	0.957-1.033	0.78			
PIQ D90 (24 h)	0.973	0.937-1.009	0.14	0.958	0.919-0.999	0.048

HR – hazard ratio, CI – confidence interval, PSA – prostate specific antigen, ADT – androgen deprivation therapy, D90 – minimal dose received by 90% of volume, ASQ – anterior-superior quadrant, PSQ – posterior-superior quadrant, AIQ – anterior-inferior quadrant, PIQ – posterior-inferior quadrant

segments were different. The segments were divided simply with the midpoint of the whole prostate on reconstructed images, and Spadinger and Sidhu *et al.* divided the segments with the midpoint of the prostate contour on each axial image [29]. Although the present dividing method has a disadvantage, in that volume deviation of the anterior and posterior regions tends to occur, the present method is simple, intuitive, and easy to apply in various situations, not only in post-implant assessment, but also in real-time planning. In particular, the present method is considered to be more useful with sagittal views, and the results of the present study showing that the information about the craniocaudal direction is important support the utility of this method. Furthermore,

Table 3B. Univariate and multivariate analyses of prognostic factors using variables obtained from post-implant CT at 1 month

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Age	0.977	0.881-1.084	0.67			
PSA	1.287	1.015-1.633	0.037	1.501	1.109-2.030	0.008
Gleason score (≤ 6 vs. 7)	4.492	1.003-20.12	0.050	15.620	2.246-108.600	0.005
T stage (T1 vs. T2)	0.751	0.168-3.357	0.71			
Risk group (low vs. intermediate)	0.158	0.019-1.311	0.087	2.379	0.133-42.670	0.56
Neoadjuvant ADT (no vs. yes)	2.244	0.434-11.62	0.34			
Number of seeds	0.963	0.907-1.023	0.22			
Prostate volume (1 month)	0.956	0.858-1.066	0.42			
Prostate D90 (1 month)	0.953	0.916-0.991	0.016	0.990	0.923-1.061	0.77
ASQ D90 (1 month)	0.971	0.940-1.002	0.067	1.012	0.961-1.066	0.65
PSQ D90 (1 month)	0.970	0.942-0.999	0.045	0.957	0.924-0.991	0.014
AIQ D90 (1 month)	1.007	0.976-1.038	0.66			
PIQ D90 (1 month)	0.994	0.965-1.024	0.71			

HR – hazard ratio, CI – confidence interval, PSA – prostate specific antigen, ADT – androgen deprivation therapy, D90 – minimal dose received by 90% of volume, ASQ – anterior-superior quadrant, PSQ – posterior-superior quadrant, AIQ – anterior-inferior quadrant, PIQ – posterior-inferior quadrant

we used only standard function of TPS, and it is thought that our method is excellent also in terms of versatility. Differences in patients' characteristics, such as ethnicity and prostate volume, can also be another reason for discrepancy in the results. The posterior region of the prostate contains a major part of the peripheral zone, and pathologically, 70% of prostate cancers arise in this zone [30]. Thus, the result that delivers an adequate dose to

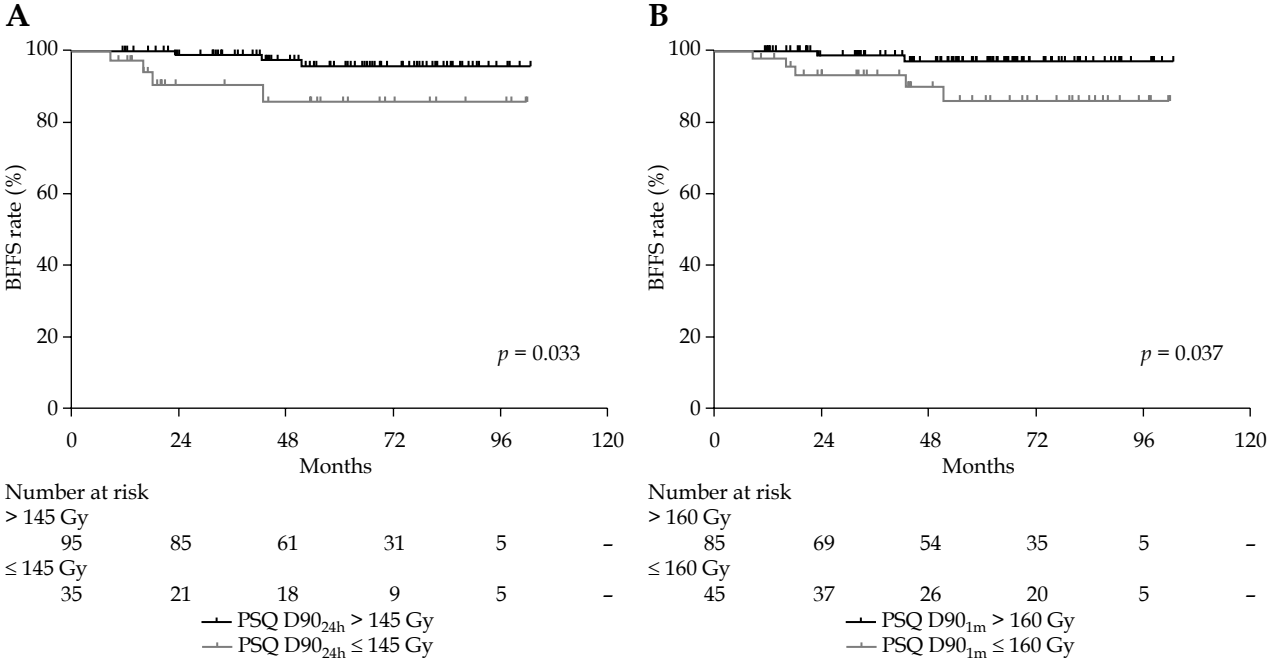

Fig. 2. A) Kaplan-Meier curves of BFFS by D_{90} of PSQ at 24 h with a cut-off value of 145 Gy. **B)** Kaplan-Meier curves of BFFS by D_{90} of PSQ at 1 month with a cut-off value of 160 Gy

BFFS – biochemical failure-free survival, PSQ $D90_{24h}$ – D90 of PSQ at 24 h, PSQ $D90_{1m}$ – D90 of PSQ at 1 month, D90 – minimal dose received by 90% of volume, PSQ – posterior-superior quadrant

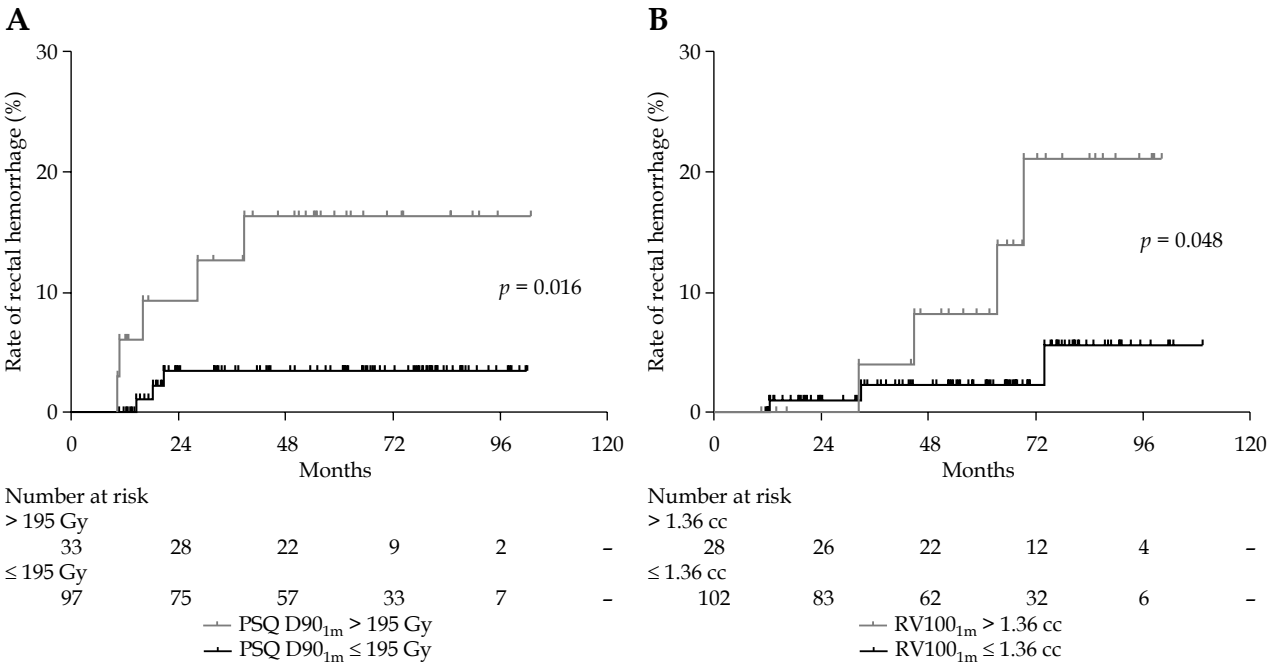

Fig. 3. A) Cumulative Kaplan-Meier curves of the rectal hemorrhage rate by D_{90} of PSQ at 1 month with a cut-off value of 195 Gy. **B)** Cumulative Kaplan-Meier curves of rectal hemorrhage rate by V_{100} of rectum at 1 month with a cut-off value of 1.36 cc

PSQ D90$_{1m}$ – D90 of PSQ at 1 month, D90 – minimal dose received by 90% of volume, PSQ –posterior-superior quadrant, RV100$_{1m}$ – V100 of rectum at 1 month

PSQ is correlated with BFFS, and is meaningful in terms of pathology of prostate cancer.

The present study indicates the utility of post-implant dosimetric analysis not only at 1 month, but also 24 h after the implant procedure. Though there are many reports about post-implant dosimetry with CT and/or MRI images obtained at 2-6 weeks after the procedure, the number of reports using images at 24 h is relatively small [16]. To the best of our knowledge, this is the first report dealing with the correlation between BFFS and regional dosimetry of the prostate using images obtained at 24 h after the procedure. The result that regional dosimetry at 24 h can predict the BFFS is meaningful, because it facilitates early compensation for a dose deficiency. A prospective study is needed to investigate whether compensating for a dose deficiency can contribute to improving BFFS.

In the present study, the cut-off value of PSQ D90 was 145 Gy at 24 h and 160 Gy at 1 month. Each value was significant for predicting BFFS. In a series of 686 patients, Shiraishi *et al.* [10] showed that D90 of the whole prostate on day 1 or day 30 was related to biochemical control on multivariate analysis. They also showed that the cut-off values for the day 1 D90 and the day 30 D90 were 163 Gy and 175 Gy, respectively. They indicated that dose escalation is needed to improve the results of LDR brachytherapy. In the present study, adequate dose distribution was shown to be needed for better BFFS, but there was no significant relationship between D90 of the whole prostate and BFFS. Considering the results of the present study, D90 of PSQ may be more useful than D90 of the whole prostate for predicting BFFS in patients with localized prostate cancer.

On multivariate analysis, PSA and Gleason score were significant factors for biochemical failure, while T stage and risk group were not significant. The following points can be considered to explain the results: (a) many of the patients in this study were classified as T1c or T2a, and there was no significant difference in risk of biochemical failure between the two groups [31]; (b) many of the intermediate-risk patients had a good prognosis, since they were classified into the "favorable intermediate-risk group" [32].

It was found that PSQ D90$_{1m}$ and V100 of the rectum are significant factors of rectal hemorrhage. It is well known that the incidence rate of rectal hemorrhage can correlate with V100 of the rectum [33,34]. Despite the significant correlation between rectal hemorrhage and "rectal dose", few reports on the relationship between rectal hemorrhage and "(regional) prostatic dose" have been published to date. Furthermore, PSQ is not anatomically closer to rectum than PIQ. One plausible reason is that PSQ is larger than PIQ, and high-dose administration to PSQ contributes more to dose escalation of rectum than PIQ. The cut-off value of PSQ D90$_{1m}$ for rectal hemorrhage was 195 Gy on ROC analysis. Although the AUC of 0.69 on ROC analysis can be considered to reflect low accuracy; the log-rank test showed that the cut-off value (PSQ D90$_{1m}$: 195 Gy) was significant for predicting rectal hemorrhage. Thus, PSQ D90$_{1m}$ may be a useful factor for predicting rectal toxicity. As mentioned above, adequate dose administration to PSQ of the prostate is needed to improve BFFS, while excessive dose escalation can lead to worsening of late complications.

In the treatment of patients who have a higher risk in PSQ from the results of biopsy or MRI study, higher

dose administration may be needed to improve BFFS. The prescription dose was 145 Gy in the present study. In a series of 686 patients, Shiraishi *et al.* [10] treated with a prescribed dose of 145 Gy or 160 Gy, and they showed that dose escalation is needed to improve results. Thus, we think that there is a room for dose escalation. In contrast, excessive dose escalation can lead to worsening of late complications. In terms of seed selection, loose seed was used in the present study, and this might have led to seed migration and unintended heterogeneity of dose distribution. Linked seed can reduce the probability of seed migration, and it may decrease excessive dose administration to the rectum or other organs.

In this study, D90 of PIQ at 24 h was significantly lower than that of other quadrants. The PIQ is a portion close to the rectum, particularly on the caudal side, and the lower dose of PIQ is considered to be a result of prostatic edema or avoiding placing the seeds in the vicinity of the rectum. On the other hand, D90 of PIQ at 1 month was not significantly lower compared with other quadrants. Possible reasons for this result are the proximity of the seeds to the rectum due to improved edema of the prostate or slight migration of the seeds to the caudal side in the prostate.

This study had several limitations. First, this study was limited by its retrospective design and single-center setting, a relatively short follow-up period, and the relatively low numbers of patients and events compared with multi-institutional studies. Although the follow-up period was relatively short, all patients reached PSA nadir after brachytherapy, and this appears sufficient to analyze biochemical control. Second, CT-MRI image fusion technique was performed with MRI images obtained at pre-planning. It is well known that the results of brachytherapy depend greatly on practitioner. Therefore, we used CT-MRI image fusion technique to mitigate variations in contouring related practitioner. The prostatic volume at post-planning differed from that at pre-planning in many patients, and the MRI images were modified to fit the CT images on TPS. Thus, the accuracy of delineation might be less than with MRI images obtained simultaneously. Third, the relationship between BFFS and biopsy information, such as number or percentage of positive cores and localization or volume of prostate cancer, was not evaluated. Fourth, neoadjuvant ADT has been administered to 60 patients (46.2%) to reduce the prostate volume, and the influence of ADT could not be completely excluded. Neoadjuvant ADT has been administered to 5 of 7 patients with biochemical recurrence, and neoadjuvant ADT showed no significant effect in BFFS on univariate analysis. Therefore, the influence of neoadjuvant ADT on results of this study is considered to be sufficiently small. Further new prospective investigation is needed to confirm the result of this study, and to assess the correlations of regional dosimetrics, biopsy information, and BFFS.

Conclusions

Post-implant D90 of PSQ is significantly associated with BFFS for localized prostate cancer not only at 1 month, but also at 24 h after implant procedure, with cut-off values of 160 Gy and 145 Gy, respectively. D90 of PSQ at 1 month is also a significant factor for rectal hemorrhage.

Disclosure

Authors report no conflict of interest.

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