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Prostate Seed Brachytherapy – Methods to Improve Implant Characteristics

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1. Introduction

Prostate cancer is diagnosed in over 230,000 men each year in the United States (Jemel, et al, 2006), and with the use of screening prostate specific antigen (PSA) the majority is diagnosed with locally confined prostate cancer. Many of these patients are good candidates for prostate brachytherapy. With the development of transperineal implantation using trans-rectal ultrasound guidance the number of patients undergoing permanent radioactive seed implants for prostate cancer has increased significantly over the past ten years. (Cooperberg, et al, 2004).

A variety of techniques have been used to deliver transperineal prostate brachytherapy, using Pd-103, I-125 and, more recently, Cs -131(Sommerkamp, et al 1988, Reed, et al, 2007, Spadlinger, et al, 2006, Meigooni, et al, 2004, Yue, et al, 2005). These sources are typically implanted as individual seeds, or as seeds that are stranded together or held together using plastic linking devices (Sommerkamp, et al 1988, Reed, et al, 2007, Spadlinger, et al, 2006). Stranded or linked seeds have the advantage that they are less likely to migrate from their implant position than individually implanted seeds (Sommerkamp, et al 1988, Reed, et al, 2007, Spadlinger, et al, 2006). Additionally, implants can be either performed via pre-plans, in which a planning ultrasound is performed before the surgery, or with intra-operative planning (Matzkin, et al, 2003).

While a linear brachytherapy source in the form of a coiled [103]Pd wire was developed, it never became available clinically (Meigooni, et al, 2004). The possibility of using a continuous linear source led to the consideration of continuously linked seeds in an implant rather than the normal use of seeds separated by spacers. The elimination of spacers would allow the same number of seeds to be implanted into the prostate with fewer needles. The number of needles used in prostate seed implants has been shown to be correlated with acute urinary morbidity after seed implantation. (Eapen, et al, 2004, Ohashi, et al, 2006, Bucci, et al, 2002, Lee, et al, 2000, Buskirk, et al, 2004, Bottomley, et al, 2007, Keyer, et al, 2009, Thomas, et al, 2008). Also, the use of fewer needles should cause less trauma to the base of the penis, which may help preserve erectile function (Macdonald, et al, 2005, Steggerda, et al, 2010).

In eliminating spacers between seeds and reducing the number of needles used for implantation, it is important that implant quality is not adversely affected. In this study a comparison of post-implant dosimetry in patients treated with conventional linked seed implants with spacers (**+S**) to those treated with a novel technique using linked seed implants without spacers between the sources (**-S**) is performed, as well as a comparison of the numbers of needles used for each technique.

2. Strategy to provide monotherapy palladium-103 implants

The day 0 post implant dosimetry of 101 consecutive patients who received monotherapy Palladium-103 implants was retrospectively reviewed. To avoid selection bias the dosimetric data from the final 48 **+S,** and the first 53 **-S** patients implanted at our institution were analyzed. Prior to this study the implant team had performed more than 800 permanent seed prostate implants. The ultrasound images taken at the time of the implant in the operating room were transferred to the Variseed ™ 7.0 software (Varian, Palo Alto, CA). The radiation oncologist then developed a treatment plan to deliver a minimum dose of 125 Gy to the prostate with a margin of approximately 5 mm anteriorly and laterally, with a smaller posterior margin. All patients were implanted using Bard® BrachyStar® seed implant needles containing Theragenics® TheraSeed® palladium-103 sources with an average activity of 2.08 (Range 1.78-2.31) linked with 0.5 mm seed-to-seed SourceLink™ links or 5 mm SourceLink™ spacer links, for the **-S** and **+S** cohorts respectively, assembled using a SourceLink™ loader. A photograph of the linked seeds without the use of spacers is shown in Figure 1, along with a schematic diagram of the linked seeds. All patients had a CT scan for post-implant dosimetry within 3 hours following the implant. A Foley catheter was in place during the implant procedure, and for the post-implant CT scan. A single radiation oncologist planned, treated, and performed post-implant contouring of the prostate.
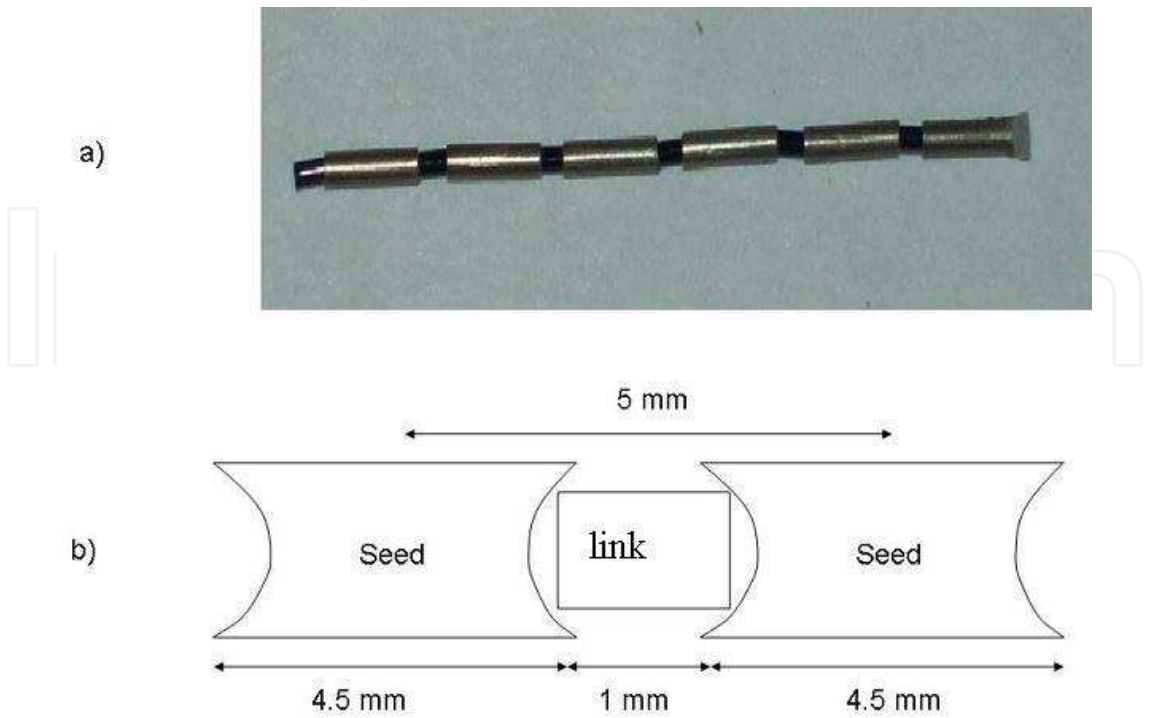

Fig. 1. Photograph (a) and schematic diagram (b) of a strand of linked seeds.

Forty-eight patients (**+S**) were implanted using linked seeds with a single spacer between each seed, except at the apex of the gland where 2 seeds were frequently placed without a spacer between them. Another 53 patients (**-S**) had implants in which all seeds were linked without spacers between them. Other than use of spacers, both groups of patients were planned and implanted in the same manner.

Using the Variseed ™ 7.0 software (Varian, Palo Alto, CA), dose-volume histograms were compiled for each patient and were used to determine the prostate V800, V400, V350, V300, V250, V200, V150, V100, V90 and V80, prostate D100, D90 and D80, and urethral D90, D30, and D10 using a point source approximation (Pd-103 M200 Corrected [NIST 99]).

The automatic seed finder was utilized to locate the Pd-103 seeds in the CT data sets, which were subsequently reviewed by the physician to assure that location of the seeds was correctly identified and that the number of seeds identified matched the number that was implanted. The post implant prostatic D90 is defined as the dose covering 90% of the prostate volume. The V100 is defined as the volume of the prostate that receives 100% of prescribed dose. The post implant dosimetric analysis was performed according to the American Brachytherapy Society's guidelines for permanent prostate brachytherapy (Nag, et al, 2000).

Statistical Methods: The dosimetric variables, as well as the average number of needles and seeds used for each group, were statistically compared using Student's t-tests to determine if there were significant differences between the two types of implants. Demographic and clinical factors including prostate volume, patient age, clinical stage, pre-implant PSA, and Gleason score were evaluated using Student's t-tests or chi-square tests of association to determine whether the two cohorts were similar. All statistical analyses were performed using SAS® Version 9.1 (Cary, NC, USA). All tests were performed using a Type I error rate of 0.05.

3.1 Demographics, disease and treatment characteristics

The clinical characteristics of our study cohorts are presented in Table 1. Statistical analysis showed no significant differences between age, mean pre-implant PSA, Gleason's score or pre-implant prostate volume. The prostate volumes were similar for the two groups (39.3 cm^3 for **+S** and 36.7 cm^3 for **-S**).

3.2 Number of needles and seeds

Comparison between the two cohorts (Table 1) showed that an average of 100.8 seeds and 23.1 needles were used for implants without spacers, while an average of 94 seeds and 31.5 needles were required when implanting with spacers. This difference in numbers of needles used was statistically significant (p<0.001), but there was no statistically significant difference in the number of seeds in the two types of implants (p=0.16).

3.3 Dosimetric parameters and outcomes

Detailed dosimetric analysis results are found in Table 2. The mean prostatic D90 for the **+S** cohort was 99.2 Gy, slightly higher than the 95.5 Gy calculated for the **-S** cohort, but this

difference was not statistically significant (p=0.22). The prostate D80 and D100 values were also not significantly different between the two cohorts (Figure 2).

Variable	+S*	-S†	p-Value
Mean Age (years)	66.2	63.5	0.068
Mean Preimplant PSA‡ (ng/ml)	6.3	6.0	0.93
Mean Combined Gleason Score	6.2	6.2	0.88
T-stage, number (%) T1c T2a T2b T2c	38 (79.2) 9 (18.8) 0 (0) 1 (2.1)	45 (84.9) 7 (13.2) 0(0) 1 (1.9)	0.45
Mean Prostate Volume (cm³)	39.3	36.7	0.31
Mean Urethral Volume (cm³)	1.4	1.4	0.97
Mean Number of Needles	31.5	23.1	<0.001
Mean number of Seeds	94	100.8	0.16
Mean number of seeds per needle	3.0	4.4	<0.001

*+S: Patients receiving implantation with spacers. † -S: Patients receiving implantation with linked seed implants without spacers between the sources. ‡PSA = Prostate Specific Antigen.

Table 1. Demographic and Clinical Cohort Comparison

Dosimetric Variable	+S*	-S†	p-Value
Prostate, Mean V800(%)	2.4	2.0	0.029
Prostate, Mean V400(%)	7.1	6.1	0.005
Prostate, Mean V200(%)	30.6	27.4	0.058
Prostate, Mean V150(%)	56.3	52.0	0.077
Prostate, Mean V100(%)	88.1	85.8	0.19
Prostate, Mean V90(%)	92.2	90.8	0.28
Prostate, Mean D100 (Gy)	44.2	45.4	0.63
Prostate, Mean D90 (Gy)	99.2	95.5	0.22
Prostate, Mean D80 (Gy)	116.8	112.3	0.15
Urethra, Mean V100(%)	41.5	51.5	0.038
Urethra, Mean V100(%)	121.4	119.7	0.70
Urethra, Mean V100(%)	139.8	137.6	0.70

*+S = Patients receiving implantation with spacers between the linked sources.

† -S = Patients receiving implantation with linked seed implants without spacers

Table 2. Summary of Dosimetric Analysis

The urethral D90 was significantly higher (p=0.038) in the group without spacers (51.5 Gy) compared to the group with spacers (41.5 Gy) shown in Figure 3.

The mean V100 for the **-S** cohort was 85.8% compared to a mean V100 of 88.1% for the **+S** cohort (p= 0.19). Also there were no statistically significant differences in the mean V80 and V90 for each of the cohorts.
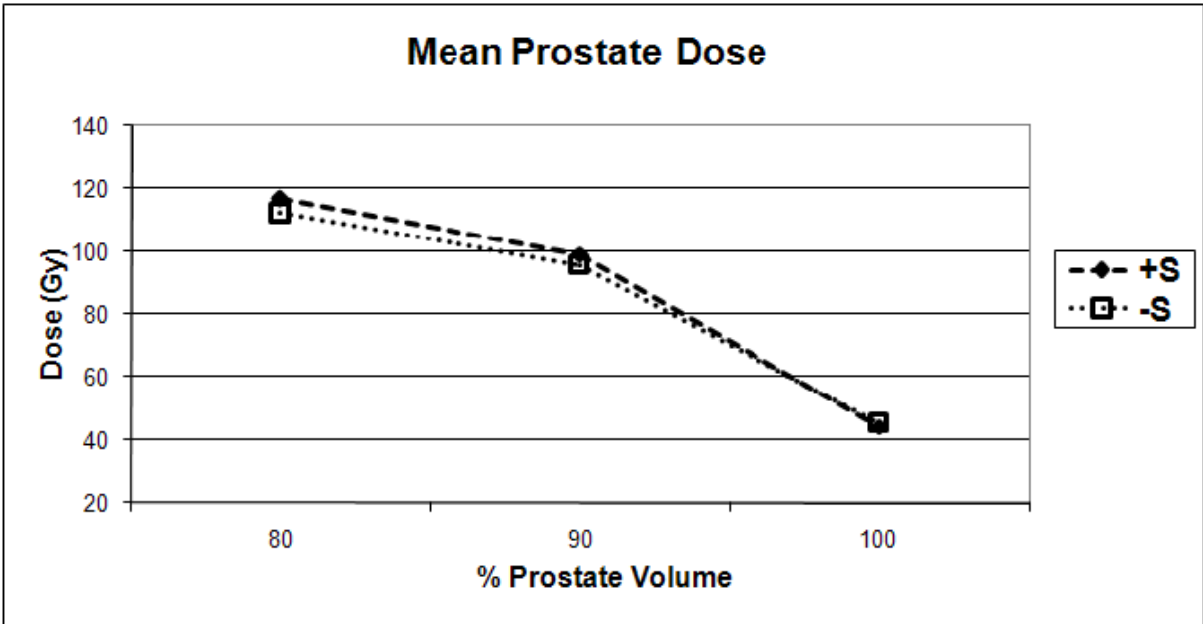
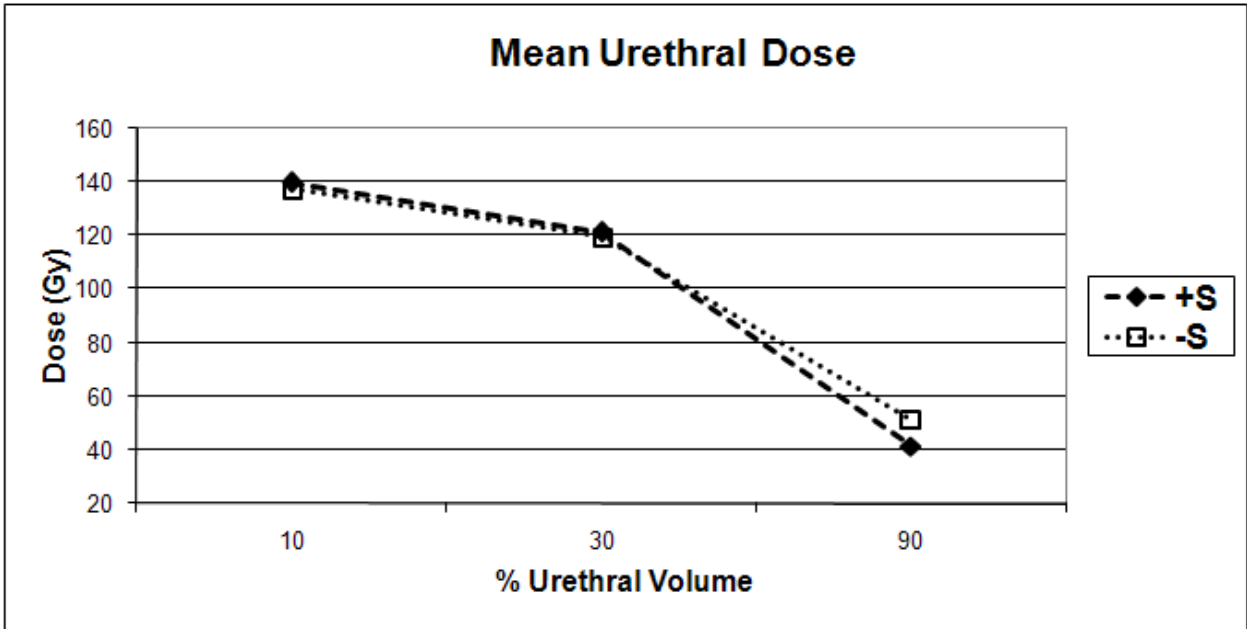Fig. 2. Mean Prostate dose for the implants performed with (+S) and without (-S) spacers.

Fig. 3. Mean urethral dose for the implants performed with (+S) and without (-S) spacers.

The mean V150, V200,V250, V300, V350, V400 and V800 were also calculated and compared between the two cohorts, as shown in Figure 4.
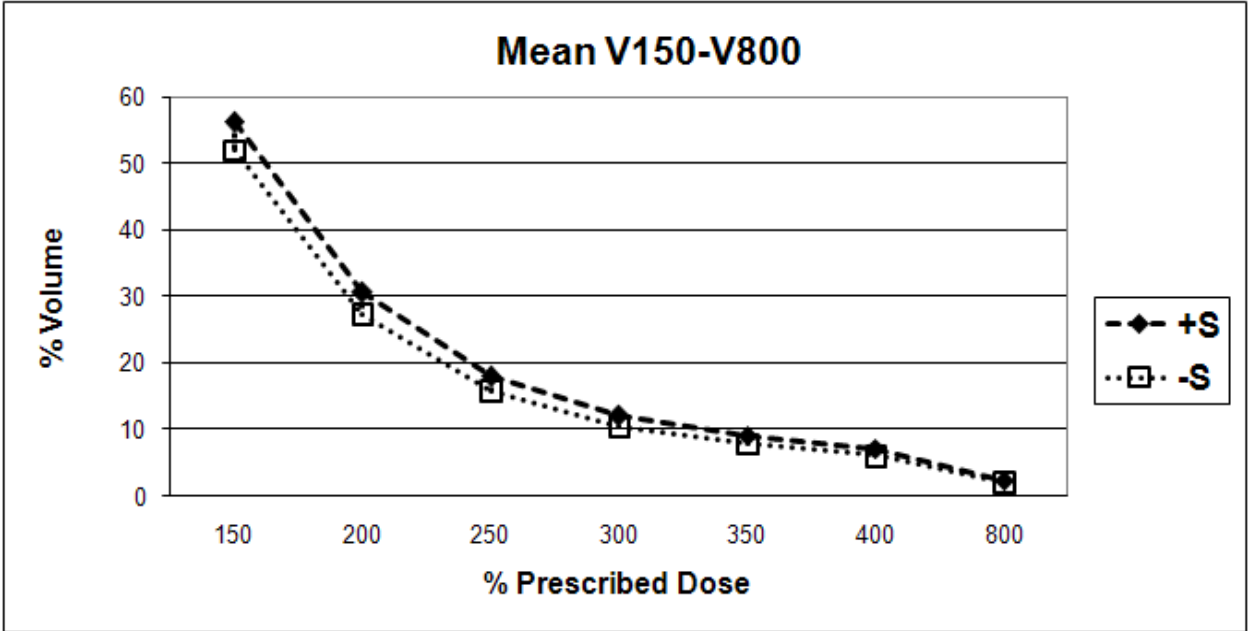
Fig. 4. Mean Prostate V150-800 for the implants performed with (+S) and without (-S) spacers.

The mean V150 and V200 for the **+S** were 56.3% and 30.6% of the prostatic volume respectively compared to 52.0% and 27.4% of the prostatic volume respectively for the **-S** group. While the differences in the V150 and V200 are surprisingly higher for the **+S** as compared to the **-S** cohort these differences failed to be statistically significant but were trending (p=0.077 and p=0.058 respectively). This trend of higher V values for the **+S** cohort as compared to the **-S** group continued. The **+S** mean V250, V300,V350, V400 and V800 are 17.9%, 12% , 9.1%, 7.1% and 2.4% of the total prostatic volume respectively and are elevated compared to these same values for the **-S** cohort which are, 15.8%, 10.5%, 7.8%, 6.1% and 2% of the total prostatic volume respectively (Figure 3). Statistical analysis demonstrated that for each of these measurements that the percentage of volume of the prostate receiving 2.5-8 times the prescribed dose was significantly higher for the **+S** cohort. A plot of total implanted activity as a function of prostate volume for both the +S and –S cohorts is shown in Figure 5. This plot shows that the total implanted activity is the same for implants using spacers or not, which confirms the dosimetric data.

4. Review of implants

The development of the RadioCoil™ linear ^{103}Pd source prompted studying the use of Pd-103 seeds linked in a continuous linear fashion, in order to decrease the number of implant needles and possibly decrease toxicity. This study was not intended to assess toxicity, but rather to compare post-implant dosimetry for patients receiving implants using conventional spacers with those whose implants used seeds continuously linked without spacers. Interestingly there are few dosimetric differences between the two groups.
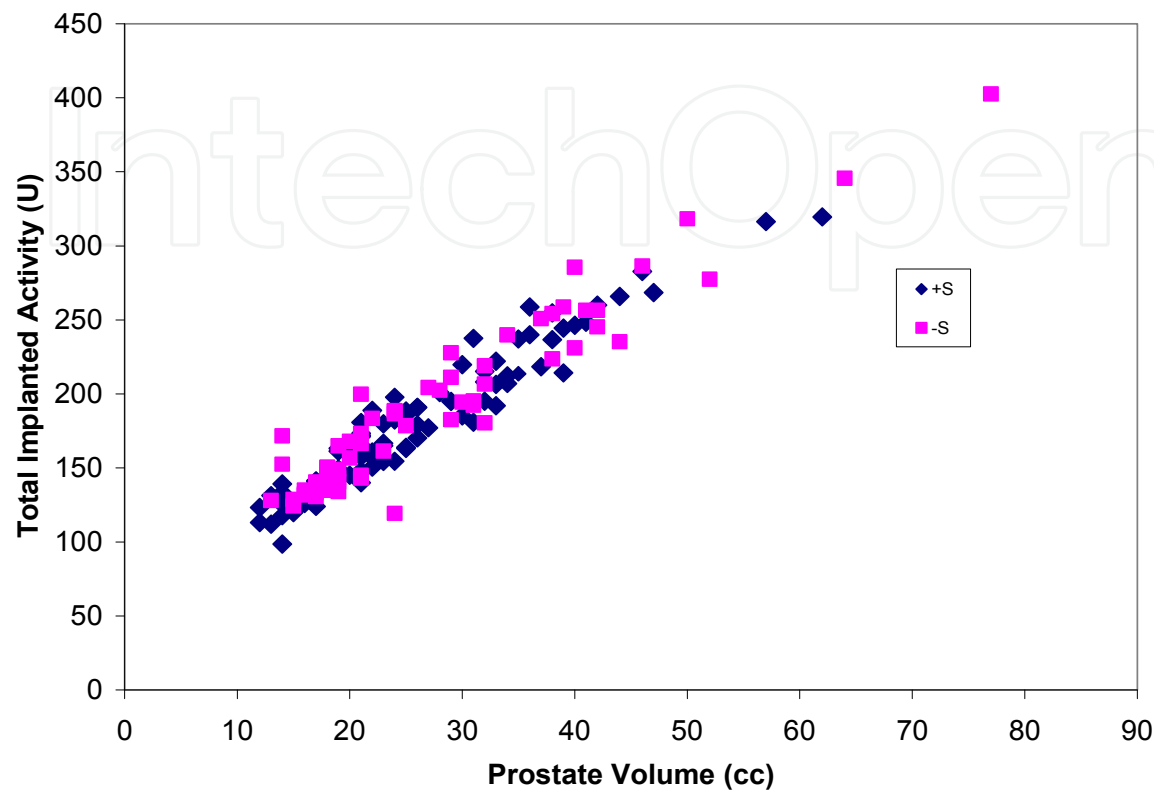
Fig. 5. Total Implanted activity as a function of prostate volume for the two arms of the study

Our data show a significant decrease in the volume of prostate tissue receiving greater that 100% of the prescribed dose (V250-V800) in the **-S** patients. This result was not expected. One of the main concerns about using continuous sources is the creation of "hot spots". However, our data show that this is not the case. All of the mean V values calculated for the **-S** cohort were less than those of the **+S** cohort.

The elimination of spacers between seeds allowed a significant decrease in the total number of needles used during prostate implants. This may prove to be clinically significant since needle trauma likely plays a role in post implant morbidity. Acute urinary toxicity is the predominant side effect of prostate brachytherapy and acute urinary retention (AUR) is a well recognized and described early toxicity (Mallick, et al, 2003). Most obstructive symptoms occur quickly after the implant procedure before the dose deposited by the sources to the surrounding tissue can reach a significant level (Bucci, et al, 2009). This suggests that prostatic trauma from the procedure is the predominant factor in obstructive urinary symptoms. Studies have been conducted to try to identify factors that predict post implant AUR.

There have been many studies reporting on AUR rates after prostate brachytherapy, with the number of needles used, the number of seeds implanted, hormonal manipulation, pre-implant prostate volume, the level of post-implant prostatic edema, and diabetes all linked to increased AUR rates(Ohashi, et al 2006, Bucci, et al, 2002, Lee, et al 2000, Buskirk, et al, 2004, Bottomley, et al, 2007, Keyer, et al, 2009, Thomas, et al 2008, Macdonald, et al, 2005). While there are no large randomized controlled trials, many of the references cited provide evidence that prostate gland trauma caused by needle insertion during brachytherapy implant plays some role in the development of post-operative AUR. Therefore, decreasing the number of needles required to perform quality implants could play a role in decreasing post implant AUR. It remains to be seen if reduced AUR is seen in patients undergoing **-S** compared to **+S**. It is important to note that decreasing the number of needles used for prostate implantation can predispose to unwanted hot or cold regions if the needle position is not placed correctly. Thus, this technique should only be undertaken by experienced brachytherapy teams.

The use of a retrospective, rather than a randomized, method to study possible dosimetric differences between the +S and –S arms of the study could have led to errors associated with all non-randomized trials. The use of Day 30, rather than or in addition to Day 0 CT scans, may have shown either differences in the data not present in the Day 0 or allowed the tracking of the dosimetric parameters as a function of time.

5. Conclusion

This study was designed as an analysis of prostate seed implants comparing the dosimetric characteristics of implants performed both with **(+S)** or without **(-S)** the use of spacers between the seeds**.** The results presented in this study show that **+S** and **-S** implants were dosimetrically similar, with a significant reduction in the number of needles required for the treatments without the use spacers **(-S)**. Analysis of the total implanted activity as a function of prostate volume are essentially identical between the two arms of the study, which helps to clarify the similarity in dosimetric characteristics of the **–S** and **+S** implants. Studies have shown that the number of needles used for brachytherapy correlates to AUR; therefore, we expect a decreased rate of AUR with this technique. It remains to be evaluated what significance implants with **-S** has on urinary quality of life.

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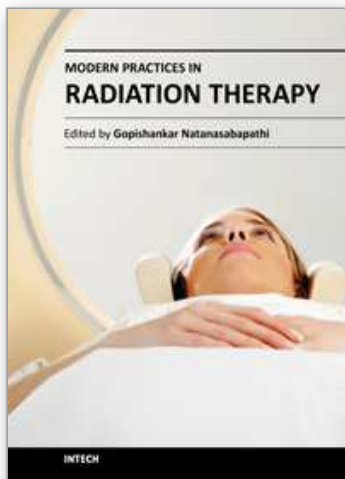
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