1-1-2005

Evaluation of an intraoperative iodine-125 brachytherapy implant technique

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EVALUATION OF AN INTRA-OPERATIVE I-125 BRACHYTHERAPY IMPLANT TECHNIQUE

by

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Bachelor of Arts
Institute of Foreign Language
Mongolia
1997

A thesis submitted in partial fulfillment
of the requirements for the

Master of Science Degree in Health Physics
Department of Health Physics
Division of Health Sciences

Graduate College
University of Nevada, Las Vegas
May 2006

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The Graduate College
University of Nevada, Las Vegas

March 1, 2006

The Thesis prepared by

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Entitled

Evaluation of an Intra-Operative I-125 Brachytherapy Implant Technique

is approved in partial fulfillment of the requirements for the degree of

MS in Health Physics

Examination Committee Chair

Dean of the Graduate College

Examination Committee Member

Examination Committee Member

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1017-53

ABSTRACT

Evaluation of an Intra-Operative I-125 Brachytherapy Implant Technique

by

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The purpose of this study was to evaluate the usefulness of an intra-operative planning method in brachytherapy prostate seed placement by comparing pre-planning and intra-operative planning techniques. This comparison was achieved by a virtual-planning technique in which the pre-planned seed and needle positions are superimposed on the intra-operatively obtained volume study. Dosimetric evaluation of each implant was based on the dose volume histogram (DVH) generated from CT studies and analysis of image and seed numbers, target volume and inferior extent of posterior planes. These parameters showed that greater dosimetric values are noted in the intra-operative technique. The study demonstrated a benefit from an intra-operative approach to seed placement as opposed to a pre-planned approach. Defining the sagittal contours of the prostate, immediately prior to implant, reduced the inferior extent of seeds placed in the most posterior aspect of the prostate, thereby decreasing the probability for rectal complication and morbidity. Additionally, more correctly delineating the tranverse

prostate contours at the time of seed placement resulted in fewer seeds placed in the periprostatic region, outside the PTV, thus reducing potential seed migration and increasing prostate dose coverage.

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ACKNOWLEDGEMENTS

This work was supported by the Radiation Oncology Center of Las Vegas. I would like to thank Dr. Ritchie Stevens and Mr. Dwight Potter, physicist for their helpful thoughts and comments on this manuscript.

CHAPTER 1

INTRODUCTION

1.1 Background

Brachytherapy is a radiotherapeutic technique that places radioactive isotopes within body cavities or directly into a tissue region with a goal of delivering a high dose to the region while sparing the normal surrounding tissue. When radium was discovered by the Curies in 1898, it became the most commonly used isotope for brachytherapy because of its long half life (1,600 years) and high photon energy (0.83 MeV average). However, the handling of this isotope involved substantial risks of radiation exposure to the physician and supporting personnel. Therefore, a number of artificially produced radioisotopes were introduced, such as Ir-192, Au-198, Cs-137, I-125 and Pd-103. These isotopes have lower photon energies with much shorter half-lives than radium; thus, decreasing the radiation hazards associated with the procedures.

1.2 Brachytherapy Techniques

In brachytherapy, there are three major treatment techniques: surface molds, interstitial therapy, and intracavitary therapy. Surface molds are used to treat small superficial areas. The sources are carefully placed on the outer surface of the mold. The distance between the source and skin surface is between 0.5 and 1.0 cm. In intracavitary

techniques, an applicator is inserted into a body cavity to reach the tumor. Intracavitary treatments are used primarily for cancers of the uterine cervix, uterine body and vagina (Khan M, 2003).

Interstitial brachytherapy is a very complex technique with implantation occurring in a surgical room while the patient is under anesthesia or sedation. Interstitial catheters are inserted directly into the tumor through the body tissue. In the case of prostate and gynecologic cases, a rubber template is sutured to the outside skin to hold the treatment catheters in position. Interstitial implants may be permanent or temporary. In temporary implants, the sources are removed after the prescribed dose has been delivered. Palladium-103 or I-125 is commonly used in permanent implants. Both temporary and permanent interstitial implants might use afterloading techniques. The significance of afterloading techniques is to reduce radiation exposure to personnel and to eliminate the direct handling of the radioactive sources.

High dose rate (HDR) brachytherapy involves the temporary placement of a tiny radioactive source with high activity, on the order of curies, into a tumor through a catheter to deliver a concentrated dose of radiation. After treatment, the radioactive source retracts into the afterloader. High dose rate remote afterloader treatment takes place in a fully shielded room with short treatment time. In Fig. 1, high dose rate remote afterloading implants achieve desired dose distributions by moving a single high strength Ir-192 source, connected to the end of a flexible cable, through one or more available channels (Khan, 2003). With the help of a computer-guided afterloader, the planning system calculates how long the radioactive source spends (dwell time) in specified 5 mm steps (dwell position) along the length of the catheter (Glen, 2003).

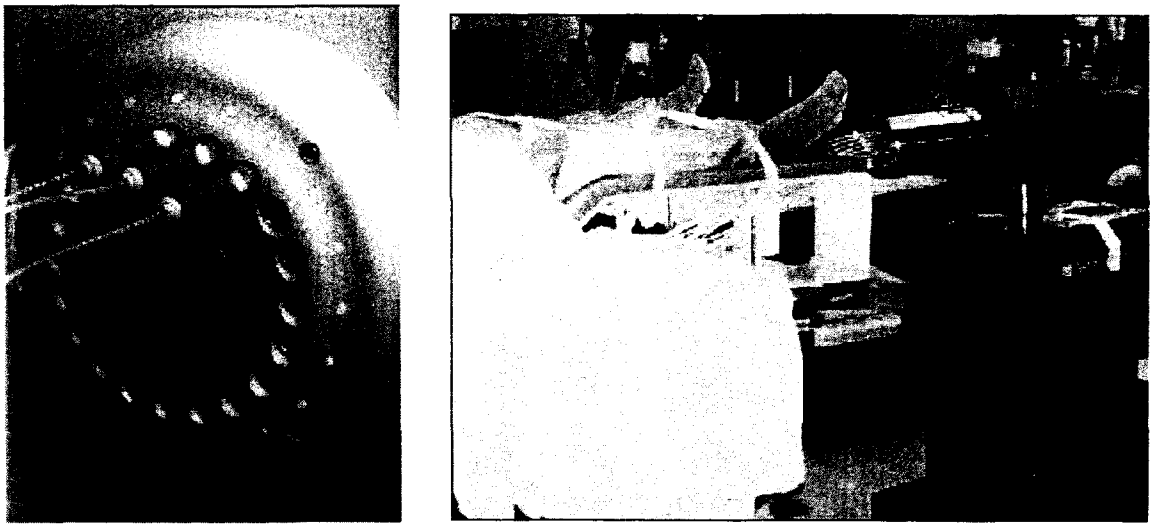

Figure 1. HDR remote afterloading brachytherapy unit employs a miniature Iridium-192 radioactive source at the end of a steel wire to deliver the radiation treatment. The steel wire is under computer control. The position of the source within the patient's body and time length can be accurately controlled (www.tampabayprostateinstitute.com).

LDR brachytherapy occurs in the operating room, with the patient under spinal or general anesthesia. For prostate cancer, the delivery of radiation is targeted directly to the prostate gland through the implantation of small radioactive pellets. Needles are inserted through the skin of the perineum. After each needle is in the proper position, the seeds are inserted according to the images seen on the ultrasound as shown in Fig. 2. These seeds emit radiation over several weeks or months, remaining in the prostate gland permanently. Most prostate implants require 60 to 120 seeds, depending on the size of the prostate.

The International Commission on Radiological Protection (ICRP) Report 38 categorizes HDR as greater than 20 cGy per minute. Cancers such as breast, gynecological, and prostate cancers can be treated with HDR. Both HDR and LDR have the ability to deliver the radiation source to the tumor while sparing the normal tissues.

The most important benefit of HDR is the shorter treatment times when compared to LDR.

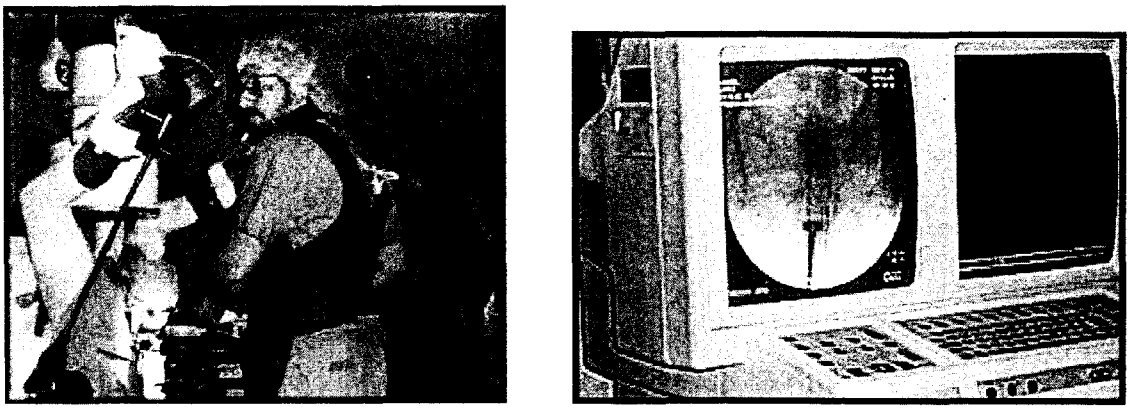

Figure 2. The physician pushes stainless steel needles through the pre-determined holes in the template, into the perineum and then the prostate, guided by the images seen on the ultrasound (www.tampabayprostateinstitute.com).

However, extra costs must be considered for room shielding and installing additional imaging equipment installation. Therefore, large number of brachytherapy treatments use LDR implants. The prescribed dose for these procedures is between 0.5 and 2.0 cGy per minute based upon size and type of tumor (Nori et al. 1990). The types of cancer treated with LDR brachytherapy are breast, head and neck, gynecologic, and prostate cancer. Even though LDR treatment is very common, it has some limitations. First, LDR treatment times are long. Any movement of the seed implant results in inadequate doses to the tumor and surrounding tissues. However, interstitial prostate brachytherapy with permanent seed implant is universally used because of its close proximity to the perineum (Sylvester et al. 1997).

1.3 Prostate cancer

Prostate cancer is the most commonly diagnosed noncutaneous malignancy in the male population. In 1999, approximately 189,000 new case of prostate cancer were diagnosed in the United States (Rietbergen et al. 1999). Prostate brachytherapy is one of the most improved treatments of early prostate cancer treatment (S. Nag et al. 2001). In the last five to ten years, with the development of imaging modalities such as computed tomography (CT), and transrectal ultrasound (TRUS) together with template-based transperineal techniques, LDR brachytherapy results have shown an improved consistency in radiation dose delivery to the entire prostate.

In addition, prostate cancer can be detected by the prostate specific antigen (PSA) test at an early stage when no symptoms are present. PSA is a substance produced by cells from the prostate. Under normal circumstances, PSA is secreted by the prostate into semen to help with reproduction by preventing the coagulation of semen. However, small amounts of PSA naturally leak into the bloodstream. When prostate cancer is present, the prostate ducts that normally secrete PSA into the urethra get clogged and more PSA leaks into the bloodstream. The PSA test can not confirm whether or not cancer is present, but it can suggest the need for further tests. By combining the patient's PSA level with his Gleason score and the clinical stage estimated by the physician, it is possible to estimate the type of prostate cancer (Peter et al. 2005).

The Gleason score allows the doctors to understand how a particular case of prostate cancer can be treated. In general, a physician gives a patient a combination of two numbers. The lowest possible Gleason score is 2 (1+1), where both the primary and secondary patterns have a Gleason grade of 1. Dr. Gleason's own simplified drawing of

the five Gleason grades of prostate cancer is illustrated in Fig 3. A very typical Gleason score might be between five to seven, and the highest possible Gleason score is ten. Dr Gleason discovered that by giving a combination of the grades of the two most common patterns he could see in any particular patient's specimen, he was better able to predict whether the patient would respond positively by a particular treatment method (Tannenbaum M, 1977).

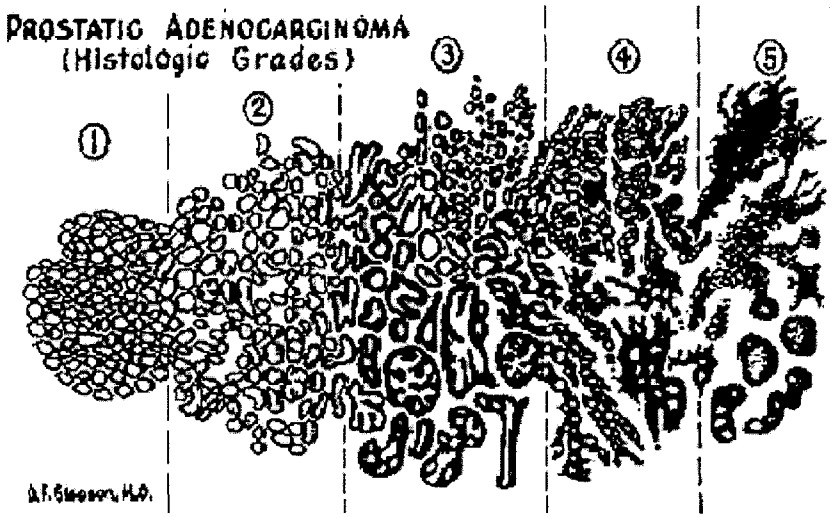

Figure 3. This illustration shows Dr. Gleason's own simplified drawing of the five Gleason grades for prostate cancer. Well differentiated Gleason grade 1 appears on the far left and poorly differentiated grade 5 on the far right. Adapted from Gleason DF. The Veteran's Administration Cooperative Urologic Research Group: histologic grading and clinical staging of prostatic carcinoma. In Tannenbaum M (ed.) Urologic Pathology: The Prostate. Lea and Febiger, Philadelphia, 1977; 171-198.

In localized prostate cancer, the tumors are classified as T1, T2, T3 and T4 (Blank et al. 2000). T1 lesions are clinically unapparent tumors. A prostate cancer stage T1c is found as a consequence only of the patient having a positive PSA result with no other clinical sign of the disease. T2 is confined within the prostate. In cancer stage T3, the

tumor extends through the prostate capsule but has not spread to other organs. T4 on the other hand, is fixed or invades adjacent structures other than seminal vesicles.

Since the number of patients having PSA tests increased rapidly in the past few years, stage T1c, T2a and T2b have become a relatively common diagnosed stage of prostate cancer (Peter et al.2005). Radioactive seed implantation has rapidly become one of the most popular treatment modalities of confined prostate cancer (Kaplan et al. 2000). Iodine-125 or Pd-103 seeds are commonly used in the treatment of early stage prostate cancer. The half-life of I-125 (59.4 days) is long when compared to Rn-222 (3.83 days) and Au-198 (2.7 days); thus it is very convenient for storage. Also, its low photon energy requires less shielding.

1.4 Treatment Planning System

In the 1980's the modern technique of seed implantation with I-125 or Pd-103 seeds being inserted into the prostate gland with the guidance of TRUS and a perineal template was developed. This procedure is nonsurgical and performed on an outpatient basis. The implant takes place in an operating room with the patient requiring a spinal anesthetic (Khan, 2003). A volume study is used to outline the loation and size of the prostate by a series of transverse ultrasound images shown in Fig 4. The patient is placed in the dorsal lithotomy position and the transrectal ultrasound prcobe is securely attached to obtain transverse images of the prostate gland from base to apex at 5-mm intervals. A grid is superimposed on each image as a coordinate system. The sagittal image is also obtained to measure the length of the gland from the base to apex. Before the volume study, the prostate gland size and the pubic arch in relation to the prostate is determined by

computed tomography (CT) scans. If the pubic arch is too narrow it will prevent the needles from reaching the target. In the case of a large gland with significant pubic arch interference, the patient may need hormonal therapy to reduce the size of the prostate. Hormonal therapy can cause a number of unpleasant temporary side effects such as hot flashes, loss of libido, impotence and weight gain (Peter et al. 2005).

A treatment-planning system specifically designed for prostate gland implants allows the target outlines from the volume study to be digitized into the computer. The computer software allows the placement of seeds on the template grid for each of the ultrasound images. Seed strength can be adjusted to deliver a prescribed minimum peripheral dose (MPD), which is the isodose surface just covering the prostate target volume.

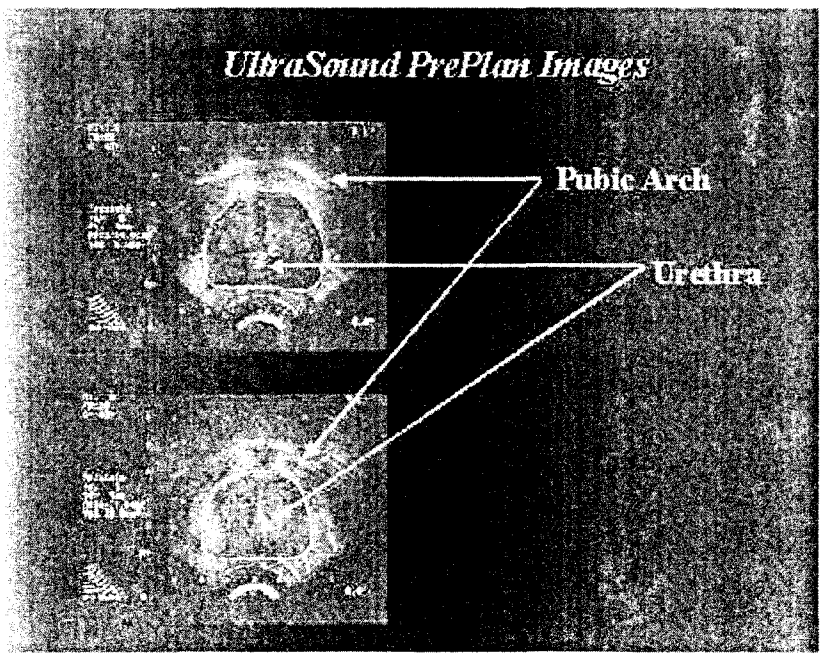

Figure 4. Ultrasound images are used to determine the size of the gland, and then to customize seed implant treatment (www.kcc.tju.edu/RadOnc/brachy/hor.htm).

Typical seed strengths are on the order of 0.336 mCi for I-125 (MPD=145 Gy) and 1.7 mCi for Pd-103 (MPD=125 Gy) (Khan, 2003). The treatment-planning methods consist of pre-implant and/or intraoperative planning.

Preplanning is the creation of a plan prior to implantation of the seeds. In most centers, prostate cancer is treated with an implant technique using only the preplanned dosimetry. However, this has three possible disadvantages. First, during the time between the preplan and the implant procedure, prostate volume and shape may change as a result of hormonal therapy or anesthesia. Secondly, the patient positioning, setup, and images acquired during the actual implant must be matched with those obtained during the pre-implant planning study. Third, in the pre-planned technique, a separate pubic arch evaluation study is required. The reason is that the pre-planned method requires a separate TRUS imaging planning study, which is awkward and sometimes difficult to schedule (Gewanter et al. 2000).

Intra-operative planning occurs in the operating room; the patient and TRUS probe stepper are not moved during the time between the volume study and seed insertion procedure. Treatment planning and the calculation of the dose distribution in real time is a new technique in the evolution of prostate brachytherapy. Currently, there are two steps in the intraoperative planning: intraoperative preplanning and interactive planning. Intraoperative preplanning is the creation of a plan in the operating room just before the implant procedure, with immediate execution of the plan. Meanwhile, TRUS is performed in the operating room, and the images are introduced in real time into the treatment planning system. The target volume, rectum, and urethra are contoured on the treatment planning system either manually or automatically. The treatment plan is created

and the seeds are implanted into the prostate based upon this treatment plan (Nag et al 2001). According to the Wilkinson et al. (2000), study, intraoperative pre-planning of prostate seed implants provides measurable improvements in dosimetric variables and greater patient comfort and convenience than the pre-planned techniques. However, intraoperative preplanning methods require additional operating room time and consequent costs. In general operating room time has decreased; therefore, the overall convenience of procedure without compromise of implant quality makes intraoperative preplanning the most suitable technique for TRUS-guided prostate brachytherapy (Gewanter et al. 2000).

Interactive planning is a stepwise improvement of the treatment plan using computerized dose calculations derived from image-based needle position feedback. In the interactive planning, the process of seed ordering, image acquisition, target definition, and organ contouring is similar to the intraoperative preplanning method (Nag et al. 2001). In other words, before the actual operative procedure, radioactive seeds are loaded into needles and a loading array is established with an autoradiograph. The prostate shape and urethra position are verified using ultrasound and a Mick applicator is used to implant seeds into the prostate (Fig. 5). Needle positioning is confirmed using transverse and sagittal ultrasound images along with fluoroscopy, with special attention to the bladder- prostate and rectal-prostate interfaces. The needles are repositioned or altered in the plan if there are adverse dosimetric consequences. The dose calculation is then updated based on actual needle location. The interval at which the dose distribution is recalculated is operator dependent. At the end of the procedure, the urologist performs cystoscopy to retrieve any lost seeds (Butler et al. 2000). In interactive planning the

calculated dose distribution is based on implanted needle position; therefore, it is difficult to account for seed movement after deposition (Nag et al. 2000).

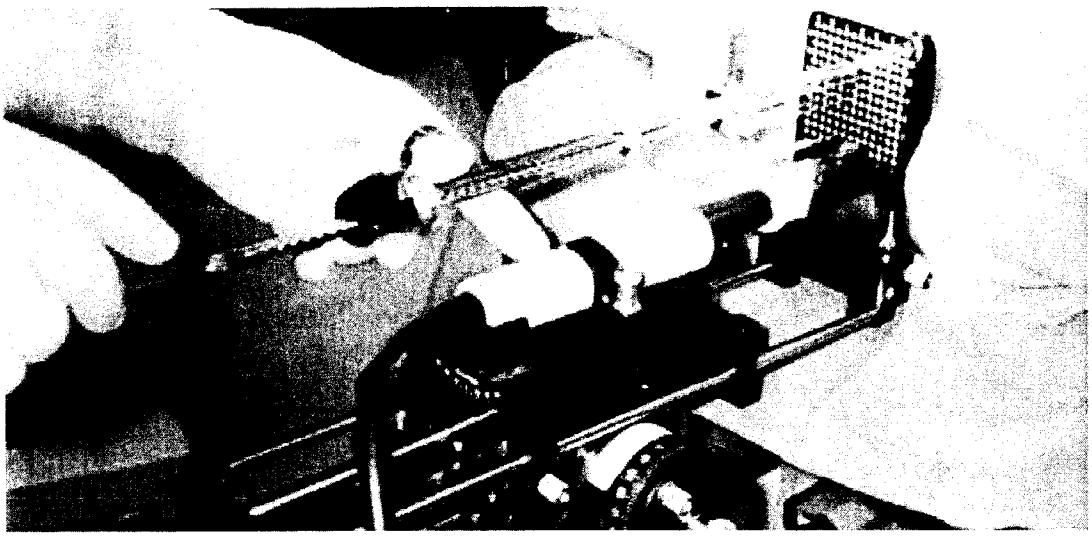

Figure 5. Cold needles are implanted prior to implanting the radioactive seeds, thus greatly avoiding radiation exposure to staff and personnel (www.micknuclear.com).

The evaluation of prostate brachytherapy implant treatment is based on dosimetric measurements of CT or ultrasound images obtained after the actual implant procedure (Doggett. 1999). Post-operative dosimetry of CT images provides immediate feedback on each implant. Currently, the American Brachytherapy Society recommends the use of CT-based, post-operative dosimetry on all patients (Nag et al.1999). The post-operative radiograph in Fig. 6 shows the radioactive seed placement. The post-op dosimetry can then be calculated and compared to pre-planned dosimetry. Swelling of the prostate in the first two weeks makes it difficult to accurately define the gland and to calculate the resulting dose. As a result the CT study is usually performed four weeks post-operation (Doggett. 1999). Bice et al. (1998) have reported that the definition of prostate target

volume on the post implant CT differed greatly between individual physicians. However, this diversity in target definition made very little difference in the calculated dose coverage of the prostate gland. On average, C100, which is the percentage of the prostate volume defined on post implant CT images that receives at least 100% of the prescription dose, was found to range from 79% to 96%. It was found that dosimetric coverage of the prostate improved with experience (Lee et al. 2000).

Since no optimal prostate implant technique has been defined, a number of techniques have developed. Two of the main approaches are (1) a pre planning technique where all calculations are made well ahead of the implant date and (2) an intra-operative technique where seed positioning is determined at the time of the operative procedure. Both methods are designed to deliver higher doses to the target while sparing surrounding normal tissues (Matzkin et al. 2003).

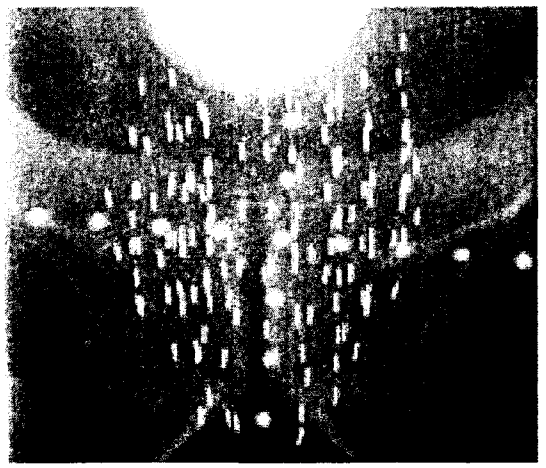

Figure 6. Post-op radiograph of a prostate seed implant (www.proste-cancer.org)

CHAPTER 2

MATERIAL AND METHODS

2.1 Patient Eligibility

As can be seen in Table 1, forty-six patients between 52 and 83 years of age with early stage prostate cancer (T1c, T2a), Gleason scores less than or equal to 7 and PSA levels less than 11 ng/ml were chosen for this study. Thirteen percent of these patients had received pre-implant androgen ablation therapy. Exclusively, two radiation oncologists, utilizing an afterloading Mick applicator performed the prostate implant procedures. Iodine-125 seeds (Model 125SL) were obtained from Mentor Corp. (Santa Barbara, CA). Seed strengths ranged between 0.287 to 0.454 mCi in order to obtain the prescribed dose of 145 Gy for all forty-six patients. All patients were implanted using an interactive ultrasound guided transperineal technique. Evaluation of the intra-operative technique was made by comparison with an artificially created (virtual) technique in which the 'preplanned' needle and seed loading was superimposed on the prostate volume obtained at the time of the implant procedure.

2.2 Pre-planned Technique

In the pre-planned technique, a volume study is obtained based upon initial transrectal ultrasound (TRUS) images acquired as much as three months prior to the actual implant procedure. This study is obtained in the office examining room with the patient unsedated

and the legs placed in a dorsal lithotomy position. The initial volume study allows the physician to evaluate pubic arch interference and, if present, the size of any transurethral resection of prostate (TURP) defects. Images of the prostate are obtained at 5 mm intervals. Using these contours a treatment plan is developed based upon the prescribed dose. This plan establishes a needle configuration and the appropriate number of seeds to be ordered (based upon available source activity).

Table 1. Baseline Characteristics of the Patient Population (n=46)

Parameters	**Number (percent)**
Age(years)	52-83
Activity(mCi)	0.287-0.454
Stage (T1c-T2a)	46
PSA(ng/ml)	
0-4	5 (10.9)
4.1-9.9	39 (84.8)
10-11	2 (4.3)
Gleason Score	
2-6	41 (89.1)
7	5 (10.9)
Androgen ablation	6 (13.0)

2.3 Intra-Operative Technique

The patient is initially taken to the operating room and following induction of general anesthesia the legs are elevated to the dorsal lithotomy position. The ultrasound probe is placed into the rectum and the prostate is centered using the lateral and posterior aspects of the prostate with special attention to the spatial orientation of the urethra (visualized adequately with a foley catheter in place). A series of sagittal and axial orientations of the prostate from base to apex are acquired at 5 mm intervals. These images are downloaded

to the treatment-planning computer, where they are digitized and a revised seed placement plan is developed prior to the implant procedure. Intra-operative dosimetric calculations on the prostate volume, corrected for relaxation of the patient following general anesthesia, are obtained. Due to the oblate spheroid shape of the prostate, an asymmetric margin is defined which varies from 2 to 5 mm in the anterior and lateral dimensions. From the apex through the mid portions of the prostate the margins are kept tight with more generous margins superiorly to allow for enhanced coverage of the seminal vesicle region at the base of the prostate. No posterior margin is defined over the entire prostate due to the close proximity of the rectum. These contoured margins define the planning target volume (PTV) and are devised and approved by the radiation oncologist. Efforts are made to place seeds within the capsule of the prostate although a limited number of extraprostatic seeds are used to achieve the desired PTV coverage described above. After-loading needles are then inserted through a transperineal template using coordinates derived from the 'intra-operative' plan. Planned seed positions can be manually modified to 'real time' positions based upon ultrasonic visualization.

2.4 Post Implants Dosimetry

Dosimetric evaluation of each procedure is initially performed utilizing dose volume histograms (DVH) generated from pre-operative and pre-implant ultrasound images. Post implant dosimetric evaluation is performed on CT images obtained approximately three to four weeks following the implant procedure (CT images tend to overemphasize prostate volume compared to ultrasound). This time period allows for acute swelling of the gland secondary to the implant procedure to subside. CT images of each slice are

taken showing both soft tissue and bone densities. On each slice, the prostate volume, rectal and bladder wall, and urethra (if foley catheter is still in place) are outlined. Isodose curves and DVH values were generated. Additional prostate dosimetric parameters including D90 (maximum dose received by 90% of the volume), V100 (volume receiving 100% of the prescribed dose), and V150 (volume receiving 150% of the prescribed dose) are obtained. Finally, a R100 (rectal volume receiving 100% of the prescribed dose) is generated to assess implant design and quality of seed placement.

2.5 Investigation Method

To evaluate the present intra-operative planning technique, a comparison was made with the pre-planned technique used by the radiation oncologist prior to obtaining the VariSeed Treatment Planning Software which permitted treatment planning in the operating room. This comparison was achieved by a virtual-planning technique in which the pre-planned seed and needle positions are superimposed on the intra-operatively obtained volume study. The superposition of the pre–planned and intra-operative volume study is achieved by the alignment within the two studies of both the transverse images of the prostate base and the sagittal images of the central prostate posterior margin. An investigation is then made of the dosimetric differences obtained utilizing dosimetry parameters (D90, V100, V150, V200 and R100). Additionally, the number of slices, the number of seeds, and the inferior extent of posterior planes are considered.

CHAPTER 3

RESULTS AND DISCUSSION

3.1 Technique Comparison

In order to evaluate the presently used intra-operative technique, comparison was made with a previously used pre-implant technique by creating an artificial virtual-technique. The virtual-technique superimposed seed and needle positions from the initial pre-implant volume study on the new volume study obtained at the time of the implant. The average number of images and seeds together with the average prostate volume obtained from both transrectal ultrasound studies (TRUS) for forty-six patients are shown in Table 2. The average number of images for both techniques is the same (9 vs. 9). Also the average prostate volume for both techniques was within 1% (43.5 cc for pre-implant technique vs. 43.0 cc for intra-operative technique).

Table 2. Comparison of average number of images, seeds and mean value of prostate volume between pre-implant and intra-operative techniques.

Technique	Images	Seeds	Volume (cc)
Pre-implant	9±1	93±11.7	43.5±12.1
Intra-operative	9±1	92±12.4	43.0±13.0

The target volume for both techniques was an asymmetric volume consisting of the prostate volume plus a margin varying from 2 to 5 mm in the anterior and lateral dimensions. Although the PTV differs for each implant procedure the average number of seeds placed within the gland differs by less than 1% between the intra-operative technique and the artificially created virtual-technique.

To evaluate the dosimetric differences between each technique, the number of seeds outside the PTV, inferiorly and anteriorly or laterally, is determined from three-dimensional CT images. Table 3 shows the number of seeds outside the PTV, inferiorly and anteriorly or laterally, determined from three-dimensional CT images. In the intra-operative technique only three patients had seeds implanted outside the PTV (inferiorly one had a single seed and a second had two seeds, laterally one had six seeds).

Table 3. Comparison between the two techniques of the number of seeds located inferiorly or anteriorly/laterally outside the PTV.

Parameters	**Number of Patients in the Intra-operative Technique (n=46)**	**Number of Patients in the Virtual Technique (n=46)**
Seeds outside PTV :		
Inferior: 0-4	44(0), 2(1-2)	21
5-10	0	11
≥11	0	14
Anterior or Lateral: 0-4	45	15
5-10	1	16
≥11	0	15

In the virtual-technique, on the other hand, extreme cases are seen, 11 or more seeds were found outside the PTV (inferiorly in fourteen patients and anteriorly or laterally in fifteen patients) indicating a decrease in dose coverage and possible rectal complication

leading to rectal morbidity if the pre-planning technique were implemented without any adaptation.

3.2 Dose Response

The dosimetric data D90 (maximum dose received by 90% of the volume), V100 (volume receiving 100% of the prescribed dose), V150 (volume receiving 150% of the prescribed dose), and V200 (volume receiving 200% of the prescribed dose) for all forty-six patients of both techniques are shown in Table 4. The average values, shown in Table 5 for V200 (24.8±2.78% vs. 19.2±2.42%), V150 (58.3±3.74% vs. 47.9±4.16%) and V100 (99.7±0.38% vs. 94.1±4.41) were greater by 29%, 22%, and 6% respectively for the intra-operative techniques. As well, the mean D90 values were higher (174.9±4.5Gy vs.157.6±14.4Gy) for intra-operative cases compared to virtual-technique. In addition, Tables 3 and 5 indicate the strong correlation between dosimetric values and the number of seeds outside the PTV in the virtual-technique providing support for the use of an intra-operative technique.

In a recent report, the Wilkinson et al. (2000) study showed the comparison of intra-operative and pre-planning techniques. Even though their dosimetric evaluation was based on earlier (2000) CT studies, Table 6 shows the average value of V100 (intra-operative) was similar to our data shown in Table 5. In our study the average value of both V150 and D90, obtained intra-operatively, was greater than the Wilkinson et al. study by 260% and 28% respectively.

Table 4. Dosimetric data D90, V100, V150 and V200 for forty-six patients of both techniques.

Patients	Intra-operative				Virtual			
	D90	V100	V150	V200	D90	V100	V150	V200
1	180.76	99.93	57.98	25.27	160.75	94.45	48.21	22.20
2	179.25	98.8	58.42	23.65	138.23	87.84	38.44	16.21
3	171.65	99.67	57.85	25.35	155.89	92.92	48.41	19.97
4	173.32	99.98	57.40	26.96	157.82	93.58	50.32	20.61
5	166.83	99.86	56.95	26.18	168.13	97.99	53.99	23.53
6	172.12	99.94	56.17	24.42	139.75	88.85	51.08	22.41
7	174.47	100	57.54	22.44	156.97	93.43	46.76	19.20
8	176.92	99.67	55.97	18.56	162.81	95.39	47.40	15.74
9	179.87	99.87	57.73	25.66	163.95	97.12	48.92	19.07
10	177.65	99.81	61.50	26.88	169.07	96.25	52.49	20.66
11	180.39	100	58.71	23.92	161.36	95.24	44.07	18.97
12	172.49	99.56	59.90	25.24	166.29	98.55	52.26	23.36
13	180.83	99.00	64.73	27.61	156.91	92.99	50.05	21.35
14	171.75	99.99	59.27	27.19	166.20	98.47	51.79	22.08
15	176.44	99.37	59.44	20.92	163.52	94.46	45.18	14.02
16	178.56	99.76	58.41	23.64	172.45	97.31	49.92	19.00
17	180.92	98.69	59.67	25.93	171.67	98.00	45.43	18.75
18	175.96	99.83	57.79	25.14	133.49	88.05	41.72	18.22
19	171.37	99.81	60.22	27.25	164.58	98.40	55.37	23.49
20	174.70	99.95	57.51	23.73	167.59	97.79	50.79	18.29
21	175.61	99.76	58.22	25.37	130.91	87.00	43.43	19.66
22	174.95	99.74	55.91	20.42	170.45	99.54	49.75	15.50
23	159.43	98.28	40.94	15.59	159.44	95.11	42.32	12.33
24	171.32	99.96	58.20	27.11	140.25	89.14	46.00	19.95
25	179.70	99.98	56.67	21.46	173.57	98.90	42.29	19.50
26	167.63	99.21	60.27	26.89	171.02	97.98	54.58	20.55
27	175.96	99.82	58.61	25.39	116.43	82.50	40.10	17.36
28	172.23	99.89	60.42	25.61	107.40	79.17	42.09	18.95
29	175.22	100	58.16	24.85	164.52	95.88	50.66	21.16
30	177.47	99.99	59.97	23.12	170.93	99.62	52.77	19.65
31	173.54	99.96	55.52	23.19	163.14	95.13	50.27	20.54
32	174.70	99.67	61.78	28.33	156.70	93.49	48.39	19.48
33	173.31	99.77	56.71	25.68	157.29	92.57	45.58	18.33
34	170.84	99.86	62.08	27.20	162.93	95.45	49.66	17.91
35	172.88	100	60.05	29.95	165.56	96.44	46.94	16.43
36	174.07	99.99	63.79	30.25	153.49	92.28	50.27	21.58
37	178.21	99.92	58.84	22.48	171.69	99.03	49.82	18.54
38	172.40	99.87	55.13	22.91	160.23	94.09	50.63	21.34
39	173.62	99.31	57.36	22.94	168.20	95.42	45.68	17.90
40	186.11	99.42	65.54	28.79	143.00	89.42	42.51	16.63
41	179.15	99.82	57.13	23.21	152.61	91.65	44.70	17.20
42	173.31	99.82	57.02	24.74	153.53	94.48	37.84	16.61
43	175.29	99.95	61.79	26.31	158.33	93.20	50.19	20.41
44	178.82	99.99	59.23	23.28	161.83	92.87	46.46	18.20
45	167.59	99.81	49.26	22.58	152.38	91.39	48.01	20.08
46	174.36	99.95	57.97	24.85	166.89	99.26	52.65	21.83

These differences result from using a minimum seed spacing of 0.5 cm in the present study (Mick applicator placement) whereas the Wilkinson et al. (2000) study using Model 7000 Rapidstrand™ seeds were limited to a minimum of 1.0 cm seed spacing.

Table 5. The averages of the parameters V200, V150, V100 and D90.

Parameters(Ave)	**Intra-operative(n=46)**	**Virtual(n=46)**
V200(%)	24.8±2.78	19.2±2.42
V150(%)	58.3±3.74	47.9±4.16
V100(%)	99.7±0.38	94.1±4.41
D90(Gy)	174.9±4.5	157.6±14.4

The Mick applicator allows the placement of individual seeds in an end to end arrangement as the plan dictates whereas Rapidstrand™ seeds are in fixed seed-spacer seed arrangement at 1.0 cm spacing.

Table 6. Comparison of V100, V150, and D90 intra-operative values with Wilkinson et al. (2000)

	V100 (%)	V150 (%)	D90 (Gy)
Wilkinson et al. study n = 61	98.5±1.9	22.5±9.8	136.5±18.8
Our study n = 46	99.7±0.38	58.3±3.74	174.9±4.5

3.3 Post Seed Implant Analysis

Evaluation of the intra-operative plan is based on CT images obtained three to four weeks following the implant procedure. The average post implant dosimetric parameters shown in Table 7 are approximately 6% lower than those values obtained intra-operatively for V150 (55.7% vs. 58.3%) and V100 (94.1% vs. 99.7), while a 8% lower mean value is noted in the post implant analysis for D90 (161.5 Gy vs. 174.9Gy). The prostate volume on the post implant CT is slightly larger for all forty-six patients compared to the intra-operative planned cases because CT images tend to over estimate prostate volume compared to ultrasound. Due to the similar density of prostate tissue and surrounding periprostatic tissue on CT images, the prostatic capsule is more difficult to define on CT than on ultrasound. Also the amount of swelling depends on the trauma of the implantation procedure (Wilkinson et al. 2000).

Table 7. Comparison of the average values V150, V100, D90 and the average prostate volume between post seed implant and intra-operative and virtual-techniques.

Parameters	Post Seed Implant	Intra-operative	Virtual
V150 (%)	55.7±10.6	58.5±2.44	48.3±3.10
V100 (%)	94.1±4.64	99.7±0.29	94.7±2.75
D90 (Gy)	161.5±14.7	173.2±5.11	158.2±9.46
Volume (cc)	44.6±12.7	42.96±13.0	43.5±12.1

Placement of seeds by the radiation oncologist typically follows a concave pattern around the lateral and posterior aspects of the prostate. The effect this seed placement has on rectal dose can be evaluated by measuring R100, the rectal volume that receives 100%

of the prescribed dose. The distribution of R100 values obtained from an analysis of post-implant CT images is shown in Table 8. Waterman et al. (2003) indicates that the volume threshold for ≤5% risk of developing Grade 2 (ulceration) late rectal morbidity (modified Radiation Therapy Oncology Group grading system) at 100 Gy, 160 Gy and 200 Gy is 3.8 cc, 1.8 cc, and 0.9 cc, respectively. Based on these data, our result of rectal volume threshold for ≤5% risk of developing Grade 2 at 145 Gy is 2.3 cc.

Table 8. R100 (the rectal volume that receives 100% of the prescribed dose) data distribution for forty-six patients.

R100 (cc)	**Number of Patients (n=46)**
0-0.5	21
0.5-1.0	13
1.0-1.7	11
1.7-2.3	0
>2.3	1

Table 8 shows that 1 case is greater than the volume threshold, 2.3 cc. This patient has not had serious rectal complications; however, the follow up time is short and close observation should be continued for 3 to 5 years. R100 overestimation can either be the result of incorrectly contouring the prostate-rectum boundary, which can be difficult to distinguish from mid gland to the apex, or the result of rectum deformation from a large amount of gas in the rectum.

CHAPTER 4

CONCLUSION

In this study the dosimetric evaluations of intra-operative and virtual-implant techniques based on the dose volume histogram (DVH) generated from CT studies were analyzed. The investigation was made of intra-operative and virtual-planning parameters (D90, V100, V150 and V200) utilizing post implant dosimetry. The parameters given in Table 5 shows that greater dosimetric values are noted in the intra-operative technique vs. virtual-planning technique for D90 (174.9 Gy vs. 157.6 Gy), V100 (99.7% vs. 94.1%), V150 (58.3% vs. 47.9%) and V200 (24.7% vs. 19.2). Additionally, a study of R100 (Table 8) was performed and an analysis was made of other parameters such as the number of images, seeds, target volume (Table 2), and the inferior extent of posterior planes, given in Table 3.

Even though the average number of seeds placed within the gland is similar (93 vs. 92) between the intra-operative and virtual-techniques, the percentage of patients with seeds outside the PTV differed significantly for each technique as can be seen in Table 9. In Table 9, 70% of the virtual-planning patients would have had more than 5 seeds and 30% more than 10 seeds placed inferior of the PTV indicating possible rectal complications, leading to rectal morbidity if the pre-planning technique were utilized without any adjustment.

Table 9. Percentage of Patients with Seeds outside the PTV in the Virtual-technique and Intra-operative Technique

Seeds outside the PTV	Percentage of Patients	
	Virtual	Intra-operative
Inferior ($\geq$5)	70	0
Inferior ($\geq$10)	30	0
Lateral/Anterior ($\geq$5)	67	2
Lateral/Anterior ($\geq$10)	33	0

Additionally, 67% of the virtual-planning patients would have had more than 5 seeds placed lateral/anterior of the PTV and 33% more than 10 seeds resulting in lower dosimetric values of parameters given in Table 5. On the other hand, in the intra-operative technique no patients had more than 5 seeds placed inferior of the PTV, and only one patient (2%) had more than 5 (6) seeds placed lateral/anterior of the PTV. Within the present limited study of forty-six patients no rectal complications or morbidity have developed. Late injury to the rectum usually occurs in the first 2-3 years after treatment (Eiffel et al. 1995). Because the seed implants occurred between 2002 and 2004, it is too early to detect potential rectal complications within these patients.

This study shows the importance of several factors that benefit from an intra-operative approach to seed placement as opposed to a pre-planned approach. The first benefit is the obvious elimination of the discomfort of catheter insertion (to accurately define the urethra location within the prostate) while the patient is sedated, as opposed to the unsedated approach used during the pre-planned technique. Second, accurately defining the inferior extent of seeds placed in the most posterior aspect of the prostate reduces the probability for rectal complication and morbidity. Third, more correctly

delineating the prostate contour at the time of seed placement results in fewer seeds placed in the periprostatic region, outside the PTV, both reducing potential seed migration and increasing prostate dose coverage. The significance of the increase in dose coverage for the intra-operative technique, which varied over the virtual-technique 29% in the V200, 22% in the V150 and 6% in the V100 values, requires future analysis. It appears to be due to shape differences (as opposed to volume differences) between the pre-planned (unsedated) prostate and the intra-operative (under general anesthesia) prostate. The increase in this study in the dosimetric values of V150 and V200 appears to be related to the technique of placing seeds at 0.5 cm spacing (as indicated by the differences with the Wilkinson et al. data). Additionally, analysis of seed placement shows that 66 % of the seeds, both peripherally and interiorly, were spaced at 0.5 cm. The influence on patient survival and/or morbidity of the relationship of dose coverage and seed separation requires a study with a larger patient population and a longer follow-up.

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