Evaluation of the dosimetric impact of loss and displacement of seeds in prostate low-dose-rate brachytherapy

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Abstract

Purpose: To analyze the seed loss and displacement and their dosimetric impact in prostate low-dose-rate (LDR) brachytherapy while utilizing the combination of loose and stranded seeds.

Material and methods: Two hundred and seventeen prostate cancer patients have been treated with LDR brachytherapy. Loose seeds were implanted in the prostate center and stranded seeds in the periphery of the gland. Patients were imaged with transrectal ultrasound before implant and with computerized tomography/magnetic resonance imaging (CT/MR) one month after implant. The seed loss and displacement had been analyzed. Their impact on prostate dosimetry had been examined. The seed distribution beyond the prostate inferior boundary had been studied.

Results: The mean number of seeds per patient that were lost to lung, pelvis/abdomen, urine, or unknown destinations was 0.21, 0.13, 0.03, and 0.29, respectively. Overall, 40.1% of patients had seed loss. Seed migration to lung and pelvis/abdomen occurred in 15.5% and 10.5% of the patients, respectively. Documented seed loss to urine was found in 3% of the patients while 20% of patients had seed loss to unknown destinations. Prostate length difference between pre-plan and post-implant images was within 6 mm in more than 98% of cases. The difference in number of seeds inferior to prostate between pre-plan and post-implant dosimetry was within 7 seeds for 93% of patients. At time of implant, 98% of seeds, inferior to prostate, were within 5 mm and 100% within 15 mm, and in one month post-implant 83% within 9 mm and 96.3% within 15 mm. Prostate post-implant V100, D90, and rectal wall RV100 for patients without seed loss were 94.6%, 113.9%, and 0.98 cm³, respectively, as compared to 95.0%, 114.8%, and 0.95 cm³ for the group with seed loss.

Conclusions: Seed loss and displacement have been observed to be frequent. No correlation between seed loss and displacement and post-plan dosimetry has been reported.

Key words: brachytherapy, dosimetry, LDR, prostate cancer, seeds.

Purpose

Low-dose-rate (LDR) brachytherapy utilizing permanent implant of radioactive seeds is a highly effective treatment option for low and intermediate risk prostate cancer patients [1-3]. In LDR brachytherapy treatment for prostate cancer patients, seed loss and seed displacement are well-recognized [4-12]. Due to inaccuracies in seed placement, blood flow, muscular forces, and edema post-implant, the implanted seeds may experience redistribution and displacement from their intended positions. Although seeds may migrate in any direction, they tend to move more easily along the needle track in the superior-inferior direction [13]. Some of the implanted seeds could even migrate to lung, abdomen, pelvis, or get excreted in urine. In some cases, even after extensive investigation and imaging, the destination of part of the seeds could not be confirmed.

In LDR prostate brachytherapy loose seeds and/or stranded seeds are used. Seed loss and migration after implant and their dosimetric effect have been studied by a number of groups. Taussky et al. studied 495 patients treated with I-125 loose seeds using an automated seed delivery system and found that the percentage of patients experiencing seed loss gradually decreased from 38% for...
the first 100 patients to 9% for the last 100 patients as they gained more experience [4]. Gao et al. simulated the effects of seed migration on post-implant dosimetry based on 14 patients treated with loose Pd-103 seeds [5]. They concluded that on average prostate D90 will decrease 1% in 2 mm mean migration and 6% in 6 mm mean migration. Prostate V100 was less sensitive to migration than D90. They also found that the range of the dose change depends on the distance of seed migration. Knaup et al. reported their studies on five patients’ plans, each of them planned with I-125, Pd-103, and Cs-131 loose seeds [6]. Their simulation was done by removing 1, 2, or 3 seeds closest to urethra or the exterior prostatic capsule. They found a reduction of 2%, 5%, and 7% in D90 for loss of 1, 2, or 3 seeds through the urethra, respectively. They also found that the dosimetric effect of seed loss near the exterior of the prostate through the prostatic veins was less severe than that of seed loss through the urethra. Pinkawa et al. studied 61 patients treated with stranded seeds [7]. Inferior displacements were found between 2.2 and 5.3 mm for four groups of seed locations. The comparison of seed loss and migration between loose seeds and stranded seeds was also investigated by several authors. Fuller et al. found that stranded seeds were associated with decreased seed migration and higher prostate and urethra dosimetry values when compared to loose seeds [8]. Saibishkumar et al. reported that the overall seed loss was greater in the stranded seed cohort than in the loose seed cohort (1.1% of total seeds vs. 0.6%) [9]. Kaplan et al. found that the average radial deviation of the loose seeds from the planned position was 3.1 mm, while that of the suture embedded seeds was 3.7 mm, and there was no improvement in the final dosimetry when suture embedded seeds were used [10]. Ishiyama et al. compared pre-plan technique, intraoperative pre-plan technique, and interactive plan technique and found no significant difference in biochemical control among the three groups but the interactive plan showed a significant reduction of the seed migration rate compared to the two other groups [12].

In the above investigations, particular emphasis was placed on either loose seeds or stranded seeds. Recently, Langley et al. reported a new one-stage prostate brachytherapy technique using a combination of stranded and loose seeds [14]. Their data showed significantly improved dosimetry (D90 and V100) for the techniques using both stranded and loose seeds when compared to stranded seeds only. In this study, we analyzed the seed loss and displacement in prostate cancer patients treated with LDR brachytherapy with loose seeds implanted in the prostate center and stranded seeds in the periphery of the gland. The dosimetric effect caused by the seed loss and displacement was also examined.

Material and methods

Patient population

In this retrospective study, data from 217 consecutive low- and intermediate-risk prostate patients treated between March 2009 and December 2012 with LDR brachytherapy at Princess Margaret Cancer Centre were analyzed. Eligibility criteria for the study were patients aged eighteen years or older with histologically confirmed prostate cancer, and no evidence of metastases. All patients studied had pretreatment planning utilizing transrectal ultrasound (TRUS), implant procedure with I-125 seeds, prescribed dose of 145 Gy, and post-implant dosimetry at one month based on magnetic resonance imaging (MRI) and computerized tomography (CT) pelvic scans.

Treatment planning

All patients were imaged with BK ProFocus trans-rectal ultrasound (TRUS) machine (BK Medical Aps, Herlev, Denmark) for prostate brachytherapy treatment planning and volume study 2-4 weeks prior to implant. The scanning was performed at 9 MHz transducer frequency. Transverse images were recorded at 5 mm slice spacing and then downloaded to the treatment planning system. Treatment planning was conducted on VariSeed (Varian Brachytherapy, Charlottesville, VA, USA) using modified peripheral loading technique. The prescription was 145 Gy minimum peripheral dose (mPD) to prostate [15]. The clinical target volume was defined as the prostate with an anterior and lateral margin of 3 mm, and a 5 mm margin in the cranial and caudal directions respecting anatomic boundaries like bladder wall and rectal wall. There was no posterior margin extended towards the rectum. For intermediate risk prostate cancer patients, lateral margins were 5 mm. Prostate contours were drawn and plans utilizing seeds with a mean air kerma strength of 0.435 ± 0.036 U were placed on images with 5 mm spacing. The measured prostate lengths were not in increments of 5 mm, so depending on the measured length of prostate, seeds were planned 2.5 to 7.5 mm below prostate.

The dosimetry goals for pre-plans were to achieve prostate V100 (the percentage of the prostate volume receiving 100% of the prescribed dose or more) greater than 99%, D90 (the percentage of the prescribed dose received by 90% volume of the prostate) between 120% and 125% of the prescription dose, and V100 (the percentage of the prostate volume receiving 150% of the prescribed dose or more) between 55% and 62%. For organs at risk, the urethral dose was to keep UD3 (the dose that is received by 5% volume of the prostatic urethra) under 150% and UD3 (the dose that is received by 30% volume of the prostatic urethra) limited to 125% of the prescription dose [16,17]. RV100 (the absolute volume of the rectal wall to receive 100% of the prescription dose or more) was planned to be less than 1.0 cm3.

Implant procedure

Permanent seed implantation was performed under general anesthesia. The patient was positioned in lithotomy as close to the exact position as possible as at the time of the mapping session. Under TRUS guidance, trans-perineal insertion of seeds utilizing template and needles was performed according to the pre-treatment plan. For each patient, I-125 loose seeds (Oncura 6711, Oncura-GE Healthcare, Arlington Heights, IL, USA) were implanted in the prostate center, while I-125 stranded seeds (Oncura

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Table 1. The mean number of seeds lost to lung, pelvis and abdomen, urine, and unknown destination per patient, and the percentage of patients experiencing seed loss to each of the above destinations

| Seed loss | Destination | Lung | Pelvis/Abdomen | Urine | Unknown | Overall |
|-----------|-------------|------|----------------|-------|---------|---------|
| Mean number per patient |             | 0.21 | 0.13 | 0.03 | 0.29 | 0.67 |
| Standard deviation |             | 0.55 | 0.41 | 0.17 | 0.66 | 1.06 |
| Percentage of patients (%) |     | 15.5 | 10.5 | 3.0 | 20.0 | 40.1 |

Results

Seed loss

The mean number of implanted seeds per patient was 110.2 (range: 75-155, standard deviation or SD: 16.4). The mean number of seeds per patient lost to lung, pelvis/abdomen, urine, or unknown destination (± SD) was 0.21 ± 0.55, 0.13 ± 0.41, 0.03 ± 0.17, and 0.29 ± 0.66, respectively. The number of seeds lost per patient, combining all destinations was 0.67 ± 1.06. Overall, 40.1% of patients experienced some kind of seed loss. Seed lost to lung occurred in 15.5% of the patients. In 10.5% of the patients, there was seed lost to the pelvis or the abdomen. Documented seed loss in urine occurred in 3% of the patients, while 20% of patients have seed lost to unknown destination. Table 1 summarized the seed loss results. Examples of seed loss to lung and pelvis are shown in Fig. 1.

Overall, the trend of seeds lost against the seeds implanted was toward the decrease. This is evident as shown in Fig. 2, where the y-axis is the number of seeds lost, and the x-axis is the number of seeds implanted, both accumulated over time. For the first 20 patients, the slope of the linear fit was 0.0145 and was much steeper than that for the next 30 implants (0.0074). The slope of the linear fit was further decreased to 0.0053 for the remaining implants.

The mean number of seeds lost per patient (± SD) was 1.35 ± 1.69, 0.77 ± 0.94, and 0.57 ± 0.96 for the first 20, the next 30, and the remaining patients, respectively.

The relationship between seed loss and the prostate volume post implant is shown in Fig. 3. The prostate volume ranged from 19.9 to 87.5 cm³ with a mean (± SD) of 42.5 ± 12.0 cm³, and was grouped with a bin size of 10 cm³. The number of seed loss per patient was 0.00, 0.17, 0.55, 0.82, 1.00, 0.80, 1.00, and 1.50 for the groups with a volume from the first bin (between 10 to 20 cm³), to the last bin (between 80 to 90 cm³), respectively. The seed loss rate (the ratio of the number of seeds lost to the number of seeds implanted) was 0.0%, 0.2%, 0.5%, 0.7%, 0.8%, 0.6%, 0.7%, and 1.0% for the corresponding groups, respectively. The mean seed loss rate of all prostate volume groups was 0.6 ± 0.2%.

Seeds inferior to prostate and seed displacement

Prostate length prior to the seed implantation procedure, measured by TRUS, was compared to prostate length one month after the procedure measured on CT/MR images. This analysis was performed to account for
the bias that may result from disparity in prostate lengths between pre- and post-implant images while calculating seed displacements. The mean prostate length (± SD) was 39.7 ± 5.1 mm (range: 26.0-56.1 mm), and 39.3 ± 4.7 mm (range: 27-57 mm), pre- and post- implant, respectively (*p = 0.4968*). Most (78.4%) of the prostate length differences between one month post-implant and pre-implant are within 3 mm, while 19.8% of them are greater than 3 mm but within 6 mm. There were only two (1.8%) implants with a prostate length difference beyond 6 mm (6.5 and 6.6 mm, respectively). The mean prostate length difference (± SD) was -0.3 ± 2.5 mm.

The change in number of seeds inferior to the prostate from pre- to post-implant was studied to quantify the seed displacement. The mean number (± SD) of the inferior seeds per patient was 9.2 ± 2.2 (range: 4-14) in the pre-plan, compared to 8.2 ± 4.5 (range: 0-30) one month post procedure.

The difference in the number of seeds inferior to the prostate from pre- to post-implant was studied to quantify the seed displacement. The mean number (± SD) of the inferior seeds per patient was 9.2 ± 2.2 (range: 4-14) in the pre-plan, compared to 8.2 ± 4.5 (range: 0-30) one month post procedure.

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Pre-implantation plan and post-implant dosimetry was -1 ± 4.5 seeds.

All seeds inferior to prostate apex were planned within 5 mm of prostate. At the implant procedure, 98.4% of these seeds were observed within 5 mm of the prostate apex, 99.8% of them were within 10 mm, and 100% were within 15 mm. The percentage of the seeds inferior to the prostate as identified in the CT/MR images one month post-implant is shown as a function of distance from the prostate apex in Fig. 4. 96.3% of all inferior seeds were within 15 mm from the prostate apex. The remaining 3.7% of the inferior seeds were located more than 15 mm beyond the prostate, two seeds of which (each from a different patient) were 30 mm below the prostate.
The one (0.056% of all inferior seeds) far most seed (found in another patient) was 33 mm inferior to the prostate apex.

**Dosimetric impact of seed loss and seed displacement**

**Seed loss**

For the whole population studied, the post-plan mean values (± SD) for prostate V\textsubscript{100} and D\textsubscript{90} were 94.7% ± 3.8% and 114.2% ± 10.6%, respectively. To find out how seed loss affected post-implant prostate dosimetry, implants were divided into two groups, one without any seed loss and another with at least one seed lost. V\textsubscript{100} mean value for the group without seed loss (n = 130) was 94.6% with a standard deviation of 3.5% (range: from 83.4% to 99.9%), while the mean value for the group with seed loss (n = 87) was 95.0% with a standard deviation of 4.2% (range: from 67.1% to 99.7%). The difference in post-plan prostate V\textsubscript{100} (p = 0.49) was not significant (Fig. 5).

The mean post-plan D\textsubscript{90} (± SD) for the group without seed loss (n = 130) was 113.9% ± 10.6% (range: 89.0-138.0%), compared to 114.8% ± 10.7% (range: 79.4-136.4%) in the group experiencing seed loss (n = 87) (p = 0.52) (Fig. 5).

The rectal wall RV\textsubscript{100} was 0.98 and 0.95 cm\textsuperscript{3} with a standard deviation 0.68 and 0.61 cm\textsuperscript{3} for the groups without and with seed loss, respectively (p = 0.80).

The post-implant prostate V\textsubscript{100}, D\textsubscript{90} and rectal wall RV\textsubscript{100} for the patient who lost 6 seeds (the maximum number of seeds lost per patient) out of 109 seeds implanted were 98.9%, 108.6%, and 0.61 cm\textsuperscript{3}, respectively. Both cases are considered acceptable.

**Seed displacement**

The mean percentage of changes in the number of seeds inferior to prostate (the change in the number of seeds inferior to prostate divided by the total seeds implanted) was -1.1% with a standard deviation of 4.1%, ranging from -11.7% to 12.7%. All extreme cases (with change beyond two times the standard deviation, or 8.2%) were identified, and their inferior seeds and prostate V\textsubscript{100} and D\textsubscript{90} post-implant along with their changes from the pre-plan were summarized in Table 2. The mean value of the post-plan prostate V\textsubscript{100} for these 12 cases was 94.7% with a standard deviation of 2.7% (a 5.0% ± 2.3% decrease from the pre-plan), and was identical to the mean value for the whole population other than these 12 cases, i.e. 94.7% ± 3.8% (a 5.2% ± 3.8% decrease from the pre-plan).

The mean post-plan D\textsubscript{90} for these 12 cases was 114.7% with a standard deviation of 8.6% (a decrease of 9.3% ± 7.6% from the pre-plan) and was similar to the mean D\textsubscript{90} for the whole population other than these 12 cases, i.e. 114.2% ± 10.7% (a decrease of 10.6% ± 10.0%).

The mean rectal wall RV\textsubscript{100} Post-implant was 0.97 ± 0.58 cm\textsuperscript{3} for the 12 cases, similar to 0.97 ± 0.66 cm\textsuperscript{3} for all other patients.

The 12 cases listed in Table 2 experiencing significant seed displacement were all acceptable and there were no differences from other cases studied, in terms of post-plan prostate V\textsubscript{100} and D\textsubscript{90} and rectal wall RV\textsubscript{100}.

**Discussion and conclusions**

The seed loss and seed displacement of 217 consecutive patients treated using LDR brachytherapy were examined. Overall, 40.1% of patients experienced seed loss to lung, pelvis and abdomen, urine, and/or unknown destination, while seed migration to lung occurred in 15.5% of the patients. The mean number of seeds lost per patient was 0.67 with a standard deviation of 1.06. The dosimetric impact of seed loss was insignificant when compared with implants without any seed loss.

The seed displacement in post-implant scans was minimal in terms of the displaced distance from prostate as well as the number of displaced seeds compared to pre-plan. The change in the number of seeds inferior to prostate

| Implant # | # Of inferior seeds | % Change of inferior seeds | Prostate V\textsubscript{100} (%) | Prostate D\textsubscript{90} (%) | Rectal wall RV\textsubscript{100} (cc) |
|-----------|---------------------|---------------------------|-------------------------------|-------------------------------|----------------------------------|
| 16        | 3 (-7)              | -8.3                      | 94.6 (-5.4)                   | 112.8 (-8.8)                  | 0.76 (0.29)                      |
| 22        | 24 (+16)            | 12.7                      | 95.7 (-4.3)                   | 120.7 (-16.4)                 | 0.62 (0.57)                      |
| 27        | 19 (+10)            | 8.5                       | 95.1 (-4.9)                   | 116.9 (-7.7)                  | 0.79 (0.57)                      |
| 72        | 16 (+8)             | 8.5                       | 95.9 (-4.1)                   | 116.9 (-7.8)                  | 0.09 (+0.08)                     |
| 123       | 1 (-7)              | -8.5                      | 95.0 (-5.0)                   | 111.3 (-11.6)                 | 0.43 (+0.23)                     |
| 125       | 0 (-10)             | -11.2                     | 96.4 (-3.6)                   | 115.7 (-7.7)                  | 1.00 (+0.95)                     |
| 130       | 2 (-9)              | -8.5                      | 96.0 (-4.0)                   | 126.4 (-2.4)                  | 1.98 (+1.70)                     |
| 140       | 1 (-11)             | -11.7                     | 88.9 (-8.8)                   | 98.0 (-14.0)                  | 1.70 (+1.44)                     |
| 146       | 17 (+11)            | 9.4                       | 96.5 (-3.4)                   | 116.9 (-4.2)                  | 1.00 (+0.61)                     |
| 196       | 30 (+17)            | 12.1                      | 94.1 (-5.6)                   | 114.9 (-7.3)                  | 1.81 (+0.86)                     |
| 198       | 25 (+14)            | 12.6                      | 90.2 (-9.8)                   | 100.5 (-27.0)                 | 0.55 (+0.19)                     |
| 200       | 4 (-9)              | -9.1                      | 98.3 (-1.6)                   | 125.7 (-1.5)                  | 0.86 (+0.23)                     |

V\textsubscript{100} – the percentage of the prostate volume receiving 100% of the prescribed dose or more, D\textsubscript{90} – the percentage of the prescribed dose received by 90% volume of the prostate, RV\textsubscript{100} – the absolute volume of the rectal wall to receive 100% of the prescription dose or more

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the prostate was within 7 seeds for 93% of patients, when compared to pre-plan. Eighty three percent of seeds inferior to prostate post-implant were within 9 mm from the prostate apex. There was no correlation between seed displacement and post-plan dosimetry in terms of prostate V100 and D90, and rectal wall RV100.

Despite our meticulous imaging with both MRI and CT scans for the dosimetry studies, in 20% of the patients, at least one seed went to unknown destination. This phenomenon is a significant contributor to the overall percentage of patients (40.1%) who experienced seed loss. While a small uncertainty in seed counting may explain this difference in some of the patients, we believe that in many of these patients the seeds lost were excreted in the urine but not documented, which may not be always accounted to seeds lost in other study [4]. Seed migration to other organs not imaged is possible and is documented in rare case reports. The relative high number of seeds implanted due to the low seed activity may also increase the probability of seed loss [19]. Our overall seed loss percentage of patients is comparable to those reported in the literature [4,20-22].

In general, the number of seeds lost per patient increased with the prostate volume. This is understandable since the number of seeds implanted increased with prostate volume. The mean seed loss rate was 0.6% and is similar to that reported in the literature [4,9,23].

Our study showed that neither seed loss nor seed displacement affects post implant prostate dosimetry. These results are consistent with the findings of Gao et al. [5] and Beaulieu et al. [19]. The possible reasons are the relative large number of seeds implanted, the optimal individual seed activity, the negligible mean number of seeds lost, and the insignificant seed displacement in terms of the displaced distance from prostate as well as the number of displaced seeds.

Pre-implant planning was performed utilizing US images, while post implant dosimetry used CT and MRI scans. This is actually the standard practice in most centers employing the pre-plan technique. Comparing images obtained by different modalities can be challenging, but as both US and MRI can identify the prostate boundaries with high accuracy, this comparison is suitable. Todor et al. described the post-implant intra-operative dosimetry using US images to identify the prostate, and cone beam CT to identify the seeds [24]. While that technique is promising, further data is needed before replacing the standard CT/MRI imaging with the US dosimetry.

While the dosimetry of the whole prostate is not affected by seed loss or migration, the dosimetry of specific sectors of the prostate may be affected. Several groups have previously shown that in I-125 seed brachytherapy, anterior prostate base receives a lower dose and apex receives a higher dose compared with pre-implant planned dose coverage [25-27]. Moreover, we have recently shown that the dose coverage of the clinical target volume of the prostate, defined as the prostate plus a 3 mm margin around it, is worse in patients with prostatic edema [28]. Clearly, seed loss in patients with prostatic edema would further worsen the dosimetry.

Regular chest X-ray imaging following LDR seed implantation is not a routine practice in most centers. The main reason that this is not done is the fact that there is not much to do once seed migration to lung is identified. Recent report about a non-smoker patient, who was diagnosed with small cell lung cancer 10 years after LDR prostate brachytherapy, with a brachytherapy seed detected in the surgical specimen, raises concern that seed migration to lung has potential consequence [29]. In this study, we showed that seed loss and migration rates were comparable to the ones reported in the literature and that it has no impact on the overall quality of the implant. Even though in this study, the implant quality was not affected by current rate of seed loss and displacements, we are now using all stranded seeds in order to avoid seed migration to critical organs.

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Disclosure

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