Original

# Prostate Cancer Permanent Seeds Implant:Interobserv Volume Reconstruction Variability and Differences in Post-Implant Dosimetry

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## Abstract

**Introduction:** An increasing number of prostate permanent seeds implant (LDR) procedures are being performed annually for localized prostate cancer (CaP). As local intraprostatic radiotherapy, LDR needs exact volume and dose calculations before and after the implant of the radioactive sources. Post-implant dosimetric analysis is mandatory and is generally evaluated by CT. As different physicians can differ in their volume definition of the prostate gland on the same post-implant CT images, the final dosimetric quality of the implant may also vary. **Material and Methods:** Our purpose is to identify the degree of agreement among three professionals skilled on prostate imaging and the dosimetric consequences of any disagreement in the sets of images from 36 consecutive patients submitted to LDR as monotherapy at Hospital A.C. Camargo (São Paulo, Brazil) from February 2005 to July 2006. **Results:** Median reconstructed prostate volumes ranged from 20.0 cc to 70.3 cc. Student´s t-test showed significant differences in the prostate volumes among the 3 observers ($p < 0.001$, $p < 0.001$ and $p = 0.010$, respectively). The Pearson´s correlation coefficient was 0.912 for prostate volumes, 0.762 for D90, 0.932 for V100 and 0.935 for V150 when all reviewers were considered. The global test revealed significant differences in D90, V100 and V150 among the reviewers ($p < 0.0001$). **Conclusion:** CT-based post-implant dosimetry allow the calculation of dose delivered to the prostate and surrounding and intra-prostatic normal tissues, but this method does not provide enough information to allow observers to reproducibly delineate the prostate volume without any discordance, which impacts in the final dosimetry.

**Keywords:** prostate neoplasm, Brachytherapy dosage

## Introduction

Prostate cancer (CaP) is classified as being low, intermediate or high-risk for biochemical failure, thus, it dramatically affects outcomes. Surgery, external beam radiotherapy, high temporary or low dose permanent brachytherapy (LDR), hormonal therapy, and watchful waiting can be used isolated or in combination to treat the different risk groups for biochemical failure.[1]

Whereas prostate LDR was first proposed almost one century ago, only in the last few decades has it emerged, thanks especially to transrectal ultrasound (TRUS), which has improved the visualization of seed implantation. In fact, an increasing number of prostate LDR procedures are being performed annually. Permanent prostate implants are currently planned by TRUS, as local intraprostatic radiotherapy needs exact volume and dose calculations before and after the implant of the radioactive sources. Once implant is completed, post-implant dosimetric analysis, generally evaluated by computed tomography (CT) imaging, is mandatory.

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The American Brachytherapy Society (ABS) has published guidelines for permanent prostate brachytherapy post-implant dosimetric analysis and it is stated that post-implant analysis should be performed on all patients, and a CT-based method is recommended. The dosimetric analysis is based on prostate volume (PV) outlined on sequential CT images.[2]

Assuming that different physicians can differ in their volume definition of the prostate gland on the same post-implant CT images, the final dosimetric quality of the implant may also vary. This study was performed to determine the degree of interobserver variability in the definition of the prostate gland on post-implant CT images, and its impact on the dosimetric parameters.

## Materials and Methods

The main objective of this study was to identify the degree of agreement among three professionals skilled on prostate imaging, regarding the delineation of the prostate on post implant. We also evaluated the dosimetric consequences of any disagreement.

Thirty-six consecutive patients with CaP, considered low risk for biochemical failure, were submitted to LDR as monotherapy at Hospital A.C. Camargo (São Paulo, Brazil) from February 2005 to July 2006. The author and two other experienced professionals on prostate imaging were recruited to participate in the study. Each observer was asked to outline the prostate gland on post-implant CT scans from the same 36 patients independently. The prostate volumes and dosimetric quantifiers resulting from these volumes were compared among the reviewers to determine the degree of agreement.

The dose prescription dose was 145 Gy, according to the American Association of Physicists in Medicine Task Group No. 43 (TG-43) formalism. All post-implant CT scans were performed 4 to 24 hours after completion of the LDR procedure. The CT scans were obtained according to an institutional protocol supervised by an experienced dosimetrist. Sequential CT images of 3 mm thickness with 3 mm spacing were obtained from L4-L5 lumbar transition until the end of the pelvis. Subsequently, all images were transferred electronically to VariSeed™ (Varian Medical Systems, Palo Alto, CA) treatment planning software. During the CT scan, all patients had a urinary Foley catheter in place and intravenously administered contrast placed into the bladder.

After delineation by the observers, 108 dose-volume histograms were generated. The prostate volumes were calculated and compared among the different observers as well as the commonly reported dosimetric parameters of implant adequacy (minimal dose received by 90% of the prostate gland [D90], percentage of prostate volume receiving 100% of prescribed minimal peripheral dose [V100] and percentage of prostate volume receiving 150% of prescribed minimal peripheral dose [V150]), using Student´s t-test and Pearson´s correlation coefficient (PCC).

## Results

Characteristics of patients are shown in Table 1. The reconstructed prostate volumes for all 36 patients according to each reviewer are presented in Table 2.

Prostate volume as assessed by TRUS for the preplan ranged from 19.3 to 49.5 $cm^3$ (median, 34.8 $cm^3$). The median number of seeds used per implant was 90 (range, 66-119), and the median activity was 0.45 mCi per seed (range, 0.29–0.49 mCi per seed).

**Table1**- Patient Characteristics

| Variable | n | % | Range | Median |
|---|---|---|---|---|
| Age (years) | | | | |
| < 60 | 13 | 36.1 | | |
| >60 <71 | 12 | 33.3 | 44-83 | 64.5 |
| > 71 | 11 | 30.6 | | |
| TNM | | | | |
| T1c | 29 | 80.6 | | |
| T2a | 4 | 11.1 | | |
| T2b | 3 | 8.3 | | |
| GS | | | | |
| < 6 | 30 | 83.3 | | |
| = 7 | 6 | 16.7 | | |
| PSAi (ng/ml) | | | | |
| < 4 | 5 | 13.9 | | |
| >4 < 10 | 29 | 80.6 | 2.9-13.1 | 6.3 |
| > 10 | 2 | 5.6 | | |
| Pre-operative Prostate volume(cc) | | | | |
| < 30 | 11 | 30.6 | | |
| >30 <40 | 16 | 44.4 | 19.3-49.5 | 34.8 |
| > 40 | 9 | 25.0 | | |
| Status | | | | |
| NED* | 35 | 97.2 | | |
| BF ** | 1 | 2.8 | | |

*no evidence of disease ** biochemical failure

Student´s t-test showed significant differences

**Table 2** – Prostate volumes by different observers

| Post-operative Prostate volume cc | Observer 1 N (%) | Observer 2 N (%) | Observer 3 N (%) |
|---|---|---|---|
| < 30 | 7 (19.4) | 2 (5.6) | 2 (5.6) |
| >30 <40 | 13 (36.1) | 11 (30.6) | 13 (36.1) |
| > 40 | 16 (44.4) | 23 (63.9) | 21 (63.9) |
| Range | 23.0-64.7 | 20.0-68.7 | 22.7-70.3 |
| Median | 39.2 | 45.7 | 46.5 |
| Standard Deviation | 10.5 | 12.7 | 12.2 |

in the prostate volumes reconstructed among the three observers, p <0.001, p <0.001 and p =0.010, respectively (Table 3).

The dosimetric parameters D90, V100 and V150 are presented in Table 4. Student´s t-test for the different dosimetric quantifiers is shown in Table 5.

PCC was 0.912 for prostate volumes, 0.762 for D90, 0.932 for V100 and 0.935 for V150 when all reviewers were considered. The global test revealed significant differences in D90, V100 and V150 among the reviewers (p <0.0001) (Table 6).

**Table 3** – Student´s t-test for the prostate volumes among three observers

| Pair | | | Paired Differences Mean | SD | 95% CI Lower | 95% CI Upper | t | p |
|---|---|---|---|---|---|---|---|---|
| Pair 1 | Obs1 | Obs2 | -5.08 | 6.25 | -7.19 | -2.97 | -4.88 | < 0.001 |
| Pair 2 | Obs1 | Obs3 | -7.41 | 5.02 | -9.11 | -5.72 | -8.86 | < 0.001 |
| Pair 3 | Obs2 | Obs3 | -2.34 | 5.11 | -4.06 | -0.61 | -2.74 | 0.010 |

**Legend:** obs = observer; SD = standard deviation; CI = Confidence Interval of the Difference; Sig = significance

**Table 4** - Mean and SD of the D90 and V100 for Observers 1, 2, and 3

| Variable | D90 (SD) | V100 (SD) | V150 (SD) |
|---|---|---|---|
| Observer 1 | 72.6-122.4 (10.7) | 18.6-60.5 (9.9) | 4.3-40.7 (8.9) |
| Observer 2 | 56.1-118.5 (16.9) | 19.2-60.9 (11.2) | 4.8-45.2 (9.1) |
| Observer 3 | 51.5-119.5 (16.2) | 21.3-62.7 (11.8) | 5.4-48.3 (9.5) |

**Legend:** D90 = percentage of dose received by 90% of the prostate volume; V100 = percentage of prostate receiving >145 Gy; V150 = the percentage of the prostate volume receiving 150% of the prescription dose.

## Discussion

The ability to accurately assess the dosimetry of a completed implant is essential. Familiarity with the anatomy is important, while avoiding the inclusion of adjacent veins or muscles in the contour is essential, but not easily reproducible for independent observers. The ABS has established parameters used to assess the quality of an implant, recommending that at least the V100, D90, and V150 must be reported for every implant.[3]

Merrick et al.[4] have suggested that a V100 >80% or a D90 >90% of the prescribed dose are the minimum values to be considered for an implant of good quality.

This study was performed to identify the degree of agreement among three skilled professionals on the delineation of the prostate and to determine the dosimetric consequences of any disagreement. Our results indicated that some discrepancy among different observers exists, and more importantly, this discrepancy has consequences for reporting the commonly used dosimetric quantifiers, the D90, V100 and V150 with two-thirds of discrepancy with statistical significance among the different observers.

One important factor is that prostate volumes determined from CT scans tend to be 25–50% larger than when the volume is determined by TRUS,[5-7] probably as consequence of the implant and edema related to implantation. It must be underscored that most post-implant CT scans in this report were obtained on the first postoperative day, the period of maximal prostate swelling, despite the use of corticosteroids administered to avoid it. Badiozamani et al. reported

**Table 5** – Student´s t-test for the different dosimetric quantifiers

| | | | Paired Differences | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Mean | SD | 95%CI | | t | p |
| | | | | | Lower | Upper | | |
| Pair 1 | d90obs1 | d90obs2 | 12.46 | 10.87 | 8.77 | 16.13 | 6.873 | 0.001 |
| Pair 2 | d90obs1 | d90obs3 | 12.21 | 10.66 | 8.60 | 15.81 | 6.868 | 0.001 |
| Pair 3 | d90obs2 | d90obs3 | -246 | 5.46 | -2.09 | 1.60 | -0.270 | 0.789 |
| Pair 4 | v100obs1 | v100obs2 | -1.45 | 4.63 | -3.02 | 0.11 | -1.880 | 0.068 |
| Pair 5 | v100obs1 | v100obs3 | -3.39 | 3.51 | -4.58 | -2.20 | -5.785 | 0.000 |
| Pair 6 | v100obs2 | v100obs3 | -1.94 | 4.15 | -3.34 | -0.53 | -2.799 | 0.008 |
| Pair 7 | v150obs1 | v100obs2 | -1.66 | 3.22 | -2.75 | -0.57 | -3.099 | 0.004 |
| Pair 8 | v150obs1 | v100obs3 | -1.06 | 2.33 | -1.84 | -0.26 | -2.723 | 0.010 |
| Pair 9 | v150obs2 | v100obs3 | 0.60 | 2.97 | -0.401 | 1.61 | 1.221 | 0.230 |

**Legend:** obs = observer; SD = standard deviation; CI = Confidence Interval of the Difference

**Table 6 –** Pearson´s correlation coefficients for the different variables

| | | v150 obs1 | v150 obs2 | v150 obs3 | v100 obs1 | v90 obs1 | v100 obs2 | v90 obs2 | v100 obs3 |
|---|---|---|---|---|---|---|---|---|---|
| v150 obs2 | Pearson´s Correlation | 0.935** | | | | | | | |
| v150 obs3 | Pearson´s Correlation | 0.970** | 0.950** | | | | | | |
| v100 obs1 | Pearson´s Correlation | 0.892** | 0.865** | 0.858** | | | | | |
| d90 obs1 | Pearson´s Correlation | 0.501** | 0.408* | 0.458** | 0.287 | | | | |
| v100 obs2 | Pearson´s Correlation | 0.807** | 0.853** | 0.824** | 0.914** | 0,225 | | | |
| d90 obs2 | Pearson´s Correlation | 0.509** | 0.341* | 0.479** | 0.351* | 0.783** | 0,272 | | |
| v100 obs3 | Pearson´s Correlation | 0.846** | 0.880** | 0.885** | 0.951** | 0.227 | 0,932** | 0,290 | |
| d90 obs3 | Pearson´s Correlation | 0.464** | 0.340* | 0.450** | 0.335* | 0.762** | 0.258 | 0.947** | 0,284 |

**Correlation is significant at the 0.01 level (2-tailed) *Correlation is significant at the 0.05 level (2-tailed) Legend: obs = observer

this evidence, observing the data of 10 patients who underwent LDR. All patients had TRUS and CT scans performed on the same day previous and post implant. The prostate was contoured on both studies by three different observers. They noted an excellent agreement between the TRUS- and CT-determined prostate volumes, as well as among the three observers, before the implant procedure, but the same degree of agreement could not be found after implantation, when a variable amount of post-implant edema was present at the time of CT imaging.[8] In view of this, it can be concluded that a better agreement in our study could have been obtained if the post-implant CT scans were performed 4 to 6 weeks after implantation, but data form have shown that post-implant CT performed on implant day and after 30 days demonstrates the same degree of discordance, and the major impact occurs in the dose to the rectum and not in the final dosimetry for the prostate, as shown by Taussky at al. [9]

The ability of defining the prostate volume is also dependent of the image acquisition method. Debois et al. investigated whether the use of MR imaging improves the ability to localize the apex of the prostate and the anterior part of the rectum for 10 consecutive patients with localized CaP. They observed that the variation of the prostatic apex location was

largest on CT (range, 0.54 to 1.07 cm) and smallest on coronal MR (range, 0.17 to 0.25 cm), concluding that the additional use of axial and coronal MR scans substantially improves the localization and delineation of the prostate.[10] Parker et al. also evaluated the differences in prostate volume definition by MR or CT. Based in phantom measurements, the authors noted that interobserver variation in prostate contouring was significantly less for MR compared to CT. [11]

Bice et al. have investigated the feasibility of performing a centralized post-implant analysis. They obtained CT images from 10 consecutive patients from five different centers. The objective was that the treating physician should delineate the prostate volume on the images, and the central reviewer also delineates the prostate volume in each case. They observed a tendency for the central reviewer to draw larger volumes relative to the treating physician ($p < 0.002$), but found no dosimetric differences despite the variation among observers.[12]

Lee et al. compared the prostate volumes and quantifiers of implant adequacy determined by five separate observers on 10 post-implant CT images from 10 patients. Prostate volumes, D90 and V100 were calculated for the different observers. As results they observed that the mean prostate volume and V100 was significantly different according to the individual reviewers, $p < 0.0001$. The reproducibility measured was fair, but was poor for the dosimetric quantifiers.

Crook et al. [13] also documented the interobserver variation in prostate contouring on post implant CT scans. They evaluated 10 patients in which implant dosimetry was calculated on four different copies of the post-implant CT scan. As results they observed a fairly good agreement between the TRUS preplan volume and the post-implant CT volume. They observed that differences in V100 ranged from 2.4% to 9.1% and for D90 from 9.3 Gy to 30.3 Gy, concluding that significant interobserver differences in prostate volume definition can exist.

Valicenti at al.[14] performed a similar study, but in that case they investigated the interobserver variation among observers on CT images used for planning of conformal external beam radiotherapy. In their study, seven different observers delineated the prostate and seminal vesicles from 10 consecutive patients. The intraclass correlation coefficient for their study was found to be 0.80 in patients simulated without contrast. These values indicate good to excellent reliability among the observers. The agreement in the study by Valicenti et al. [14] was lower than in the present study, which may be related to the long experience in prostate delineation of the observers recruited in this study, [14] but it must be emphasized that a good correlation does not connote good agreement, which can be observed in the final dosimetric results of our analysis, where the PCC was 0.912 for prostate volumes and lower for D90 (0.762) the most common parameter used for dosimetric analysis.

In conclusion, CT-based post-implant dosimetry has improved the calculation of dose delivered to the prostate and surrounding intraprostatic normal tissues, such as the rectum and urethra, but after prostate brachytherapy this method does not provide enough information to allow observers to reproducibly delineate the prostate volume without any discordance, especially without sufficient experience. If this is the case, it is possible that complementary imaging modalities, such as ultrasonography or MRI, can increase the reproducibility. We have found, and others have demonstrated, that with experience the prostate volume can be contoured with acceptable accuracy on CT imaging.

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