

## Quantifying Iodine-125 Placement Accuracy In Prostate Brachytherapy Using Post-Implant Transrectal Ultrasound Images

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### Abstract

#### PURPOSE:

The quality of a prostate brachytherapy implant depends on the accurate placement of sources. This study quantifies the misplacement of iodine-125 sources from the intended location using intra-operative ultrasound images.

#### METHOD AND MATERIALS

Iodine-125 sources were manually identified in the post-implant ultrasound images and compared to the pre-operative plan. Due to the subjective nature of the identifying sources, only sources identified with high confidence were included in the analysis. Misplacements from the original intended coordinate were measured along the X, Y and Z-axes and were stratified between overall misplacements and regions of the prostate gland.

#### RESULT

1619 iodine-125 sources using 357 strands were implanted in 15 patients' prostate glands, with 1197 (74%) confidently identified for misplacement analysis. The overall mean displacement was 0.49 cm and in the X, Y and Z direction was 0.13, 0.15 and 0.38 cm respectively. Greater source misplacement occurred in the anterior part of the prostate gland than the posterior part of the prostate gland by a factor 1.33 ( $p < 0.0001$ ). Comparing sources in the lateral vs. medial regions of the prostate, no statistically significant differences on source misplacement were observed. Comparing misplacement in the base vs. mid-gland vs. apex identified the greatest difference between the base and mid-gland by a factor of 1.29 ( $p < 0.0001$ ).

#### CONCLUSIONS

This study has identified significant misplacement of iodine-125 sources from their intended locations with the greatest error misplacement occurring in the Z direction. Source misplacement tends to occur more commonly in the anterior gland and in the base of the prostate.

Keywords: Prostate, brachytherapy, stranded sources, I125, misplacement

Conflict of interest: The authors have no conflicts of interest to declare.

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## Introduction

Permanent interstitial prostate brachytherapy using iodine-125 is an effective treatment option for men with localized prostate cancer [1] [2] [3] and has become a standard treatment with excellent ten-year biochemical relapse-free survival and overall survival. Brachytherapy has gained popularity due to its safe toxicity profile in comparison with external beam radiotherapy with higher doses that can safely be achieved to the prostate gland and lower doses to the organs at risk [4]. The goal of an implant is to achieve high quality post-operative dosimetry. The American Brachytherapy Society Guideline recommends that the prescription dose for monotherapy for iodine-125 sources is 145 Gy and suggests reporting the dose that covers 90% (D90) and 100% (D100) of the prostate volume and the percentage of the prostate volume receiving the prescribed dose (V100) from the DVH [5]. A good quality prostate brachytherapy implant depends on how close the dosimetry achieved post implant is in relation to these recommendations. These measures correlate with clinical outcomes, as studies have suggested that a D90 > 140 Gy is associated with a lower risk of relapse [6][7].

Source placement accuracy is defined as the difference between actual and planned source location [8] and will be referred to as source misplacement throughout this document. It is one of the limiting factors that can compromise the dose distribution for permanent prostate implants. Implant quality can be compromised due to errors in source placement caused by: 1. needle deflection; 2. prostate movement during insertion; 3. subsequent source displacement due to intraoperative edema of the prostate gland caused by trauma from the needle insertions; 4. prostate displacement by pressure applied during ultrasound image acquisition; and 5. effect of drag force on the source string as the needle within the prostate tissue is retracted [9].

Our study aims to quantify source placement accuracy for prostate brachytherapy patients planned pre-operatively, using post-implant intraoperative transrectal ultrasound images.

## Method and materials

### Patient characteristics

This study was approved by the local institutional ethics committee. Patients with low-risk prostate cancer (Gleason score of 6 and less, prostate-specific antigen less than 10ng/ml, and clinical staging T1a to T2b) and low-tier intermediate risk prostate cancer (defined as organ-confined disease and either Gleason score of 7 and PSA of 10 ng/mL or lower, or PSA of 10-20 ng/mL and Gleason score of 6 or lower) using brachytherapy as monotherapy (i.e. without androgen deprivation therapy or external beam radiotherapy) for their treatment were eligible for the study.

### Implant technique and image acquisition

Our technique has been described in detail before [10]. Briefly, 4 to 6 weeks prior to the prostate brachytherapy implant, a planning TRUS of the prostate is performed with the patient in dorsal lithotomy position. Axial and sagittal images of the prostate are taken with a transrectal ultrasound operating at 6 MHz (8088 Biplane Transducer on BK Pro Focus UltraView 800) and imported into VariSeed 8.0.1 (Build 4512) planning system (Varian Medical systems), while

visualizing the urethra with aerated KY gel. The clinical target volume (CTV) was the prostate gland with a 3 mm lateral, anterior and inferior margin for the planning target volume (PTV). A non-uniform distribution of sources in the prostate and periprostatic tissue was used to plan a PTV V100 of at least 98% while limiting the periurethral tissue to a  $D_5 < 150\%$ , and rectal  $D_{1cc}$  to  $\leq 145\text{Gy}$ .

For the implantation, patients underwent general anesthesia and seeds were placed with the patient in the dorsal lithotomy position. The planning setup was replicated using the TRUS and needles containing 0.400 mCi (0.508 U) stranded iodine-125 sources (Amersham, OncoSeed, 6711) were inserted using a transperineal technique, using a template for guidance.

The base is first identified using sagittal images, with corresponding axial images used for confirmation, and serves as a reference point for the Z coordinate ( $Z=0$ ). Typically, both axial and sagittal images were utilized for image guidance during needle insertion. A rapid movement was used to insert the needles into the prostate. Axial images were utilized for confirmation of the needle position in the XY plane, while sagittal images were utilized for confirmation of the needle position in the Z plane. The strands were inserted row wise from the anterior prostate to the posterior prostate, with needles inserted from the patient's right to the patients left in each row. Throughout the case, the location of the base was confirmed on the sagittal and axial images, with adjustments made to ensure that the base remains at the  $Z=0$  location.

At the end of the procedure, a series of axial ultrasound images were taken at 5 mm interval from the base down to 5 mm below the apex of the prostate gland caudally and imported into the VariSeed planning software.

### **Measuring distance of source from intended coordinates**

The contouring tool in VariSeed was used to delineate the prostate gland and urethra. Using the preoperative plan as reference to intended needle coordinates, needle tracks, including sources that were clearly visible were identified on VariSeed and labeled with the coordinate accordingly at every axial image. For tracks that were not clear on the axial images, the interpolation function in VariSeed was used. Sagittal and coronal image reconstruction also helped to identify unseen tracks from the axial images (See Figure 1).

Once the tracks of individual coordinates were created, each iodine-125 source was identified within each track. Reference to the preplanning information was used to identify the source coordinates (X and Y plane), number of sources per strand and their location on each strand (Z plane). For each track location we classified the ultrasound appearance and characteristics into 4 categories: 1. definitely no source, 2. likely no source, 3. source highly likely, 4. definitely source (see Figure 2). Highly echogenic areas on ultrasound that corresponded with highly likely or definitely to contain source location were further assessed for misplacement in the X, Y and Z dimensions. Measurements in the X and Y plane were done using the measuring tool in VariSeed. Measurements were done from the center of the highly echogenic region to the intended coordinate on the reference plan.

The prostate gland was subdivided into virtual sectors to evaluate the influence of source misplacement based on the different regions of the prostate gland. Using the sector analysis tool in the VariSeed planning software, anterior and posterior division was created based on the center of projection of the prostate gland. The prostate gland was also segmented into base, mid-gland and apex (see figure 3a and 3b). Segmentation of the prostate gland into medial and lateral regions was done manually by measuring at the largest lateral dimension of the prostate gland on the axial view to the center of the prostate gland with the urethra conventionally located in the center 'D line'. At each slice, the prostate was divided equally into 4 regions and any sources located in the 2 central regions were assigned as 'medial', while any sources located in the peripheral regions were assigned as 'lateral' (Figure 3c).

Misplacements of identified sources were tabulated and analyzed using GraphPad Prism 5. Descriptive statistics were used for source misplacement in the X, Y, Z differences directions and overall misplacement. We used the unpaired two-way Student's *t*-test to compare the difference of misplacement within different regions of the prostate gland.

## Result

### Patient characteristics

Fifteen patients consented to participate in this study. The mean age was 62 years (range 53 to 79 years). The mean volume of the prostate gland was 50.7 cc (range 28.3 cc to 76.7 cc). The characteristics of the study population are summarized in Table 1, with 7 patients with low risk and 8 patients with intermediate risk disease.

### Misplacement results

#### Overall results

357 strands with 1619 sources were used in total. Of the 1619 sources implanted, 1197 (73.87%) were confidently identified, i.e. with scores of 3 or 4 using the scoring system. The overall mean misplacement was 0.49 cm ( $\pm 0.02$  cm) (Table 2) and in the X, Y and Z directions was 0.13 cm ( $\pm 0.01$  cm), 0.15 cm ( $\pm 0.01$  cm) and 0.38 cm ( $\pm 0.02$  cm) respectively.

#### Anterior versus posterior

Dividing the prostate into anterior and posterior regions, mean source misplacement was 0.57 cm ( $\pm 0.014$  cm) for anteriorly placed sources and 0.43 cm ( $\pm 0.012$  cm) for posteriorly placed sources, demonstrating 32.5% more displacement for sources placed in the anterior region ( $p < 0.0001$ ). The differences in misplacement between anterior and posterior located sources were also statistically significant for all axes ( $p < 0.0001$ ).

#### Medial versus lateral

No statistically significant results were noted in the difference when dividing the prostate into lateral vs. medial regions. The overall mean misplacement for the sources was 0.49 cm for both

medially and laterally placed sources. This was also true when medially vs. laterally placed sources were compared on the X, Y and Z-axes ( $p=0.7519$ ,  $0.3454$ , and  $0.589$  respectively).

### **Base vs. mid gland vs. apex**

Comparison of the mean misplacement of sources between base vs. mid gland, base vs. apex and mid-gland vs. apex was also conducted. The mean overall misplacement for sources placed in the base was  $0.57$  cm ( $\pm 0.016$  cm), mid gland  $0.44$  cm ( $\pm 0.014$  cm) and apex  $0.45$  cm ( $\pm 0.017$  cm). In comparing these regions, it was found that there was greater misplacement of sources in the base of the prostate compared to the mid-gland (i.e. 29% greater misplacement at the base region compared to the mid-gland ( $p < 0.0001$ )), and 26% greater at the base when comparing base vs apex ( $p < 0.0001$ ). The greatest amount of misplacement occurred in the Z direction, with 48% greater misplacement at the base when compared to the mid-gland ( $p < 0.0001$ ) and 39% greater misplacement when compared to the apex ( $p = 0.02813$ ). In contrast, there was no significant difference in misplacement between the mid-gland and apex. In the anterior base portion in the Z direction, 187 sources were misplaced inferiorly by a mean of  $0.58$  cm ( $\pm 0.029$  cm) and only 1 source was misplaced superiorly. In the posterior base portion 279 sources were misplaced inferiorly by a mean of  $0.38$  cm ( $\pm 0.027$  cm) compared to 9 sources misplaced superiorly.

## Discussion

Current practice guidelines issued by AAPM and GEC-ESTRO recommend that dosimetry be performed for all TIPPB patients after the operative procedure for quality assurance purposes, with both groups recommending the use of CT-imaging for source evaluation [11]. MRI, plain x-rays of the implanted zone taken at different angles, and ultrasound are additional techniques that can be used for source detection.

In ultrasound, the lack of clear visualization of the implanted sources remains a major challenge. A study by Roberson et al. on source placement error using ultrasound and CT fusion reported a 74% identification rate for stranded sources [9]. Their study of 3 patients identified mean misplacement of 0.46 cm (in the X-Y plane) which is similar to our overall misplacement of 0.49 cm (in X, Y and Z). Their study also observed that needles tend to splay at the periphery of the prostate gland. A separate study by Han et al. evaluated the use of post-implant transrectal ultrasound images to detect loose sources intraoperatively with a mean sensitivity of detecting sources of 74% (range 51-83%) [12]. These authors were skeptical of the utility of ultrasound in identifying sources accurately, highlighting one of the limitations of our study. Our study pick up rate of 73% was similar to the studies above. Our utilization of the VariSeed software using a 3-dimensional view of the needle tracks and its interpolation capability enhanced our source pick up rate.

The greatest misplacement identified in this study occurred in the anterior regions of the prostate, with a mean displacement of 0.57 cm. This is similar to the results by Usmani et al. that quantified migration of stranded sources in 10 clinical cases using fiducial markers placed before the implant as reliable fixed reference points. Their study demonstrated that strands located in the anterior region of the prostate have the greatest degree of migration. It was postulated that this migration was primarily a result of the resolution of edema, with observations of strands migrating laterally by a magnitude of +0.22 mm, +0.41 mm superiorly, and +0.22 mm anteriorly [13]. A more detailed analysis of prostate edema after brachytherapy implants by Sloboda et al. studied prostate gland sizes using serial MRI images at day -1, 0, 12, and 28 in 40 patients [14]. In this study, prostate volumes were 18% larger on day 0 compared to day 30, with relative dimensions on day 0 of  $1.01 \pm 0.07$  in the left-right directions,  $1.11 \pm 0.09$  in the anterior-posterior dimensions, and  $1.08 \pm 0.13$  superior-inferior dimensions. These values correlate well with our current results, as the misplacement was noted to be greatest in the anterior vs. posterior comparisons, with no significant differences identified in the lateral vs. medial comparisons.

A review of the literature identifies additional studies that have analyzed source misplacement during brachytherapy using different techniques. Meyer et al. compared planned vs. delivered treatment in 10 clinical cases using variable angle x-ray images with a C-arm immediately after sources were delivered intraoperatively, with images taken both with the ultrasound probe in place and when the ultrasound was withdrawn [15]. The mean delivery error reported by this group, i.e. the difference between the planned location and the actual delivered location, was 4.6 mm, which is comparable to our results. The greatest error was identified in the cranial-caudal direction and was speculated to be due to uncertainties of insertion depth or source clumping in the Z direction. This study identified a 21.6% reduction between the planned and

delivered D90. Similarly, in our study the greatest misplacement occurred in the Z direction, particularly in the base of the prostate, where sources were misplaced inferiorly by 0.57 cm in the anterior base compared to 0.38 cm in the posterior base. Another study by Pinkawa et al. used day 0 and day 30 CT scans in 51 patients with placement of sources compared to the pelvic bones to quantify displacement of stranded sources [16]. This study identified significant movement of sources posteriorly by 1 mm and inferiorly by 3.8 mm, suggesting these movements were the result of the resolution of prostatic edema. This study found a correlation between prostate volume decreases and an increase of D90 at day 1 compared to day 30. A simulation planning study of 20 cases of I-125 and Pd-103 sources performed by Dawson et al. used a random number generator to place each source in the implant at randomly generated distances from the preplanned locations. Mean source deviations of 3.01 mm in the X and Y direction led to dose variations from -8% to 15% for I-125 sources [17]. Together, these studies demonstrate that small movements or misplacements of sources from their intended locations can significantly alter the dosimetry of prostate implants. The dosimetric impacts of the source misplacements identified in our study were not analyzed and were beyond the scope of this study.

Phantom studies have shown that beveled tip prostate brachytherapy needles inserted in a fixed orientation deflect by about 2.8 mm [18] and that deflection varies with depth of insertion of needles [19]. Our experience is that needles tend to splay as they are inserted, with greatest misplacement at the base of the prostate and seeds tending to bunch together at the prostate apex. This is consistent with our findings of greater misplacement of seeds at the base compared to the apex. Our technique also involves us confirming the accuracy of the XY placement of strands in one plane. As a result, it is possible that needles deviate from this XY coordinate in other planes, leading to variations in misplacement in different regions of the prostate.

A number of factors may be identified as strengths of the design of this study. First and foremost, to the authors' knowledge this is the first study to evaluate source placement accuracy using TRUS in clinical cases. The majority of studies quantifying source migration or displacement compare source position from the day of implant to a later date, with studies in placement accuracy lacking in the literature. The advantage of using our approach is that the positions of the patients were preserved at the time of post-implant imaging. This allowed us to make precise comparisons between pre-operative planning and post-operative implant coordinates, without being confounded by changes in patient positioning or deformation of the prostate associated with the ultrasound probe being removed from the rectum [20]. Another strength of our study was the utilization of a single imaging modality allowing for easy comparisons of images at different time points. We also collected data for this study prospectively using patients that were uniformly treated with an adequate sample size of sources to allow for comparative analysis between regions. Finally, the cases were done by a single experienced brachytherapist, minimizing the risk of intra-operator variability of source insertion.

The authors also acknowledge some limitations of this study. The most apparent limitation is utilizing TRUS images to visualize seeds, as was described earlier in the discussion. In



In addition, the images were acquired after all sources had been placed in their intended locations, thus assuming that the relative position of the prostate and the ultrasound setup were consistent from the beginning of the case to the end, as any movement or changes such as prostate edema could have occurred in that period of time. Ideally, a more precise study would have involved acquiring images following the insertion of each needle; however, this would have been time consuming and was not possible in clinical practice. We also recognize that our method of measurement in the Z axis was limited to 5 mm increments, instead of a continuous variable, leading to measurements in this direction being less precise. Our study was also not able to take into account source misplacements that were intentionally made from preplanned location by the oncologist in the operating room.

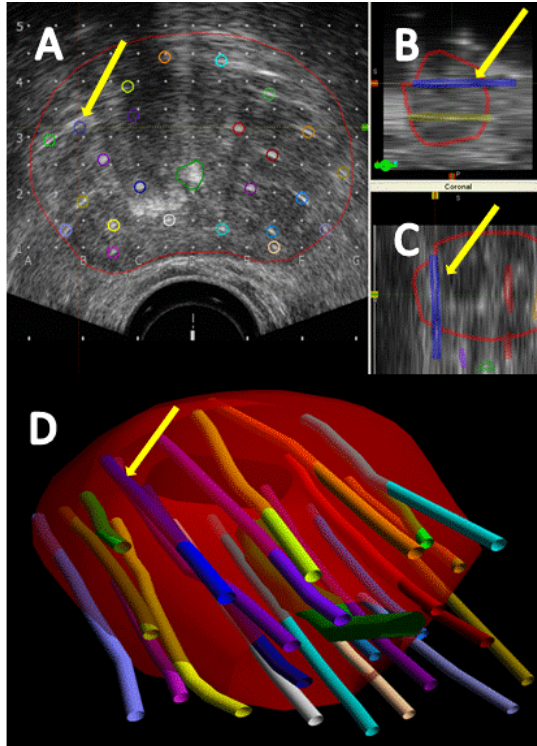
This paper reinforces our concern of misplacement of seeds inferiorly, which tends to be of greatest concern in the anterior portion of the prostate gland. As a result of these findings, we have paid special attention when depositing stranded sources to the anterior portion of the prostate gland by using more sagittal imaging to allow us to appreciate if there is any migration in the Z direction. As well, we have also taken extra caution during the process of depositing stranded sources in the anterior prostate to ensure sources ended up in the intended Z coordinates.

## Conclusion

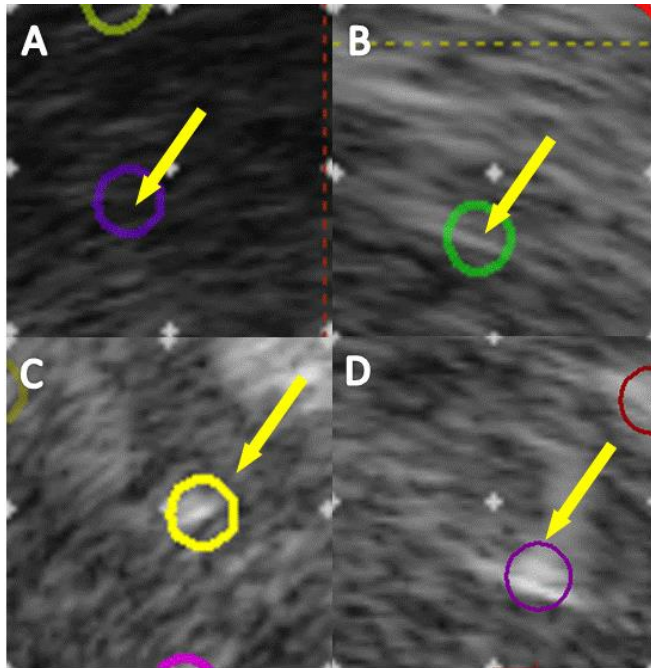
Despite efforts by an experienced oncologist to place sources accurately during prostate brachytherapy implants, this study identified placement errors in the implanted locations of sources. The greatest degree of misplacement occurred in the Z direction. Analyzing the different regions of the prostate identified the greatest degree of misplacement anteriorly, with greater misplacement also occurring in the base of the prostate compared to the mid-gland and apex, particularly in the X and Z directions. These misplacement errors are likely a reflection of needle deflection during the insertion of sources and prostatic edema caused by the trauma of needle insertion.



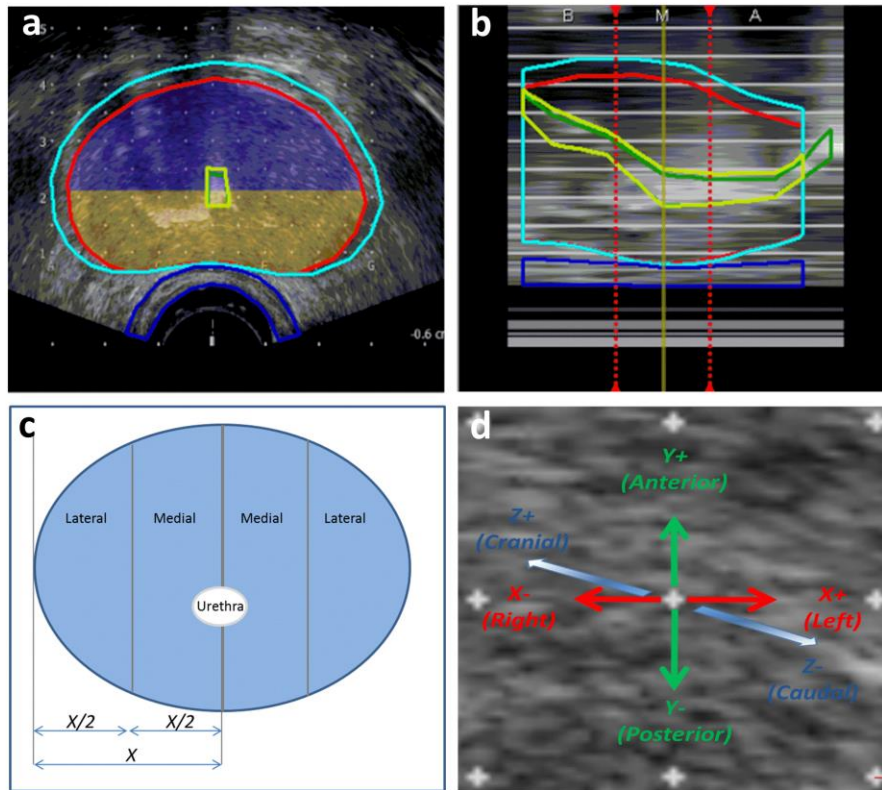
## Figures



**Figure 1. Localizing a needle track.** In this example, the needle track is created by a needle inserted at coordinate B3. The axial image (A), with sagittal reconstruction (B) and coronal reconstruction (C) helped to identify the individual needle tracks. A 3D reconstruction view (D) also helped to visualize individual needle tracks.



**Figure 2. Identifying sources.** For each track evaluation there are 4 possibilities based on the ultrasound image characteristics: A. definitely no sources; B. likely no sources (only needle tracks are seen as slightly higher echogenicity from the background); C. likely source (higher intensity echogenicity compared to background); D. definitely source (higher intensity echogenicity compared to background coupled with the 'comet tail' artifact).



**Figure 3. Regions of the prostate.** Division of the prostate gland into: (a) anterior and posterior regions; (b) base (B), mid-gland (M) and apex (A); and (c) medial and lateral. (D) Measurement of source misplacement in the X, Y and Z directions.

## Tables

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Table 1 Summary of patient and disease characteristics

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<b>Age (Years)</b>	63 (53 to 79)
<b>PSA, (ng/ml)</b>	8.7 (3 to 15.5)
<b>Prostate Volume (ml)</b>	47.5 (28.3 to 76.7)
<b>Clinical T Classification, n (%)</b>	
<i>T1c</i>	6 (40.0)
<i>T2a</i>	7 (46.7)
<i>T2b</i>	2 (13.3)
<b>Gleason Score, n (%)</b>	
3+3	7 (46.7)
3+4	7 (46.7)
4+3	1 (6.6)
<b>Risk Category, n (%)</b>	
<i>Low</i>	7 (46.7)
<i>Intermediate</i>	8 (53.3)

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Table 1. Summary of patient and disease characteristics. Data are represented as median (range), unless otherwise specified.

Region Of Prostate Gland	Mean Source misplacement (cm)							
	X Axis		Y Axis		Z Axis		Overall	
<b>Whole gland (n=1197)</b>	0.13	±0.006	0.15	±0.008	0.38	±0.021	0.49	±0.018
<b>Anterior (n=542)</b>	0.15	± 0.005	0.18	± 0.007	0.43	± 0.016	0.57	± 0.0140
<b>Posterior (n=655)</b>	0.11	± 0.003	0.13	± 0.004	0.33	± 0.014	0.43	± 0.0117
<i>p-Value of Difference</i>		< 0.0001		< 0.0001		< 0.0001		< 0.0001
<b>Lateral (n=599)</b>	0.13	± 0.004	0.16	± 0.006	0.37	± 0.015	0.49	± 0.0126
<b>Medial (n=598)</b>	0.13	± 0.005	0.15	± 0.005	0.38	± 0.015	0.49	± 0.0135
<i>p-Value of Difference</i>		0.7519		0.3454		0.589		0.9686
<b>Base (n=466)</b>	0.15	± 0.006	0.15	± 0.006	0.46	± 0.018	0.57	± 0.0159
<b>Mid (n=375)</b>	0.12	± 0.005	0.15	± 0.006	0.31	± 0.017	0.44	± 0.0137
<b>Apex (n=356)</b>	0.12	± 0.005	0.15	± 0.008	0.33	± 0.019	0.45	± 0.0168
<i>p-Value Comparing Base vs. Mid Gland</i>		0.0007		0.6793		< 0.0001		< 0.0001
<i>p-Value Comparing Base vs. Apex</i>		0.0021		0.9598		0.0281		< 0.0001
<i>p-Value Comparing Mid Gland vs. Apex</i>		0.7322		0.7685		0.4662		0.4724

**Table 2. Misplacement of sources in different regions of the prostate gland.**

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