ORIGINAL ARTICLE

Preimplant Factors Affecting Prostate D90 after Transperineal Interstitial Prostate Brachytherapy with Loose ^{125}I Seeds

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The dose received by 90% of the prostate volume (D90) is the key parameter of dosimetric analysis in prostate brachytherapy. The aim of this analysis was to identify preimplant factors affecting prostate D90 after transperineal interstitial prostate brachytherapy with loose ^{125}I seeds. We reviewed the records of 210 patients who underwent transperineal interstitial prostate brachytherapy with loose ^{125}I seeds for clinical T1/T2 prostate cancer at our institution. Patients who received supplemental external-beam radiation therapy were excluded. One hundred and nine patients (51.9%) received neoadjuvant hormonal therapy (NHT). One month after seed implantation, postimplant computed tomography and dosimetric analysis were performed. Univariate and multivariate analyses were carried out to identify preimplant factors affecting postimplant prostate D90. The postimplant prostate D90 values ranged from 123.3 to 234.1 Gy (mean ± standard error, 177.1 ± 1.4 Gy). Postimplant prostate D90 differed significantly between patients who had and had not undergone NHT ($P = 0.001$). In addition, simple regression analyses showed positive correlations with the estimated preimplant prostate D90, preimplant prostate volume by transrectal ultrasound (TRUS), total radioactivity, number of needles, and number of seeds. On stepwise multiple regression analysis, postimplant prostate D90 showed significant negative correlations with NHT and preimplant prostate volume by TRUS, and a significant positive correlation with total radioactivity. In conclusion, NHT, preimplant prostate volume by TRUS, and total radioactivity are significant preimplant factors affecting postimplant prostate D90 in prostate cancer patients treated with transperineal interstitial prostate brachytherapy with loose ^{125}I seeds.
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Keywords: **brachytherapy, dosimetry, ^{125}I, prostate cancer, seed**

Introduction

There are a number of treatment options for clinically localized prostate cancer; treatment selection depends on life expectancy, the clinical stage, the serum prostate-specific antigen (PSA) level, the Gleason score, competing medical conditions, concerns about the effects of treatment on quality of life, and other factors. The treatment alternatives for localized prostate cancer include watchful waiting, androgen deprivation therapy, radical prostatectomy, external-beam radiation therapy, and brachytherapy.

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In recent years, transperineal interstitial prostate brachytherapy with radioactive seeds has become a popular treatment option for localized prostate cancer. Substantial advantages of prostate brachytherapy include better potency preservation, less risk of urinary incontinence, and greater patient convenience.[1] Previous investigators have suggested that outcomes with prostate brachytherapy in selected patients are equivalent to those with other treatment modalities for localized prostate cancer, including radical prostatectomy and external-beam radiation therapy.[2]

With the widespread use of prostate brachytherapy, there is growing interest in quality assurance that includes dosimetric analysis.[3–6] It is recommended that preimplant and postimplant dosimetric analyses for prostate brachytherapy be performed routinely.[7,8] In brief, before implantation, the prostate is contoured on transrectal ultrasound (TRUS) images, and radioactive seed placement is planned with a computer-assisted treatment planning system. Then, a dose–volume histogram is generated, and dosimetric parameters, such as the dose received by 90% of the prostate volume (D90), are calculated. After implantation, dosimetric analysis is also performed with computed tomography (CT) images.

Prostate D90 is one of the key parameters of dosimetric analysis in prostate brachytherapy.[7–11] In 1998, Stock and colleagues were the first to describe prostate D90 as an indicator of implant quality that showed a good correlation with the probability of achieving biochemical control.[11] They showed that a prostate D90 of 140 Gy is a highly significant factor in predicting PSA relapse-free survival.[11] A subsequent publication by Potters and coworkers confirmed the correlation between prostate D90 and the probability of achieving biochemical control.[9] Moreover, Stock and colleagues suggested in a later study of the results of posttreatment biopsies that a prostate D90 > 160 Gy was associated with increased tumor control and that a prostate D90 > 180 Gy was associated with an increased risk of long-term urinary toxicity from brachytherapy.[10] The American Brachytherapy Society recommends that prostate D90 should be reported after prostate brachytherapy.[7,8]

We sometimes encounter results in which the postimplant prostate D90 value is higher or lower than expected. Previous investigators have suggested that it is difficult to achieve the exact preplanned dose coverage because of seed misplacement, seed migration, and postimplant prostatic swelling.[12–16] These factors cannot be predicted preoperatively. It is important to evaluate preimplant factors associated with postimplant prostate D90 because suboptimal or excessive values of prostate D90 are associated with increased biochemical failure or increased morbidity, respectively. The present study was undertaken to identify preimplant factors affecting postimplant prostate D90 in prostate cancer patients treated with transperineal interstitial prostate brachytherapy with loose ^{125}I seeds.

Materials and Methods

We reviewed the records of 210 patients who underwent transperineal interstitial prostate brachytherapy with loose ^{125}I seeds for clinical T1/T2 prostate cancer at Keio University Hospital. Patients who received supplemental external-beam radiation therapy were excluded from this analysis. Neoadjuvant hormonal therapy (NHT), which consisted of a luteinizing hormone-releasing hormone agonist and antiandrogens, was generally administered to patients with a prostate volume >40 cm^3 and to those with pubic arch interference at the preimplant volume study by TRUS.[17] Hormonal therapy was not continued past the date of seed implantation.

One month before seed implantation, a preplan was obtained with TRUS images taken at 5-mm intervals from the base to the apex of the prostate with the patient in the dorsal lithotomy position. The prostate contour was outlined at each level by a single radiation oncologist (AS). The planning target volume included the prostate gland and a margin of 3 mm anteriorly and laterally and 5 mm in the cranial and caudal directions. No margin was added posteriorly at the rectal interface. Treatment planning used a peripheral or a modified peripheral approach. For the 210 patients, the prescribed brachytherapy dose was 145 Gy for the first 133 patients and 160 Gy for the subsequent 77 patients. Preplan dosimetry aimed for a prostate D90 of <125% of the prescribed dose, a prostate V100 (% of the volume receiving the prescribed dose or greater) of >99%, and a prostate V150 (% of the volume receiving 150% of the prescribed dose or greater) of <60%. VariSeed 7.1 (Varian Medical Systems, Palo Alto, CA, USA) software was used both in the planning and in the calculation of the final dosimetry. TG 43 formalism was used in the preplanning and postimplant dosimetry analyses.[18] All 210 patients were treated with loose ^{125}I radioactive seeds using a Mick applicator (Mick Radio-Nuclear Instruments, New York, NY, USA). Postimplant axial CT images of the prostate at 2.5- to 3.0-mm intervals were undertaken 1 month after seed implantation. The prostatic margins were outlined by a single radiation oncologist (AS). Postimplant dosimetry calculations were performed.

The following information was recorded: patient characteristics, implant characteristics, preimplant prostate D90, and postimplant prostate D90. The following parameters were included as preimplant predictive variables: patient age, serum PSA, whether the patient had undergone NHT, Gleason score (<7 vs. 7), preimplant prostate D90, preimplant prostate volume by TRUS, total radioactivity, radioactivity per unit volume, number of needles, and number of seeds.

Table 1 Patient characteristics (n =210)

Variable	Value	Range
Age, years	68.9 ± 0.4	(53 – 80)
Initial PSA, ng/mL	7.47 ± 0.24	(4.01 – 19.88)
Gleason score <7, n (%)	130 (61.9)	
Gleason score =7, n (%)	80 (38.1)	
NHT (+), n (%)	109 (51.9)	
NHT (–), n (%)	101 (48.1)	
Preimplant prostate volume by TRUS, cm^3	23.0 ± 0.4	(9.3 – 40.8)

Data are presented as mean ± standard error (range) or number (percent) of patients.
PSA, prostate-specific antigen; NHT, neoadjuvant hormonal therapy; NHT (+), patients who received NHT; NHT (–), patients who did not receive NHT; TRUS, transrectal ultrasound.

Table 2 Implant characteristics (n =210)

Variable	Value	Range
Preimplant estimate of prostate D90, Gy	184.8 ± 0.9	(148.0 – 208.9)
Total radioactivity, MBq	920.5 ± 11.6	(482.9 – 1300.0)
Radioactivity per unit volume, MBq/cm^3	41.1 ± 0.4	(27.6 – 63.1)
Number of needles	24.4 ± 0.3	(12 – 37)
Number of seeds	72.2 ± 0.8	(40 – 95)

Data are presented as mean ± standard error (range).
D90, dose received by 90% of the volume of the prostate.

Statistical analysis

Data are presented as the mean ± standard error (SE). A paired t test was performed to determine if there was a difference between preimplant and postimplant prostate D90 values. Student's t test was used to compare postimplant prostate D90 values between patients who had and had not undergone NHT and between patients with a Gleason score <7 and with a Gleason score of 7. Simple regression analyses were performed to investigate the relationship between postimplant prostate D90 and continuous preimplant variables. Stepwise multiple regression analysis was performed to identify independent predictors of postimplant prostate D90 from preimplant variables. A P value of <0.05 was considered statistically significant.

Results

Tables 1 and **2** summarize the patient and implant characteristics, respectively, for all 210 patients. The postimplant prostate D90 values ranged from 123.3 to 234.1 Gy. There was a significant difference between the preimplant and postimplant D90 (184.8 ± 0.9 vs. 177.1 ± 1.4 Gy, P < 0.001). **Figure 1** shows postimplant prostate D90 values vs. preimplant prostate D90 values for all 210 patients. The mean ± SE postimplant prostate D90 was 169.4 ± 1.7 Gy in patients who had received NHT and 185.3 ± 2.0 Gy in those who had not received NHT (P = 0.001). Postimplant prostate D90 was 175.5 ± 1.8 and 179.6 ± 2.2 Gy in patients with Gleason score <7 and Gleason score =7, respectively (P = 0.148). Postimplant prostate D90 showed positive correlations with preimplant prostate D90 (r =0.355, P < 0.001), preimplant prostate volume by TRUS (r =0.338, P < 0.001), total radioactivity (r =0.490, P < 0.001), number of needles (r =0.372, P < 0.001), and number of seeds (r =0.482, P < 0.001), but did not show significant correlations with age (r =0.068, P = 0.327), serum PSA (r = –0.018, P = 0.794), and radioactivity per unit volume (r = –0.034, P = 0.626) in simple regression analyses (**Table 3**).

Postimplant prostate D90 showed significant negative

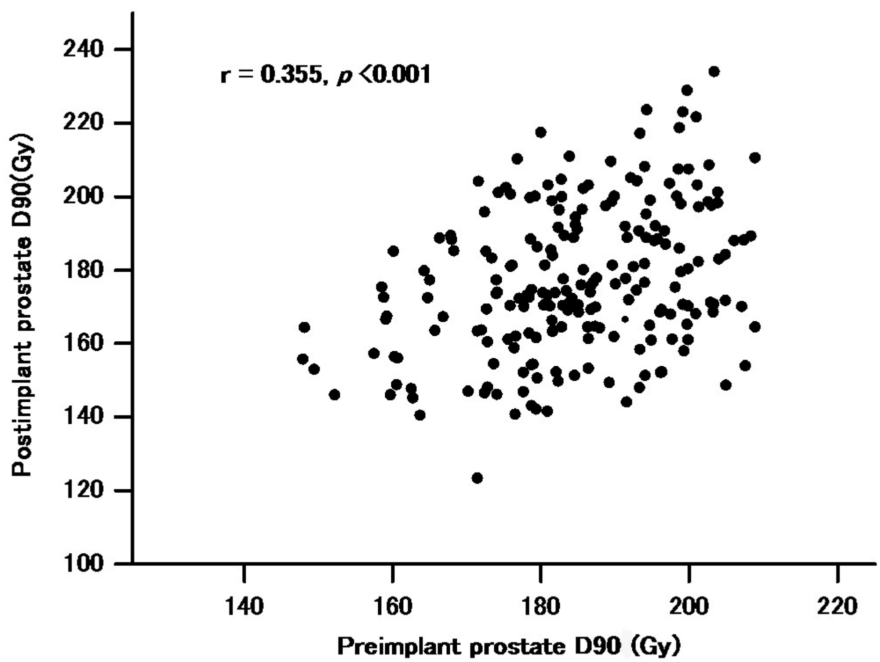

Fig. 1 Postimplant prostate D90 vs. preimplant prostate D90.
Data are shown for all 210 patients. D90, dose received by 90% of the volume of the prostate.

correlations with NHT ($P < 0.001$) and preimplant prostate volume by TRUS ($P < 0.001$), and a significant positive correlation with total radioactivity ($P < 0.001$) in the stepwise multiple regression analysis (**Table 3**).

Discussion

The purpose of the present study was to identify preimplant factors affecting postimplant D90 in prostate cancer patients treated with transperineal interstitial prostate brachytherapy with loose ^{125}I seeds. The results showed that NHT, preimplant prostate volume by TRUS, and total radioactivity are significant independent factors affecting postimplant prostate D90.

In univariate and multivariate analyses, NHT was associated negatively with postimplant prostate D90, meaning that a patient receiving NHT had a lower D90 than a patient who did not receive NHT. These results are in agreement with a previous report.[19] Ash and coworkers reported that postimplant prostate D90 was significantly different between patients who had and had not undergone NHT (130.8 vs. 145.1 Gy, $P \leq 0.001$).[19] A possible explanation for the negative effect of NHT on postimplant prostate D90 is that NHT is associated with an increase in prostate volume after implantation, which results in a lower D90.[19] Ash and coworkers reported that the ratio of the postimplant CT scan volume to the preimplant TRUS volume of the prostate (CT/TRUS volume ratio), which indicates the volume change of the prostate from before to after implantation, was significantly different between patients who had and had not undergone NHT (1.17 vs. 0.98, $P < 0.001$).[19] Our previous study also showed that the CT/TRUS volume ratio was significantly different between patients who had and had not undergone NHT (1.30 vs. 1.05, $P < 0.001$), meaning that patients who had undergone NHT had a greater increase in prostate volume after implantation.[20]

The next factor affecting postimplant prostate D90 was the preimplant prostate volume by TRUS. Simple regression analysis revealed that preimplant prostate volume by TRUS was positively correlated with postimplant prostate D90, although the correlation was weak (r =0.228, $P < 0.001$). This result is in agreement with those of previous reports.[21,22] McNeely and coworkers reported that a larger gland was associated with a higher D90 in univariate analyses.[21] Moreover, Stock and colleagues reported that preimplant prostate volume by TRUS was a factor that significantly affected postimplant prostate D90, although the correlation was weak in univariate analyses (r =0.223, $P < 0.001$).[22] Their possible explanation was that the activity per volume table calls for a greater activity in large glands than may be needed to achieve the desired dose.[22] From the results of these previous studies, it seems that larger glands tend to have higher D90s. However, in multiple linear regression analysis in the present

Table 3 Univariate and multivariate analyses for postimplant prostate D90

Covariate	Simple regression *P* value	Stepwise multiple regression *P* value	B	SE
Age, years	0.327			
Initial PSA, ng/mL	0.794			
Gleason score =7 vs. Gleason score <7	0.148*			
NHT (+) vs. NHT (−)	0.001*	<0.001	−12.146	2.449
Preimplant prostate D90, Gy	<0.001			
Preimplant prostate volume by TRUS, cm^3	<0.001	<0.001	−1.521	0.386
Total radioactivity, MBq	<0.001	<0.001	0.095	0.014
Radioactivity per unit volume, MBq/cm^3	0.626			
Number of needles	<0.001			
Number of seeds	<0.001			

*Student's *t* test was used.
D90, dose received by 90% of the volume of the prostate; B, unstandardized coefficients; PSA, prostate-specific antigen; NHT, neoadjuvant hormonal therapy; NHT (+), patients who received NHT; NHT (−), patients who did not receive NHT; TRUS, transrectal ultrasound.

study, preimplant prostate volume by TRUS had a significant negative effect on postimplant prostate D90. These results seem contradictory. A possible explanation for the discrepancy might be that for a larger gland, a given amount of radioactivity tends to have a lower D90.

The last significant factor affecting postimplant prostate D90 was total radioactivity. In univariate and multivariate analyses, total radioactivity was associated positively with postimplant prostate D90. Thus, a higher amount of radioactivity leads to a higher D90. It is obvious that the dose received by the prostate should increase with the increase in total radioactivity when the volume of the prostate is given. The other possible reason is that the negative effect of seed misplacement or seed migration on the dose coverage of the prostate would decrease with the increase in total radioactivity.

The results of the present study show that the preimplant prostate D90 value calculated by the computer-assisted treatment planning system was not adequate for predicting postimplant D90. Although postimplant prostate D90 showed a positive correlation with preimplant prostate D90 in the simple regression analysis, the correlation was not strong (r =0.355, $P < 0.001$) (**Fig. 1**). Moreover, in the stepwise multiple regression analysis, preimplant prostate D90 was not a significant independent factor affecting postimplant prostate D90. These results indicate that we should not depend solely on preimplant prostate D90 values calculated by a computer-assisted treatment planning system. It is recommended that preimplant factors shown to affect postimplant prostate D90 should be considered.

The present results indicate that postimplant prostate D90 is often lower in patients with a larger prostate gland and in patients who have undergone NHT. To achieve optimal dose coverage of the prostate, this group of patients may need more seeds than that calculated by the computer-assisted treatment planning system. Moreover, when suboptimal dosimetric results are predicted and prostate brachytherapy is not considered to be an appropriate treatment, especially for patients with larger prostates and those who have undergone NHT, other treatment options such as radical prostatectomy or external-beam radiation therapy can be offered.

In conclusion, the results of the present study show that NHT, preimplant prostate volume by TRUS, and total radioactivity are significant preimplant factors affecting postimplant prostate D90. Thus, the combination of these three factors can be used to predict postimplant prostate D90 in prostate cancer patients treated with transperineal interstitial prostate brachytherapy with loose ^{125}I seeds.

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