Prostate volume delineation and seed localization using a 3-T magnetic resonance spectrometer

Jason Eric Davis
University of Nevada, Las Vegas
PROSTATE VOLUME DELINEATION AND SEED LOCALIZATION USING A 3-T MAGNETIC RESONANCE SPECTROMETER

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Jason Eric Davis

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Jason E. Davis

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Dean of the Graduate College

Examination Committee Member

Graduate College Faculty Representative
ABSTRACT

PROSTATE VOLUME DELINEATION AND SEED LOCALIZATION USING A 3-T MAGNETIC RESONANCE SPECTROMETER

by

Jason Eric Davis

Dr. Phillip W. Patton, Examination Committee Chair
Associate Professor of Health Physics
University of Nevada, Las Vegas

With approximately one in six men affected by prostate cancer at some point in their lives, effective treatment of the disease remains a focus of oncology research. Effective treatment using radiation requires the delivery of a significant dose to the prostate volume while sparing surrounding sensitive structures. Treatment success can then be determined by localization of the seeds following implantation and the calculation of a dose distribution across the target volume. Magnetic Resonance Imaging (MRI) yields images with soft tissue contrast that is superior to CT or ultrasound, but has been under-appreciated as a dosimetric tool due to the difficulty in localizing the implanted seeds.

To optimize scan parameters for seed localization, a phantom was constructed of tissue-equivalent gelatin. Seeds were implanted during construction so various scan protocols could be tested for seed visualization and volume calculation prior to patient studies. Five healthy volunteers and five patients with permanently implanted seeds were then imaged to validate the phantom studies. Images were evaluated based on anatomical clarity and seed visualization rates.
Optimization of the scan protocols for use with this equipment yields images with clearly defined anatomical boundaries as well as clearly defined seeds. Phantom volume measurements deviated from known values by less than 2.5% T2-weighted images provide superior anatomical delineation, but suffer from broad susceptibility artifacts that make determination of seed locations difficult. Proton density-weighted images clearly show seed locations and tissue margins. The selection of a 1 mm slice thickness and a 4 mm interslice gap allowed maximum seed visualization rates of 93.3%.

Keywords: prostate, brachytherapy, dosimetry, magnetic resonance imaging
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CHAPTER 1

INTRODUCTION

With an estimated 234,460 new cases projected to be diagnosed yearly, prostate cancer is the second most common cancer among men (ACS 2006). In fact, based on incidence rates from 2001-2003, it is estimated that one in six men will be diagnosed with the disease at some point in their lives (NCI 2006), and that 27,350 lives will be lost to prostate cancer in the year 2006 alone (ACS 2006).

Although early stages of the disease are either asymptomatic, or display symptoms that resemble those of others common conditions, such as lower back pain, urine flow obstructions, or burning during urination, routine screening through the prostate specific antigen (PSA) blood test has allowed more than 90% of the cancers to be diagnosed in the earlier local and regional stages. With appropriate treatment, patients diagnosed in these stages have a 5-year survival rate of nearly 100% (ACS 2006). The challenge to any kind of cancer treatment using radiation is delivering a therapeutic dose to the targeted volume while sparing surrounding healthy tissues.

Prostate Anatomy and Surrounding Structures

About the size of a walnut in younger men, the prostate is a small, somewhat triangular gland situated low in the male pelvis. As shown in Fig. 1, it is framed
anteriorly by the pubic symphysis, posteriorly by a layer of fat that separates the prostate from the rectum, inferiorly by the urogenital diaphragm, and superiorly by the bladder (Pollack 2003).

![Diagram of prostate location within the pelvis.](UUHSC2006)

Figure 1. Prostate location within the pelvis. (UUHSC 2006)

Although classically thought of as a histologically homogeneous organ, the four regions of the prostate are actually different in regards to tissue composition and pathologic susceptibility (McNeal 1981). However, since nearly 99% of the prostate is composed of glandular tissue, it is hardly surprising that more than 95% of malignant neoplasms in the prostate are adenocarcinomas, or tumor cells arising from glandular
epithelial cells (Pollack 2003). Adenocarcinomas tend to be slow-growing and have historically been believed to require the achievement of a tumor volume of over 4 cm$^3$ before metastasizing (Crawford et al. 2001). It is this tendency toward slow growth that makes adenocarcinoma an ideal candidate for treatment with radiation therapy, since the tumor can generally be detected through routine screening methods well in advance of extracapsular migration.

While the prostate itself is generally considered to be fairly radioresistant, this observed resistance to radiation does not necessarily extend to the surrounding tissues and structure. The proximity of the rectal wall to the anterior edge of the rectum makes avoidance of incidental irradiation of the rectal mucosa extremely difficult in most forms of radiation treatment. With a tolerance dose of 70 Gy, accidental irradiation of the rectal wall may cause atrophy of the mucosa, serosal breakdown, stenosis, and fibrosis leading to prolonged obstructive effects (Hall 2000). Despite this biological limitation, there is no generally accepted limit on rectal dose during prostate treatment (Potters 2003). The American Association of Physicists in Medicine (AAPM) Task Group No. 64 does however recommend limiting the rectal dose to less than 90 Gy to reduce incidence of rectal bleeding and ulceration (Yu et al. 1999).

Because of their locations, the urethra and urinary bladder are also of great consideration during radiotherapy of the prostate. Although the bladder is in intimate contact with the base of the prostate, the urethra’s location within the prostatic volume makes it an organ of primary concern in the planning of any treatment of the prostate. The fact that the urethra does not follow a straight-line path through the prostate volume
may further complicate efforts to spare this organ without precise image guidance (McNeal 1981).

The urinary bladder is composed of basal cells with a relatively high renewal rate making any radiation induced cell damage possible with relatively low doses. Although occurring in a minority of cases, instances of fibrosis, urinary stricture, hematuria, and focal ulceration have been reported in patients receiving a dose of between 65 and 70 Gy (Milosevic and Gospodarowicz 2003). Differences in implant technique, the use of combination therapies, methods of urethral delineation, and other factors have complicated the ability of researchers to set dose limits to minimize the risk of urinary stricture or fibrosis of the urethra. However, studies performed before the introduction of peripheral loading techniques have suggested that a dose in excess of 400 Gy can be associated with an increased risk of urethral morbidity (Crook et al. 2005). Additionally, the incidence of urinary morbidity may be further enhanced in patients with a recent history of transurethral resection of the prostate (TURP) to treat benign prostatic hyperplasia (Potters 2003).

Permanent Brachytherapy

Due to the lack of a surface dose and the sparing of surrounding tissues, permanent interstitial brachytherapy allows for the delivery of a higher localized dose than external beam therapies. The highly conformal nature of the treatment allows the physician and treatment staff to create a treatment plan that is capable of minimizing the dose to sensitive structures like the prostatic urethra. This treatment may also appeal to patients that seek non-surgical treatment on an outpatient basis which will result in a minimal
disturbance of the patients’ lifestyle (Potters 2003). Since the process is minimally invasive, recovery is rapid relative to radical prostatectomy, allowing patients to return to work and normal activities within a few days (Ragde et al. 2000).

Brachytherapy is generally reserved for patients with early stage prostate cancer, when the tumor is still relatively slow growing and still confined within the prostatic capsule (Pollack 2003). For this treatment, small seed pellets are placed directly into the prostate, approximately one centimeter apart, through small needles. Currently, the seeds, numbering from 40 to more than 100, are inserted through the perineum in order to help ensure a more uniform seed placement, as well as avoid complications that may arise from pubic arch obstruction of the needle placement (Potters 2003).

The seeds may be placed by one of two methods. The first involves the use of a pre-scan trans-rectal ultrasound (TRUS) to delineate the prostate volume. Images from these scans are used to formulate a treatment plan that includes pre-determined needle locations, and a planning target volume with a 2-3 mm margin, which is manually delineated by a physician (Potters 2003). The seeds are then placed through pre-loaded needles. The principal disadvantage of this technique is that it relies on the prostate being in the exact same position during treatment as during the pre-planning scans (Pollack 2003). There is also a risk of prostate volume changes if the preplanning scans are carried out more than 2-3 weeks before treatment. This risk is especially evident in patients undergoing hormonal therapy for volume reduction (Yu et al. 1999).

The intraoperative planning method is an alternative to preoperative treatment planning. In this method, seed placement is monitored throughout the procedure either through fluoroscopy, CT, MRI, or TRUS. Seeds are placed individually through the
Mick applicator system, which gives the treatment staff more control over the seed spacing. As the procedure progresses, the seed locations are noted on the planning computer and a profile of the seed placement in three dimensional space is developed. This method is not without its drawbacks, however. The treatment time is increased due to the individual placement of the seeds which, in turn, increases the total cost of performing the treatment (Pollack 2003). Additionally, this method does not account for the possibility that the seeds may migrate following implantation, thus altering the dose distribution.

Rationale for Post-Implant Dosimetry

The ability to accurately assess the dosimetry of the implant is considered the most important factor in understanding the relationship between implant quality and treatment efficacy (Prete et al. 1998). A study performed by Stock et al. (1998) suggested that the dose delivered to the target volume is the most significant predictor of biochemical failure following $^{125}$I implants. In fact, it was shown that patients that received a $D_{90}$, the dose covering 90% of the target volume, greater than or equal to 140 Gy had a 4-year rate of freedom from biochemical failure of 92%. By comparison, those patients that received a $D_{90}$ of less than 140 Gy had a biochemical failure freedom rate of only 68%.

Since dose is inversely proportional to the square of the distance from the source, it is not surprising that the dose distribution is largely dependant on the implant geometry. Due to gland deformation, needle deviation, and gland swelling, however, the actual geometry of the implant is not the same as the planned geometry. Accurate post-implant dosimetric analysis allows for the identification of areas of the gland that may have
received a suboptimal dose. These regions may then be treated either through a second 
brachytherapy procedure or through external beam radiation (Ravindran et al. 2006).

Further, information obtained during the imaging component of a post-implant 
dosimetric study can be used to evaluate or even predict post-treatment complications. 
Visualization of an implanted seed that has localized in or overly close to the urethra, 
penile bulb, or neurovascular bundle may be useful for the urologist if a patient presents 
with hematuria, urinary obstruction, or erectile dysfunction (Coakley et al. 2001).

Additionally, as is the case with many medical procedures, the quality of a prostate 
implant depends on the skill and experience of the procedure staff (Yu et al. 1999). It has 
been demonstrated that there is a learning curve associated with performing permanent 
implantation brachytherapy (Lee et al. 2000), which has led Yu and colleagues to 
recommend that institutions continuously monitor implant quality to allow for technique 
improvements and to avoid perpetuation of errors that may compromise implant quality. 
Based on these factors, post-implant dosimetry is considered mandatory by both the 

Dosimetric Methods

Methods for calculating the dose from a permanently implanted brachytherapy source 
are detailed by the AAPM Radiation Therapy Committee Task Group No. 64 (Yu et al. 
1999). Commonly, the isotropic point source approximation is used for dose calculation. 
From this model, the total dose delivered at a distance $r$ by an $^{125}\text{I}$ or $^{103}\text{Pd}$ seed is given by 

$$D = \bar{D}_0 \times 1.443 \times T_{1/2}.$$ 

(1)
In this equation, $T_{1/2}$ is the half-life of the implanted isotope and the initial dose rate is given by

$$D_0 = \frac{S_k \Lambda g(r)\bar{\phi}_{an}}{r^2},$$

(2)

where $S_k$ is the air kerma strength with units of cGy cm$^2$ h$^{-1}$, $\Lambda$ is the dose rate constant, $g(r)$ is the radial dose function, and $\bar{\phi}_{an}$ is a dose anisotropy constant. The radial dose function accounts for scatter and absorption in the tissue and is only defined along the transverse axis of the source. Also accounting for absorption, scatter, and other dose distribution effects around the source, the dose anisotropy constant is an approximation of the dose anisotropy function that can be used only when the point source approximation given above is used. This factor also takes into account self-absorption within the source and the absorption of photons within the encapsulating material. Both the radial dose function and the dose anisotropy constant are tabulated for the most common brachytherapy materials in the recommendations by AAPM Radiation Therapy Task Group No. 43 (Nath et al. 1995). From these simplified equations, it is evident that accurate dosimetric evaluation requires precise determination of the prostate volume, as well as the seed location within that volume.

Imaging Studies

Historically, prostate implants have been imaged using plane film radiography. While this allows for excellent visualization of the implanted seeds, as seen in Fig. 2, the soft tissue of the prostate itself does not image well using traditional radiography. Additionally, despite the fact that the implanted seeds image well on film, localization
is complicated by the fact that their arrangement leads to image overlapping of almost 25% of the seeds (Su et al. 2004).

With its wide availability, low expense, and potential for intra-operative use, ultrasound is considered an attractive option for prostate imaging both before and after implantation (Han et al. 2003). There are technical issues that limit ultrasound’s usefulness in determining prostate volume, however. Typically, prostate volumes from ultrasound are calculated using the ellipsoid formula

\[ V = l \times w \times h \times \frac{\pi}{6}, \]  

(3)

where \( V \) is the total prostate volume, \( l \) is the length or transverse diameter measured at the point of maximal diameter, and \( w \) is the width or diameter measured in the anteroposterior plane. Finally, \( h \) is the longitudinal diameter of the gland, measured
along the midsagittal plane between the genitourinary diaphragm and the bladder neck. This method has been shown to underestimate the prostate volume by as much as 30% (Matthews et al. 1996). The ellipsoid formula method of volume calculation is intrinsically imprecise due to the fact that the prostate is not perfectly elliptical in shape. Additionally, variations in the choice of the three planes of measurement may exist between sonographers or even between scans for the same sonographers because transducer orientation relative to the prostate volume is operator dependent (Rahmouni et al. 1992).

A prostate volume interobserver variability ranging from 20% to 50% is a testament to the difficulty of accurately delineating the prostate volume on TRUS images (Smith et al. 2003). This variability is most notable near the base and apex, and along the anterior edge. As illustrated in Fig. 3, this variability may be further complicated by the fact that implanted seeds will degrade the image along the prostate borders (Smith et al. 2003).

![Pre-implant and Post-implant TRUS images](image)

Figure 3. Pre- and post-implant TRUS images demonstrating the prostatic margin obscuring effects of the implanted seeds (Smith et al. 2003).
The determination of seed location using ultrasound is also limited by technical issues. Most notably, as seen in Fig. 4, the seeds appear as small bright spots on a background that is already cluttered by bright speckles, making them difficult to isolate. Additionally, the implanted sources are difficult to distinguish from calcifications and other structures that are echogenic. Finally, the brightness of the seeds on the ultrasound image is dependant on the orientation of the seeds relative to the transducer (Wei et al. 2006). This orientation is also operator dependant and may vary between scans (Rahmouni et al. 1992). These factors combine to limit the ability of even experienced staff to delineate and localize the seeds. A study performed using four brachytherapists showed that the locations and identities of only 20% of the seeds were agreed on by all four of the therapists (Han et al. 2003).

![Pre-implant and Post-implant TRUS images showing bright spots (arrows) that may be interpreted as implanted sources.](image)

Figure 4. Pre- and post-implant TRUS images showing bright spots (arrows) that may be interpreted as implanted sources (Han et al. 2003).
Although better at imaging the implanted seeds than ultrasound, CT also has limitations that prevent its use as a single imaging modality for pre- and post-procedural studies. Because CT uses x-rays to create images similar to traditional radiography, contrast between different tissue types is dependant on the density of the tissues. Unfortunately, the prostate and surrounding tissues are very similar in density, which makes discrimination between the tissues difficult. For instance, definition of the prostatic urethra is extremely difficult without the use of a Foley catheter. The inability to distinguish the prostate from the anterior wall of the rectum, the levitator ani muscles, and the neurovascular bundles contributes to the subjective nature of volume determination using CT. The unintentional inclusion of portions of these tissues within the contoured prostate volume may also lead to an overestimation of the prostate volume, which will impact the calculated dose in both pre- and post-implant studies (Yu et al. 1999).

Currently most implants are carried out with an ultrasound scan for pre-planning to preserve anatomic detail and a CT for post-implant studies to maximize the ability to determine seed positions. This multi-modality imaging method has limitations as well. TRUS is typically performed in the supine lithotomy position in order to more easily access the rectum and to mimic the position the patient will be in during the implantation procedure. Because of limitations in the bore of most CT equipment however, the post-implant CT is generally performed in the standard supine position (Narayana 1997). Due to this difference of positioning and because of normal prostate motion between the scans, errors may be produced in the registration of the two images, which may lead to inaccuracies in seed registration (Wei et al. 2006).
In order to compare the prostate and seed locations in the two different image types, clinicians must align the images using implanted fiducial markers or anatomic landmarks. Many clinicians align the two images based on the observed locations of either the rectum or the urethra. This technique may not lead to a perfect registration because of the fact that the urethra does not image well on CT without catheter administered contrast (Narayana et al. 1997b). Additionally, the ultrasound is performed using a transrectal probe which may cause a rectal and prostate deformation which is not seen on the CT images. These registration errors may be further complicated by the difference in volume estimations produced using ultrasound and CT. Studies have shown that prostate CT images, even when performed pre-implant, are an average of 47% larger than the estimated ultrasound volumes (Narayana et al. 1997a). In order to minimize these errors, many researchers are focusing on ways to use the same imaging modality for both pre- and post-implantation imaging studies.

MR Physics

Magnetic resonance imaging takes advantage of intrinsic properties of atomic nuclei and their behavior in the presence of a strong magnetic field. Protons, neutrons, and electrons each have an intrinsic property called spin. Since subatomic particles and nuclei carry a charge or charge distribution, and because magnetic fields are generated by the movement of a charge through space, the rotation of these particles about a central axis induces a magnetic moment. This moment causes individual nuclei to behave like a magnet with a north and south pole.
Similar to rotating celestial bodies or a spinning top, subatomic particles also exhibit a second-order motion known as precession, which is the result of an interaction between an external force and the spinning object. For magnetic resonance, this is the interaction of the externally applied magnetic field with the spinning particles. Precession is the rotation of the magnetic moment about the axis of the rotating body. The frequency $\omega$ of this precession depends on the strength of the magnetic field and gyromagnetic ratio of the rotating body, and is shown by the Larmor equation

$$\omega = \gamma B$$

In this equation, $B$ is the external magnetic field and $\gamma$ is the gyromagnetic ratio of the precessing body. The gyromagnetic ratio is unique to each element and is the ratio of the element’s magnetic moment to its angular momentum (Bushberg et al. 2002).

Because the magnetic moment is a vector quantity, it can be thought of as being composed of different components of the transverse and longitudinal planes. The component of the magnetic moments parallel to the external magnetic field is known as the longitudinal vector $M_z$. Perpendicular to the external magnetic field is the transverse component $M_{xy}$. While the magnitude of the magnetic moment vector is the same for like particles, the orientation of these magnetic moments in the absence of an external magnetic field is random, producing a net magnetization of zero. When placed in a strong magnetic field, the magnetic moments of the nuclei are observed to align with the direction of the magnetic field (Bushberg et al. 2002).

A microscopic view of the process reveals that it is actually the precessional axis that aligns with the magnetic field. Since the transverse spin orientations are still random in this configuration, there is no net magnetization perpendicular to the externally applied
field ($B_0$) and the observed net magnetization is parallel to $B_0$. The nuclei align either parallel or anti-parallel to the external field. The majority of the nuclei align themselves in the lower energy state, or parallel to the field. In actuality, the population difference between these two states is approximately three in one million nuclei. Given the large quantity of hydrogen nuclei in a given sample volume, however, this difference is generally sufficient to produce a detectable change in the magnetic field (Brown and Semelka 2003).

Production of an MR signal is actually an application of Faraday’s law of electromagnetic induction. When a proton precesses so that its magnetic field intersects the plane of a coil of wire, a current is induced in the coil. This current can then be detected as an MR signal (Hendee and Ritenour 2002). In order to generate this signal, a radiofrequency (RF) pulse at the Larmor frequency is applied to the sample, rotating the longitudinal component of the magnetic moment into the transverse plain. Additionally, this applied RF pulse induces a phase coherence in the $M_{xy}$ component of the magnetic moment so that the individual protons precess in phase with one another. The combination of the phase coherence of $M_{xy}$ and the rotation of $M_z$ into the transverse plane maximizes the magnitude of the magnetization in the transverse plane. Since this plane is perpendicular to the coil, this translates to a maximum signal intensity.

Inhomogeneities in the material cause the protons to begin to precess at different frequencies. As the protons begin to de-phase, the vector components of the transverse magnetization begin to cancel each other, resulting in a loss of signal intensity. This process is time dependent and is known as free induction decay (FID). The FID decays as phase coherence is lost between the individual spins caused by differences in the local
magnetic field. This exponential relaxation decay is called the T2 relaxation time and is determined by the molecular structure of the material. This characteristic allows for improved contrast over CT between layers of materials that may have different molecular compositions but similar densities.

Returning the excited protons back to the equilibrium magnetization is a long process relative to the loss of signal due to the de-phasing of transverse magnetization. Each individual excited spin must release its energy to the lattice. This exponential regrowth is called spin-lattice relaxation and relies on the characteristics of the spin interaction with the lattice. The time necessary to recover 63% of the equilibrium magnetization following a 90 degree radiofrequency pulse is known as the T1 relaxation time (Bushberg et al. 2002).

MRI Prostate Studies

It has been demonstrated that over or underestimating the prostate volume can have an impact on the dose distribution throughout the prostate volume (Reynier et al. 2004). Given the small dimensions of the prostate, it is evident that even small changes in prostate border delineation can have a large impact on the calculated volume and dose distributions. For example, overestimating the border of a 3 cm x 5 cm x 4 cm elliptical prostate by as little as 3 mm increases the calculated volume by 25% (Prete et al. 1998). In order to minimize dose distribution errors, the ideal imaging modality for treatment planning and post-implant dosimetry should be able to determine the prostate volume as accurately as possible. Studies comparing MRI contoured prostate volume calculations to measured prostate volumes following prostatectomy have shown that MRI estimates
are as close as 92% of measured values with the discrepancy being attributed to the periprostatic tissues contained in the excised specimen volume that would not be accounted for in imaging studies (Rahmouni et al. 1992).

To improve the signal-to-noise ratio and, subsequently, the spatial resolution of prostate MR images, many clinics use an endorectal coil. These coils may be contraindicated in some patients, however, including those with a recent history of pelvic radiotherapy or surgery. Additionally, the endorectal coil suffers from motion artifacts caused by rectal peristalsis. Furthermore, as described by Sosna and colleagues (2004) pressure from the insertion of the coil causes a deformation of the posterior border of the prostate. This deformation is demonstrated by the warping of a spectroscopy grid when used as an overlay to an anatomic image as shown in Fig. 5.

![Prostate deformation due to insertion of an endorectal probe. The picture on the left shows a probe-in image of the prostate with associated spectroscopy grid. The image on the right is probe-out and shows how the spectroscopy grid must be warped to contain the same tissue volume. (Alterovitz et al. 2006).](image)
Such deformation has been shown to cause seed displacement as much as 9.377 mm from the position without the endorectal probe (Alterovitz et al. 2006). Perhaps more notably, the images are also somewhat inhomogeneous because of the near field effect that causes a region of signal hyperintensity near the rectum with a rapid fall off of signal near the anterior border of the gland. This region of signal fall off can lead to unsatisfactory visualization of the prostatic apex and neurovascular bundles (Torricelli et al. 2006). Each of these artifacts can be seen in Fig. 6.

![Figure 6](image_url)

**Figure 6.** Representative axial T2-weighted image using an endorectal coil at 1.5T. This image reveals some of the shortcomings of using the endorectal coil, including artifacts from bowel peristalsis seen in the left-right direction shown by the gray arrow, near-field brightening that affects the peripheral zone shown by the white arrow, and some distortion of the posterior border of the gland shown by the black arrows (Sosna et al. 2004).

Recent work by Sosna et al. (2004) and Torricelli et al. (2006) demonstrates that image quality obtained at 3.0 Tesla (T) with an external phased array coil is comparable to those obtained at 1.5 T with an endorectal coil without the associated gland deformation or peristaltic motion artifacts. Despite the fact that some of the criteria used
to define image quality are subjective, it has been determined that the external 3T technique has clinical relevance for those patients that are contraindicated for endorectal coil usage or who refuse the use of an endorectal coil for personal or psychological reasons (Torricelli et al. 2006).

Source Localization

MR has not seen widespread acceptance as a post-implant imaging tool because of the difficulty in localizing the implanted seeds. Although used to investigate extraprostatic seed distribution following permanent seed implant brachytherapy, MR has not been widely utilized for dosimetric analysis due to the difficulty in distinguishing individual seeds from one another and from other structures with low signal (Coakley et al. 2001). Shown in Fig. 7, the seeds show up on the image as a signal void, which may resemble the appearance of blood vessels or air bubbles.

Figure 7. Transverse T2-weighted fast SE MR image of 3-mm-thick section of prostate treated with brachytherapy. Multiple radiation therapy seeds are in the position of the neurovascular bundle (arrows) bilaterally (Coakley et al. 2001).
However, sequences can be optimized to either accentuate the lack of signal from the sources, allowing a skilled reader to distinguish blood vessel signal voids from those produced by other sources. In this case, proper identification is the result of noting that the signal void surrounding a blood vessel is also surrounded by an area of increased signal intensity adjacent to the signal void due to the chemical shift between the blood and surrounding tissues (Dubois et al. 1997).

Pulse sequences must be chosen carefully, however. As demonstrated by McLaughlin et al. (2002), the signal distortion produced by the presence of the seeds may obscure the margins of T1-weighted images to the point where there is no volume determination benefit over CT. Careful selection of sequence parameters may minimize the susceptibility artifact around the implants, allowing for a more accurate representation of the seed location within the glandular space.

The aim of this work is to explore the usefulness of magnetic resonance imaging as a single imaging modality for pre- and post-implant imaging studies. Specifically, the goal is to determine whether images acquired from a variety of pulse sequences using a cardiac coil coupled with 3T MRI will be adequate for pre-implant treatment planning and post-implant dosimetric analysis of permanently implanted brachytherapy seeds. Adequacy will be determined by the degree to which anatomic detail allows for precise delineation of prostate boundaries, as well as the ability to accurately localize the implanted seeds.
CHAPTER 2

PHANTOM STUDIES

Introduction

An anthropomorphic phantom allows for the development and repeated testing of imaging protocols without the need to inconvenience patients. Additionally, creation of the phantom in the lab allows for the prostate volume and seed locations to be measured during construction, creating a baseline of measurements for comparison to later measured results. In order for a phantom to be useful for MR imaging, it must be stable at room temperature and should closely mimic the density and magnetic properties of the tissues that are being represented.

From the wide range of values available in the literature, the target T2 relaxation time for the simulated prostate volume was chosen to be 80 ms and the target T2 relaxation time for the surrounding tissues was chosen to be 150 ms. A target T1 relaxation time of 937 ms was selected for the prostate volume and a relaxation time of 207 ms was used for the surrounding tissues. These values were chosen to correlate with the central gland and peripheral zone, respectively, of the prostate as determined by Gibbs et al. (2001).
Materials and methods

Phantom construction

In order to approximate the T1 and T2 relaxation times of the prostate and surrounding tissues, a phantom composed of mixtures of animal hide gelatin and agar gel was constructed. It has been shown by Blechinger et al. (1988) that adjusting the concentrations of agar gel and animal hide gelatin in a phantom allows a researcher to control T2 relaxation times. In general, increasing the concentration of animal hide gelatin with respect to the total phantom volume increases the T2 relaxation time (Blechinger et al. 1988). Work performed by D'Souza et al. (2001) has also shown that the addition of a copper chloride salt (CuCl$_2$·2H$_2$O), with ethylenediaminetetraacetic acid (EDTA) used as a chelating agent, lowers the T1 relaxation time values.

Using the ratios presented by Blechinger (1988), it was determined that a ratio of 30% animal hide gelatin to 70% agar gel should be used for the prostate volume, and a ratio of 80% animal hide gelatin to 20% agar gel should be used for the surrounding tissues. For comparison of images obtained with varying numbers of seeds, three separate 50 ml phantoms were constructed to represent the prostate.

To make each prostate volume, 50 ml of distilled water was heated to boiling. A mixture of 3.48 g of dry animal hide powder and 1.58 g of dry agar powder was slowly added to the water while continuously stirring. The dry powders were sifted very slowly into the water to avoid clumping. Similarly, the mixture was stirred slowly to avoid the introduction of air bubbles into the gel. After the dry powder mixture had been dissolved, air bubbles were skimmed off the top of the mixture and discarded.
Enough distilled hot water was added to 0.0515 g of EDTA to dissolve the chelating agent in a separate beaker. To this volume, 0.03 g CuCl₂ was added, stirred in, and allowed to dissolve completely before adding to the gel mixture. Finally, 0.15 ml of formaldehyde was stirred into the mixture directly before pouring the molten mixture into the 50 ml mold. The mold capsule was then partially submerged in an ice water bath to allow the phantom material to cool and solidify. During this step, the capsule was occasionally agitated gently by hand to avoid gravitational sedimentation. This entire process was repeated to create a total of three prostate phantoms.

Initially, it was decided that placement of the seeds between successive layers of gelatin in the prostate phantom would yield relatively consistent seed placement with no air voids resulting from piercing the gel to place the seeds. The imitation seeds were produced by trimming a 0.8 mm diameter titanium wire to 5 mm lengths. Each seed was placed by hand on top of a 2 mm thick layer of cooled gelatin. Another layer of gelatin was then poured on top of the seeds and allowed to cool. As shown in Fig. 8, placing

Figure 8. Prostate phantom showing seed orientation perpendicular to the central axis of the phantom.
the seeds by this method results in a seed orientation that is perpendicular to the central axis of the completed phantom. This orientation is more consistent with the older retropubic method of seed placement. Since the purpose of this study is the creation of a tissue mimicking phantom to evaluate current brachytherapy methods, an orientation perpendicular to the axis of the phantom is not optimal for this study. Therefore, it was determined that the seeds must be placed parallel to the central axis of the phantom.

To closely mimic current implant procedures, a template was constructed that would allow the seeds to be placed uniformly into the gelatin material. The template had holes that were pre-drilled with a 1 cm space between each hole to ensure uniform spacing of the implanted dummy seeds (Fig. 9).

Figure 9. Seed placement template shown from the top (a) to show the spacing of the holes and from the side (b) to show the placement of the prostate phantom beneath the template.
For each implanted seed, an 18 gauge needle was inserted into the gelatin material through the pre-drilled template hole. A seed was dropped through the needle, and a separate length of wire threaded through the needle was used to stabilize the implanted seed while the needle was withdrawn. Seeds were placed with a lateral spacing ranging incrementally from 2 mm to 10 mm, with the majority of the seeds spaced between 4 mm and 6 mm apart. To fill any air voids left by the needle, a small amount of molten phantom material was poured onto the top of the phantom.

Due to material losses during transfer of the gelatin between vessels, as well as the addition of material to fill voids left by seed placement, it was necessary to confirm the volume of the prostate phantom before placement within the surrounding material. To this end, the volume of one phantom was measured by immersion. A 200 ml beaker was filled approximately to the 100 ml line with DI water and the fluid level marked. The phantom was then completely immersed in the beaker and the resulting fluid level was marked. Water was then removed from the beaker by pipet and transferred to a 100 ml graduated cylinder until the fluid level in the beaker matched the level marked before immersion of the phantom. The volume of displaced fluid was recorded and would serve as the basis for comparison with volume measurements made from the MRI images.

The surrounding tissue phantom was created in much the same manner as the prostate volume phantom. To avoid having to cut through the surrounding material phantom to insert the prostate phantom, the larger phantom was made in four separate stages with cooling in between so that the prostate phantoms could be placed on top of a solid layer. A complete list of materials used for the phantom sections can be seen in Table 1.
Table 1. Composition of tissue mimicking prostate and surrounding tissues.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Material Used</th>
<th>Quantity Per Layer</th>
<th>Total Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surrounding Tissue</td>
<td>DI Water</td>
<td>1890 ml</td>
<td>7560 ml</td>
</tr>
<tr>
<td></td>
<td>Agar Powder</td>
<td>17.01 g</td>
<td>68.04 g</td>
</tr>
<tr>
<td></td>
<td>Animal Hide Powder</td>
<td>350.60 g</td>
<td>1402.04 g</td>
</tr>
<tr>
<td></td>
<td>EDTA</td>
<td>1.95 g</td>
<td>7.79 g</td>
</tr>
<tr>
<td></td>
<td>Copper Chloride</td>
<td>1.15 g</td>
<td>6.05 g</td>
</tr>
<tr>
<td></td>
<td>Formaldehyde</td>
<td>15.12 ml</td>
<td>60.48 ml</td>
</tr>
</tbody>
</table>

| Prostate         | DI Water             | 50 ml             | 150 ml         |
|                  | Agar Powder          | 1.58 g            | 4.74 g         |
|                  | Animal Hide Powder   | 3.48 g            | 1.04 g         |
|                  | EDTA                 | 0.05 g            | 0.15 g         |
|                  | Copper Chloride      | 0.03 g            | 0.09 g         |
|                  | Formaldehyde         | 0.15 ml           | 0.45 ml        |

With the large quantities used, slow mixing and stirring becomes even more important in order to avoid the excessive production of air bubbles and material losses through clumping. After mixing the first stage, the gelatin was poured into a two gallon plastic bucket and allowed to cool in an ice water bath before placing the first prostate volume phantom on top of the solidified gelatin. It was noted that briefly touching the flat edge of the prostate phantom to boiling water before placing on the solidified surrounding material layer allows the two phantoms to bond without the formation of air pockets at the borders. The subsequent surrounding material layer was poured into the mold, enveloping the prostate phantom. The entire phantom was then allowed to cool in an ice water bath until solid.

Several trials of this procedure were conducted in order to perfect seed placement, mixing technique, and cooling methods. In order to minimize material losses while
testing adjustment to techniques, smaller phantoms were constructed and imaged before moving on to a full-scale example.

**Imaging protocol development**

The phantoms were imaged using the 3 Tesla Philips Intera Achieva™ MR system with a SENSE Cardiac Coil. In order to minimize artifacts that may be produced by the interface between the bucket and the gelatin material, the final phantom was removed from the container prior to scanning. The phantoms' sizes are such that they were completely covered by the coil elements with the phantom center of mass centered within the coil. Imaging was completed using the scan list pre-installed on the Philips Intera Achieva system, as well as a proton-density (PD) weighted sequence (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Prostate phantom imaging parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scan Type</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>T1W_TSE_Ax</td>
</tr>
<tr>
<td>T2W_TSE_Ax</td>
</tr>
<tr>
<td>T2W_TSE_Cor</td>
</tr>
<tr>
<td>THRIVE_1mm</td>
</tr>
<tr>
<td>PDW_TSE</td>
</tr>
</tbody>
</table>

Emphasis was placed on the T2-weighted and PD-weighted imaging sequences as suggested in the literature for imaging the prostate following implant placement (DuBois et al. 1997 and McLaughlin et al. 2002).
Phantom volumes were calculated using the MIPAV* software application. MIPAV was used to manually delineate the boundary between the prostate phantom and surrounding tissue. These measurements were then used by the program to calculate the cross sectional area of each slice. The area of each slice was then multiplied by the slice thickness to yield a slice volume. Summing the slice volumes gives an approximation for the total prostate volume that can be compared to that recorded during construction of the phantom. Because the dependence of reconstructed volume on slice thickness has been previously evaluated, this dependency was not re-investigated for this project (Kurmis et al. 2004).

Results

Images produced of the first phantom had a mottled appearance and showed no distinction between the mock prostate and the surrounding materials (Fig. 10). The mottled appearance was attributed to air bubbles formed during the gelatin mixing process and was corrected on subsequent phantom trials. Review of lab notes from the creation of this phantom revealed that the lack of distinction between the two layers was a result of an error in measuring the quantities of gelatin and agar powder to be used. The result of this error was that both masses within this phantom had identical compositions.

* Medical Image Processing, Analysis, Visualization; Center for Information Technology, National Institutes of Health; Bethesda, MD.
In order to confirm the ratios of animal hide gelatin and agar powder were adequate for visual discrimination between the regions using MRI, a phantom was constructed with two discreet layers. One layer represented the prostate material while the other represented the surrounding tissue. To test the hypothesis that air bubbles introduced during rapid stirring of the gelatin created the speckled images, the gelatin for this phantom was stirred slowly until pouring. Images produced of this phantom yielded much better distinction between the two layers and a smoother texture, confirming that the mottled appearance of the first phantom was the result of air being introduced during stirring.

These images also revealed the presence of textured patches assumed to be ice crystals in both gelatin layers, and a large mass indicating the phase separation of different components of the gelatin during the cooling process (Fig 11). A subsequent
phantom that was produced with the same chemical ratios but allowed to cool in an ice water bath confirmed that slowing the cooling process prevented the formation of the textured patches (Fig. 12). A single dummy seed was placed between the layers to

Figure 11. T2-weighted phantom image showing boundary between two gelatin layers (white arrow) and texture indicating the formation of ice crystals (black arrow) and phase separation of mixed chemicals (gray arrows).
Figure 12. a) T2-weighted image of a slowly cooled gelatin/agar phantom showing clear distinction at the boundary between the representative central gland (top) and peripheral zone (bottom) layers. b) Axial T2-weighted image showing the signal intensity variations between the peripheral zone (arrow) and central gland.

indicate the location of the boundary in the event that a lack of contrast between layers was again discovered upon imaging. Images of this phantom reveal a reasonable correlation between the signal intensities of the phantom and human images.

The final phantom produced images with a clear boundary between the two different masses and distinct signal voids indicating the locations of the implanted seeds. A ring of reduced signal intensity also presents itself. This artifact is caused by vibrations induced in the gelatin material by the motion of the MRI system. Elimination of this artifact was achieved by trimming off some of the surrounding material while leaving enough to show a contrast between the prostate phantom and its surroundings (Fig. 13).
Figure 13. Axial T2-weighted image of the prostate phantom showing a ring of reduced signal intensity (left) and the same section after trimming away some of the surrounding material (right).

Without magnification, individual seeds could be visually resolved at seed spacing as close as 3 mm for both scan types (Fig. 14). When seeds were spaced less than 3 mm apart, the boundaries of the individual voids could not be resolved.

Figure 14. Magnified axial T2-weighted image of the prostate phantom showing seed spacing. The white arrows indicate a seed spacing of 3 mm and the black arrow indicates a seed spacing of 5 mm.
Volume measurements taken using the proton density weighted and T2-weighted images were 51.92 ml and 52.58 ml, respectively. This represents an underestimation of the 52.9 ml creation volume by 0.60% for the T2-weighted images and 2.05% for the PD-weighted images.

Conclusions

The combination of agar gelatin and animal hide gelatin in appropriate ratios was used to create a phantom with MRI signal intensities that are visually equivalent to those seen in the central gland and peripheral zone of the human prostate. The materials used allowed the phantom to be structurally stable enough for use without a containment vessel, thus avoiding the possibility of signal attenuation or artifacts caused by a containment vessel. With the addition of formaldehyde as a thermal stabilizer, the phantom was able to withstand several months of imaging and transportation to and from the MRI suite, with outside temperatures ranging from 25° C to 43° C.

These phantoms allowed for the testing of various MRI scan sequences to localize implanted brachytherapy seeds. Analysis of the resulting images indicates that proton density weighted and T2-weighted MRI sequences with a 3 T field strength have the potential for use in differentiating the prostate from surrounding tissues while producing distinct signal voids indicating the location of implanted seeds.

It was not immediately evident in the phantom studies whether the extent of the signal void would adversely impact the usefulness of MRI in post-implant dosimetric studies, however. In the phantom studies, no seeds were placed close enough to the capsule walls to be able to determine whether the signal void would interfere with the ability to
delineate the prostate volume. It was also unclear from these results whether the size of
the signal void would hinder the ability of a reader to precisely determine the seed
location relative to anatomical features and to the other seeds.

Planimetric volume estimates derived from image sets deviated from the known
values by less than 2.5%. This is consistent with results from previous 1.5 T studies
conducted using volumetric flasks (Tuttle 2006) as well as those comparing image-based
estimates to pathologic specimens (Sosna et al. 2003). For reference, when compared
with MRI, CT tends to overestimate the prostate volume by as much as 20-40% (de
Brabandere et al. 2006).

These results suggest that post-implant dosimetric analysis is feasible using a 3 T
MRI scanner and a cardiac coil. Tissue boundaries are clearly visible using both T2-
weighted and proton density-weighted scans, allowing for contouring of the prostate
volume. Using these same two scan techniques, implanted seeds are visible and may be
resolved at spacings of 3 mm and above.
CHAPTER 3

PATIENT STUDIES

Introduction

In theory, higher field scanners offer the promise of a higher signal-to-noise ratio, higher spatial resolution, and higher spectral resolution with similar or shorter acquisition times over lower field strength magnets (Cunningham et al. 2005). Recent work by Sosna et al. (2004) and Torricelli et al. (2006) demonstrates that image quality obtained at 3.0 T with an external phased array coil is comparable to that obtained at 1.5 T with an endorectal coil. Additionally, an experiment performed by Sosna et al. (2003) showed a close correlation between in vivo and ex vivo volume determinations performed using 3T MRI. However, one of the principal drawbacks to operating at higher field strength is the increase in susceptibility artifacts surrounding metallic implants, which may obscure tissue anatomy or the location of nearby seeds (Frayne et al. 2003).

Materials and methods

Pre-implant patients

The primary goal of this study is to determine whether a set of scan protocols using a non invasive cardiac coil may be appropriately developed to allow for the localization of permanently implanted brachytherapy seeds while preserving anatomical detail. To that
end, six healthy volunteers allowed for various scan protocols to be tested and evaluated based on these two criteria. As a starting point, it was noted that the Philips Intera system has a pre-installed exam card for imaging prostate anatomy and detection of prostate cancer. This exam card includes an axial T1 weighted turbo spin echo (T1W_TSE), axial and coronal T2 weighted turbo spin echoes (T2W_TSE), an axial 1mm THRIVE scan, and a single-shot, diffusion-weighted image (SSh_DWI). The parameters for each of these scans are listed in Table 3.

<table>
<thead>
<tr>
<th>Scan Type</th>
<th>TR (ms)</th>
<th>TE (ms)</th>
<th>FOV (mm²)</th>
<th>Matrix</th>
<th>NSA thickness</th>
<th>Slice Number of Slices</th>
<th>Slice Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1W_TSE_Ax</td>
<td>470</td>
<td>10.0</td>
<td>160</td>
<td>256</td>
<td>3</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>T2W_TSE_Ax</td>
<td>4768</td>
<td>90.0</td>
<td>160</td>
<td>512</td>
<td>3</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>T2W_TSE_Cor</td>
<td>3997</td>
<td>80.0</td>
<td>160</td>
<td>512</td>
<td>3</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>SSh_DWI</td>
<td>2500</td>
<td>64.0</td>
<td>160</td>
<td>128</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>THRIVE_1mm</td>
<td>3.4</td>
<td>1.53</td>
<td>395</td>
<td>256</td>
<td>1</td>
<td>1</td>
<td>125</td>
</tr>
</tbody>
</table>

Although these scan parameters were designed for the detection of prostate cancer, it was noted that they may not be adequate for visualization of implanted metallic seeds or for the delineation of the prostate from surrounding tissues. In order to determine which, if any, would be suitable for inclusion in a pre- and post-implant study, a healthy volunteer was imaged using the pre-installed scan parameters. Additionally, based on the findings of previous research studies, a proton density weighted (PDW) sequence with a TR of 2200 ms, a TE of 40 ms, one signal average, 160 mm FOV, and a slice thickness of
3 mm was added (Dubois et al. 1997). Each of the images was then visually evaluated on their suitability for a pre- and post-implant volume estimates and based on overall image clarity and distinctness of prostate anatomy.

Following the elimination of inappropriate scan sequences, the remaining sequences were varied to determine which would yield the clearest anatomical boundaries, as well as minimize the total scan time. Adjustments were made to the number of signal averages (NSA) acquired as shown in Table 4. All other parameters were held constant to determine what effect the increase in the number of signal averages would have on the image quality.

Table 4. Variation in scan time with increasing number of signal averages

<table>
<thead>
<tr>
<th>Scan Type</th>
<th>NSA</th>
<th>Slice thickness (mm)</th>
<th>Number of Slices</th>
<th>Slice Gap (mm)</th>
<th>Scan Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDW_TSE_Ax</td>
<td>2</td>
<td>1.00</td>
<td>24</td>
<td>4.00</td>
<td>05:21.2</td>
</tr>
<tr>
<td>PDW_TSE_Ax</td>
<td>4</td>
<td>1.00</td>
<td>24</td>
<td>4.00</td>
<td>10:42.4</td>
</tr>
<tr>
<td>PDW_TSE_Ax</td>
<td>6</td>
<td>1.00</td>
<td>24</td>
<td>4.00</td>
<td>16:03.6</td>
</tr>
<tr>
<td>PDW_TSE_Ax</td>
<td>8</td>
<td>1.00</td>
<td>24</td>
<td>4.00</td>
<td>21:24.8</td>
</tr>
</tbody>
</table>

Post-implant patients

With one exception, each of the five patients was selected for this study based on a history of prostate cancer treated with permanent implant brachytherapy. The exception to this inclusion was the first patient imaged, who had undergone external beam radiation therapy of the prostate, but had three fiducial markers implanted before treatment. This
patient was included to evaluate the ability to visualize individual implanted seeds without interference from field disturbances resulting from other nearby seeds.

General protocols for imaging this group of patients were similar to that used for imaging the healthy volunteer group, with patients undergoing proton density-weighted scans. In the case of the post-treatment patients, emphasis was placed on adjusting parameters to maximize the visualization of the seeds. Slice thickness was varied between patients to determine which slice thickness would allow for clear anatomical boundaries while producing distinct signal voids indicating seed locations. Table 5 details the parameters varied.

| Table 5. Post-implant prostate patient imaging parameter variations used |
|--------------------|-----|-----|-----|-----|-----|-----|
| Scan Type          | TR (ms) | TE (ms) | FOV (mm$^2$) | Matrix | NSA | Slice thickness | Slice Gap | Number of Slices |
| PDW_TSE_Ax        | 2200  | 40   | 160  | 256  | 4   | 4.0            | 1.0       | 16               |
| PDW_TSE_Ax        | 2200  | 40   | 160  | 256  | 4   | 3.0            | 0.4       | 20               |
| PDW_TSE_Ax        | 2200  | 40   | 160  | 256  | 4   | 2.0            | 0.4       | 24               |
| PDW_TSE_Ax        | 2200  | 40   | 160  | 256  | 4   | 1.0            | 0.4       | 40               |
| PDW_TSE_Ax        | 2200  | 40   | 160  | 256  | 4   | 1.0            | 2.0       | 14               |
| PDW_TSE_Ax        | 2200  | 40   | 160  | 256  | 4   | 1.0            | 4.0       | 14               |

Images were evaluated for general clarity and anatomical detail, as in the case of those images acquired during the healthy volunteer portion of the study. Additionally, the images were examined to determine whether or not the seeds were visible and whether or not the prostate margins were obscured by the seeds.
Variations in slice thickness between the two modalities made direct comparison between CT and many of the MRI data sets impractical. For the data set with a 1 mm slice thickness with no gap, as well as the 1 mm slice thickness with a 4 mm gap, the data images were compared to sets of CT images that had previously been dosimetrically evaluated by a trained physicist using the Variseed 7.1\textsuperscript{1} treatment planning system. Seeds were noted whenever they were visualized on one modality but not the other.

For seed localization and counting, two observers examined each set of images multiple times in a randomized order with no prior knowledge of the number of seeds placed. Along with printed data sets, both observers were given information on slice thickness and slice gap. Where applicable, seed locations were compared on successive slices in order to systematically omit those signal voids that indicate a single seed present in multiple slices. Observers were asked to keep a tally of the number of seeds counted. The number of seeds counted was then compared to the number implanted, as recorded in the patients' procedural notes.

Results

Pre-implant studies

It was immediately recognized that some of the resultant images would not be adequate for inclusion in this study based on the lack of anatomical detail. For instance, while useful for a pathological evaluation of the prostate tissue, the diffusion-weighted image shows little anatomical detail (Fig. 15). Similarly, the T1-weighted images, while having a faster acquisition time than T2-weighted images, show little tissue contrast between the prostate itself and surrounding musculature (Fig. 16). Because the

\textsuperscript{1} Varian Medical Systems, Palo Alto, California, USA.
Figure 15. Diffusion-weighted image in the axial plane of a healthy male prostate.

Figure 16. T1-weighted image of the male pelvis in the axial plane showing the lack of contrast between the prostate (white arrow) and levitator ani muscles (black arrows).
THRIVE 1 mm sequence is designed for use with contrast enhancement; these images without contrast injection do not exhibit the degree of soft-tissue contrast for the areas being considered that would allow for easy delineation of the prostate tissue (Fig. 17). Evaluation of the THRIVE scan revealed little signal contrast between the anterior rectal wall, the prostate, and the levitator ani muscles.

![Image](image_url)

**Figure 17.** THRIVE 1 mm scan of the male pelvis in the axial plane. Note the lack of contrast between the prostate (white arrow) and surrounding tissues (gray arrows).

Shown in Fig. 18, it was immediately apparent that the T2-weighted images yielded excellent soft tissue contrast and anatomical detail in both the axial and coronal planes. Using these scan parameters, the boundaries between the prostate and surrounding tissues
were readily discernable, as was the prostatic urethra. No changes were made to the T2-weighted scan parameters based on these results.

Figure 18. T2-weighted images of a healthy male prostate in the axial (left) and coronal (right) planes. In both images, the prostate itself is indicated by the white arrow and the levitator ani muscles are indicated by the gray arrows.

The images from the proton-density weighted scans appeared grainy in comparison to the T2-weighted scans, suggesting a lower signal to noise ratio (SNR). In order to be useful in this study, the overall image quality needed to be improved to accurately delineate the prostate volume. This was achieved by increasing the number of signal averages (NSA) from two to four, six, and eight averages (Fig 19). Although increasing the number of averages increases the signal to noise ratio by measuring and summing the signal received for a given slice multiple times, there is a tradeoff in time of acquisition. Total measurement time is directly proportional to the NSA such that, when increasing from two to eight averages, there is an increase in the total scan time from 215 to 730 s.
Figure 19. Axial proton density weighted images of a healthy male pelvis showing the increase in overall image clarity achieved by increasing the NSA from (a) 2 to (b) 4, (c) 6 and (d) 8.

Post-implant studies

Figure 20 illustrates how image quality varies as a function of slice thickness for PD-weighted scans. The 1 mm slice thickness images showed distinct signal voids and clear
anatomical boundaries. In comparison, the signal voids in the images acquired with a 3 mm slice thickness appear broadened (Fig. 20). This effect is even more pronounced in the

Figure 20. Axial proton density weighted images of the male pelvis following implantation. Images were acquired using (a) 1 mm, (b) 2 mm, (c) 3 mm, and (d) 4 mm slice thicknesses.
images acquired with a 4 mm slice thickness. Additionally, images acquired using a 4 mm slice thickness reveal superimposed signal voids from the inclusion of more than one seed on different planes in the same slice selection (Fig. 21).

![Figure 21](image.png)

**Figure 21.** Axial proton density weighted image of a male pelvis acquired using a 4 mm slice thickness. Dual signal artifacts are indicated by white and black arrows.

On images with a small slice thickness, seeds were readily visualized within the gland itself, along the glandular borders, and outside of the prostate capsule (Fig. 22). Close seed grouping was not found to be a factor in the number of seeds counted within these data sets. In general, the number of seeds implanted (maximum 90) allowed for a seed distribution that was spaced such that individual seeds could be readily distinguished from their neighbors. In the instances where two or more seeds were placed sufficiently close to cause the two voids to merge, the size of the void was significantly larger than
neighboring voids. A similar effect was noted in the corresponding CT images, with an enlarged area of signal hyperintensity indicating the presence of multiple seeds.

One instance was noted in which a seed was visualized on a CT image without being counted on the corresponding MR image. This patient consented to a second MRI session in which the absence of a seed in that plane was confirmed. An assumption was made based on the previous experience of the physicist that performed the dosimetric evaluations that the seed had likely migrated to the urethra and had been subsequently expelled in the urine. Because the CT scan was not repeated, however, no conclusions could be drawn as to the source of this anomaly.

Figure 22. Axial proton density weighted images of a male pelvis showing seed locations within the gland (white arrow), along the prostate capsule (black arrow), and outside of the gland (gray arrow).
When the image sets were evaluated with no prior knowledge of the number of seeds implanted, an overall average of 70 out of 86 seeds were visualized across all slice thicknesses. The 1 mm slice thickness with a 4 mm gap had the highest number of seeds visualized at 84 out of 90, while the 4 mm slice thickness with a 1 mm gap had the lowest visualization rate with 60 out of 78. Table 6 lists the percentage number of seeds visualized for each data set.

<table>
<thead>
<tr>
<th>Data Set</th>
<th>Slice Thickness (mm)</th>
<th>Slice Gap (mm)</th>
<th>Average Percentage of Seeds Visualized</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0</td>
<td>1.0</td>
<td>68.8±16.8</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>0.4</td>
<td>76.4±13.1</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>0.4</td>
<td>81.3±12.4</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>0.4</td>
<td>85.2±17.2</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>2.0</td>
<td>91.7±1.6</td>
</tr>
<tr>
<td>6</td>
<td>1.0</td>
<td>4.0</td>
<td>93.3±2.2</td>
</tr>
</tbody>
</table>

Conclusions

Pre-implant studies

Three of the five image sequences pre-installed on the Philips Intera system were found to be unsuitable for inclusion in this study. For the T1-weighted and THRIVE_1mm scans, the lack of anatomic detail and soft-tissue contrast make delineation of the glandular borders difficult and prone to the same subjective judgment
necessary for CT-based glandular delineation (Al-Quaisieh et al. 2001). In the case of the THRIVE_1mm scan, this lack of inherent contrast was expected since this scan is typically used in contrast studies following the intravenous administration gadolinium.

From the images reviewed, the T2-weighted scans provided the best soft tissue contrast and anatomical detail in both the axial and coronal planes. Accordingly, this scan was included in the final protocol as an anatomy baseline for comparison to the other scans selected. Although not as clear as the T2-weighted scans, the PDW scan also yielded clear glandular borders and was included in the parameters evaluated for their usefulness in determining seed locations following the implant procedure.

Post-implant studies

Data suggests a direct correlation between image slice thickness and the percentage of seeds counted. A 4 mm slice thickness yielded the worst visualization rate with 68.8% of seeds visualized, while a 1 mm slice thickness yielding the highest percentage of seeds visualized with between 85.2% and 93.3%, depending on the spacing between slices. These findings are consistent with previous studies that evaluated the effect of slice thickness on seed localization using both CT and MRI (De Brabandere et al. 2006, Prete et al. 1998). A large slice thickness increases the chance that more than one seed may intersect the scan plane and contribute to the loss of signal at that position. For an observer, it may not be possible to tell whether the signal void is produced by a single seed or multiple seeds. This effect is also seen in post-implant CT images when a seed appears on contiguous slices.
Reduction of the slice thickness to 1 mm improves seed definition, while allowing for precise determination of prostate boundaries. However, the tradeoff to the slice thickness adjustment is a decrease in the signal to noise ratio, resulting in images with a grainy appearance. To compensate for the decreased signal to noise ratio while maintaining a constant FOV, each slice must be acquired multiple times with the resulting data summed, which results in increased scanning times. Increased scan times may lead to greater patient discomfort and motion, which can degrade image quality. Using four signal averages appears to be a suitable compromise, yielding clear images while maintaining a scan time of just less than eleven minutes in order to minimize patient discomfort.

As an alternative solution to the decreased SNR from thinner slice thicknesses, the gap between slices may be increased, which results in a reduction in the total number of slices needed to cover the entire prostate volume. Broadening the slice gap has the added advantage of simplifying the seed localization and counting process by reducing the number of images through which signal voids must be tracked.
CHAPTER 4

SUMMARY AND CONCLUSIONS

Summary

Magnetic Resonance Imaging (MRI) yields images with soft tissue contrast that is superior to CT or ultrasound, but has been under-appreciated as a dosimetric tool in LDR brachytherapy due to a perceived difficulty in localizing the implanted seeds. Compared to 1.5 T MRI with a whole body coil, the use of a SENSE compatible cardiac coil coupled to a 3 T MR spectrometer yields a higher signal to noise ratio and increased spatial resolution. Work by Sosna et al. (2004) and Torricelli et al. (2006) demonstrates that image quality obtained at 3.0 Tesla (T) with an external phased array coil is comparable to those obtained at 1.5 T with an endorectal coil without the associated gland deformation or peristaltic motion artifacts. However, one of the principal drawbacks to operating at a higher field strength is the increase in susceptibility artifacts surrounding metallic implants, which may obscure anatomical information or the location of other implants (Frayne et al. 2003).

The aim of this work was to determine whether images acquired from a variety of pulse sequences using a cardiac coil coupled with 3T MRI are adequate for pre-implant treatment planning and post-implant dosimetric analysis of permanently implanted brachytherapy seeds. Adequacy was determined by the degree to which anatomic detail
allows for precise delineation of prostate boundaries, as well as the ability to accurately localize the implanted seeds at least as well as with CT.

To that end, a series of phantoms were created using a combination of animal hide gelatin and agar gelatin that allowed for the testing of various MRI scan sequences to localize implanted brachytherapy seeds. Analysis of the resulting images indicates that proton density weighted and T2-weighted MRI sequences on a 3 T spectrometer have the potential to differentiate the prostate from surrounding tissues while producing distinct signal voids at implanted seed locations.

Although some have argued that variations in prostate volume determination from CT images have little impact on dosimetric quality factors, it is important to note that this assertion is only valid when a periprostatic margin is included as part of the target volume (Bice et al. 1998, Merrick et al. 1999). As has been noted previously, the inability to distinguish the prostate glandular boundary from the surrounding tissues is the strongest factor in volume determination uncertainty (Al-Quaisieh et al. 2001). An assessment of the impact of imaging uncertainties on dosimetric evaluation of prostate brachytherapy implants concluded that volume calculation uncertainties had a larger impact on tumor control probability than either seed detection rates or seed localization uncertainties (Lindsay et al. 2003).

Volumes calculated from image sets were less than 2.5% smaller than those measured during phantom creation. Volume estimates may be further improved through a reduction in slice thickness (Kurmis et al. 2003), but at the expense of increased scan times, which may increase patient discomfort, movement, and subsequent image degradation.
The inclusion of the proton density weighted sequences with a short TE allowed for more precise determination of seed locations by minimizing the signal void surrounding the seeds and decreasing the incidence of signal void overlap that can obscure both anatomy and seed position. Using this sequence, seeds were resolved at spacings as low as 3 mm.

Seed detection rate was found to be dependent on slice thickness used for the image acquisition. In general, smaller slice thicknesses had higher detection rates with the 4 mm slice thickness yielding the worst visualization rate with 68.8% of seeds visualized, and the 1 mm slice thickness yielding the highest percentage of seeds visualized with between 85.2% and 93.3%, depending on the spacing between slices. These findings are consistent with previous studies that evaluated the effect of slice thickness on seed localization using both CT and MRI (De Brabandere et al. 2006, Prete et al. 1998).

Although the detection rates for this study were below the 95% suggested by Yi Su et al. (2005) for accurate estimation of dose quality parameters, the maximum detection rate of 93.3% is above those reported for T2-weighted MRI studies (Bloch et al. 2007.) Additionally, research conducted by Dubois et al. (1997) suggests that there is a learning curve associated with the detection of implanted sources on MR images. Dubois further suggests that this curve may be mastered in as few as five cases by initially using CT images along side the MR images as a learning guide.
CONCLUSIONS

The results of this study suggest that images acquired using a 3 T magnetic resonance spectrometer coupled to a cardiac coil may be used to reliably identify permanently implanted brachytherapy seeds in the prostate without the use of an endorectal coil. The optimized protocols may be seen in Table 7. Tissue boundaries are clearly visible using both T2-weighted and proton density-weighted scans, allowing for contouring of the prostate volume. Additionally, the short TE of the proton density-weighted scans minimizes the susceptibility artifact surrounding the seeds to allow the seeds to be clearly visualized while preserving anatomical boundary information. Slice thickness may be reduced to maximize both volume estimates and seed detection rates, while interslice spacing may be increased to shorten image acquisition times and simplify the seed counting process.

<table>
<thead>
<tr>
<th>Scan Type</th>
<th>TR</th>
<th>TE</th>
<th>FOV</th>
<th>Matrix</th>
<th>NSA</th>
<th>Slice thickness</th>
<th>Slice gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2W_TSE_Ax</td>
<td>4800</td>
<td>90</td>
<td>160</td>
<td>512</td>
<td>3</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>T2W_TSE_Cor</td>
<td>4800</td>
<td>90</td>
<td>160</td>
<td>512</td>
<td>3</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>T2W_TSE_Sag</td>
<td>4800</td>
<td>90</td>
<td>160</td>
<td>512</td>
<td>3</td>
<td>3</td>
<td>0.3</td>
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<td>160</td>
<td>256</td>
<td>4</td>
<td>1.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>
REFERENCES


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Figure 1 (page 899)


Figure 2 (page 447)

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APPENDIX II

PATIENT CONSENT FORM
TITLE OF STUDY: Investigation of Magnetic Resonance Imaging as a tool for Brachytherapy
Permanent Seed Implantation Treatment of Prostate Cancer

INVESTIGATOR(S): Jason Davis, Phillip Patton

CONTACT PHONE NUMBER: 702-895-3555 (Phillip Patton), 702-328-2368 (Jason Davis)

Purpose of the Study
You are invited to participate in a research study. The purpose of this study is to investigate the use of Magnetic Resonance Imaging (MRI) as a method of imaging the prostate that will allow physicians to accurately plan a permanent implant cancer treatment and evaluate the success of these treatments.

Participants
You are being asked to participate in the study because you have been diagnosed with prostate cancer, are considered a candidate for implantation therapy, and have no known medical conditions such as claustrophobia, metal implants, etc. that would prevent you from being imaged by MRI.

Procedures
If you volunteer to participate in this study, you will be asked to do the following: lie on your back in an MRI tube for approximately 45 minutes while the scan is completed. After your treatment, you will be asked to repeat the scan.

Benefits of Participation
There may not be direct benefits to you as a participant in this study. However, we hope to learn how MRI may be used to plan prostate cancer treatments and evaluate the success of these treatments.

Risks of Participation
There are risks involved in all research studies. This study may include only minimal risks. Because the process requires that you remain completely still, you may become uncomfortable during the scanning process. Additionally, you may experience some claustrophobia while in the MRI tube.

Cost/Compensation
There will not be financial cost to you to participate in this study. The study will take approximately 90 minutes of your time, or 45 minutes each on two separate days. You will not be compensated for your time. The University of Nevada, Las Vegas may not provide compensation or free medical care for an unanticipated injury sustained as a result of participating in this research study.
UNLV UNIVERSITY OF NEVADA, LAS VEGAS

INFORMED CONSENT
Department of Health Physics

TITLE OF STUDY: Investigation of Magnetic Resonance Imaging as a tool for Brachytherapy
Permanent Seed Implantation Treatment of Prostate Cancer

INVESTIGATOR(S): Jason Davis, Phillip Patton

CONTACT PHONE NUMBER: 702-895-3555 (Phillip Patton), 702-328-2368 (Jason Davis)

Contact Information
If you have any questions or concerns about the study, you may contact Jason Davis at (702)328-2368 or Phillip Patton, PhD at 702-895-3555. For questions regarding the rights of research subjects, any complaints or comments regarding the manner in which the study is being conducted you may contact the UNLV Office for the Protection of Research Subjects at 702-895-2794.

Voluntary Participation
Your participation in this study is voluntary. You may refuse to participate in this study or in any part of this study. You may withdraw at any time without prejudice to your relations with the university. You are encouraged to ask questions about this study at the beginning or any time during the research study.

Confidentiality
All information gathered in this study will be kept completely confidential. No reference will be made in written or oral materials that could link you to this study. All records will be stored in a locked facility at UNLV for at least 3 years after completion of the study. After the storage time the information gathered will be shredded.

Participant Consent:
I have read the above information and agree to participate in this study. I am at least 18 years of age with no medical conditions such as claustrophobia, metal implants, or implanted cardiac pacemaker that prevent me from being imaged using a magnetic resonance imaging spectrometer. A copy of this form has been given to me.

Signature of Participant __________________________ Date __________

Participant Name (Please Print) __________________________

Participant Note: Please do not sign this document if the Approval Stamp is missing or is expired.
APPENDIX III

MRI IMAGE ACQUISITION METHODS
PROSTATE MRI SCAN ACQUISITION NOTES

Pre-Scan Setup

1. Select ‘Patient’ on the menu bar.

2. Select ‘New Exam.’

3. Enter the following information:
   a. Patient’s coded name.
   b. Registration number.
   c. Patient’s date of birth (MM/DD/YYYY).
   d. Patient gender as male.
   e. Patient’s weight (in kg).
   f. Any additional comments.
   g. The other fields can be left blank.

4. Clink ‘Enter.’

5. Click ‘Proceed.’ The system will not automatically switch to scan mode.

Patient Positioning

1. Instruct patients to remove all metallic objects that may be on their person, including watches and jewelry.

2. If the patient has a metallic zipper or metal rivets in their clothes, allow them to change into a set of scrubs or a hospital gown.

3. Lower the couch to the parking position using the Out/Down tumble switch located on the control panel. So the patient should be able to comfortably easily sit and then lay on the couch, stopping the couch somewhat above the parking position may be necessary.

4. Place the cardiac coil on the couch. Do not plug the coil into the scanner at this time. Add other mattresses, knee cushions, and pillows as needed for patient comfort. Be sure the patient is as comfortable as possible to minimize motion artifacts. Blankets, sheets, or parkas may be used as the room may become cool.
during the procedure. Each patient should also be provided with a set of ear plugs to minimize discomfort due to machine noise.

5. Instruct the patient to lie on their back with feet pointed in toward the bore. Align the patient’s pelvic crest with the top of the cardiac coil. The patient may lie with their arms above their head or folded across their chest, so long as the position is comfortable enough to minimize motion. Raise the couch using the Up/In tumble switch.

6. Press the ‘light visor’ button on the control panel. This will activate the laser registration grid lines. Using the laser beams, place the patient so the approximate location of the prostate lies in the middle of the illuminated cross. The coil may now be plugged into the scanner. Press ‘Travel-to-scanplane’ button on the control panel. The laser beams will turn off automatically. Use the Up/In tumble switch to place the patient into the tube. The couch will stop moving once the isocenter has been reached.

7. Once all the scans have finished, remove the patient from the tube. Use the Out/Down tumble switch on the control panel until the couch is in the parking position, or to a position where the patient is able to step down safely.

8. Be sure to tightly close the exam room door before starting any scans.

Imaging Scan

1. Select the ‘Hospital’ folder in the Exam Cards under Toolbar.

2. Select the folder ‘User Defined.’

3. Scroll down and select the ‘UNLV’ folder.

4. Select the first scan list ‘UNLV Prostate.’

5. Copy the scans and paste them in the Exam Cards.

6. In the Exam Cards, click on the Survey scan to open up the scan. Make sure the geometry (GEO) field is blank or the survey scan will not run. Click ‘Proceed,’ then ‘Start Scan’ to start the Survey.

7. When the Survey has finished, click on the Exam Cards for the Ref_SCC_SENSE to open up the scan. Make sure the coil selected is the cardiac coil. Respiratory compensation should be set to ‘Breath Hold.’ Click ‘Proceed’ to start the
Ref_SCC_SENSE scan. Following the on-screen prompts, tell the patient when to hold their breath and when to begin breathing again.

8. When the reference scan has finished, select the appropriate reference scan image to begin planning the other scans. Double click the next scan in the current exam card window to open that scan for planning. A colored box should appear in the reference scan image. Align this box so that the entire region of interest is covered. For coronal reference views, the center circle within the planning volume should line up just below the bladder trigone and the top of the box should line up approximately with the center of the femur head. For sagittal reference scans, the lower edge of the scan volume box should line up with the fold of the leg (between the bottom of the leg and the top of the buttock). On axial scans, the prostate should be visible above the darkly colored rectum and between the two femurs.

9. Under the 'Initial' tab, use the Survey scan as a guide and adjust the field of view (FOV) to the desired size. Ensure that foldover suppression is set to 'Yes,' then click 'Proceed,' then 'Start Scan' to begin scanning.

10. While the first scan is running, steps 8 and 9 can be repeated for the remaining scans. If the first scan has not finished and the planning has been completed for each of the subsequent scans, clicking 'Proceed' for the subsequent scans will allow the scans to proceed without interruption once the previous scan has finished.
VITA

Graduate College
University of Nevada, Las Vegas

Jason Eric Davis

Home Address:
6854 Baby Jade Court
Las Vegas, Nevada 89148

Degrees:
Bachelor of Science, Health Physics, 2005

Thesis Title: Prostate Volume Delineation and Seed Localization Using a 3T Magnetic Resonance Spectrometer.

Thesis Examination Committee:
Chariperson, Dr. Phillip Patton, Ph.D.
Committee Member, Dr. Steen Madsen, Ph.D.
Committee Member, Dr. Ralf Sudowe, Ph.D.
Graduate Faculty Representative, Dr. Harvey Wallmann, Ph.D.