Characterization of the performance of the new MOSkin dosimeter as a quality assurance tool for pulsed dose-rate (PDR) prostate brachytherapy, and the effect of rectal heterogeneity on the dose delivered to the rectal wall

Ian S. Kwan
University of Wollongong


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CHARACTERIZATION OF THE PERFORMANCE OF THE NEW MOSKIN
DOSIMETER AS A QUALITY ASSURANCE TOOL FOR PULSED
DOSE-RATE (PDR) PROSTATE BRACHYTHERAPY, AND THE EFFECT OF
RECTAL HETEROGENEITY ON THE DOSE DELIVERED TO THE RECTAL
WALL

by

Ian Samuel Kwan

A thesis submitted in fulfilment of the
requirements for the Doctor of Philosophy
degree in the School of Engineering Physics at the
University of Wollongong

03/06/2009

Thesis supervisors: Professor Anatoly Rosenfeld, Dr. Michael Lerch, Dr. Joseph Bucci
(St. George Hospital)
CERTIFICATION

I, Ian Samuel Kwan, declare that this thesis, submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the School of Engineering Physics, University of Wollongong, is wholly my own work unless otherwise referenced or acknowledged. The document has not been submitted for qualifications at any other academic institution.

Ian Samuel Kwan

June 03, 2009
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ABSTRACT

Brachytherapy is a common treatment modality used for treating prostate cancer. The radiation is emitted from within the prostate, which focuses the damage on the tumour rather than the surrounding healthy tissue. However, due to the close proximity of the rectum to the prostate, there is a possibility that the rectum will receive too much radiation dose during prostate treatment. This may lead to post-treatment rectal complications that range in severity from general rectal discomfort and bleeding, to the development of a rectal fistula that may require surgical intervention. Currently, there is no real-time quality assurance tool used to verify that the rectum does not receive too much radiation dose.

The Centre for Medical Radiation Physics (CMRP) at the University of Wollongong, Australia, has developed a new MOSFET dosimeter called the MOSkin with a unique packaging design that should demonstrate some benefits over other MOSFET dosimeters. The MOSkin can potentially serve as a real-time rectal dosimeter for use during a PDR or HDR brachytherapy treatment.

The general aim of this research is to characterise the performance of the new MOSkin dosimeter, and to determine whether the unique design of the MOSkin demonstrates dosimetric advantages over other dosimeters for brachytherapy, and in certain other applications. The performance characteristics of the MOSkin were explored by exposing it to a 6 MV x-ray field delivered by a linear accelerator (LINAC), and also with an Ir-192 PDR brachytherapy source.

The MOSkin was irradiated with a 6 MV, 10×10 cm$^3$ photon beam with the gantry set to 100 cm source-to-surface distance, and its dose response was compared to the response of a CC13 compact ionization chamber, and a couple of fiber optic dosimeters.
The fiber optic dosimeters had either a 0.5 or 1 mm diameter scintillating crystal attached to one end of the optical fiber. The MOSkin’s ability to measure the skin dose to a depth of 0.07 mm, which corresponds to the nominal depth of the basal cell layer of the epidermis, was compared to Attix chamber and fiber optic dosimeter measurements, along with skin dose measurements reported in other studies found in the literature. My research was primarily concerned with dosimetry at shallow depths in the phantom because it was believed that the MOSkin’s packaging design would prove advantageous over other dosimeters at such depths.

With regards to brachytherapy, the dose response of the MOSkin was compared to the response of a RADFET dosimeter within a rectal phantom. Brachytherapy treatment planning systems (TPS) calculate the dose by assuming that the human body is a large, homogeneous water-equivalent material. The effect that a hollow, air-filled rectal cavity has on the anterior rectal dose was investigated by measuring the dose delivered to the inner wall of a rectal phantom while it was empty, and comparing dose measurement to the dose measured within a homogeneous rectal phantom, and the dose calculated by the TPS. The results were also corroborated by Monte Carlo simulations written with the Geant4 toolkit.

The results of an early stage, Phase II clinical trial at St. George Cancer Care Centre are discussed. The MOSkin was used to measure the dose delivered to the anterior wall of the patient’s rectum during PDR brachytherapy patients during treatment, and the results are compared to the dose calculated by the TPS. The results were also compared to the observations made during the phantom study.
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Refereed Publications


Conferences


5. Ian S. Kwan, Andrew Howie, Dean Cutajar, Joseph Bucci, Peter Metcalfe, Martin Butson, Martin Carolan, Michael Lerch, and Anatoly Rosenfeld, "Suitability of the new MOSkin detector for Skin Dosimetry”, *Engineering and the Physical Sciences in Medicine (EPSM)*, Oral Presentation, October 2007, Fremantle, Australia.


CHAPTER 1
INTRODUCTION

Brachytherapy is a common treatment modality used to treat prostate cancer. The radiation is given off inside the tumour, allowing the damage to be focused on the tumour rather than the surrounding normal tissue. High dose-rate (HDR) and pulsed dose-rate (PDR) prostate brachytherapy are two similar forms of treatment that involve the transfer of an Iridium-192 ($^{192}$Ir) source through a set of catheters, and into the prostate so that the tumour is irradiated from within the prostatic capsule. Pulsed Dose-rate (PDR) brachytherapy is similar to the delivery of an HDR brachytherapy treatment, except that the Ir-192 source used in PDR brachytherapy has a smaller amount of Ir-192 being contained within the source’s steel casing. Consequently, the activity of the source is lower, the source’s physical dimensions are slightly shorter in length, and the treatment times are greater.

HDR/PDR brachytherapy provides radiobiological and dosimetric advantages over external beam radiotherapy. [8] By treating the disease with a source contained within the prostate, the dose is distributed so that it conforms well to the size and shape of the prostate, and is better than the distribution achievable using external conformal treatment modalities such as intensity modulated radiotherapy (IMRT). The steep dose gradient that surrounds an Ir-192 source ensures that the large majority of the dose is delivered within a distance of around 10 mm from the source, and that relatively low doses are delivered to tissue located beyond approximately 20 mm from the source. However, due to the close proximity of the urethra and rectum to the prostate, there is a possibility that non-cancerous cells will receive a very high radiation dose. A high dose to the rectum may lead to rectal complications following treatment. Symptoms of rectal toxicity include general rectal discomfort, bleeding, and if the rectum is severely over-irradiated, then the
development of a fistula that may require surgery. The incidence of late rectal complications depends on a number of factors, but the clearest causation of post-treatment rectal complications is the total radiation dose delivered to the rectum. [9]

Currently, there is no real-time quality assurance tool to verify that the prostate disease is treated according to the plan, or to ensure that the rectum does not receive a high radiation dose. Thermoluminescent dosimeters (TLD) have been used as a form of quality assurance for HDR/PDR brachytherapy, but the dosimetric information provided by TLDs is acquired many hours following the treatment, which does not aid the oncologist to avoid over-irradiating the prostate while the treatment is in progress. The successful development of a small, real-time dosimeter would be of great appeal for those who wish to have a dosimeter capable of providing dosimetric information while the patient is being treated.

The Centre for Medical Radiation Physics (CMRP) at the University of Wollongong (Australia) has developed a new MOSFET dosimeter called the MOSkin. Like all MOSFET dosimeters, the MOSkin is capable of providing real-time dosimetric information to the radiation oncologist and radiotherapist while the patient is being treated. The MOSkin differentiates itself from other commercially available MOSFET dosimeters with its unique packaging design, which should exhibit some benefits over conventional MOSFET dosimeters. These benefits will be explored in Chapter 3 and 4.

The general aim of this research is to characterize the performance of the new MOSkin dosimeter, and to determine whether the unique design of the MOSkin demonstrates the advantages over other real-time dosimeters as intended.

Chapter 2 of this thesis is divided into three main sections. The chapter begins with a discussion on the potential radiobiological advantage of treating prostate cancer with
HDR brachytherapy. Specifically, the low $\alpha/\beta$-ratio of prostate cancer, and the radiobiological significance of the prostate’s slow rate of proliferation on treatment fractionation are discussed. This is followed by a general discussion on prostate cancer, including how the severity of prostate cancer is graded and staged, and the different methods in which prostate cancer may be treated. A number of ideas and clinical terminology are introduced in this section that are necessary to fully understand the discussion in subsequent chapters. The final section discusses the effects of radiation on the physical properties of a MOSFET, and how these changes can be measured, and related back to the absorbed dose.

Chapter 3 introduces the MOSkin dosimeter, where its performance characteristics are explored when irradiated with a 6 MV photon beam delivered from a linear accelerator (LINAC). The results are compared to the response of a CC13 compact ionization chamber, and a couple of fiber optic dosimeters with either a 0.5 or 1 mm diameter scintillating crystal attached to one end of the optical fiber cable. Emphasis is placed on the dosimetric ability of the MOSkin near the surface of the phantom, and in the build-up region of the depth dose curve (0–15 mm depth in water), where the MOSkin’s unique packaging design is believed to offer its greatest advantage over other types of small, real-time dosimeters. The MOSkin’s ability to measure the skin dose, particularly at the basal cell layer of the epidermis (70 $\mu$m skin depth), is compared to that of the RADFET dosimeter, a commercially available MOSFET dosimeter product. The surface dose response of the two MOSFET dosimeters is compared to the response of both an Attix chamber, and a parallel-plate extrapolation ionization chamber.

In Chapter 4, the performance characteristics of the MOSkin dosimeter are explored when irradiated with an Iridium-192 PDR brachytherapy source. The ability of the MOSkin to measure the dose at various distances from the source, and from various angles of irradiation, are investigated and compared to the response of the RADFET dosimeter when
irradiated under the same conditions. The rectal cavity, which is treated as a completely homogeneous, water-equivalent organ by brachytherapy treatment planning systems, is emptied prior to treatment. The effect that the gas in the rectal cavity has on the dose distribution was investigated, and compared to the dose calculated by the planning software. Experimental dose measurements are obtained with the MOSkin and RADFET within a solid water-equivalent rectal phantom, and are compared to the dose calculated by the treatment planning system. The experimental results are also corroborated with dose estimates acquired via Monte Carlo simulations written using the Geant4 toolkit. The relationship between rectal cavity diameter, source distance, and the effect that the air contained in the rectal cavity has on the scatter dose distribution, and the rectum dose, is also explored via Monte Carlo simulation.

Chapter 5 describes the early stages of the Phase II clinical trial at St. George Cancer Care Centre, where the MOSkin was used to measure the rectal dose of PDR brachytherapy patients during treatment. The PDR prostate brachytherapy procedure at St. George Cancer Care Centre is described in detail. It is necessary to understand the treatment procedure in order to understand the experimental methodology, because additional steps were added to the procedure over time in order to obtain optimal results. The dose measurement obtained for each treatment is analysed and compared to the dose calculated by the PLATO Brachytherapy treatment planning system, while the evolution of the methodology, and the implication of each change, is described. The chapter concludes with a discussion on how the dose information obtained with the MOSkin dosimetry system can be applied clinically, which should be different from the analysis used for this study.
CHAPTER 2
LITERATURE REVIEW

2.1 Radiobiology and treatment complications

This discussion begins with a section that covers basic radiation physics, radiation biology, and the biological basis for treating prostate cancer with HDR brachytherapy rather than other forms of treatment. The study of radiation interactions is quite broad, so the emphasis in this discussion will concentrate primarily on the physical and chemical effects of photon interactions that are relevant to this thesis. This will be followed by a discussion on radiation biology, which will cover the mechanisms for inducing DNA strand breaks, the mechanism of cell killing, the effect of fractionation and dose-rate on cellular response, and the significance of the $\alpha/\beta$ ratio on prostate cancer treatment. The last few subsections should provide insight as to how the delivery of 5–7 Gy per fraction in HDR brachytherapy may provide a radiobiological benefit over other treatment modalities, which usually deliver standard 2 Gy fractions.

2.1.1 Quick Introduction to Radiation Physics

Ever since Roentgen first discovered a new and mysterious kind of ray that he later called the $x$-ray, as it could blacken photographic film contained inside a light-proof box, the potential of x-rays for diagnostic and therapeutic applications was realized. [7, 10] Antoine Henri Becquerel discovered radioactivity in 1898, and soon performed the very first radiobiology experiment on himself by accidentally leaving a small vial of radium in his pocket. He noted the skin erythema that appeared 2 weeks later, and the several weeks it required to heal. The same experiment was deliberately repeated later by Pierre Curie,
using his own forearm as the target of the "radium burn". While the study of radiation effects on biology was very crude, and in hindsight, extremely dangerous in the late 1800s, the study of radiobiology today has advanced alongside our understanding of radiation physics.

The absorption of energy during an interaction between radiation and matter will either lead to an excited state, or an ionization. Excitation occurs when an electron in an atom or molecule gains energy due to some external factor such as heat or a photon interaction with the molecule, and rises to a higher energy level. The electron may de-excite later so that it falls back down to a lower energy level, releasing energy in the form of radiation. If the interaction with the target material is energetic enough for an electron to exit the material, this radiation is referred to as ionizing radiation. The important characteristic of an ionization event is the release of around 33 eV of energy, which is more than enough energy to break a chemical bond. Ionizing radiation can be further broken down into electromagnetic (EM) radiation such as x-rays, and particulate radiation. Particulate radiation includes neutron particles and charged particle radiation such as electrons, protons, alpha (α) particles (doubly-charged helium), and heavy charged particles. Charged particles are characterized by their ability to directly ionize atoms, disrupting the atomic structure of the target material as they pass through. This is in contrast to electromagnetic radiation, which does not cause changes directly. The term heavy charged particles refer to the nuclei of elements such as carbon and neon, which are accelerated to energies of up to 400 MeV per nucleon in order to be energetic enough for radiotherapeutic applications. [11] While there is a great deal of interest in the application of protons and heavy ions for radiotherapy, the application is still quite rare. The discussion here will consider only EM radiation such as x- and gamma-radiation, while particulate radiation will not be discussed further.

Most radiobiological experiments have studied cellular response following their exposure
to x-rays and gamma (γ) radiation. These two types of EM radiation are identical in their physical character, differing only in their origin. X-rays are produced outside the nucleus, usually from the deceleration of high energy electrons when made to strike a target material. The kinetic energy lost by the electrons is converted into photons. In contrast, γ-rays are produced by unstable nuclei, or radioactive material. When converting into a more stable form, a nucleus emits its excess energy in the form of γ-rays.

In a vacuum, EM radiation moves at a velocity equal to the speed of light, \( c \), or \( 3.0 \times 10^8 \text{ m/s} \). The speed of light in air is nearly equal to its speed in a vacuum, so the slight difference in speed is usually not accounted for when considering air as the medium. Conceptually, x-rays and γ-rays can be thought of as waves that vary with time, and can be described by both its frequency (\( \nu \)) and wavelength (\( \lambda \)). The distance between two directly neighbouring peaks of the wave is described as its wavelength, while the number of waves that pass a particular point per second is described as the frequency of the wave. The total speed of the wave is equal to the frequency multiplied by the wavelength of the wave, or

\[
c = \nu \lambda
\]  

An x-ray can also be thought of as a discrete bundle of energy, or photon. The energy of a single photon is related to the frequency of the EM radiation, \( \nu \), and proportional to Planck’s constant, \( h \),

\[
E = h \nu
\]  

For example, if the EM frequency is large, the energy of the photon is also large, while the wavelength must be short (Eq. 2.1). When discussing radiobiology, the concept of x-rays being comprised of bundles of energy is more important than the wave properties they exhibit, as the effect of energy deposition in cells and tissue by incident radiation is the major focus of radiobiology.
2.1.2 Interactions of X-rays with Matter

When x-rays strike a target, the type of interaction that occurs will depend mainly on the energy of the x-rays, but also on the composition of the absorbing material. In soft tissue, the type of interaction most dominant at photon energies $< 30$ keV is called the *photoelectric effect*, sometimes referred to as *photoelectric absorption*. In the photoelectric effect, the incident x-ray photon interacts with an electron in the K, L, or M shell of an atom of the target material, although photoelectric interactions with an electron in the most inner shell, the K-shell, is most probable. The energy of the photon is absorbed entirely by the electron, which now has enough energy to leave the atom. The product of this interaction is a free electron, or *photo-electron*, that is released from its orbit, and a vacancy left in the atomic shell of the atom. Some of the energy absorbed by the electron is used to overcome the binding energy with the atom, while the remaining energy is manifested as the electron’s kinetic (motion) energy. This process is illustrated in Figure 2.1.

The kinetic energy of the ejected electron allows it to travel over a short distance in the target material and cause damage to other atoms by ionizing them, breaking chemical bonds. Following the emission of the photoelectron from an atomic shell, the atom relaxes by filling the new vacancy in the shell with an electron from an outer shell. Electrons in outer shells have a greater amount of energy than those electrons which reside in shells closer to the atomic nucleus. When the vacancy left by the photoelectron is filled by an electron from an outer shell, the excess energy released by the electron is either emitted as an x-ray of characteristic energy, or transferred to another electron, resulting in a second electron emission. The x-ray emitted as a result of electron migration from a outer shell to an inner shell is referred to as a *characteristic x-ray*, as the energy of the newly emitted photon can only be of certain energies — namely, the energy difference of the
two shells. The photon energy is very low, and of such little biological significance that it is generally ignored. The emission of a second electron from the interaction is called the Auger effect, and the second electron is referred to as an Auger electron. The interaction of secondary electrons produced from the primary interaction is what is observed as biologic damage, not the interaction of the incident photon itself.
The Compton Effect is another type of photon interaction that may occur in the medium. At photon energies $> 30 \text{ keV}$ in soft tissue, the probability of an incident photon undergoing a Compton interaction in tissue becomes greater than the probability of undergoing
photoelectric interaction. In the Compton process, the incident x-ray has a far greater energy than the binding energy of the electron it interacts with. Rather than absorbing all the photon energy, only a small fraction of the photon energy is imparted to the electron during an interaction. This energy is enough to free the electron. The scattered photon continues to travel through the material with the remaining energy, and either participates in more Compton scatter interactions, or is absorbed in a photoelectric interaction. The overall products of a Compton interaction are a photon of decreased energy, and a Compton electron that escapes its orbital. The amount of energy lost by the photon in the interaction varies over a large range; sometimes it transfers a lot of energy to the electron, and sometimes it transfers very little. The energy transferred to a Compton electron is related to the scatter angle, or change in travel direction between the incident and scattered photons. In practice, an x-ray beam delivered by a medical linear accelerator (LINAC) contains a large number of photons, and these photons will interact with the vast number of atoms in the target material, scattering at all possible angles. Due to the number of photons incident on a material, nearly all possible energy losses are produced at some point during irradiation.

The probability of photoelectric absorption occurring in the target material is described by the mass absorption coefficient, which varies greatly with the atomic number (Z) of the target material, and the energy of the photon. In fact, the mass absorption coefficient is approximately proportional to $Z^3$. While the probability of a Compton scatter interaction is far less dependent on Z. [12] Diagnostic radiology (imaging) takes advantage of the differential in absorption probability in soft tissue, fatty tissue, and bone. By using 40–125 keV photons, photoelectric absorption still constitutes a large proportion of the interactions in the body, making high-Z materials in the body, such as bone, easily differentiable from soft tissue. Lower energy photons (< 40 keV) that are more favourable to photoelectric absorption are not chosen for diagnostic imaging, as they would mostly
be absorbed by the body, whether it’s bone or soft tissue. This would lead to poor differentiation between different tissue types, while also providing unnecessary radiation to the patient due to the high probability of photon absorption. Accordingly, photons with energies $> 200 \text{ keV}$ are not used for imaging applications due to their low probability of being absorbed in the body, and greater probability of undergoing a Compton interaction. As Compton scatter is mostly independent on $Z$, it would provide minimal differential in scatter probability between materials of different atomic number. [12]

2.1.3 The Biological Effect of X-rays on DNA

2.1.3.1 DNA Strand Breaks
As summarized nicely by Hall [13] and Metcalfe et al., [14] the biological effects of radiation are likely the result of damage to the target cell’s DNA. Deoxyribonucleic acid (DNA) is a molecule comprised of two strands held together with hydrogen bonds, and twisted to form a double-helix structure. The structure is analogous to a ladder, where the two DNA strands are analogous to the two vertical beams of the ladder, and the hydrogen bonds between strands are analogous to the rungs of the ladder that hold the two beams together. Unlike the damage caused by charged particle radiation such as $\alpha$-rays and protons, or uncharged particles such as neutrons, the interaction of a photon with a target cell is seen as an indirect action, meaning the x-rays themselves do not damage a cell’s DNA directly. Instead, photons pass all, or part, of their energy to the electrons in tissue, which cause damage to the DNA. Approximately 80% of a cell is composed of water, so for this discussion, assume that the photon energy is transferred to the electrons of the water molecules, resulting in $\text{H}_2\text{O}^+$. The ionized water molecules react with the surrounding uncharged water molecules, decaying quickly into hydroxyl ion (OH$^-$), a type of free radical that can diffuse a short distance and cause damage to a critical target in the cell. The term free radical refers to an atom or molecule with an unpaired electron, making them chemically unstable. As the free radicals and electrons migrate away from
the site of interaction, their energy is deposited along the path, or *track*, they travel. In this case, the damage caused by the photons is indirect, since the energy must first be transferred to the target material before eventually being transferred to the cellular DNA, where strand breaks are induced.

If cells are irradiated with x-rays, breaks will occur along one, or both, of the DNA strands. Double-strand breaks may result in cell killing, mutation, or carcinogenesis (the initiation of cancer formation). Single-strand breaks are usually of little significance due to the repair mechanisms employed by the cell. The type of radiation damage that is of most biological consequence are the *double-strand breaks*, where the breaks occur in both strands, and are separated by 4 base pairs or less. [14] If multiple breaks occur in both strands, but the breaks are well separated, the repair mechanism is still quite effective at repairing the broken strands because the breaks are handled separately by the repair mechanism. The distance between the strand breaks is radiobiologically important, as the repair mechanism is unable to use the opposite strand as a template if two breaks occur directly opposite each other, or within four base pairs of each other.

2.1.4 Cell Killing
Radiobiologists frequently discuss the relationship between radiation dose, and the proportion of cells that survive the radiation exposure. Double-strand breaks are repairable in mammals, but the repair mechanism is error-prone, leading to possible mutation and carcinogenesis despite an attempt to repair the aberration. The number of chromosomal aberrations increase with the dose received by the cells, as a higher dose corresponds to a greater number of x-rays (at a given photon energy) impinging the target cells, while a lower dose corresponds to a lower number of incident x-rays. At low doses, the probability of inducing a double-strand break at small doses is low, as the probability that a single interaction will produce two chromosomal lesions is low. Accordingly, the average
distance separating two chromosomal breaks is greater at low doses, so the probability of two single-strand breaks occurring in close proximity is also low at low doses. The probability of cell survival (S) after receiving a radiation dose (D) is mathematically described by the expression

\[ S = e^{-\alpha D} \quad (2.3) \]

where \( \alpha \) is a coefficient that describes the probability of inducing lethal cell damage from a single interaction.

At higher absorbed doses, the induction of a double-strand break is most likely induced by the electron and free radical produced from two separate interactions, rather than a single interaction. A double-strand break produced in this manner can be thought of as two single-strand breaks in close proximity, induced by two separate interactions. The probability of this occurring increases with dose, as the number of photons impinging on the target is greater, and the average distance separating individual interactions in the target material become shorter. Of course, double-strand breaks may also occur due to a single interaction that produces two (or more) strand breaks, as described for low doses. However, the probability of this occurring is relatively low. This is why the probability of inducing a double-strand break is low for low doses, as there is only one mechanism of inducing two breaks when the dose is low. The probability of cell survival from a multi-hit interaction pathway is described by the expression

\[ S = e^{-\beta D^2} \quad (2.4) \]

where \( \beta \) is a coefficient that describes the probability of cell survival after multiple hits.

The cumulative damage to cells from both interaction pathways can be described by Equation 2.5, where the two components of \( \alpha \) and \( \beta \) are referred to as the linear and quadratic components of cell survival, respectively.
\[ S = e^{-\alpha D - \beta D^2} \] 

(2.5)

2.1.4.1 Cell Survival and Fractionated Doses

This leads us to a discussion on fractionated dose delivery, and how this affects cell survival. Radiation damage is either described as *lethal*, which is irreversible and cannot be repaired, or *sub-lethal*, which describes damage that can be repaired in several hours unless additional radiation dose is delivered. A great deal of research was done in the 1960s on mammalian cells under different physiological and environmental parameters, which showed that if the dose delivered to a cell culture is split into two fractions separated by a time interval, some of the sublethal damage produced by the first irradiation are repaired in the period separating the delivery of the two fractions. [14, 15] Normal cells and tumour cells are both capable of sublethal damage repair in the time interval that separate the delivery of a two fraction treatment; however, normal cells are more capable of repairing this damage than tumour cells. The main goal of fractionated radiation treatment delivery is to produce differential cell damage between normal and tumour cells by taking advantage of the difference in their ability to repair sub-lethal damage. [16] The idea of sub-lethal damage, fractionated doses, and dose rate are all clinically relevant to the radiation treatment of prostate cancer, as patients are *always* treated with a multi-fraction regimen, whether the treatment is delivered by high energy photons from a linear accelerator, or by low dose-rate or high dose-rate brachytherapy.

To understand the reason for this phenomena, one must look again at how double-strand breaks are formed. The component of cell killing that results when a single photon interaction produces two chromosomal breaks is not affected by fractionating the dose delivery, nor is it dependent on the number of fractions used to treat the patient. Since only a single hit is involved in causing both breaks, a double-strand break would occur whether
the dose is delivered in a single fraction, or delivered in multiple fractions with a rest period in between. The same cannot be said when two chromosomal breaks are the product of two single strand breaks, one break originating from each fraction of the treatment. When each fraction of the treatment induces a single break on the same chromosome, the break that results from the first fraction may be repaired before the second fraction is delivered. [16, 14, 8] In this case, the superior repair mechanism of normal cells would lead to a cell survival advantage over tumour cells. Accordingly, the rest period between fractions would have no effect on double strand breaks induced by two photon interactions which occurred during the same exposure.

The explanation above can also be used to explain the effect of dose-rate on cell survival. [15] If a given dose is delivered at a really low rate, or over a long exposure period, the biological effect of the absorbed radiation dose is reduced when compared to the same dose delivered via a high dose rate treatment modality. This dose-rate effect is also due to the repair of sublethal damage, except the repair occurs during the irradiation rather than in the time interval between fractions. The likelihood that a second break occurs before the first break has been repaired is higher at high dose rates than at low dose rates. In fact, continuously delivered low-dose rate radiation exposure can be thought of as a large number of small fractionated doses, which provides some opportunity for many cells to repair.

2.1.4.2 The Relevance of $\alpha/\beta$ Ratio in Prostate Radiation Therapy

As discussed by Hall, [16] Brenner, [17] and Duchesne, [8] the $\alpha/\beta$ ratio represents the dose from which a greater proportion of normal cells would die when compared to tumour cells exposed to the same radiation dose. Most types of tumours are said to have a large $\alpha/\beta$ ratio of around $10\ Gy$, and are generally referred to as early responding tissue because they respond to radiation damage after a short time. The differential efficacy of repair between normal and tumour cells is the reason why radiation treatments
are generally delivered with a large number of 2 Gy fractions rather than a single large fraction. The delivery of a lower dose per fraction results in a greater surviving fraction of normal cells when compared to tumour cells. Normal cells generally have an $\alpha/\beta$ ratio of around 3 Gy, and are referred to as late responding, as they generally don’t respond to radiation for days, weeks, or possibly months post-irradiation. For a given total dose, late reacting tissues are much more dependent on the dose per fraction due to their lower $\alpha/\beta$ ratio, although the reason for this is inconclusive. [8, 18] One hypothesis is that the $\alpha/\beta$ ratio of a cell population is determined by its age distribution, where slowly proliferating tissues with relatively long cell cycles, and hence, only a small proportion of cells undergoing cell division at any given time, will be more sensitive to large doses delivered per fraction. In contrast, quickly proliferating cells, such as those found in most tumours, contain a greater number of cells that are either in, or entering, the mitotic cycle.

However, prostate tumours are different from most tumours, as research has suggested that prostate tumours are actually late-responding tumours with a $\alpha/\beta$ ratio of $1.5 - 3$ rather than early-responding, as originally believed. [8,17,19,20,21] This means the $\alpha/\beta$ of a prostate tumour may be lower than that of normal tissue, making it a late-responding tissue relative to most normal tissue. Prostate cells appear to have a very small proportion of cells undergoing mitosis at a given moment, with many of its cells stuck in interphase, the section of the cell cycle where the cell is not undergoing cell division (mitosis). Unlike most types of tumours, which tend to have short doubling time, prostate tumour cells have a potential doubling time that ranges from 16 – 61 days [17], making it one of the slowest proliferating human tumours. If the advantage of fractionated treatment delivery is to spare normal tissue from radiation damage effects by taking advantage of their lower $\alpha/\beta$ ratio, then the same rationale doesn’t appear to be applicable to prostate cancer.

To determine the efficacy of a fractionated treatment for prostate cancer, one must also
consider the $\alpha/\beta$-ratio of nearby organs that are at risk of suffering post-treatment toxicity, such as the rectum, and how its $\alpha/\beta$ compares to that of prostate tumour cells. Evidence from animal studies suggest that the $\alpha/\beta$ ratio of the rectum is $>4$ Gy, [19,20] perhaps as high as 6 Gy, [18] which is higher than most normal tissue. The $\alpha/\beta$ estimates for prostate tumours should be used with caution in human studies, as they are not conclusive due to the methodology used to determine its value. [18] Regardless of the precise value of the $\alpha/\beta$, it is believed that the $\alpha/\beta$-ratio for prostate cancer is lower than that of the rectum, and consequently, there is indeed a benefit of a fractionated treatment for prostate cancer, particularly hypofractionated treatment and high dose-rate brachytherapy. Hypofractionation, or the delivery of fewer fractions at a greater dose per fraction, should produce greater tumour control and fewer rectal and urinary complications than both fractionated external beam radiotherapy (EBRT) and low-dose rate (LDR) brachytherapy, as suggested by Brenner. [20]

2.1.5 BED, SED, and the benefits of High Dose-Rate treatment

The biological effect of dose on living tissue isn’t as predictable as it first appears, since it depends on more than just the total absorbed dose. Fractionated treatments exemplify this notion, as the biological effect of a large single dose is not equal to the effect of a fractionated treatment. The dose delivered per fraction ($d$), and the number of fractions ($n$) used to deliver the treatment are parameters that change the effectiveness of a total absorbed dose. If the parameters $n$ and $d$ used to treat a patient are different from what is considered a standard treatment regimen at the treatment facility in question, the biological effect of the treatment will also be different, even if the total dose delivered during the treatment is the same. The linear quadratic model of cell survival described earlier (Equation 2.5) can be used to calculate the many combinations of $n$ and $d$ that will produce a constant biological effect (i.e., a constant cell survival probability).
The Biological Effective Dose (BED) was introduced to quantify the effect of parameter changes away from the standard treatment. At many treatment facilities, a treatment is delivered in 2 Gy/fraction, although this value varies between treatment facilities. The BED is calculated by assuming that the patient is treated with many infinitely small fractions (i.e., when \(d\) approaches zero) rather than the standard treatment. The resultant BED is equal to the total dose required to produce the same biological outcome as a standard treatment. Starting from the linear quadratic model of cell survival described earlier (Equation 2.5), and assuming \(n\) fractions and \(d\) dose per fraction, the overall surviving fraction \(S\) of cells from the treatment is equal to the product of the surviving fractions resulting from each individual fraction. So

\[
S = \left[e^{(-\alpha D - \beta D^2)}\right]^n = e^{-nd(\alpha + \beta d)}
\]

where \(nd\) is equal to the total dose \(D\). The BED is calculated by assuming that \(d \to 0\), and then equating the surviving fraction \((S)\) of this treatment to the surviving fraction of the standard delivery:

\[
S_{standard} = S_{BED} = e^{- BED(\alpha + \beta \times 0)}
\]

\[
nd(\alpha + \beta d) = \alpha BED
\]

\[
BED = nd\left(1 + \frac{d}{(\frac{\alpha}{\beta})}\right)
\]

where the values of \(n\) and \(d\) are equal to the delivery parameters of the standard treatment used at the cancer centre. If one aims to alter the dose delivered per fraction \(d\) away from the standard value, this equation can be used to calculate the number of fractions \(n\) necessary to deliver the same overall biological effect. The same can be done if \(n\) is altered, and the dose per fraction \(d\) required to induce the same biological effect is unknown.
The standard effective dose (SED) is a quantity that’s similar to the BED, except the equivalent dose is delivered in 2 Gy fractions rather than infinitely small fractions. The most common dose delivered per fraction in radiotherapy is approximately 2 Gy/fraction, so a comparison of the biological effect of treatments that differ from the standard 2 Gy per fraction may be quite useful. The SED can be calculated from the BED equation as shown:

\[ SED = nd \left(1 + \frac{d}{\alpha/\beta}\right) \left(1 + \frac{2}{\alpha/\beta}\right) \]

\[ = nd \frac{BED}{\left(1 + \frac{2}{\alpha/\beta}\right)} \]

A real example can be used to convey the fundamental idea behind SED, and the importance of the fractionation parameters used to treat a patient, by comparing the biological effectiveness of a combined EBRT and HDR brachytherapy treatment to that of external beam monotherapy.

Assume that the brachytherapy component of the combined HDR and EBRT treatment is delivered in 3 fractions at 6.5 Gy/fraction, for a total dose of 19.5 Gy; while the EBRT component of the treatment is delivered in 23 fractions at 2 Gy/fraction, for a total dose of 46 Gy. The total dose delivered in such a treatment is 65.5 Gy. However, as it was described earlier, the biological effect of a treatment is not dictated simply by the total dose absorbed by the target volume. If the \( \alpha/\beta \)-ratio of prostate cancer is approximately 1.5 Gy, the SED to the prostate using the combined treatment is calculated as follows:
While 65.5 Gy is delivered to the prostate tumour using the combined HDR and EBRT treatment, it actually has the same biological effectiveness as the delivery of 90.6 Gy using a 2 Gy/fraction treatment. It is important to note that the HDR component of the treatment is the sole reason for the increased effectiveness of the treatment, not the external beam component. The EBRT component was delivered using the standard treatment parameters, and so the SED delivered with EBRT (46 Gy) is simply equal to the total absorbed (46 Gy). If the same biological effectiveness is to be achieved using external beam monotherapy, a total dose of 90.6 Gy would be required. Clearly, delivering 65.5 Gy is far more desirable than delivering 90.6 Gy, especially if the biological effect of the two treatments would yield an identical biologic effect.

To understand the impact of HDR brachytherapy on the effective dose to the rectum, the SED delivered to the rectum can be calculated for both the combined HDR brachytherapy + EBRT therapy, and external beam monotherapy. Assume that the goal of the oncologist is to achieve the same level of tumour control using both the combined treatment, and EBRT delivered alone. As illustrated previously, this is achieved if a total dose of 65.5 Gy is delivered using the combined treatment, and 90.6 Gy is delivered using EBRT alone. At St. George Cancer Care Centre (Sydney), the treatment plan is defined so that the dose delivered to the rectum does not exceed 70% of the total dose prescribed to the prostate. This rectal dose constraint is pre-defined by the centre, and so each treatment plan is created using the same dose constraint. With regards to the combined treatment,
where a total of 65.5 Gy is delivered to the prostate, the maximum dose delivered to the rectum is would be 45.9 Gy. In comparison, a patient treated with only EBRT should receive a rectal dose that does not exceed a dose of 63.7 Gy. However, as discussed earlier, the total dose does not determine the biological effect of the radiation dose on cell survival. The SED of the combined treatment is far greater than the total dose would indicate due to the HDR brachytherapy component of the treatment.

To calculate the SED delivered to the rectum after the combined treatment, where the $\alpha/\beta$ ratio of the rectum is assumed to be 4 Gy:

$$ SED = (19.5 \times 0.70) \left( 1 + \frac{6.5}{4} \right) \left( 1 + \frac{2}{2} \right) + (46 \times 0.70) \left( 1 + \frac{2}{2} \right) \left( 1 + \frac{2}{2} \right) $$

$$ = (34.125 \times 0.70) + (46 \times 0.70) $$

$$ = 56.1 \text{ Gy} $$

The SED delivered to the rectum is 56.1 Gy for the combined treatment, while the SED delivered to the rectum from EBRT alone would be simply equal to 70% of the total dose to the prostate (90.6 Gy), or 63.7 Gy, as discussed earlier.

In conclusion, a patient treated with a total absorbed dose of 65.5 Gy via the combined treatment will have an SED of 90.6 Gy delivered to the prostate, and 56.1 Gy delivered to the rectum. In contrast, a patient treated with a total radiation dose of 90.6 Gy via EBRT alone will have an SED of 90.6 Gy delivered to the prostate, and an SED of 56.1 Gy delivered to the rectum. The same level of tumour control was achieved using a lower dose if the patient is treated with EBRT combined with HDR brachytherapy, rather than EBRT delivered as the sole form of treatment. Furthermore, patients treated with the combined therapy will also suffer from fewer post-treatment complications from rectal
toxicity due to the lower SED to the rectum. This illustrates why HDR brachytherapy is such an effective form of treatment for prostate cancer.

2.1.6 Implications of Low $\alpha/\beta$-ratio in Prostate Treatment

HDR brachytherapy treatment of prostate cancer is usually delivered as an adjunct to EBRT rather than as the sole form of treatment. It is always delivered as a form of hypofractionated treatment, where the dose per fraction is approximately 6 Gy/fraction. If HDR brachytherapy was delivered as a monotherapy, and used the same dose per fraction as a standard EBRT treatment (2 Gy/fraction), the treatment would take weeks to deliver. This isn’t feasible when treating with HDR brachytherapy, because the patient would be confined to a hospital bed for weeks, with plastic catheters pierced through his perineum and into his prostate until all prescribed fractions have been delivered. Larger dose per fraction $d$ were originally chosen to reduce the number of fractions required for treatment, thus reducing the treatment time. Initially, there was no radiobiological basis for using a larger dose per fraction $d$, as the low $\alpha/\beta$ of the prostate was not realized until quite recently. There are a few reports of HDR brachytherapy being delivered as monotherapy for the treatment of localized prostate cancer, [21, 22, 23, 24] but delivering HDR brachytherapy in conjunction with EBRT is far more common. While brachytherapy has always been delivered using 5–7 Gy/fraction, the realization that larger fractions may be beneficial in treating prostate cancer due to the uncommonly low $\alpha/\beta$-ratio means that adjunctive HDR brachytherapy has always been radiobiologically advantageous, even if this advantage was unintentional when first introduced.

Increasing the dose delivered per fraction is still not common practice with regards to other radiation therapy modalities, as the theoretical evidence illustrating the benefit of increased fractionation isn’t entirely conclusive. [17, 20] While there is a general agreement that the $\alpha/\beta$-ratio of the prostate is far lower than most types of tissue, a widely
accepted $\alpha/\beta$ value has not been agreed upon yet, nor has the $\alpha/\beta$ of the rectum. Consequently, it is unclear how much the dose delivered per fraction can be increased without increasing the patient’s risk of experiencing late complications such as rectal toxicity. Furthermore, the amount of benefit gained by increasing the dose delivered per fraction is unknown.

Currently, there are few reports on the treatment outcome of delivering larger fraction sizes and reducing the number of fractions, but some results are appearing from studies conducted at institutions such as Memorial Sloan-Kettering Cancer Center (New York City, U.S.A.) and University of Wisconsin (Madison, U.S.A.) that compare the effectiveness of an increased dose-per-fraction delivered. At Memorial Sloan-Kettering, the study compares a high-dose IMRT treatment, with the outcome of a combined IMRT and HDR brachytherapy treatment. St. George Hospital Cancer Care Centre (Sydney, Australia) is moving from a 3-fraction brachytherapy treatment, to a two-fraction treatment on June 16th, 2008. Rather than deliver 3 fractions at 6.5 Gy/fraction, patients will be treated using 2 fractions at 9 Gy/fraction.
2.2 Overview of Prostate Cancer

There is a plethora of reports in the literature regarding prostate cancer treatment,[9, 20–25, 40, 47, 48, 51–54] and they vary greatly in terms of quality, breadth, patient selection, definition of tumour control, and biochemical failure endpoints. What they have in common is a requirement for the reader to have a basic understanding of how prostate cancer is detected, how the severity of a patient’s disease is graded and staged following a biopsy, and how radiation-induced post-treatment complications are graded following the treatment. An understanding of these concepts is not only crucial in understanding prostate disease in a general sense, but is required if the reader wants to understand the clinical studies found in the literature, as clinical studies often involve patients that fit within a range of risk factors, and determine treatment success using a certain biological or biochemical endpoint.

For the benefit of the reader, the relevant background information and terminology will be introduced in a natural, progressive manner before discussing the risk of morbidity from radiation therapy in the next section. The primary focus of this thesis is high dose rate (HDR) prostate brachytherapy; however, much of the content is applicable to other forms of radiation treatment. Furthermore, HDR brachytherapy is generally delivered as an adjunct to some form of external beam radiotherapy (EBRT), so attention will also be directed towards external beam radiotherapy. The first two sections will discuss risk factors for prostate cancer, which include the effects of age, race, and hormones (mostly testosterone). This will be followed by a discussion on prostate specific antigen (PSA), biopsies, and Gleason scores, as this terminology appears in all scientific publications that discuss prostate radiotherapy. The final section will briefly discuss the successes and failures of HDR brachytherapy.
2.2.1 The Risk of Prostate Cancer Incidence

The prostate is a glandular organ of the male reproduction system that produces seminal fluid. It is approximately the size of a walnut, or around 4 cm in length. The prostate is located within the pelvic region, on the anterior side of the rectum, and under the bladder. The urethra passes through the prostate, which produces some of the constituents of semen. The semen is carried through the urethra during ejaculation. According to the *Australian Incidence and Mortality* books, [26] a collection of patient and mortality data collected and summarised by the Australian government’s *Australian Institute of Health and Welfare* (AIHW), prostate cancer was Australia’s most frequently diagnosed malignant cancer in 2004, and is the second leading cause of cancer-related death in Australian men. While non-melanoma skin cancer is known to be the most common type of cancer in Australia, it is generally excluded from the list of most frequently diagnosed cancers because basal and squamous cell carcinoma are not notifiable cancers. There were 15,759 incidences of prostate cancer in 2004; in comparison, there were 12,126 incidences of breast cancer. The incidence rate of prostate cancer has increased steadily since the mid-1990s, while the mortality rate has decreased due to improved detection and treatment methods. In 2004, men were being diagnosed with prostate cancer at a younger age than in the past, with a clear shift in the average age of detection towards younger ages. [26] The increased incidence rate of prostate cancer is in contrast to the overall incidence rate of all forms of cancer, which has remained steady in Australia over the past 10 years. Prostate cancer risk is even more severe in the United States, where the proportion of men who suffer from prostate cancer is greatest. [27] These statistics do not include those men who unknowingly suffer from prostate cancer, and die of other causes.

2.2.2 Risk factors of Prostate Cancer

There are numerous factors attributed to the risk of suffering prostate cancer, such as race, genetics, age, diet, and hormones. The biggest factor appears to be age, which is closely
related to both the incidence of prostate cancer, and the risk of suffering complications induced by the treatment. The incidence rate of prostate cancer is negligible for men 45 years of age and younger, but becomes more common when men reach an age greater than 65–70. The risk of suffering a recurrence of the disease following the treatment, along with treatment-induced toxicity also increases with the age of the patient at the time of treatment.

Androgens, testosterone in particular, stimulate the growth of cancer cells in the prostate. Testosterone is produced almost entirely in the testes, so eunuchs are known to not suffer from adenocarcinoma of the prostate. [27, 28] Male hormones can also play a role in the treatment of prostate cancer, as Androgen Deprivation Therapy (ADT), also known simply as hormone therapy, is a popular mode of supplementary treatment delivered prior to a radiation treatment. When ADT is administered, the patient’s androgen levels are reduced with the intention of reducing the size of the tumour. Race plays a role, as black men have a higher level of testosterone than white or hispanic males, and hence have a higher incidence of prostate cancer. Furthermore, white and hispanic males are at a higher risk of prostate cancer than men from Asian descent. Scandinavian men also have an inherited predisposition to prostate caused by a genetic mutation of the BRCA1 and BRCA2 genes, which are passed through historical lineage. [29]

High (animal) fat diets have been suggested to increase the risk of developing prostate cancer, while a diet that is rich in soy appears to decrease the risk of prostate cancer by 70%, according to a study conducted on Adventists in the United States. [30] Soy protein is the most commonly consumed source of isoflavones, which decreases a person’s blood androgen level by increasing the level of SHBG (sex-hormone binding globulin) in the blood. [30,31,32] SHBG binds to testosterone so that the testosterone level in the body is reduced. This dietary risk factor, which is tied to the hormonal factor, may help explain
why the risk of developing prostate cancer is so low in men of Asian descent, as the consumption of isoflavones in countries like Japan, Korea, China, and Taiwan is more than ten times higher than in Westernised countries such as the United States. [32]

2.2.3 Testing for Prostate Cancer

Testing for the presence of prostate cancer normally involves a digital rectal examination (DRE), and a test for prostate specific antigen (PSA). A DRE is a technique that requires a doctor to insert a gloved, lubricated finger into the rectum and rub the prostate through the rectal wall, feeling for bumps or abnormalities. The prostate should be soft and smooth. Lumps or local, hard areas of the prostate are considered abnormalities, and may indicate the presence of cancer. When a tumour in the prostate is small, a DRE is ineffective at detecting the presence of prostate cancer. However, if an abnormality is found during a DRE, a biopsy will then be required, regardless of whether the patient’s PSA was found to be low. [33]

A test of a patient’s PSA level is performed to check for the amount of PSA in the blood. PSA is a type of protein produced by both normal and cancerous cells of the prostate gland. Generally, an elevated PSA level is the first sign that would raise concern, and would ultimately lead to other tests to verify the presence or absence of the disease. During a prostate cancer screening, a doctor takes a blood sample, and the PSA level in the blood is measured in a laboratory. PSA is usually reported in units of nanograms per millilitre (ng/ml). Generally, a PSA level above 4 ng/ml is considered to be elevated, but studies have found cases where men with a PSA below 4 ng/ml have prostate cancer. [34, 35] An elevated PSA level alone doesn’t necessarily equate to a benign tumour or cancer of the prostate, just as a low PSA doesn’t always mean that no cancer is present. [33, 36, 34, 37, 35] In fact, due to the slow-growing nature of prostate cancer, and the high age factor related to prostate cancer risk, few men die as a result of prostate
cancer. Overdiagnosis and follow-up testing is an issue, as are the benefits and risks of treatment. After all, if the diagnosis and treatment of prostate cancer will not have a positive effect on the quality of the patient’s life, then there isn’t much benefit in either diagnosis or treatment.

The following PSA ranges have been suggested by doctors, although slight variations in the ranges may exist between treatment facilities. It was taken from the *National Cancer Institute* in the United States. [33]

- 0 to 2.5 ng/ml is normal.
- 2.6 to 4 ng/ml is slightly elevated.
- 4 to 10 ng/ml is slightly to moderately elevated.
- 10 to 20 ng/ml is moderately elevated.
- > 20 ng/ml is considered significantly elevated.

A low level of PSA in the bloodstream is considered normal for men. The onslaught of either prostate cancer and/or benign tumours in the prostate can increase PSA concentration in the blood. Many doctors feel that men with a PSA level greater than 4 ng/ml should undergo a biopsy, while some feel that men with a PSA greater than 2.5 ng/ml should receive a biopsy. Generally, the higher the PSA concentration, the more likely that prostate cancer is present. If a patient’s PSA levels are high, while the DRE results are normal, a typical course of action taken by a physician would be to conduct a transrectal ultrasound (TRUS), which is simply an ultrasound image of the prostate that is used to identify abnormal areas of the prostate that require a biopsy for further inspection. If the results of the TRUS are normal, the PSA test may be repeated several months later. [36] There are several other variables that a doctor may consider when a patient’s PSA is borderline, and a DRE and/or biopsy does not provide a clear understanding of the situation. This includes measuring the PSA density, PSA velocity, and PSA doubling
For example, the PSA density is calculated by dividing the patient’s PSA value by the prostate size, which is determined from the TRUS. The higher the PSA density, the greater the probability that the patient suffers from prostate cancer. A high PSA density does not necessarily mean that the PSA level of the patient is high, only that the PSA level is high for a prostate of this size.

A biopsy is the next test considered by a physician once the PSA and DRE tests indicate the possibility of an abnormality. It requires a doctor to take small tissue samples from separate areas of the prostate. The cells are examined in order to confirm or deny the presence of prostate cancer.

2.2.4 Grading and Staging of Tumour during Biopsy

A patient biopsy involves the grading and staging of the patient’s tumour cells taken during a biopsy. The cell samples are examined in a lab under a microscope. Using the Gleason grading system, which is the most popular system used for grading the severity of prostate cancer, a grade is given to cells taken from two areas of the prostate. The prostate is comprised of different areas of tissue, and each area may contain tumour cells of a different grade, and this is accounted for using this method. The cells taken from the two largest, most predominant cell patterns are each given a grade from 1–5, depending on how dissimilar the cancer cells appear compared to normal cells, and how quickly the cells are growing. The two scores are added together to determine the total Gleason Score, which ranges from 2–10. [39, 38] If the cells resemble normal prostate cells closely, they are given a Gleason grade of 1. If the cells appear irregular in shape when compared to normal prostate cells, they are assigned a Gleason grade of 5. A Gleason grade between 2–4 is assigned to tumours that fall somewhere in between. Figure 2.3 illustrates the types of cells observed in each Gleason grade. [40] To the right of the image are the Gleason grades assigned to the appropriate cells.
Figure 2.3: Cancerous cell shape and size at different Gleason grades.
Staging of the cancer is the determination of the size and spread of the disease. It is performed in order to indicate to others how it is growing, and where it is located in the body. There are two different systems used to stage prostate cancer. The first is the Tumour, Node, Metastases (TNM) staging system, an international system developed by the American Joint Committee on Cancer. [38] The other method is the Whitmore-Jewett, or A, B, C, D system, which will not be discussed in detail here. [40]

TNM staging is the most common method of staging prostate cancer. The T staging describes the tumour size and spread with great specificity, and is given one of the following descriptors: TX, T0, T1, T1a, T1b, T1c, T2, T2a, T2b, T2c, T3, T3a, T3b, and T4. A T0 specification is given when a primary cancer is not evident; a T1 specification refers to a tumour that is only evident in a small percentage of the biopsy sample; a T2 specification indicates a larger tumour size that involves either one lobe, or both lobes; and a T3 specification indicates how far the tumour has extended beyond the prostate capsule wall, without having spread to other anatomy. A T4 specification is given to the most severe disease, with the tumour spread beyond the seminal vesicles and into other areas of anatomy such as the rectum, bladder, and pelvic wall. The most important distinction between the different stages is whether or not the cancer has spread to other anatomical organs. A T1 or T2 stage cancer has remained in the prostate and has not spread beyond the prostate, while a T3 and T4 stage cancer has spread beyond the prostatic capsule, and therefore, is more difficult to treat.

N-staging indicates the level of regional lymph node involvement, while M-staging describes the presence or absence of metastases. N staging and M staging are generally not commonly used to determine which patients are eligible to participate in a clinical study, nor are patients groups formed based on their N and M staging results.
2.2.5 Assessment of Available Treatment Options

After the oncologist has made a careful diagnosis of the patient’s prostate condition, there are numerous options available to treat prostate cancer, each with their own strengths and weaknesses. The main treatments of prostate cancer include surgical procedures such as radical prostatectomy, cryosurgery, and transurethral resection, while radiation therapy modalities include external beam radiation therapy (EBRT), 3D-conformal radiotherapy, intensity modulated radiotherapy, proton therapy, and brachytherapy. Men with tumours confined to the prostate, and have a life expectancy of greater than 10 years, have numerous treatment options available to them, each associated with particular benefits with regards to biochemical control, potential for relapse, and the patient’s quality of life following treatment in both a short-term and long-term sense. The form of treatment that is best for a particular patient is too subjective for one to state with absolute certainty due to the lack of randomized controlled trials, but recommendations can be made based on the literature that exists today.

Comparing the clinical outcome of separate studies is quite difficult, as there appears to be an inconsistency in the methodology, both in terms of how the treatment was delivered, and the differences in assessment criteria for biochemical failure and relapse defined in each study. As the prescribed treatment dose increases with advancement in imaging techniques and dose conformity, are the results of clinical studies completed 5–10 years ago comparable to studies performed today or in the near future? The significance that the clinical experience of those involved in the research may be a factor, and is not an issue that would be easy to account for between studies. The clinical experience of the radiologist responsible for interpreting patient images as a significant effect on how well the severity of a patient’s disease is assessed, as demonstrated in numerous studies, \[41,42,43,44\] particularly in a study by Harris et al. \[44\] Luckily, recommended guidelines such as the European Association of Urology’s (EAU) Guidelines on Prostate
Cancer [45] and the NCCN’s Clinical Practice in Oncology: Prostate Cancer Early Detection [36] exist to help clinicians sift through the results from patient studies found in the literature to provide an insightful summary of the results from major clinical studies, along with the potential of major patient studies currently taking place at the time of publication.

2.2.5.1 Radical Prostatectomy

A radical prostatectomy involves the surgical removal of the prostate along with nearby tissue where the cancer has spread. Small, localized tumours are effectively treated by radical prostatectomy and radiotherapy. Large tumours that have spread to the lymph nodes or other areas are not effectively treated by removing the prostate. The effectiveness of a prostatectomy will depend on the stage and grade of the disease. In patients under the age of 75, and with a cancer-free life expectancy of greater than 10 years, radical prostatectomy is the predominant treatment modality. The prospect of surgically removing a localized tumour from the body is usually appealing to the patient, as it provides perceived finality. [46]

There are two common forms of radical prostatectomy, although more than two methods exist: radical retropubic prostatectomy, and radical perineal prostatectomy. In a radical retropubic prostatectomy, the tumour is removed through an incision in the lower abdomen. The prostate, and the seminal vesicles attached to the prostate, are removed. A small part of the bladder closest to the prostate, and the pelvic lymph nodes may also be removed if necessary. [40] A nerve-sparing technique may be used during retropubic prostatectomy, where the nerves surrounding the prostate are spared when possible during surgery. Sparing the nerves reduces the chance of suffering adverse effects from the procedure, usually sexual and urinary dysfunction. A radical perineal prostatectomy is similar, except that an incision is made in the perineum rather than the lower abdomen.
The perineum is the narrow region between the scrotum and anus. This procedure is currently more predominant than retropubic prostatectomy, and requires less time in surgery. Both procedures require the patient to rest for several days in the hospital followed by 3–5 weeks of rest at home. A catheter is inserted during surgery to allow for urination during the first several weeks of the healing process.

2.2.5.2 Clinical Side Effects of Radical Prostatectomy

The possibility of experiencing side effects from radical prostatectomy treatment, even 24 months post-treatment, is significant. A study conducted by Stanford et al. [47] was particularly effective at highlighting the negative impact that radical prostatectomy may have on the quality of life of patients following treatment. The study was conducted on patients treated with radical prostatectomy in 1994 and 1995, on a cohort of 1291 patients of African-American, White, and Hispanic descent, residing in numerous American cities throughout the United States. In the study, 45.6% of men suffered occasional urinary leakage, 16.9% suffered frequent leakage, and 5.4% of men complained of having no urinary control 6 months following radical prostatectomy. The complete or partial loss of voluntary control over urination and defecation is called incontinence. The frequency of incontinence of all patients was high, with 41.1% experiencing incontinence ≤ twice per day, and 29.0% experienced incontinence ≥ twice per day. The situation of most patients improved 24 months after their treatment, but 40.2% of men still suffered from slight urinary leakage, 6.8% frequent leakage, and 1.6% still had no urinary control approximately 24 months after diagnosis (and ≥18 months post-surgery). Over time, the frequency of incontinence improved slightly for those only suffering infrequent incontinence, while the situation improved greatly for those who suffered from incontinence more than twice a day. Patient age is the biggest risk factor with regards to suffering from urinary dysfunction post-treatment. For those who suffer from incontinence following treatment, patients younger than 60 years old experienced less frequent incontinence,
and regain function sooner than older patients.

Similar results were observed with regards to sexual function. After 24 months, 59.9% of men reported that their erections were not firm enough for sexual intercourse, and 44.2% were unable to have any erections. Results were slightly improved when a nerve-sparing technique was used during the prostatectomy procedure. Lower interest in sexual activity, inability to maintain an erection, and lower frequency of sexual activity were also reported by patients.

2.2.5.3 External Beam Radiotherapy

The aim of radiotherapy is to deliver a large, homogeneous radiation dose to a target volume while minimizing the dose to surrounding normal tissue. The current application of external beam radiotherapy (EBRT) aims to achieve this by using three-dimensional (3D) volume reconstructions, so that the tumour and surrounding tissue can be visualized in 3D. This allows for clearer treatment margins, modulation of the beam intensity in certain sections of the radiation field, and alteration of the shape of the radiation field using multi-leaf collimators (MLC). Since the radiation is usually delivered to the target using multiple x-ray fields originating from different angles, the ability to visualise the target volume in 3D allows each field to be sculpted to the shape of the tumour. With regards to prostate cancer, excellent conformity of the dose distribution to the tumour leads to a reduction in the rectum and bladder volume that is situated within the 90% and 80% isodose regions of the dose distribution. A reduction in the volume of normal tissue exposed to intermediate/high doses during treatment has been shown to reduce the risk of inducing late toxicity effects. This was illustrated by Hille et al. [48] in a study on the impact of rectal balloons on the dose-volume histogram of the treatment plan. When the rectal balloon is inflated, the volume of the rectal wall that’s situated within the high dose region is reduced because the balloon pushes the posterior section of the rectum further
away from the prostate during irradiation. With 60 ml of air injected into the balloon, the
dose reduction to the rectal wall appeared significant. A less significant amount of dose
sparing was observed when the balloon was only filled with 40 ml of air, as the balloon
did not push the rectal walls out as far.

An alternative benefit of a more conformal dose delivery is the potential to increase the
total dose to the prostate, without increasing the risk of the patient suffering from post-
treatment complications. In the literature, this is commonly referred to as dose escalation.

2.2.5.4 Brachytherapy

Radical prostatectomy and EBRT are the most common treatment modalities for early
stage prostate adenocarcinoma (T1 and T2), although brachytherapy, or the implantation
of radioactive sources directly into a patient, is also popular. Irradiation of the target
volume by implanting radioactive sources is not a new idea, as Alexander Graham Bell
first suggested it at the beginning of the 20th Century. [49] Brachytherapy has gained
popularity over the years due to its potential to spare surrounding normal tissue from un-
necessary radiation dose. It has been performed for nearly a century, but the method was
crude and implant placement accuracy was never assessed. Whitmore and Carlton pop-
ularized prostate brachytherapy in the 1960s and 1970s using the retropubic approach,
although the results were disappointing. [50, 51] In a study performed on patients from
1970 to 1987, Whitmore and Zelefsky reported a greater than expected incidence of local
relapse 15 years following treatment, in a study done on 1078 patients. The poor out-
come is believed to be due to the technical limitations of the retropubic technique, which
resulted in poor distribution of the isotope within the prostate. [51]

There are three brachytherapy methods used to treat prostate cancer: high dose-rate (HDR),
pulsed dose-rate (PDR), and low dose-rate (LDR) brachytherapy. LDR brachytherapy
will be discussed first, as it was initially the only form of brachytherapy.

2.2.5.5 Low Dose Rate Prostate Brachytherapy Treatment
In LDR brachytherapy, radioactive seeds the size of a grain of rice are permanently inserted inside the organ of interest. The radiation is given off inside the tumour, allowing the damage to be focused on the tumour rather than the surrounding healthy tissue. Due to the limited range of the photons emitted by an LDR brachytherapy source, the dose gradient is steep, decreasing quickly with distance from the source. As a result, the majority of the dose is delivered within close proximity of each source. This ensures that the majority of the radiation dose is delivered to the target volume, while the normal tissue peripheral to the prostate is spared.

The insertion of the needles is performed in an operating room and takes between 30–45 minutes. The prostate is an ideal organ to treat using brachytherapy because it is located so close to the perineal epidermis, making catheter insertion a simple procedure. Following the delivery of general anaesthesia to the patient, an ultrasound probe is inserted into the rectum to visually monitor the prostate and needles while the catheters are being inserted. A total of 60–120 individual Iodine-125 (I-125) or Palladium-103 (Pd-103) seeds are deposited into the prostate using approximately 18–22 catheter needles. Iridium-192 has also been used for LDR brachytherapy, although I-125 and Pd-103 are far more common today.

Iodine-125 has a radioactive half-life of 59.4 days and emits x-rays with a mean energy of 29 keV. [52] while Pd-103 has a half-life of 17 days and emits photons with a mean energy of 21 keV. [53] The characteristics of I-125 and Pd-103 are similar, in that they both emit low energy photons, and they both deliver their dose at a low rate. However, they differ in their half-life, photon energy, and initial dose rate. While the mean photon energy emitted by Pd-103 is lower than that of I-125, the initial dose rate of Pd-103 is
20–24 cGy/hr, which is far greater than the initial dose rate of I-125, which is typically 7–10 cGy/hr. Photons emitted by I-125 will penetrate further through tissue due to their greater energy, so the use of I-125 reduces the chances of leaving under-dosed regions within the prostate. These regions are sometimes referred to as ”cold spots”, and are due to seeds being spaced too far apart to provide adequate dose coverage to the target volume. The longer half-life of I-125 means that its dose rate does not drop off as rapidly as a Pd-103 source; however, the initial dose rate is far lower than that of Pd-103. While I-125 remains the most common source used for LDR brachytherapy, the higher initial dose rate of Pd-103 is supposed to offer radiobiological advantages over I-125. However, there is a lack of clinical data that shows that delivering a greater dose initially, but with a faster drop-off in dose rate, leads to the purported benefits over I-125 that is proposed in theory.

According to a study at Memorial Sloan-Kettering Cancer Center, [55] isotope selection had no significant effect on patient outcome, regardless of the theoretical benefits of selecting one source over the other. Blasko et al. [53] recommends that I-125 be used on patients that exhibit a low Gleason score, while Pd-103 is selected when the Gleason score is high. This recommendation was made based on their clinical experience at the Seattle Prostate Institute, where 233 patients with early stage T1 and T2 prostate cancer were treated with Pd-103 seeds from January 1st, 1988, to December 31st, 1995. However, the definition of biochemical failure used in the study differs from that defined by the ASTRO Consensus Conference definition of biochemical failure, which is 3 consecutive rises in a patient’s serum PSA post-treatment. [54] This makes their results more difficult to compare with other studies.

2.2.5.6 Downside of LDR Brachytherapy
One issue with permanent seeds is that they tend to redistribute themselves in the prostate over time. Their migration within the prostate means that despite accurate initial seed
placement within the prostate, overall dose coverage of the target volume over the course of treatment may still leave cold spots. The radiation emitted from the seeds may damage a greater volume of normal tissue, and treat a smaller region of the target volume than required. In fact, there is a possibility that the seeds would migrate out of the prostate completely, and enter the bladder, urethra, rectum, or lungs, resulting in unwanted damage to nearby surrounding structures. This issue is avoided by using stranded seeds. [56,57] Furthermore, even with accurate seed placement, long-term radiation exposure to non-target regions such as the urethra may cause urinary discomfort for a patient during treatment.

Another issue with LDR brachytherapy is with regards to radiation protection. The permanent seeds require months to deliver the prescribed dose to the patient. A radioactive source is considered active for a time period of 5 half-lives. This equates to approximately 300 days using I-125. When the patient returns home, he may irradiate family, friends, and care-givers that get into close contact to him over the first few months of treatment, although the dose is low and of no concern if precautions are taken. [58] The biggest risk of LDR brachytherapy is to the general public. Loose brachytherapy seeds may be lost from the body, which may escape from the patient during urination, ejaculation of semen during sex, or via the gastro-intestinal tract at some point during treatment. Furthermore, if the patient were to die during treatment, the radioactive corpse cannot be dealt with as freely as a typical corpse. [59] For example, it is prohibited to cremate the body of an LDR brachytherapy patient, even if it was the wish of the deceased.

2.2.5.7 High Dose Rate Brachytherapy

HDR brachytherapy is most typically delivered in conjunction with EBRT as a boost to the BED delivered to the tumour, rather than alone as a monotherapy. The reasons were discussed in Section 2.1.6. HDR brachytherapy treatment is delivered using \textit{Iridium-192} (Ir-192), a highly radioactive source when compared to low energy, low dose-rate
emitters like I-125 and Pd-103. Iridium-192 emits photons of a weighted mean energy of around 390 keV, and has a half-life of 73.83 days. [60] Unlike LDR sources, which are implanted permanently into the prostate, the Ir-192 source used in HDR brachytherapy is re-usable, as it is never contaminated through direct implantation into the body.

HDR brachytherapy can be delivered in a number of ways. It is used as an intra-operative treatment, where an HDR applicator is sutured to the skin surface just above a tumour bed so that this region can be irradiated in the surgical theatre. [61] This form of treatment is regularly utilized immediately following a lumpectomy performed on a breast tumour, where irradiation of the cavity resulting from the excision of the tumour reduces the risk of tumour recurrence. HDR brachytherapy may also be used to treat cervical cancer, which is a simpler procedure, as catheter application isn’t complex.

With regards to prostate cancer treatment, the source is transferred into the body via plastic, steel, or nylon catheters inserted through the perineum and into the prostate with the guidance of a TRUS probe. The TRUS probe provides axial images through the prostate volume, although it is also capable of providing sagittal and coronal views. A separate x-ray imaging unit is also used to provide clearer images of the catheter placement from a coronal viewpoint. Typically, the catheters are inserted into the patient using a template placed in front of his perineum. The template consists of a two-dimensional coordinate grid system, with a catheter hole at each grid coordinate. The coordinates allow the position of each catheter to be correlated to the coordinates seen in the axial images provided by with the TRUS, making both catheter insertion, and post-operative referencing of the catheters, simpler. Typically, a total of 18–22 catheters are inserted into the patient, although the number depends on the number allowed by the HDR remote afterloader. A cystoscopy may be performed by a urologist, where the catheters are inserted further than necessary, intentionally piercing the bladder. This provides the oncologist with a degree of flexibility with regards to how deep the source can be placed inside the body, as it
ensures that the needles are deep enough to provide adequate dose coverage to the base of the prostate. Such precaution may prove invaluable if the prostate were to swell, or if the catheters were to slide outwards.

The Ir-192 source is physically welded to a stainless steel cable, and housed in a machine called an *HDR remote afterloader* when not in use. The afterloader is responsible for dispensing the source during treatment. The afterloader is positioned in the treatment room during irradiation, but is operated remotely via a control unit located outside the treatment room, preventing harmful radiation from being delivered to clinical staff. The Ir-192 source is transferred from the afterloader towards the catheter via a set of *transfer tubes*. One end of each transfer tube is connected to the afterloader unit, while the other end is connected to a catheter protruding from the patient’s perineum. The number of transfer tubes connected to the afterloader unit is equal to the number of catheters used to treat the patient. During the treatment, the afterloader transfers the source through the transfer tube, and towards the end of the catheter. The afterloader then pulls the source back towards the afterloader in 2.5 or 5 mm increments.

Unlike LDR brachytherapy, a single source is used in HDR brachytherapy. The dose distributioned in the target volume is determined by the amount of time the source spends at each source position, commonly referred to as the *dwell position*. The shape of the dose distribution is controlled by varying the amount of time that the source spends at each position. The amount of time the source spends at a particular dwell position is typically referred to as its *dwell time*. The ability to adjust the dwell time at each source position is a clear advantage over most LDR brachytherapy treatments, which use permanent seed implants whose position and dwell times are fixed. Furthermore, seed migration is not an issue in HDR brachytherapy like it is in LDR brachytherapy.

Once the catheters have been placed into the prostate, either a CT scan or regular x-ray
image is taken in order to visualize the location of the catheters in relation to surrounding organs. The main difference between CT and radiography-based brachytherapy is that CT-based brachytherapy allows for imaging in three dimensions (3D), whereas radiography based brachytherapy only allows for imaging in two dimensions (2D), unless orthogonal images are taken and reconstructed. The reconstruction of the orthogonal images can provide a 3D image, but does not provide segmentation of internal organs. Using CT-based treatment planning, the set of CT images can be reconstructed to form a 3D image of internal organs, which allows the dose distribution to be considered in three-dimensions to be considered. The patient’s transaxial CT image set is imported into the treatment planning software (TPS), where the prostate gland, urethra, and rectum are outlined on each image, along with the position of each catheter. The TPS can create a 3D representation of each anatomical feature by interpolating between the user-defined organ outlines, while the dose distributed throughout the target volume can be controlled by adjusting the dwell positions and dwell times. By controlling these two parameters, the shape of the dose distribution can be matched to the shape of the prostate. This level of conformity is not possible using the other treatment modalities discussed earlier.

Figure 2.4 represents the sagittal view of a real HDR brachytherapy patient treated at St. George Cancer Care Centre, Kogarah, Australia. The image was constructed using a large number of axial CT scans of 4 mm thickness, which were imported into Nucletron’s Oncentra Image Registration software package (Nucletron, The Netherlands). The prostate, catheters, template grid, rectum, and a foley (urinary) catheter are clearly delineated in the image. The catheters can be seen traversing the template, perineum, and the prostate. The acquisition of a new Philips Brilliance Big Bore CT machine at St. George allowed the centre to transition towards using 1 or 2 mm slices for their CT treatment planning.
Figure 2.4: Sagittal view of the reconstructed patient CT images taken of an HDR brachytherapy patient at St. George Cancer Care Centre. Nucletron’s *Oncentra* software was used to contour the prostate and critical organs.
2.2.6 Benefits and drawbacks of using CT images in brachytherapy

There are numerous advantages and disadvantages in using CT imaging for brachytherapy. Firstly, the variation in inter-observer contouring of the target volume and surrounding critical structures using CT-based planning software has been noted in a number of studies. [62, 63, 64] Ultrasound imaging provides better delineation of the prostate and other soft tissue structures than CT. The contouring of pertinent organs and structures in a CT image is a rather subjective process, which explains the inter-observer variation in the contouring of anatomical structures. However, CT images provide clearer delineation of catheters than an ultrasound image. Furthermore, the course of the urethra through the prostate is also difficult to discern in ultrasound images, [65] although the insertion of a Foley catheter, or the injection of an aerated gel into the urethra, makes it easy to see. With regards to LDR brachytherapy, it is easier, and more accurate, to locate individual seeds in a CT image than in an ultrasound.

Lastly, CT-based treatment planning does not allow for real-time planning and delivery of HDR brachytherapy treatments. Ultrasound imaging allows a treatment plan to be created in the operating room immediately following the insertion of the catheters. This negates the need to transport the patient to a CT machine so that the implant can be checked using CT images. By performing all the tasks in the operating theatre, catheter migration isn’t a great concern, as the patient isn’t moved between different beds throughout the day, or transferred between different rooms in the hospital. This eliminates the catheter migration attributed to patient transport.

2.2.7 Pulsed Dose-Rate (PDR) Brachytherapy

Pulsed Dose-rate (PDR) brachytherapy is similar to the delivery of an HDR brachytherapy treatment, except that the Ir-192 source used in PDR brachytherapy has a lower activity, and consequently, delivers dose at a lower rate. The physical length of a PDR source,
approximately 3 mm in length, is also shorter than a typical HDR brachytherapy source, which have a length of approximately 5 mm.

2.2.8 Benefit of HDR/PDR over LDR brachytherapy

The potential for loose LDR seeds to migrate away from its intended position within the target volume, and perhaps even migrate out of the prostate, is one downside of LDR brachytherapy when compared to HDR brachytherapy. In HDR and PDR brachytherapy, there is no concern of seed migration because the sources are contained within plastic, steel, or nylon catheters. The use of catheters also allows the Ir-192 source to be placed in the peripheral region surrounding the prostate gland in order to provide better dose coverage to the marginal volume, which can’t be done using traditional loose LDR seeds. Loose seeds would migrate away if they were placed outside the prostate capsule. The higher mean energy of the photons emitted by Ir-192 means that the photons emitted by the source at each dwell position will, on average, penetrate further into the tissue. This reduces the risk of leaving under-irradiated 'cold spots’ in the prostate. In comparison, an individual I-125 or Pd-103 seed deposits its dose to a far smaller volume. For this reason, LDR brachytherapy is typically reserved for low-risk patients, and patients with smaller prostates. The number of seeds used in LDR brachytherapy could technically be increased in order to provide dose coverage over a larger volume, but the cost of the treatment would escalate, as the seeds are expensive. In Australia, the seeds are purchased in allotments of 60, rather than individually. At St. George Cancer Care Centre (Sydney, Australia), the number of seeds implanted into a patient is limited to 120 in order to make the treatment financially feasible. The use of stranded seeds, such as Rapid STRAND™ by Oncura (Illinois, U.S.A.), reduces the problems observed with loose seeds, [56, 57] but they also deliver higher urethral dose than loose seeds.
2.2.9 Complications arising from HDR Prostate Brachytherapy

Despite the difference in technique and radiation source strength of the various radiation treatment modalities used to treat prostate cancer, they pose the same risks to all organs in close proximity to the prostate — namely the rectum, urethra, and bladder. [50] The numerous treatment modalities for prostate cancer generally result in relatively comparable disease control, so the probability of inducing complications, and severity of these complications, are factors that are equally important when assessing the effectiveness of a particular treatment. The most common morbidity experienced by HDR brachytherapy patients occurs at the rectum, which manifests as rectal discomfort, pain, spasms, diarrhea, rectal bleeding, hemorrhaging, proctitis, and incontinence. [66, 67] A patient will generally not suffer from all these complications, but a combination of them. All of these complications impede the patient’s ability to partake in common daily activities, and may severely affect their lifestyle. The severity of the complication is determined by the level of discomfort suffered by the patient, and the amount of medical intervention necessary to alleviate the problem. A desire by the *European Organization for Research and Treatment of Cancer* (EORTC) for a common, consistent toxicity reporting criteria eventually led to the scoring of late effects in normal tissue currently in use. Studies of rectal toxicity typically use a late-effect grading criteria developed by the *Radiation Therapy Oncology Group* (RTOG), which was developed through a collaborative effort between physicians interested in fast neutron therapy, and the RTOG group. The Late Radiation Morbidity Scoring Scheme is highly detailed, and a concise summary can be found in an article published by Cox et al. [67] Briefly, the scoring scheme grades complications based on the severity of the complications at various tissue sites. The grading scale ranges from 0–5. A grade of 0 indicates that no negative radiation-induced effect was observed, while a grade of 5 is an effect that led to death. In many research publications, severe toxicities are defined as anything beyond a Grade 3. Assessment of late radiation effects require a great deal of long-term observation, as the effects may worsen over time, or may only be observed after several months following the conclusion of treatment.
The RTOG criteria has been criticized due to its severe limitations. For example, the grading system does not consider the specific type, or types, of rectal complications suffered by the patient, nor the number of complications. Instead, all of the patient's rectal complications are given a single score to indicate the overall severity. It is impossible to determine whether the patient is suffering from a single rectal complication, or from multiple toxicities, based on the score. Furthermore, the current grading system does not have a method for scoring a patient's severity when each complication is at a different level of severity; corollary to this, a single score cannot indicate which complication suffered by the patient requires the most attention. [66] However, the scoring criteria must be understood due to its widespread use in clinical studies.

While rectal complications are also prevalent in EBRT, IMRT, and LDR brachytherapy treatment of prostate cancer, the large dose per fraction used in HDR brachytherapy treatment, means that the dose absorbed by the rectum requires a greater amount of attention. As discussed earlier, the overall survival rate of prostate cancer sufferers has increased significantly since diagnosis and treatment techniques have improved. Consequently, the trend in patient studies has steered towards analysing the 'quality of life' of the patient following treatment rather than simply examining survival rates, as all treatment modalities are effective at controlling the disease. Ideally, normal levels of bowel, bladder, urinary, sexual, and rectal function would be unaffected by a treatment. Urinary function is most affected in men treated with radical prostatectomy, while bowel function is most affected by those receiving EBRT and brachytherapy. Sexual problems are present in many patients prior to treatment due to the presence of prostate disease, but may be intensified by a treatment, particularly radical prostatectomy. [68]

The advent of modern radiotherapy techniques such as Intensity Modulated Radiation Therapy (IMRT) and 3D Conformal Radiotherapy (3D-CRT) have reduced the radiation
delivered to normal tissue that surrounds the prostate, while allowing for an increase in the prescription dose. Rate of local control, biochemical freedom from disease, and overall patient survival have all improved due to this increase in dose. [69, 70, 71] Unfortunately, this is congruent to the risk and severity of late rectal toxicity, which also increases with the total dose, and the volume of the rectum that is irradiated. Despite the ability of IMRT to deliver dose that conforms to the target volume, no external radiotherapy technique can match the level of conformity offered by brachytherapy, [72] except perhaps proton or hadron therapy, although their clinical application is rare due to the small number of such facilities in existence. The incidence of late rectal complications of any grade following HDR prostate brachytherapy, as defined by the RTOG, is approximately 10–25%. The incidence rates reported in the literature vary widely between different treatment centres. Many studies are concerned mainly with rectal complications that are considered Grade 2 or higher, while some studies would consider a treatment successful if the number of Grade 3 or worse complications was minimal.

The rate of incidence of complications depends on a number of factors, such as the number of fractions and dose/fraction used in the treatment, [8, 73] and the severity of the disease prior to treatment. [23] It also depends on whether HDR brachytherapy was delivered as a boost to EBRT, [9] or delivered alone as monotherapy. [23, 22] The benefits of increasing the total dose delivered during prostate treatment has been illustrated in dose escalation studies involving EBRT treatment, [69, 70, 72, 9, 73] so research in HDR prostate brachytherapy appears to have recently shifted towards increasing the dose delivered per fraction, and hence, increasing the overall SED to the prostate.

As discussed in the previous section, hypofractionated prostate treatment, or the delivery of fraction sizes larger than the standard 1.5 to 2 Gy/fraction, has been explored in numerous studies. A study by Akimoto et al. [73] analysed the incidence and severity of Grade 2, or worse, rectal bleeding in patients treated with hypofractionated EBRT,
where the dose delivered per fraction was escalated from the standard 2 Gy/fraction, up to 3 Gy/fraction, where the patient was treated at a frequency of 3 fractions per week. The total dose delivered to the patient was 69 Gy, all delivered using hypofractionated EBRT. This study was performed after reports showed that the response of prostate cancer to radiation may be similar to that of late-responding normal tissue, indicating that hypofractionated treatment may improve local control rates. Particular emphasis was placed on the correlation between the total rectal dose, calculated from the dose-volume histogram (DVH), and the incidence rate of Grade 2 or worse rectal bleeding in patients.

Of the 52 patients included in the study, 13 patients (25%) developed Grade 2 or worse rectal bleeding. Increasing the dose delivered per fraction resulted in improved tumour control, but at the expense of a high incidence of Grade 2 or worse rectal bleeding. This prompted a subsequent study by Akimoto et al. [9] on patients treated with hypofractionated EBRT delivered in conjunction with HDR brachytherapy. In the study of 100 patients, only 10 out of 100 patients (10%) developed Grade 2 or worse rectal bleeding, showing significant improvement over their first study in this regard. There was also a benefit in terms of tumour control, or biochemical non-evidence of disease (bNED).

The use of HDR brachytherapy delivered as a monotherapy has also been explored, most notably by Martinez et al., [23] and by Yoshioka et al. in Japan. [22, 21] The benefits of hypofractionated treatment, as hypothesized from studies of the $\alpha/\beta$-ratio of prostate cells, means that the full potential of HDR brachytherapy may be realised if delivered as a monotherapy. By delivering HDR brachytherapy in conjunction with an external beam treatment, the benefit of hypofractionation isn’t fully realised. In a study by Yoshioka et al., [21] 43 patients were treated with HDR brachytherapy monotherapy at Osaka University Hospital between 1995 and 2001. Patients were treated with a total of 54 Gy, delivered in nine fractions at 6 Gy/fraction. Two fractions were delivered daily, separated by $\geq 6$ hour intervals. Of the 43 patients involved in the study, 8 patients (2%) suffered from Grade 1 toxicity, 12 patients (28%) suffered from Grade 2 toxicity, and 1 patient
suffered from Grade 4 (Grade 3 or higher) toxicity. The use of HDR brachytherapy delivered as a monotherapy resulted in good local control and bNED rates when compared to EBRT and combined EBRT and HDR brachytherapy outcomes. Late toxicity effects arose in 5 patients (four suffered Grade 1, and one suffered a Grade 2 rectal ulcer) > 2 years following treatment, but none of them complained of incontinence, pain, or any symptom other than bloody stool.

2.2.10 Potential Benefits Of Using A Rectal Dosimetry System

The probability that a patient will suffer from rectal toxicity is correlated to the total radiation dose absorbed by the rectum. Therefore, the best way to reduce this risk is to ensure that the radiation dose to the rectum is no greater than the expected dose, as defined in the plan. This requires that the treatment delivered to the patient is congruent with the treatment plan. If the dose delivered to the rectum could be monitored while the treatment was in progress, then the risk of the patient suffering rectal complications could be reduced by either stopping, or adjusting, the treatment when the measured dose is greater than expected. Potentially, the total accumulated dose delivered to the rectum could be measured in one minute intervals after the start of the treatment, and compared to the calculated rectal dose in order to verify that they are in agreement.

An alternative application of such a dosimetry system would be to use it to measure the total rectal dose delivered during a treatment, and adjust the treatment plan of the following fraction if the rectal dose was too high. For example, if the rectal dose measured during the first fraction is greater than expected, the treatment plan used to deliver the second fraction could be adjusted to ensure that the rectum is under-irradiated during the next fraction. However, this may be difficult to accomplish in practice, because these adjustments may have ramifications on the quality of the treatment. The dose distributed throughout the tumour volume must remain high enough to adequately treat the disease.
Further discussion regarding the application and considerations to be taken in real-time dosimetry will be presented in Chapter 5, where the progress of a Phase II clinical trial related to rectal dosimetry in PDR brachytherapy will be discussed.
2.3 MOSFETs in radiation dosimetry

The use of semiconductor detectors in radiation dosimetry has become quite popular due to several inherent advantages they have over ionization chambers. The most obvious advantage of a semiconductor-based dosimeter is its small physical size compared to gas-filled ionization chambers. While semiconductor detectors can be made quite large for particular high energy applications, they can also be scaled down to sub-micron dimensions. The main focus of the research presented in this report is the performance of a new metal oxide semiconductor, field effect transistor (MOSFET) dosimeter, and its potential application as a real-time dosimeter in HDR brachytherapy.

The effect of radiation on the performance of a MOS device was first noted by Hughes and Giroux, having discovered the trapping of positive charges in the oxide layer following irradiation. Prior to their observation, irradiation of a MOS structure was believed to have little effect on a MOS device because charge carriers produced in the silicon shouldn’t have an effect on the current flow through the MOSFET, and therefore, shouldn’t have a detrimental effect on performance. Radiation induced charge trapping in insulators had already been observed and explored by that time, yet nobody thought that similar effects in the insulating layer of MOS devices would cause an observable performance degradation.

The use of the MOSFET as a means to measure cumulated dose was suggested by Holmes-Siedle as early as 1974. [7] The first special ”dosimetric MOSFET” was created by an Oxford (UK) based company started by Holmes-Siedle, which would later become Radiation Experiments and Monitors (REM) in 1985. This device, called the TOT200, was used to measure space radiation in 1978. In recent years, there has been major work done to develop a MOSFET dosimeter towards medical applications, as work
by Hughes et al. [74], Gladstone et al. [75] and Rosenfeld et al. [76] has shown the potential benefits of a MOSFET in vivo dosimeter.

The aim of this section is to explore the structure of the MOSFET, and illustrate the special properties of MOSFETs that enable it to be used as a radiation dosimeter. The field of radiation effects in electronic components is enormous due to its relevance in aerospace electronics. [77] The applicability of this research in medical physics is serendipitous rather than intentional. MOS devices were not designed for radiation dosimetry, and radiation-induced effects in MOS devices are normally considered a nuisance rather than valuable. The constant radiation emitted from minerals contained within rocks and mountains, can cause electronic components to degrade and function improperly over time, while cosmic radiation may cause the device to malfunction or shut down due to a single ionizing event. This section will provide an overview of radiation effects in a MOSFET, and how these effects can be measured and then converted into a value for absorbed dose.

The section is divided into three subsections. The first section will provide an overview of MOS devices, including a brief review of p-type and n-type doped semiconductors, energy bands, and conductivity. Section 2 describes the radiation-induced effects that are produced in silicon dioxide following radiation exposure, particularly the generation and migration of electron–hole pairs through the oxide. The third and final section of this chapter describes the characteristics of the charge traps in detail, and the relationship between accumulated radiation defects, and the bias voltage applied to the gate electrode of the MOSFET during irradiation. An understanding of charge trapping, and charge annealing processes may be able to explain certain performance characteristics that have been reported by researchers who have examined various MOSFET dosimetry systems. This chapter will hopefully present itself as a useful source of information on MOSFETs aimed squarely at those interested in MOSFETs from a medical physics perspective, rather than from the perspective of one who is concerned about the ramifications
of radiation-induced effects in electronics intended for use in aircrafts, nuclear weapons, satellites, and the aerospace industry.

2.3.1 An Overview of Semiconductor Materials

2.3.1.1 Semiconductor Band Structure

A semiconductor is a type of solid or liquid material that conducts electricity better than an insulator, but worse than a metal. Metals such as copper, silver, and aluminium can conduct electricity well when a voltage is applied to it, while insulators such as diamond are very poor conductors. At room temperature, the electrical conductivity of semiconductor materials is somewhere in between that of a metal and insulator. When the discrete energy levels of individual atoms merge together to form a solid, bands of energies that contain a large number of closely spaced energy levels are produced. [78] While a single, isolated atom has a very distinct and well defined energy level, this isn’t the case when describing atoms that are bound within a crystal lattice. The Pauli Exclusion Principle requires that no two electrons ever have identical quantum numbers, so when individual atoms join together and form a crystalline lattice structure, energy bands within the lattice are formed from the individual energy levels. The energy levels that form the band are slightly shifted in energy so that they aren’t identical. Therefore, an energy band is comprised of a number of closely spaced energy levels that appear as a broad band, and the energy of an electron within the lattice must have an energy that falls within one of the energy bands. Each band is separated by a range of forbidden energies that cannot be occupied by an electron. Consequently, the range of forbidden energies that separate two energy bands is referred to as the forbidden gap, or band gap energy. The band structure of a material is the property that determines whether a material is a conductor, insulator, or semiconductor. Typically, only the valence electrons in the outer shell are of concern, while the lower energy electrons that have filled the lower shells do not contribute to conductivity, and are not allowed to wander through the lattice. The next, higher energy
band is called the conduction band. As its name implies, electrons in this band are free to migrate around the crystal, and contribute to the conductivity of the material. The difference between an insulator and conductor material is the relative size of the forbidden gap. A semi-conductor has a forbidden gap that is of an intermediate size when compared to insulators and metals. Insulators have a much larger band gap, while metals have a relatively narrow band gap.

2.3.1.2 Formation of P-type and N-type Silicon

In a pure semi-conductor, all the electrons in the conduction band and all the holes in the valence band would be caused entirely by thermal excitation. [78] Furthermore, there would be an equal number of electrons and holes in an intrinsic semi-conductor, as each electron excited into the conduction band must leave a single hole behind in the valence band. In practice, this sort of situation is virtually impossible to achieve, as low levels of impurities are contained within all semi-conductors.

Impurities may also be introduced to a semi-conductor intentionally. An impurity in a semi-conductor material tends to behave as a substitute in place of a normal atom. In silicon, an impurity would take the place of a normal silicon atom within its crystalline lattice. One type of impurity regularly used to dope silicon belong to Group V in the periodic table, and have five valence electrons. Group IV atoms, or tetravalent atoms such as silicon ($^{28}_{14}$Si) differ from Group V atoms because they have only four valence electrons, and are characterized by their desire to form four covalent bonds with surrounding atoms in order to have a total of eight valence electrons in its outer orbital. When a Group V impurity such as phosphorus ($^{31}_{15}$P) is substituted for a Si atom in the silicon lattice, the phosphorus forms four single bonds with four surrounding Si atoms in the lattice, just as a normal Si atom would in a pure Si crystal. However, the phosphorus impurity’s fifth valence electron would not participate in a bond. This is illustrated in Figure 2.5. The
Figure 2.5: A schematic diagram depicting the impact of doping a silicon crystal with a Group V donor impurity such as phosphorus. The donor impurity introduces electrons to the crystal without increasing the number of positively charged holes, thereby increasing the electron concentration without increasing the hole concentration. The donor electrons require little energy to be excited into the conduction band.

fifth electron is not held to the crystal strongly. It occupies an energy level within the forbidden energy gap just below the conduction band, so only a small amount of energy is required to excite it to the conduction band. Impurities of this type are normally referred to as donor impurities because they contribute electrons to the conduction band without introducing additional positive vacancies behind in the valence band. Furthermore, the energy difference between the donor impurity and conduction band is small,
Figure 2.6: A schematic diagram depicting the impact of doping a silicon crystal with a Group III acceptor impurity such as boron. The acceptor impurities result in positive hole vacancies in the valence band without introducing additional electrons, thereby increasing the hole concentration without increasing the electron concentration. Very little energy is required to excite valence electrons to fill the vacancies, and so holes are formed readily in the valence band.

which ensures that the donor electrons almost always have enough energy to jump to the conduction band. The term *n-type silicon* is used to describe silicon that is doped with Group V impurities.

Silicon doped with Group III, trivalent atoms, such as boron ($^{11}$B), produces a *p-type silicon*. [79] A p-type silicon derives its name from the high concentration of positively
charged holes in the valence band as a result of substituting a Group III impurity for an Si atom in the silicon crystal. A Group III atom has three valence electrons, so when an impurity such as boron is substituted for a silicon atom, the boron can only form three bonds with the surrounding Si atoms rather than four. Consequently, one of the neighbouring silicon atoms will only form three bonds rather than four, leaving a positively charged vacancy (i.e. a "hole") where a silicon has nothing to bond to. The energy level of the vacancy introduced by the impurity lies in the forbidden gap, slightly above the valence band. This is illustrated in Figure 2.6 Holes are left behind in the valence band whenever a valence electron is excited to the energy level of the impurity. This process is quite similar to the holes formed when valence electrons are excited up to the conduction band. However, in the case of acceptor impurities, holes created in the valence band do not correspond to an increase in the number of free electrons in the conduction band, as they fill the vacancy introduced by the impurity instead. Furthermore, the energy difference between the energy level of the vacancy and the top of the valence band is small, which ensures that the impurities are readily filled by thermally excited valence electrons.

2.3.2 MOSFET Structure, and the Effects of Irradiation

2.3.2.1 Typical MOSFET Structure

The structure of a typical MOS device is shown in Figure 2.7. The components include a thin, micron-scale, insulating silicon-dioxide layer sandwiched between a metallic gate electrode and either an n-type or p-type silicon substrate. The role of each component in a functional MOSFET device will be illustrated more clearly as the section progresses, but a brief description of each component is provided here as an introduction to the general operation of a MOS device. The gate is given its name because it is used to control the conductivity of the semiconductor material. The electrical conductivity of the silicon substrate is controlled by altering the magnitude of a bias voltage that is applied to the gate. In the absence of a gate bias, the conductivity of the semiconductor material is
low, and the device does not conduct current. This is also true if the magnitude of the
gate voltage is below a certain voltage; the minimum gate voltage required to induce a
current through the silicon is called the threshold voltage, $V_{th}$. The gate is approximately
1 $\mu$m thick, and can be made of a metal, or a material such as polysilicon. Polysilicon is utilized as the gate material because the threshold voltage of a MOS device with a
polysilicon gate is lower than a similar device that utilizes a metallic gate. [7] The charge
carriers that constitute the current flow through the silicon originates from an electrode
called the source. When the magnitude of the gate voltage is greater than the $V_{th}$, charge
carriers can flow from the source, through the bulk of the semiconductor, and towards an
electrode on the opposing end of the insulating oxide. This electrode is called the drain.
The current exits the semiconductor at the drain.

Silicon dioxide (SiO$_2$) is formed when silicon is exposed to oxygen or air. The SiO$_2$ layer found in electronic components is 'grown' under well-controlled conditions and higher temperatures to minimize the number, and type, of flaws present in the silicon. The reaction involved in the production of SiO$_2$ is [80]

$$Si + O_2 \rightarrow SiO_2$$

$$Si + 2H_2O \rightarrow SiO_2 + 2H_2$$

The reason SiO$_2$ was chosen as the ideal insulator for MOS devices, and many other Si devices, is due to the near-perfect interface properties between silicon and silicon dioxide. During SiO$_2$ production, oxygen atoms are diffused into a bulk piece of silicon, reacting with the silicon atoms and forming an oxidized region. The result is an ideal match along the interface between SiO$_2$ and Si layers. This near-perfect match along the SiO$_2$–Si interface isn’t observed when other insulators are used instead of SiO$_2$. [80]

### 2.3.2.2 Production and Recombination of Electron–hole Pairs in Silicon Dioxide

When an electronic device is struck by charged particles, neutrons, or electromagnetic (EM) radiation such as x-rays and $\gamma$-rays, it may result in ionization or atomic displacement in the device, and possibly permanent radiation damage. The basic radiation-induced processes can be separated into four separate stages: electron–hole generation, charge migration/transport, charge-trapping processes in the SiO$_2$ layer, and charge-trapping along the SiO$_2$–Si interface, where the insulator and semiconductor materials are joined. An overview of the common photon interactions were previously described in Chapter 2, albeit in terms of a radiobiological context.
When a MOSFET is irradiated by photons, the interactions that occur within the oxide volume of a MOSFET result in the generation of electron–hole charge pairs. Electron–hole pairs are produced in the oxide when an incoming photon transfers all, or part, of its energy to a valence electron of a SiO$_2$ molecule. The energy imparted to the electron may provide it with sufficient energy to reach the conduction band of the SiO$_2$ lattice, leaving a positively charged atom behind in the lattice. The probability that the electron–hole pairs will recombine following an ionizing event depends primarily on the \textit{linear energy transfer} (LET) of the radiation, and the magnitude of the bias voltage applied to the gate. LET is a quality of radiation that describes the average energy deposited by an incident particle per unit distance along the path it takes while traversing through the material. [6] The LET of the radiation depends on the type of radiation, the energy of the radiation, and the type of absorbing material. Higher LET radiation will leave a denser electron–hole concentration along its track so that the mean distance between electron–hole pairs is short. The close proximity of the electron–hole pairs produced by high LET radiation increases the likelihood that they will recombine. The magnitude of the bias voltage applied to the gate during irradiation also has a large impact on the probability of electron–hole recombination, as the electric field induced by the gate voltage is responsible for separating the charge-pairs generated within the oxide. A stronger electric field is more effective at separating the charge-pairs produced during irradiation. For radiation dosimetry applications, a gate bias of positive polarity is usually applied to the gate during irradiation. This will be discussed in greater detail in Section 2.3.7.

Several researchers have studied the response of MOS devices when exposed to different radiation sources, radiation types, and radiation energies. Several models were created to describe the strength of the recombination process, and try to fit the experimental results. The most fundamental models are the \textit{columnar recombination} and \textit{Onsager germinate} models. The Onsager germinate model works well when the model is limited to high LET.
radiation that produces dense ionizations and charge pairs along its track; while the ger-
minate recombination model is effective at describing the recombination of charge pairs
that are, on average, spaced relatively far apart. Dozier and Brown measured the response
of a MOS device when exposed to photons of intermediate energies. [6] These interme-
diate photon energies appear most relevant to the work presented in this paper. Figure 2.8
represents the fractional yield of non-recombined charge pairs in SiO$_2$ when irradiated
at different photon energies. Photons of various energies were delivered by five different
radiation sources: $^{60}$Co $\gamma$-rays, Mo x-ray tube (17.4 keV), Cu x-ray tube (8.04 keV), Cr
x-ray tube (1.49 keV), and synchotron radiation (70 eV). Each photon produces a sec-
ondary electron with an energy that is nearly equal to the energy of the primary photon.
The secondary electron is responsible for the energy deposition in the oxide. As the pri-
mary photon (and secondary electron) energy decreases from 10 keV, the stopping power
increases by a factor of 4–5, resulting in a much denser track of charge pairs from which
stronger recombination is expected. This approaches the lower limit of the columnar
model. A bias voltage of $3 \times 10^5 \text{V/cm}$ was applied to the MOSFET gate during irradiation. As the yield of non-recombining pairs also depends on the strength of the electric field, and consequently, the bias voltage applied to the gate during irradiation, a larger gate bias will yield improved charge separation, resulting in fewer recombining charge pairs. This dependence on the gate voltage is experimentally observed as independent of radiation LET. [81]

2.3.3 Migration of Holes through SiO$_2$

Holes cannot physically migrate through a crystal lattice. Under the influence of an electric field, holes respond quickly, undergoing an apparent motion via a complex process of electron charge motion. Hole migration is described as ”apparent” motion because it is actually the result of electron migration. An electron is usually trapped with a single hole, but may move from hole to hole by thermally activated ”hopping” when it has enough energy. [78, 6] At low temperatures, electrons move very slowly through the crystal. When an electron migrates away from a hole and combines with another, the hole with which it combines is eliminated, while a new hole is left behind at the electron’s initial position. The hole appears to have migrated to a new location, when in fact, its apparent motion is the result of electron hopping, which eliminates one hole and creates another. The hole migration process through an insulator is called polaron hopping, [6] and is far slower than electron transport. The transport of electrons towards the gate electrode is comparatively quick, as electrons migrate through the conduction band.

2.3.4 Description of Charge Trapping

The role of the insulating oxide layer in MOS devices is to act as a barrier between the metal and semiconductor so that there is no current flow between the top metal gate, and the semiconductor. One of the effects that ionizing radiation may have on the oxide is a
reduction of the energy barrier along the SiO$_2$–Si interface, which would allow charges to transfer between the semi-conducting and insulating materials. Another effect is the formation of a semi-permanent charge sheet within the SiO$_2$, where the majority of holes are trapped. This charge sheet produces its own field, which alters the conductivity of the material by bending the energy bands of the material. While both electron and hole traps are present in the oxide, the concentration of trapped holes is greater than the electron concentration by a factor of $10^3$ to $10^6$. As the number of trapped holes increase near the SiO$_2$–Si, the strength of the electric field that surrounds the positive charge sheet also increases, which makes the migration of newly-formed holes towards the silicon increasingly difficult. [6]

There are two types of oxide traps that are of importance. The first type are the traps located within the major bulk of the oxide, introduced by the presence of impurity ions that are incorporated into the lattice during the growth of the oxide layer. These traps are called oxide states or traps. The remainder of the traps are located along the SiO$_2$–Si interface, and appear due to the imperfect match between the silicon and silicon dioxide. They are commonly referred to as interface states or traps. [7, 6, 80, 82, 83] While the interface formed between this particular pair of semiconductor–insulator materials was earlier described as ”nearly perfect”, a small concentration of imperfections do exist within several nanometers of the interface.

The distribution and characteristics of the charge traps in the oxide can be quite different, depending on their distance away from the SiO$_2$–Si interface. The majority of oxide traps are concentrated within a narrow region that begins at a distance of approximately 2 nm from the SiO$_2$–Si interface, but the behaviour of traps along the interface are not fully understood yet. Various unified models have been proposed based on research by Griscom and others to describe the behaviour of the traps with respect to distance from the interface. [7] In 1988, Helms described the oxide volume near the SiO$_2$–Si interface
as being divided into five (somewhat) distinct regions, each with their own trapping characteristics. The regions are differentiated by the type of charge trapping and migration processes that occur, and described with respect to their distance from the SiO$_2$–Si interface. Based on this description, Holmes-Siedle et al. [7] provided a summary of the behaviour of the holes in each region, particularly the process of charge trapping, and the decay of interface trapped charges ($Q_{it}$) over time. The behaviour of the traps in the five regions will be described here.

The region located along the interface is called the SiO$_x$ region, characterized by the presence of interface traps along the SiO$_2$–Si interface, where the SiO$_2$ and silicon lattice are joined. The proximity of this region to the interface is labelled "Region 1" in
Figure 2.10: Representation of the ionizing interaction, charge transport, and various hole-trapping processes that occur in the interface region during irradiation of a MOS-FET. The positive charge sheet ($Q_{ot}$) that forms can clearly be seen.

Figure 2.9. This region is located within an atomic bond length of the SiO$_2$–Si interface, or approximately 0.2 nm. When an electron-hole pair is produced during an ionizing event, the bias applied to the gate induces an electric field that forces the hole to migrate towards the silicon, which may become trapped by an interface trap. The trapped charge is generally referred to as an interface trapped charge, $Q_{it}$. Interface traps are described as fast interface states, as the charge state in this region changes rapidly with the Fermi energy level between the SiO$_2$ and Si. The rapid exchange of charges between the oxide and the silicon substrate results in the quick annihilation of interface trapped holes by electrons that tunnel into the oxide from the silicon bulk, resulting in a rearrangement of the atomic bonds along the SiO$_2$–Si interface.

The presence of bulk oxide traps is used to define the third region described by Helmes.
Region 3 is located beyond the near-interface region, and within 20 nm distance from the SiO$_2$–Si interface. This region contains the majority of the shallow and deep hole traps; consequently, the majority of hole-trapping occurs in Region 3. Region 4 is situated between Region 3 and the gate electrode, and represents the remainder of the oxide volume. The size of Region 4 is larger than Regions 1–3 combined by several orders of magnitude, encompassing nearly the entire oxide volume; thus, electron–hole pairs can be assumed to originate entirely within Region 4. Despite its physical size, Region 4 contains very few charge traps when compared to the regions closer in proximity to the silicon substrate. As a result, the majority of holes created in the oxide encounter very few traps while migrating towards the bulk oxide traps in Region 3. The concentration of oxide traps peaks along the interface plane between Regions 2 and 3, and declines sharply at distances greater than 20 nm from the substrate. In contrast, the oxide and interface regions represent a rather insignificant portion of the total oxide volume, yet they contain nearly all the charge traps. Under the influence of a gate bias voltage, holes produced in Region 4 are driven to the oxide traps in Region 3, where the concentration of charge traps becomes increasingly dense. The build-up of $Q_{ot}$ in Region 3 is mainly responsible for the shift in $V_{th}$ observed following MOSFET irradiation. A portion of the holes trapped within the first few nanometres of the Si–SiO$_2$ interface are eventually cleared by electrons originating from the silicon, resulting in a region free of $Q_{ot}$ and $Q_{it}$ build-up, and a "sheet" of positive trapped charges ($Q_{ot}$) within a narrow band in Region 3, generally referred to as a charge sheet. The holes trapped along the charge-sheet comprises nearly all oxide-trapped charges remaining in the oxide following the clearance of traps. The charge sheet, and the region devoid of trapped holes as a result of electron tunneling from the silicon are both depicted in Figure 2.10.

Region 2 is generally referred to as the near-interface region, and is located between Regions 1 and 3. Region 2 is located slightly further away from the SiO$_2$–Si interface than the SiO$_x$ region, but still within close proximity of the interface. Region 2 contains what
are known as *border traps*, while holes that become trapped in this region are referred to as border-trapped charges, $Q_{bt}$. The term "border trap" refers to the mixed characteristics of the traps found in this region. Generally, interface traps are characterized by the rapid exchange of charges with the silicon, while oxide traps are long-lived and do not interact with the silicon. Border traps in the near-interface region blur this distinction, as it contains traps that exhibit the behaviour of interface traps, and traps that behave like oxide traps. The border traps in the near-interface region differ from interface traps mainly by the speed at which their traps can be filled by an electron originating from the silicon. Some border traps can be filled with charge from the silicon within about 1 minute, although some may also take several years. These times are far slower than the filling of interface traps present in the SiO$_x$ region, which have a fill-time on the order of picoseconds. As the process of clearing $Q_{it}$ and $Q_{bt}$ in these two regions requires an amount of time on the order of the total irradiation time, it has time-dependent effect on MOSFET performance, which will be described in a later section.

Region 5, which has not been discussed actually refers to the thin layer of silicon closest to the SiO$_2$–Si interface, and directly faces the SiO$_x$ region of the oxide. The charge trap structure of the SiO$_x$ region is affected by its proximity to this silicon region, as the charge state of the region is heavily dependent on the Fermi level of the silicon.

2.3.5 Positive Gate Bias During Irradiation

The gate bias voltage used to separate the electron–hole charge pair produced during irradiation has been assumed to be of positive polarity so far in this chapter. A positive voltage at the gate induces a field that drives holes towards the substrate, and electrons towards the gate. A negative bias may also be applied during irradiation, but this has a dramatic effect on the amount of charge trapping that occurs in the oxide. Under the influence of a negative gate bias, holes would migrate in the direction of the gate electrode,
while electrons would migrate quickly towards the silicon. However, only the holes produced in the near-interface region (i.e.: Region 2) can become trapped in Region 3, since they would encounter Region 3 while migrating towards the gate. In contrast, holes that are generated in the remainder of the oxide would migrate towards the gate electrode and exit the oxide, while the corresponding electrons are driven towards Region 3, clearing the charge sheet of trapped holes. Since Regions 1 and 2 represent only a minute fraction of the total oxide volume, very few electron–holes generated in the oxide become trapped.

With regards to employing MOSFET devices for dosimetric applications, the use of a negative gate bias during irradiation is undesirable. The fraction of the radiosensitive oxide volume being utilized is too small to cause significant change in the MOSFET’s electrical properties. The use of MOSFET relies on the measurement of the electrical changes caused by the build-up of $Q_{it}$ and $Q_{bt}$ in the oxide, and the application of a positive gate bias results in greater electron–hole generation and charge build-up.

2.3.6 Structure of Oxide Defects

The oxide defect, or hole trap, responsible for the radiation-induced trapping of positive charges in the oxide has been identified by electron spin resonance (ESR), and commonly referred to as an $E'$ centre. [83, 84] An $E'$ centre is a trivalent silicon atom with an unpaired electron in a dangling orbital, which is back-bonded to oxygen atoms ($\cdot Si \equiv O_n$). $E'$ centres are the product of radiation-induced trapping, expressed as follows

$$\equiv Si - Si \equiv \rightarrow \equiv Si \cdot Si \equiv + e^-$$

(2.6)

where the three back-bonds are to oxygen atoms. The structure of this type of defect is entirely radiation-induced. The structure of other types of defect centres have been identified, and due to the presence of Cl, OH, and H impurities in the oxide. At temperatures
above 100 K, $E'$ centres tend to undergo annealing (relaxing) within minutes or hours following radiation exposure. [84] The time required for the annealing depends on the type of defect being considered, along with the temperature of the oxide. Annealing may occur within minutes like it does in $E'$ centres, or it may take several years in a very stable variant of a defect. The OH concentration in the oxide plays a role in post-irradiation anneal kinetics, as do radicals produced when O$_2$ reacts with an $E'$ Centre.

Interface traps exist due to the imperfect formation of bonds between the Si and SiO$_2$ lattices, including disconnected chemical bonds, and the presence of impurities. The amount of charge that is trapped along the interface can change quickly, as it depends on the number of electrons tunnelling through the interface and into the oxide volume. The probability of electron tunnelling is dependent on the size of the potential barrier along the interface, which in turn, is dependent on the strength of the electric field at the interface. The electric field in the oxide is mainly due to the bias voltage applied to the gate, so the size of $V_g$ indirectly influences the concentration of interface-trapped charges. However, as the number of holes trapped in the oxide increases with radiation exposure, the strength of the net electric field becomes increasingly dependent on the electric field that surrounds the charge-sheet ($Q_{ot}$) in Region 3 of the oxide. The net electric field is comprised of two independent components: the electric field induced by the gate bias voltage $V_g$, and the electric field that surrounds the positive charges trapped in the oxide. Since the $V_g$-induced component of the electric field does not change if $V_g$ is held constant, any changes observed in the net electric field at the interface during irradiation can be entirely attributed to a change in the concentration of holes trapped within the oxide.
2.3.7 The Effect of Oxide and Interface Charge Build-up on the Threshold Voltage ($V_{th}$)

In this chapter so far, the discussion of radiation-induced changes in the MOSFET has primarily focused on electron–hole production, charge migration, and hole trapping. In electronics, the consequence of radiation-induced damage in silicon dioxide would result in the loss of function and reliability, and eventual failure of the MOS device. Clearly, this is undesirable in many industries, particularly the aerospace and aviation industries. How does the build-up of damage in SiO$_2$ affect the gate voltage, and how does a change in the gate voltage enable us to use MOSFETs as radiation dosimeters?

The gate voltage discussed up to this point has been a positive bias applied during irradiation in order to separate the electron–hole pairs produced in the silicon dioxide later by an ionizing event. This voltage is sometimes referred to as the irradiation gate voltage ($V_i$), and has been assumed to be of positive polarity regardless of whether the MOSFET comprised of a p-type or n-type semiconductor. The type of semiconductor found in a MOSFET has no effect on the creation of charge pairs in the oxide, or charge transport processes during irradiation. However, to qualitatively describe the function and performance of a MOSFET device after irradiation, the type of silicon is critical, as it determines the polarity of the bias voltage which must be applied to the gate in order for a MOSFET to function, or ‘switch on’. An n-channel MOSFET refers to a MOSFET device comprised of a p-type silicon substrate and requires a positive gate bias to function (i.e. while it’s not being irradiated), while a p-channel MOSFET has an n-type silicon substrate and requires a negative gate bias. In order to understand how the two types of MOSFETs function, and how they differ, they must be discussed separately.
2.3.7.1 N-channel MOSFET

An n-channel MOSFET is made of a p-type silicon substrate that contains a high concentration of holes in the valence band, and a far lower concentration of electrons in the conduction band. In the theoretical situation where there are no holes trapped in the SiO$_2$ layer, and no bias voltage applied to the gate, the electron concentration throughout is the same throughout the entire silicon bulk. If a positive bias voltage was applied to the gate electrode, this bias would attract electrons in the p-type silicon towards the SiO$_2$–Si interface. Since it was assumed earlier that no positively-charged holes are trapped in the oxide, the applied bias on the gate is the only source of potential available to draw electrons towards the SiO$_2$–Si interface region situated between the source and drain. A schematic diagram of a MOSFET is illustrated in Figure 2.7. If the gate voltage is increased, the concentration of electrons gathered along the SiO$_2$–Si interface will also increase. When the gate bias reaches a certain threshold, the electron and hole concentrations are equal along the interface. At this bias voltage, the narrow region of the substrate situated between the source and drain is no longer dominated by the positive charges in the p-type silicon, nor is it dominated by the negative charge of the electrons that were attracted towards the interface. The gate voltage required to equalize the electron and hole concentrations is called the *threshold voltage* ($V_{th}$). If $V_g$ is increased further so that $V_g > V_{th}$, the concentration of electrons between the source and drain becomes greater than the concentration of holes, resulting in the formation of a negative charge channel along the interface. This negative charge channel, or *n-channel*, is essentially a small, localized volume of n-type silicon material that exists within the p-type silicon substrate. However, this n-type region only exists in the presence of $V_g$, where $V_g > V_{th}$.

In reality, a distribution of positive trapped charges ($Q_{ot}$) are present in the oxide at all times, even prior to irradiation. Due to the attraction between the trapped charges present in the oxide and free electrons within the silicon bulk, the attraction of electrons towards the SiO$_2$–Si interface can be attributed to two independent factors, rather than just the
Figure 2.11: A typical $I_D-V_g$ curve for an n-channel MOSFET. Curve $A$ is the characteristic $I_D-V_g$ relationship of a pre-irradiated MOSFET, while $B$ is the shifted $I_D-V_g$ curve that follows irradiation. Curve $C$ represents a MOSFET that has been exposed to a significant amount of total radiation dose, and suffers from leakage current.

When $V_g > V_{th}$, the conductivity within the n-channel region, and consequently, the current that flows from the source electrode to the drain ($I_D$), will increase linearly with $V_g$. This relationship is usually expressed in the form of an $I_D-V_g$ curve that characterizes each MOS device. An example of an $I_D-V_g$ plot for an n-channel MOSFET can be
seen in Figure 2.11. The threshold voltage of a MOSFET can be obtained by steadily increasing the gate bias until a non-zero drain current is observed at the drain electrode, assuming a small bias voltage (labelled \( V_D \) in Figure 2.7) is applied to the drain to induce current flow in the n-channel. The gate voltage at which an \( I_D - V_g \) curve intersects the horizontal axis is equal to \( V_{th} \), as the appearance of a current through the silicon substrate can only occur in the presence of a charge channel. The curve labelled \( A \) in Figure 2.11 represents the \( I_D - V_g \) curve of a pre-irradiated MOSFET, while \( B \) represents the \( I_D - V_g \) characteristic of the same MOSFET following radiation exposure. Notice the shift in \( V_{th} \) towards a lower gate voltage following an exposure to radiation.

The shift in the threshold voltage (\( \Delta V_{th} \)) following irradiation is the result of an increase in oxide-trapped charge concentration, which affects the net potential difference (and electric field) in the oxide and interfacial region. The increased \( Q_{ot} \) concentration results in a stronger net electric field, which subsequently attracts a greater number of free electrons in the p-type silicon towards the n-channel. However, the net electric field required to induce an n-channel in the silicon is dependent solely on the concentration of dopants in the p-type silicon material; since this is a material property, the minimum electric field required to create an n-channel in the silicon does not change following radiation exposure. Consequently, an increase in the \( Q_{ot} \)-induced component of \( \bar{E}_{net} \) reduces the voltage-induced component required to maintain a negative charge channel in the substrate. The change in the threshold voltage observed post-irradiation is directly proportional to the dose absorbed in the oxide layer. By measuring the threshold voltage before and after exposing the MOSFET to ionizing radiation, the dose delivered to the MOSFET can be calculated.

When a MOSFET device is irradiated continuously, the total dose absorbed in the oxide, and the concentration of \( Q_{ot} \), increases with time. The resultant increase in the n-type
conductivity in the charge channel leads to a further reduction in $V_{th}$. Eventually, a sufficient number of holes will be trapped in the oxide to establish an n-channel even in the absence of a gate voltage, causing a leakage current to flow from source to drain at all times. This is represented as curve $C$ in Figure 2.11.

2.3.7.2 P-channel MOSFET

A p-channel MOSFET utilizes an n-type silicon substrate, which has a higher concentration of conduction electrons than holes. The application of a negative bias voltage at the gate, rather than a positive bias voltage, should drive conduction electrons in the silicon away from the Si–SiO$_2$ interface and attract holes, increasing the concentration of holes in this region. When the magnitude of $V_g$ is equal to a particular threshold voltage, the concentration of holes and electrons near the interface become equal. At gate voltages less (i.e.: more negative) than $V_{th}$, a positive charge channel, or p-channel, forms within the n-type silicon between the source and drain, allowing for current flow between the two electrodes. This charge channel is essentially a small, localized volume of p-type material located within the larger n-type silicon substrate.

When a p-channel MOSFET is irradiated, the holes that become trapped in the oxide attract electrons in the substrate toward the SiO$_2$–Si interface. As the strength of the $Q_{ot}$-component of $\vec{E}_{net}$ increases, electrons are attracted back towards the interface, decreasing the threshold voltage. This decrease in $V_{th}$ occurs for the same reason a decrease is also observed in n-channel MOSFETs; however, with regards to a p-channel MOSFET, where a negative gate voltage is needed to induce a p-channel, an increasingly negative $V_{th}$ means that a p-channel becomes increasingly difficult to form as an n-type MOSFET is irradiated. This is illustrated in Figure 2.12, where curve $B$, which represents the $I_D-V_g$ curve of an irradiated MOSFET, requires a more negative threshold voltage than a MOSFET prior to being irradiated, represented by curve $A$. Once the MOSFET is
exposed to a large enough radiation dose, the magnitude of the gate voltage required to induce a p-channel becomes so great that it becomes nearly impossible to form a charge channel, and therefore, impossible to induce a charge channel for a current to flow. [7]

![Figure 2.12: A typical I\(_D\)–V\(_g\) curve for a p-channel MOSFET. Curve A is the characteristic I\(_D\)–V\(_g\) relationship of a pre-irradiated MOSFET, while B is the negatively shifted I\(_D\)–V\(_g\) curve observed following irradiation of the MOSFET. The MOSFET requires a more negative voltage to switch on post-irradiation. Curve C represents a MOSFET with a large (negative) V\(_{th}\), making it difficult to switch on.]

To summarize p-channel and n-channel MOSFET operation concisely, the negative threshold voltage shift that results following the irradiation of a MOSFET renders a n-channel MOSFET easier to switch on, and a p-channel MOSFET more difficult to switch on.

2.3.8 Further Dependencies on the Threshold Voltage

A model which was developed to describe the threshold voltage shift caused by Q\(_{ot}\) is described below

\[
\Delta V_{th} = -\left(\frac{q}{\epsilon_{ox}}\right) \cdot K_g \cdot f_y \cdot f_t \cdot t_{ox}^2 \cdot D
\]

(2.7)
where \( q \) is equal to the charge of the electron, \( \epsilon_{ox} \) is the permittivity of the oxide, \( K_g \) is the energy dependent charge generation coefficient, \( f_y \) is the field-dependent free-charge yield (i.e. non-recombining charge pairs), \( f_t \) is the field-dependent fraction of holes that become trapped in the oxide while migrating, \( t_{ox} \) is the oxide thickness, and \( D \) is the absorbed dose. The recombination of electrons and trapped holes, and the hole annealing process tends to limit or reduce the change in \( \Delta V_{th} \).

There are several points regarding Eqn. 2.7 that require further explanation. The first is that \( \Delta V_{th} \) is dependent on the square of the oxide thickness \( t_{ox}^2 \), or possibly \( t_{ox}^n \), where \( n \) varies from 1.5–2. [7] A thick oxide offers a greater volume from which to collect charge, although in submicron technology, it is believed not to apply when the thickness of the oxide is less than 30 nm. Secondly, the process of hole trapping isn’t 100% effective, which is why the terms \( f_y \) and \( f_t \) exist in Equation 2.7. Both terms are field-dependent and are heavily influenced by the strength of the bias voltage applied to the gate while being irradiated. A stronger bias increases charge yield by reducing electron–hole recombination immediately following their production (\( f_y \)), while reducing the probability of holes being trapped while migrating silicon (\( f_t \)). The proportion of holes that will become trapped in the oxide also depends on the mean trap density of the oxide, \( \bar{N}_{ht} \), and the hole capture cross-section, \( \sigma_{ht} \). The fraction of holes that become trapped in the oxide (\( f_t \)) is expressed as

\[
f_t = \bar{N}_{ht} \cdot \sigma_{ht} \cdot \Delta X
\]  

(2.8)

where \( \Delta X \) is the physical width (thickness) of the hole trap distribution (i.e.: the charge sheet described in Section 2.3.4), usually equal to around 5 nm or so. While the majority of radiation-generated holes slowly "hop" towards the silicon and get trapped in the charge sheet, a small number of these holes migrate past the charge sheet. These
untrapped holes continue to migrate towards the interface, eventually recombining with electrons that tunnel into the oxide from the silicon, or becoming trapped along the interface. This tunnelling process, or *tunnel annealing*, is responsible for the time-dependent, long-term annealing of $\Delta V_{th}$. Annealing also occurs when an ionizing event generates an electron–hole pair in the near-interface region between the charge sheet and silicon. The electrons generated by the event are swept towards the dense positive charge sheet, reducing $Q_{ot}$.

Taking all of the above into consideration, an general equation used to describe the change in the threshold voltage MOSFET dosimeter with a bias voltage applied to the gate during irradiation is [76]

$$\Delta V_{th} = 0.04 \cdot D \cdot t_{ox}^2 \cdot f$$  \hspace{1cm} (2.9)

where $D$ represents the absorbed dose, $t_{ox}^2$ is the thickness of the oxide, and $f$ represents the field-dependent free-charge yield (identical to $f_y$ used in Eqn. 2.7), or the proportion of electron–hole pairs that do not recombine after they’re produced.
CHAPTER 3
CHARACTERIZATION OF THE NEW MOSKIN DOSIMETER IN A HIGH-ENERGY PHOTON BEAM

3.1 Importance of Skin Dosimetry

The dose delivered to human skin has been of interest in numerous studies, using a variety of different dosimeters and techniques. [85, 86, 87, 88, 1, 89, 90, 91] When a patient is treated with a megavoltage photon beam, the dose delivered to the surface is mainly due to electron contamination originating from the LINAC treatment head, and the air volume between the treatment head and patient. [92] A large number of other factors affect the surface dose such as the field size, angle of beam incidence, and the use of various types of beam modifiers and collimators.

The skin dose is of interest because the skin is always irradiated during an external radiotherapy modality, and yet treatment planning systems (TPS) are incapable of accurately predicting the dose within 1 mm or 2 mm of the patient’s surface. CT images used for CT-based TPSs use voxels with dimensions on the order of millimetres. This is much larger than the epidermal and dermal layers of the skin, so planning software do not have the resolution required for dose calculations in steep dose gradient conditions. At greater depths in tissue, where charged-particle equilibrium conditions are met, the measurement and verification of the dose deposition is far more simple, as all common detectors employed today are capable of accurate measurements at depth in water. The emergence of radiotherapy treatment techniques such as 3D-conformal radiotherapy, IMRT, and HDR brachytherapy, which offer improved dose conformity to the target volume, have lead
oncologists to deliver larger doses to the target volume without increasing the risk of radiation toxicity in nearby normal tissue. Unfortunately, improved beam conformity to the target does not reduce the dose absorbed by the skin that is exposed. It only decreases the total area of skin that is exposed during treatment. Additionally, the recent interest in hypofractionated delivery schemes in the treatment of certain cancers has pushed the total dose delivered in a treatment, and consequently, the skin dose, to an even greater level.

In the field of medical physics, the term 'skin dose' is defined as the amount of dose absorbed by the basal cell layer of the epidermis, the critical layer for carcinogenesis. [93, 87] Exposure of the skin to high radiation doses may cause an early response called erythema, followed by the loss of epidermal basal cells, which may result in either a dry or moist desquamatory response 3–6 weeks following treatment. In the most severe cases, late skin reactions such as telangiectasia and necrosis may appear several months following treatment. [94] What complicates the process of determining the skin dose is the fact that different skin reactions originate from different depths of the epidermis and dermis, and also by the fact that the thickness of the skin varies widely across the body surface. For example, the epidermal layer is approximately 0.04 mm thick, while the epidermal layer at the sole of the foot is approximately 1.5 mm thick. [95] To simplify the matter, both the International Commission on Radiological Protection (ICRP) [94] and the International Commission on Radiation Units and Measurements (ICRU) [96] recommend that the skin dose be measured at a depth of 0.07 mm below the surface, which is the nominal depth that was chosen. An ideal dosimeter for skin dosimetry would be capable of measuring the dose delivered to an infinitesimally thin volume at 70 \( \mu m \) depth in tissue. Unfortunately, a detector with an infinitesimally thin sensitive volume does not exist, so the best, and most realistic option is a dosimeter with a micron or nano-scale sensitive volume, and a shallow effective point of measurement. The effective depth of measurement of most commonly used dosimeters range from several micrometres in
water (GaFChromic HD-810 film), to several millimetres (Roos chamber), while the sensitive volume of most detectors are $\geq 1 \text{ mm}$ thick.

Skin complications are an important factor when deciding on the dose prescription delivered during radiotherapy, such as the treatment of the breast, and the head and neck regions. To avoid unwanted skin reactions in situations where the risk of the patient suffering skin complications is high, the skin dose, and the dose deposition within the first several millimetres of the build-up region, should be tracked while the treatment is being delivered.

### 3.2 Common Dosimeters in Use

#### 3.2.1 Ionization chambers

In conventional radiation therapy, ionization chambers and TLDs are two of the most commonly used dosimetry tools. Ionization chambers are considered the most reliable dosimeters, frequently used as the standard to which other dosimeters are compared. Ionization chambers measure the number of ion pairs generated by ionizing events that occur within a medium. This medium is typically a gaseous medium contained within a chamber, although the medium can also be a solid or liquid. When an ionization chamber is irradiated, ionizing events that occur within the chamber result in the production of an positive-negative charge pair, which are attracted to two conducting electrodes contained within the gaseous chamber. The positive ion charges, and corresponding electrons, produced from the ionizing events move to the electrodes of opposite polarity, and the electric current is measured. This current is proportional to the amount of energy deposited within the gas-filled chamber. The chamber may be in the form of a coaxial cylinder, where the wall of the cylinder acts as one of the electrodes, while a stem oriented along the central axis of the cylinder acts as the other electrode. The electrodes of the ionization chamber may also be in the form of two parallel plates of opposite polarity.
Generally, ionization chambers are relatively bulky when compared to other forms of dosimeters. Their relatively large sensitive volume does not allow for point dose measurements. Instead, the dose is deposited throughout the chamber. Consequently, the response of the detector is only indicative of the average dose deposited throughout the gaseous chamber, rather than the dose at a precisely defined point. In the absence of a dose gradient, this *volume effect* is not an issue, as the dose delivered to any point within the chamber is equal. However, in practical dosimetric applications, some form of dose gradient exists, and dose-averaging over the chamber volume leads to an uncertainty in the reading. The measurement uncertainty associated with dose-averaging increases with the steepness of the dose gradient in which the detector is placed, and the volume of the chamber. This is a factor within the first few millimetres of a medium irradiated with either a photon or electron beam delivered by a linear accelerator (LINAC), which is characterized by a steep dose gradient. Complex lateral dose gradients may also be present in IMRT. The point of measurement of a cylindrical ionization chamber is considered to be along the central electrode, and so the position of a cylindrical ionization chamber is always defined with respect to this electrode. However, the *effective* point of measurement is slightly closer to the radiation source due to the predominantly forward direction of the secondary electrons, so a correction factor must be applied to the reading in order to account for the slight shift in the point of measurement. The effective depth of a cylindrical ion chamber makes them unsuitable for surface or superficial dose measurements in the build-up region of a photon beam delivered by a LINAC, while their high electrical demands makes them ill-suited for *in vivo* dosimetric applications.

In the past, plane-parallel ionization chambers were often used to measure dose in the buildup region of high energy photon and electron beams, as recommended by the American Association of Physicists in Medicine’s (AAPM) Task Groups 21 and 25. However, investigations into the accuracy of this type of detector revealed that these
chambers overresponded in the build-up region of normally incident photon beams due to electron in-scattering from the chamber’s side walls. [3, 4] While most plane-parallel ion chambers feature electrical guarding, few chambers have a guard ring of sufficient width to offer adequate radiation guarding. Gerbi [3, 101] has shown that an RMI model 449 fixed separation parallel-plate ionization chamber, or Attix chamber (named after its designer), overcomes the shortcomings of other parallel-plate chambers in both a high-energy photon and electron beam. The Attix chamber proved capable of skin dose measurements to within 0.5% of an extrapolation ionization chamber. It has a 0.125 cm$^3$ collecting volume, and a 4.8 mg/cm$^2$ (or 0.025 mm) thick entrance window made of conducting kapton film loaded with graphite. [101, 102, 103] The chamber has a diameter of approximately 6 cm, while the entrance window has a diameter of approximately 4.6 cm. Extrapolation chambers determine the surface dose by measuring the dose at several depths in tissue, and extrapolating to the zero volume, and are used as the standard to which other surface dosimeters are compared. However, due to its size and electrical requirements, ionization chambers are more appropriate for phantom measurements and quality assurance testing of radiotherapy units. For clinical applications, a small detector that requires minimal or no power to operate is capable of measuring the dose in water under both charged-particle equilibrium conditions, and in the build-up region of a depth dose distribution.

3.2.2 Thermoluminescent dosimetry

Thermoluminescent dosimeters (TLD) are a popular option in patient dose verification due to their small size, and are used for dosimetry in a wide range of applications, including HDR brachytherapy and small field IMRT, and stereotactic radiosurgery. When stringent handling, calibration, pre-annealing, and post-annealing procedures are followed, TLDs can provide accurate dosimetric information. However, this requires a significant investment towards adequate training of clinical staff. Furthermore, as they must
be annealed in an oven following irradiation, they are not capable of real-time, in-vivo dosimetry. TLDs can only provide prospective dosimetric information. The small size of TLDs is advantageous for clinical applications, where a point dose measurement is desired. Unfortunately, when placed in a steep dose gradient, they suffer from the same limitations as most types of ionization chambers, albeit less severely. While TLDs of less than 1 mm thickness are accurate for dose measurements in a shallow gradient, they do not provide the spatial resolution required for the effects of dose averaging to be disregarded when the gradient is steep. This ‘volume effect’ has been well documented in numerous studies involving the assessment of ionization chambers of various volumes, and various types of detectors. [85, 86, 104, 105, 106] Furthermore, while an LiF TLD of 1 mm thickness will have an effective point of measurement of approximately half its thickness, its effective depth of measurement in water will be equal to approximately 1.2 mm after adjusting for the relative difference in density between LiF (approximately 2.6 g/cm$^3$) and water (1 g/cm$^3$). This is not adequate for surface measurements.

A number of research groups have devised methods to utilize TLDs to measure the dose in the build-up region of a photon beam delivered by a LINAC. Using an extrapolation method similar to the method described for parallel-plate extrapolation chambers, the skin dose can be obtained by measuring the surface dose using TLDs of various thicknesses, and extrapolating to the reference skin depth of 70 $\mu$m. [85, 2] However, similar to the time-consuming use of a extrapolation ionization chamber for determining the surface dose, this TLD extrapolation method is rather labourous and time consuming. The ultra-thin TLDs are very fragile, particularly the corners, which are easy to chip. This was an issue for Kron et al., who noticed a significant effect on the dose response of individual TLDs related to the difference in mass between TLDs from the same batch. When the response of individual TLDs from a single batch were compared, a response variability of up to 16% was observed from the batch of ultra-thin 0.14 mm TLDs. [2] Furthermore, the skin dose response is obtained through an indirect calculation rather than
via direct measurement, which is impractical for clinical applications. Another study by Stathakis et al. [87] used ultra-thin LiF TLDs with dimensions of $0.3 \times 0.3 \times 0.1$ mm to determine the skin dose, but this was accomplished through correlation of the dose to this depth with results taken from a Monte Carlo simulation, rather than through direct measurement. While the depth dose measurements taken with the ultra-thin TLD were in good agreement with the depth dose curve distribution obtained by Stathakis et al. from a Monte Carlo simulation, neither the results obtained through measurement or simulation was in agreement to the normalized surface dose measurements reported by others (approximately 16% of the dose measured at $d_{\text{max}}$ for a 6 MV, $10 \times 10$ cm$^2$ photon beam, 100 cm source-to-surface distance). [85, 1, 88, 89, 107, 3]

3.2.3 Radiochromic Films

The usefulness of radiochromic films in clinical radiation dosimetry has been demonstrated in numerous studies, particularly by Butson et al. [88, 108, 109, 110, 111, 112] Radiochromic films have active monomer components that polymerizes to form a permanent polymer coloured-dye when irradiated. Unlike radiographic film, no chemical processing steps are required to develop radiochromic film because the colourless dyes in the film become coloured by the deposited energy. To read out radiochromic film, only a simple flatbed scanner is required, making them attractive in diagnostic procedures and industrial applications. [113, 109] Polymerization of the film is visible immediately following an exposure to radiation, but continues to polymerize slowly for up to 24 hours post-irradiation. The generally accepted rule for reading out radiochromic film is that the film should be stored in a dark room with the temperature set cooler than 20°C and left for 24 hours post-irradiation to allow for the polymerization process to taper off.
Radiochromic films such as GaFCHROMIC EBT, HS, and XR-T dosimetry films (International Specialty Products, New Jersey, USA), allow for high spatial resolution measurements to be made in three-dimensions. The spatial resolution along two-dimensional surface of the film is on the order of microns, while the thickness of the radiosensitive active polymer ranges from approximately 5–40 μm, depending on the type of film being considered. The active polymer of all radiochromic films is sandwiched between two sheets of transparent polyester, each with a thickness ranging from approximately 1–100 μm. In consequence, the effective depth of most types of radiochromic film is approximately 150 μm,1 although certain GaFChromic film models, such as HD-810, have a shallow effective measurement depth of approximately 4 μm. [1] Radiochromic film can be cut into shapes and sizes without affecting their dosimetric characteristics, while the flexibility of film allows it to be bent slightly in order to conform to an outer body contour, such as the breast. The large surface area of an uncut sheet of radiochromic film is advantageous when the dose distribution delivered by a radiation source is unknown, and is often used to map the dose distribution of the delivery. After irradiating the film, the film requires 6–24 hours to self-develop, which doesn’t allow for their application in real-time dosimetry. While a report by Rink et al. [114] has shown that GaFChromic EBT film is capable of real-time dosimetry, the response of the film was non-linear with dose, and both the method and equipment required to extract the dose information from the film in real-time does not appear suitable for in-vivo clinical dosimetry due to its complexity.

3.2.4 Fiber-Optic Dosimeters

Fiber-optic dosimetry (FOD) is one of the more interesting developments in dosimetry because dosimeters that utilize a scintillator crystal are capable of real-time dosimetry. Organic scintillators are inherently water-equivalent, their response is linear to the dose

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rate, and the detector is available in a small volume comparable to most TLDs. [115,116] A scintillation-based dosimetry system is composed of three main elements: a scintillating detector probe, a fibre-optic light guide, and some form of photodetector. The radiosensitive detector is usually a small-volume plastic scintillator attached to the optical fiber. Scintillating fibres may also be selected. [106] The light produced by the scintillator is transported through an optical fiber and towards a photodetector, where the light is converted into a readable signal. The photodetector can be either a photomultiplier tube, or a photodiode.

A disadvantage of fiber-optic dosimeters is the Cerenkov radiation and fluorescent light produced in the optical fibre during irradiation. [117] The total signal detected at the photodetector is comprised of the scintillated light produced by the scintillating crystal, and two noise components: the Cerenkov radiation, and the fluorescence signal. The Cerenkov radiation component of the signal noise is commonly referred to in the literature as the 'stem effect'. Fluorescent light is produced when radiation interacts with the optical fibre rather than the crystal. Boer et al. [117] have shown that a fluorescent signal is produced in an optical fibre whether it is irradiated with a 20 MeV electron beam, or a 125 kVp x-ray beam. Cerenkov radiation is produced when charged particles pass through the fiber at a speed greater than the speed of light in the fiber. [115] Unlike the fluorescent signal, the amount of Cerenkov radiation produced in the fiber is dependent on the angle of irradiation. [117, 118] In the case of photon irradiation, the charged particles responsible for producing the Cerenkov radiation are the fast electrons produced when the photon interacts within the fiber, and the electrons produced in the material surrounding the fiber. Cerenkov radiation has a continuous spectrum that spans from the ultraviolet to infrared wavelengths, and varies with intensity according to $\lambda^{-3}$. [119] Therefore, Cerenkov radiation is stronger in the UV and blue region of the visible spectrum, and far weaker in the red and infrared. [119, 117, 118]
Currently, the Cerenkov and fluorescent noise is removed from the total light signal through a background subtraction technique. When a 'dummy' fiber optic cable with no scintillating material is placed beside a primary FOD, the Cerenkov and fluorescent background signal induced in the two cables is assumed to be equal. By subtracting the signal measured in the dummy fiber from the signal originating from the FOD, the total signal from the FOD should be comprised entirely of scintillated light. The use of two fiber optic cables increases the size of the detector, and consequently, negates the benefit of a single fiber’s small size. The amount of Cerenkov can be reduced further by selecting a scintillator with a spectral emission profile shifted to longer wavelengths in order to take advantage of the Cerenkov signal’s $\lambda^{-3}$ relationship. By utilizing a scintillator with a peak emission wavelength $\geq 500 \text{ nm}$, the Cerenkov component of the total signal, which is comprised mainly of wavelengths $< 400 \text{ nm}$, can be selectively filtered out of the primary signal. [106, 120]

Another issue which is the size and shape of the scintillator. Research on small volume scintillators typically utilize cylindrical scintillators with a 1 mm diameter, and a length of 5 or 10 mm. [106, 121, 122] As noted by Archambault et al., [106] Laub et al., [105] and Leybovich et al., [104] the size and dimensions of a detector’s sensitive volume are critical factors in dosimetric accuracy when measuring the dose in radiation fields characterised by complex lateral gradients, such as the ones utilized in IMRT. The ideal detector would have a short length, width, and thickness, or perhaps be symmetrical in three dimensions. A shorter scintillator would be more appropriate for use in complex radiation fields, but this would come at the expense of light output and signal-to-noise, which varies linearly with detector length.
3.2.5 MOSFET dosimeters

MOSFET detectors may offer a solution to the issues addressed so far. MOSFET dosimeters share many of the benefits of fiber optic dosimeters such as small size, a nearly-constant electron stopping power ratio between silicon and water over a wide range of electron energies delivered from a LINAC, and the ability to measure accumulated dose in real-time. The sensitive volume of a MOSFET is the thinnest amongst the medical dosimetry discussed here, which allows for high spatial resolution. [76] Unlike the dosimeters discussed earlier, the dimensions of the MOSFET sensor are short enough in all three dimensions to ensure that the orientation of the dosimeter in relation to the direction of the gradient is of no concern. The sensitive volume of a MOSFET dosimeter is typically less than 1 µm thick, allowing for high spatial resolution slightly better than achievable using radiochromic film, and yet MOSFETs are also capable of real-time dosimetry, and can be used to measure the dose delivered in multiple fractions of a radiotherapy treatment. The main concern of most commercially available MOSFET dosimeters is the epoxy resin typically used to encapsulate most MOSFET dosimeter designs. The epoxy helps protect the sensor from physical damage and abrasion, and hermetic seals the electronics to prevent damage caused by moisture. The epoxy also serves as a build-up layer of material, which increases the detector’s effective depth of measurement. Reports have shown that the effective depth of measurement of a MOSFET dosimeter with an epoxy effective depth is approximately 1 mm, [123, 91, 124] which mitigates the benefit of having a thin sensitive detector volume for accurate dosimetry in the build-up region of a 6 MV photon beam. You can shift the position of the dosimeter so that the epoxy is accounted for, but this is tricky in the build-up region of the depth dose curve. Butson et al. [89] have shown that a bare MOSFET with its encapsulating layer removed is capable of measuring the superficial dose when compared to an Attix chamber. Similarly, Scalchi et al. have shown that while an unmodified Thomson & Nelson TN-RD-50 model MOSFET dosimeter had a large effective depth of 1.8 mm (epoxy side) and 0.8 mm (flat underside), [125] a modified version of the same MOSFET model
with its encapsulation partially removed, can measure the dose at an effective depth of around 70 \( \mu m \) in tissue. [91] Modification of the encapsulation was required to reduce the detector’s effective depth of measurement. However, the modification of the TN-RD-50 dosimeters resulted in large discrepancies between individual MOSFET dosimeters, which was attributed to the poor reproducibility of this modification.

3.3 Materials

3.3.1 MOSFET Detector Design

![Diagram of typical MOSFET dosimeter and MOSkin](image)

(a) Typical MOSFET dosimeter (left: side view, right: top view)

(b) MOSkin (left: side view, right: top view)

Figure 3.1: Comparison between the overall design and packaging of a typical MOSFET dosimeter, and the MOSkin.

Conventional MOSFET dosimeters utilize an epoxy resin material to physically protect the sensor from damage and moisture. A schematic representation of such a MOSFET dosimeter can be seen in Figure 3.1 The resin is placed on top of the sensor and is in the physical shape of a dome, or “bulb”, but with an oval-shaped base. The epoxy is
designed with an oval base in order to accommodate the sensor, whose base has a rectangular shape. This shape is intended to maximize the uniformity of the epoxy thickness surrounding the sensor at all angles of irradiation, and therefore, minimize the dependence of the dosimeter’s response on the angle of irradiation. However, the response of MOSFETs with such a design have been shown to be dependent on the angle of irradiation in several MOSFET studies. [126, 127, 123] Angular dependence was reported using a number of different MOSFET dosimeters from different manufacturers.

3.3.2 MOSkin Design

The dosimeter of interest in this report is the new MOSkin detector, a MOSFET-based detector designed by the Centre of Medical Radiation Physics (CMRP) at the University of Wollongong, Australia. What makes the MOSkin unique is the design of the packaging, which uses a “drop in” design. The MOSFET sensor is dropped into a thin layer of kapton, and hermetically sealed with a water-equivalent, flexible polyimide film of highly reproducible thickness. This thin film prevents damage to the electronics caused by moisture, prevents direct contact between the patient and the electronics of the dosimeter, and acts as a carrier of the thin aluminium contact leads that connect to the MOSFET sensor. Furthermore, the film acts as a thin build-up layer. The flexible film layer provides the sensitive detecting volume with an effective depth of approximately 70 µm in tissue, although the thickness of the film can be varied at the time of manufacturing to suit the biological region of dosimetric interest. Using a thin film rather than an epoxy bulb encapsulation minimizes both the encapsulating build-up layer, and the variability in the thickness of the build-up material between separate detectors. The utilization of a thin film encapsulating layer should overcome the issues described by Scalchi et al. [91, 125] when measuring the surface dose. A schematic representation of the MOSkin design is shown in Figure 3.2.
The MOSFET sensor found on the MOSkin has dimensions of $0.8 \times 0.6 \times 0.35$ mm$^3$, a gate oxide thickness of 0.55 $\mu$m, allowing for high spatial resolution measurements. The MOSkin device is 10 mm long and 1.8 mm wide, but the packaged device is approximately 0.45 mm thick. The MOSkin design is optimized to measure dose in a steep dose gradient, such as the one encountered at the air-tissue interface of the skin surface.

Figure 3.2: A schematic diagram of the MOSkin detector, design at the Centre for Medical Radiation Physics (Australia). The MOSkin is shown from a side view in (a), and from above the detector on the sensor side of the device in (b).

The MOSkin was compared to a MOSFET dosimeter called the RADFET (REM Oxford, UK), which uses an epoxy resin to encapsulate the radiosensitive detector inside. Further information on the RADFET detector can be found in publications by Holmes-Siedle, [128] and Price et al. [129] In summary, the RADFET’s sensor is mounted to a thin PCB carrier and encapsulated by a black epoxy "bulb". The thin PCB carrier of the
detector has dimensions of $55 \times 9$ mm, while the dimensions of the epoxy bulb are approximately $3 \times 4$ mm, and $0.8 - 1$ mm thick. The MOSFET sensor is contained within the epoxy bulb. In comparison, the MOSkin is approximately 1 mm long and 2.5 mm wide. The MOSkin’s sensor is only $400 \, \mu$m thick, but the packaged device is approximately 1 mm thick.

Both the MOSkin and RADFET detectors are read out by a portable, battery-powered reader designed by the CMRP. A 15 V irradiation bias is applied to the MOSFET gate during irradiation to separate the charge-pair produced in the oxide (as described in Chapter 2); however, the reader is also capable of applying a 5 V bias voltage, or 0 V (passive mode) to achieve a lower sensitivity in high-dose applications (e.g. synchrotron irradiation) in order to extend the useful life of the MOSFET sensor. For large dose applications, the application of a lower bias voltage to the gate, or perhaps no voltage at all, reduces the concentration of holes that become trapped in the oxide for a particular absorbed dose. In total, five dual-sensor MOSFET detectors can be attached to the reader simultaneously if desired, enabling five low-sensitivity and five high-sensitivity MOSFET sensors to be active during irradiation. However, for phantom measurements using clinically relevant photon energies, the higher bias setting is generally selected in order to increase the sensitivity of the MOSFET dosimeter, and the linearity of its response.

3.3.3 Fiber Optic Dosimetry System

The two optical fiber dosimeters used in this study both utilize a Bicron BCF-20 cylindrical plastic scintillating fibre, a type of organic scintillator produced by Saint-Gobain Crystals. Plastic scintillating fibers are clad with a thin layer of non-scintillating polymethylmethacrylate (PMMA), which potentially improves light collection by reducing the scintillator’s dependence on having a perfectly polished surface for efficient light collection. [106] The PMMA cladding also protects the scintillator’s surface from physical
damage. The two detectors only differ by the diameter of the scintillating element. One scintillator has a 0.5 mm diameter, while the other has a 1 mm diameter. The 0.5 mm diameter FOD used to obtain the measurements presented here was randomly selected from a batch of 20. Most FOD studies have utilized a 1 mm diameter scintillator, while few reports could be found in the literature using 0.5 mm diameter scintillators for radiation dosimetry. The sensitive volume of the 1 mm diameter crystal is larger than the 0.5 mm diameter crystal by a factor of 4, and should produce a greater amount of scintillated light, decreasing the signal-to-noise ratio. When the BCF-20 scintillating fiber is irradiated, it emits a green light with an emission peak at 492 nm. This signal is sent down the length of the fiber optic cable towards a photodiode. The radiosensitive scintillating volume is 1 mm diameter and 10 mm in length, and is connected to a 10 m long polymethylmethacrylate (PMMA) optical fiber (model CK-40) produced by Mitsubishi Inc (Japan). The cable has a refractive index of 1.49. The other end of the fiber is connected to a Hamamatsu S1336-18BK photodiode, which converts the light from the fiber into a signal that gets passed to an amplifier. The output signal from the amplifier is sent to a laptop computer via a data acquisition card from National Instruments. The computer collects the data and graphically displays the incoming pulses in real time via a software application created in LabVIEW 7 (for Microsoft Windows XP).

The Hamamatsu S1336-18BK photodiode was chosen due to its sensitivity characteristics with respect to wavelength. [130] As illustrated in Figure 3.3, this particular photodiode model is insensitive to light with a wavelength of less than approximately 400 nm. At wavelengths of greater than 400 nm, the sensitivity increases almost linearly with respect to wavelength. The emission spectrum of the BCF-20 scintillating fiber begins at a wavelength of around 470 nm, rising rapidly until reaching a peak at around 492 nm. Beyond a wavelength of 492 nm, the spectrum decreases gradually with increasing wavelength. The selection of an S1336-18BK photodiode and a BCF-20 scintillator fiber should minimize the Cerenkov background noise.
A second, identical dummy fiber was also irradiated for the background subtraction of signal noise, but the amount of noise generated in the fiber at normal beam incidence was negligible in this case. As discussed by Beddar et al. [116] Cerenkov radiation is of greater concern when electron (i.e. charged particle) beams are concerned, where the maximum Cerenkov is produced at an incident beam angle of 45°. At an angle of 0°, the amount of Cerenkov is at a minimum. When the stem effect was ignored, a maximum error of 0.3% was reported by Beddar et al. when comparing the normalized depth dose response of a 1 mm diameter FOD when compared to the normalized response of an ionization chamber. The pairing of the BCF-20 FOD with a S1336-18BK photodiode
further reduced the background noise in this experiment, and so the dummy fiber was not required for this experiment.

3.4 Methods

3.4.1 Response Linearity
The linearity of the MOSkin and 1 mm diameter FOD’s response were checked in a 6 MV photon beam, 100 cm SSD, with the field size set to $10 \times 10 \text{ cm}^2$. Measurements were performed with the detectors placed at a depth of $d_{\text{max}}$ in a Solid Water$^{\text{TM}}$ phantom. With the LINAC set to deliver dose at a rate of 400 cGy/min, the response of the MOSkin was measured following the delivery of dose ranging from 50–400 cGy in increments of 50 cGy. As the response of scintillator dosimeters is dependent on the incident dose rate rather than the total, the dose-rate response linearity of the 1 mm diameter FOD was examined by measuring the light response of the FOD when irradiated at dose rates of 80, 160, 240, 320, 400, and 600 cGy/min. Each MOSkin measurement was taken three times, and averaged. The FOD data was obtained by irradiating the dosimeters for approximately 10 seconds at each dose rate, and the mean signal amplitude was obtained by averaging the signal amplitude over a 5 second interval in the middle of the irradiation period. The signal obtained during the first 2 seconds of irradiation, where the response quickly rises, was never used in the calculation of the mean signal. The FOD was irradiated twice at each dose rate, and the mean signal amplitude obtained was then averaged.

3.4.2 Depth Dose Determination
The dose distribution of the photon beam was measured at depths ranging from 0–100 mm in a water-equivalent phantom made from Solid Water material (Gammex RMI), with the detectors placed inside the phantom. The detectors used for comparison are the MOSkin, the two BCF-20 FODs, and the CC13 compact ion chamber (3 mm radius)
from Wellhöfer (Scanditronix). The detectors were individually irradiated with a 6 MV photon field delivered by a Varian 2100EX linear accelerator (LINAC). In order for slabs of Solid Water material to be placed atop the detectors for the depth dose measurement, the detectors were placed within a narrow, shallow groove that etched atop one slab of Solid Water™ phantom material. The groove allowed for accurate positioning of the detectors at the geometric centre of the radiation field, minimizing the response uncertainty caused by a non-uniform lateral dose profile. A wax used to eliminate air gaps between the detectors, and the walls of the groove. The LINAC was set to deliver a 6 MV photon beam, 400 MU/min, at an SSD of 100 cm. Photon field sizes of 5×5, 10×10, 20×20, and 40×40 cm² were used to observe the effect of field size on the surface dose. The response of the FOD was obtained by irradiating the detector for a total of 10 seconds, and calculating the mean response over a 5 second interval. With regards to the MOSkin measurements, a 1 minute wait period was incorporated between the end of irradiation, and readout of the $V_{th}$ in order to minimise the effects of creep-up, as described by Ramani et al. [131] The 0.5 mm diameter FOD was only used to measure the depth dose distribution of the 10×10 cm² photon field. Its inclusion was mainly used to demonstrate the relationship between scintillator diameter and the ability to measure the dose in the build-up region. It was also used to illustrate whether there was a direct correlation between the scintillator volume of the 0.5 mm and 1 mm FODs, and the size of the signal produced, as measured by the photodiode. The FOD’s effective depth of measure was assumed to be equal to its radius, and located along the scintillator’s central axis. Throughout the experiment, the FODs were positioned so that the central axis of the FODs were located at the depth of interest. Similarly, the thickness of the RADFET’s epoxy encapsulating layer was accounted in the depth dose measurement. Adjustments to the measurement depth was achieved by applying an appropriate amount of wax underneath the detector while it was positioned within the groove. However, surface dose measurements were taken with the detectors placed on the surface of the phantom, with no correction for each detector’s effective depth of measurement. The response of each detector was normalised to the
reading taken at 15 mm depth ($d_{\text{max}}$), where the dose is a maximum. The normalized dose value will be referred to as the \textit{percentage depth dose} (PDD) for the remainder of this report. The CC13 ion chamber cannot be used for accurate dose determination near the phantom surface. Instead, the dose measurements obtained with the MOSkin and two FODs in this region were compared to readings taken with an Attix chamber.

3.4.3 Surface Dosimetry

To illustrate the benefit of the MOSkin’s packaging with regards to surface dosimetry, the MOSkin’s ability to accurately measure surface dose was compared to the RADFET, a commercially available MOSFET dosimeter (REM Oxford, UK). The RADFET differs from the MOSkin with regards to its packaging. Rather than utilizing a layer polyimide film to encapsulate the MOSFET sensor, an epoxy material is used to form a 1 mm thick "bulb" of build-up material over the sensor. The RADFET is described in greater detail in Chapter 4. The detectors were placed atop a Solid Water™ phantom and irradiated at normal incidence (0°), and again at oblique angles of 30°, 60°, and 75° relative to the normal beam axis. The readings were then compared to Attix chamber readings. The response of the detectors were normalized to the dose response obtained at $d_{\text{max}}$. Measurements were taken with the LINAC set to deliver a 6 MV photon beam, 400 MU/minute, at an SSD of 100 cm. Readings were taken using photon field sizes of $5 \times 5$, $10 \times 10$, $20 \times 20$, and $40 \times 40$ cm$^2$ in order to observe the effects of field size on the dose response of the three dosimeters. The MOSkin and RADFET dosimeters were each irradiated five times at $d_{\text{max}}$ with the gate electrode facing the beam, and the mean $\Delta V_{th}$ was calculated.

3.4.4 Inter-batch Response Reproducibility of MOSkin Dosimeters

An advantage of encapsulating the MOSFET with a thin polyimide film of high manufacturing reproducibly is a decrease in the response variation between individual detectors, a
problem noted by Scalchi et al. [91] using modified MOSFETs. The steep dose gradient at the surface of a phantom means that even slight variations in the effective depth of each MOSkin will lead to clearly dissimilar dose responses at the surface. Therefore, the manufacturing reproducibility of the polyimide film layer is likely the largest determinant of response variation between individual MOSkin dosimeters. To verify the claim that the polyimide film used to encapsulate the MOSkin dosimeter has a high manufacturing reproducibility, a total of seven individual MOSkin detectors were irradiated at the surface of the phantom by a 6 MV photon beam set to a field size of $10 \times 10 \text{ cm}^2$. Each MOSkin was irradiated three times at the surface of a phantom, and the mean response of each dosimeter was normalized to the response at $d_{\text{max}}$. The MOSkins used for measurement were taken from the same batch, and produced during the same manufacturing run in order to eliminate the possibility of inter-batch variability in manufacturing.

3.4.5 Discussion on MOSkin response uncertainty

The overall response uncertainty of the MOSkin reading is a combination of several attributing factors. One contributing factor to the uncertainty of a MOSkin reading is the limited resolution of the readout system. The reader is capable of measuring $V_T$ to within $\pm 1 \text{ mV}$. Throughout the experiment, the total absorbed dose delivered to the MOSkin and RADFET was large enough to ensure that the change in the MOSkin’s $V_{th}$ was $> 100 \text{ mV}$, which equates to a readout uncertainty of less than $\pm 1\%$. The surface measurements were repeated five times using a single MOSkin to minimize the statistical uncertainty of the measurement.

The significance of voltage creep-up is dependent on the amount of time between the end of irradiation, and the read-out of $V_{th}$ of a MOSFET dosimeter. By consistently reading out the MOSFET immediately following the end of the irradiation period, or 1 minute later, the response uncertainty related to the voltage creep-up is not an issue. As described
by Ramani et al. [131], creep-up is characterized by a sharp rise in voltage, which peaks 10 seconds following the end of irradiation. The voltage gradually decreases towards the equilibrium, or 'true', threshold voltage of the MOSFET after approximately 1 minute. However, even at its peak, an increase of only 4 mV was observed by Ramani et al., so the significance of voltage creep-up is dependent on the total dose delivered to the MOSFET dosimeter, and therefore, the size of $\Delta V_{th}$. This voltage effect becomes even less significant if the MOSFET is not read out 10 seconds following irradiation. With regards to clinical applications, where the doses delivered are large, voltage creep-up is not a factor. To be thorough, the voltage creep-up of the MOSkin was studied prior to the commencement of the experiment. At its peak, the threshold voltage increased by 3–4 mV when the MOSkin was read out 5–15 seconds post-irradiation, but was not observable if it was read out 35 seconds post-irradiation.

The most significant form of uncertainty is related to the positioning accuracy of the detector, particularly with distance away from the source. While this is less of a concern at depths beyond $d_{max}$, where charge-particle equilibrium conditions are met, the issue was of greater concern in the build-up region, where sub-millimetre inaccuracies in positioning equate to large dose discrepancies between the measured and expected dose response.

3.5 Results

3.5.1 Response Linearity

The linearity of the MOSkin and FOD can be seen in Figure 3.4(a) and (b). The vertical axis represents the dose response of the MOSkin normalized to the response of the detector when 50 cGy was delivered. The MOSkin response was found to increase linearly with dose from 50–400 cGy, as shown in Figure 3.4(a). Deviations from the best fit line through the data points never exceeded $\pm1.3\%$ ($R = 0.999$). The 1 mm diameter FOD also exhibited excellent response linearity ($R=0.999$). The data points were within
Figure 3.4: Dose response linearity of the MOSkin and 1 mm diameter fiber optic dosimeter when exposed to a 10×10 cm² photon beam.
±1.2% of the best fit line through the data set. This is in agreement with observations by Beddar et al. [116] with regards to the dose-rate response proportionality of the FOD. No dose effect was exhibited by either dosimeter.

3.5.2 Depth Dose

3.5.2.1 Build-up Region (0–15 mm)

The MOSkin, two fiber optic dosimeters, and the CC13 ionization chamber were used to measure the dose at depths ranging from 0–100 mm in the phantom. Readings obtained with the MOSkin, FOD, and CC13 ionization chamber in the build-up region of the depth dose curve can be seen in Figure 3.5, while surface dose values are summarized in Table 3.2. The 0.5 mm diameter crystal was only irradiated with the 10×10 cm² photon beam, so the response of the smaller 0.5 mm fiber optic dosimeter is only illustrated in Figure 3.5(b).

When the dosimeters were used to measure the dose at the phantom’s surface (depth of 0 mm), a significant response discrepancy between the detectors was evident. When irradiated with a 10×10 cm² 6 MV photon beam, the MOSkin recorded a mean PDD of 17.7±0.3%, which is similar to the 16% PDD obtained with the Attix chamber. In comparison, surface PDDs of 31.5±3% and 40.9±3% were obtained using 0.5 mm and 1 mm diameter FODs, respectively. The response of the MOSkin at the phantom’s surface was in better overall agreement with the Attix chamber response than the scintillator detectors at all field sizes, illustrating the advantage of the MOSkin’s shallow effective depth of measurement over the FOD’s 0.5 mm and 1 mm diameter scintillating crystal. With regards to the fiber optic dosimeters, the smaller 0.5 mm diameter FOD was able to perform better than the 1 mm diameter FOD, as expected. However, this advantage over the 1 mm FOD isn’t of practical significance, since the smaller diameter of the 0.5 mm FOD doesn’t make it effective at skin dosimetry either.
Figure 3.5: Percentage depth dose values measured using a MOSkin, 1 mm fiber optic dosimeter, and a CC13 ionization chamber. The 0.5 mm fiber optic dosimeter was only irradiated when a $10 \times 10 \text{ cm}^2$ beam was used.

The difference in response between the MOSkin and Attix chamber may be attributed to a slight difference in their effective depth of measurement. As discussed in Section 3.2.1, the Attix chamber was designed with a 0.025 mm thick entrance window made from graphite-loaded kapton film, which is equivalent to 0.048 mm in water. [1] It was not designed to measure dose at an effective depth that corresponds to the depth of the basal layer (70 $\mu$m), or to any specific, biologically relevant depth in tissue. While the response of the MOSkin is slightly greater than the Attix chamber response at the surface, the MOSkin’s response corresponds better to the nominal depth of the basal layer, as specified by the ICRP and ICRU. [94, 96]

The response of the FODs can be compared to readings taken by Devic et al., [1] Kron et al.,
[2] Gerbi, [3] and Cross, [4] who reported their PDD measurements acquired within 1 mm from the surface of the phantom. Devic et al. utilized numerous detectors, but in terms of their effective depth of measurement, the most relevant dosimeters for comparison are: a set of 0.15 mm and 0.4 mm thick LiF TLDs, an Attix chamber with 1 sheet of XV-2 Kodak Ready pack film placed on top of the chamber (0.305 mm), Attix chamber + 2 sheets of XV-2 film (0.562 mm), and an Attix chamber + 3 sheets of XV-2 film (0.819 mm). Devic et al. used the sheets of film to increase the Attix chamber’s effective depth of measurement, and consequently, increase the number of dose points in his near-surface depth dose measurements. The report by Kron et al. includes measurements taken with 0.14 mm, 0.37 mm, and 0.88 mm thick LiF TLDs. Table 3.1 compares the surface dose response of the 0.5 mm and 1 mm FODs obtained in this experiment, to the results obtained by Devic et al. and Kron et al. The effective measurement depth of the TLDs listed in Table 3.1 was scaled to the density of water, as LiF has a density of approximately 2.6 g/cm³.

Based on the effective measurement depth of the detectors utilized in this experiment, the surface response of the 0.5 mm diameter FOD obtained in this experiment should fall between the response of the 0.15 mm TLDs, and the Attix chamber + 1 sheet of XV-2 film. However, this was not observed. The response obtained with the 0.5 mm diameter FOD (31.5±2%) was greater than the response of the Attix chamber with 1 sheet of film atop the chamber window, despite the shallower effective depth of the 0.5 mm diameter FOD. The reading taken with the 0.5 mm FOD was in greatest agreement with the response of the Attix chamber + 2 sheets of film, which has an effective depth that’s greater than the thickness of the 0.5 mm FOD itself. Similarly, the surface response obtained with the 1.0 mm diameter FOD should fall between the PDD value obtained with the 0.4 mm TLD (as reported by both Devic et al. and Kron et al.), and the Attix chamber + 2 sheets of XV-2 film. Instead, its response is most comparable to the response of the Attix chamber + 3 sheets of film, and the 0.88 mm thick TLD.
Table 3.1: Comparison of the normalized surface dose response obtained using a 0.5 mm and 1 mm diameter fiber optic dosimeter (FOD), with results presented by Devic et al., [1] Kron et al., [2] Gerbi, [3] and Cross. [4]

<table>
<thead>
<tr>
<th>Dosimeter</th>
<th>Effective depth in water (mm)</th>
<th>Percentage Depth Dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mm diameter FOD</td>
<td>0.250</td>
<td>32 ± 3</td>
</tr>
<tr>
<td>0.15 mm TLD (Devic)</td>
<td>0.185</td>
<td>21 ± 4</td>
</tr>
<tr>
<td>0.14 mm TLD (Kron)</td>
<td>0.190</td>
<td>21 ± 6</td>
</tr>
<tr>
<td>Attix + 1 sheet of film (Devic)</td>
<td>0.305</td>
<td>25</td>
</tr>
<tr>
<td>Attix + 2 sheets of film (Devic)</td>
<td>0.562</td>
<td>32</td>
</tr>
<tr>
<td>1.0 mm diameter FOD</td>
<td>0.500</td>
<td>41 ± 3</td>
</tr>
<tr>
<td>0.4 mm TLD (Devic)</td>
<td>0.495</td>
<td>29 ± 4</td>
</tr>
<tr>
<td>0.4 mm TLD (Kron)</td>
<td>0.495</td>
<td>28 ± 3</td>
</tr>
<tr>
<td>Attix + 2 sheets of film (Devic)</td>
<td>0.562</td>
<td>32</td>
</tr>
<tr>
<td>Attix + 3 sheets of film (Devic)</td>
<td>0.819</td>
<td>38</td>
</tr>
<tr>
<td>0.88 mm TLD (Kron)</td>
<td>1.16</td>
<td>39 ± 3</td>
</tr>
<tr>
<td>Extrapolation chamber (Gerbi)</td>
<td>0.80</td>
<td>39.1%</td>
</tr>
<tr>
<td>Extrapolation chamber (Cross)</td>
<td>1.0</td>
<td>40%</td>
</tr>
<tr>
<td>Extrapolation chamber (Devic)</td>
<td>1.0</td>
<td>43%</td>
</tr>
</tbody>
</table>

There are some slight discrepancies between the PDD response values obtained with the FODs in this experiment, and the values reported in the literature. There is a possibility that either the FODs are over-responding when used to measure surface dose, the TLDs used by both Devic and Kron et al. are under-responding, or both scenarios are true. If the 39±3% PDD obtained with the 0.88 mm TLD (effective depth of 1.16 mm) by Kron et al. is compared to the 43% PDD obtained by Devic et al. using an extrapolation chamber at 1 mm depth, the 39.1% PDD at 0.8 mm obtained by Gerbi [3] with an extrapolation chamber, and the 40% PDD at 1 mm obtained by Cross [4] with an Attix Chamber, it appears that the 0.88 mm TLD under-responded. At an effective depth of 1.16 mm in water, the 0.88 mm TLD response should have been significantly greater than the PDD values obtained by Devic, Cross, or Kron et al. In contrast, the 38% PDD reading taken by Devic et al. using an Attix chamber with 3 sheets of film on top (effective depth of
Table 3.2: The percentage depth dose at the surface of the phantom, measured by the MOSkin, 0.5 mm and 1 mm diameter BCF-20 scintillators, and Attix chamber when irradiated using a photon beam at field sizes of 5×5, 10×10, 20×20, and 40×40 cm².

<table>
<thead>
<tr>
<th>Detector Type</th>
<th>Percentage Depth Dose (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5×5 cm</td>
</tr>
<tr>
<td>Attix chamber</td>
<td>10</td>
</tr>
<tr>
<td>MOSkin</td>
<td>11.4</td>
</tr>
<tr>
<td>1 mm BCF-20</td>
<td>37.1</td>
</tr>
<tr>
<td>0.5 mm BCF-20</td>
<td>-</td>
</tr>
</tbody>
</table>

0.819 mm) is very similar to the 39.1% PDD reported by Gerbi using an Attix chamber at the same depth, which validates Devic’s method of simply placing film on top of the Attix chamber to increase the amount of build-up material, and effective depth of measurement of the device. While the under-response of the TLDs may partially account for the large disparity between the FOD responses, and the response of the TLDs taken by Devic et al. and Kron et al., the under-response of the TLDs does not account for all the PDD discrepancies observed. The FODs still appear to over-respond when compared to Attix chamber readings at similar effective depths.

The response of the MOSkin and FODs already begin to converge at a depth of 2 mm for all photon field sizes, and are in excellent agreement at depths ≥4 mm, as shown in Figure 3.5. While the MOSkin’s shallow effective depth enable it to measure the surface dose better than the 0.5 mm and 1 mm diameter FODs, this advantage does not appear to be a factor beyond a depth of 4 mm. At this depth, a detector with a sub-micron thick sensitive volume does not appear to exhibit an observable advantage over a detector with a 1 mm thick sensitive volume in terms of dosimetric accuracy in the build-up region of the depth dose distribution. With regards to the CC13 ionization chamber, the depth at which the MOSkin and FOD response become comparable to the CC13 ionization chamber depends on the field size. When using the largest field size used in this study, 40×40 cm²,
the response of the CC13 is in agreement with the MOSkin and FOD starting at a depth of 4 mm, despite the CC13 chamber’s relatively large 3 mm radius. In comparison, when irradiated with a $5 \times 5$ cm$^2$ photon beam, the response of the CC13 chamber was not in agreement with the MOSkin or FOD until a depth of 10 mm. This observation can be explained by the inverse relationship between field size, and the amount of electron contamination that occurs at the surface. Surface dose increases with field size because the use of a larger photon beam increases the number of photons that interact with the collimator jaws inside the gantry head, and increases the number of interactions with air molecules situated between the gantry head and patient surface. Electrons are produced from the interactions, and a proportion of the electrons will reach the patient and deposit their energy at shallow depths in tissue. A larger field results in a greater surface PDD, so the slope of the dose gradient isn’t as steep when increasing towards the maximum dose (i.e. a PDD of 100%). In Figure 3.5(d), it’s apparent that the PDD profile of a $40 \times 40$ cm$^2$ beam already begins to flatten out at depths $\geq 4$ mm. The dose is nearly a maximum at 7 mm, and therefore, the dose gradient is nearly disappears at this stage. Dosimeters with a larger dosimetric volume appear to struggle to measure the dose accurately until the gradient becomes very gradual.

As the MOSkin and FODs are better suited for dosimetry at shallow depths in phantom, agreement with the CC13 ionization chamber within the first few millimetres in the phantom isn’t of utmost importance. However, the depth at which the response of the MOSkin, FODs, and CC13 ionization chamber become comparable is interesting to note, as it represents the depth from which the dose gradient no longer has a negative effect on the CC13 ion chamber’s ability to measure dose in the build-up region.
Figure 3.6: Percentage depth dose values measured using a MOSkin, 1 mm fiber optic dosimeter, and a CC13 ionization chamber. The 0.5 mm fiber optic dosimeter was only irradiated when a $10 \times 10 \text{ cm}^2$ beam was used.

3.5.2.2 Depths Greater than $d_{\text{max}}$

The MOSkin and 1 mm diameter FOD was in excellent agreement with the CC13 ionization chamber. The normalized response of the MOSkin was within $\pm 2.3\%$ of the CC13 chamber response at all depths and photon field sizes, although the majority of measurements were within $\pm 1.5\%$. The only exceptions include a -3.1% discrepancy from the CC13 chamber response at a depth of 100 mm when irradiated by a $20 \times 20 \text{ cm}^2$ photon beam, and a -3.6% discrepancy at a depth of 80 mm when irradiated by a $40 \times 40 \text{ cm}^2$ beam. These discrepancies do not appear to correlate with either the depth of measurement, or field size. The MOSkin results are comparable to the results obtained by Chuang et al. [132] using an epoxy MOSFET dosimeter, whose readings were within 3.3% agreement of an ionization chamber. The 1 mm FOD response was within
±3% of the CC13 ionization chamber response at all depths and field sizes.

3.5.3 Surface Dose

When the dosimeters were irradiated by the 10×10 cm² photon field at normal incidence, the mean PDD of the MOSkin was 17.7±0.3%. This is slightly greater than the 16% obtained with the Attix chamber; however, the Attix chamber has an effective depth of measurement of only 48 µm in water. The MOSkin’s slightly greater dose response should be seen as a positive indication, although it should be compared to the surface PDD of an extrapolation chamber. There are numerous reports in the literature of readings taken with an extrapolation chamber, but they’re usually extrapolated to the surface of the phantom (i.e. 0 mm depth) rather than to 70 µm depth in water. Devic et al. reported an extrapolation chamber reading of 17.0% PDD at a depth of 70 µm, which appears to correlate well with the MOSkin reading of 17.7±0.3% surface PDD. In the literature, the surface PDD obtained using an Attix chamber ranged from 15–16% (48 µm depth in water) when a Varian-branded LINAC was used for irradiation. [3,1,89] In studies which utilized a different brand of LINAC for their experiment, the surface PDD measured with the Attix chamber fell outside this range, [4] and haven’t been used for comparison in this report. In comparison to the MOSkin, the RADFET detector reported a mean PDD of 35.8±2% at normal incidence, which is greater than the response of the Attix chamber by a factor of 2. Relative to the Attix chamber readings taken by Devic et al., the water equivalent thickness of the epoxy bulb is between 0.7–0.8 mm, as expected.

With regards to irradiation at oblique angles, the normalized response of the MOSkin increased with the angle of irradiation. This is apparent for all field sizes in Figure 3.7. The relationship between the detector response and beam angle was expected, as the photon beam must traverse a greater path length through the MOSFET’s sensitive volume as the beam angle increases. An increase in beam angle also corresponds to an increase in the
Figure 3.7: Normalize surface dose values obtained using a 1 mm fiber optic dosimeter, and a CC13 ionization chamber. The 0.5 mm fiber optic dosimeter was only irradiated when a $10 \times 10$ cm$^2$ beam was used.

path length through the flat polyamide film layer atop the MOSkin, and the entrance window of the Attix chamber. In contrast, the RADFET dosimeter’s epoxy encapsulating ‘bulb’ was expected to provide a more constant path length through the build-up layer at all beam angles due to its rounded shape. For these reasons, it was initially hypothesized that an increase in beam angle would lead to a greater increase in response in the MOSkin and Attix chamber than observed with the RADFET. As illustrated in Figure 3.7, this was verified experimentally. The largest increase in response was observed using the Attix chamber, although Gerbi [3] found that the Attix chamber over-responded by a factor of 1.2 at an incident beam angle of 75$^\circ$ relative to an extrapolation chamber. When irradiated with either a $5 \times 5$ or $10 \times 10$ cm$^2$ photon beam, the MOSkin and Attix chamber responses increased by a similar amount in relation to the beam angle until an angle of
where the response of the Attix chamber is greater than the MOSkin. A similar relationship between response and beam angle was observed with the RADFET, as can be seen by the similar shape of the response curves in Figure 3.7.

Overall, the MOSkin’s response closely follows the response of the Attix chamber until a beam angle of either $75^\circ$ or $60^\circ$ is used, depending on field size. As the MOSkin is far smaller than an Attix chamber, and has far lower power requirements, it is a practical tool for skin dosimetry in a clinical setting. It can be treated as a viable alternative to radiochromic films in this regard, which are capable of providing a surface dose profile at the skin surface, but not capable of real-time dosimetry in a practical sense.

3.5.4 MOSkin response reproducibility

The response of the MOSkin proved to be quite reproducible. When the surface PDD was measured using seven individual MOSkin detectors taken from the same batch, the mean PDD obtained using seven individual MOSkin dosimeters was found to be $18.1 \pm 1.1\%$. The lowest and highest PDD reported by the seven MOSkins were $17.2 \pm 0.4\%$ and $20.4 \pm 0.6\%$, respectively. The response reproducibility of individual MOSkin dosimeters was quite high. In comparison, the response reproducibility of an individual Thomson & Nielson MOSFET dosimeter with a modified epoxy encapsulating layer was around $\pm 1.3\%$ when placed at the surface of a phantom, as reported by Scalchi et al. [91]. The low response variation ($\pm 1.1\%$) between each MOSkin is an indication of a relatively high manufacturing reproducibility of the encapsulating film layer. Using a manual method of altering the epoxy layer of a MOSFET, Scalchi et al. [91] reported a $\pm 1.9\%$ variation in PDD response between nine altered MOSFET dosimeters. Using a manual method of altering the epoxy layer of a MOSFET, the manufacturing reproducibility of the modified epoxy, and therefore, the response reproducibility of the dosimeter, was not as good as that of the MOSkin. The response reproducibility of individual MOSkin detectors taken from
different batches has not yet been explored.

3.5.5 Scintillator responsivity with respect to volume

It was hypothesized that the sensitivity of the smaller 0.5 mm diameter scintillator would be lower than the 1 mm diameter scintillator by a factor of 4 due to their relative difference in volume. Comparing the results obtained by both fiber optic dosimeters at $d_{\text{max}}$, the 0.5 mm dosimeter appears to be less sensitive by a factor of approximately 3.2–3.5. A lower sensitivity may not have much bearing on the results obtained in this particular experiment, but it may be an issue when the radiation dose is delivered at a low rate.

3.6 Conclusion

The shallow effective depth and thin sensitive volume of the MOSkin enabled the MOSkin to measure the dose at the surface of a solid water phantom, and within 4 mm depth from the surface of the phantom. Measurements obtained with the 0.5 mm and 1 mm diameter fiber optic dosimeters indicate that they over-respond at depths ranging from 0–4 mm. However, at depths beyond 4 mm, the shallower effective depth and micron-scale sensitive volume of the MOSkin did not appear to offer a dosimetric advantage over the FODs. This was true at any photon field size. Beyond 4 mm, all the dosimeters utilized in the study were capable of measuring depth dose. The manufacturing reproducibility of the MOSkin’s thin polyimide encapsulating layer could be seen from the low variation in PDD observed between individual MOSkin dosimeters.
CHAPTER 4
CHARACTERIZATION OF THE NEW MOSKIN DOSIMETER FOR USE IN HIGH DOSE-RATE PROSTATE BRACHYTHERAPY, AND THE HETEROGENEIC EFFECT OF THE RECTAL AIR CAVITY ON THE RECTAL WALL DOSE

4.1 Introduction
Pulsed Dose-rate (PDR) brachytherapy is a highly fractionated treatment that uses a single stepping source. The delivery of the treatment is similar to the delivery of an HDR brachytherapy treatment, except that the Ir-192 source used in PDR brachytherapy has a lower activity, and consequently, delivers dose at a lower rate. However, the same risks that correspond to HDR brachytherapy also apply to PDR brachytherapy. The incidence of late rectal complications from HDR/PDR prostate brachytherapy of any severity, or grade, as defined by the Radiation Therapy Oncology Group (RTOG), [67] varies widely between treatment centres, what is clear is that the incidence and severity of rectal toxicity has been shown to increase with the total radiation dose delivered to the rectum. [9]

At St. George Cancer Care Centre (SGCCC) in Sydney, Australia, PDR brachytherapy is delivered in conjunction with EBRT in the treatment of intermediate to high-risk prostate patients. Treatment plans are carefully created to ensure that the anterior rectal wall receives a dose no greater than 70% of the dose prescribed to the prostate. However, the close proximity of the rectum to the prostate, and the steep dose gradient that surrounds an Ir-192 source, means that the probability of delivering too much dose to the rectum is still high, despite careful planning. The catheters may shift in the superior–inferior direction during patient transport, or in the period of time between the creation of the
treatment plan, and delivery. This would change the source dwell positions with respect to the prostate, and result in a discrepancy between the intended dose distribution defined in the treatment plan, and the dose delivered to the patient’s rectum during treatment. Some form of Quality Assurance (QA) is necessary to ensure that anatomical motion, and the movement of catheters from their intended position during treatment does not lead to post-treatment complications such as rectal bleeding and incontinence. If the dose delivered to the rectum during the treatment procedure could be monitored in real-time, the treatment could be stopped or altered before an excessive amount of dose was deposited in the rectum. Alternatively, if the total rectal dose delivered during a fraction is greater than expected, the dwell positions and dwell time parameters of the treatment plan could be altered so that the rectal dose delivered in the next fraction is low, thus compensating for the overdose to the rectum from the previous fraction.

A detector that is designed for rectal dosimetry must be capable of measuring the dose at the anterior rectal wall in order to determine whether the rectum is receiving more radiation than expected. Late radiation damage to the rectum is primarily due to radiation dose absorbed throughout the entire thickness of the wall, [133] so ideally, the dose delivered throughout the rectal mucosa and submucosa should be measured. Although desirable, it isn’t physically possible to measure the dose to the submucosa, as it would require dosimeters to be implanted within the rectal wall itself. However, the ability to measure the dose delivered to the inner side of the rectum’s anterior wall, and compare it to the dose calculated by the treatment planning software is a good alternative, as the anterior rectal wall is an easily identifiable reference position that is already used by oncologists to define the rectal dose constraint in many treatment facilities. Unfortunately, a dosimeter’s effective depth of measurement has a significant effect in dosimetry near an Ir-192 source, since the dose gradient surrounding the source is so steep.

A detector’s effective depth is attributed to the thickness of the material that covers the
detector’s sensitive volume, the (electron) density of this material, and the thickness of the sensitive volume itself. For these reasons, the dose measured by a dosimeter is actually measured at a depth inside the dosimeter. This distance, which must be converted into an equivalent distance in water (if the material isn’t water equivalent already), must be accounted for when trying to position a dosimeter so that it’s a certain distance from a source. Due to the effective depth of measurement of most dosimeters, most dosimeters are not capable of measuring the dose directly at the anterior rectal wall. Instead, the dose would be measured a short distance away from the rectal wall, the distance being equal to the dosimeter’s effective depth of measurement. This distance is significant in HDR brachytherapy due to the steep dose gradient surrounding an Ir-192 source. The dose decreases quickly with distance from the source, so even if a detector’s effective depth is shallow, it may still have a significant effect on its ability to measure the dose at the anterior wall. Generally, MOSFET dosimeters have a sensitive volume of less than 1 µm thickness. If the encapsulating build-up layer were not present, MOSFETs would be an ideal detector for rectal dosimetry. However, an unencapsulated MOSFET with an exposed sensor would be a safety hazard to patients, since it is an electronic device. Furthermore, the dosimeter would be very prone to physical damage, and damage due to moisture. The MOSkin dosimeter overcomes these issues because the polyamide film atop the sensitive volume is only several microns thick. If you consider the thickness of both the MOSkin’s polyamide film layer, and its sub-micron sensitive volume, the MOSkin appears to overcome the shortcomings that prevent other dosimeters from being able to accurately measure the rectal dose at the level of the mucosa.

Another area of concern is related to the effect that tissue heterogeneities have on photon scatter. Generally, treatments are planned using treatment planning software (TPS) such as PLATO, and a set of the patient’s transaxial CT images taken following the catheter insertion procedure. The TPS uses the images to construct a three-dimensional representation of the prostate, urethra, catheters, and prostate. The dose rate around an Ir-192 source
is calculated by brachytherapy TPSs according to the Task Group Report 43 (TG43) protocol, developed by the American Association of Physicists in Medicine (AAPM). The TG43 protocol was developed as a means of calculating the dose delivered to any point away from an Ir-192 source by taking both the distance from the source, and the angle relative to the source’s perpendicular bisector, into account. A TPS determines the overall dose distribution within the 3D image construction by considering the position of the dwell positions, and the dwell times required to effectively treat the target volume. [134, 135] However, brachytherapy TPSs assume an infinitely large, homogeneous, water-equivalent medium surrounds the patient anatomy in three dimensions, without ever considering the effect of tissue heterogeneities on the scatter and absorption probability. Instead, the TPS treats the entire reconstructed image volume, including the rectal cavity, as a water-equivalent tissue when the TPS performs the dose computations. Since the rectum is emptied before an HDR brachytherapy treatment begins, this study was conducted to determine whether the dose delivered to the wall of an ‘empty’ (air-filled), heterogeneous rectum differs from the dose delivered to a ‘full’, homogeneous, water-equivalent rectum. In essence, this is a study that aims to quantify the effect that air contained in the rectal cavity has on the backscatter dose contribution.

Numerous studies have illustrated the effect of tissue heterogeneities on the dose delivered by an HDR brachytherapy source through both experimental measurements, and Monte Carlo simulations. [136, 137, 138, 139, 140] To investigate the effect that a rectal heterogeneity has on the dose delivered to the rectal wall, dose measurements were taken in a rectal phantom in both homogeneous and heterogeneous conditions. The results were also compared to the dose estimated via Monte Carlo simulation, and the dose calculated by an HDR brachytherapy TPS.
4.2 Materials and Methods

4.2.1 MOSFET Detectors

Figure 4.1: A schematic diagram of the commercially available RADFET dosimeter from REM Oxford, UK.

A full description of the MOSkin design is provided in Chapter 3. In summary, the MOSkin is characterized by its small size and thin polyamide film layer atop the MOSFET sensor, providing minimal build-up material, and consequently, a shallow effective depth of measurement. The MOSkin design is optimized for dose measurements in a steep dose gradient, and on the surface of the a water phantom or human skin. The small amount of build-up material atop the sensor allows dose measurements to be taken along the inner rectal wall during an HDR brachytherapy treatment.

The MOSkin was compared to the performance characteristics of a RADFET, a commercially available MOSFET dosimeter which utilizes an epoxy encapsulation. A schematic
diagram of the RADFET can be seen in Figure 4.1. The RADFET, designed by REM Oxford (UK), has a MOSFET sensor mounted to a thin PCB carrier and encapsulated by a black epoxy 'bulb'. [128] The epoxy bulb protrudes approximately 1 mm thick from the PCB carrier, and has an oval-shaped base that’s 4 mm long, and 3 mm wide. The thin PCB carrier of the detector is 55 mm long and 9 mm wide. In comparison, the MOSkin is 10 mm long and 1.8 mm wide. The chip on the MOSkin itself is only around 400 µm thick, but the packaged device is approximately 0.46 mm thick. In this experiment, the RADFET detector was connected to the portable, battery-powered readout unit designed for the MOSkin by the CMRP, so the same 15 V was applied to the gate electrode of the RADFET and MOSkin during irradiation, and read-out of the threshold voltage is identical for both dosimeters.

4.2.2 Detector calibration

To convert the voltage readings from the reader into an absolute dose value, a dose conversion factor was required for the MOSkin and RADFET detectors. The dose calibration factor was determined using a 6 MV x-ray beam with a 10×10 cm² field size and source-to-surface distance of 100 cm, produced by a Varian 2100EX linear accelerator (LINAC). The two detectors were positioned at the depth of maximum dose (d_{max}), or 15 mm, with the source-to-surface distance (SSD) set to 100 cm. They were not read out until 1 minute post-irradiation in order to eliminate the effects of voltage creep-up. [131] However, the dose delivered to the detector was sufficient to ensure that the response uncertainty associated with the MOSkin reader (±1 mV), and voltage creep-up (≤ 4 mV) would equate to less than 1% of the threshold voltage change, even if creep-up had not been accounted for. Readings were compared to a CC13 compact ion chamber from Scanditronix Wellhöfer (Germany).

The calibration factors that were obtained using the LINAC was then compared to the
calibration factors obtained separately by irradiating the MOSkin and RADFET with a Nucletron microSelection Ir-192 v1 pulsed dose rate (PDR) source. The detectors were calibrated by irradiating them for 2 minutes at a distance of 18.6 mm from the PDR source. This was repeated three times, and compared to the TG43 calculated dose.

4.2.3 Phantom design

The dose was measured within a water-equivalent, solid medium with full build-up and backscatter materials to ensure charge particle equilibrium conditions. The phantom is made from Plastic Water™ (CIRS, Norfolk, VA, USA), and was purchased from Gammasonics Pty (Sydney, Australia). It is comprised of numerous solid slabs of plastic of various thickness, which are placed in a stacked configuration. The distance between the source and detector is altered by inserting a combination of slabs in between the detector and catheter slabs. Additional phantom material was placed above the source and below the detector in order to provide adequate backscatter conditions. To irradiate the detector, the afterloader system transports the Ir-192 source down the source cable and into the plastic catheter, which is inserted into a phantom slab designed to hold the catheter.

4.2.4 Response of detectors at depth

The MOSkin and RADFET dosimeters were used to measure the dose in the water-equivalent phantom at various distances from the Ir-192 source in order to illustrate their dosimetric accuracy when irradiated by an Ir-192 source. The depth dose response of the detectors were then compared to the dose calculated by the PLATO TPS (v.14.2.5) to calculate the dose around brachytherapy sources. This was measured over a range of 14–54 mm distance from the Ir-192 source. The additional thickness of the RADFET’s epoxy encapsulation was accounted for during placement on the phantom. While distances $\leq 20$ mm from the source are of greater clinical concern with regards to rectal
dose, readings in this experiment were taken starting from 14 mm rather than shallower depths of 5 or 10 mm due to the large potential for setup error, and the large repercussions that placement uncertainty would have on the dose response. As described earlier, a 1 mm deviation from a depth of 10 mm would result in a 21% change in the dose rate, and so the placement accuracy required for an accurate dose measurement is difficult to achieve. This proved to be an issue for Lambert et al., [122] where measurements taken at 10 mm distance resulted in a 10% dose discrepancy when compared to calculated values.

4.2.5 Angular dependence of the MOSkin’s response
A dosimeter intended for rectal dosimetry during HDR brachytherapy patient treatments will be subjected to radiation from a large number of distances and angles during treatment. In order to provide accurate dosimetric information, the response of the dosimeter in question must not be dependent on the angle of radiation incidence. To see whether the MOSkin’s response is dependent on the angle of irradiation, its angular response was characterized at various angles along two planes. First, the MOSkin’s response was measured at numerous points around the central axis of the MOSkin dosimeter, assuming the ‘central axis’ is in the direction of the MOSkin dosimeter, and the cable to which it is attached. The points of measurement reside on an orthogonal plane that bisects the MOSkin’s sensor. This is illustrated in Figure 4.2(a). The water-equivalent phantom used to conduct the angular measurements is illustrated in Figure 4.2(b). In order to vary the irradiation angle without changing the distance between the source and dosimeter, the detector was placed along the central axis of a 21 mm diameter cylindrical piece of water-equivalent material, and inserted into a 30 mm thick slab of water-equivalent material. The cylindrical piece is actually comprised of two halves, with a thin groove etched along the central axis in order to allow the MOSkin and cable to fit snugly within the groove. This is depicted in Figure 4.2(b). The groove is just long enough to ensure that the perpendicular bisector of the MOSkin detector and Ir-192 source are aligned. By
Figure 4.2: Angular response measurement around the MOSFET’s central axis. This dose was compared to the dose calculated using the TG43 formalism.
placing the cylindrical piece into the 21 mm diameter hole through the side of the 30 mm thick phantom slab, the irradiation angle could be adjusted without changing the source distance. A separate cylindrical piece was designed to house the RADFET. The air gaps between the epoxy bulb of the RADFET, and the walls of the groove in which it’s placed were filled with a water-equivalent wax material to ensure adequate scatter conditions. The dose response was obtained as the angle was increased in 10° increments at angles ranging from 0–90°. Between angles of 90–330°, the angle was increased in 30° increments.

Further measurements were made at various azimuthal angles. Rather than simply delivering a constant dose to the detector from various azimuthal angles, and obtaining the response at each angle, the source angle was adjusted by using a single catheter aligned parallel to the dosimeter and source cable, and irradiating the detector with the PDR source placed at a number of different dwell positions. This is illustrated in Figure 4.3(a). Irradiating the MOSkin in this manner better exemplifies how the MOSkin would be irradiated during an actual patient treatment, where the total dose delivered to a point is equal to the sum of the doses delivered from each dwell position. As the Ir-192 source moves along the catheter, both the source distance and azimuthal angle change simultaneously. Measurements were taken in a tank filled with tap water, rather than a Plastic Water™ phantom used earlier. The water phantom was a 25×25×25 cm³ perspex tank, with holes drilled into the side of the tank to allow catheters to be inserted. A liquid water phantom was chosen for this measurement because of its larger size and greater versatility with regards to catheter geometry around the PDR source. The source was positioned 20 mm above the perpendicular bisector of the MOSkin’s sensor, and the azimuthal angle (and source–dosimeter distance) was adjusted by stepping the source in 5 mm and 10 mm increments in the axial direction. The performance of the RADFET was not assessed in this scenario, as the device was too large to fit into the catheter. The dose was measured at symmetric points around the reference position, 0 mm. The response was
Figure 4.3: Angular response measurement at various azimuthal angles and distances. Results were compared with the dose calculated using the TG43 formalism.
compared to the calculated dose at those points using PLATO TPS, which accounts for changes in irradiation angle, distance, and the anisotropic dose distribution that surrounds brachytherapy sources.

4.2.6 Dose measurements along the rectal wall

To measure the absorbed dose delivered to the inner wall of an empty rectal cavity, a 30 mm thick slab of water-equivalent material with a 21 mm diameter cylindrical air cavity along its side was created. This slab is 30 mm thick, with a hole of diameter 21 mm through its side. To simulate a 'full' rectum, a separate cylindrical piece was designed to
be inserted into the rectal cavity, filling the cavity. A thin groove was etched along the
surface of the cylindrical piece to allow the MOSkin and cable to fit snugly within the
groove. The groove runs parallel to the central axis of the cylinder, and its length ensures
that the perpendicular bisector of the MOSkin detector and Ir-192 source are aligned. A
separate cylindrical piece was designed to hold the RADFET against the wall of the rectal
cavity. the cylindrical piece is inserted into the rectal phantom, with either the MOSkin or
RADFET situated within the groove of the cylindrical piece described in Section 4.2.3.
The dose delivered to the wall of the 'full' rectal cavity is essentially a measurement
of the dose delivered to a single depth in homogeneous water-equivalent medium. By
rotating the cylinder clockwise or anti-clockwise, the MOSkin can be positioned at any
point along the inner wall of the phantom. The anterior rectal wall dose was measured
with the detector positioned at the anterior side of the rectal phantom. In this discussion,
the 'anterior' wall of the phantom is defined as the point on the rectal wall closest to the
Ir-192 source, labelled as 0° in Figure 4.4. The distance between the source and anterior
wall is 18.6 mm. A moderate distance of 18.6 mm was chosen because while it is far
enough away to reduce the uncertainty due to slight placement errors, the source is still
close enough to the rectal cavity to be representative of a typical distance between the
catheters closest to the rectum, and the inner anterior rectal wall. The anterior wall dose
in an empty rectal cavity was taken by securing the detector to the cavity wall using an
adhesive tape. The reading was repeated five times, and the detector was removed and
reattached after each measurement in order to account for positioning reproducibility. No
correction was made to account for the additional distance introduced by the epoxy build-
up layer for the rectal dose measurements. This was followed by dose measurements at
90°, 180°, and 270° relative to the anterior rectal wall measurement, as labelled in Fig-
ure 4.4.
4.2.7 GEANT4 Monte Carlo simulation

The rectal dose measurements obtained with the MOSkin and RADFET detectors were further corroborated by results obtained through Monte Carlo simulations. The simulations were written in C++ using the Geant4 toolkit (version 4.9.0), a powerful collection of C++ libraries used for simulating particle transport through matter, and the interactions that may occur along the particle path. Geant4 adopts an object-oriented approach in which separate classes exist for each aspect of the simulation process. [141] Geant4 is popular in the field of high energy physics, but is also designed for medical applications requiring simulations of lower energy particles passing through a medium. Specific details pertaining to the simulation are provided below.

4.2.7.1 Model of Ir-192 PDR source

The Nucletron microSelection Ir-192-v1 (older version) pulsed dose rate (PDR) 2.0Cl source was precisely modelled and positioned within a 30×30×30 cm³ cubic block of Plastic Water™, a type of water-equivalent plastic material. Ramaseshan et al. assessed the water equivalency of Plastic Water™ for photon energies ranging from 18 kVp to 18 MeV. [5] Table 4.1 contains mass proportional composition information for water, Solid Water™, and Plastic Water™. The information for Solid Water™ in Ramaseshan’s paper was originally taken from ICRU 44. [142]

The dimensions of the Ir-192 mPDR v1 (classic) source was taken from a Nucletron Certification for Sealed Sources, which describes the source in detail, and also described in detail by Karaiskos et al. [143] The physical design of the Ir-192 source, as defined in the Geant4 code, was visualized and can be seen in Figure 4.5. The radioactive Ir-192 pellet is contained within a 0.55 mm radius cylindrical shell made from AISI 316L steel. The radioactive Ir-192 pellet contained within the source shell is 1.0 mm long, with a 0.30 mm radius. One end of the cylindrical shell is sealed by a solid steel hemisphere, or
Table 4.1: Elemental composition of Plastic Water™ compared with other materials. Taken from Ramaseshan et al. [5]

<table>
<thead>
<tr>
<th>Element Name</th>
<th>Atomic Number (Z)</th>
<th>Mass Fraction Composition (%) Water</th>
<th>Plastic Water™</th>
<th>Solid Water™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen</td>
<td>1</td>
<td>11.2</td>
<td>7.4</td>
<td>8.1</td>
</tr>
<tr>
<td>Boron</td>
<td>5</td>
<td>-</td>
<td>2.26</td>
<td>-</td>
</tr>
<tr>
<td>Carbon</td>
<td>6</td>
<td>-</td>
<td>46.7</td>
<td>67.2</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>7</td>
<td>-</td>
<td>1.56</td>
<td>2.4</td>
</tr>
<tr>
<td>Oxygen</td>
<td>8</td>
<td>88.8</td>
<td>33.52</td>
<td>19.9</td>
</tr>
<tr>
<td>Magnesium</td>
<td>12</td>
<td>-</td>
<td>6.88</td>
<td>-</td>
</tr>
<tr>
<td>Aluminium</td>
<td>13</td>
<td>-</td>
<td>1.4</td>
<td>-</td>
</tr>
<tr>
<td>Chlorine</td>
<td>17</td>
<td>-</td>
<td>0.24</td>
<td>0.1</td>
</tr>
<tr>
<td>Calcium</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>2.3</td>
</tr>
<tr>
<td>Weighted mean Z</td>
<td>-</td>
<td>6.6</td>
<td>6.43</td>
<td>5.96</td>
</tr>
</tbody>
</table>

'dome'. Attached to the other end of the cylindrical shell is a steel cable that connects the PDR source to the afterloader. The steel cable was defined to be 10 cm in length for the simulation. It is necessary to include the steel cable in the simulation, as PLATO accounts for the additional scatter contribution from the cable. The presence of the steel cable attached to one side of the Ir-192 source results in a dose that is 10.2% greater at points ahead of the cable when compared to the dose delivered to symmetrical points within the steel cable. [140] The steel cable was assumed to have the same 0.55 mm radius as the PDR source shell. The origin of each primary photon emission was selected randomly from within the physical volume of the radioactive Ir-192 pellet, and its energy is determined randomly, weighted by the emission spectra of a microSelectron Ir-192 HDR source, as reported by the National Research Council of Canada (NRCC). [144] Bare Ir-192 spectra have also been presented by Glasgow and Dillman, [145] Kocher, [146] and by Duchemin and Coursol, [147, 148] but the differences in the data are, in practical terms, insignificant. The AAPM has not recommended a photon energy spectra for Ir-192 to be used for Monte Carlo simulations of brachytherapy dose deposition. The
bare Ir-192 emission data reported by the NRCC is based on the most recent report by Duchemin and Coursol, [148] although many Monte Carlo studies use the data reported by Glasgow and Dillman from 1979. [149, 143, 138]

Figure 4.5: A schematic of the Ir-192 source, as modelled for the simulation. The image is a screen capture taken during the simulation, when the visualization feature was enabled

4.2.7.2 Photon interactions
A total of $2 \times 10^9$ photon emissions was chosen for the water-phantom measurements in order to achieve good statistics. This is particularly important at the posterior rectal wall located about 40 mm from the source, where few interactions are expected to occur. Each simulation was performed five times, and the mean dose is reported here. The initial direction of the emitted photon is randomly generated in the x, y, and z-directions using three separate randomized values. The seed used to initialize the random number generator is dependent on the start time of the simulation to ensure that subsequent simulations do not generate an identical sequence of randomized values, and consequently, identical initial direction vectors. Following the generation of a photon, it must then traverse through the steel capsule that surrounds the Ir-192 pellet before reaching the
phantom. Photons are transported through the geometry and undergo interaction processes. The low-energy electromagnetic interaction extensions available in Geant4 were utilized to handle the photon processes in the simulation, while G4LowEnergyIonisation, G4LowEnergyBremsstrahlung, and G4MultipleScattering processes were utilized to handle particular charged particle processes. The classes are included with the Geant4 package. Electron tracking was performed so that secondary particles with a range greater than 0.05 mm were generated. The remaining particles deposit their energy locally, and not tracked. We observed that changing the cut range from 0.001 mm to 0.1 mm had no noticeable effect on the total dose absorbed in the scoring volume. The negligible contribution of electrons to the dose rate was also mentioned by Ballester; [150] however, electron tracking was included in our simulation.

4.2.7.3 Benchmarking of Monte Carlo simulation

Benchmarking of the Monte Carlo simulations was performed by comparing the depth dose distribution obtained through simulation in Geant4, and the TG43 calculated dose distribution. The simulated and calculated depth dose distribution was obtained within a $30 \times 30 \times 30$ cm$^3$ cubic water phantom, along the perpendicular bisector of the Ir-192 source. In both cases, the dose was normalized to the air kerma strength ($S_k$) of the source. The air kerma strength is defined as the product of the air kerma rate ($\dot{K}_{air}(d)$) at a point along the perpendicular bisector of the source, in free space, and the square of the distance ($d$) away from the source, or $S_k = \dot{K}_{air}(d) \cdot d^2$, with units of U (1 cGy h$^{-1}$ cm$^2$).

With regards to the Monte Carlo simulated depth dose distribution, the air kerma strength of the source had to be obtained via simulation using an approach as described by Ballester. [150] The dose cannot be simply normalized to the source activity, as the source provided by Nucletron includes only the apparent activity of the source, rather than the true activity of the radioactive Ir-192 pellet contained within the steel capsule of the source. The simulations were repeated three times, except at distances beyond 40 mm, where five
simulations were performed due to the poor statistics achieved at these distances from the source. Variable sized scoring volumes were used in the simulation. At distances of less than 20 mm from the source, the sensitive volume was defined as a $0.50 \times 0.50 \times 0.2$ mm volume. At distances $\geq 20$ mm, the dimensions of the sensitive volume was increased to $2 \times 2 \times 1$ mm to increase the energy deposition. Furthermore, the distance between dose points at distances $< 20$ mm is smaller because the dose changes more rapidly in this region of the depth dose distribution, and therefore, more dose points are necessary in order to accurately characterise the shape of the curve. The sensitive volume dimensions used for this experiment should not result in volume-averaging errors caused by a non-zero sensitive volume thickness, or by anisotropic-related, as discussed by Melhus et al. [151] and Wong et al. [152]

4.2.7.4 Rectal wall dose in homogeneous and heterogeneous situations

Following the validation of the Monte Carlo code, simulations were performed in order to estimate the dose absorbed when the rectal cavity was air-filled, and again when the rectum was a water-equivalent, homogeneous medium. The simulations were performed five times at each position, and the average dose was calculated. The relative difference in anterior rectal wall dose was calculated. The scoring volume was defined as a $1 \times 1 \times 0.02$ mm$^3$ volume of SiO$_2$ material located 18.6 mm away from the centre of the Ir-192 source. This distance was chosen because it is identical to the source–detector distance in our experimental measurements. The source and scoring volume were contained within a water phantom of dimensions $30 \times 30 \times 30$ cm$^3$. Rather than use the true thickness of a MOSFET’s radiosensitive SiO$_2$ layer in the simulation, which is less than 1 $\mu$m thick, a sensitive volume of 20 $\mu$m thickness was defined in order to increase the number of interactions that occur within the volume, while decreasing the computation time and statistical uncertainty of the estimated dose response. Increasing the thickness of the scoring volume to 20 $\mu$m should not lead to any errors in the dose estimated by
the simulation. Although the dose decreases non-linearly with distance away from the source, the dose gradient passing through such a thin scoring volume is essentially linear, and so the negative effects attributed to averaging the dose in a non-linear dose gradient can be ignored. At the posterior wall (180°), which is approximately 40 mm distance from the source, the thickness of the sensitive volume was increased to 50 $\mu$m to increase the number of interactions in the oxide.

4.2.7.5 Relationship between source distance and rectal diameter on the anterior wall dose

In order to determine whether a relationship exists between the relative dose discrepancy observed due to the rectal heterogeneity, and the distance separating the source and rectum, further simulations were performed. Simulations were performed at a shorter source distance of 10 mm, and again at a longer distance of 40 mm, assuming the rectal diameter is constant (20 mm). The simulation reported earlier, where a source distance of 18.6 mm and rectal diameter of 20 mm were defined, were repeated for this experiment to ensure that all the simulation parameters presented in this section were identical. Figure 4.6 is a representation of the parameters used for the simulation, as described.

The percentage dose discrepancy observed at source distances of 10, 18.6, and 40 mm were compared. The simulations were executed using the same phantom dimensions described previously so that the simulation conditions are consistent with the experimental setup. Five simulations were performed at each source position, and the mean dose is presented in this report. A total of $2 \times 10^9$ primary particles were emitted by the source for the simulation. Variable scoring volumes were used in this study. At a source distances of 10 mm, the scoring volume was defined with dimensions of $1 \times 1 \times 0.01$ mm$^3$; at 18.6 mm distance, the scoring volume had dimensions of $1 \times 1 \times 0.1$ mm$^3$; and the scoring volume at 40 mm distance was defined as a $2 \times 2 \times 0.25$ mm$^3$ volume.
Figure 4.6: Illustration of the simulation performed to measure the effect that source distance has on the magnitude of the dose discrepancy caused by the presence of the air in the rectal cavity. In the simulation, irradiation distances of 10, 18.6, and 40 mm are used, while the diameter of the rectum is kept at a constant 20 mm.

It is reasonable to assume that a relationship exists between the source distance and the magnitude of the dose discrepancy. The presence of an air cavity within the rectum reduces the probability that a photon will undergo a scatter interaction within this volume, thereby altering the dose distribution in the phantom or patient. Since the cavity is situated behind the anterior wall of the rectum, the cavity should mainly reduce the number of backscatter photons, and therefore reduce the total dose absorbed at the anterior wall of the rectum. However, for a given rectum size, an increase in the source distance would slightly reduce the angle that subtends the width (i.e., diameter) of the cylindrical rectal cavity. This reduction in subtending angle should reduce the magnitude of the dose discrepancy.

Further simulations were performed to determine whether a relationship exists between the dose discrepancy observed in an empty and full rectal cavity, and the diameter of the rectal cavity. For this simulation, the source distance was held at a constant 18.6 mm, while the rectal diameters used were 10, 20, and 40 mm. A relationship between rectal
diameter, and the dose delivered to the anterior wall of the rectum is particularly interesting because it would have clear clinical dosimetric implications. In order to insert the MOSkin into a patient’s rectum, it was proposed that the MOSkin be attached to the outside of an inflatable rectal balloon, and then inserted into the patient’s rectum. The balloon would be inflated until it fills the patient’s rectum, and is taut enough to not slide out of the patient. The size of the rectum will naturally differ between patients, so the amount of air required to fill the balloon, and the diameter of the rectal balloon, will also differ between patients. At a given source distance, an increase in rectal diameter will increase the angle subtending the width of the rectum, which should affect the travel path of a greater proportion of the primary photons emitted in the direction of the cavity, and consequently, reduce the number of backscatter photons. This increase in subtending angle is illustrated in Figure 4.7, where $\theta_1$, which corresponds to the 20 mm diameter rectum, is smaller than the angle subtended by the 40 mm diameter rectum, $\theta_2$. There is also a relationship between the subtending angle of the rectum, and the source distance, as explained earlier.
To determine whether there is a relationship between rectal diameter and the dose discrepancy, simulations were performed for rectal diameters of 0, 20, and 40 mm, as illustrated in Figure 4.7. Of course, a rectal diameter of 0 mm is simply a simulation within a homogeneous phantom, where the rectum is treated as a water-equivalent organ. These simulations were also performed for source distances of 10 and 40 mm. The effect of increasing the rectal diameter on the subtending angle should be greatest at a source distance of 10 mm, and smallest at 40 mm distance.

4.2.8 Effects of Finite Patient Volume

The simulations described so far have been conducted using a rather typical phantom dimensions, and a single dwell position. This is typical in dosimetric studies in brachytherapy using a phantom, and in Monte Carlo simulations. The dosimetric significance of assuming that the rectum is empty during treatment has been explored thus far. However, the dose discrepancy observed both experimentally and in corresponding Monte Carlo simulations may be further impacted by secondary heterogeneities located close to the prostate. These heterogeneities include the effects of a finite patient volume, the close proximity of the prostate to the perineum and abdomen, and the numerous air-filled catheters inserted into the patient. These factors may have a further effect on the rectal dose, particularly when compared to the dose calculated by the TPS, as the TG-43 formalism does not account for such heterogeneities.

The human-sized phantom was defined as a three dimensional block of water material with a 70 cm long torso (i.e. superior–inferior direction), a 35 cm left–right lateral width across the waist (as opposed to shoulder-to-shoulder width), and 20 cm anterior–posterior patient “thickness”. These dimensions are nominal values, although the author feels they are realistic estimates for an average-sized male. Rather than positioning the source at the geometric centre of the phantom like in other studies, an approximation of the prostate’s location within the male body was used. In this simulation, the source was positioned
(a) A schematic of the phantom dimensions, and relative position of the source dwell positions

(b) Relative position of source dwell positions.

Figure 4.8: Sagittal view of the human-sized phantom, with five dwell positions located in close proximity to the inferior end of the patient, which corresponds more realistically to the position of a human prostate.

7 cm from the inferior end of the phantom, and at the medial distance along both the anterior–posterior axis, and left–right lateral axis. Accordingly, the opposite end of the phantom is designated the “superior” end. This is illustrated in Figure 4.8, where the catheters and five dwell positions used for the simulation are on the inferior end of the
phantom, close to the perineum of a patient.

The radiation was delivered by a single Ir-192 PDR source from five different dwell positions. The scoring volume is a $0.50 \times 0.50 \times 0.2$ mm volume located along the perpendicular bisector of the PDR source when it is located at the centre dwell position, as illustrated in Figure 4.8(b). The centre dwell position is considered the origin in the simulation. Two other dwell positions are located along the same transverse axis as the central dwell position, and hence, are situated along the same catheter. The first dwell position is located 2 cm superior to the origin, while the second is located 2 cm inferior to the origin. Another two dwell positions are positioned 2 cm towards the patient’s left and right sides, respectively. The catheter material was assumed to be water equivalent, as plastic catheters are used at SGCCC rather than steel. Russell et al. [136] has shown that the scatter and attenuation effects of the catheter material can be approximately by water if the physical property of the wall material is similar to water. [136] Plastic and nylon catheters may be assumed to be water-equivalent in the simulation. The five dwell positions all reside on the same coronal plane of the patient in order to vary the distance and angle of the incoming radiation which strikes the scoring volume in both the superior–inferior direction, and left–right lateral direction adjacent to the source. A total of $2 \times 10^9$ primary particles were emitted from the source. The irradiation time at each dwell position was given equal weighting so that $4 \times 10^8$ particles, or 20% of the primary photon used in the simulation, were emitted from the source at each dwell position. A greater number of dwell positions were not used in the simulation, as the increased distance away from the scoring volume would have reduced the number of interactions which occurred in the sensitive volume, and increased the statistical uncertainty of the results. Increasing the thickness of the sensitive volume would have increased its size, and therefore, increased the number of interactions. However, due to the non-linear nature of the dose gradient passing through the sensitive volume, the effect of volume-averaging of the dose would have been apparent. This is particularly true for the dwell position that’s situated
1 cm from the scoring volume. Likewise, increasing the length and width of the sensitive volume would also increase the size of the scoring volume. However, this would increase the solidangle of the scoring volume with respect to the source. The isodose distribution surrounding the source is curved rather than linear, and this curvature may lead to inaccuracies caused by dose averaging. However, when the length and width of the catheter is small, such an error is avoided. [151]

The rectum was defined as air-filled cylindrical cavity with a diameter of 4 cm, and a length of 20 cm. A diameter of 4 cm was chosen, as it is similar to the rectal diameter of a patient being treated with a MEDRAD Immobilizer Prostate Stabilization Device (MEDRAD, Indianola, PA, U.S.A.) inside the rectum, and inflated with 60 ml of air. The MEDRAD Immobilizer device, which will be referred to as the ”rectal balloon” for the remainder of this report, is a disposable device which stabilizes the prostate, rectal wall, and surrounding male anatomical structures during both imaging and radiation treatment procedures. This device will be discussed in greater detail in Chapter 5, where the methodology and results obtained in a Phase II clinical patient trial are discussed. To simplify the simulation, the phantom was assumed to be a block of liquid water rather than separate materials such as muscle, soft tissue, and four-component tissue, as defined in ICRU 44. [142]

4.3 Results

4.3.1 Detector Calibration

A dose calibration factor was found for the MOSkin and RADFET detector, irradiating with both a LINAC and Ir-192 PDR source. Using the PDR source, the MOSkin and RADFET were found to have a mean dose calibration factor of 216 ± 7 mV/Gy and 150 ± 6 mV/Gy, respectively. Calibrating the MOSkin and RADFET with the LINAC yielded calibration factors of 207 ± 3 mV/Gy and 137 ± 4 mV/Gy, respectively. The
slight difference between LINAC and PDR brachytherapy calibration is due to an decrease in a MOSFET’s sensitivity as the threshold voltage increases with accumulated dose. The MOSFETs were calibrated for the LINAC before they were calibrated for brachytherapy, so the initial threshold voltage for each calibration procedure was different.

The reason for the increase in a MOSFET’s threshold voltage with accumulated dose was discussed in Section 2.3.7, while the decrease in MOSFET sensitivity was noted in a study of MOSFET dosimeters by Zilio et al. [153] In the study by Zilio et al., he notice a small sensitivity decrease of 0.045±0.008 per voltage increase in $V_{th}$. A sensitivity correction factor could be applied to the MOSFET response, but in the case of brachytherapy treatment for prostate cancer, this isn’t necessary due to the low dose delivered to an HDR/PDR brachytherapy patient. As discussed in Section 2.1.5, a relatively low accumulated dose, but a high effective dose, is delivered in brachytherapy. A typical 3 fraction prostate treatment would deliver a dose of 6 Gy/fraction, or a total of 18 Gy, to the patient’s prostate. The patient’s rectum would receive a lower accumulated dose.

4.3.2 Response of detectors at depth

The dose readings taken by the detectors were in good agreement with the TG43 calculated value, although the discrepancy between the measured and calculated doses appeared to increase with distance from the source. In terms of absolute dose, the dose measured with the MOSkin and RADFET at a depth of 54 mm were only 1.0 cGy and 0.9 cGy less than the dose calculated by PLATO, respectively. However, when the discrepancy is expressed in terms of percentage, the dose measured with the MOSkin and RADFET were 9.1% and 8.2% less than the calculated dose, respectively. This can be seen in Figure 4.9(b), where the dose measured at each depth is scaled by the distance squared ($r^2$).
Figure 4.9: Dose measurements taken with the MOSkin and RADFET dosimeters in a water-equivalent solid phantom at various distances (r) from an Ir-192 HDR brachytherapy source in order to make a comparison with PLATO. $Dose \times r^2$ was also plotted against depth to better illustrate the deviation between the calculated dose and the MOSkin at large distances from the source.
The discrepancies at large distances can be attributed to two factors. One factor is the low dose (11 cGy) delivered to the dosimeters by the PDR source at this depth, and the small threshold voltage change in response to this dose. The readout unit’s inherent uncertainty of ±1 mV becomes more significant as the magnitude of the dose, and dose response, decreases with source distance. Although the response uncertainty appears large when expressed as a percentage, the absolute uncertainty, expressed in terms of voltage, is within the readout unit’s smallest degree of precision, or 1 mV. The significance of this uncertainty could have been reduced to ±1% of $\Delta V_{th}$ if the response of both dosimeters was greater than 100 mV. However, on the day the experiment was performed, it would have required an irradiation time of approximately 35 minutes to produce a 100 mV change in threshold voltage at 54 mm distance. As the percentage discrepancy is only high due to the low accumulated dose delivered in this experiment, it shouldn’t be a deterrent to using the MOSkin for dosimetry.

Another contributing factor to the high percentage dose discrepancy is the incomplete scatter environment provided by our water-equivalent phantom. According to studies by Melhus et al. [151] and Pérez-Calatayud et al. [154] on the effect of phantom size in brachytherapy dosimetry studies, a spherical phantom must have a diameter of 80–100 cm to provide full scatter conditions for an Ir-192 source. The use of a spherical phantom with a diameter smaller than 100 cm resulted in a lower dose delivered to a point located a distance $r$ from the source. This under-dosage was observed at any distance $r$ in the smaller spherical phantom when compared to the dose delivered to the same distance $r$ in the 100 cm diameter phantom. This under-dosage only became significant at large distances from the source, as $r$ approached the phantom’s outer boundary. According to results obtained by Melhus et al., the phantom used in this study, standing 25 cm high, would result in a dose that’s approximately 4% lower at $r = 50 \text{ mm}$ than the dose delivered within an infinitely large phantom.
A dose discrepancy between the measured and calculated dose was also observed at 14 mm depth, where the MOSkin response was 4.8% greater than the calculated value, and the RADFET response was 6% lower than expected. This error at 14 mm is believed to be due to a setup error involving the placement accuracy of the dosimeters. According to PLATO, even a 1 mm change in distance from the source would result in an 16% change in dose rate due to the steepness of the dose gradient at a depth of 14 mm. Setup errors were also experienced by Lambert et al. [122] at distances close to an HDR Ir-192 source. The significance of such placement errors on the dose delivered to the dosimeter decreases with increasing distance from the source.

4.3.3 Angular dependence of the MOSkin’s response

The response of the MOSkin dosimeter was measured at angles ranging from 0–90° in 10° increments, and from 90–330° in 30° increments around the central axis of the MOSFET device and cable, as illustrated in Figure 4.2(a). The response of the MOSkin can be seen in Figure 4.10(a), and does not appear to vary with the angle of irradiation. The response was within ±2% of the mean response for nearly all eighteen measurements taken from 0–330° except at three angles, where the response deviated from the mean by 3–4%. The variation in response appears to be due to statistical fluctuations in response, as there does not appear to be a correlation between dose and changes in irradiation angle in the eighteen readings taken.

The response of the RADFET was measured at angles ranging from 0–330° in 30° increments. Unlike the MOSkin response to changes in irradiation angle, the RADFET exhibited a pattern of significant response variation that correlates to the angle of irradiation. When irradiated from the top-side of the RADFET, which corresponds to angles from 0–90° and 270–360° (as illustrated in Figure 4.2(a)), the response was greater than
Figure 4.10: Response of the MOSkin and RADFET at various angles around the central axis of the dosimeter and attached cable.

the mean. When irradiated from the detector’s under-side, the response was less than the mean. Furthermore, the response pattern appears to be asymmetric rather than symmetric. Using the phantom illustrated in Figure 4.2(b), the distance between the source and dosimeter does not change as the dosimeter is rotated. The most likely explanation for the asymmetry is that the sensor is slightly off-centre rather than at the geometric centre
of the epoxy bulb, although a rather symmetric response was observed in Section 3.5.3, where the angular response of the RADFET was characterised for skin dosimetry.

With regards to the MOSkin readings taken at various angles along the azimuth, the response was in good agreement with the dose calculated by PLATO at all angles. The response was generally around ±3% of the calculated dose at the source dwell positions used for this measurement, although most measurements were within ±2%. The results can be seen in Figure 4.11. The ability of the MOSkin to accurately measure dose with changes in both distance and azimuthal angle is of utmost importance if the MOSkin is intended for clinical HDR brachytherapy dosimetry, as the dose delivered to a point along the rectal wall is the sum of the dose delivered from all dwell positions along a catheter.

Figure 4.11: Response of the MOSkin at various azimuthal angles and distances.
4.3.4 Validation of Monte Carlo code

The dose estimated by Geant4 dose was found to be in good agreement with the PLATO TPS dose calculation until a source distance of 40 mm, where the Geant4 simulation appears to underestimate the dose slightly, as shown in Figure 4.12. However, the discrepancy is <2%, even at 50 mm. The use of variable sized scoring volumes appears important, particularly at dose points located near the source, where the dimensions of the sensitive volume should be small relative to the source in order to avoid volume-averaging errors related to the steep dose drop-off with radial distance from the source, and the anisotropical dose distribution surrounding the source. The uncertainty values in the percentage difference seen in Figure 4.12 are based on the statistical variation of results obtained from repeated simulations.

4.3.5 Absorbed Dose in a Heterogeneous and Homogeneous Rectal Phantom

The values in Table 4.2 represent the percentage difference in the dose measured in the ‘empty’ rectal phantom to the dose measured in a ‘full’, homogeneous rectal volume at a source distance of 18.6 mm. The effect of the air cavity is evident along the anterior and posterior rectal walls, labelled 0° and 180° in Table 4.2, respectively. The dose measured by the MOSkin and RADFET in an empty rectal cavity were 14.7 ± 0.2% and 13.7 ± 0.6% lower than the dose measured in a homogeneous rectal phantom, while the simulation reported a 13.2 ± 0.6% discrepancy in the rectal wall dose, corroborating the observations observed experimentally. The effect of rectal heterogeneity cannot be ignored, as it appears to be significant. This discrepancy will particularly affect studies that examine dose volume histograms and try to relate absorbed dose to rectal complications. [9,155,48,156] Studies by Hille et al. [48] and van Lin et al. [155] incorporate rectal balloons into their study of rectal dose, and the size of the balloon depends on the amount of air used to inflate the balloon. The heterogeneity will also affect the method used to assess the efficacy of a rectal dosimetry system in clinical patient trials, as the dose measured in the rectum
Figure 4.12: Comparison of the depth dose distribution calculated using the TG43 formalism, and the Monte Carlo simulated depth dose distribution. Dose values were normalized to air kerma strength.
Table 4.2: Percentage difference between the dose readings taken in an empty rectal cavity, and readings taken in a homogeneous rectal cavity

<table>
<thead>
<tr>
<th></th>
<th>0°</th>
<th>90°</th>
<th>180°</th>
<th>270°</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOSkin</td>
<td>(−14.7 ± 0.2) %</td>
<td>(2.8 ± 0.3) %</td>
<td>(22 ± 1) %</td>
<td>(0.2 ± 0.3) %</td>
</tr>
<tr>
<td>RADFET</td>
<td>(−13.7 ± 0.6) %</td>
<td>(4.1 ± 0.3) %</td>
<td>(26 ± 2) %</td>
<td>(3.3 ± 0.3) %</td>
</tr>
<tr>
<td>Geant4</td>
<td>(−13.2 ± 0.6) %</td>
<td>(1.4 ± 0.1) %</td>
<td>(22 ± 2) %</td>
<td>(0.83 ± 0.07) %</td>
</tr>
</tbody>
</table>

cannot simply be compared to the rectal dose calculated by the brachytherapy TPS. The incorporation of a rectal balloon into the treatment would alter the shape and diameter of the rectal walls, which is expanded to different sizes through an injection of air.

The observations discussed here are similar to the backscatter effects reported by Raina et al., [137] who discussed the dose discrepancy between their experimental dose measurements, and dose values calculated by the TPS in intraoperative high-dose rate brachytherapy (IOHDR). In IOHDR treatments, applicators through which the HDR source is transferred are typically sutured directly onto the tumour bed, delivering a high dose of radiation to the target site immediately following surgical excision of the tumour. For example, IOHDR has been employed to the small breast cavity immediately following the surgical removal of a breast tumour, and in the treatment of soft tissue sarcomas. [61, 157] The brachytherapy TPS does not account for the absence of scatter material in the region above the applicators, which is mostly air. Raina et al. observed a large discrepancy between the calculated and measured doses by using an array of applicators placed directly onto the surface of a water-equivalent plastic phantom. The dose delivered to the phantom surface was measured with various thicknesses of tissue-equivalent bolus material placed on top of the applicators. With no backscatter material present, the dose delivered to the phantom was 15% lower than the dose delivered when more than 10 cm of bolus material was on top of the applicators. This result is comparable to the discrepancy reported here, except that a cylindrical air cavity is physically smaller than the room-size air medium in the experimental setup of Raina et al. A dose overestimation of 14% by the TPS was
also observed in an experiment by Mangold et al., where PDR brachytherapy was used following the surgical treatment of breast cancer. [139] Kinhikar et al. [90] reported that the TPS overestimated the skin dose by approximately 9% by comparing the TPS dose calculation with MOSFET and TLD measurements.

Readings taken at the posterior end of the rectal wall were greater in the presence of the empty volume, differing from the full rectum measurements by $22 - 26\%$. This outcome should be unsurprising, as the photons emitted by the Ir-192 source are attenuated less through air. The uncertainty of the Geant4 simulated data was relatively high at the posterior wall ($180^\circ$) when the rectal cavity was water-equivalent. The poor statistical uncertainty is due to the relatively low number of interactions that occur at the posterior wall, which is 40 mm from the source. While a simple solution to this problem would be to increase the number of primary photon emissions from the Ir-192 source in order to increase the number of interactions within the sensitive volume, increasing the simulation time beyond the 2000 hours of CPU processing time that was required to obtain the data presented in this report would be impractical.

The doses delivered to the $90^\circ$ and $270^\circ$ positions within the rectum were not significantly affected by the presence of the air medium, reporting only a slight increase in dose when the rectal cavity was filled with air.

While Table 4.2 illustrates the relative difference in dose that can be expected when the rectum is assumed to be an empty air-filled cavity rather than homogeneous, it does not illustrate the effect of the RADFET’s encapsulating layer on its ability to measure the absolute dose measurement at the rectal wall. Earlier, the RADFET was shown to be capable of accurately measuring the absorbed dose with increasing distance from the source. However, the thickness of the epoxy was always taken into account in the dose calculation. Table 4.3 compares the dose calculated by the TPS to measurements taken
Table 4.3: Comparison of the anterior rectal wall dose measurements taken in both a heterogeneous and homogeneous rectum environment, and the PLATO calculated anterior wall dose. The differences between the measured and calculated values are expressed in terms of percentage.

<table>
<thead>
<tr>
<th></th>
<th>Calculated Dose (cGy)</th>
<th>Full Rectum</th>
<th>Empty Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Measured (cGy)</td>
<td>% Diff</td>
<td>Measured (cGy)</td>
</tr>
<tr>
<td>MOSkin</td>
<td>37</td>
<td>37±1</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>RADFET</td>
<td>37</td>
<td>33 ± 1</td>
<td>−10%</td>
</tr>
<tr>
<td>RADFET (with epoxy correction)</td>
<td>33</td>
<td>33 ± 1</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

with both the MOSkin and RADFET when the thickness of the epoxy material was not accounted for in the source distance used for calculation. The difference between the measured and calculated doses are also presented in terms of percentage. When the RADFET was placed against the anterior wall of the phantom, the absolute dose reading obtained with the RADFET was 10% lower than the expected dose at the anterior wall. However, when the 1 mm of epoxy material was taken into account in the source distance used for calculating the dose, the dose discrepancy was < 1%. Clearly, the discrepancy observed is completely related to the physical design of the epoxy resin. This is true whether the dosimeter is placed in a homogeneous or heterogeneous rectal environment, although for other clinical applications, the presence of the epoxy bulb may not matter. However, by accounting for the extra distance introduced by the epoxy material, the calculated dose is not representative of the dose delivered to the rectal wall, nor to the rectal dose constraints used for planning. Dose measurements taken with the RADFET will always misrepresent the anterior wall dose due to the epoxy. One solution would be to use the TPS to calculate the point dose approximately 1 mm from the rectal wall. However, this level of precision and accuracy is difficult to achieve precisely due to the fixed voxel sizes, which have dimensions at the millimetre scale. This same issue was discussed in the previous chapter of this thesis with regards to skin dose calculations.
4.3.6 Relationship between source distance and rectal diameter on the anterior wall dose

There is a clear relationship between the anterior rectal dose, and the diameter of the rectal cavity, as can be seen in Figure 4.13.

![Graph showing the relationship between rectal diameter and percentage dose difference from homogeneous rectum](image)

Figure 4.13: Relationship between the diameter of the rectal cavity, and the percentage dose deviation from the dose estimated in a homogeneous environment

The dose discrepancy at the anterior wall was greater when the diameter of the rectal cavity used for the simulation was 40 mm rather than 20 mm. This was observed at source distances of 10, 18.6, and 40 mm. A larger rectal cavity affects the travel path of a larger proportion of the photons emitted from the source, since the angle from the source that subtends the diameter of the rectal cavity is greater. However, the 40 mm diameter cavity did not significantly increase the magnitude of the dose discrepancy when compared to the dose estimate using a 20 mm diameter cavity. This was particularly true at large distances from the source. For example, at a source distance of 10 mm, dose discrepancies of $15.7 \pm 2.2\%$ and $19.9 \pm 2.7\%$ were estimated for rectal diameters of 20 mm
and 40 mm, respectively. The 40 mm diameter rectal cavity, which is twice the diameter and four times the volume of 20 mm cavity, only results in a slightly lower dose estimate relative to the estimate for the 20 mm diameter rectal cavity. When the source distance was increased to 40 mm, the dose discrepancies were only $-3.2 \pm 0.8\%$ and $-5.1 \pm 1.5\%$ for rectal diameters of 20 mm and 40 mm, respectively. It appears that the heterogeneities did not reduce the dose to the anterior rectum wall significantly using either rectal diameter.

Based on the results presented in Figure 4.14, the magnitude of the dose discrepancy is also strongly dependent on the source distance. There are two reasons for this. First, changing the source distance also changes the subtending angle of the rectum. This angle decreases as the separation distance between the source and anterior rectum wall increases. A larger subtending angle affects the travel path of a larger proportion of the photons when compared to a smaller attenuating angle, so increasing the source distance reduces the impact of the heterogeneity on the rectal dose.

If the decrease in subtending angle was solely responsible for the decrease in dose discrepancy as the source distance increases, then the dose discrepancy should remain constant if the rectal diameter ($d$) increased with source distance ($r$) so that the subtending angle of the rectum remained constant at all source distances. However, based on the data plotted in Figure 4.13, this is not the case. The subtending angle of the cavity at $r = 10 \ mm$ and rectal diameter $d = 20 \ mm$ (90°) is similar to the angle when $r = 18.6 \ mm$ and $d = 40 \ mm$ (94°), and yet the dose discrepancies are clearly dissimilar, at $15.7 \pm 2.2\%$ and $10.1 \pm 2.9\%$, respectively. The heterogeneity must be having an effect on the rectal dose or scattered photons that has not been considered so far.

According to a report by Russell et al., [136] increasing the source distance affects the
(a) Dose plotted against distance from the source (r)

(b) Percentage dose difference plotted against the source distance (r)

Figure 4.14: Relationship between the source distance, and the percentage dose deviation from the dose estimated in a homogeneous environment
ratio between the primary and scatter dose deposited at a point along the perpendicular bisector of the source. *Primary photon dose* is defined as the dose deposited by photons that had not yet interacted with the phantom medium prior to interacting within the sensitive volume. Therefore, all primary photons that deposit energy within the sensitive volume were initially emitted from the source in the direction of the sensitive volume. This differs from *scatter photon dose*, which is deposited by photons that have undergone at least one scatter interaction prior to depositing energy within the sensitive volume. In their report, Russell et al. showed that the scatter contribution to the dose along the perpendicular bisector increases with source distance because the probability that a photon has not interacted with the medium decreases with source distance. The primary photon dose decreases with distance accordingly. The dose deposited just beyond the Ir-192 source’s steel capsule is almost entirely due to primary photons, while the number of backscatter and side-scatter photons is very low. However, at a source distance of approximately 60 mm, the primary and scatter dose component become equal, each contributing 50% of the total dose.

Russell et al. [136] also showed that if the source is positioned close to an air-water interface, and this interface runs parallel to the source’s perpendicular bisector, the scatter dose contribution would be effected due to the reduction in side-scattering photons. The proportion of the total dose contributed by scatter photon dose still increased with source distance, but it increased at a much lower rate when compared to the increase observed within a fully homogeneous phantom. This relative decrease in scatter dose deposition was attributed to the absence of scatter material on one side of the bisector axis, which consequently reduced the number of scatter photons. Since the air-water interface is continuous along the bisector axis, the apparent size of the heterogeneity is proportional to the source distance. It has a continuous affect on the scatter photons from the source to the sensitive volume. This air-water interface did not affect the primary dose deposition because it was never in the direct path of primary photons travelling from the source and
sensitive volume.

With regards to the experiment being discussed in this thesis, the rectal cavity is positioned directly *behind* the sensitive volume rather than parallel to the perpendicular bisector. Unlike the air-tissue interface used by Russell et al. in their experiment, the apparent size of the rectal cavity with distance, as reflected in the decrease in the subtending angle of the rectal cavity. However, as described earlier, the dose discrepancy is not simply due to a simple a geometric factor such as the subtending angle of the heterogeneity. Another factor is the increase in the proportion of the total dose delivered by scatter photons as the source distance increases. If the subtending angle did not vary with distance, then the effect that a heterogeneity has on the dose discrepancy should actually *increase* with source distance. However, rather than observing an increase in the dose discrepancy in this experiment, a decrease was observed because the air contained within the rectum only reduces the probability of photons scattering backwards towards the sensitive volume, and not side-scatter or forward-scatter photons. The interaction probability of photons travelling through the phantom medium between the source and sensitive volume is not affected by the heterogeneity. At shorter distances from the source, where the rectal diameter is relatively long when compared to the source distance, both the number of back-scatter and side-scatter photons are affected by the heterogeneity. The explains why the dose estimate in a heterogeneous phantom medium becomes quite low at a source distance of 40 mm, and is not solely due to the subtending angle of the heterogeneity.

The uncertainty of the dose discrepancy, as shown in Figure 4.14(b), appears to be significantly larger at a source distance of 10 mm than it is at 18.6 and 40 mm. Since the dose discrepancy is calculated using the Monte Carlo rectum dose estimates in both a heterogeneous and homogeneous phantom, the size of each error bar in Figure 4.14(b) is dependent only on the magnitude of the uncertainty of these two dose terms. The primary
cause of the large error bars observed is the relatively large 2% statistical uncertainty observed for the rectum dose estimate within the fully homogeneous phantom at r=10 mm. In comparison, the statistical uncertainty of the homogeneous rectum dose was much smaller ($\leq 0.5\%$) at source distances of 18.6 and 40 mm than at 10 mm, and as a result, the uncertainty of the dose discrepancy is also smaller at these distances. In the presence of either a 20 or 40 mm diameter air cavity, the uncertainty in the dose discrepancy was $\leq 0.6\%$ at all source distances.

The statistical uncertainty of the dose in the homogeneous phantom was greater at a distance of 10 mm than at 18.6 mm or 40 mm due to the small dimensions of the sensitive volume defined in our Monte Carlo simulation at this source distance. A thin sensitive volume (0.01 mm) was defined in order to reduce the effects of volume-averaging in such a steep dose gradient. However, the number of photon interactions that occurred within the sensitive volume was relatively low due to its small dimensions, and so a greater degree of statistical fluctuation occurs between simulations.

4.3.7 Dose results obtained in a human-sized phantom

The dose results calculated within the finite patient volume described in Section 4.2.8 is expressed in terms of the percentage difference between the anterior rectal dose estimated in a heterogeneous, air-filled cavity, and the dose when the rectum is water equivalent. The dose at the anterior wall of the empty rectal cavity was $19.5 \pm 1.8\%$ lower than the dose delivered to the same distance within a homogeneous rectal phantom. This result is in good agreement with the $19.9 \pm 2.7\%$ dose discrepancy reported earlier using a source distance of 10 mm and rectal cavity diameter of 40 mm. As this simulation was performed using the same source distance and rectal diameter, issues related to the finite patient volume, presence of the surrounding catheters, and the close proximity of the source dwell positions to the perineum do not appear to have a noticeable effect on the dose. However, at a greater source distance of 40 mm, the incomplete side-scatter conditions that exists
due to the prostate’s close proximity to the perineum may have an increased effect, as the sidescatter contribution to the dose increases with distance from the source.

4.4 Conclusion

There are several important conclusions that can be made from this experiment. The assumption that the rectum is a homogeneous, water-equivalent medium means that the dose reportedly delivered to the anterior rectal wall by a treatment planning system is overestimated, as illustrated in Table 4.2 and 4.3. This finding has a consequence in studies that examine the dose volume histogram reported by treatment planning systems to quantify the proportion of the rectal wall that receives 90% or 100% of the prescribed dose, and studies that try and relate the risk of complications to the rectal dose. [9, 73, 158, 156] Assessment of the performance of a rectal dosimeter will also be affected, as the accuracy of a dosimeter cannot simply be ascertained by comparing the calculated dose as determined by the TPS, to the dose measured by the dosimeter. This comparison cannot be made until tissue heterogeneities were somehow accounted for in the calculation formalism like they are in treatment software used to plan external beam treatments. Another solution may be to use Monte Carlo simulation-based planning, but only when computing power increases dramatically to allow Monte Carlo simulations to be applied in a clinical setting. It would be quite interesting to explore the relationship between the radius of the rectal cavity and the absorbed dose at the rectal wall, although Raina’s report shows little difference between the effect of a room-sized air cavity, and the relatively small heterogeneity introduced into the phantom in this report. [137] The dose calculated within the finite patient-sized phantom did not differ greatly from the results obtained from a simulation which used a cubic 30×30×30 cm³ phantom.

The importance of the packaging of a MOSFET dosimeter in quality assurance during HDR brachytherapy was illustrated when comparing the measured dose at the anterior
wall of the rectal cavity wall, to the theoretical dose. The MOSkin and RADFET detectors both reported comparable percentage dose differences between the dose measured in an empty and full rectal cavity, and corroborated by Geant4 simulated results. However, in terms of absolute dose, the RADFET exhibited a 10% underresponse at the anterior rectal wall when compared to the expected dose, and the dose measured by the MOSkin. The reduced build-up material atop the MOSkin sensor allowed it to measure the dose against the rectal wall, while a correction would likely have to be applied to the RADFET to account for the thickness of the build-up layer, which increases the distance between source and detector. This illustrates the importance of using a detector with a shallow effective depth of measurement.
CHAPTER 5
RESULTS FROM PHASE II CLINICAL TRIAL AT ST. GEORGE HOSPITAL

5.1 Introduction
The risk and severity of complications arising from a particular form of prostate cancer treatment has become a significant topic of interest, as the available radiation therapy modalities used to treat prostate cancer are all capable of providing effective tumour control. While rectal complications are a concern following external beam radiotherapy (EBRT), intensity-modulated radiotherapy (IMRT), low dose-rate (LDR) brachytherapy, and high dose-rate (HDR) brachytherapy, the large dose delivered per fraction in HDR/PDR brachytherapy treatment, along with the high dose-rate delivery to the rectum situated nearby, means that a great deal of concern regarding rectal dose surrounds HDR/PDR brachytherapy treatment. The most common morbidity experienced by HDR brachytherapy patients occur at the rectum, which manifests itself as rectal discomfort, pain, spasms, diarrhea, rectal bleeding, hemorrhaging, proctitis, and incontinence. [66, 67] A patient who suffers from rectal complications following treatment will generally not suffer from all these complications, but a combination of them. Some of these complications will impede the patient’s ability to partake in common daily activities, which may severely affect their lifestyle.

The growing concern over rectal toxicity stems mainly from the escalation of the total dose delivered during a treatment, and the trend towards using larger fraction sizes for treatment due to the low $\alpha/\beta$-ratio of prostate tumour cells when compared to many other types of tumour cells. [8, 19, 20] This was discussed in detail in Chapter 1. The rate of clinical and biochemical freedom from disease have been shown to improve when the
total dose delivered to the prostate was increased from approximately 70 Gy, to a total
dose of 76–80 Gy, or greater. [69, 159, 70, 71, 160, 161] A similar improvement is evident
when the prostate is treated with EBRT in conjunction with HDR brachytherapy, or when
HDR brachytherapy is delivered as a monotherapy. [23, 22, 21, 24]

Progression towards the delivery of larger doses, and larger fraction sizes, significantly in-
creases the need for quality assurance (QA) measures during HDR/PDR prostate brachyther-
apy. Treatment plans are tailored to each individual patient using each patient’s transaxial
CT images; however, the images are taken hours prior to treatment delivery. Many hos-
pitals do not re-plan the treatment prior to the deliver of each fraction, and consequently,
organ motion, catheter migration, and slight changes in prostate size are not accounted
for. This is an issue when dealing with a treatment where a 1 mm change in source
distance would result in a large discrepancy between the delivered dose, and the dose
calculated by the TPS.

Rather than rely on the dose distribution calculated by a CT-based TPS, a dosimetry
system that allows for real-time rectal dose measurements would be invaluable in de-
termining whether the rectal dose is in agreement with the dose calculated by the TPS
at a time \( t \) following the start of the treatment. The dose information provided by the
dosimeter would take anatomical changes and catheter migration into account, which is
not possible using dose calculations by the TPS. Potentially, a rectal dosimeter designed
for QA of an HDR/PDR brachytherapy treatment would be able to measure the total dose
delivered to the rectum at regular time intervals during the treatment, and then compared
to the dose calculated by the TPS. If the measured dose is not in agreement with the cal-
culated dose within a certain margin, as defined by the clinician, the treatment may be
interrupted prior to the onset of chronic toxicity. To complicate matters, the brachyther-
apy TPSs in use today calculate the dose without accounting tissue heterogeneities, and
their effect on the dose distribution throughout the patient volume. [134] The assumption
that a patient is a block of homogeneous water does not accurately portray a patient’s anatomy, as the prostate is typically situated only several centimetres superior to the perineum, and 0.5–1 cm anterior to the rectal cavity which is emptied prior to treatment. The effect of the rectal heterogeneity on the dose was discussed in detail in Chapter 4, and compared to observations by Raina et al. [137], Mangold et al. [139] in their study on breast treatment; and Anagnostopoulos et al. [138] in their study of the effects of the spinal cord and finite tissue volume on oesophageal treatment.

In this clinical study, we measured the dose delivered to the patient’s anterior rectal wall during the pulsed dose-rate (PDR) brachytherapy component of the prostate treatment at St. George Hospital Cancer Care Centre (Kogarah, Sydney, Australia), which is delivered in conjunction with EBRT. Pulsed dose-rate brachytherapy is delivered at St. George rather than HDR brachytherapy due to shielding issues in the treatment room. A PDR source is similar to an HDR brachytherapy source, except a PDR source has a lower activity, and is physically shorter than an HDR source. The rectal dose measurements were taken using the MOSkin, a MOSFET detector developed by the Centre for Medical Radiation Physics (University of Wollongong, Australia).

5.2 Methods and Materials

5.2.1 Patient Selection

Intermediate and high risk patients were used in the study. At SGCCC, intermediate risk patients are defined as patients with $< T3$ stage disease, combined with either a Gleason score of 7, or a PSA ranging from 10–20. High risk patients include those that meet any of the following criteria: a Gleason score of 8–10, PSA $> 10$, or disease at stage $\geq T3$. The patient selection process was random, as all intermediate and high risk patients were eligible to participate.
5.2.2 PDR brachytherapy Treatment Procedure

The brachytherapy operation was performed with the patient under general anaesthesia. With the patient in the lithotomy position, a template grid was sutured to the upper thighs so that it covered the perineum. Holes are located at each grid point on the template, where the catheters are inserted. Holes in the template hole are spaced 5 mm apart in both the vertical and horizontal directions. The insertion procedure was guided by real-time images taken with a trans-rectal ultrasound (TRUS) probe, as well as an x-ray machine used to acquire images from a coronal viewpoint. The TRUS probe was connected to a mechanical stepper carriage, and the cylindrical probe itself was covered with a condom, followed by lubricant. The stepper carriage was locked in place, only allowing the TRUS
Figure 5.2: Images of the MEDRAD Immobilizer rectal balloon device deflated (left) and inflated with 60 ml of air (right). The concavity of the device cradles the prostate, minimizing prostatic motion.

...
Indianola, PA, U.S.A.) was inserted into the rectum following needle insertion to a depth decided upon by the radiation oncologist. Approximately 60 ml of air was injected into the rectal balloon following insertion. The depth of insertion is determined qualitatively, and differed between patients.

The MEDRAD rectal balloon is a disposable, one-time use device. Its concave face stabilizes the prostate during both treatment planning, and delivery when inflated with air. When filled with 60 ml of air, the balloon introduces a 35 mm diameter air cavity of predictable size and shape inside the rectum. Figure 5.3(a) is a photon to illustrate the size of the balloon when completely deflated, while Figure 5.3(b) is a photo of the same balloon inflated with 60 ml of air. The incorporation of a rectal balloon into a prostate treatment procedure has been shown to reduce the total dose absorbed by the rectal wall, [155, 156, 48] with the efficacy of the MEDRAD balloon and other balloons studied by van Lin et al. [155] The MEDRAD balloon device, and MOSkin were approved for use in the clinical trial by Therapeutic Goods Administration (TGA) in Australia prior to the commencement of the trial. Furthermore, it is currently the only rectal balloon approved for clinical use in Australia, although an alternative rectal balloon produced by a different manufacturer is currently in the process of gaining approval.

For the trial, the MOSkin detector was attached to the concave side of the MEDRAD balloon prior to being inserted into the patient’s rectum. The detector was attached to the balloon using Telesis 5 (Telesis, USA), a silicone-based, medical grade adhesive. A photo of the MOSkin dosimetry system, complete with portable read-out unit, MOSkin dosimeter, and MEDRAD rectal balloon, can be seen in Figure 5.3(a) and 5.3(b). When the balloon is inserted into the rectum and inflated, the wall of the balloon pushes the MOSkin against the anterior wall of the rectum so that they are in physical contact. This allows for dose measurements to be taken at the wall. The glue was applied to the geometric centre of the concave balloon surface using a sterilized cotton swab, and the MOSkin
was placed on the adhesive for approximately 5 minutes to allow the adhesive to dry.

![Image of MOSkin, MEDRAD rectal balloon, and Skin readout unit.](image1)

(a) A photo of the MOSkin, MEDRAD rectal balloon, and Skin readout unit.

![Image of MOSkin attached to the rectal balloon, and covered with a condom.](image2)

(b) MOSkin attached to the rectal balloon, and covered with a condom.

Figure 5.3: Visibility of the MOSkin device in a set of CT images. The handle of the MEDRAD rectal balloon device is clearly visible in nearly every CT image in the set.
Following the needle insertion procedure, and the insertion of the MEDRAD rectal balloon, patients were allocated a rest period of 1 hour before commencing the CT-based imaging procedure. Transaxial CT images were taken using a Philips Brilliance Big Bore CT machine. CT images of 2 mm thickness were taken of the patient, and transferred to the PLATO TPS in order to create the treatment plan. The distance between the two fiducial markers located at the base of the prostate, and the one marker at the apex of the prostate, is measured and used as a reference for subsequent CT scans of the patient. The distance between markers should not change in subsequent CT scans, as this would signify that the prostate has changed in size since the CT images were taken. The catheters are also checked during simulation to ensure that they are inserted far enough into the patient to provide adequate dosimetric coverage of the prostate, particularly the base. This is achieved by inserting a set of plastic needles into each catheter, each with a dummy PDR source marker at the end. To provide adequate dose coverage, the most superior source dwell position must be at least 5 mm beyond the fiducial markers located at the base of the prostate. If the catheter tips were not inserted far enough to provide 5 mm of clearance, the catheters must be pushed further into the patient, and the CT scan is repeated. The CT images were uploaded to Oncentra Masterplan (Nucletron, The Netherlands) for image registration, where the outline of the prostate, urethra, and rectum were contoured in each CT image. The position of each catheter was also registered in each image for reconstruction. Using the reconstructed images from Oncentra, treatment plans were created by a medical physicist using PLATO TPS, and later approved by a radiation oncologist.

The point dose delivered to the MOSkin was calculated by first locating the detector in the appropriate image slice from the CT image set, and then allowing PLATO TPS to calculate the point dose delivered to the specified location at the rectal wall. Either the MOSkin dosimeter or cable is clearly visible in the set of CT images, appearing as a white point located at the anterior rectal wall. The MOSkin cannot be visually differentiated from the
Figure 5.4: Visibility of the MOSkin device in a CT image. The handle of the MEDRAD rectal balloon device is clearly visible in nearly every CT image in the set.
cable in a CT image, as they both appear as a white point. However, the detector is designed so that the sensitive detecting volume is located 4 mm from the tip of the MOSkin, so the tip can be used as a reference. The MOSkin’s sensitive volume is specified in the CT image set by first finding the CT images where neither the MOSkin or cable appear in the image (Figure 5.4(a)), and then shifting through the CT image set in the patient’s inferior direction until the first image in which the MOSkin device appears is found. This image should be of the tip of the MOSkin dosimeter. Once this image is found, the sensitive volume is assumed to be located 2 images in the inferior direction (Figure 5.4(b)), since each image is 2 mm thick, and the MOSkin’s sensitive volume is 4 mm from the tip.

A total of 9 patients were included in this ongoing preliminary study. The treatment was delivered by a Nucletron microSelection remote afterloader. The fractionation scheme for the PDR component of the treatment composed of 2 fractions, with 9 Gy delivered per fraction. The first fraction was delivered on Monday in the late afternoon, while the second fraction was delivered the following morning. This corresponds to a period of approximately 19–20 hours between the first and second fraction. A separate treatment plan was created for each fraction to ensure that changes in the patient’s anatomy were properly accounted for.

The first patient included in the study was treated with 3 fractions (6.5 Gy/fraction) rather than 2 fractions, as he was treated just prior to a change in the fractionation scheme at SGCCC. A single treatment plan was created for the first patient. The treatment plan was created prior to the delivery of the first fraction, while the same plan was used for the second and third fractions. Furthermore, each axial CT image slice used to plan the treatment was 4 mm thick rather than the 2 mm image slices used in subsequent treatment plans. The treatment methodology used to treat the first patient in this study is very representative of the method used by the majority of other treatment facilities. The use of 4 mm or 5 mm thick CT images is the norm, as the number of images that need to be
contoured by the oncologist is reduced by 50% when compared to the use of 2 mm image slices. Clinically, there is no significant benefit of using thinner CT images in terms of treatment quality, as there is no real need for the accuracy. The shape and relative positions of the prostate, rectum, and urethra do not change so significantly between adjacent images that a treatment plan would require 2 mm resolution in order to be effective. Unfortunately, image thickness has a significant effect on this trial, as the trial requires that the MOSkin’s axial position be accurately determined so that the TPS’s calculation of the dose expected at the MOSkin’s position is also accurate. A resolution of 4 mm isn’t high enough to determine the location of the MOSkin’s sensitive volume within the rectum using our method, where we use the image in which the tip of the MOSkin first appears as a reference point. The use of 2 mm slices means that the uncertainty in the MOSkin’s position within the CT image set is only $\pm 1 \text{ mm}$. With regards to basing the delivery of all three fractions on a single treatment plan, most centres deliver all the fractions based on a single treatment plan because each plan may take 1–2 hours to create. In most centres, a new treatment plan would only be created for the second or third fractions if the CT images taken prior to their delivery indicate that the internal anatomy of the patient has changed significantly since the delivery of the first fraction. Inter-fraction catheter migration can usually be accounted for without creating a new treatment plan, as the position of each catheter can be physically adjusted until their position relative to the fiducial markers is similar to their position in the first set of CT images. The advantage of creating an individual treatment plan for each fraction is also evaluated in this report.

5.2.3 Experimental Considerations

In order for a comparison to be made between the measured and calculated rectal dose, the treatment must be delivered in the same conditions in which the treatment was planned. The relative position of the MOSkin must not move with respect to the source dwell positions within the catheter. This requires that the catheter insertion depth, prostate size,
and the position of the MEDRAD rectal balloon have not changed from the time the CT images were taken, to the delivery of the treatment fraction. The balloon must not experience rotational motion while the patient is transported to different rooms in the hospital.

Figure 5.5: An illustration of the steep dose gradient that the MOSkin would be situated in if the MEDRAD balloon were positioned too far superiorly relative to the prostate.

The protruding length of the MEDRAD rectal balloon was measured immediately prior to imaging the patient via CT, and again prior to treatment delivery. If the balloon had moved in the superior–inferior direction by a distance $\Delta x$ since the CT images were taken, it was noted. Balloon adjustments are difficult to perform while the patient is lying on his bed. Rather than correct for the observed balloon migration immediately prior to treatment delivery, PLATO was used to calculate the dose delivered to the MOSkin, with $\Delta x$ accounted for. In total, the expected dose to the MOSkin is calculated twice: before and after accounting for $\Delta x$. Balloon migration in the superior–inferior direction
may have a severe effect on the dose actually measured by the MOSkin due to the shift in the point of measurement, especially if the dosimeter was originally positioned closer to either the base or apex end of the prostate. A steep dose gradient in the superior-inferior direction exists at both ends of the prostate. As a result, a small degree of balloon migration in this region, either superiorly or inferiorly, would have a great effect on the measured dose. Figure 5.5 illustrates the steep dose gradient that the MOSkin would be situated in if the balloon were positioned too far superiorly relative to the position of the prostate. If the balloon was initially positioned directly posterior to the prostate’s geometric centre, which is the ideal location for dosimetry, then a slight displacement of the balloon wouldn’t have a significant effect on the dosimetry, as the movement would be along an isodose curve.

5.3 Results

5.3.1 Analysis of Measurements Taken from Patient 1

The first patient included in the study was treated with a three-fraction treatment rather than the two-fraction treatment received by other patients in the study. The measured dose following the third fraction was 90% lower than the expected dose, but after shifting the point dose calculation to account for the $\Delta x = 2 \ cm$ balloon displacement in the superior direction, the dose discrepancy was reduced to -65%, as it is shown in Figure 5.6. Even after accounting for $\Delta x$ in the TPS dose calculation, the measured dose is clearly lower than anticipated, and an indication of an experimental error that needed to be explored.

The large dose discrepancy observed during the third fraction was due to a combination of factors, the most important factor being related to the treatment plan, and the insertion of the balloon too far into the prostate. The treatment plan created for the first fraction was clearly not representative of either the patient’s internal anatomy, or the position of the rectal balloon relative to the prostate. If balloon migration was the sole reason for the low dose delivered to the MOSkin, it would have been accounted for when the dose
was recalculated to account for $\Delta x$. However, this was not observed, as recalculation of the dose to account for $\Delta x$ only reduced the magnitude of the discrepancy from -90% to -65%. The presence of heterogeneities such as the 40 mm diameter air-filled rectal cavity can account for a -15% or -20% dose discrepancy, but not a -65% discrepancy. However, the balloon was initially inserted into the rectum too far superiorly with respect to the prostate, and as a result, was situated in a steep dose gradient region. Both the $\pm 2\ mm$ uncertainty in MOSkin position, and the $\pm 2\ mm$ uncertainty in $\Delta x$ are significant factors when the dose was recalculated for $\Delta x$. According to the treatment plan, shifting the dose point 2 mm in the superior direction would have reduced the expected dose by 20% in this particular case. Inter-fraction anatomical changes must have also played a significant factor in this underdosage.

If the treatment was re-planned, inter-fraction balloon migration, catheter migration, and anatomical changes would have been accounted for in the calculation of the expected dose to the MOSkin so that its effect on dosimetric accuracy isn’t so evident. In fact, our experience with the first patient was the reason that 2 mm thick CT images were used for all subsequent treatments. The additional images also added a significant amount of time to the planning procedure, but it was necessary if poor results were to be avoided in the future.

5.3.2 Analysis of Measurements Taken of Subsequent Patients

Following the measurements taken of the first patient, SGCCC changed their HDR brachytherapy treatment procedure to a 2-fraction treatment, with 2 mm images used to create individual treatment plans for each fraction, as described earlier. The decision to move to a 2 fraction treatment was independent to this particular study at SGCCC; however, the use of 2 mm CT images was used to improve the precision in locating the MOSkin’s sensitive volume in the image set. The percentage deviation of the measured dose relative to the expected dose at the anterior rectal wall is presented in Figure 5.7 for each
Figure 5.6: Percentage deviation between the measured dose at the anterior rectal wall for the first patient, who was treated with 3 fractions at 6.5 Gy/fraction. Only a single treatment plan was created for this patient.

Fraction. Rectal dose measurements were taken in a total of 9 patients, where a total of 19 measurements were obtained. Since an individual treatment plan was created for each treatment fraction, the measurements did not have to be analysed on a patient-by-patient basis. Instead, each rectal dose measurement was analysed on a fraction-by-fraction basis.

A total of 14 measurements were included for analysis, while 5 measurements were excluded for various reasons. Two patients complained of a discomfort that they found unbearable on their second day of treatment prior to the delivery of the second fraction. In order to remedy the discomfort, the rectal balloon was deflated and subsequently removed from the rectum. As a result, the rectal dose was not measured during the second fraction for these patients. After an investigation and patient enquiry, the discomfort appears to have been caused by a build-up of gas in the patient’s rectum and colon, which
could not be expelled while the rectal balloon blocked the opening of the anus. This is a design drawback of the MEDRAD rectal balloon, but the manufacturer has promised to address the situation in a new design. Of course, a new design may also need to undergo a lengthy re-testing by the TGA. In another case, the rectal balloon ruptured inside the rectum, and deflated in the process. Consequently, improper contact between the MOSkin and anterior rectal wall did not allow the rectal dose to be measured. The measurement was taken at a rather arbitrary location inside the rectal volume, and was excluded from the study. A fourth measurement was excluded from analysis because the rectal balloon, and the MOSkin attached to it, was rotated more than 90° away from the anterior rectal wall, providing limited useful dosimetric information. Throughout the study, involuntary of the muscles around the rectum and the anus caused the balloon to displace further into the rectum. However, in some patients, a rotational movement would be evident, which was difficult to correct. The fifth measurement excluded from Figure 5.7 was the third measurement taken from the Patient 1, who was discussed in the previous section.

![Percentage Deviation from Expected Dose vs Fraction](image.png)

Figure 5.7: Percentage deviation between the measured dose at the anterior rectal wall, and the dose calculated by the PLATO TPS for each fraction.
The results presented in Figure 5.7 are presented in chronological order, where *fraction 1* corresponds to the earliest measurement in the trial, while *fraction 14* corresponds to the most recent. The first 7 measurements presented in Figure 5.7 were generally around 10–35% lower than the dose expected to the MOSkin, although there was significant variability in the dose discrepancies observed. In contrast, the results obtained for fractions 8–14 in Figure 5.7 are approximately 5–17% lower than the expected dose, exhibiting less inter-fraction and inter-patient variability between individual measurements.

The most probable reason for the greater absolute dose deviation observed in our earliest rectal dose measurements (fractions 1–7 in Figure 5.7) is a refinement in our experimental methodology as the trial progressed. The degree of balloon migration that occurs prior to the treatment appears to be a strong factor in determining whether a comparison between the measured and calculated dose delivered to the MOSkin is meaningful. The degree of balloon migration (\( \Delta x \)) ranged from 0–20 mm, which means the balloon moved by up to 20 mm during the time that separates the imaging procedure, and the treatment. If the degree of migration is excessive, it would be imprudent to expect the measured dose to be comparable to the TG43 calculated dose, as the rectal dose calculation is based on a snapshot of the patient’s internal anatomy at the time the images were acquired. Furthermore, whenever balloon migration was observed, it always occurred in the superior direction, which means the balloon always moved between 0–20 mm further into the patient’s rectum. Early attempts to account for \( \Delta x \) required the MOSkin dose to be recalculated by the TPS following the treatment by going back to the TPS, shifting the dose point specified in the plan by distance \( \Delta x \), and recalculating the dose at the new point. The measured dose was then compared to the new calculation. Adjustments to the balloon position just prior to the treatment, while the patient is lying on his bed, could have been performed as an alternative method to account for \( \Delta x \). However, such adjustments are too difficult to perform in a clinical situation, so recalculating the dose post-irradiation appeared to be the best solution at the time. The uncertainty associated with each measurement of
the balloon handle was estimated to be $\pm 2 \text{ mm}$ on each end of the handle; therefore, the estimated uncertainty in $\Delta x$ is approximately $\pm 4 \text{ mm}$. The uncertainty in $\Delta x$ stems from the difficulty in accurately measuring the length of the balloon handle between the patient’s legs, and parallax error. Recalculation of the dose doesn’t provide enough accuracy when considering the estimated 4 mm uncertainty in $\Delta x$, in addition to the $\pm 1 \text{ mm}$ uncertainty that corresponds to our determination of the balloon position.

Without the computing capacity to run full-scale Monte Carlo simulations using the dwell positions and dwell times from each treatment plan, it is impossible to determine the dose discrepancy to be expected between the dose delivered to the rectal wall at the point where the MOSkin was positioned, and the expected dose at this point. As discussed in Chapter 4, the magnitude of the dose discrepancy is dependent on both the source distance, and the diameter of the rectal cavity. Consequently, the dose discrepancy should vary between fractions, and between patients. This will be discussed later in this section.

As shown in the results obtained from both the phantom study and the Geant4 simulations discussed earlier, the anterior rectal dose was 5–20% less than the expected dose due to the presence of a 40 mm diameter rectal heterogeneity. A $-20\%$ discrepancy was estimated for a source distance of 10 mm, while a $-5\%$ discrepancy was calculated for a distance of 40 mm. This does not take the effects of balloon and catheter migration into account. Figure 5.8 is an image taken from the treatment plan of a real HDR brachytherapy patient treated at SGCCC, which shows the distribution of catheters within the prostate volume, and the relative distance separating the MOSkin and the individual catheters. As this is a 2D image, the distribution of dwell positions along each catheter, and their distance from the MOSkin, is not shown in the figure. The prostate, rectum, and urethra were contoured by a radiation oncologist. With regards to the rectal contour, only the outer rectal wall is contoured by the radiation oncologist. The inner rectal wall shown in Figure 5.8 is contoured automatically by the TPS, which assumes that the rectal wall
Figure 5.8: CT image of a patient used to plan for treatment planning. The contour of the prostate and rectum are labelled in the image. The TPS assumes that the rectum is 5 mm thick.

is 5 mm thick.

While an inter-patient and inter-fraction variation in the dose discrepancy was expected for the reasons discussed earlier, an acceptable range of discrepancies may be determined using the results presented in the Chapter 4 as a basis. Based on qualitative observation, the distance between the inner anterior wall of the rectum and the nearest catheter typically ranges from 10–15 mm, which would result in a percentage dose discrepancy of 15–20% with the TPS. However, the rectum is irradiated by the source from over 100 dwell positions distributed around the prostate, so the rectum is irradiated from dwell positions that are, on average, further away than 10–15 mm. However, this ”average” source distance may not be much greater than the closest catheters due to the exponential dose drop-off observed with increasing distance from the source. The majority of the
dose delivered to the MOSkin is delivered predominantly when the source is at dwell po-
sitions located nearest to the rectal wall. The most distant catheters, which is comprised
of those catheters that are located within the anterior-left and anterior-right quadrants of
the prostate, and the catheters situated along the far-left and far-right prostatic capsular
wall, would contribute a very small proportion of the total dose. There are also a number
of dwell positions within the closest catheters that are rather far from the MOSkin due to
their position along the superior-inferior axis. An overall dose discrepancy ranging from
10–15% is a reasonable estimate of what to expect, as it corresponds to source distances
of around 20–30 mm. However, this range of dose discrepancies does not account for
any changes in the measured dose as a result of balloon migration, which ranged from
0–20 mm in the trial, nor does it account for catheter migration.

It should be clearly and explicitly stated in this report that the 10–15% dose discrepancy
is a hypothesized range. There should be no expectation that the discrepancy should be
a single consistent value between fractions for a single patient. In fact, the discrepancy
should vary between patients, and between fractions, because the treatment and anatom-
ical conditions do not remain static. If the measured dose is anywhere between 10–15%
less than the calculated dose, then the treatment is being delivered according to plan.
Consistency between measurements isn’t indicative of a successful study, or dosimetric
accuracy, and so the variability in the results shown in Figure 5.7 is of little significance
to the study. What is important is whether the measured the dose is between 10–15% less
than the calculated dose. Only when the dose discrepancy falls outside of this range is
the treatment not being delivered as expected. While an expected range of discrepancies
was qualitatively determined in this report, it is difficult to make a conclusive statement at
this point with regards to what range of dose discrepancies are acceptable, and would not
require intervention by an oncologist or radiotherapist during treatment. The expected
range of dose discrepancies was determined without considering the effect that catheter
and rectal balloon displacement may have on the results, as well as the $\pm 5 \ mm$ uncertainty in position along the anterior–posterior axis.

5.3.3 Refinements in Experimental Methodology

![Figure 5.9: Three-dimensional image from a sagittal reconstructed from a patient’s set of CT images. The MEDRAD rectal balloon, and the MOSkin attached to it, were positioned on the superior end of the prostate, where a steep dose gradient exists.](image)

The procedure pertaining to the clinical trial was revised several times during the study to include an adjustment of the rectal balloon while the patient lay supine on the bed of the CT machine, immediately prior to image acquisition. This balloon adjustment was originally added to the procedure because the amount of balloon migration that occurred between the time of the acquisition of the CT images, and the delivery of the treatment, appeared to be related to whether the balloon was positioned too far superiorly (i.e., into the rectum) at the time of imaging. If the balloon appeared to be positioned too far superiorly at the time of the CT image acquisition, the balloon was more likely to move by a
greater distance later, based on the balloon handle measurement taken immediately prior to treatment. However, if the centre of the balloon appears to be aligned properly with the centre of the prostate in the 3D reconstructed image created by the TPS, the amount of balloon displacement appeared limited to several millimetres. The reduced balloon migration observed is most likely due to good surface contact between the concave face of the rectal balloon, and the rectal wall when it is directly posterior to the prostate.

Figure 5.9 is an image taken from an earlier patient whose rectal balloon was positioned too far superiorly relative to the prostate. No adjustment was made to the balloon’s position prior to imaging. The MOSkin is located at the central point of the balloon’s concave face (Figure 5.3(b)), and yet relative to the prostate, its position is clearly towards the superior end of the prostate. Adjustments made to the balloon’s position along the superior-inferior direction are performed based on what is seen on the monitor display as the axial CT images are acquired. This assessment is clearly a subjective one, as nothing can be verified until contouring and image registration is complete. When this is completed, the MOSkin and prostate can be viewed either from a 3D or sagittal viewpoint. Several CT scans of the patient are taken. The first scan at SGCCC is a quick transaxial scan using 5 mm slices to determine the region of interest for subsequent scans. It can also determine if the patient has rolled in his bed slightly, which may affect the clarity of subsequent images. Based on this first image set, the region of interest can be reduced to include only the anatomical regions of the patient that are relevant for the treatment, thus reducing the radiation exposure to the patient from subsequent scans. The patient’s position may also be adjusted. If the MOSkin appears to be too far into the rectum, a crude adjustment of the balloon is performed so that the MOSkin is located more towards the inferior. Rotational misalignments are easily seen in an axial CT slice, and the balloon can be rotated if necessary. Unlike the balloon’s position in the superior–inferior direction, its rotational position is clearly discernible in almost any CT image from the set, since either the MOSkin or the cable attached to it will be visible in most images.
In order to measure the maximum dose delivered to the rectum, the MOSkin’s position should be positioned at the most anterior point along the inner rectal wall.

In order to adjust the position of the balloon, 30–60 ml of air must be removed from the balloon before it is moved in order to reduce the level of pain felt by the patient. After the adjustment, the length of the balloon handle is noted, and used later to calculate $\Delta x$ prior to the delivery of the treatment. The amount of adjustment required at this stage is based on qualitative judgement, and is only meant to improve the MOSkin’s position rather than "correct" it, as the MOSkin’s position relative to the prostate can only be assessed after image reconstruction using the TPS, as noted earlier. After the treatment plan is created by the oncologist, the patient is taken to the treatment room, where the length of the balloon handle protruding from the patient is measured. At this point, $\Delta x$ is calculated. The dose delivered to the MOSkin can be recalculated in order to account for the balloon migration $\Delta x$.

The adjustments that were made have evolved, and have been refined over time. In consequence, the most recent measurement were obtained using the most refined methodology, and may be of higher quality than earlier measurement data. Regardless, the MOSkin appears to be capable of measuring the rectal dose within the expected range of dose discrepancies.

5.4 Discussion

There are certainly a large number of ways in which such a dosimetry system could be applied. Although the data acquired in this study was done by manually reading out the information from the reader unit, the aim is to eventually utilize an automated data acquisition system that can display the dosimetric data in real-time. A software application called MOSPLOT has already been developed by the CMRP in a separate project that is capable of reading out the MOSkin device at regular intervals, allowing the user to track
the total accumulated dose delivered to the dosimeter while the treatment is in progress. It can also provide a visual graphical display of the accumulated dose increasing with time. If the Cartesian co-ordinate of each source dwell position, and the dwell time spent at each co-ordinate, could be output from the TPS, then perhaps the accumulated dose measured by the MOSkin after \( t \) minutes could be compared directly to the expected dose. This would require co-operation from the developers of the brachytherapy treatment planning system’s, who would need to provide a method for this information to be outputted to the MOSPLOT software. The relevant information pertaining to each dwell position can already be printed from the software, so outputting the data to MOSPLOT should be feasible from a technical standpoint. If the discrepancy between the measured and expected accumulated dose is less than a certain threshold, which indicates that the MOSkin is being over-irradiated, then the software could automatically stop the treatment. Perhaps an visual and/or audio warning could be issued to alert the end user of the software that human input may be required, if manual interruption of the treatment is preferred.

When the dosimetry system measures an overdose after time \( t \), stopping the treatment midway is a good approach for PDR brachytherapy, but may not be the best approach for HDR brachytherapy due to the shorter treatment times. Shorter treatment times would allow a shorter opportunity to interrupt the treatment unless the interruption process was applied automatically. If the rectum received too much radiation dose during the first fraction (out of a total of 2 fractions), perhaps the best approach for HDR brachytherapy would be to create a treatment plan for the next fraction that compensates for the overdose. For example, the subsequent treatment plan could be designed so that the dwell times used at positions closest to the rectum are shorter, ensuring that the anterior wall of the rectum receives a dose that’s lower than the rectal dose constraint.

Perhaps how the dose measurement is analysed should be adjusted to be more convenient for clinical applications beyond this study. In this report, the measured dose was
always compared to the rectal dose expected at the MOSkin’s position in the rectum, as calculated by the TPS. A response that was either greater or less than the predicted dose was considered undesirable, as it meant that something had changed in comparison to the treatment plan. The change may have been anatomical, or perhaps related to balloon and/or catheter displacement from their assumed position. However, balloon migration was only tracked in this study because it had a direct effect on how well the measured and expected doses compared, not because it is clinically relevant to an oncologist. After all, the rectal dose is unaffected by balloon migration, and HDR/PDR brachytherapy treatments are delivered successfully at most treatment facilities without the use of a rectal balloon for immobilization (although their popularity is increasing). If the MOSkin dosimetry system is intended to be used as a tool for providing quality assurance for HDR/PDR brachytherapy prostate treatments, then the maximum absorbed dose delivered along the anterior rectal wall is what should be of primary concern, not how well the measured dose compares to the calculated dose at the MOSkin’s position in the rectum. This means the position of the MOSkin’s sensitive volume should not have to be specified in the TPS, nor does balloon migration need to be noted in order for the MOSkin dosimeter to be useful in a clinical setting. What matters is the absorbed dose, which should not exceed the maximum dose constraint anywhere along the anterior rectal wall by a clinically significant margin.

However, a radiation oncologist isn’t realistically going to employ this dosimeter in the same cautionary manner used for this study. It is more realistic to assume that a radiation oncologist would insert the rectal balloon (and MOSkin) into the patient’s rectum, and would measure the dose during treatment without ever knowing where the maximum dose is going to be delivered along the rectal wall. Assuming a moderate approach is taken, lets say the rectal dose should not exceed 5.7 Gy anywhere along the anterior wall of the rectum. This corresponds to a -10% dose discrepancy from the calculated dose, and is based on the 9 Gy/fraction delivered at SGCCC. A single measurement of less than 5.7 Gy is a positive indicator, but is not truly meaningful because only a single MOSkin
was used. The dose may be greater at another position. What is needed for the practical application of the MOSkin, or any rectal dosimeter, is a linear array of dosimeters. If the dosimetry system consisted of 4 detectors that were spaced 5 mm apart on the balloon, then the dosimeter becomes much more practical to use, and easier to apply. Again, I personally do not expect an end user of such a dosimetry system to use the same amount of caution and care when handling the dosimeter, nor should an end user be expected to do so in order to extract useful information.

Another point worthy of discussion is with regards to how an under-dosage should be treated by a radiation oncologist. If the dose delivered to the rectum is lower than 5.7 Gy by a considerable amount after the first fraction, does this provide the oncologist the liberty to increase the dose to the prostate (and rectum) for the second fraction if he/she feels that this would improve the clinical outcome of the treatment? It is probably in the best interest of the oncologist not to view a low rectal dose measurement as an opportunity to increase the dose for the second fraction of the treatment. By increasing the dose further, there appears to be little to gain, as the probability of a successful treatment with HDR/PDR brachytherapy is already very high. In contrast, the risk of inducing some level of rectal toxicity may increase by a clinically significant amount.
CHAPTER 6
CONCLUSION

The potential of the MOSkin for use as a quality assurance tool has been investigated, particularly in the context of high dose-rate brachytherapy treatment of prostate cancer, where currently, no quality assurance testing is performed. Generally, it’s the unique packaging that differentiates the new MOSkin from other MOSFET dosimeters. The MOSkin’s sub-micron thick sensitive volume and shallow effective depth was found to enable the MOSkin to measure the dose accurately at an air-tissue interface. When the MOSkin was placed at the surface of a solid water phantom and irradiated by a $10 \times 10$ cm$^2$, 6 MV photon beam delivered by a LINAC, it was shown to be capable of measuring the dose at an effective depth of measurement of approximately 70 $\mu$m in water, as recommended by the ICRP [94] and ICRU. [96] Its normalized response was in good agreement to both an Attix Chamber and parallel-plate extrapolating ionization chamber. In comparison, the RADFET was incapable of accurately measuring the surface dose at any angle of irradiation, consistently overresponding by a factor of two relative to the response of the MOSkin, Attix chamber, and extrapolation chamber. This was true at angles of irradiation ranging from 0–75$^\circ$. Based on comparisons with surface dose measurements as reported by Devic et al. [1], Kron et al., [2] Gerbi, [3] and Cross, [4], the RADFET’s effective depth of measurement was approximately 0.8 mm. The MOSkin’s thin film encapsulation offered a significant advantage over the thicker bulb of epoxy resin that encapsulates the MOSFET sensor of the RADFET with regards to its ability to measure the skin dose.

The MOSkin’s performance characteristics were also compared to a 0.5 mm and 1 mm diameter fiber optic dosimeter up to a depth of 100 mm in the phantom. Overall, the
MOSkin dosimeter was capable of accurately measuring the depth dose distribution when compared to the CC13 ionization chamber. The 0.5 mm and 1 mm diameter fiber-optic dosimeters were equally capable of accurately measuring the dose at depth, except in the build-up region from 0–4 mm depth in water, where only the MOSkin did not over-respond relative to an Attix and extrapolation ion chamber. The CC13 compact ionization chamber over-responded until a depth of 7 mm in water. In the build-up region is where the MOSkin’s shallow effective depth and micron-scale sensitive volume demonstrates its greatest dosimetric advantage over the FODs. However, beyond a depth of 7 mm, all the detectors investigated were capable of accurately measuring the dose when irradiated with a LINAC.

The advantage of the MOSkin’s thin film packaging design extended to rectal dosimetry in HDR brachytherapy treatment, where it was capable of measuring the dose along the rectal wall of a rectal phantom. The MOSkin and RADFET detectors both reported comparable percentage dose differences between the dose measured in an empty and full rectal cavity, and were corroborated from results of a Monte Carlo simulation written with the Geant4 toolkit. However, in terms of absolute dose, the RADFET under-responded by 10% when compared to the expected dose at the anterior rectal wall, and the dose measured by the MOSkin. This is due to the epoxy bulb encapsulating the RADFET, which physically only allows the RADFET to measure the dose a slight distance away from the rectal wall, rather than at the rectal wall when pressed directly against it. The reduced build-up material atop the MOSkin sensor allowed it to measure the dose against the rectal wall, while a correction would likely have to be applied to the RADFET to account for the thickness of the build-up layer, which increases the distance between source and detector. This illustrated the importance of using a detector with a shallow effective depth of measurement for rectal dosimetry in HDR brachytherapy.

The MOSkin exhibited no angular dependence around the central axis of the dosimeter.
device (0–330°), or in the azimuthal direction. The manufacturing reproducibility of the MOSkin’s thin film encapsulation was quite high. The mean overall PDD, calculated using seven individual MOSkin dosimeters, was 18.1±1.1%, while the lowest and highest PDD reported by the seven MOSkins were 17.2±0.4% and 20.4±0.6%, respectively. The response uncertainty of each individual MOSkin was typically lower than ±0.5%, while the overall uncertainty of the mean PDD, based on readings from seven individual MOSkin dosimeters, was ±1.1%. In comparison, the response reproducibility of a single Thomson & Nielson MOSFET with a modified epoxy encapsulating layer was approximately ±1.3% when placed at the surface of a phantom, while the uncertainty of the mean PDD of nine MOSFET dosimeters with an altered epoxy layer was ±1.9%, according to the data reported by Scalchi et al. [91] The low response variation between individual MOSkins is an indication that the polyamide film layer was manufactured with a high level of reproducibility. Altering the epoxy layer of a Thomson & Nielson MOSFET dosimeter resulted in poorer epoxy reproducibility, and therefore, resulted in poorer response reproducibility between individual dosimeters.

The effect of rectal heterogeneity on the dose delivered to the rectal wall was examined by first measuring the anterior rectal wall dose in a full, homogeneous rectal cavity, and comparing the result to rectal wall measurements taken in an empty rectal cavity, and calculating the percentage difference. The assumption by brachytherapy treatment planning systems that the rectum is a homogeneous, water-equivalent medium rather than a hollow, air-filled rectal cavity meant that the calculated dose to the anterior rectal wall is overestimated by between 10–20%. The exact value of this discrepancy between the measured dose and calculated value was shown to be related to the source distance, and the diameter of the rectal cavity. The dose discrepancy caused by the air-filled rectal cavity decreased with increasing rectal cavity diameter, and increased with decreasing distance from the source. The results obtained with the MOSkin and RADFET are in agreement with results reported by Raina et al., [137], Mangold et al., [139], and Kinhikar et al. [90]
They were also corroborated by Geant4 Monte Carlo simulation results.

Further Geant4 simulations were performed to study the effects of the finite patient volume, which may affect the dose like the rectal heterogeneity explored earlier. The finite volume of a patient, the close proximity of the prostate to the perineum and chest wall, and the numerous air-filled catheters inserted into the patient had the potential to have an effect on the rectal dose, and so their impact on the rectal dose needed to be explored. A phantom with dimensions that are believed to be realistic dimensions for an adult male (70×35×20 cm$^3$), with the prostate assumed to be located 7 cm superior from the perineum, was defined for this simulation, but it did not reveal any statistically significant difference in the dose discrepancy calculated in this simulation, and the dose estimate obtained in the 30×30×30 cm$^3$ water phantom, where the source and detector were located near the geometric centre of the phantom. The dose delivered to the anterior wall of the empty rectal cavity of the "human-sized phantom" was 19.5 ± 1.8% lower than the dose delivered to the same point within a homogeneous phantom. This result is in good agreement with the 19.9 ± 2.7% dose discrepancy observed when the phantom was defined as a 30×30×30 cm$^3$ block of solid water, which indicates that a finite patient volume, a potential form of heterogeneity near the rectal environment, does not further reduce the rectal dose when compared to the dose calculated within a homogeneous tissue environment.

The MOSkin rectal dosimetry system was utilized in a Phase II clinical trial at St. George Cancer Care Centre, and when used in combination with a rectal balloon, it was capable of measuring the rectal dose within expectations. The MOSkin was clearly visible in the CT images, and locating the sensitive volume of the MOSkin is not difficult. The degree of balloon migration that occurs prior to the treatment appears to be a strong factor in determining whether a comparison between the measured and calculated dose delivered to the MOSkin is meaningful. While initial measurements were even lower than the
5-15% dose discrepancy we expected to observe due to the air-filled MEDRAD rectal balloon inserted into the patient’s rectum, improvements in our experimental methodology eventually lead to more consistent results that fell within the expected range of doses.

Further research should utilize an array of MOSkin dosimeters so that balloon migration, which typically occurs in the superior direction, does not affect our ability to measure the maximum dose delivered to the anterior rectal wall.
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