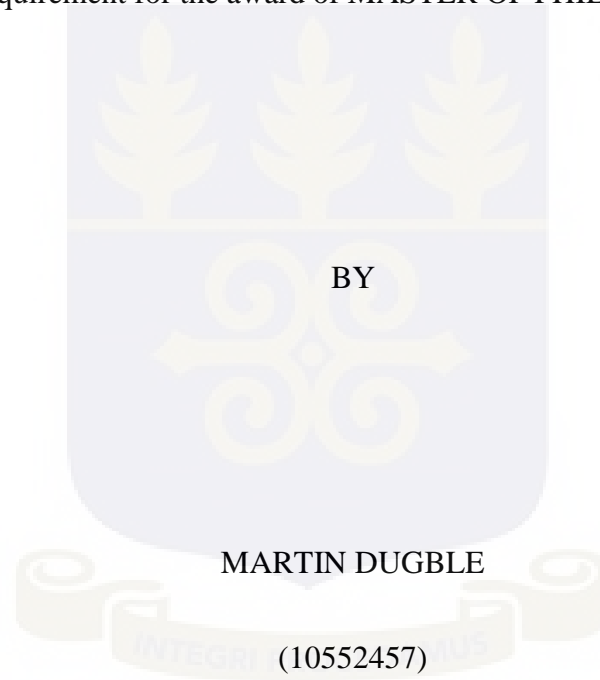


**COMPARATIVE ASSESSMENT OF INTRAOPERATIVE AND POST-IMPLANT  
DOISIMETRY AND VOLUMETRY IN PROSTATE PERMANENT IMPLANT  
BRACHYTHERAPY WITH I-125 SEEDS**

This thesis is submitted to the University of Ghana, Legon In partial fulfilment of the  
requirement for the award of MASTER OF PHILOSOPHY



JULY, 2017

## DECLARATION

Candidate's Declaration:

I hereby declare that except for the references to other publications, which have been duly cited, this thesis is the result of my own research work and that it has neither in part nor whole been presented for any degree elsewhere

.....  
MARTIN DUGBLE  
(STUDENT)

.....  
DATE

.....  
DR. JOEL YARNEY  
(PRINCIPAL SUPERVISOR)

.....  
DATE

.....  
DR. STEPHEN INKOOM  
(CO-SUPERVISOR)

.....  
DATE

.....  
MR. S.N.A. TAGOE  
(CO-SUPERVISOR)

.....  
DATE

## ABSTRACT

Post implant dosimetry has become the gold standard for prostate implant evaluation. The goal of this research was to compare the dosimetry of intraoperative real-time ultrasound plan to CT postimplant plan in permanent prostate seed implant brachytherapy. A retrospective study of 20 patients treated with  $^{125}\text{I}$  prostate seeds implant were performed. All plans were created using VariSeed 8.0 planning system. Intraoperative real-time ultrasound images were acquired using 0.5 cm slice thickness. Post plan CT images were acquired 3-4 weeks after implant.  $^{125}\text{I}$  seed activities varied between 0.352 -0.747 U per seed. The load pattern varied slightly between patients depending on the prostate size. Statistical analysis of intraoperative real-time and CT postimplant plans for prostate volumes V150 % and D90 and prostate volumes were performed and reported using SPSS (version 20.0). The intraoperative real-time prostate volume and the CT postimplant prostate volume average size were 35.128 cc and 36.384 cc respectively. Average Prostate volume parameters, V150 % was 59.225 % and 65.291, D90 was 141.839 Gy and 140.99 Gy for intraoperative real-time dosimetry and CT postimplant dosimetry respectively. There was no statistically significant difference between the intraoperative real-time and CT postimplant prostate volumes (P value= 0.137) and the D90 (P value=0.441). However there was a significant difference between V150 % values (P value = 0.005) which was most likely due to prostate edema. In conclusion, the postimplant dosimetry using CT image set showed similar D90 dose coverage to the intraoperative real-time dosimetry using ultrasound image data. This study showed that our prostate seed implant have consistently delivered adequate therapeutic dose to the prostate. Further studies to correlate other dose parameters should be performed.

## **DEDICATION**

To my parents Mr. and Mrs. Agordzo for their support, love, care and prayers. They taught me the importance of education, learning and doing what should be done.

To my lovely family, lectures and all my colleagues.



## ACKNOWLEDGEMENT

To God be the Glory, the creator of the Heaven and earth for blessing me with knowledge, wisdom, understanding and the will-power which has enabled me complete this work successfully.

I wish to express my profound gratitude to my supervisors Dr. Joel Yarney, Dr. Stephen Inkoom and Mr. S.N.A. Tagoe for their directives and guidance without which I may not have produced this work.

I am grateful to the staff of the National Centre for Radiotherapy and Nuclear Medicine for their warm reception given to me. Also my appreciation goes to Mr. Evans Sasu for his immersed contribution towards this work. In fact if not for him, this work would not have been a reality. I say thank you so much and may the good Lord continue to bless and protect you.

My sincere thanks go to Dr. Francis Hasford (Head of Medical Physics Department) for his encouragement, help and advice during this hectic period. To Mr. E.K.T. Addison who open my mind towards medical physics

My endless thanks go to my parents, siblings, family, colleagues and anyone one who helped make this dream a reality.

“Finally, I humbly express my gratitude to all lecturers of SNAS and all the staff for their cooperation. I say may God bless you all abundantly”.

**TABLE OF CONTENT**

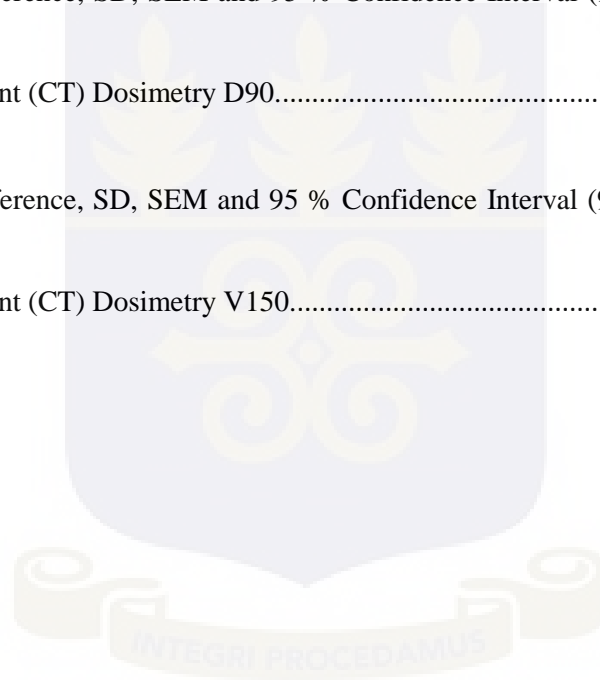
<b>DECLARATION</b> .....	ii
<b>ABSTRACT</b> .....	iii
<b>DEDICATION</b> .....	iv
<b>ACKNOWLEDGEMENT</b> .....	v
<b>TABLE OF CONTENT</b> .....	vi
<b>LIST OF TABLES</b> .....	ix
<b>LIST OF FIGURES</b> .....	x
<b>CHAPTER ONE</b> .....	1
<b>INTRODUCTION</b> .....	1
<b>1.1 Background</b> .....	1
<b>1.2 Statement of the Problem</b> .....	6
<b>1.2 Objective of Study</b> .....	6
<b>1.3 Relevance and Justification</b> .....	7
<b>1.4 Organization of the Thesis</b> .....	7
<b>2.1 Dosimetry associated with brachytherapy</b> .....	8
<b>2.1.1 Interstitial treatment</b> .....	8
<b>2.1.2 Dose Distribution around Source</b> .....	9
<b>2.1.3 AAPM TG 43 algorithm</b> .....	9
<b>2.2 Radioisotopes used in prostate brachytherapy.</b> .....	11
<b>2.2.1 Classification of brachytherapy sources</b> .....	11
<b>2.2.2.1 Iodine -125</b> .....	11
<b>2.2.2.2 Palladium-103</b> .....	14
<b>2.2.2.3 Iridium-192</b> .....	15
<b>2.2.2.4 Cesium-137</b> .....	16
<b>2.2.2.5 Cobalt -60</b> .....	17
<b>2.2.2.6 Gold-198</b> .....	17
<b>2.3 Causes of prostate cancer</b> .....	19
<b>2.4 Treatment selection criteria according to European ESTRO/EAU/EORTC guidelines</b> .....	20

<b>2.5: International guideline towards prostate cancer brachytherapy implant...</b>	<b>23</b>
<b>2.5.1: The European’s ESTRO/EAU/EORTC guideline.</b> .....	<b>23</b>
<b>2.5.2 The American Brachytherapy Society (ABS) guidelines.</b> .....	<b>23</b>
<b>2.6 Treatment modalities for Prostate cancer patients.</b> .....	<b>24</b>
<b>2.6.1 Hormone therapy</b> .....	<b>24</b>
<b>2.6.2 Chemotherapy Treatment</b> .....	<b>24</b>
<b>2.6.3 Cryotherapy Treatment</b> .....	<b>25</b>
<b>2.6.4 External Radiation Treatment (Teletherapy)</b> .....	<b>26</b>
<b>2.7 Selected Cure Rate Studies of Prostate Implant</b> .....	<b>27</b>
<b>2.8 Selected complication rates studies of prostate implants</b> .....	<b>29</b>
<b>2.8.1 Urinary complication</b> .....	<b>29</b>
<b>2.8.2 Rectal complications</b> .....	<b>30</b>
<b>2.9 Impact of imaging modality on dose reporting</b> .....	<b>30</b>
<b>2.9.1 Ultrasound Imaging</b> .....	<b>31</b>
<b>2.9.2 CT Imaging</b> .....	<b>32</b>
<b>2.9.3 MR Imaging</b> .....	<b>34</b>
<b>2.9.4 Timing of imaging on dose reporting</b> .....	<b>35</b>
<b>2.9.5 Effect of prostate edema on brachytherapy dosimetry</b> .....	<b>36</b>
<b>CHAPTER THREE</b> .....	<b>38</b>
<b>MATERIALS AND METHODS</b> .....	<b>38</b>
<b>3.1 Materials</b> .....	<b>38</b>
<b>3.1.1 The implant needles</b> .....	<b>38</b>
<b>3.1.2 The ultrasound unit, rectal probe and Gel</b> .....	<b>39</b>
<b>3.1.3 The stepper and the template grid</b> .....	<b>40</b>
<b>3.1.4 Mick applicator</b> .....	<b>42</b>
<b>3.1.5 The survey meter</b> .....	<b>43</b>

3.1.6 Anesthesia .....	44
<b>3.2 The real time implant procedure.....</b>	<b>45</b>
3.2.1 Volume study .....	45
3.2.2 Needle identification.....	46
3.2.3 Delivery of seeds .....	46
3.2.4 Dose planning.....	47
<b>3.3 CT postimplant procedure.....</b>	<b>48</b>
3.3.1 Selection of patients.....	48
3.3.2 Organ sedimentation.....	49
3.3.3 Contouring of organs on the CT images .....	49
3.3.4 Source identification. ....	49
3.3.5 Dosimetry. ....	50
3.3.6 Statistical analysis. ....	50
3.3.6.1. P-value .....	50
3.3.6.2. T-test.....	51
3.3.7 Limitations in the post implant dosimetry .....	51
<b>CHAPTER FOUR.....</b>	<b>53</b>
<b>RESULTS AND DISCUSSION .....</b>	<b>53</b>
<b>4.1 Results.....</b>	<b>53</b>
<b>4.2 Discussion .....</b>	<b>55</b>
<b>CHAPTER FIVE .....</b>	<b>61</b>
<b>CONCLUSION AND RECOMMENDATION .....</b>	<b>61</b>
<b>Recommendation .....</b>	<b>61</b>
<b>APPENDICES.....</b>	<b>67</b>

## LIST OF TABLES

Table 1 characteristics of isotopes used in brachytherapy .....	18
Table 2 The selection criteria for patients and their recommendation (Ash et al., 2000) .....	22
Table 3 Dose limits for prostate brachytherapy .....	48
Table 4 prostate volumes (cm <sup>3</sup> ) measured before and after 1 month of needle insertion .....	53
Table 5 Mean Difference, SD, SEM and 95 % Confidence Interval (95 % CI) for Intraoperative (IO) and postimplant (CT) Dosimetry D90.....	53
Table 6 Mean Difference, SD, SEM and 95 % Confidence Interval (95 % CI) for Intraoperative (IO) and postimplant (CT) Dosimetry V150.....	54



**LIST OF FIGURES**

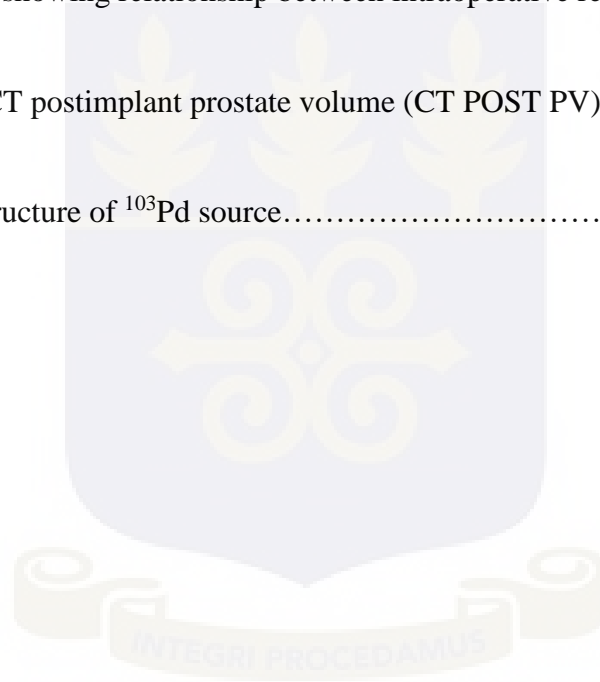
Figure 2.2 the geometry and the definitions used for the TG 43 protocol.....10

Figure 3.2. Example of I-125 seed 6711 model used currently for prostate brachytherapy  
implant radiotherapy physics: theory and practice. CRC Press.....13

Figure 4.1 The pictures shows the implant needles used during real-time procedure .....39

Figure 5.1 Graph showing relationship between intraoperative real-time prostate volume  
(IORT PV) and CT postimplant prostate volume (CT POST PV) .....56

Figure 2.4 the structure of  $^{103}\text{Pd}$  source.....15



## LIST OF ABBREVIATIONS

AAPM	American Association of Physicist in Medicine
ABS	American Brachytherapy Society
AP	Anterior-Posterior
ASTRO Oncology	American Society of Therapeutic Radiology and
Au	Gold
AUA	American Urological Association
PCa	Prostate Cancer
Cc	Cubic centimeter
cGy	Centigray
Co	Cobalt
Cs	cesium
CT	Computed Tomography
CTV	Clinical Target Volume
D90	Dose covering 90% of the prostate
DRE	Digital rectum examination
DVH	Dose volume histogram
EAU	European Association of Urology
EBRT	External beam radiation therapy
EORTC Cancer	European Organization for the Research and Treatment of
ESTRO	European Society for Therapeutic Radiology and Oncology
$\gamma$	Gamma
GBq	Giga Becquerel
HDR	High Dose Rate
HVL	half Value Layer
I	Iodine
IAEA	International Atomic Energy Agency

ICRU Measurement	International Commission on Radiation Units and
IGRT	Image guided radiation therapy
IORT	Intra-operative radiation therapy
IPSS	International prostate symptom score
Ir	Iridium
KBTH	Korle-Bu Teaching Hospital
KeV	Kilo electron volt
LDR	Low Dose Rate
mCi	milli curie
MDR	Medium Dose Rate
MeV	Mega electron volt
mm	millimeter
MRI	Magnetic Resonance imaging
ng	nano gram
PBRT	Proton beam radiation therapy
Pd	Palladium
PSA	Prostate specific Antigen
PTV	Plan Target Volume
RD	Rectal dose
TG	Task group
TPS	Treatment planning software
TRUS	Transrectal Ultrasound
TURP	Transurethral resection of the prostate
UrD30	Dose covering 30% of the urethra
US	Ultrasound
USA	United State of America
V100 prescribed dose	Volume of prostate covered by 100 % of the

V150	Volume of prostate covered by 150% of the prescribed dose
$\alpha$	Alpha
$\beta$	Beta
U	Seed factor or unit of air kerma strength.

### LIST OF SYMBOLS AND CONSTANTS

$P(r_0, \theta_0)$	Reference point that lies on the transverse bisector of the source at a distance of 1 cm from the origin
$D(r, \theta)$	The dose rate at point, r, in the medium from a radioactive source
$G(r, \theta)$	Geometry factor
$F(r, \theta)$	Anisotropy function
$S_K$	Air kerma strength of the source
$\Lambda$	Dose rate constant
$\Theta$	angle with respect to the long axis of the source
$g(r)$	Radial dose function
$r_0$	Reference point on the transverse axis

## CHAPTER ONE

### INTRODUCTION

#### 1.1 Background

Brachytherapy is a term used to describe the short distance treatment of cancer with radiation from small, encapsulated radionuclide sources. This type of treatment is given by placing sources directly into or near the volume to be treated. The dose is then delivered continuously, either over a short period of time (temporary implants) or over the lifetime of the source to a complete decay (permanent implants). Most common brachytherapy sources emit photons; however, in a few specialized situations beta or neutron emitting sources are used. There are generally two main types of brachytherapy treatment; Intracavitary, in which the sources are placed in body cavities close to the tumour volume and interstitial, in which the sources are implanted within the tumour volume. (Rosenberg, 2008)

Two methodically different brachytherapy treatment modalities can be used in the treatment of prostate cancer. These are either permanent low dose rate (LDR) seed implantation employing iodine-125 or palladium-103 or the temporary afterloading technique using iridium-192 (high-dose rate, HDR brachytherapy) with a removable stepwise mobile radiation source. In LDR brachytherapy the seeds are stored in titanium cases usually referred to as brachytherapy seeds. As the name permanent brachytherapy suggests, the seeds are permanently left inside the prostate gland over the course of their radioactive lives emitting low radiation until they decay completely. The HDR brachytherapy uses single radioactive seed made of Iridium-194 which is sometimes referred to as an iridium wire. Soft flexible catheters are inserted through the perineum and

into the prostate gland. The procedure involves an overnight stay in the hospital during which a patient undergoes two or three treatments with the wire through each catheter. In LDR brachytherapy, tiny radioactive particles each of size  $3.8 \times 0.5 \text{ mm}^2$  are implanted directly into the tumor (Khan, 2003). These particles are called “seeds” and they can be inserted together as strands or individually into the prostate. Because the seeds are implanted directly into or very close to the tumour, they deliver high doses of radiation to the tumour with minimum effect to the normal healthy tissues around it. This means the procedure is less damaging than conventional radiation therapy where the radioactive beam irradiates other organs. (Podgorsak, et al., 2005a).

Both methods can achieve the application of a high target dose in the prostate with a radiation quality of short distance efficacy resulting in a minimal radiation exposure of the periprostatic tissues. The use of HDR brachytherapy without additional external beam saturation for the treatment of prostate cancer can at present only be recommended as part of controlled clinical trials. With permanent seed implantation, however, there is enough experience to assess the usefulness of this method adequately. Results are not significantly different when palladium or iodine seeds are used. (Rosenberg, 2008, Podgorsak, et al., 2005b).

Brachytherapy has gained wide acceptance as a treatment modality for early stage prostate cancer, in which the disease is confined to the prostate gland. Prostate brachytherapy has been performed over the years with a variety of approaches and with state-of-the-art technology during each era. Implantation techniques have evolved from intraurethral insertion of a temporary source in the early decades of last century, to permanent interstitial implantation using a retro pubic approach, and eventually to the current ultrasound-guided

transperineal techniques. In 1965, radioactive I-125 was introduced to clinical practice for permanent implantation. With a half-life of just under 60 days and a relatively low energy radiation (average = 32 kV), it is well suited for permanent brachytherapy. During the 1970s and early 1980s, retropubic implants with I-125 were popular. As with many innovations in medicine, the initial enthusiasm was dampened by reports of poor source and dose distribution and high recurrence rates. The technique proved to be difficult to reproduce widely, and many implants were judged to be inadequate, even by the comparatively primitive imaging and dosimetry capabilities available at that time. Most practitioners abandoned this procedure; however, a few understood that with improvements in case selection and technique, the fundamentals remain sound. (Beyer, 2001)

Prostate brachytherapy came into the modern era with a preliminary report in 1983 by Holm et al, who described the use of transrectal ultrasonography to guide transperineal insertion of needles into the prostate to permanently deposit I-125 into the gland. This concept was studied by a number of investigators, but Blasko et al., are generally credited for developing and popularizing the current techniques. With the passage of time and the publication of numerous large studies with long-term results, prostate brachytherapy has undergone a worldwide renaissance, with more patients choosing this treatment each year. (Beyer, 2001)

It has long been appreciated that the quality of a prostate seed implant is important in the long term outcome of the patient. Recent updates by Potters *et al.*, and Stock *et al.*, have correlated the significance of D90% (minimum dose covering 90% of the prostate volume) to PSA freedom from recurrence and post-implant biopsy results. This quality of care

indicator may be analogous to a margin radical prostatectomy”. “Uniform dosimetric reporting in accordance with American Brachytherapy Society guidelines has allowed dosimetry coverage to be correlated with different seed delivery techniques. There are two main delivery techniques of prostate brachytherapy.

One is described as the interactive or real-time technique in which the actual seed placement is determined at the exact time of the procedure. This delivery technique begins with a volume assessment, but relies extensively on continuous biplane ultrasound imaging with a multi-positional cradle system and fluoroscopic guidance at repeated junctures throughout the brachytherapy procedures to optimize final seed positioning. The other is the preplan, preloaded needle technique which basically implants the patient with an arrangement of seeds and needles that was prearranged at least a week or two in advance.(Shanahan et al., 2004)

Prostate implants are generally planned to deliver a prescribed minimum dose. However, it has been shown that the minimum dose planned can rarely be achieved due to seed placement errors which are inherent in the procedure. Furthermore, postimplant edema can further reduce the dose delivered by the implant. Hence it cannot be assumed that the patient would receive the dose prescribed in the pre- treatment dosimetric plan. Postimplant dosimetric evaluation was traditionally carried out using multiple radiographs. Although such plane films are adequate for reconstruction of the relative seed positions, they cannot provide the dose delivered to the prostate because the prostate cannot be visualized on a radiograph. Postimplant dosimetry was limited to a calculation of the matched peripheral dose (MPD), a parameter that has been shown to be an unreliable indicator of the dose delivered to the prostate. The dose delivered to the prostate and other organs can be

determined by performing a postimplant computer tomography (CT)-based dosimetric analysis. The advantage of CT-based dosimetry is that the prostate and other organs, such as the rectum, can be visualized. This capability allows dose-volume histograms (DVHs) to be generated, which provide detailed information on dose coverage and implant quality. At present, a postimplant CT study is the most direct method for carrying out quantitative dosimetric evaluation. CT-based dosimetric evaluation is particularly important during the early stages of a new prostate seed implant program to aid the team in progressing up the learning curve as quickly as possible. Continuous evaluation of implant quality permits improvement in techniques as the program develops.

Otherwise, problems which compromise implant quality may go undetected and be perpetuated indefinitely. (Anderson, Mellenberg, Waterman, Wu, & Blasko, 1999)

I-125 and Pd-103 are the most commonly used radioactive isotopes used in permanent prostate brachytherapy seed implant. Implant can be delivered either with I-125 which has a half-life of 60 days or Pd- 103 which has a half-life of 17 days. (Ash et al., 2000). Because of the differences in dose rates between I-125 and Pd-103, it has become common practice to utilize I-125 for slower-growing, low-grade prostate cancers (Gleason score 3–6) and to use Pd-103 for more rapidly growing, high-grade prostate cancers. (Gleason score 7–10). For I-125, the prescribed minimum tumor dose (MTD) has been 160 Gy for transperineal prostate implant alone (Peschel et al., 1999). Other radionuclides such as gold-198, caesium-131 and iridium-192 are used in LDR and HDR. At Korle-Bu Teaching Hospital, I-125 is used for prostate brachytherapy treatments. This is because I-125 seeds have low energy which is convenient for storage as it requires less shielding as well as longer half-

life which is more appropriate for clinical use. Palladium-103 is an alternative nuclide for the treatment”.(Podgorsak, et al., 2005b)

## **1.2 Statement of the Problem**

One of the requirements for effective implementation of permanent implant prostate brachytherapy programme is post-implant dosimetry. Though the noticed discrepancies in the dose distributions used to treat the patient and what had been planned cannot be corrected during post-implant dosimetry, the procedure can be used as a quality assurance tool to enhance one's dose optimization effectiveness. Also the ability to know accurately the dose distributions within the irradiated region would help in explaining observed clinical outcomes. It has been acknowledged that the dose distributions within an irradiated region create the only reliable and verifiable link between the chosen treatment parameters, and the observed clinical outcome for a specified treatment technique. With reference to this, postimplant-dosimetry can be used to perfect one's implant technique.

## **1.2 Objective of Study**

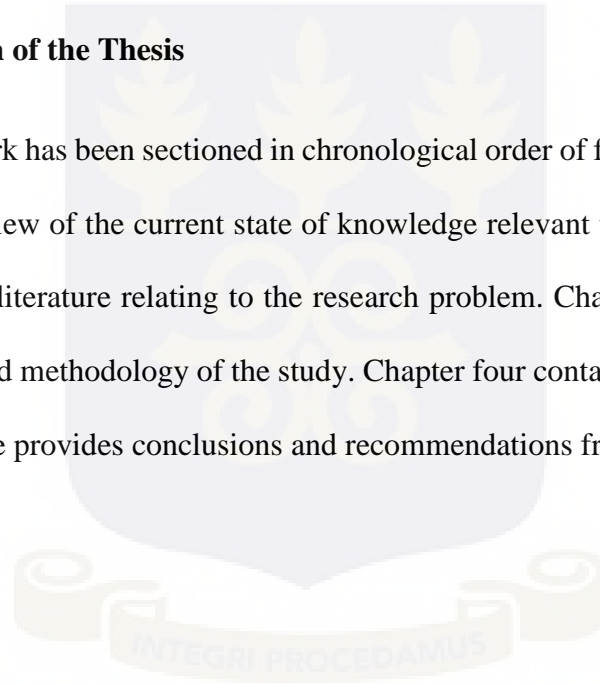
To assess and ascertain the effectiveness of dose optimization by comparing dosimetric values obtained during Ultrasound guided intraoperative real-time implant and CT-postimplant permanent implant prostate brachytherapy with I-125 at the Korle Bu Teaching Hospital; to boost confidence level of the various professionals involved in this treatment modality, and make the necessary recommendations to enhance the treatment delivery process, which would go a long way to improve the quality of life of patients treated with permanent prostate brachytherapy at the hospital.

### **1.3 Relevance and Justification**

This research study seeks to address prostate volume variations and their dosimetric effects on tumor at different stages in the prostate brachytherapy procedure using real-time ultrasound guided images and post-implant CT images. The prostate volume and dosimetric parameters such as D90, D100 (dose covering 100% of the volume), V100 and V150 (volume covered by 150% dose) using US images would be compared with those obtained from CT images acquired nearly 30 days of post-implantation.

### **1.4 Organization of the Thesis**

This research work has been sectioned in chronological order of five chapters. Chapter one focuses on overview of the current state of knowledge relevant to the study. Chapter two reviews existing literature relating to the research problem. Chapter three focuses on the materials used and methodology of the study. Chapter four contains results and discussion while chapter five provides conclusions and recommendations from the findings.



## CHAPTER TWO

### LITERATURE REVIEW

This chapter makes available a general idea on prostate cancer, prostate cancer treatment modalities, and international guideline on prostate cancer treatment.

#### **2.1 Dosimetry associated with brachytherapy**

In brachytherapy, radiation dose falls off with the inverse square of the distance from the source. Therefore placing a source close to the target gives the target very high dose. Hence if some distance can be kept away from normal tissue structures, then the dose be lower there hence sparing them from damage.

##### **2.1.1 Interstitial treatment**

The dosimetry information for reporting on interstitial implant according to recommendations in ICRU report No. 58, consist of;

- i. Explanation of the target volume
- ii. The sources, procedure and implant time, the total air kerma
- iii. Explanation of the dose: prescription point/ surface, prescription dose reference doses in the central plan, mean central dose and the peripheral dose.
- iv. An explanation of high and low dose region and dose uniformity indices and dose-volume histograms (DVHs)

The report highlights the need to report, as a minimum, four different dose related quantities to adequately describe an implant treatment. In addition to the total reference air kerma, the next important parameter is the mean central dose, which is representative of

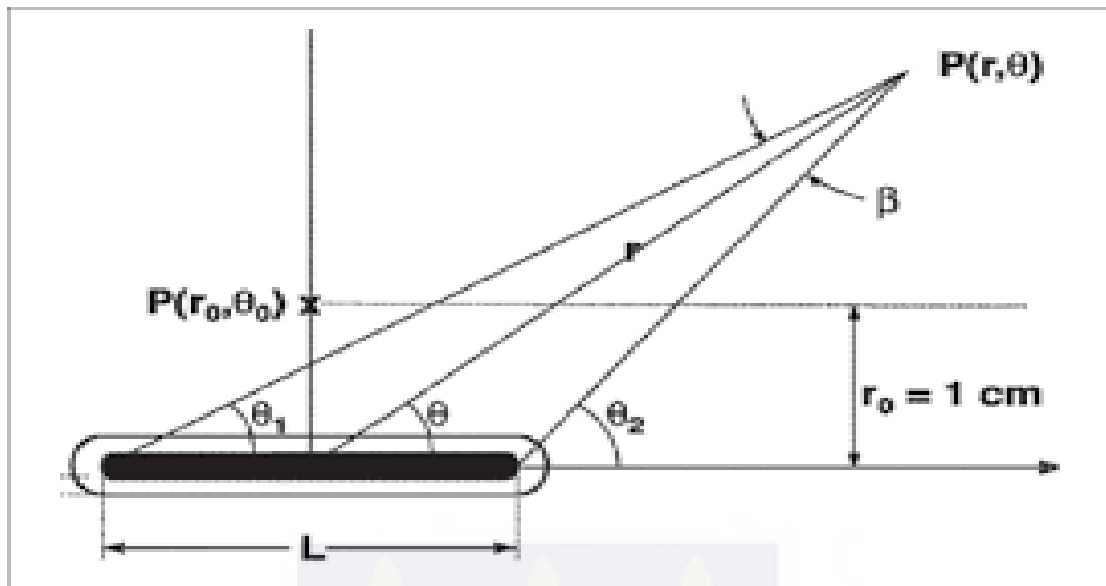
the plateau dose region inside the target volume. The minimum dose is important in tumour control, hence the need to report the peripheral dose. To help correlate dose and any late damage, high dose regions ( $>150\%$  of the mean central dose) and low dose regions ( $<90\%$  of the peripheral dose) are also to be reported.

### **2.1.2 Dose Distribution around Source**

Dose calculations are presented in this research for photon emitting sources only. The dose calculations are divided into two categories: the first category represents the AAPM TG43 formalism, which can be considered as the most complete formalism available today”. “This approach is used in modern TPSs and is suitable as a method for commissioning and the second category (independent protocol developed on the center) may be used for quick checks and verification of treatment plans.

### **2.1.3 AAPM TG 43 algorithm**

In 1995 the AAPM introduction in TG 43 a dose calculation formalism to establish the 2-D dose distribution around cylindrically symmetric sources. It is based on measured quantities such as dose rate constant, geometry factor, anisotropy function, and radial dose function and air kerma strength.



**Figure 2.1 “the geometry and the definitions used for the TG 43 protocol”.**

The quantities used in the calculation of absorbed dose in the TG-43 formalism is measured for the specific type of source. This implies that, aside the photon spectrum and medium, the TG-43 depends on the source construction and geometry as well. Figure above summarizes the geometry and coordinates definitions used in the TG-43 dosimetry protocol. A source of an active length,  $L$ , the encapsulation geometry and the guidance wire as shown. This is the usual configuration of a PDR iridium source. The origin of the coordinate system is positioned at the center of the active core of the source. The  $z$ -axis is along the tip of the source. A cylindrical symmetry for the activity distribution within the core here assumed. The point of interest,  $P$ , is at a radial distance,  $r$ , from the origin and has a polar angle coordinate,  $\theta$ , in the cylindrical coordinate system.

According to the protocol, the dose rate at a point  $p(r, \theta)$  in water can be expressed as

$$D(r, \theta) = \Lambda S_k \frac{G(r, \theta)}{G(r_0, \theta_0)} g(r) F(r, \theta) \dots \dots \dots 2.1$$

Where r is the distance from origin to the point of interest P, and  $\theta$  is the angle with respect to the long axis of the source, as shown in Figure 2.1  $\theta_0$  defines the source transverse plane and is equal to  $\theta/2$  radians,  $S_k$  is the air kerma strength of the source,  $\Lambda$  is the dose rate constant in water,  $G(r, \theta)$  is the geometry function,  $g(r)$  is the radial dose function, and  $F(r, \theta)$  is the anisotropy function. (Rivard et al., 2004)

**2.2 Radioisotopes used in prostate brachytherapy.**

**2.2.1 Classification of brachytherapy sources.**

The use of radioactive materials for diagnostics and therapy purpose has been in the field of medicine since the 19<sup>th</sup> century, however more innovations came up along the way since some of the radioactive sources have very long half-life and higher energy hence not suitable for clinical use and difficult for radiation protection. Thus, it is necessary to have a detailed description of these radioisotopes. The commonly used prostate brachytherapy sources are described below”.

**2.2.2.1 Iodine -125**

<sup>125</sup>I has gained a wide use for permanent implants in radiation therapy. The advantages of this isotope over radon and <sup>198</sup>Au are its long half-life (59.4 days), which is convenient for suitable, and its low photon energy, which needs less shielding. However, the dosimetry of I-125 is much more multifarious than the conventional interstitial sources.

Three I-125 seed models, designated 6701, 6702, and 6711, have been manufactured, which are identical in size and encapsulation but are different in the active source design.

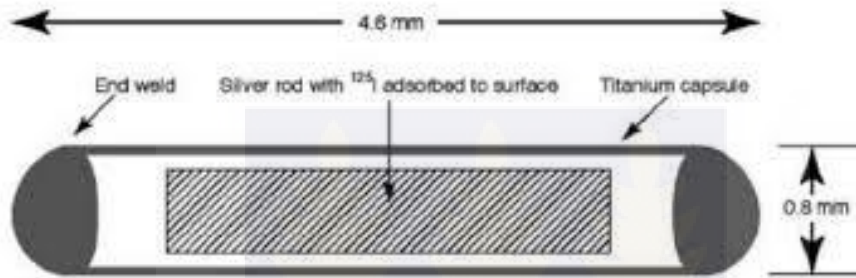
The earlier model 6701 is now out-of-date. The encapsulation consists of a 0.05-mm-thick titanium tube soldered at both ends to form a cylindrical capsule of dimensions  $4.5 \times 0.8$  mm. The model 6702 seed contains ion-exchange resin beads, which are saturated with  $^{125}\text{I}$  in the form of the iodide ion. The model 6711 seed contains a silver wire with the active material, silver iodide (AgI), adsorbed on its surface.

In the new seed design, namely model 6711, the silver wire is readily visible on radiographs and shows seed position as well as orientation. The model 6702 seed is radiographically less visible, although the titanium end welds can be seen when surrounded by reduced thickness of tissue.  $^{125}\text{I}$  decays exclusively by electron capture to an excited state of  $^{125}\text{Te}$ , which spontaneously decays to the ground state with the emission of a 35.5-keV  $\gamma$  photon. Characteristic x-rays in the range of 27 to 35 keV also are produced due to the electron capture and internal conversion processes”.

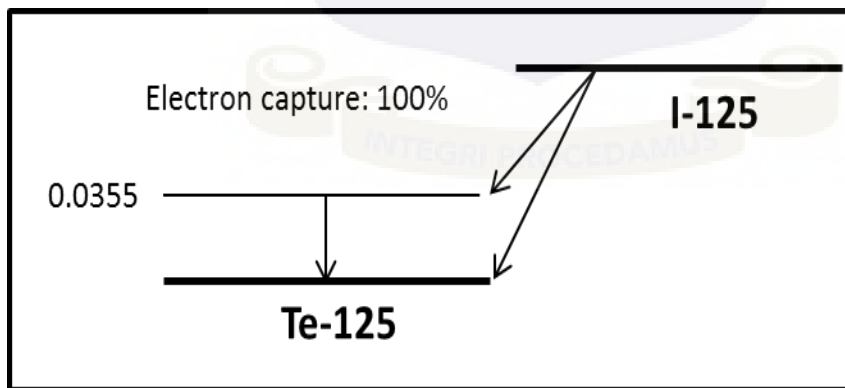
Titanium encapsulation serves to absorb liberated electrons and x-rays with energies less than 5 keV. The model 6711 seed emits two additional photons at 22.1 keV and 25.2 keV energies. These are fluorescent (characteristic) x-rays produced by the interaction of  $^{125}\text{I}$  photons with the silver wire.

Because of the presence of titanium end welds, the dose distribution around iodine seeds is highly anisotropic. This can pose problems of creating cold spots near the source ends. The users of  $^{125}\text{I}$  implants either ignore this problem or try to minimize the extent of cold spots by creating random seed distributions. Although the basic problem still remains, most treatment-planning systems do not take into account anisotropy around individual sources. Significant differences exist in the published values of exposure rate constant for  $^{125}\text{I}$ . Schulz et al., have reported a calculated value of  $1.464 \text{ Rcm}^2 \text{ mCi}^{-1} \text{ h}^{-1}$  for an unfiltered

point source. As will be discussed, the use of the exposure rate constant for unfiltered point sources to calculate dose distribution around actual sources of complex designs such as  $^{125}\text{I}$  has serious accuracy limitations. (Nath et al., 1997). Figure 2.2 shows the structure of  $^{125}\text{I}$  seed 6711 model use currently for permanent prostate brachytherapy with its encapsulation



**Figure 2.2.** Example of I-125 seed 6711 model used currently for prostate brachytherapy implant (Mayles, P., Nahum, A., & Rosenwald, J. C. (Eds.). (2007). Handbook of radiotherapy physics: theory and practice. CRC Press.



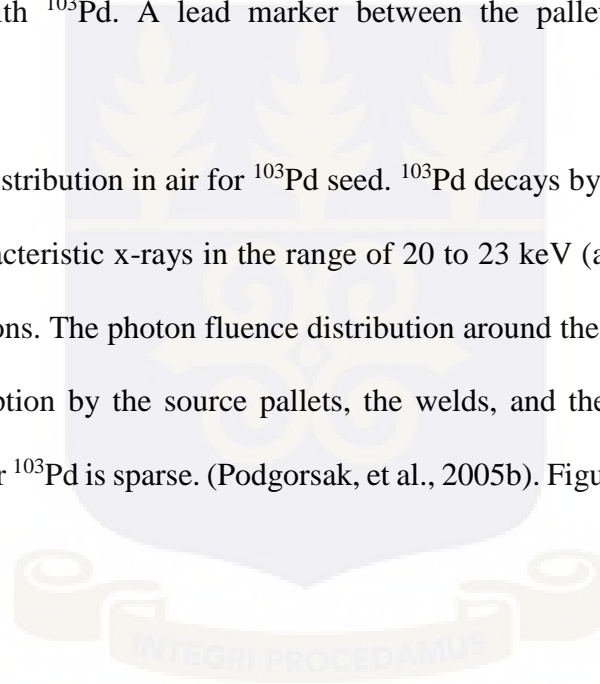
**Figure 2.3.** The decay scheme of I-125 (nucleide, 2013)

### 2.2.2.2 Palladium-103

$^{103}\text{Pd}$  seeds have recently become available for use in brachytherapy. Their clinical applications are similar to those of  $^{125}\text{I}$ . Having a shorter half-life (17 days) than that of  $^{125}\text{I}$  (59.4 days),  $^{103}\text{Pd}$  may provide a biologic advantage in permanent implants because the dose is delivered at a much faster rate.

The  $^{103}\text{Pd}$  seed model 2003 consists of a laser-welded titanium tube containing two graphite pallets plated with  $^{103}\text{Pd}$ . A lead marker between the pallets provides radiographic identification.

Photon fluence distribution in air for  $^{103}\text{Pd}$  seed.  $^{103}\text{Pd}$  decays by electron capture with the emission of characteristic x-rays in the range of 20 to 23 keV (average energy 20.9 keV) and Auger electrons. The photon fluence distribution around the source is anisotropic due to the self-absorption by the source pallets, the welds, and the lead x-ray marker. The dosimetry data for  $^{103}\text{Pd}$  is sparse. (Podgorsak, et al., 2005b). Figure 2.4 shows the structure of  $^{103}\text{Pd}$



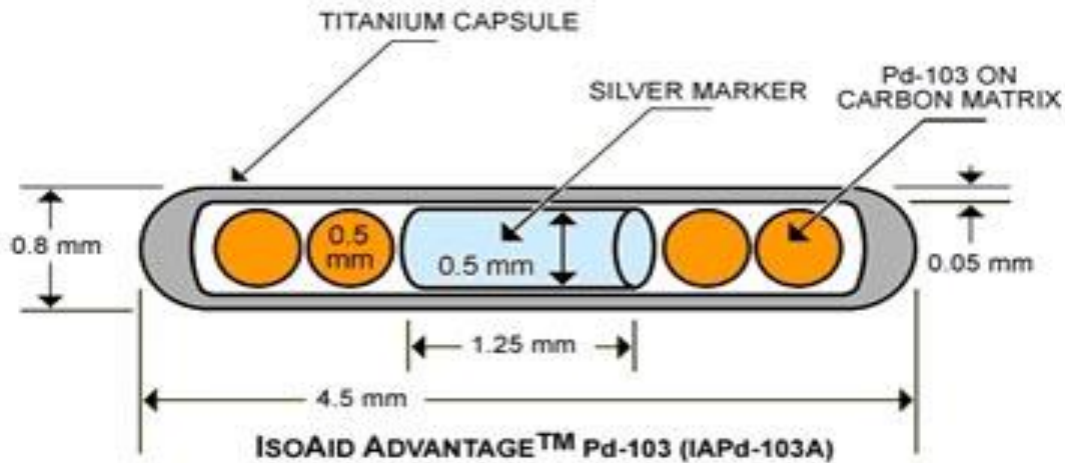


Figure 2.4 the structure of  $^{103}\text{Pd}$  source

### 2.2.2.3 Iridium-192

Iridium-192 (alloy of 30% Ir and 70% Pt) sources are fabricated in the form of thin flexible wires that can be cut to desired lengths. Nylon ribbons containing iridium seeds 3 mm long and 0.5 mm in diameter, spaced with their centers 1 cm apart, are also commonly used. Both the wires and the seed ribbons are quite suitable for the afterloading technique.

$^{192}\text{Ir}$  has a complicated  $\gamma$ -ray spectrum with an average energy of 0.38 MeV. Because of the lower energy, these sources require less shielding for personnel protection.  $^{192}\text{Ir}$  has the disadvantage of a short half-life (73.8 days). However, the half-life is long compared to the average treatment time so that the sources can be used in nonpermanent implants similar to radium and cesium. The activity varies by only a few percent during an average implant duration. (Podgorsak, et al., 2005b)

#### 2.2.2.4 Cesium-137

Cesium-137 is a  $\gamma$ -ray-emitting radioisotope that is used as a radium substitute in both interstitial brachytherapy. It is supplied in the form of insoluble powders or ceramic microspheres, labeled with  $^{137}\text{Cs}$ , and doubly encapsulated in stainless steel needles and tubes. The advantages of  $^{137}\text{Cs}$  over radium are that it requires less shielding and is less hazardous in the microsphere form. With a long half-life of about 30 years, these sources can be used clinically for about 7 years without replacement, although the treatment times have to be adjusted to allow for radioactive decay (2% per year).

$^{137}\text{Cs}$  emits  $\gamma$  rays of energy 0.662 MeV. The decay scheme shows that  $^{137}\text{Cs}$  transforms to  $^{137}\text{Ba}$  by the process of  $\beta$ -decay but 93.5% of the disintegrations are followed by  $\gamma$  rays from the  $^{137}\text{Ba}$  metastable state. The  $\beta$  particles and low-energy characteristic x-rays are absorbed by the stainless steel material, so that the clinical source is a pure  $\gamma$  emitter.

Any practical source will have a finite size and would necessitate corrections for photon attenuation and scattering. The  $\gamma$  rays from cesium have nearly the same penetrating power as radium  $\gamma$  rays in tissue. Meisberger et al. have compared the measured and calculated depth dose values along the transverse axes of the sources and showed that the exposure in water to exposure in air ratio is the same for radium and cesium for depths up to 10 cm. Significant differences, however, exist between radium and cesium doses at points along oblique angles (near the longitudinal axis) due to the filtration effect. Not only is the attenuation of  $\gamma$  rays in steel and platinum quite different, but also cesium emits monoenergetic  $\gamma$  rays while radium emits  $\gamma$  rays of wide energy range. (Murphy et al., 2004)

#### 2.2.2.5 Cobalt -60

$^{60}\text{Co}$  has been used for brachytherapy but is rarely used now. The main advantages of  $^{60}\text{Co}$  is its high specific activity, which allows fabrication of small sources required for some special applicators. However, it is more expensive than  $^{137}\text{Cs}$  and has a short half-life (5.26 years), necessitating more frequent replacement and a complex inventory system.

Cobalt brachytherapy sources are usually fabricated in the form of a wire that is encapsulated in a sheath of platinum iridium or stainless steel. The sources can be used to replace  $^{226}\text{Ra}$  in intracavitary applications. Curie-sized cobalt sources have also been used in a unit called the Cathetron. This is a remote-loading device and provides high dose rates for intracavitary therapy. (Podgorsak, et al., 2005b)

#### 2.2.2.6 Gold-198

Seeds or “grains” consisting of a radioactive isotope of gold,  $^{198}\text{Au}$ , are used for interstitial implants. They are used in the same way as radon seeds have been used for permanent implants.  $^{198}\text{Au}$  has a half-life of 2.7 days and emits a monoenergetic  $\gamma$  ray of energy 0.412 MeV”. “ $\beta$  rays of maximum energy 0.96 MeV are also emitted but are absorbed by the 0.1-mm-thick platinum wall surrounding the seed. A gold seed is typically 2.5 mm long with an outer diameter of 0.8 mm. Because of its lower  $\gamma$ -ray energy, personnel protection problems with gold are easier to manage than those of radon. Moreover, radon seeds continue to exhibit low-level  $\gamma$  activity for many years due to bremsstrahlung, arising from high-energy  $\beta$  particles emitted by its long-lived daughter products”. It is suspected that this chronic irradiation may be carcinogenic. For these reasons, gold seeds replaced radon

seeds for many years, until  $^{125}\text{I}$  seeds gained more widespread acceptance.(Podgorsak, et al., 2005b, Kalolo, 2013).Table 1. Shows some isotopes and their characteristics used in prostate brachytherapy

**Table 1 characteristics of isotopes used in brachytherapy**

Isotope	Energy(kev)	Half-life	HVL in lead (mm)	Source form	Clinical application
$^{125}\text{I}$	28	59.6 days	0.025	Seeds	LDR-permanent interstitial
$^{103}\text{Pd}$	22	17 days	0.013	Seeds	LDR-permanent interstitial
$^{131}\text{Cs}$	29	10 days	2.54	Seeds	LDR-permanent interstitial
$^{192}\text{Ir}$	380	78.3 days	2.5	Seeds and flexible wires	HDR-permanent interstitial
$^{198}\text{Au}$	410	2.7 days	2.5	Grains, seeds and wires	LDR-permanent interstitial
$^{60}\text{Co}$	1250	5.27 years	13	pellets	HDR-permanent interstitial

### **2.3 Causes of prostate cancer**

Like all types of cancer, the exact cause of prostate cancer is not easy to determine. In many cases, multiple factors may be involved. Ultimately, mutations in the DNA, or genetic material, lead to the growth of cancerous cells. These mutations cause cells in the prostate to start growing uncontrolled and abnormally. Abnormal or cancerous cells continue to grow and divide until a tumor develops. If you have an aggressive type of prostate cancer, the cells may metastasize or leave the original tumor site and spread to other parts of the body. In developed countries, prostate cancer is the second most frequently diagnosed cancer, and the third most common cause of death from cancer in men". Nobody really knows the causes of prostate cancer, however age, diet, ethnic origin and a positive family history is probably the strongest known risk factor. Age is considered as the primary risk factor. The older a man is, the higher is his risk. Prostate cancer is rare among men under the age of 45 years, but much more common after the age of 50 years. Statistics indicate that genetics is definitely a factor in prostate cancer risk.

A man whose brother or father had had prostate cancer runs twice the risk of developing it, compared to other men. It is more common among certain racial groups - in the USA prostate cancer is significantly more common and also more deadly among Afro-Americans than White-Americans. According to the American Cancer Society (ACS), approximately 5-10 percent of prostate cancer cases are caused by inherited mutations. It's been linked to inherited mutations in several different genes, including: RNASEL, formerly known as HPCI, BRCA1 and BRCA2, which have also been linked to breast and ovarian cancer in women, MSH2, MLH1, and other DNA mismatch repair genes and HOXB13. A

diet that is rich in red meat and high-fat dairy products may also be a risk factor for prostate cancer. (Damber & Aus, 2008)

#### **2.4 Treatment selection criteria according to European ESTRO/EAU/EORTC guidelines**

“For prostate brachytherapy, different tests are considered before a patient undergoes the procedure. There are two aspect of the patient selection. One is to identify patients who are likely to have a good outcome in terms of biochemical disease free survival and the other to identify patients who will have a good functional outcome. The most significant prognostic factors for disease free survival are initial prostate-specific antigen (PSA), Gleason score and the stage. For functional outcomes the initial prostate volume and lower urinary tract symptom score (IPSS) provides the best guide to outcome. Patients with a Gleason score of 6 or less do well with brachytherapy alone. Gleason score 7 tumours have an approximately 50% probability of biochemical relapse within 5 years”. “Patients with a Gleason scores 6 and 7 should be distinguished according to the predominant grade (3 or 4) since a predominant grade 4 indicates a worse prognosis. Those with Gleason score 8-10 tumors do badly and should be considered for other adjuvant treatment. Patients with low volume localized disease with a small risk of extra-capsular spread do well with brachytherapy alone, i.e. stages T1C-T2B. Some extra information on the risk of extra-capsular spread can be gained by evaluating the number of biopsies involved and the proportion of each core which contains malignancy and the presence or absence of perineural spread. If brachytherapy is to be used as the sole treatment T<sub>3</sub> cases should be excluded. For minimal T<sub>3</sub> disease patients should be considered for external beam radiation

with brachytherapy used as a boost using techniques which cover the extent of known extra-capsular spread. It should, however, be remembered that although many patients may have disease outside the prostate capsule it is within 2 or 3 mm of the capsule in a very high proportion and still within the volume encompassed by brachytherapy. The patient symptom score before treatment is the most sensitive predictor of urinary morbidity after brachytherapy. Those with a score of 0 - 8 do well with a low risk of acute retention and prolonged urethritis. Those with an IPSS score of more than 20 on the other hand have a 30-40% risk of acute retention and prolonged urethritis". "Transrectal ultrasound should be performed on all patients to more accurately assess the local extent of disease and measure prostate volume. It can also be used to assess the probability of pubic arch interference. All patients should have biopsy proven adenocarcinoma. It is usual to take six to 12 biopsy cores with ultrasound guidance. The number of positive biopsies should be recorded to estimate tumour volume. Those with a prostate volume of 35 cm<sup>3</sup> or less have a relatively low incidence of acute retention and urinary morbidity. This is higher for those with larger volumes. Those patients with a volume of greater than 50-60 cm<sup>3</sup> should have hormonal cyoreduction if they are to be considered as candidates for brachytherapy. (Ash et al., 2000).

There are different treatment options available for early stage prostate cancer, these include; hormone therapy, chemotherapy, cryotherapy, permanent seed implant brachytherapy, external beam radiation therapy and prostatectomy. (Heidenreich et al., 2011). Each form of treatment has its own associated risk and side effects. Surgical removal of the prostate contains an increased likelihood that patients will experience erectile dysfunction and urinary incontinence. Sexual dysfunction and irritative

gastrointestinal and genitourinary side effects are commonly associated with external radiation treatment for early stage prostate cancer. In permanent seed implant brachytherapy complications such as urinary retention, urinary incontinence and radiation proctitis may occur (Ash et al., 2000; Stone & Stock, 2002). Table 2. Shows the criteria for selection of patients for permanent prostate brachytherapy

**Table 2 The selection criteria for patients and their recommendation (Ash et al., 2000)**

	RECOMMENDED DO WELL	OPTIONAL FAIR	INVESTIGATIONAL DO POORLY
PSA (ng/ml)	<10	10-20	>20
GLEASON SCORE	5-6	7	8-10
STAGE	T1c-T2a	T2b-T2c	T3
IPSS	0-8	9-19	>20
PROSTATE VOLUME (g)	<40	40-60	>60
Q <sub>MASS</sub> ml/s	>15	15-10	<10
RESIDUAL VOLUME cm <sup>3</sup>			>200
TURP ±			+

## **2.5: International guideline towards prostate cancer brachytherapy implant.**

### **2.5.1: The European's ESTRO/EAU/EORTC guideline.**

The Europeans have made the guidelines towards permanent I-125 seed implant for localized prostate cancer. Some of the parameters to be reported after the implant are, prostate volume implanted (cc), number of needles, number of seeds, prescribed dose (Gy), and total activity implanted (mCi), dosimetric parameters D90, V100 % and V150 %. The Europeans also provided some restriction for defining the target and organs at risk and some dosimetric parameters.

'The European guidelines recommends also CT- imaging for post-implant evaluation. The dosimetric parameters to be considered for CT-post implant are as follows; prostate: D90(%), V100(%), V150(%), Urethra: UrD10(Gy) and Rectum: RD2cc(Gy), V100% and V150% respectively. (Salembier, Lavagnini, Nickers, Mangili, & Rijnders, 2007)

### **2.5.2 The American Brachytherapy Society (ABS) guidelines.**

The American Brachytherapy Society (ABS) has also issued various guidelines for seed implants. The guideline for dosimetric parameters for real time implant to be considered are D100(Gy), D90(Gy),V100(%) and to minimize the length of urethra receiving 200% of the prescribe dose. (Anderson et al., 1999)

Likewise ABS recommends CT-imaging for post-implant evaluation. The dosimetric parameters to be reported for CT post-implant evaluation are D100,D90 and D80 for prescribed dose, V200,V150,V100,V90 and V80(%) for volume coverage, Urethra and Rectal doses, post-implant volume(cc) and number of days between implant and the date of imaging study.(Nag, Beyer, Friedland, Grimm, & Nath, 1999). The recommendations

from Europe and America do differ in that ABS adds D80, V90 and V80 and recommends minimizing the length of urethra receiving 2005 of the prescribe dose.

## **2.6 Treatment modalities for Prostate cancer patients.**

Treatment of prostate cancer involves the use of both high dose rate (HDR) and low dose rate (LDR) ionizing radiation as well as other modalities. Some of the modalities are as described below,

### **2.6.1 Hormone therapy**

Prostate cancer hormone therapy is the systemic ablation of the body's testosterone which, for a period of time, will slow or stop the growth and spread of prostate cancer. Hormone therapy may also be called androgen deprivation or androgen ablation. The male sex hormone, testosterone, causes the growth of the prostate gland and other sex organs in the developing male. Even as men pass through the age of puberty, testosterone continues to contribute to the growth of the organ. Testosterone will fuel the growth of any prostatic cell: the chemical cannot discriminate between the receptors of healthy tissue and cancerous tissue. Prostate cancer hormone therapy removes the chemical that "feeds" cells and can stop or slow the growth and spread of the tumour" (Bastian et al., 2012)

### **2.6.2 Chemotherapy Treatment**

Prostate cancer chemotherapy is usually used as salvage treatment during hormone refractory prostate cancer or for advanced prostate cancer with distant metastasis and has shown success in extending the life and quality of life in many patients. Most cases of prostatic adenocarcinoma usually grow very slowly, meaning the cells divide at a rate that

is similar to that of healthy cells. “Chemotherapy, therefore, is usually not effective for early adenocarcinoma of the prostate as chemotherapeutic drugs are both toxic and systemic. Toxic because they damage cells so badly that upon division, the cell dies. Systemic because chemotherapy affects all the cells of the body as it circulates through the blood stream. Like radiation therapies, chemotherapy does not destroy the entire body because only cells that divide soon after being treated will die. Unfortunately, chemotherapy cannot be focused to any particular area of the body. All quickly-dividing cells of the body therefore are affected, including, those in the hair follicles, skin, gastrointestinal tract, and bone marrow. The severe and sometimes dangerous side effects of chemotherapy drugs have often outweighed their benefits as an early prostate cancer treatment. However, for patients with advanced disease, chemotherapy can be beneficial in both extending the life and decreasing pain. The earlier use of chemotherapy has been helpful in slowing the advancement of the disease (Heidenreich et al., 2011)

### **2.6.3 Cryotherapy Treatment**

Also referred to as cryosurgery and cryoablation, prostate cryotherapy is a minimally invasive surgery capable of using controlled freeze and thaw cycles to destroy the disease. Because cryotherapy is relatively new, that is, lacking numerous long-term survival rate studies, cryotherapy is not used as often as radiation therapy for primary treatment. Cryotherapy, however, is effective in treating cases of prostate cancer that are radio resistant and recur as a result. Some doctors believe that the use of freezing temperatures rather than stronger doses of radiation therapy is more effective for radio resistant prostate cancer. Prostate cryotherapy works because as cells freeze, ice crystals form inside and around them. The freezing and thawing processes destroy cells through dehydration, drastic

changes in the pH levels, or prevention of the flow of red blood cells”. “Subjecting the prostate gland to freezing temperatures, specifically negative 40 degrees Celsius, also activates an anti-tumour response in the body. An anti-tumour response begins with the production of anti-bodies that work to eradicate the tumour. Cryotherapy is an effective primary treatment for those who are in the early stages of prostate cancer with low risk for tumour extension. This treatment may also be an excellent alternative for those who are not good candidates for radical prostatectomy. Cryotherapy may be used if EBRT fails and the cancerous prostate cells are deemed radioresistant. Some advantages of include the one day in-hospital treatment, though some patients will stay overnight depending on their general health. (Heidenreich et al., 2011)

#### **2.6.4 External Radiation Treatment (Teletherapy)**

External beam radiotherapy (EBT) is a type of radiation therapy that uses a machine to aim high energy rays at the prostate cancer from outside the body. During external beam radiation therapy, a beam of radiation is directed through the skin to the cancer and the immediate surrounding area in order to destroy the main tumour and any nearby cancerous cells. Usually the treatments are administered five days a week, Monday through Friday, for a number of weeks, where an average of 4500 cGy of radiation is given to each patient in number of fractionations. This allows the cancerous cells to be destroyed while repairing the healthy body cells. The radiation are generated by a cobalt-60 machine which produces gamma radiation or linear accelerator capable of producing high-energy X-rays and electrons for the treatment of prostate cancer. Using high-technique treatment planning software, the treatment team controls the size and shape of the beam, as well as how it is directed to the targeted area. The goal of treatment is to irradiate a targeted area with as

much energy as possible while avoiding the neighboring organs. Advanced radiotherapy techniques include three-dimensional conformal radiotherapy (3D-CRT), intensity modulated beam radiation therapy (IMRT), image-guided radiation therapy (IGRT), intra-operative radiation therapy (IORT), proton beam radiation therapy (PBRT), tomotherapy, systemic radiation therapy, radio immunotherapy (RIT), and hypo-fractionated radiation therapy. Proton beam therapy is becoming a more widely accepted treatment for prostate cancer, while neutron beam therapy is still in the experimental stages. (Heidenreich et al., 2011, Kalolo, 2013, Podgorsak, et al., 2005)

## **2.7 Selected Cure Rate Studies of Prostate Implant**

Cure rates in prostate brachytherapy are measured as overall survival, disease-specific survival, and biochemical control. Because prostate cancer grows slowly, survival studies are difficult to perform, with most investigators presenting outcomes, even long-term outcomes, as biochemical disease free survival (BDFS). There is some evidence that the use of PSA control as a surrogate for disease-specific survival is appropriate. (Zelevsky et al., 2017). A multi-institutional analysis of long-term BDFS in 2693 hormone naive patients treated with brachytherapy alone found that risk group was the strongest predictor of outcome.(Elefsky et al., 2007). These are undeniably good results, but dosimetric data were available for less than one-fourth of the patients analyzed from the 11 contributing institutions. Although the analysis was not broken down by institutions, it is clear that not all institutions had equal success. Several studies have shown that clinical outcomes in prostate brachytherapy, both for the retropubic approach and the TRUS-guided technique, correlate with dose coverage parameters”. “The extensive clinical experience of Memorial Sloan-Kettering Institute (1078 patients with retropubic approach surgery) from 1970–

1987 was presented by Zelefsky and Whitmore. Two recent retrospective studies of the TRUS technique also demonstrate that the clinical outcome depends on dose delivered and prostate volume coverage. Both studies were based on post-implant dosimetry taken from CT scans.(Zelefsky et al., 2017). Stock et al. reported on an experience of 134 prostate cancer patients implanted with 125I as the sole treatment modality (not treated with external beam therapy (EBRT) or hormonal therapy). They assessed rates of freedom from biochemical failure as a function of the D90 dose. D90 was defined as the minimum dose in the hottest 90% of the target volume. A significant increase in freedom from biochemical failure (92% vs. 68% after 4 years) was observed ( $p=0.02$ ) for patients ( $n=69$ ) where  $D90 \geq 140$  Gy. (Stone & Stock, 2002).

In a later study Potters et al. recently reviewed the impact of various dosimetry parameters on biochemical control for their experience of 719 patients treated with permanent prostate brachytherapy. Many of these patients also received EBRT (28%) or hormone therapy (35%). Furthermore, 84% of the implants used 103Pd with the remainder using 125I. Their results indicated that patient age, radionuclide selection, and use of EBRT did not significantly affect biochemical relapse-free survival (PSA-RFS). The only dose-specification index that was predictive of PSA-RFS was D90. The close correlation between D90 and PSA-RFS and a dose response in the clinical dose range of 100 to 160 Gy are strong justifications for improved information and accuracy in the dosimetry for interstitial brachytherapy, hence the focus of this work.(Potters et al., 2001)

## **2.8 Selected complication rates studies of prostate implants**

There is very little consensus, not only with regard to doses, but also which organs should be considered at risk for causing complications. Multiple well performed studies show conflicting results. Several investigators have looked at dose to the prostate gland as a portent of complications. Given a reproducible implant technique, high doses to the gland point to high doses to the critical structures, which lead to complications. This hypothesis obviates the need for drawing the critical structures or what dose limits they might require. For example, urinary frequency and increase in International Prostate Symptom Score (IPSS) have been shown to correlate with  $D_{90} > 180$  Gy, while increased V150, V200, and D90 seem to correlate with urethral structure. D90 values greater than 160 Gy tend to compare with a decrease in potency. Just as importantly there is also indication that high-dose regions within the gland, which D90 and V150 convey, do not mean complications. (Stone, 2005)

### **2.8.1 Urinary complication**

Dose to more than 10 mm of the urethra exceeding 250% of the prescribed dose in brachytherapy is likely to lead to RTOG Grade 2 or 3 morbidity but with only modest urethral sparing techniques, such high doses are virtually unseen in the modern era. Most short-term, acute urinary complications such as urinary obstruction or an increase in IPSS may be attributed more to needle trauma and to a lesser extent to dose and dose rate. With regard to urinary complications, only excessive dose to the membranous urethra appears to be a sensible dose restriction to prevent urethral complications. (Group, 2009)

### **2.8.2 Rectal complications**

Investigations have shown that dose to the rectum correlates with rectal complications. However, no two investigations seem to perform rectal dosimetry in quite the same fashion. Variants range from dose to the anterior rectal wall to dose to the surface of the outer rectal wall to dose to the annular volume between the outer and inner rectal walls. The most useful of the resultant dosimetry guidelines was promulgated by Snyder et al. which based rectal dose constraints on an annular dose volume histogram of the rectum, targeting to achieve less than 1.3 cm<sup>3</sup> to receive 160 Gy for iodine monotherapy. This rule is often modified by practitioners who prescribe 145 Gy minimum peripheral dose (mPD) to read less than 2.0 cm<sup>3</sup> to receive 145 Gy as this is also evident from the publication". The mPD was defined by Rao et al., 1981 as the lowest dose at the intersection of the periphery of each seed array and a plane halfway between the planes carrying the seeds. (Snyder et al., 2001, Rao et al., 1981). .

### **2.9 Impact of imaging modality on dose reporting**

The AAPM TG-64 and the American Brachytherapy Society (ABS) as well as European Groups recommend the use of CT to evaluate the implant. Dosimetric parameters  $D_i$  and  $V_i$  that are used to score an implant are dependent on accurate identification of source position, dose calculation, and target delineation. Most inconsistencies in dose reporting are a result of disparity in target delineation. Various imaging modalities can be used to evaluate an implant. Plane films provide source positions but lack soft-tissue contrast. The ultrasound images provide prostate definition but cannot offer unambiguous seed positions. The use of CT to evaluate the implant is currently the standard of care. CT images of the

pelvis provide excellent source definition within the limits of axial slice spacing and partial-volume artifact, and exhibit reasonable soft-tissue contrast. However they are not as reliable as MR images for prostate or normal tissue delineation. MR imaging requires multiple scans for optimal viewing of the soft tissue and sources. The effect of various imaging modalities on delineating target volumes and their impact on dose reporting is addressed below.

### **2.9.1 Ultrasound Imaging**

The use of ultrasound for implantation but not for evaluation was recommended by both ABS and ESTRO (European Society of Therapeutic Radiology and Oncology). The PTV is the prostate as visualized using a transrectal ultrasound probe. In addition to the prostate, the rectal wall and urethra are clearly visible on ultrasound. Prostate volume definition on ultrasound is superior to the CT definition of the prostate. Despite the clarity of the prostate image on ultrasound there is a tendency to contour the lower sphincter on the ultrasound as prostate, and care should be taken to avoid this common oversight. Studies have shown that inter- and intraobserver prostate volume definition can be minimized using 3D ultrasound scans. The superior prostate definition on ultrasound would make this imaging modality the choice for implant evaluation over CT if the sources could also be visualized. Source identification on ultrasound is challenging and ambiguous. Sources that are not oriented perpendicular to the ultrasound beam are not clearly visualized. Therefore, ultrasound images should be used with other imaging modalities like CT or fluoroscopic images to provide better source identification. Attempts made to register the ultrasound

prostate images to the CT images are prone to problems arising from the ultrasound prostate distortion due to the presence of the probe in the rectum and the movement of the probe as it steps through the entire length of the prostate. Techniques to register fluoroscopic seed positions to the ultrasound prostate images can provide a means of real-time dosimetry with accurate prostate volume delineation and source position definition. Such a fusion, if accurately performed in conjunction with newer ultrasound equipment that does not distort the prostate during imaging, would reduce the variability in dose reporting. (Ash et al., 2000, Nag et al., 1999)

### **2.9.2 CT Imaging**

Dose indices routinely reported in the literature, such as D90, are CT based, and quality of the implant based on D90 is a standard. While CT is used to establish source positions, the clarity of CT images is inadequate to contour the prostate accurately. This is the primary cause of reported large variations of inter and intraobserver values of D90 and V100. In general, it is more difficult to identify accurately normal structures adjacent to the prostate in CT images than on MR because of lower soft-tissue contrast with CT compared to MR images. Also, it is difficult to distinguish the inferior part of the prostate, the apex, on CT, and the prostate volume tends to be overestimated by the observer. (Roach et al., 2005). The superior part of the prostate, the base, can also be particularly challenging to contour. (McLaughlin et al., 2005). Large glands obliterate the bladder neck and may not be contoured as prostate on CT. And the intact bladder neck for small glands is difficult to distinguish from the prostate and may be contoured as prostate. A prominent median lobe

penetrating the bladder as in is easily identified on ultrasound. Because such median lobes are almost impossible to implant adequately, they are usually resected by the urologist prior to implant)". "Furthermore, post-implant scans are distorted due to the presence of seeds and edema from the implant procedure". "Despite accurate determination of seed position and dose calculation, the wide variation in doses reported is testimony to the difficulties in contouring the prostate on CT. Inaccurate delineation of the prostate after implantation can potentially lead to incorrect conclusions. Overestimation of the prostate apex due to inadequate soft-tissue contrast can falsely result in a change in D90 and V100". Underestimating the base on large glands and overestimating the base on small glands can also potentially lead to incorrect conclusions regarding base coverage. (Han et al., 2003). Generally, most CT-based dose and volume indices reported in literature are limited due to the lack of consensus in contouring. Increased awareness of prostate anatomy and training in CT contouring can increase the agreement in dose reporting. Contouring normal structures responsible for urinary, rectal, and erectile function and determining the dose to these structures is crucial to delivering and evaluating optimal therapy. Outlining normal structures adjacent to the prostate responsible for these functions are also equally challenging on CT. The urethra cannot be distinguished on CT unless a Foley catheter with a contrast material is used. Seeds placed in the posterior region of the prostate obliterate the prostate-rectum interface and make contouring the outer rectum difficult". "The inner rectum or the rectal mucosa, which is the radiation sensitive component of the rectum, cannot be unambiguously delineated on CT. The neurovascular bundle and structures associated with erectile function cannot be identified unambiguously on CT. Because of the difficulty in outlining normal structures while using CT-based evaluation, attempts

have been made to correlate dose to the prostate and normal tissue complication. Other groups have reported dose to the normal structure by outlining the structures as viewed on CT or use surrogates. The geometric center of the prostate has been used as a dose point for the urethra. It is common to use the penile bulb dose as a substitute for erectile function. (Salembier et al., 2007, Narayana et al., 2005)

### **2.9.3 MR Imaging**

Magnetic Resonance (MR) imaging provides improved soft-tissue contrast such as base and apex definition and determination of the prostate rectal interface as compare to CT. T2-weighted images provide identification of the prostate and critical normal tissue adjacent to the prostate. The rectal wall comprising of the outer rectal muscle and the inner rectal mucosa can be distinguished on T2-weighted axial MR. The dose to the bladder, urethra, rectum, upper and lower sphincter, corpus cavernosum, penile bulb, neurovascular bundle, and pudendal arteries can further be determined using MR imaging and correlated to dose-toxicity and quality of life studies. The variability in volume definition is reduced with MR images due to the clarity of the images. A pulse sequence that improves volume definition, however, does not allow the unambiguous determination of seed position. Seed localization is performed either on CT or planar images and fused with MR images". Image registration involving two or more modalities introduces uncertainties depending on the timing of the scans. Difference in bladder and rectal filling can be significant even when CT and MR scans are obtained one immediately following the other with similar patient positioning. In addition, ideal anatomical registration can only be achieved over a certain

region of interest and not over the entire volume of the patient. Endorectal MR imaging has been used to determine both the seed position and to delineate anatomy. While the use of endorectal coil increases patient discomfort and reduces the reliability of dose determination to the rectum, it removes the need for fusion between different imaging modalities and associated uncertainties. MR images provide better anatomical definition but increase the cost of imaging. It should therefore be used only when a clear medical benefit has been identified. With improved instruction and education in contouring most structures can either be outlined or surrogates determined on CT. Training guidelines to contour the CT base and the apex reproducibly will improve consistency in reporting the existing dose parameters. (McLaughlin et al., 2002, Moerland et al., 1997, Amdur et al., 1999)

#### **2.9.4 Timing of imaging on dose reporting**

Studies have shown that the post-surgical edema and its resolution can alter the dose delivered by an implant. The dynamics of edema resolution and the decay of radioactivity can lead to large changes in the dose delivered if this effect is not taken into account. The magnitude of this effect further depends upon the timing of imaging after the implant for the purpose of dose evaluation and dose reporting. For a normal implant, between 50 and 150 sources are placed into the prostate through transperineum guiding needles. At least 15 and sometimes more than 30 guiding needle insertions are needed to place the sources to various spatial locations in the gland". "The mechanical trauma caused by the needle insertion, the intraprostatic bleeding resulting from the needle penetrations, and the general inflammatory response to the needle perforations together cause the prostate gland to swell initially and reach a maximum volume shortly after the completion of procedure followed

by gradual resolution of the swelling. Except for a few reports demonstrating a weak negative correlation of the procedure induced percentage volume increase with the pre-implant prostate volume, published studies have not found any consistent correlation of either the amount of edema or its temporal resolution pattern with the known characteristics of a patient such as age, pre-implant gland volume, use of hormones, or with the details of the procedure such as radionuclide type, number of needles used, number of implanted sources, and total source strength. In general, the degree of procedure-induced prostate edema and its rate of resolution varied significantly from patient to patient and remained unpredictable for individual patients at the completion of the procedure. (Badiozamani et al., 1999, Taussky et al., 2005, Yamada et al., 2003)

### **2.9.5 Effect of prostate edema on brachytherapy dosimetry**

The effects of edema can be fully incorporated into the dosimetry calculation within the TG-43 dose calculation formalism, if the temporal variation of each implant's edema is known. Edema-induced dosimetric errors resulting from conventional post-implant dosimetry change from underestimation to overestimation as a function of post-implant dosimetry time, hence conventional post-implant dosimetry performed at a judiciously selected time could also provide an accurate estimation of the delivered dose if the individual implant's edema characteristics are known. However, patient-specific edema characteristics can only be obtained, at present, by performing comprehensive post-implant imaging studies for each implant, which can be time consuming and inconvenient. In absence of this information, simulation studies have shown that a nominal optimum time exists for each radionuclide at which the errors resulting from conventional post-implant

dosimetry are not zero but are clinically acceptable for all edema characteristics. For edemas that follow exponential resolution, the nominal optimal time for performing post-implant dosimetry was found to be  $10\pm 2$  days,  $16\pm 2$  days, and  $42\pm 2$  days, respectively, for  $^{131}\text{Cs}$ ,  $^{103}\text{Pd}$ , and  $^{125}\text{I}$  implants. The maximum error resulting from conventional implant dosimetry performed at these nominal optimal times would be less than 5% regardless of the edema characteristics.

(Speight et al., 2000, Whittington et al., 1999).



## CHAPTER THREE

### MATERIALS AND METHODS

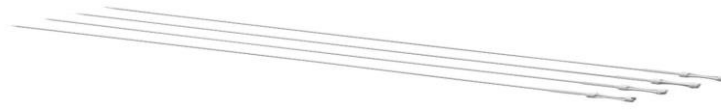
This chapter forms the theoretical and experimental background of the project. It is made up of two parts; part one describes the real-time implant and part two describes the post-plan procedure.

#### 3.1 Materials

Real-time implant was done in the surgical theatre. This study was done for the purpose of quality assurance of patients undertaking prostate brachytherapy and for patients who would undergo prostate brachytherapy in the future. This segment describes briefly the real time implant in the theatre. The equipment used during real-time implant were: Iodine-125 Radionuclide (radioactive seeds), seed planning software (VariSeed 8.0 model), mick compatible needle, treatment planning software, ultrasound unit and rectal probe, stepper or probe carrier, B and K template (the perineum template), stabilization device, gel, mick applicator, anesthesia and survey meter”.

##### 3.1.1 The implant needles

During the real time implant technique the needles were inserted base on the ultrasound image guidance. The needles were fixed on the template grid with holes on each side to allow the seeds to be deposited in the patient body. In general, patient under prostate brachytherapy could be implanted with needles ranging from 15-20 and with seeds ranging from 45-90.(Podgorsak, et al., 2005b). Figure 3.1 is an example of implant needles use for permanent implant brachytherapy procedure.



**Figure 3.1. The pictures shows the implant needles used during real-time procedure**

### **3.1.2 The ultrasound unit, rectal probe and Gel**

Ultrasound is the usage of high frequency sound waves (1-10 MHz) and their corresponding echoes to create pictures of the internal structures of patients. It is a harmless modality which produces images of the inside of the body using sound waves.

In LDR prostate brachytherapy, an ultrasound probe is inserted into the rectum and images from the probe are used to evaluate the size and shape of the prostate. This is to help the medical team to decide the right radiation dose for each patient. The insertion of the seeds into the exact location began as identified at the beginning of the procedure, this took about 1-3 hours. No surgical opening was needed. Through the skin between the scrotum and the rectum, the radioactive seeds were inserted into the prostate gland using needles which were passed with the help of the ultrasound probe.

The ultrasound machine had a seed implant software package which helped to display a grid pattern on the screen, it also displayed the sagittal in addition to the transverse planes of the prostate volume. This feature was very useful in identifying the superior prostate capsule to guide individual needle insertion, in visualizing the movement of the prostate

volume as needles are inserted and in confirming that the seeds are deposited correctly at the cephalad-most portion of the prostate.

“The ultrasound gel a conductive medium that is used in ultrasound diagnostic technique and treatment therapies”. “The gel is applied between the transducer and the skin to displace the air and minimize large reflections that would interfere with the ultrasound transmission into the patient. The transducer is use to send and receive sound wave”



**Figure 3.2. A pictorial view of ultrasound unit and rectal probe used at the theatre for the procedure**

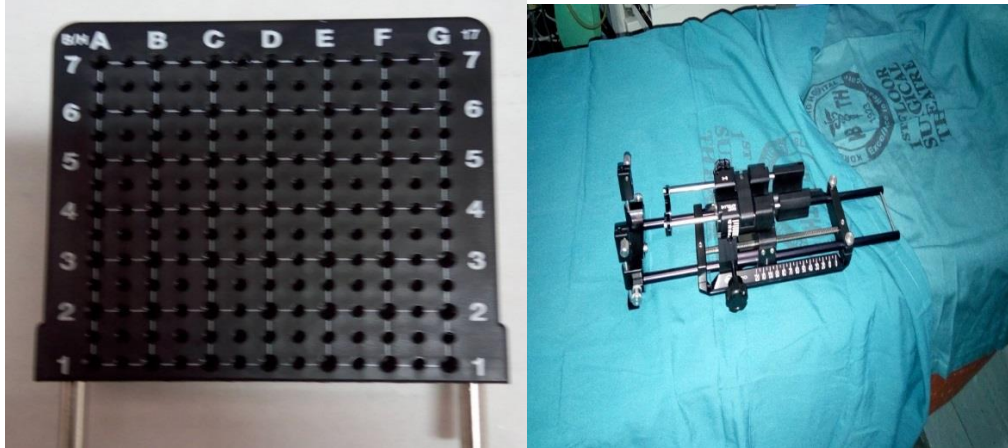
### **3.1.3 The stepper and the template grid**

The needle pattern has holes which can accept 17 or 18 gauge needles arranged typically in a 13x13 matrix, at 5 millimeters spacing. The template may be designed to mount

directly to the rectal probe in some systems, in which it moves together with the probe, or it may be mounted on the probe carrier, in which it remains stationary with respect to the region of the abdomen surrounding the urogenital and the openings as the probe is moved. In either circumstance, the hole on the needle template matched to the grid points displayed on the TRUS monitor screen. The stabilizing mechanism, immobilizes the entire rectal probe system against the operating table or floor, to prevent accidental motion of the probe and needle template during the implant procedure. The template is placed at close proximity to the perineum to minimize needle spreading in the target volume.

The template grid corresponds precisely with the electronic grid of the ultrasound machine, the grid is used to guide the needles into the perineal area, the coordinates or the map references on this grid or template is used to pinpoint the exact positions in the prostate where the seeds are to be placed. At the time of volume study and implant, both the ultrasound probe and the template are fixed on the stepper. The stepper has a scale and a knob which is adjusted at 5 mm interval when studying both sagittal and transverse sections of the prostate through the rectum.

The stepping device allows the rectal probe to be attached to the stabilizing mechanism while permitting the in and out movement of the patient's rectum in precise steps. The square lightweight stepper has a universal grid array and can be sutured to the patient. The stepper holder is available for various ultrasound stepper devices. The advance needle fixation design uses a plate that locks all needles in a single action. Figure 3.3 shows the template grid and stepper use during the implant procedure



**Figure 3.3 A pictorial view of stepper and template grid used during the implant**

### **3.1.4 Mick applicator**

During real-time implant procedure, iodine-125 radioactive seed are attached to the Mick applicator, after which the needles are fixed to the applicator. The whole assembly is place into the prostate gland through image guided ultrasound procedure. The oncologist then shoots the radioactive seeds from the magazine to the prostate volume through needles, usually each magazine contains 15 radioactive seeds. The applicator works like a gun by shooting the seeds to all the needles until the entire prostate volume is effectively implanted. Figure 3.5 shows a Mick applicator which was during the intraoperative real-time implant at the Korle-Bu Teaching Hospital.



**Figure 3.5 Picture of the mick applicator used for the implant**

### 3.1.5 The survey meter

The survey meter is used to measure radiation dose rates and also assess radiation leakage. In the course of the implant procedure, an accident may occur in which seeds may drop on the floor. Therefore at the close of the procedure, the theatre room must be thoroughly checked to confirm that no radioactive seeds have dropped. This is mostly done by the medical physicist with aid of the survey meter to measure dose rates and assess any possibility of radiation leakage. Figure 3.5 shows a survey meter which was used during the procedure in the theatre



**Figure 3.5 A survey meter**

### **3.1.6 Anesthesia**

It is the short-term induced loss of consciousness or awareness. Anesthesia enables the painless performance of medical procedures that would cause severe or unbearable pain to an anaesthetized patient. Three broad groups of anesthesia exist, these include general anesthesia which overturns the central nervous system activities and results in unconsciousness and total lack of feeling. Sedation anesthesia overpowers the central nervous system to a lesser degree, inhibiting both anxiety and creation of longstanding memories without resulting in unconsciousness. Regional or local anesthesia blocks transmission of nerve impulses between targeted part of the body and the central nervous system, causing loss of sensation in the targeted body part. A patient under regional or local anesthesia remains conscious unless general or sedation anesthesia is administered at the same time. After the procedure the anesthetist reverses the anesthetic effect. In this study the patient is given general anesthesia during the real-time implant and the anesthesia

machine is to monitor the patient throughout the procedure”. Figure 3.6 shows the anesthesia machine used for the procedure



**Figure 3.6 The anesthesia machine used at the theatre for the procedure**

### **3.2 The real time implant procedure**

The implant of seeds is done carefully so as to avoid unnecessary radiation to the patient. In view of this, the patient’s prostate volume is studied.

#### **3.2.1 Volume study**

Volume study using ultrasound to be used for the implant was done 2-3 weeks before the implantation so as to minimize changes in the prostate volume particularly if the patient is under hormonal therapy. This is done mostly by the urologist and the oncologist after the seeds were obtained from the manufacturer (BARD COMPANY, USA) based on the volume

of estimated. The volume study helped to know the number of seeds to be ordered. The volume study consisted of a number of consecutive axial images which were obtained from a 5 mm spacing from the prostate to the apex with the template pattern superimposed on the each image. Sagittal ultrasound images are often obtained from base-apex length measurement to ensure that the proper number of slices were obtained.

### **3.2.2 Needle identification**

At the treatment theatre the patient was positioned in a lithotomy position. B and K template attached to interplant stepper was brought to the perineum of the patient and the ultrasound probe was introduced into the rectum while connected to the ultrasound machine. The urologist, oncologist and the medical physicist identified each needle planted around the peripheral of the prostate around the template. Both physical and electronic templates matched. As the urologist was planting the needles, the oncologist and the physicist were identifying the position of each needle on the screen of the ultrasound.

### **3.2.3 Delivery of seeds**

The plan of the implant was based on ultrasound cross sectional images. The intended treatment volume generally was the entire prostate gland with a small margin of periprostatic tissue (usually 0.2 cm). The number of seeds required and their geometric location in the target volume was determined through optimized computer dose planning. The recommended total radiation to the periphery of the target volume was 150-160 Gy for I-125. Transverse ultrasound images were obtained at 5 mm increment and digitally entered into the interplant treatment planning computer. Contours of the prostate, urethra and

rectum were drawn digitally. Treatment plan was generated and optimized electronically. Generally, a peripheral loading system was used. Adjunct template guide holes were seldom used, with diagonal positions being preferentially loaded. More centrally located needles contained seeds loaded only at the base and apex. The interplant system provides straightforward tool for the operator to set these parameters. Anatomical boundaries from the contour structures were automatically integrated and applied to set the limits of the pattern". (Podgorsak, et al., 2005b).

### **3.2.4 Dose planning**

The dose planning software used to perform the dose computation was the VariSeed 8.0 version, with online connection to the ultrasound system which also contains screen volume calculation. In this study the prescribed doses were 110 Gy for partial implants and 160 Gy for full implants. The most important observation for the dose planning was to ensure that large areas with high doses were to be avoided, moderate dose to urethra and as low dose as possible to the rectum. Table 3 shows the dose limits for prostate brachytherapy

**Table 3 Dose limits for prostate brachytherapy**

Dose parameter	Dose limit
Prostate	
V200 [%]	<50%
V150 [%]	<70%
V100 [%]	>95%
Urethra	
UrD(90) [%]	<90%
UrD(30) [%]	<130%
UrD(10) [%]	<140%
Rectum	
V100 [%]	<1%

These dose limits correspond with international limits for Europe and America.

### 3.3 CT postimplant procedure

#### 3.3.1 Selection of patients

Patients who had already undergone permanent prostate brachytherapy and had CT scans of the pelvis taken 3-4 weeks after the implant were selected for this procedure in respective of age, time of implant, religious or ethnic backgrounds. In all 20 patients were chosen, with 11 of them receiving a prescription dose of 110 Gy( partial implant) and 9 receiving

a prescription dose of 160 Gy( full implant). The post CT images were uploaded onto the treatment planning machine with the patients identification numbers assigned to them. The CT images were taken at 2.5 mm interval.

### **3.3.2 Organ sedimentation**

The CT images uploaded are then carefully sorted to select only images which contain the sources.

### **3.3.3 Contouring of organs on the CT images**

After sorting and selecting images with sources, organs of interest were contoured by the medical physics and other professionals. Care was taken not to overestimate the prostate and other organs of interest.

### **3.3.4 Source identification.**

The VariSeed 8.0 software comes with a full package including a seed finder algorithm. This function helps to automatically detect the sources present in the prostate on the CT images. Unfortunately, the algorithm at the Korle-Bu Teaching Hospital could not function during the period of the study. Hence the need for alternative methods and ways of identifying the source on the CT images.

The Hounsfield Unit (HU) was very useful in this regard. As the pointer is passed over the sources, their HU values are displayed below. Sources with high HU of about 1200 and above were considered as “real sources” while sources with low HU of about 1100 and below were classified as shadows or artifacts. Another challenge encountered was identifying and distinguishing of merged sources. Here the expertise and experience of the

medical physicist and other professionals involve in the process were brought to bare in dealing with this challenge.

### **3.3.5 Dosimetry.**

“After the contouring and identification of all the expected sources in the prostate, the VariSeed 8.0 software automatically calculates doses received by various organs using the AAPM TG 43 dose calculation algorithm. These doses which are displayed on the screen were recorded for all patients and saved for statistical analysis”.

### **3.3.6 Statistical analysis.**

Mean prostate volume was compared by pair-sample T-test with two significance. Prostate doses D90 and V150 results were compared by paired-sample test with 95% confidence interval (CI). The dose ratio were compared with unity (ratio=1) by one-sided T-Test with two tailed significance. Analysis was performed with SPSS (Version 20.0).

#### **3.3.6.1. P-value**

P-value is the level of marginal significance within a statistical hypothesis test representing the probability of the occurrence of a given event. The P-value is used as an alternative to rejection points to provide the smallest level of significance at which the null hypothesis would be rejected. A smaller P-value means there is stronger evidence in favor of the alternative hypothesis.

P-values are calculated using p-value tables or spreadsheet/statistical software. Because different researchers use different levels of significance when examining a question, a

reader may sometimes have difficulty comparing results from two different tests. For example, if two studies of returns from two particular assets were undertaken using two different significance levels, a reader could not compare the probability of returns for the two assets easily

### **3.3.6.2. T-test**

A t-test is an analysis of two populations means through the use of statistical examination, a t-test with two samples is commonly used with small sample sizes, testing the differences between the sample when the variance of two normal distributions are not know

The formula used to calculate the test is a ratio: The top portion of the ratio is the easiest portion to calculate and understand, as it is simply the difference between the means or averages of the two samples. The lower half of the ratio is a measurement of the dispersion, or variability, of the scores. The bottom part of this ratio is known as the standard error of the difference. To compute this part of the ratio, the variance for each sample is determined and is then divided by the number of individuals that compose the sample, or group. These two values are then added together, and a square root is taken of the result.

### **3.3.7 Limitations in the post implant dosimetry**

In this study there were some challenges encountered. First and foremost was the failure of the VariSeed 8.0 seed finder to function. The seed finder which was supposed to be used for identifying the radioactive sources on the CT images couldn't work, hence the need for alternative way of identifying the radioactive sources. The Hounsfield unit (Hu) was very useful in this regard. Sources with high Hu of about 1200 and above were selected as real

sources while sources with low Hu of about 900 and below were classified as shadows or artifact from the real sources.

Another challenge faced was identification of merged sources. Here the experience of the medical physicists and other professional were brought to bare in distinguishing these sources.



## CHAPTER FOUR

### RESULTS AND DISCUSSION

#### 4.1 Results

20 patients were chosen for the study after undergoing permanent prostate brachytherapy (prescription dose, 160 Gy and 110 Gy).

The mean intraoperative real-time prostate volume measured before the needle insertion was 35.13 cm<sup>3</sup> and that measured after 1 month of implant was 36.38 cm<sup>3</sup> with a mean ratio of 0.97 (p= 0.137) as shown in table 4.

**Table 4 prostate volumes (cm<sup>3</sup>) measured before and after 1 month of needle insertion**

Variables	Before implantation	1 month after implantation
Mean	35.13	36.38
Median	31.605	34.065
Range	14.69-75.97	13.69-76.23
P value		0.137

“The mean D90 value measured for the intraoperative real-time implant was found to be 141.84 Gy and post CT D90 value was found to be 140.99 Gy with a mean ratio of 0.844 (p = 0.441). The difference in the D90 values are shown in table 5 below”.

**Table 5 Mean Difference, SD, SEM and 95 % Confidence Interval (95 % CI) for Intraoperative (IO) and postimplant (CT) Dosimetry D90.**

Dose	Mean	Mean difference	SD	SEM	95% CI	P Value
IO90	141.84					
CT90	140.99	0.844	4.798	1.073	-1.401-3.090	0.441

However, there was a large difference values obtained for the intraoperative real-time V150 and the post CT V150. The mean volume measured for the intraoperative real-time was 59.23 % and the post CT V150 was 65.29 % with a mean difference of 6.066 % (p= 0.005). Table 6 shows the comparison between the two values.

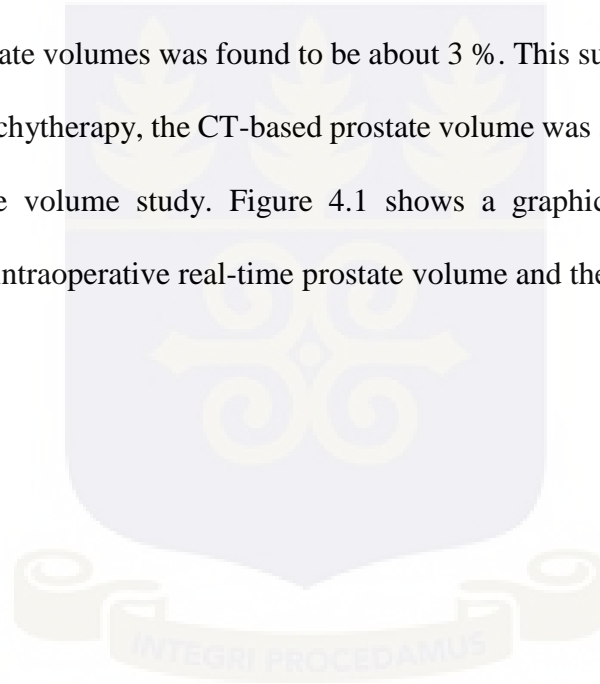
**Table 6 Mean Difference, SD, SEM and 95 % Confidence Interval (95 % CI) for Intraoperative (IO) and postimplant (CT) Dosimetry V150.**

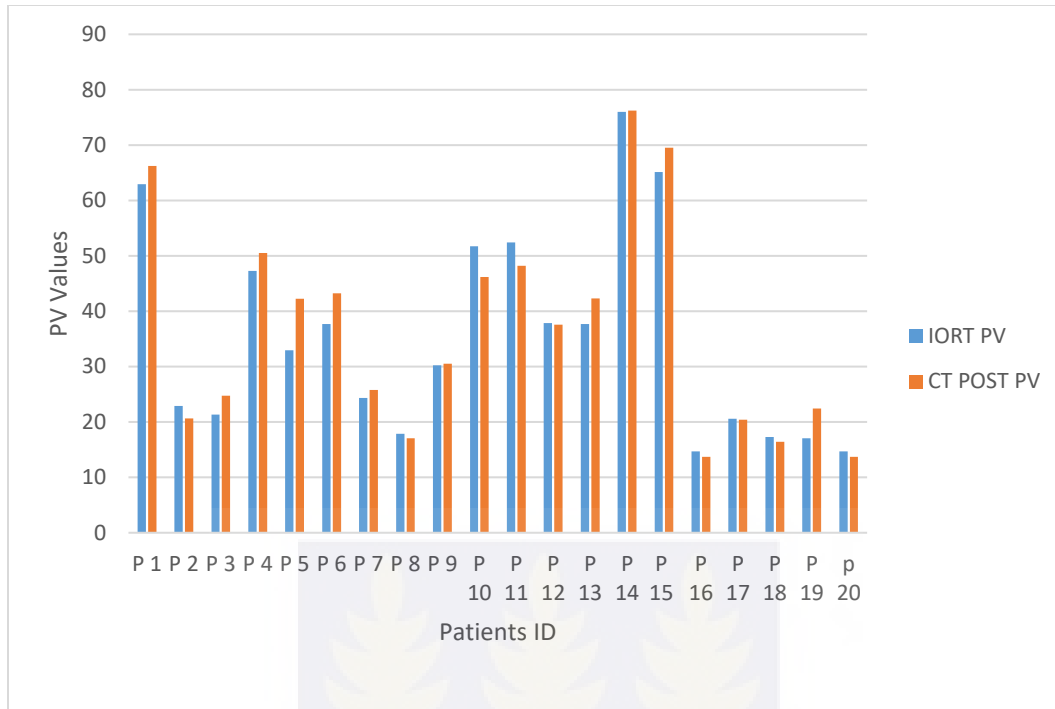
Dose	Mean	Mean difference	SD	SEM	95% CI	P Value
IO V150	59.23					
CT V150	65.29	6.066	8.564	1.915	-10.074-2.058	0.005

## 4.2 Discussion

This study demonstrate that the dosimetric representation system provides a close match to the 1 month postimplant dosimetry results. In this initial phase, no attempt was made to change or optimized the dosimetry results for the intraoperative procedure. Rather, emphasis was placed on determining whether the result of the intraoperative system were similar to the postimplant dosimetry results.

The mean difference between the intraoperative real-time prostate volume and the CT postimplant prostate volumes was found to be about 3 %. This suggests that on average, at 1 month after brachytherapy, the CT-based prostate volume was slightly larger than that in the intraoperative volume study. Figure 4.1 shows a graphical representation of the difference in the intraoperative real-time prostate volume and the CT postimplant prostate volume.





**Figure 4.1 Graph showing relationship between intraoperative real-time prostate volume (IORT PV) and CT postimplant prostate volume (CT POST PV)**

This however could be as a result of overestimation during contouring of the prostate on the CT base images. US images provide better soft tissue contrast and well defined borders of the prostate when compared with CT images where it is difficult to define boundary of the prostate, hence the prostate may be overestimated leading to increase in the CT postimplant prostate volumes. Secondly, US images are acquired at the end of the implantation session with the patient in the dorsal lithotomy position and under anesthesia similar to the patient setup used for intraoperative real-time planning and seed implantation”. “However, CT postimplant images are acquired using a supine head-first patient position at about 4 weeks post-implantation with different bladder and rectal fillings. According to (Waterman et al., 1999, Yue et al., 1998, Amdur et al., 1999) the prostate volumes measured using twister US imaging immediately post-implantation can

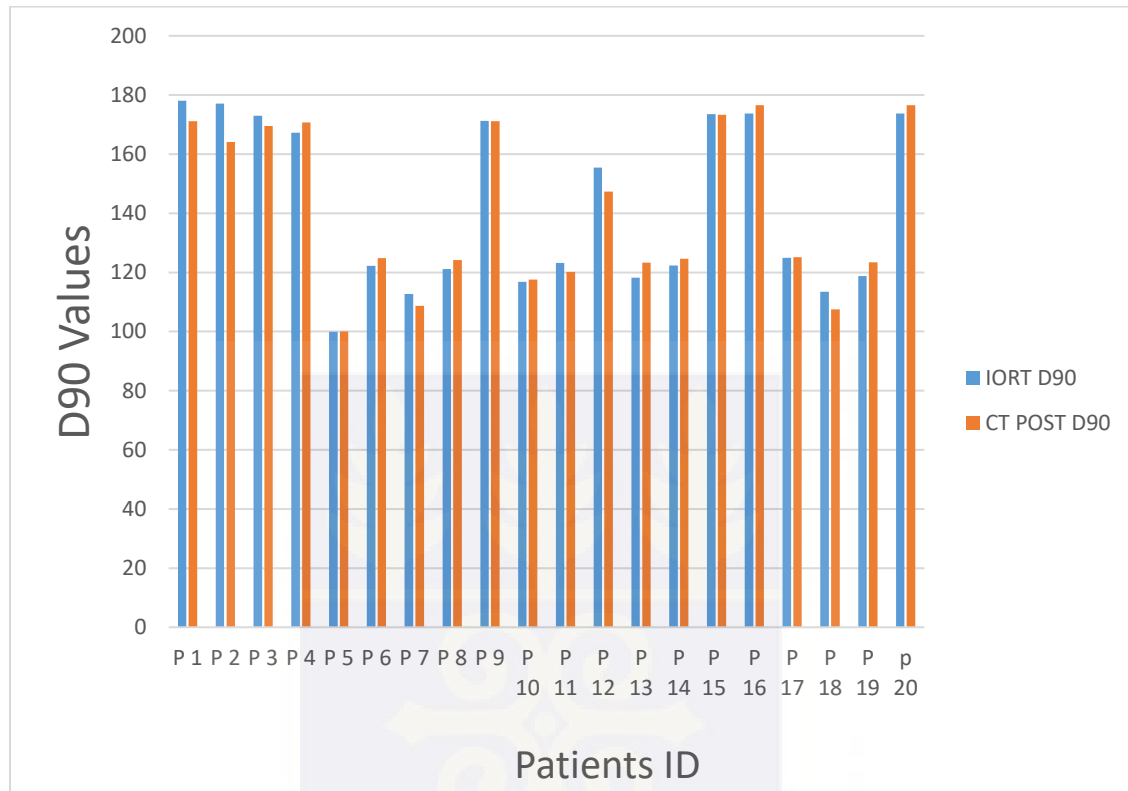
charge as large as 50 % from the volume measured using stepper US imaging prior to needle insertion in the operating room”.

During the actual implantation, the seeds are placed within the prostate capsule, and as the needle is withdrawn from the gland, they assume a more conformal position. The end result is that the seeds are placed within the target rather than on it or just outside of it, yielding a higher D90. The greater amount of high-dose regions seen on the CT study also result from the more conformal nature of the implant than what is represented in the operating room study.

For patients who undergo seed implantation within the preplan technique, patients' position realignment, prostate gland motion and needle insertion variability often made achieving planning doses difficult. The intraoperative real-time technique was developed to overcome many of these problems but as data from the study has demonstrated, planning doses are also not always achieved. “In a study of 297 men, Stock demonstrated that 98.5% of the patient who were implanted had a  $D_{90} \geq 140$  Gy, 25% of the patients had a  $D_{90}$  between 180 and 199.9 Gy and 18% had a  $D_{90} > 200$  Gy. To maximize disease control and limit morbidity, delivered doses should probably be kept with a narrower range. It has been suggested that, the  $D_{90}$  range for I-125 should be 140-180 Gy.

In this study, the difference in the  $D_{90}$  between the intraoperative real-time procedure and the post CT implant procedure was 0.85, suggesting that the intraoperative real-time dosimetry system is a true representation of the post implant dosimetry results. In addition the ratio of the intraoperative real-time results to the CT  $D_{90}$  result was 1.006. The 95 % CI was within 5 % suggesting that for the critical dose, very close approximation is

possible. Figure 4.2 shows a graphical representation of the comparison of the two parameters.

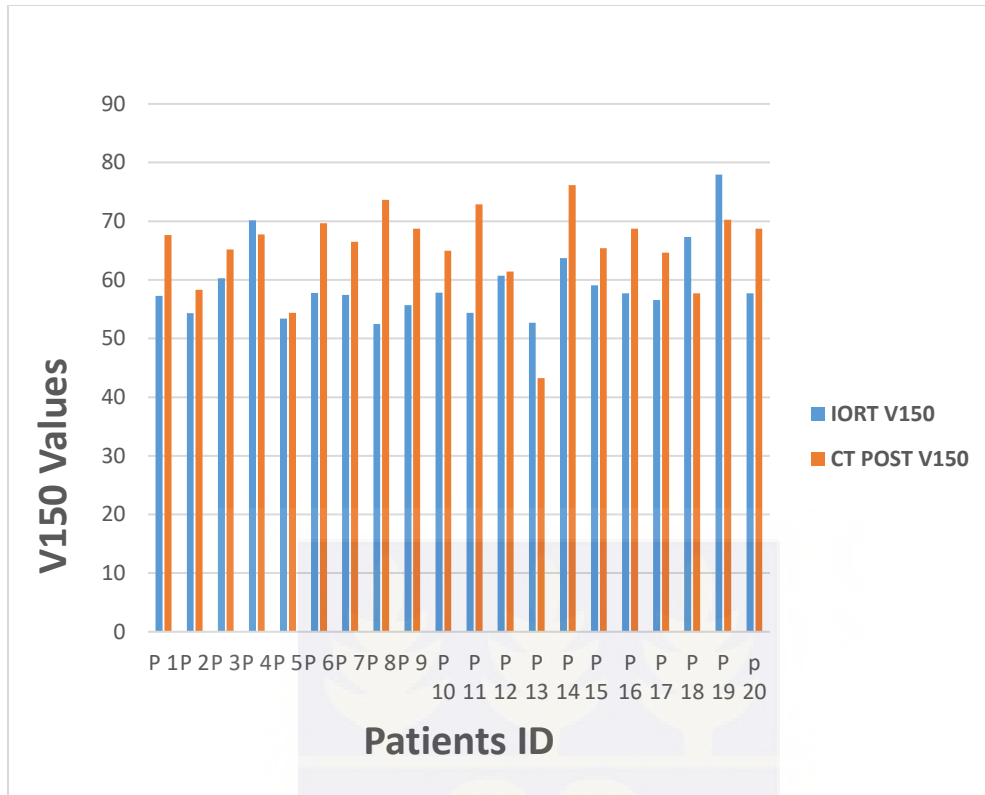


**Figure 4.2 Graph of intraoperative real-time D90 and CT postimplant D90**

However not all the patients have such close results, some of the discrepancies between the two can be explained by changes in prostate volume and shape because of edema during and after the implantation. The large difference in the V150 values between the intraoperative real-time and the CT Postimplant based dosimetry could be explained by the following, poor demarcation of the prostate gland and less certainty in localizing the apex and the base of the prostate gland on the CT scans during contouring, hence the prostate is overestimated. A slight change in the contour can significantly change these parameters. CT scans uses ionizing radiation which adds extra unwanted dose to the patient which

could increase the doses of the various parameters in the CT postimplant dosimetry which is not the case in the intraoperative real-time US images". Figure 4.3 shows a graphical comparison of the intraoperative real-time V150 and the CT postimplant V150 values





**Figure 4.3 Graph of intraoperative real-time V150 and CT postimplant V150**

## CHAPTER FIVE

### CONCLUSION AND RECOMMENDATION

The study sample in this research work was 20 patients who were treated with permanent prostate brachytherapy over the years. The selection of the 20 patients was random and was not based on any criteria. Despite the small sample size for the study, it was possible to analyze the results and compare the values obtained from the two dosimetric systems involved in the implant procedure. The intraoperative real-time was developed to obtain radioactive dose representation during the implant procedure. From the study, though small differences exist between the intraoperative real-time dosimetry and the CT postimplant dosimetry system because of changes in prostate volume and other factors, the results obtained suggest that the intraoperative real-time implant dosimetry system provides a good representation of the actual dose delivered and received by patients.

#### **Recommendation**

In this study the implanted seeds on the CT images were identified manually using the Hounsfield unit, Density and the experience of the professionals involved. It is therefore recommended that the seed finder algorithm of the VariSeed 8.0 software at the facility be worked on to make future study easier, faster and accurate.

Also, it is recommended that the facility design an in-house protocol for performing of postimplant dosimetry for all patients who undergo permanent prostate brachytherapy to determine the dose received by the patient so as to be able to trace any clinical complications arising from the procedure. Factors such as the duration for taking post

implant CT scan, specifications of the scan, professionals to be involved in the post implant dosimetry procedure, catheterization and others should be outlined clearly in the protocol.



## REFERENCES.

- Anderson, L. L., Mellenberg, D. E., Waterman, F. M., Wu, A., & Blasko, J. C. (1999). Permanent prostate seed implant brachytherapy : Report of the American Association of Physicists in Medicine Task Group No . 64 a ... , (64), 2054–2076.
- Ash, D., Flynn, A., Battermann, J., Reijke, T. De, Lavagnini, P., & Blank, L. (2000). ESTRO / EAU / EORTC recommendations on permanent seed implantation for localized prostate cancer, *57*, 315–321.
- Bastian, P. J., Boorjian, S. A., Bossi, A., Briganti, A., Heidenreich, A., Freedland, S. J., ... Zelefsky, M. J. (2012). High-risk prostate cancer: From definition to contemporary management. *European Urology*, *61*(6), 1096–1106.  
<http://doi.org/10.1016/j.eururo.2012.02.031>
- Beyer, D. C. (2001). The Evolving Role of Prostate Brachytherapy.
- Damber, J.-E., & Aus, G. (2008). Prostate cancer. *The Lancet*, *371*(9625), 1710–1721.  
[http://doi.org/10.1016/S0140-6736\(08\)60729-1](http://doi.org/10.1016/S0140-6736(08)60729-1)
- Elefsky, M. I. J. Z., Uban, D. E. A. K., Evy, L. A. B. L., Otters, P., Eyer, D. A. C. B., Lasko, J. O. H. N. C. B., ... Orwitz, E. R. I. C. M. H. (2007). MULTI-INSTITUTIONAL ANALYSIS OF LONG-TERM OUTCOME FOR STAGES T1 – T2 PROSTATE CANCER TREATED WITH PERMANENT SEED IMPLANTATION, *67*(2), 327–333. <http://doi.org/10.1016/j.ijrobp.2006.08.056>
- Faiz, M. (n.d.). No Title.

- Group, A. pm T. (2009). *on Dose Prescription and Reporting Methods for Permanent Interstitial Brachytherapy for Prostate Cancer Report of AAPM Task Group 137*.
- Heidenreich, A., Bellmunt, J., Bolla, M., Joniau, S., Mason, M., Matveev, V., ... Zattoni, F. (2011). EAU guidelines on prostate cancer. Part 1: Screening, diagnosis, and treatment of clinically localised disease. *European Urology*, 59(1), 61–71.  
<http://doi.org/10.1016/j.eururo.2010.10.039>
- Murphy, M. K., Piper, R. K., Greenwood, L. R., Mitch, M. G., Lamperti, P. J., Seltzer, S. M., ... Phillips, M. H. (2004). Evaluation of the new cesium-131 seed for use in low-energy x-ray brachytherapy. *Medical Physics*, 31(6), 1529–1538.  
<http://doi.org/10.1118/1.1755182>
- Nag, S., Beyer, D., Friedland, J., Grimm, P., & Nath, R. (1999). American brachytherapy society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *International Journal of Radiation Oncology Biology Physics*, 44(4), 789–799. [http://doi.org/10.1016/S0360-3016\(99\)00069-3](http://doi.org/10.1016/S0360-3016(99)00069-3)
- Nath, R., Anderson, L. L., Meli, J. a, Olch, a J., Stitt, J. a, & Williamson, J. F. (1997). Code of practice for brachytherapy physics: report of the AAPM Radiation Therapy Committee Task Group No. 56. American Association of Physicists in Medicine. *Medical Physics*, 24(56), 1557–1598. <http://doi.org/10.1118/1.597966>
- Otters, L. O. P., Ao, Y. I. C., Alugaru, E. M. E. L. C., Orre, T. A. T., Earn, P. A. U. L. F., & Ang, X. I. A. O. O. N. G. W. (2001). A COMPREHENSIVE REVIEW OF CT-BASED DOSIMETRY PARAMETERS AND BIOCHEMICAL CONTROL IN PATIENTS TREATED WITH PERMANENT PROSTATE BRACHYTHERAPY,

50(3), 605–614.

Peschel, R. E., Ph, D., Chen, Z., Ph, D., Roberts, K., Nath, R., & Ph, D. (1999). Long-Term Complications with Prostate Implants : Iodine-125 vs . Palladium-103, 288(November 1998), 278–288.

Podgorsak, et al., 2005. (2005a). Radiation Biology: a Handbook for Teachers and Students. *Training Course Series*, 42, 166. <http://doi.org/10.1007/s00247-008-1027-2>

Podgorsak, et al., 2005. (2005b). Radiation Oncology Physics : A Handbook for Teachers and Students.

Rivard, M. J., Coursey, B. M., Dewerd, L. A., Hanson, W. F., Ibbott, G. S., Mitch, M. G., & Williamson, J. F. (2004). Update of AAPM Task Group No . 43 Report : A revised AAPM protocol for brachytherapy dose calculations, (43), 633–674. <http://doi.org/10.1118/1.1646040>

Rosenberg, I. (2008). Radiation Oncology Physics: A Handbook for Teachers and Students. *British Journal of Cancer*, 98, 1020. <http://doi.org/10.1038/sj.bjc.6604224>

Salembier, C., Lavagnini, P., Nickers, P., Mangili, P., & Rijnders, A. (2007). Tumour and target volumes in permanent prostate brachytherapy : A supplement to the ESTRO / EAU / EORTC recommendations on prostate brachytherapy, 83, 3–10. <http://doi.org/10.1016/j.radonc.2007.01.014>

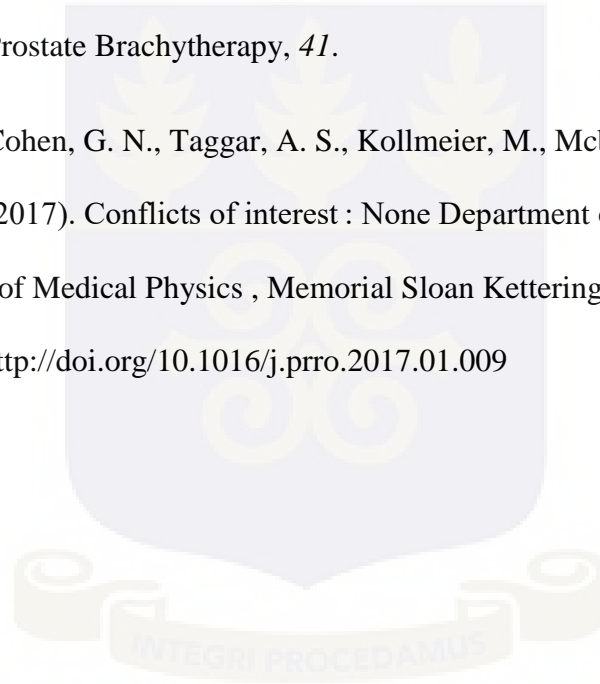
Shanahan, T. G., Mueller, P. W., Roszhart, D. A., Severino, W. C., Bhate, A. D., Nanavati, P. J., ... Maxey, R. B. (2004). Image guided I125 prostate brachytherapy

with Hybrid Interactive Mick technique in the community setting: How does it compare? *Technology in Cancer Research & Treatment*, 3(2), 209–215.

Stone, N. N. (2005). URINARY MORBIDITY AND INCONTINENCE FOLLOWING TRANSURETHRAL RESECTION OF THE PROSTATE AFTER BRACHYTHERAPY, 173(March), 808–812.  
<http://doi.org/10.1097/01.ju.0000152698.20487.0e>

Stone, N. N., & Stock, R. G. (2002). European Urology Complications Following Permanent Prostate Brachytherapy, 41.

Zelevsky, M. J., Cohen, G. N., Taggar, A. S., Kollmeier, M., McBride, S., Mageras, G., & Zaider, M. (2017). Conflicts of interest : None Department of Radiation Oncology , Department of Medical Physics , Memorial Sloan Kettering. *Practical Radiation Oncology*. <http://doi.org/10.1016/j.prro.2017.01.009>



## APPENDICES

## APPENDIX A

**Patients' information obtained after real-time implant using VariSeed 8.0 software**

<b>Patient ID</b>	<b>Age</b>	<b>Year of treatment</b>	<b>Country</b>	<b>Prostate volume</b>	<b>Prescribed dose(Gy)</b>	<b>Number of needles</b>	<b>Number of sources</b>	<b>Source activity(U)</b>
P1	47	2015	Ghana	62.91	160	21	80	0.685
P2	65	2015	Ghana	22.9	160	15	47	0.583
P3	70	2015	Ghana	21.31	160	12	39	0.677
P4	72	2016	Ghana	47.3	160	21	68	0.688
P5	58	2016	Ghana	32.96	110	19	67	0.352
P6	61	2015	Ghana	37.68	110	19	58	0.465
P7	58	2015	Ghana	24.35	110	13	41	0.493
P8	61	2016	Ghana	17.85	110	15	33	0.46
P9	60	2016	Benin	30.25	160	18	57	0.575
P10	69	2016	Bukina Faso	51.74	110	18	70	0.455
P11	67	2015	Ghana	52.4	110	20	58	0.569
P12	71	2015	Ghana	37.85	160	18	53	0.677
P13	64	2014	Ghana	37.69	110	18	43	0.629
P14	66	2013	Ghana	75.97	110	22	80	0.583
P15	59	2016	Ghana	65.14	160	22	75	0.747

P16	68	2015	Ghana	14.69	160	13	34	0.583
P17	70	2016	Ghana	20.56	110	13	44	0.386
P18	63	2016	Ghana	17.28	110	14	35	0.497
P19	70	2016	Ghana	17.04	110	15	44	0.46
P20	69	2016	Ghana	14.69	160	13	34	0.583



**APPENDIX B**

**Patients' information obtained after CT postimplant dosimetry using VariSeed 8.0 software**

<b>Patient ID</b>	<b>Age</b>	<b>Year of treatment</b>	<b>Country</b>	<b>Prostate volume</b>	<b>Prescribed dose(Gy)</b>	<b>Number of needles</b>	<b>Number of sources</b>	<b>Source activity(U)</b>
P1	47	2015	Ghana	66.25	160	21	80	0.685
P2	65	2015	Ghana	20.63	160	15	47	0.583
P3	70	2015	Ghana	24.75	160	12	39	0.677
P4	72	2016	Ghana	50.53	160	21	68	0.688
P5	58	2016	Ghana	42.24	110	19	67	0.352
P6	61	2015	Ghana	43.21	110	19	58	0.465
P7	58	2015	Ghana	25.77	110	13	41	0.493
P8	61	2016	Ghana	17.05	110	15	33	0.46
P9	60	2016	Benin	30.53	160	18	57	0.575
P10	69	2016	Burkina Faso	46.17	110	18	70	0.455
P11	67	2015	Ghana	48.18	110	20	58	0.569
P12	71	2015	Ghana	37.6	160	18	53	0.677
P13	64	2014	Ghana	42.32	110	18	43	0.629
P14	66	2013	Ghana	76.23	110	22	80	0.583
P15	59	2016	Ghana	69.53	160	22	75	0.747

P16	68	2015	Ghana	13.69	160	13	34	0.583
P17	70	2016	Ghana	20.39	110	13	44	0.386
P18	63	2016	Ghana	16.45	110	14	35	0.497
P19	70	2016	Ghana	22.46	110	15	44	0.46
P20	69	2016	Ghana	13.69	160	13	34	0.583



## APPENDIX C

Patient ID	Age	Year of treatment	Prescribed dose(Gy)	Source activity(U)	Prostate	Prostate	Difference ( %)
					Real-time volume(cc)	CT postimplant volume(cc)	
P1	47	2015	160	0.685	62.91	66.25	5.309
P2	65	2015	160	0.583	22.9	20.63	-9.913
P3	70	2015	160	0.677	21.31	24.75	16.143
P4	72	2016	160	0.688	47.3	50.53	6.829
P5	58	2016	110	0.352	32.96	42.24	28.155
P6	61	2015	110	0.465	37.68	43.21	14.676
P7	58	2015	110	0.493	24.35	25.77	5.832
P8	61	2016	110	0.46	17.85	17.05	-4.482
P9	60	2016	160	0.575	30.25	30.53	0.926
P10	69	2016	110	0.455	51.74	46.17	-10.765
P11	67	2015	110	0.569	52.4	48.18	-8.053
P12	71	2015	160	0.677	37.85	37.6	-0.661
P13	64	2014	110	0.629	37.69	42.32	12.284
P14	66	2013	110	0.583	75.97	76.23	0.342
P15	59	2016	160	0.747	65.14	69.53	6.739
P16	68	2015	160	0.583	14.69	13.69	-6.807
P17	70	2016	110	0.386	20.56	20.39	-0.827

P18	63	2016	110	0.497	17.28	16.45	-4.803
P19	70	2016	110	0.46	17.04	22.46	31.808
P20	69	2016	160	0.583	14.69	13.69	-6.807

**Comparison of patients prostate volume between real-time and CT Postimplant**



**APPENDIX D****Comparison of patients D90 between real-time and CT Postimplant**

<b>Patient ID</b>	<b>Age</b>	<b>Year of treatment</b>	<b>Prescribed dose(Gy)</b>	<b>Source activity(U)</b>	<b>D90 (Gy) Real-time</b>	<b>D90 (Gy) CT postimplant</b>	<b>Difference (%)</b>
P1	47	2015	160	0.685	178.07	171.12	4.061
P2	65	2015	160	0.583	177.14	164.15	7.913
P3	70	2015	160	0.677	172.93	169.51	2.018
P4	72	2016	160	0.688	167.29	170.7	-1.998
P5	58	2016	110	0.352	99.98	100.00	-0.020
P6	61	2015	110	0.465	122.24	124.8	-2.051
P7	58	2015	110	0.493	112.71	108.69	3.699
P8	61	2016	110	0.46	121.1	124.19	-2.051
P9	60	2016	160	0.575	171.3	171.14	0.093
P10	69	2016	110	0.455	116.85	117.61	-0.646
P11	67	2015	110	0.569	123.16	120.19	2.471
P12	71	2015	160	0.677	155.4	147.35	5.463
P13	64	2014	110	0.629	118.18	123.33	-4.176
P14	66	2013	110	0.583	122.34	124.64	-1.845
P15	59	2016	160	0.747	173.49	173.31	0.104
P16	68	2015	160	0.583	173.71	176.53	-1.60

P17	70	2016	110	0.386	124.97	125.16	-0.15
P18	63	2016	110	0.497	113.45	107.51	5.53
P19	70	2016	110	0.46	118.76	123.43	-3.73
P20	69	2016	160	0.583	173.71	176.53	1.60



## APPENDIX E

## Comparison of patients V15 % between real-time and CT Postimplant

Patient ID	Age	Year of treatment	Prescribed dose(Gy)	Source activity(U)	V150 % Real-time	V150 % CT postimplant	Difference (%)
P1	47	2015	160	0.685	57.28	67.65	18.104
P2	65	2015	160	0.583	54.33	58.28	8.181
P3	70	2015	160	0.677	60.26	65.19	-3.420
P4	72	2016	160	0.688	70.17	67.77	1.817
P5	58	2016	110	0.352	53.38	54.35	20.564
P6	61	2015	110	0.465	57.77	69.65	15.833
P7	58	2015	110	0.493	57.41	66.5	40.358
P8	61	2016	110	0.46	52.48	73.66	23.335
P9	60	2016	160	0.575	55.71	68.71	12.366
P10	69	2016	110	0.455	57.82	64.97	33.983
P11	67	2015	110	0.569	54.38	72.86	1.087
P12	71	2015	160	0.677	60.73	61.39	-17.938
P13	64	2014	110	0.629	52.68	43.23	19.504
P14	66	2013	110	0.583	63.73	76.16	10.680
P15	59	2016	160	0.747	59.08	65.39	19.054
P16	68	2015	160	0.583	57.73	68.73	14.192
P17	70	2016	110	0.386	56.58	64.61	-14.275

P18	63	2016	110	0.497	67.32	57.71	-9.817
P19	70	2016	110	0.46	77.93	70.28	19.054
P20	69	2016	160	0.583	57.73	68.73	19.054

