Dosimetry of Modulated Arc Prostate Radiation Therapy using Gafchromic EBT3 Film Deployed on a Spacer Device

Kemal Berk
University of Wollongong, kb967@uowmail.edu.au

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Dosimetry of Modulated Arc Prostate Radiation Therapy using Gafchromic EBT3 Film Deployed on a Spacer Device

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Kemal Berk
BMedRadPhys

Centre for Medical Radiation Physics
School of Physics
Faculty of Engineering

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ABSTRACT

Radiotherapy is one of the most widely used treatment modalities in modern oncology; it is constantly improving, with many high precision tools such as rectal spacers to decrease rectal wall toxicity being used to improve patient outcomes. This thesis explores the idea that in-vivo rectal wall measurements can be performed using Gafchromic EBT3 film deployed on a rectal spacer device known as Rectafix®.

Two of the most complex and advanced radiotherapy prostate treatment modalities, Volumetric Modulated Arc Therapy (VMAT) and TomoTherapy® high precision prostate boost treatments were investigated by utilising a CIRS head and neck phantom with a modified Rectafix that allows film to be housed during treatment.

An initial benchmarking study was carried out to test the response of film to a varying angle of incidence and depth of exposure. This method employed proved to be robust and the dose profile obtained from the Treatment Planning System (TPS) against the measured profile were a successful match according to report TRS-43071.

High precision prostate boost plans for VMAT and TomoTherapy were created utilising existing patient data superimposed onto the CIRS head and neck phantom. The results were compared by extracting superior – inferior line profiles on the most anterior portion of the Rectafix® because it is the most at risk portion of the rectal wall to toxicity.

A gamma analysis was performed with dose difference/Distance to Agreement (DTA) parameters set to 3%/3mm, 3/1%, 2%/1mm and 1%/1mm with VMAT scoring 100%, 98.7%, 98.2% and 89.2% with repeated measurements scoring 100%, 99.0%, 98.2% and 86.0% respectively. The same dose difference/DTA parameters were utilised with TomoTherapy, scoring 100%, 98.5%, 97.3% and 85.0% and repeat TomoTherpy® measurement scoring 100%, 100%, 100% and 91.0% respectively.
The method investigated can provide enough information to verify whether treatment has been delivered to an acceptable level of accuracy. The dose objective set for the treatment plan was to limit the dose to the rectal wall to 14-16 Gy, but VMAT delivery delivered a much higher dose, 23.9 Gy to a portion of the rectal wall that risked unwanted toxicity. It was agreed that further investigation is needed before concluding the treatment; however the TomoTherpy® delivery was within the limits of the dose objectives so it was deemed safe to continue the treatment.

The procedure outlined in this thesis shows this method detected deviations that could potentially deem the treatment to be unsafe to deliver. These may include small deviations in the setup, inter leaf leakage, or other unlikely variations in the parameter between the planned and delivered dose. With the help of the outlined procedure in this thesis, unwanted side effects can be predicted before they occur and avoided by replanning the treatment in order to increase positive outcomes for the patient.
STATEMENT OF ORIGINALITY

This is to certify that the work described in this thesis is entirely my own, except where due reference is made in the text.

No work in this thesis has been submitted for a degree to any other university or institution.

Signed

Kemal Berk
10th of January, 2017
ACKNOWLEDGEMENTS

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1 Introduction

1.1 A relatively new paradigm for fractionated prostate radiotherapy

Based on the low alpha beta ratio\(^1\), hypo-fractionated prostate radiotherapy is now being examined in several new clinical trials\(^2\). A hybrid technique which involves standard fractionation with two large dose fractions as a boost is part of clinical trial in Australia.\(^3\) This trial enables either spacer Gel or Rectafix® to be used to optimise the space between rectal tissue and the prostate target.

With such a high dose per fraction applied to the boost, delivering a precise dose to the rectal tissue is paramount. This thesis explores the hypothesis that it is better to ensure that the dose delivered to the rectal wall matches the dose calculated by the radiotherapy treatment planning computer, and thus avoid unexpected toxicity. This can be validated by the “end to end” pre-treatment QA dosimetry method devised and reported in this thesis. This proposed dosimetry method he uses EBT3 film wrapped onto a Rectafix® immobilisation spacer device.

1.2 Thesis Aims

This thesis addresses an investigation of the potential use of EBT3 film as an in-vivo dosimeter when attached to a rectal immobilisation and spacer device known as Rectafix®. All the experiments were pre-clinical and were carried out in a dosimetry phantom environment. The research questions we addressed in this investigation are as follows:
i. Can EBT3 film be positioned on Rectafix® device such that it simulates a dose at the rectal prostate interface?

ii. Can EBT3 film be calibrated and used at high dose per fraction doses (typically 8 Gy)?

iii. What is the accuracy and reproducibility of the EBT3 film measurements?

iv. How do the pre in-vivo EBT3 film measurements compare with radiotherapy treatment planning dose estimates for simple fields and for volumetric modulated arc (VMAT) dose delivery?

v. How do the in phantom EBT3 film measurements compare with radiotherapy treatment planning dose calculations for TomoTherapy® delivery?

1.3 Prostate Cancer

The prostate consists of glandular, fibrous and muscular elements. It is positioned inferiorly to the base of the bladder and houses the beginning of the urethra. The vas deferens and seminal vesicle glands are attached to the posterosuperior section of the prostate. The prostate consists of four zones: the central, transition, fibromuscular, and the largest; the peripheral zone.12

Prostate carcinomas most commonly i.e. ~75% occur in the peripheral zone, while benign prostatic hyperplasia (BPH) mostly occurs in the transition zone. Prostate cancer can extend to any of the other zones, as well as into the seminal vesicles, rectum and neck of the bladder. The likelihood of metastases to the lymph nodes and other regions of the body depends on the size and degree of differentiation of the primary tumour.12

Various methods are used to treat prostate cancer, and while there are a number of options there is no consensus on which is best. The optimal options which are best addressed by Urologists and or Oncologists and which the meet standard of care, vary somewhat depending on the grade/stage of tumour and patient performance and health status.19
The options available include active surveillance, radical prostatectomy, interstitial prostatic brachytherapy, external beam radiotherapy and cryotherapy. It has been shown by level 1 data that radical prostectomy or radiotherapy confer longer overall survival and cancer specific survival compared with no treatment.  

There is no available data to prove the superiority of prostatectomy vs brachytherapy vs radiotherapy as there hasn’t been any randomized clinical trials which compared these treatments, prostate cancer progresses slowly and clinical selection is subject to selection bias.

In deciding for the most suited treatment for the patient the severity of the disease, life expectancy and patients’ base line performance. With low to intermediate risk patients who have a life expectancy of 10 years or less, treatment is not recommended. For patients with poor baseline performance when surgery is not recommended surveillance or radiotherapy may be the modality of choice.

For young patients surgery may provide a better long term benefit. Radical prostatectomy is widely used in order to treat prostate cancer of any risk level. For patients with intermediate to high risk, the prostate and seminal vesicles, as well as the pelvic lymph nodes are removed. This may be performed via open surgery approach or minimally invasive laparoscopic approach with or without robotic assistance, with equal oncologic outcomes.

Interstitial brachytherapy, in which small seeds of iodine 125 or palladium 103 are inserted stereotactically into the prostate under the guidance of ultrasonography, delivers a localized dose to the prostate while sparing nearby critical organs at risk. This may be performed using low dose rate brachytherapy were the seeds are left inside the prostate permanently or by using high dose rate brachytherapy in which seeds are inserted for a period of time and then removed.

External beam radiotherapy, in which electrons, protons or neutrons are used to deliver radiation via an external source, although appear to have theoretical advantages, provide similar clinical efficiency. It has been proven effective in low,
intermediate and even high risk cancer when used in combination with androgen deprivation. It is non-invasive and effective at delivering a high dose to the target area with better uniformity in comparison to brachytherapy, but also delivers a higher dose of radiation to the surrounding critical structures. 12

There is some evidence that an increased dose increases the local control of the tumour.20,21 Dose escalation in an external beam has mainly been at 2Gy per fraction, but dose escalation using an external beam with a brachytherapy boost has historically used a large dose per fraction.18,20

Hypofractionation is a beneficial method possibly because the prostate has a low $\alpha/\beta$ ratio, but due to the increased total treatment dose and dose per fraction, the need to verify an accurate delivery is an important factor.

Historically, increased fractionation has been regarded as providing an increased therapeutic advantage because it spares late responding normal tissue more than tumours which respond like early responding tissue. This is still the paradigm for most tumours and clinical sites treated with radiotherapy. The $\alpha/\beta$ ratio in the linear quadratic (LQ) equation can be used as a measure to understand that fractionation spares late responding tissue, i.e. a low $\alpha/\beta$ ratio more than early responding tissue with a high $\alpha/\beta$ ratio. 1,12-14

Prostate cancer may be the exception to the general rule due to having an $\alpha/\beta$ ratio for tumour that is similar to or even lower than the surrounding late responding normal tissue. 1,12-14

Brenner and Hall stated that prostatic cancer appears to be much more sensitive to changes in fractionation than other cancers, and estimated the $\alpha/\beta$ ratio to be approximately 1.5 Gy. 1 There have been several other low values quoted for the $\alpha/\beta$ ratio; Brenner et al giving $\alpha/\beta =1.2$ Gy14; Demanes et al. 1.2 Gy15; Martinez et al. 1.2 Gy; Lukka et al 1.12; Gy16 and Kupelian et al. 1.1 Gy17

Another view which contradicts this argument was proposed by Nahum et al. where severe hypoxia in the prostate in certain cases is what limits the overall cure rate of
cancer treated using conventional radiotherapy. Nahum states that the $\alpha/\beta$ ratio or the clonogen number must be extremely low to explain the response of prostate cancer to external beam therapy or brachytherapy. Despite Nahum’s view, the consensus now as evidenced by several independent analyses of $\alpha/\beta$ is that the value for prostate cancer is very low.

### 1.4 External Beam Radiotherapy

External beam radiotherapy is one of the most common techniques used to treat cancer, with approximately 50% of all cancer patients receiving some form of radiotherapy as part of an optimal treatment. The aim is to administer a prescribed dose to the organ or area being treated, while minimising the dose received by the surrounding normal tissue. Obviously it is important to minimise acute and late side effects while preserving or increasing a patients’ quality of life. Radiation causes strand breaks by direct damage or indirect damage from free radical production. The effectiveness of radiotherapy is well recognised and has contributed significantly to improved cure rates and survival in recent decades.

### 1.5 Radiobiological modelling and optimisation

Radiobiology is a study of the effects of ionising radiation on human cells where radiobiological models are used to predict the effect of ionizing radiation on tumour cells and normal tissue cells. A number of models based on cell survival data are used to predict the very complex radiobiology mechanism effect that ionizing radiation has on tumours and normal tissue.

The goal of radiotherapy is to eradicate tumour clonogens (tumour regenerating cell) by maximising damage to these cells while minimising damage to normal tissue cells in order to maximise the benefit and minimise any unwanted side effects. As local tumour control increases, the side effects that follow must also be reduced because patients are surviving for longer periods of time post radiotherapy. Predictions from
radiobiological models combined with the outcomes of clinical trials are used by clinicians to tailor dose distributions according to tumour control and normal tissue toxicity. Radiobiology theories and the response of cells to ionization radiation are constantly changing and being updated. In the discussion following in this thesis the linear quadratic radiobiological model is covered for tumour control and the Lyman Kutcher-Burman model for normal tissue toxicity. While the models are not an integral part of the dosimetry experiment, they do help to explain how radiobiological modelling is shaping prostate clinical trials.

1.5.1 The mechanism of cell killing

Radiotherapy is based on the principle of killing tumour clonogens whilst minimising the damage done to surrounding normal tissue. Ionization radiation deposits energy into DNA strands and causes damage to the cells via either direct or indirect cell death. Direct cell deaths occur when electrons cause a double strand break (DSB) and single strand break (SSB) in the DNA. Although there are mechanisms in which cells can repair, not all the DSB are repaired or not, leading to cell death. Indirect cell death occurs as a result of free radicals, the most dominant one being the –OH molecule, produced by the ionization of water molecules.

The linear quadratic model can be used to increase our understanding of how changes in the parameters can affect cell survivability. The linear quadratic (LQ) model states that:

\[ s = \exp(-nd (\alpha + \beta d)) \]  

(1.1)

Where \( S \) is the surviving fraction of cells and \( d \) is the radiation dose in Gy per fraction, \( n \) is the number of fractions, and \( \alpha \) and \( \beta \) are the radiosensitive parameters which dictate the sensitivity to change between different types of tissue. This difference in sensitivity between tumour and normal cells dictates the fractionation regimen, because the \( \alpha/\beta \) ratio is a recognised historical method of determining the sensitivity to change in different tissues.
1.6 Hypofractionation

There has been interest in the fraction size used in the treatment of prostate cancer. Standard radiotherapy treatment fraction size in 2 Gy per fraction. Hypofractionated radiotherapy is when a dose higher than 2 Gy per fraction is delivered reducing the time of the treatment. The $\alpha/\beta$ ratio in the linear quadratic equation can be used as a measure to understand that fractionation spares late responding tissue, i.e. a low $\alpha/\beta$ ratio has more than with early responding tissue compared with a high $\alpha/\beta$ ratio. The $\alpha/\beta$ ratio is the dose in which the linear component and the quadratic component of the linear quadratic equation cause equal amount of cell death. Thus better tumour control can be achieved with a higher dose per fraction, with similar side effects. 1,12-14

Prostate cancer may be the exception to the general rule because it is thought to have an $\alpha/\beta$ ratio for tumour that is similar or even lower than the surrounding late responding normal tissue. 1,12-14

Brenner and Hall stated that prostatic cancer appears to be much more sensitive to changes in fractionation than other cancers, and estimated the $\alpha/\beta$ ratio to be approximately 1.5 Gy. 1 There have been several other low values quoted for the $\alpha/\beta$ ratio; Brenner et al giving $\alpha/\beta = 1.2$ Gy14; Demanes et al. 1.2 Gy15; Martinez et al. 1.2 Gy; Lukka et al 1.12; Gy16 and Kupelian et al. 1.1 Gy17.

This low $\alpha/\beta$ for prostate implies that the prostate BED may always be greater than late responding normal tissue, which is why hypofractionation is of benefit in radiotherapy for prostate cancer because it delivers a higher than standard (2Gy/fraction) dose in fewer fractions. This fractionation regime has 2 advantages compared to a standard fractionation regime; first it allows for a reduction in late rectal BED for an equivalent prostate BED compared to a standard fractionation regime, and it provides a greater prostate BED for an equivalent prostate BED compared to a standard fractionation regime.
Another view which contradicts this argument was proposed by Nahum et al. who argued that severe hypoxia in the prostate in certain cases is what limits the overall cure rate for cancer treated by conventional radio therapy. Nahum states that the $\alpha/\beta$ ratio or the clonogen number must be very low in order to explain the response of prostate cancer to external beam therapy or brachytherapy.\textsuperscript{18} Despite the view of Nahum, the consensus view now, as evidenced by several independent analyses of $\alpha/\beta$, is that the value for prostate cancer is very low.

1.7 Volumetric modulated Arc Radiotherapy (VMAT)

Many technological advances have been made in the delivery of external beam radiotherapy. The use of multi leaf collimators (MLCs) to create conformal and modulated dose distributions has helped to reduce the dose to normal surrounding tissue, although there is still some dose to normal tissue due to combinations of scattered and leaked radiation. This low dose may still induce a probability of late effects or short term toxicity, induced secondary malignancies, all of which emphasises the need for a careful characterisation of planned dose to the patient.\textsuperscript{30}

Volumetric modulated arc therapy (VMAT) is a technique for delivering intensity modulated radiotherapy (IMRT) in a continuous manner while the linac rotates in an arc around the patient.\textsuperscript{31} The dynamic aperture shaping of a multi lead collimator (MLC) of a conventional linear accelerator makes VMAT possible. Like IMRT, VMAT can produce intensity modulated dose distributions and deliver them in a much shorter time frame.\textsuperscript{32} Unlike IMRT, VMAT makes use of all the gantry angles, but without any instantaneous beam intensities.

To produce plans with much shorter treatment times than IMRT, VMAT delivery utilises MLC segments spaced equidistantly apart and then inversely optimised; the level of modulation dictates the gantry spacing required. This treatment planning system approximates the continuous dose delivery through a coarse representation of an arc, e.g. every 4 degrees, and means that the patient dose will be under-sampled at
distances further away from the rotational axis (i.e. the isocentre). Treatment planning software allows this parameter to be adjusted. VMAT planning demands that a linear accelerator is able to deliver a number of different MLC shapes in an arc, with each of them having a number of different monitor units. However, due to physical restraints of the linac the dose rate and/or the gantry speed must be modulated between each control point. The MLC speed is what ultimately determines the dose rate and the gantry speed. Modern control systems can now vary these parameters individually, this means the gantry speed, dose rate, and individual MLC speed are all controlled individually to achieve a highly conformal dose delivery.

1.8 TomoTherapy®

TomoTherapy® is another method for delivering EBRT. Helical TomoTherapy® is a technology that allows IMRT to be delivered with 3D image guidance capability, while providing modulated dose maps during a linac arc, just like VMAT. However, the delivery method is significantly different to VMAT because it uses a 6 MV linear accelerator which rotates while producing binary modulated fan beams on a slip ring CT gantry to deliver a dose helically.

The fan beam is produced by a 64 leaf binary MLC set up where the fan beams are modulated as a function of the gantry angle. A very high level of intensity modulation can be achieved by using a large number of beam angles per gantry rotation, along with the MLC open-close time being small (20 ms to open or close), pneumatically operated MLCs moving at 100 times the speed of a conventional linac makes this possible.

Binary MLCs produce a 1D profile that is continually modified, and when combined with the continuous rotation of the beam, produces a 2D profile. The couch moves through the bore of the gantry, which allows the dose to be painted helically around the patient and minimise any potential overdosing or underdosing at any point.
This system can acquire MVCT images via the on board CT detectors; this helps to verify the pre-treatment setup, dose reconstruction, delivery verification, and carry out regular quality control procedures.  

The pitch, modulation factor, and widths of the collimator are planning parameters that may be adjusted during the treatment planning phase to achieve the desired dose modulation, treatment time, and resolution. The distance the couch travels in the time it takes for a complete gantry rotation with respect to the width of the beam on the axis of rotation is defined as the pitch. The trade-off between the freedom and optimisation of the plan to allow for variations of beam intensities to achieve its goals is called the modulation factor (MF). 

The pitch chosen can introduce an unwanted dosimetric artefact known as the helical tomotherapy thread effect where beam junctioning appears to create dose ripples artefacts. This is a unique effect for tomotherapy and it is minimised by making use of a pitch value equal to p=0.86/n (n is an integer).

With the advancements in radiation therapy techniques high precision treatment techniques such as VMAT and TomoTherapy have proven to be better at better coverage of the PTV also while sparing the OAR more than conventional IMRT. Although there have been planning studies comparing these two modalities, there is no agreement as to which technique is superior. Although it is observed that VMAT provides a faster treatment time.

S. Awakada et. al have performed a study in which they have performed a comparison study using the same dose-volume parameters of VMAT and HT for prostate cancer by using the identical dose prescription to 95% of the PTV. Identical treatment plans were created for 15 patients and prescription dose delivered was 74.8 Gy in 34 fractions for 95% of the PTV to receive 90% of the prescription dose in both plans. It was observed that there were a number of significant differences in a number of volume parameters but they were not so large. While TomoTherapy plans provided a more homogenous dose distribution in PTV and lower rectum doses, while the VMAT plans were observed to have more conformable plans, lower bladder doses and shorter delivery time.
1.9 Rectal Toxicity

Limiting the dose and the volume of rectal wall irradiated is an important factor in minimising acute rectal effects post radiotherapy. These effects may become apparent during or soon after radiotherapy and include softer or diarrhoea like stools, and rectal tightness along with cramping and frequent pain. In some cases superficial ulceration may cause bleeding that may require endoscopic cauterisation known as radiation induced proctitis. Other complications may also arise 3 to 4 years post treatment that are classified as late effects, and may include stricture, decreased rectal compliance, and decreased storage capacity which causes small and frequent bowl movements. In more severe cases where injury has occurred to the anal musculature, other problems may arise such as fecal incontinence or stricture; these injuries can be severe and have a negative effect on patient’s quality of life.

During CT scans and subsequent treatment, the rectum is more likely not to be in the same position due to movement caused by interfraction and intrafraction variations in rectal filling, and intestinal gas and bladder filling. This creates uncertainty during treatment.

The most frequently quoted endpoint used in published data make use of either rectal bleeding or the Radiation Therapy Oncology Group (RTGO) Grade rectal toxicity scoring system\textsuperscript{21}. The RTGO scale considers Grade 2 toxicity to include moderate diarrhoea and colic, more than 5 bowel movements per day, excessive rectal mucus, or some bleeding. Grade 3 toxicity includes obstruction or bleeding which requires surgery; but Grade 4 necrosis/perforation fistula is rarely encountered in the current radiation therapy modalities. A summary of the incidence of toxicity endpoints can be found in Table 1-1.

At lower doses a large amount of rectal volume must be subjected to intermediate doses before substantial toxicity is seen. The convergence of dose-volume data at >70Gy and <20% volume obtained from multiple centres implies that toxicity is mostly associated with the high dose range\textsuperscript{22}.
For a conservative treatment plan the dose-volume constraints should be used as a starting point: $V_{50} < 50\%$, $V_{60} < 35\%$, $V_{65} < 25\%$, $V_{70} < 20\%$, and $V_{75} < 15\%$. The NTCP models predict that following this guideline should limit Grade $\geq 2$ late rectal toxicity to $<15\%$ and the probability of Grade $\geq 3$ late rectal toxicity to $<10\%$ for prescriptions up to 79.2 Gy in standard 1.8- to 2-Gy fractions.

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>Endpoint</th>
<th>Total prescribed dose (Gy)/f</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tucker et al.(^{23})</td>
<td>Grade $\geq 2$ RTOG</td>
<td>68.4, 73.2, 79.2/1.874, 78/2</td>
<td>13.5</td>
</tr>
<tr>
<td>Söhn et al.(^{24})</td>
<td>Grade $\geq 2$ Common Terminology Criteria for Adverse Events (CTCAE) v3.0</td>
<td>70.2, 72, 73.8, 75.6, 77.4, 79.2/1.8</td>
<td>16</td>
</tr>
<tr>
<td>Rancati et al.(^{25})</td>
<td>Grade $\geq 2$ bleeding</td>
<td>64–79.2/1.8–2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Grade $\geq 3$ bleeding</td>
<td>70–79.2/1.8–2</td>
<td>6.9</td>
</tr>
<tr>
<td>Peeters et al.(^{26})</td>
<td>Bleeding</td>
<td>68 (n = 234), 78 (n = 234)/2</td>
<td>4.9</td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>68 (n = 234)/2</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>Fecal incontinence</td>
<td>6.8</td>
<td></td>
</tr>
<tr>
<td>Cheung et al.(^{27})</td>
<td>Grade $\geq 2$ toxicity, modified scale</td>
<td>78/2</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td>Without haemorrhoids</td>
<td>16.7 (14/ 84)</td>
<td>16.7</td>
</tr>
<tr>
<td>Burman et al.(^{28})</td>
<td>Severe proctitis, necrosis, fistula, and stenosis</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 1-1 Description of endpoints, Lyman-Kutcher-Burman NTCP model parameters for published analyses \(^{22}\)
Patients treated with IMRT are reported to have lower rates of complication than those treated with standard 3D-CRT\textsuperscript{29}.

1.10 Rectafix®

The distance between the prostate (target) and the rectum (organ at risk) is close, which leads to a compromise between dose to target and organ at risk.\textsuperscript{42}

The Rectafix® is a device designed to reduce the dose received by the rectal wall to reduce side effects from rectal wall irradiation. A Rectafix® is a rod inserted into the rectum, angled in the posterior direction, and secured by a vertical column. Once the Rectafix® is inside the rectum, it is then moved posteriorly to move the rectum away from the prostate by 20-25 mm. Rectafix® has found a niche in proton therapy boosts and photon boosts to treat prostate cancer.\textsuperscript{42,43,44}

A study carried out by Sarah Alnaghy et.al. placed MOSkin™ detectors onto a surrogate Perspex Rectafix® device to obtain real time dose measurements along the rectal wall. They used single detectors to measure the dose at the rectal wall with ±5% of the TPS on 87.5% of the detectors. They then used a dual MOSkin™ system to obtain acceptable agreement with all the detectors.\textsuperscript{45} A graph of measured absorbed dose to TPS on the anterior edge of the solid Perspex probe can be found in Figure 1-1.
The benefit of running MOSkin™ detectors is that they are real time dosimeters and can feed dose data online while treatment is taking place; this means that errors can be detected during treatment and intervention can occur before the patient has received an incorrect dose. The study carried out in this thesis was able to obtain the dose received by a large portion of the rectal wall with high resolution, giving it the ability to detect high variations of dose over a small distance. A 2-D dose map can be created of the dose received by the rectal wall; this is much better than the high dose gradient setting in which this experiment was conducted.

A study performed by Isacsson et al (2010) compared treatment plans with and without rectal wall retraction in the same 9 patients. All the patients in this study were biopsy proven with localised adenocarcinoma of the prostate. A cylindrical Perspex rod of 1.5 cm in diameter was inserted into the rectum and then retracted posteriorly. 3 radiopaque markers were used for position verification using both the planning CT scans and x-rays. The patients were given a proton boost of 20 Gy in four fractions of 5 Gy, as well as a dose of 50 Gy in 25 fractions of 2 Gy using
conventional photon beam treatment. Comparative treatment planning showed that the volume of rectal wall retraction significantly reduced the volume of wall receiving high doses, in all patients. The volume that received 70 Gy in 2 fractions during the boost was reduced by 5-96% (average of 67%). The average dose reduction received by the rectum was 5. An average difference of 0.4 mm was found between the retractor markers on the planning CT and the images taken during treatment. 42

Nilsson et al compared two different treatment plans for 10 different patients being treated for prostate adenocarcinoma. Treatment plans were produced using VMAT for ten patients with and without rectal retraction, and a hypofractionation scheme of 42.7 Gy in seven fractions was used. Four dose volumetric criteria were used to evaluate the rectal wall dose: $V_{40.1\text{ Gy}}$, $V_{38.3\text{ Gy}}$, $V_{36.5\text{ Gy}}$, and $V_{32.6\text{ Gy}}$. This recreation of the rectal wall increased the distance between the rectal wall and the prostate. Moreover, the rectal wall volume decreased to zero for all dose measurements except $V_{32.6\text{ Gy}}$, which was 0.2 cm$^3$ on average when the rectal retractor was used. This operation was carried out without compromising the dose coverage of the panning target volume (PTV). 43

1.11 Fiducial Marker

Fiducial markers are used in a wide range of medical imaging applications. Modern radiation therapy techniques such as computed tomography (CT), Magnetic resonance imaging (MRI) and position emission tomography (PET) accurately define the target and deliver radiation in a safe manner to better localise a tumour. 51

Tumour and normal tissue motion intra-fraction and inter-fraction poses a major challenge to the delivery of highly conformal radiation therapy techniques. Since a prostate is a highly mobile target due to errors arising from setting patients up, because there are no nearby structures visible to kVCT or MVCT imaging pre-treatment, and also due to bladder volume, rectal distension, levator contractions, and even respiration. 52
Fiducial markers are a very useful tool to assist with registration, tracking inter-fraction and intra-fraction motion, and measuring any difference between the position, from the process of simulation to treatment planning to treatment guidance.53

Fiducial markers are commonly placed within the target volume or adjacent to it prior to radiotherapy simulation as a surrogate for the target volume because tumours are often difficult to visualise using the 2D IGRT modalities presently available. Fiducial markers should be easy to identify and be visible in simulation and treatment verification images. This aids in pre-treatment verification of the target position in order to treat the target precisely while also helping to spare the surrounding normal tissue.53 This is vital in prostate cancer because the rectal wall is sensitive to radiation, and when irradiated it can cause complications for the patient.

Daily localisation has become routine in many radiotherapy clinics thanks to the linac based on-board kVCT and the time saving MVCT orthogonal fiducial imaging, unlike conventional CBCT.53 Fiducials can also be used with CBCT where soft tissue contrast is low.

As MRI emerges into a useful modality for treatment planning54, having fiducial markers that are visible to the MRI and CT imaging modalities is vital, during treatment and simulation.53

PolyMark (CIVCO Medical Solution, Orange City, IA) fiducial markers were used here because they are visible in CT, CBCT and MRI, but have poor visibility in EPID-MV. Chan et. al. noted that attention should be given to the CT protocol and the MR sequences in order to reduce image artefacts and unclear visibility of the markers.53

PolyMark™ (CIVCO Medical Solution, Orange City, IA) is the first polymer based biocompatible marker. It contains a stainless steel core with a PEEK-optima shell. It has dimensions of 1 x 3 mm, its density is 1.32 g/cm³, relative electron density if
1.24 and a relative opaque thickness of 1 during kV imaging. It minimizes artifacts and is visible during kV based IGRT, MRI and is optimized for proton therapy. A study carried out by Alnaghy et al. used MOSkin™ detectors on top of a probe during a TomoTherapy® boost SRS treatment. The rotational positioning of the probe was an issue because while the MV scans performed pre measurements, the MOSkin™ detectors were invisible because they were too small to be seen in this imaging modality. In the KV images taken pre measurements, the MOSkin™ detectors were difficult to image because the kV energy x-rays experience beam hardening, scatter and Poisson noise when exposed to high Z materials that lead to streak artefacts.

To overcome the rotational positioning problem that occurred in this study, polymark® fiducials were inserted into the Rectafix®. These fiducials are optimised for MR and are visible in CT; so they were used as a parallel study on the visibility of fiducials utilising MRI scans. This increased geometric accuracy of the Rectafix® device one of many imaging techniques in use, i.e. CT, VMAT and tomotherapy scans.

### 1.12 In vivo dosimetry

In-vivo dosimetry is a method of monitoring the actual dose delivered to a patient instead of relying on the planned dose being accurate; it can be used as a safety measure in treatment delivery. A dosimeter is placed inside or on the top surface of the patient being treated, wherever the dose must be measured. It has been stated in the ICRU report 24 (1976) that the best way to check the actual dose received by a patient is by performing in-vivo dosimetry.

In-vivo dosimetry is therefore an appealing method to verify the dose received by the rectal wall, so in-vivo dosimetry of the anterior section of the rectal wall would enable the dose received by the section that usually receives the highest dose to be measured. Due to the high doses delivered during hypofractionation schedules to the prostate and anterior rectal wall, this dose must be calculated to correlate the rectal...
toxicities to the delivered dose. In-vivo dosimetry would also help to verify the calculated target dose, and since the anterior rectal wall is included inside the PTV, a dosimeter placed inside the rectal wall would be a surrogate for the PTV dose at the posterior end of the volume. There has been a focus on implantable in-vivo dosimeters to verify target doses, as reported by Beyer et al 2007\textsuperscript{46}, Black et al 2005\textsuperscript{47}, Kry et al 2009\textsuperscript{48}, Fagerstrom et al 2008\textsuperscript{49}, Scarantino et al 2005, 2008\textsuperscript{50, 49}. These methods can be used for prostate radiotherapy, while the implanted dosimeter can be used for position verification and to move the rectal wall away from the prostate to reduce its volume and the dose received by the prostate\textsuperscript{48}.

1.13 Properties of EBT3 film and suggestions for use

Gafchromic EBT3 film is a type of commercial radiation-induced auto-developing photon and electron-beam analysis film that is available for therapeutic radiation dosimetry in radiotherapy applications to provide accurate in-vivo dosimetry measurements\textsuperscript{56}. This film uses the principle of a polymer changing colour when irradiated; film that displays this property is generically referred to as radiochromic film.

In this study we used Gafchromic EBT3 (lot number 12171302, Ashland specialty Ingredients, NJ, USA) radiochromic film because it allowed large field areas to be detected with an adequate dose response in terms of energy dependence and linearity. It has a high dose range and a high spatial resolution that is restricted mainly by the resolution of the densitometer. Moreover, its high dose capability allows it to be used to study high dose gradients in the penumbra, it also has a linear dose response over a large range of dose, and it is also tissue equivalent which makes it ideal for an in vivo study.\textsuperscript{56, 67, 82, 83, 84, 85}

Gafchromic EBT3 radiochromic dosimetry film consists of a single active layer, nominally 27 μm thick, that contains an active component, marker dye, stabilisers and other additives that give the film its low-energy dependence. The yellow marker dye decreases UV/light sensitivity, and when used in conjunction with an RGB film
scanner permits the use of multi-channel dosimetry. The active layer is between two, 120 μm transparent polyester substrates; this symmetric arrangement ensures consistent response regardless of which side of the film is facing the light source of the scanner. This composition can be visualised in Figure 1-2. The polyester substrate has a unique surface treatment with microscopic silica particles that maintain a gap between the surface of the film and the glass window in a flatbed scanner. Since the gap is almost ten times the wavelength of visible light, it prevents the formation of Newton’s Rings interference patterns in images obtained using the flatbed scanners.\textsuperscript{57}

![Polyester - 120μm](image1)

![Active Layer - 27μm](image2)

![Polyester - 120μm](image3)

Figure 1-2 Gafchromic EBT3 film composition

Gafchromic EBT3 film is self-developing, which reduces the possibility of error due to variations in chemical processing analysis, as long as a strict protocol such as time to read out is followed; it is not very sensitive to visible light, it is not brittle and can be bent and shaped to a certain degree, and it does spring back into its original shape as long as a crease is not induced while bending.

There are also some challenges that arise using EBT3 film which should be considered; for example, its sensitivity varies with temperature and UV light; its self-development takes a couple of days; it’s response is non-linear at low doses, and
there are possible variations in zero dose EBT3 film response caused by interbatch and intrabatch variations. \textsuperscript{58, 67, 84} Adhering to a fixed and consistent protocol is crucial in EBT3 film dosimetry to gain reproducible results.\textsuperscript{59}

When Gafchromic EBT3 film is exposed to ionizing radiation, colouration due to an attenuation of some of the visible light coming through the developed EBT3 film occurs, which darkens its appearance. This reduction in light passing through the EBT3 film is a measure of its “blackness” or “optical density” (OD). It is assumed that the dose to the EBT3 film is shown by the resulting optical density. The relationship for optical density is:

\[
\text{Net } OD = \log_{10}\left(\frac{I_o}{I}\right)
\]

Equation 1-2

Where \(I_o\) is the light intensity with EBT3 film given no dose and \(I\) is the light intensity after EBT3 film is exposed to a dose of radiation.\textsuperscript{60, 67, 83, 84}

To calibrate the EBT3 film, it is irradiated by a known calibrated linac dose at a known distance from the source to the EBT3 film. When the change in colour is analysed there is an OD which represents the dose absorbed in the particular irradiation; this is then repeated with different times, calibrated dose or distances, and from which a trend is determined.

Since Gafchromic EBT3 film batches have a linear response to an increasing dose (after \(~50\) cGy)\textsuperscript{61}, a calibration factor emerges that will allow the dose incident on any EBT3 film of the same batch to be determined.

The response of radiochromic dosimeters can be influenced by the temperature and relative humidity, and in some cases by ambient light and gases, and since the conditions between calibration and practical use may differ, variations of response with the surrounding conditions must be determined and corrected.\textsuperscript{62, 67, 84}
Gafchromic EBT3 film is designed to be handled in interior room light, so it is recommended that the EBT3 film be kept in the dark when not in use and exposure to sunlight be avoided.\textsuperscript{60, 67, 84}

These EBT3 films are placed inside an envelope when not in use to avoid the effect of ambient light and other light sources during storage. It is important to minimise their exposure to light so any ambient light should be approximately equal for all EBT3 film; therefore all EBT3 film batches should be housed together to maintain their consistency. This also ensures the same thermal background for all the EBT3 film because EBT3 film is sensitive to temperature.\textsuperscript{60, 67, 84}

EBT3 film may be stored at room temperature (20˚ - 25˚C) but is best stored at refrigerator temperature, or less. Brief exposures (e.g. < 1min.) at temperatures of 50˚C should not affect EBT3 film, but sustained exposure of unexposed EBT3 film to temperatures >60 °C may cause a significant change in sensitivity.\textsuperscript{62}

Gloves should be used while handling EBT3 film to keep it clean and free of oil. Cotton gloves seem to be appropriate. Care should be taken not to stain or scratch the EBT3 film because it will affect the colour and in turn, the results.\textsuperscript{63} Prior to use, EBT3 films should be visually inspected and handled with care. The EBT3 film will turn from clear to a milky white at a damaged location, while the cut edges may be stressed and should be avoided for dosimetry analysis. It is recommended that the light beam of the scanner be kept about 1.5 mm away from a cut edge.\textsuperscript{62, 67, 84}

Gafchromic EBT3 film is easy to work with and shape, it is not brittle so it can be bent and shaped according to what it will be used to measure.\textsuperscript{62}

The lot number and model number of the EBT3 film should be recorded for each and subsequent experiments; this will enable the user to verify any manufacturing variations in the EBT3 film.\textsuperscript{62}

The orientation and alignment of the EBT3 film should be noted, and since EBT3 is non- polarised it is not angular dependent like its predecessor EBT2 film, however it
is important to record film orientation during irradiation and scanning to have a record of orientation. One method is to consistently mark and number the same corner of the film; this also keeps track of where the film was used. 62

The film should be placed inside a phantom that is appropriate for the experiment being undertaken. For calibration purposes, EBT3 film should be placed between layers of solid water and perpendicular to the linac beam, with at least 10cm underlying backscatter material. 64 The orientation of the film should be noted and laser alignment points marked for analysis at a future time. 64 Almost full colour development of all radiochromic formulations is very rapid, generally occurring in a few milliseconds, but several chemical effects in plastic systems induced by radiation require some time to reach chemical completion after irradiation. 62, 65, 67, 83, 84

Keeping within the same time period between irradiation and scanning of films is crucial in obtaining measurements to minimise potential uncertainties due to dose dependent post irradiation darkening. 62, 65, 67, 82

Although the main part of colour development occurs immediately during exposure, radiochromic films exhibit a strong dose dependent darkening of up to 20% OD during the first couple of hours after irradiation. 59

Moreover, a 22 hour period of irradiation to scanning time induced OD changes below 0.45% per hour for EBT3 film. Therefore, uncertainties of 2h-time delays remain within the tolerable uncertainty limits (<2%) and a 20h to 24h time window between irradiation and scanning can be assumed as being accurate enough. 59, 67, 82

A 48 hour irradiation to scan time is ideal, 64 so a 42 to 50 hour window was used in this study scan the films post irradiation because it offered practical benefits for the user and it maximised the potential post irradiation colour development.
2 Materials and Protocols

2.1 Linac

An Elekta Synergy linear accelerator (Elekta Oncology Systems, Crawley, UK) was used to calibrate the film and deliver the VMAT plan. The TomoTherapy® machine was a TomoTherapy® HI-ART II superposition-convolution system; both machines are located at the Liverpool Cancer Therapy Centre in Western Sydney.

2.2 Treatment Planning System (TPS)

Computerised treatment planning systems (TPS) were used to calculate dose maps on CT data sets prior to patient treatment and the CT data sets were obtained using a 2 mm slice thickness on the Siemens Sensation 4 Multislice CT scanner (Siemens Medical Solutions, Malvern, PA); these calculations can also be performed on phantoms by using CT data sets. One main objective of this study was to compare the dose delivered on the Rectafix® with the dose predicted by the treatment planning system.

The TPS used to calculate the dose from the linear accelerator VMAT deliveries was a Pinnacle treatment planning system (Philips Radiation Oncology Systems, Fitchburg, WI Version 9.0). Pinnacle incorporates the collapsed cone dose method of calculation. A 1.00 x 1.00 1.00 mm³ dose grid was used to calculate all the doses via a collapsed cone convolution.
The TomoTherapy® planning station version 4.2 (Accuray Incorporated) TPS was utilised to calculate all the doses for the TomoTherapy® system before dose delivery; this consisted of a 2.00 x 2.00 2.00 mm³ dose grid for dose calculations using a convolution superposition method.66

2.3 Phantom

A Solid Water phantom (Gammex RMI, Middleton, WI) with the uniformity, water equivalence, and ability to vary thickness was utilised to carry out calibration and simple field tests.

An IMRT Head and Torso Freepoint Phantom (CIRS, model 002H9K) was used for Rectafix® measurements. This phantom is constructed from tissue equivalent, epoxy materials with cylindrical cavities that allow rods to be inserted. These rods that can hold an ionization chamber or they can be made from bone equivalent material. The cylindrical cavities could also be rotated and placed in different positions. It is these cavities into which the Rectafix® was inserted. 45

2.4 Rectafix® sleeve

The diameter of the insertion point on the CIRS phantom was wider and longer than the Rectafix® device, so a sleeve was made from polyoxymethylene to obtain a secure fit between the Rectafix® and the phantom. Polyoxymethylene was used because the Rectafix® is constructed from polyoxymethylene. The sleeve also houses the film and secures it in place around the Rectafix® device.

Polyoxymethylene (CH₂O)n is an engineering resin with mechanical properties that make it suitable to be used prototyping and manufacture of laboratory apparatus. The characteristics of Polyoxymethylene include metal-like machining and dimensional stability, as well as thermal stability. 88
The Rectafix® is 20 mm in diameter, the insertion point on the CIRS phantom is 25 mm in diameter, and the film is ~1mm thick. The sleeve has an outside diameter of 25 mm and an inside diameter of 21 mm; it is 120 mm long so that it fills the gap in the length of the insertion point on the CIRS phantom. This ensures that the insertion point is filled with polyoxymethylene, it has no air gap, and the Rectafix® and film is securely in place.

Figure 2-1 Image of the Rectafix® sleeve.

The inside diameter of the sleeve was machined and polished to avoid damaging the film whilst inserting and removing it from the sleeve.

2.5 Fiducials

Fiducial markers are placed inside the Rectafix® device to verify its position inside the phantom by using the on board imaging modalities offered by the Elekta Synergy linear accelerator and TomoTherapy® HI-ART II machines.

Since the Rectafix® is cylindrical and measurements are taken in a high dose gradient, even a small rotational error in the set up could produce a large readout error on the film.
Three Polymark fiducial markers were placed onto the Rectafix®; two were placed 5 cm apart on the superior edge of the Rectafix® and one marker was placed between the other 2 fiducial markers at 90°. This orientation allowed for the Rectafix® to be corrected in the sagittal, coronal and axial planes, as well as corrections for any rotation that may occur in a phantom set up.

By using imaging data obtained pre-treatment, the fiducial markers were used as a reference point for the detector and to verify the position of the Rectafix® before commencing treatment.

### 2.6 Film Cutting

Since there is only a set of guidelines and no protocol recommended for dosimetry with EBT3 film, being consistent with each individual method in order to have data that can be inter-compared and be consistently reproduced over multiple experiments is very important. This report uses methods that are a conjugate of several suggested protocols, including A. Niroomand-Rad et. al. (1998) 62, N. Farah et. al. (2014) 63, S. Devic et. al. (2005) 64, C. Huet et. al. (2014) 65, P. Papaconstadopoulos et. al. (2014) 67, N. Bennie and P. Metcalfe 68.
At least one publication suggests cutting film with scissors because the equal pressure from the scissors helps keep the sandwich type layers from separating. With film, scissors should be used although good results can also be obtained by using a scalpel, a guillotine cutter, or a sharp knife.

The cut edge of the film may be stressed and cause OD abnormalities which should be avoided for dosimetry analysis. It is also recommended that the light analysis beam be kept about 1.5 mm away from the cut edge.

Since the outer layers of EBT3 films are polyester they can be marked with a felt tip permanent marker or pen without damaging the active layer. If the marks interfere with scanning or other measurements, they can be removed with a soft rag or tissue moistened with a solvent which does not damage the polyester. These marks may also be removed using image analysis software.

The lot number and model number of the film was noted for each box of film; this helps the user trace any manufacturing variations to a particular batch of film.

2.7 Flatbed scanner

Although not specifically intended for radiochromic film dosimetry, document scanners can be used for measurements in various film dosimetry applications. Flatbed document scanners intended for high quality photographic scanning that prefer to operate in transmission mode often use a fluorescent light source with a broadband emission spectrum and a linear charge coupled device (CCD) array detector. These scanners permit transmission scans in up to a 48-bit red-green-blue (RGB) mode, e.g., 16bits per colour.

The scanner used in this experiment was an Epson V700 (Epson, NSW, Australia) digital scanner with software that allows for raw image data acquisition, and with no colour corrections made to the image; it also has a good signal to noise ratio. The
scanner should be warmed up for 30 minutes and then 10 scans made to stabilise its light source and ensure it is at operating temperature.\textsuperscript{59}

The scanners are not flat over the entire scanning field; there may be differences of approximately 2\% in response, with the largest being within 2-3 cm of the left and right sides of the scan field. To take advantage of field flatness, the films be placed in the centre of the scan area, away from the edge.\textsuperscript{59}

Scanner resolution must be set to compromise between image resolutions, file size and scan time, so in this study I utilised 72 dpi because a 72 dpi resolution allows for 28 pixels per cm.

It is important to save scans in 48 bit RGB tiff format because it is a lossless data compression technique and most software analysis is compatible with this format, and it also allows for split channels to obtain the required colour channel from subsequent analysis. No colour correction options should be used while scanning because they could cause significant automatic manipulation of the OD values which cannot be easily tracked.\textsuperscript{64,65}

\textbf{2.8 Film Use Protocol}

EBT3 film should be calibrated using a large well-characterised uniform radiation field. Each batch of film obtained from the distributor must be calibrated. The dose response curve and film sensitivity should be obtained in the dose range estimated to be of interest in the subsequent experiment.
Figure 2-3 Image of varying film colour in response to an absorbed dose. The dose read out from left to right: 0 Gy, 1 Gy, 2.5 Gy, 5 Gy, and 7.5 Gy.

For a typical calibration and experiment carried out in this thesis, 5 pieces of film were irradiated at doses ranging from 1 to 14.82 Gy. The films were cut into $5.0 \times 4.0 \text{ cm}^2$ pieces such that the irradiation field was considered to be uniform and limited within a field size of $10 \times 10 \text{ cm}^2$.

The calibration strips were chosen so they were large enough to give good statistics and also small enough to allow multiple samples to be cut from the same sheet of film.

Pixel Intensity is associated with films exposure, we can relate pixel value to OD using equation 1-2. Each film is irradiated to a known dose value, hence OD and dose relationship can be obtained. Darker colour density represents higher dose.

The films were positioned between two water equivalent solid water phantoms. A build-up of 1.5 cm thick solid water was placed between the source field and the irradiated sample and 10 cm thick solid water lay behind the sample as back scatter, in the direction of beam propagation. The slabs were all 30 cm x 30 cm by varying the thicknesses (2mm to 4cm).

There was no significant influence between the low and high field sizes from $3 \times 3 \text{ cm}^2$ up to $25 \times 25 \text{ cm}^2$ on the dose response, so only the previously mentioned $10 \times 10 \text{ cm}^2$ configurations were implemented. The relative uncertainty of the delivered dose is around 2%, which is the standard conventional value used clinically when continuous quality control procedures are implemented using ionization chamber methods.
Each film was read after 3 warm up scans, and then readings were recorded for 3 actual subsequent scans.

After acquiring the image it was opened with ImageJ and then converted from a 16 bit format into a 32 bit format to help extract the information required without losing data to size restrictions.

![ImageJ interface](image1.png)

Figure 2-4 Converting the image into 32 bits using Image J.

The image was then split into image data sets which represented three colour channels, red, green and blue.

![ImageJ interface](image2.png)

Figure 2-5 Splitting the image into 3 colour channels using Image J.
A two-colour protocol is suggested for 3 model based radiochromic film dosimetry system using only the reflection mode in a dose range of 0–8 Gy; for low doses (0–2 Gy) calibration is performed with the red channel, while for higher doses (>2 Gy) calibration is performed with the green channel. The dose range we want in this study is well above 2 Gy. As part of film validation experiments, and to validate a prostate boost dose exceeding 2 Gy/F, and typically around 8 Gy, the green channel was used for the analysis reported in this thesis. 67

The green channel is used to obtain the pixel value of the selected area or line of interest from the film; this is done using the box or line function to outline the area of interest and then using the MEASURE function under the ANALYZE tab. For a box selection of a region of interest (ROI), the readout will be the average pixel value of the ROI, while for a line selection it will readout the pixel value per pixel, from the start to the end of the line of interest.

Figure 2-6 Using the area selection tool on Image J to select the desired area on film.
Figure 2-7 Using the Measure tool on Image J to obtain the pixel value of selected area on film.

The net OD is then calculated using equation:

\[ Net \ OD = \log_{10}\left[\frac{I}{I_0}\right] \]

Equation 1-2

Where \(I\) is the pixel value of the film post irradiation and \(I_0\) is the pixel value of the film pre-irradiation.

To investigate the relationship between changes in optical density against known dose values, a calibration curve must be produced to obtain the relationship between the OD values obtained from film to dose. It is also important to check this curve to increase confidence in future results.
By relating the net optical density of each of the calibration strips to their known dose values from irradiation, a calibration curve is produced. By calculating the equation of the line for this calibration curve using the line of best fit function with a 3rd degree polynomial curve in Microsoft Excel, any other unknown dose values within the range of the dose limit of the calibration curve can also be calculated.

The accuracy of this calibration curve was then validated by irradiating film strips at a different depth and a different monitor units (MU) to the calibration points. Since MU is directly proportional to dose, this in turn equates to a different dose delivered. The dose to these strips was found using the calibration curve, and also calculated using Pinnacle TPS. The measured and calculated values were then compared to increase confidence in the calibration curve.

### 2.9 Data Analysis

Film analysis was performed using ImageJ. A line profile constructed superior-inferior plane corresponding to the Centre on the film, which would be closest to the prostate of each of the images. The pixel value obtained was then converted to dose using the calibration curve previously obtained.

![Figure 2-8 Marks on film corresponding to the section most anterior on the Rectafix®.](image-url)
Figure 2-9 Using the straight segmented line tool in ImageJ to select the profile of interest.

Figure 2-10 Using the Plot Profile function followed by the List tab on ImageJ in order to obtain the PV at each pixel along selected profile.
The dose along the same line was also calculated using pinnacle RTP in order to compare the measured versus calculated dose values along the rectal wall closest to the prostate.

The measured values for the superior-inferior line profiles were then filtered using MATLAB and a fifth order one dimensional median filter. The function medfilt1 was used in MATLAB to smooth out the curve and better match the measured vs calculated curves; the measured curve is noisy due to film or scanner not having perfect uniformity, or a stain, markings or damage due to use.
Figure 2-11 Comparison of unfiltered film profile on top vs filtered film profile on the bottom
The measured and calculated central vertical lines for each film were then plotted as dose profiles on the same axis to compare the difference between the calculated vs measured dose for each scenario.

2.10 Error Analysis and Tolerance Criteria for Acceptability

When calculating tolerances for dose calculations, there are always differences between measurements and calculations, but these differences depend on the location within the beam and on patient geometry. There is no simple statement about the criteria of tolerances because the accuracy of dose calculations depends on the algorithm and the region within the beam, and the region within the patient. Tolerances must be analysed with this concept in mind.

One method to analyse and compare calculations and measurements is to represent deviations statistically; there may be a tolerance set to each point value, but overall acceptability is not based on matching the tolerances at each point.

An acceptable decision is made using confidence limits, or similar statistical data, and while not all the data points may meet a certain tolerance, they may still be acceptable as long as say, 95% of the points fall within this limit.

Different people may look at the same types of tolerance data and decide on different values, so our expectations depend on the state of the algorithm and the type of situation being analysed.

The deviation between the calculated and measured data can be expressed as a percentage of the locally measured dose:

\[
\delta = 100 \times \frac{(D_{\text{calc}} - D_{\text{mean}})}{D_{\text{mean}}}
\]

Equation 2-1
Where \( \delta \) is expressed as a percentage, \( D_{calc} \) is the dose calculated at a particular point in the phantom, and \( D_{mean} \) is the dose measured at the same point in the phantom.\(^{70}\)

A statistical assessment can be performed using a set of criteria defined by Venselaar et. al. on the acceptability of different tolerances for \( \delta \). This is based on information which states that the high dose gradient regions of the beam require a different assessment; this can be seen in Figure 2.12 and Figure 2.13. This information is utilized in the IAEA TRS 430 report, which is aimed at quality assurance measurements of TPS.\(^{71}\)

<table>
<thead>
<tr>
<th>Tolerance</th>
<th>Homogeneous, simple geometry</th>
<th>Complex geometry (wedge, inhomogeneity, asymmetry)</th>
<th>More complex geometries, i.e. combinations of 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \delta_1 ) (central beam axis data) high dose, small dose gradient</td>
<td>2%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>( \delta_2 ) build-up region of central axis, penumbra region of the profiles high dose, large dose gradient</td>
<td>2 mm or 10%</td>
<td>3 mm or 15%</td>
<td>3 mm or 15%</td>
</tr>
<tr>
<td>( \delta_3 ) (outside central beam axis region) high dose, small dose gradient</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>( \delta_4 ) (outside beam edges) low dose, small dose gradient</td>
<td>30%</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>( RW_{50} ) radiological width</td>
<td>2 mm or 1%</td>
<td>2 mm or 1%</td>
<td>2 mm or 1%</td>
</tr>
<tr>
<td>( \delta_{50-90} ) (beam fringe)</td>
<td>2 mm</td>
<td>3 mm</td>
<td>3 mm</td>
</tr>
</tbody>
</table>

Figure 2-12 Proposed tolerances for \( \delta \) at different configurations.\(^{71}\)
The criteria acceptable for small dose gradient regions is that express tolerances as a percentage, whereas in regions with a large dose gradient, the tolerance value should preferably be expressed in a mm shift of the relevant isodose line.

2.10.1 Suggested tolerances for individual points

Venselaar et al have suggested criteria for acceptability in different test configurations of a beam. Figure 2.12 shows different acceptability criteria for a variety of different test configurations.

It is suggested that as long as many data points of comparable situations are evaluated, some of the points that do not satisfy the accuracy criteria may not necessarily lead to a negative overall result, as long as the overall result is satisfactory.

2.10.2 Gamma analysis

Gamma analysis is a useful tool for determining how closely a treatment planning system and the delivered dose correlates with one another at different locations.
around the target. For a gamma analysis to produce a positive dose correlation, the 2 systems measured must match within a set spatial displacement and dose displacement tolerance. The gamma analysis can be performed in a 2D space or a 3D space.

Distance to agreement (DTA) is calculated by locating a pixel with a known dose, correlating this position to the treatment planning system, finding the corresponding coordinate and then measuring the distance between these two points. 73

Gamma analysis incorporates this DTA with a calculation of dose difference. The gamma index is given by the following equation:

\[
\Gamma(r_m, r_c) = \sqrt{\frac{r^2(r_m-r_c)}{\Delta d_M^2} + \frac{\delta^2(r_m-r_c)}{\Delta D_M^2}}
\]  

Equation 2-2

The radial distance between the treatment plan pixel \( r_m \) and the calculated pixel \( r_c \) is given by \( r \). The dose difference between the two pixels is \( \delta \), the dose difference criteria set is given by \( \Delta d_M^2 \) and the DTA criteria set is given by \( \Delta D_M^2 \).

In using this technique a tolerance level is set, i.e. if 3mm is chosen as the tolerance level, and if the two points between the measured and calculated pixel on TPS lie within a 3mm radius of one and another, the point passes the DTA. This can be seen as a test where the pixels either pass or fail.

A gamma index of 1 and above is an indication that the test has failed. Due to the elliptical distribution of the gamma function, as explained in equation 2-3, a point where the DTA and the dose tolerance criteria are within the accepted limit may still fail the gamma test. For a more detailed explanation of gamma analysis, see the study done by Low D. A. et. al. 74

Gamma analysis was performed using Matlab software. This analysis was performed for a line profile because the results obtained in this study are used to compare the line profiles between the treatment planning system and measured dose on film.
Basran et. al. suggested that the tolerance for an IMRT treatment plan should be set at a 95% pass rate for gamma analysis with a tolerance criteria of 3%/3mm (dose difference/DTA), and for more complex IMRT treatments the pass rate should be decreased to 88%. 75

T. Kairn et. al. utilised a tolerance of 3%/3mm and 2%/1mm to study complex IMRT, RapidArc and TomoTherapy® fields during prostate radiotherapy. 76

While 3%/3mm is probably the most commonly used quantity, there is considerable debate about which quantities are optimal, depending on the clinical scenario. For the high precision treatments considered in this thesis it would be hypothesised that tight acceptance criteria would be of greater benefit.

The plans delivered in this study are a high precision treatment which requires a high level of accuracy in delivery. The acceptance criteria to be studied are 3%/3mm, 3%/1mm, 2%/1mm and 1%/1mm.

2.10.3 Error Analysis

There are many sources of uncertainty that effect these measurements including reproducibility of the optical density measurement, photon output reproducibility and scanner reproducibility as well as uncertainties in the film calibration curve, effect of the film positioning and small SSD variations between the applications, temperature and humidity effects, dust, fingerprints, scratches and the fitting function. 67, 82

The effects of scanner performance, variations in the linear accelerator performance and any differences the film may have intra sheet, are error corrections that cannot be made because this is a statistical analysis of data and varies with the time and environmental changes.

Any errors in the film manufacturing process, set up errors, human errors, non-uniformities in the light field of the scanner and storage of the film are random errors
that cannot be corrected for. Because the differentiating factor when calculating this uncertainty is that it is not based on statistical data, these errors may be corrected or possibly eliminated.

Uncertainties were minimised by following a strict protocol with the use of film and its analysis; as discussed in previous sections.

The calibration curve measurements were repeated 3 times and the average of all 3 data was used to construct a mean curve. The error of each dose point was calculated using a t-test with a confidence interval of 95%.
3 Calibrating Film

3.1 Aim

To measure the dose at the rectal wall during a prostate boost high precision treatment, EBT3 film was calibrated according to the batch being used, and then partially wrapped around a Rectafix® device.

3.2 Materials and Method

The Gafchromic EBT3 film used in all the following experiments is from lot number 12171302, Ashland speciality Ingredients, NJ, USA.

The films were irradiated in a solid water phantom at $D_{\text{max}}$ 100 SSD with 1.5 cm build up and 10 cm underlying backscatter material. The measurement at $D_{\text{max}}$ ensured that the MU recorded was equal to the dose in units of cGy where 1 MU is equal to 1 cGy. The 10 cm underlying backscatter material ensured there was enough Solid Water producing back scatter to meet requirements. The irradiation field was 10 x 10 cm$^2$ and was considered to be uniform; this set up is shown in Figure 3-1.
Figure 3-1 Film calibration set up.

Film was analysed using the method outlined in sections 2.7, 2.8 and 2.9. The green channel was used to analyse dose values that are well above 2 Gy, but for doses around 2 Gy and below, the red channel is better suited for data analysis.

The film is left for 48 hours to develop and then scanned in accordance with the protocol previously outlined.
The OD for the green and red channels was measured separately, and then the net OD is calculated using Equation 2.1. This ensures that any variation of pre irradiation OD between each strip of film is accounted for.

### 3.3 Green Channel Calibration

Figure 3-2 Calibration curve using the green channel

Any dose values below 2 Gy were not included in the green channel calibration curve because this is not favourable, as outlined in section 2.8.

The OD for each point is averaged and then an error analysis using the student t-test is carried out to give the possible variation of each point within a confidence interval chosen to be 95%.
The error for each dose point was studied according to the calibration curve in Figure 3-2, and the error of each point is as follows.

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Dose CD (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.65</td>
<td>±0.014</td>
</tr>
<tr>
<td>5.30</td>
<td>±0.024</td>
</tr>
<tr>
<td>7.95</td>
<td>±0.065</td>
</tr>
<tr>
<td>10.59</td>
<td>±0.14</td>
</tr>
<tr>
<td>12.71</td>
<td>±0.21</td>
</tr>
<tr>
<td>14.83</td>
<td>±0.29</td>
</tr>
</tbody>
</table>

Table 3-1 Errors calculated for each dose point in the green channel using the t-test with a confidence level of 95%

To find a mathematical relationship between net OD and dose that will relate other values of net OD within the range measured to the value of a dose, a line of best fit with a 3rd degree polynomial fit was overlaid onto the graph using Microsoft Excel by fitting a curve of best fit (add trend line function). The equation was then obtained to be:

\[ D = 1.5553x^3 + 36.64x^2 + 7.5077x \]  
Equation 3-1

A confidence level >95% is also satisfied because the confidence of this line of best fit to the green calibration curve is 99.9% and the line can be accepted as a proper fit.

A calibration curve for the red channel was also calculated, as shown in Figure 3-3.
3.4 Red Channel Calibration

Figure 3-3 Calibration curve using the red channel

To achieve a straight line for the calibration curve, only the film strips within the relevant dose range for the red channel are used. The net OD is then calculated using Equation 3-2.

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Dose CD (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.53</td>
<td>±0.014</td>
</tr>
<tr>
<td>1.01</td>
<td>±0.0086</td>
</tr>
<tr>
<td>2.65</td>
<td>±0.0097</td>
</tr>
</tbody>
</table>

Table 3-2 Errors calculated for each dose point in the red channel using the t-test with a confidence level of 95%
A line of best fit using a 3rd degree polynomial in Microsoft Excel was again utilised to obtain a relationship between the net OD and dose.

\[ D = 5.8198x^2 + 12.835x - 0.2873 \quad \text{Equation 3-2} \]

A confidence >95% is also satisfied because the confidence of this line of best fit to the red calibration curve is 100% and the line can be accepted as a proper fit.

### 3.5 Validation of Calibration

To validate the calibration curve, 2 strips of film were placed inside 5 cm deep solid water with 10 cm underlying backscatter material, which was then placed in the beam at 100 SAD with a 10 x 10 cm\(^2\) size field. One strip was exposed to 450 MU and the other to 750 MU; this set up is shown in Figure 3-4.
Figure 3-4 Set up used to calibrate the test film.

The film was analysed using protocol described previously and the green channel calibration. The dose the film should have measured was also calculated using Pinnacle TPS, and then the calculated and measured dose was compared.
The difference in error was calculated using the equation:

\[
\%\text{Error} = \frac{\text{Calculated} - \text{Measured}}{|\text{Calculated}|}
\]

Equation 3-3

The dose received by each film was:

<table>
<thead>
<tr>
<th>MU</th>
<th>Dose Measured (Gy)</th>
<th>Dose Calculated (Gy)</th>
<th>% Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td>3.81</td>
<td>3.80</td>
<td>0.3</td>
</tr>
<tr>
<td>750</td>
<td>5.65</td>
<td>5.70</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 3-3 Dose measured and calculated on calibrated test film with the resulting error.

By making use of the criteria of acceptability in the IAEA TRS 430 report\textsuperscript{71}, for a homogenous field at the central axis, any error below 2\% is acceptable. Since the error between the calculated dose and the one measured using the calibration Equation 3-1 is within this limit, as seen by Table 3-3, the protocol used for film analysis and the calibration equation obtained can be used within a 2\% tolerance.

### 3.6 Discussion

The confidence gained from using the protocol and from calibrating this batch of film means that any increase in dose difference is specific to that delivery task and not to any major error in dose measurement.
4 Non Modulated Field Experiments

4.1 Aim

Although calibration was successful, moving forward to the desired test measuring dose in a high precision prostate boost plans in VMAT and TomoTherapy® is complex because both are multi leaf collimated rotational IMRT delivery techniques.

4.2 Materials and Methods

The CIRS phantom was used because it is non-homogenous due to the Rectafix® and its polyoxymethylene sleeve is denser than the tissue equivalent solid water.

The Rectatix® device with polyoxymethylene sleeve inserted into the CIRS phantom becomes non-homogenous due to density difference.

The film used in the simple field experiments was flat, but it was folded into a semi-circle to conform to the Rectafix® device with the Rectafix® sleeve fitted over the film and inserted into the CIRS phantom.

Furthermore, a 1 dimensional profile can be extracted from the measurement film and matched to the TPS to validate the accuracy of the TPS at the rectal wall with the Rectafix® inserted. This is the key to these experiments.

To validate every feature in this experimental set up would help in measuring the desired high precision prostate boost plan, so a series of tests where each step is
divided into simpler scenarios was carried out to increase confidence in the experimental set up.

This film does spring back and it resists bending into small radius, so it can only be shaped if held firmly in place; this characteristic means it cannot be wrapped completely around the Rectafix®, as shown Figure 4-1. Furthermore, the cut edge can be damaged so it should be kept 1.5 mm away from the other edge; this also reduced the area of rectal volume that was analysed. Since we are only interested that section of film closest to the prostate, in the higher dose region this did not hinder the project.

Figure 4-1 Rectafix®, film and sleeve set up showing the sleeve holding the film in place around the Rectafix®.

The film used to wrap around the Rectafix® should be large enough to give good data and still be able to wrap around the Rectafix®. In this case a strip of film 4.5 cm wide by 11 cm long was a good compromise because it covered the entire length of the Rectafix®.

Each film was marked at the centre of the most superior edge of the Rectafix® device because it reciprocates the area closest to the rectal wall and the prostate; that area of the rectal wall that would receive the highest dose.
The beams traversed different thicknesses of material, from various angles and different densities. The film was wrapped around the Rectafix®, and the stress of sliding in and out of the sleeve was also tested.

First, 12x12 cm² film is placed inside a solid water phantom with a 10 cm build up and 10 cm underlying backscatter material, and then irradiated by a 6 MV beam with 5x5 cm² field with 3 dose fields from 3 angles - 270°, 0° and 90°. Each beam is the same weight so 300 MU is delivered with each run at 100 SAD, as shown in Figure 4-3.
In the next step, 12x12 cm² film was placed inside a solid water phantom with a 10 cm build up and 10 cm underlying backscatter material. This experiment was carried out with a 5MV arc beam and 5x5 cm² size fields, 180° continuous movement around the phantom starting from 270° and ending at 90° at 100 SAD. In total 600 MU was delivered. This set up is shown in Figure 4-4.
These 3 beam configurations were then implemented again with the solid water phantom swapped for the CIRS phantom set up shown in Figure 4-2. The CIRS phantom is aligned so that the gantry at the centre of the Rectafix® is 100 SAD. This set up is shown in Figure 4-5.
The arc beam set up was implemented with the CIRS phantom set up utilised as shown in Figure 4-2. The CIRS phantom is aligned so that the gantry to the centre of the Rectafix® is 100 SAD. This set is shown in Figure 4-6.
These experiments were carried out and the protocol for film analysis was followed as discussed previously in section 2.9.

Image software was then used to extract a 1d line profile between the 2 marks that correspond to the centre of the image, or in the superior-inferior direction in case of the CIRS phantom and Rectafix® set up in Figure 4-2. The pixel values were then converted to OD and then to dose using the calibration curve.

The dose obtained is smoothed using a 5th order median filter on Matlab. This was performed twice for each profile to remove noise spikes in the film because the pixel value at each point differed slightly before a dose is given or any minor scratches that resulted from taking the film out of the box to when it was scanned. The
corresponding dose profile for each measurement was also extracted from the TPS, and then the measured and calculated line profiles were compared by superimposing both profiles.

The accuracy between the measured and calculated profiles was checked by using Equation 2-3 to check the percentage difference between each and then validating the result using the acceptance criteria for a dose profile, as outlined in the report TRS-430.71

4.3 Results

![Graph showing TPS and Film dose profiles using Solid Water 3 beam set up.]

Figure 4-7 Film and TPS dose profiles using Solid Water 3 beam set up.
Figure 4-8  Film and TPS dose profiles using CIRS phantom 3 beam set up.

Figure 4-9 Film and TPS dose profiles using Solid Water arc beam set up.
Figure 4-10 Film and TPS dose profiles using CIRS phantom arc beam set up.

<table>
<thead>
<tr>
<th>Configuration</th>
<th>$\delta_1$</th>
<th>$\delta_2$</th>
<th>$\delta_3$</th>
<th>$\delta_4$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 fixed field solid water phantom</td>
<td>0.2%</td>
<td>2.6%</td>
<td>0.7%</td>
<td>15.2%</td>
</tr>
<tr>
<td>3 fixed field CIRS phantom</td>
<td>2.3%</td>
<td>6.7%</td>
<td>2.3%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Arc field solid water phantom</td>
<td>0.9%</td>
<td>13.6%</td>
<td>1.5%</td>
<td>14.1%</td>
</tr>
<tr>
<td>Arc field CIRS phantom</td>
<td>1.4%</td>
<td>1.7%</td>
<td>1.3%</td>
<td>25.5%</td>
</tr>
</tbody>
</table>

Table 4-1 Tolerance criteria of sections of the dose profiles obtained from IAEA TRS-430.  

4.4 Discussion

By using the acceptance criteria limits set for a simple geometry homogenous phantom in the central beam for the solid water set up, and the acceptance criteria for a complex geometry non-homogenous limits for the CIRS phantom with the Rectafix® set up, it was noted that the error at each point outlined in the TRS-430
report and the profiles are within the limits allowed. This means the measured profiles are an acceptable match to the TPS.

The $\delta_2$ measurement for the arc field solid water measurements are outside the TRS-430 tolerances for dose difference, but are accepted due to being within the DTA measurement.

Figure 6.3 shows that an equal amount of solid water was traversed by the beam before it reached the central profile of the film, although most of the dose was delivered edge on to the film. Each dose is overlapped by 3 separate beams and a high uniform dose with a high dose gradient at the penumbra region is delivered.

This result means the line profile can be extracted and successfully matched with the TPS, and it also indicates that the film can also measure the dose from edge on.

Figure 4-4 shows that the beam traversed varying thicknesses of phantom and from many different angles; this also occurred at a high dose and high dose gradient at the penumbra.

The good match between the measured and calculated profiles indicates that the film can measure a dose accurately from many angles and through varying thicknesses of material, and the continuous beam had no negative effect on the dose measured.

This result is important because the CIRS phantom is elliptical and the film will be measuring a dose from materials with varying thicknesses.

The set ups shown in Figures 4-5 and 4-6 show that the film and the TPS matched well, as also shown in Figures 4-8 and e 4-10.

This indicates that the non-homogenous composition, and any damage to the film by inserting the sleeve or stress caused by bending, had no negative impact on measuring the dose. Moreover, the shape of the film is also not a factor when measuring the dose.
The dose between the solid water and the CIRS phantom set ups are different even though the same plan is delivered due to the film in the CIRS phantom sitting on top of the Rectafix® – while 100 SAD was taken as the centre of the Rectafix®.

Since a line profile is being measured, any rotation or tilt in positioning the Rectafix® will impact on the profile measured because the dose is being measured in a high dose gradient. By making use of the fiducials and room lasers pre irradiation, the Rectafix® was aligned precisely into the correct position.

Figure 4-11 Stain or damage marks on film

Figure 4.11 shows there are spikes in the graph at random sections that relate to a stain, a scratch, or a mark on the film; they are therefore irrelevant to the overall outcome of these experiments.
5 VMAT Experiment

5.1 Aim

Having refined the experimental technique with the simple 3 field and non-modulated arc beam experiments, the next step was to measure the dose using a prostate high precision boost treatment.

5.2 Materials and Method

A plan was created by superimposing an existing patient plan for a high precision prostate boost therapy using VMAT, onto the CIRS phantom with the Rectafix® insertion using Pinnacle TPS. This allowed for contours of volumes such as the PTV, the clinical target volume (CTV), as well as organs and critical structures to be copied onto the CIRS phantom. The set up is described in Figure 4-2.

![Figure 5-1 VMAT plan view with isodose lines obtained from Pinnacle TPS.](image)
The CTV includes the prostate and extraprostatic disease, as well as an extracapsular extension or seminal vesicle invasion. The PTV was set for a 5mm extension to the CTV margin in every direction but the posterior margin, which was set for a 3mm extension. The rectum in this plan is curved, while the rectal wall utilised on the phantom is straight, so an insert on the CIRS head and neck phantom is used to replicate a rectum. The dose measured with film to TPS data has no negative impact on the scope of this thesis.

The plan parameters were set in accordance with the phase II Prometheus trial where a high precision boost for prostate cancer was delivered with a hypo-fractionated schedule of 21.1 Gy in 2 fractions. The prescribed dose is set so that 90% of the dose (19 Gy) of the target maximum covers a minimum of 95% of the planning target volume (PTV). To achieve a sharp fall off in the dose, an in homogenous distribution is acceptable.

The objective of this treatment plan is to limit the dose to the rectum to 14-16 Gy, with the maximum dose occurring in the overlap region between the rectum and PTV, but there is a chance that the PTV adjacent to the rectal volume may receive a minimum dose of 16 Gy while the urethra would receive a maximum dose of 21 Gy.

The phantom was aligned using the fiducial markers and room lasers, and then the experiment was repeated twice.

The phantom was then shifted 3 mm in the anterior direction and the dose measured once again using the same set up.

The film was then scanned according to the protocol outlined previously in section 2.8. A line profile was extracted from each of the 3 films in the superior-inferior direction on the most anterior section of the Rectafix®, converted to net OD using Equation 2-1 and then to a dose using Equation 3-1. The profile was then filtered twice using the medfilt1 function on MATLAB with a dimension of order 5, and then TPS was used to extract a line profile corresponding to the same position. The
calculated and measured profiles at the rectal wall - Rectafix® interface were then superimposed with each other. The calculated and measured profiles were then analysed with a gamma analysis by calculating the dose on the measured profile and the TPS at 1 mm intervals, so that each profile could be assessed at the same position on the curve. Matlab was used to perform the gamma analysis, and $\gamma < 1$ was accepted as a pass while a $\gamma \geq 1$ was taken to be a fail.

The gamma analysis was then plotted as a visual representation of how well each figure matched the TPS. A plot comparing the dose profiles measured between the rectal wall and a 3mm shift in the anterior direction was also produced.

C. Huet et al. have already investigated the variation in mean pixel value on a neutral film as a function of the number of scans on different days and concluded that measurements were not reproducible. This along with a film variation inter sheet and an inter batch render the film not reproducible for dose measurement modality.
5.3 Results and Discussion

In utilising the 3%/3mm acceptance criteria, 100% of the points passed the gamma analysis, as shown in Figure 5-3.

Figure 5-2 Film measured against TPS calculated VMAT delivery profile

Figure 5-3 3%/3mm gamma analysis of Figure 5-2 VMAT delivery. Pass rate: 100%
The DTA was then reduced and the 3%/1mm acceptance criteria measured. The pass rate for the selected criteria is 100%, which means the gamma parameters can be tightened even further. This is shown in Figure 5-4.

![Gamma vs Distance Graph](image)

Figure 5-4 3%/1mm gamma analysis of Figure 5-2 VMAT delivery. Pass rate: 100%

The gamma parameters were then changed to 2%/1mm and a failed gamma point can be observed. The pass rate for this test was 98.8%, which is still within the acceptable limit. This is shown in Figure 5-5.
Figure 5-5 2%/1mm gamma analysis of Figure 5-2 VMAT delivery. Pass rate: 98.8%

The gamma parameters were tightened again to determine how tight they can be made before the pass rate is unacceptable at <95%. The parameters this time were 1%/1mm and the pass rate was 89.2% which is below the minimum acceptable value of 95%. This is shown in Figure 5-6.

Figure 5-6 1%/1mm gamma analysis of Figure 5-2 VMAT delivery. Pass rate: 89.2%
This result indicates that gamma analysis can only be tightened to 2%/1mm utilising this method. For a further investigation, the same gamma parameters were studied through all the film vs TPS comparisons. This will be analysed at a later point in a table format.

To determine the reproducibility of the measured data, 2 measurements were obtained from each treatment plan, and then the VMAT delivery was repeated. A comparison between the repeat film measurement and the TPS is shown in Figure 5-7.

![Graph](image.png)

**Figure 5-7** Film measured against TPS calculated VMAT second delivery profile

A gamma analysis was then carried out utilising the acceptance criteria 3%/3mm, 3%/1mm, 2%/1mm and 1%/1mm which are shown+ in Figure 5-8, Figure 5-9, Figure 5-10, and Figure 5-11 respectively.
Figure 5-8 3%/3mm gamma analysis of Figure 5-7 VMAT delivery Pass rate: 100%

Figure 5-9 3%/1mm gamma analysis of Figure 5-7 VMAT delivery Pass rate: 100%
Figure 5-10 2%/1mm gamma analysis of Figure 5-7 VMAT delivery Pass rate: 98.3%

Figure 5-11 1%/1mm gamma analysis of Figure 5-7 VMAT delivery Pass rate: 89.2%
To compare the initial and repeat measurements obtained from the VMAT delivery, the two film measurements were graphed together to give the visual representation shown in Figure 5-12.

![VMAT Profile and VMAT Profile Repeat Comparison](image)

**Figure 5-12 VMAT profile and VMAT profile repeat comparison**

A gamma analysis utilising 2%/1mm acceptance criteria was then carried out to compare both film measurements. This can be seen in Figure 5-13. A pass rate of 100% was obtained.
Figure 5-13 2%/1mm gamma analysis, VMAT profile and VMAT profile repeat. Pass rate: 100%
The reproducibility comparison shows a good gamma analysis with 100% pass using 2%/1mm acceptance criteria.
The dose measured along the rectal wall was then compared to the dose measured with a 3 mm anterior shift to determine what the outcome of a positional error would have on the results. This is shown in Figure 5-14.

Figure 5-14 VMAT rectal wall profile against 3 mm anterior shifted profile
The film measurement with a 3mm anterior shift resembles the TPS at the rectal wall at the initial portion of the curve, but then deviates markedly. An error such as this would incur a large variation in the shape of the curve because the film is placed in an area with a large dose gradient so it is very unforgiving of positional errors.

Moreover, if the rectal wall was misplaced 3mm anterior into the higher dose region then a larger portion of the rectal wall would receive a substantially higher dose and hence increase the risk of greater rectal toxicity.

None of the gamma points in Figure 5-2 failed, however the initial portion of the curve up to 1.6 cm had the highest gamma value at 0.88; this corresponds to that section of the curve with the highest dose gradient.

A spike in gamma occurred in areas with a rapid change in the dose gradient.

There is a similar trend in Figures 5-3, 5-4, and 5-5 but in Figure 5-5 the gamma failed in the 1 cm to 1.5 cm range; this plan is still considered to be acceptable because 95% of the points passed the gamma test.

High dose gradients are a worse match because the dose changed rapidly over a short distance, causing the dose threshold component of the gamma analysis to quickly fall outside the range. This was explained by M. Stasi \(^{77}\), where even if a poor pass rate is present in a high dose gradient, the plan may still be accepted. Gamma analysis is open to interpretation in the region to which it is applied.

Although a spike in the gamma is visible in Figure 5-3 in the same region, it still passes at 100% of the points.

This difference can be contributed to either a slight positional error during analysis, or starch or stain on a particular region, as explained previously in Figure 4-11.

The good match in the measured and calculated profiles and the high pass rate of gamma seen in Figures 5-3, 5-4, and 5-5 show that a good match of calculated and
measured dose profiles can be obtained on the anterior rectal wall. These repeat measurements also prove that the results can be successfully duplicated.

The objective of the treatment plan is to limit the dose to the rectum to 14-16 Gy, with the maximum dose occurring in the overlap region between the rectum and PTV because the PTV adjacent to the rectal volume may receive a minimum dose of 16 Gy.

The region that received the highest dose is visible at 3.92 cm along the profile with a dose of 11.95 Gy. Since the prescription will be delivered in 2 fractions, the rectal wall will receive double this dose, 23.90 Gy. This is substantially higher than the limit of 14-16 Gy to the rectum that was prescribed and hence will need further investigation before treatment can continue.

5.4 Conclusion

Successfully measuring the dose profile at the anterior rectal wall in a prostate boost high precision VMAT plan has proven that the method used is successful while in this pilot the phantom study detected shifts of 2mm with a dose difference of 1%.
6 TomoTherapy® Plan Measurements

6.1 Aim

The aim is to use the same method employed for VMAT delivery in chapter 5, in a prostate high precision boost treatment delivered with TomoTherapy®.

6.2 Materials and method

The TomoTherapy® Hi-Art II TPS v.4.2.2 uses a collapsed cone algorithm to calculate the dose to medium.

The TomoTherapy® plan was created by superimposing the same patient treatment plan outlined in chapter 5. This allowed for contours of volumes such as the PTV and clinical target volume (CTV), as well as organs and critical structures to be the same as the VMAT case. The set up described in Figure 7.1 was used.

The same patient data utilised in chapter 5 was set for a high precision prostate boost with TomoTherapy® was used and optimised for the CIRS phantom by utilising a 2.00 x 2.00 2.00 cm³ dose grid. Each slice was 2 mm thick for calculation.

The same plan parameters and treatment plan objectives were used as with VMAT, outlined in Section 5.2.
Without a dose control system to maintain a constant dose output within the limit of 2%, the output of the TomoTherapy® unit drops as a function of time.\textsuperscript{78,79} Since the output of the machine fluctuates more than 2% if the beam is on for more than 7 minutes, the fraction is split into 3 parts and is delivered in 3 passes so that each pass is less than 7 minutes. To achieve this result, the clinical plans are modified to include 6 fractions instead of 2.

The CIRS phantom and Rectafix® set up seen in Figure 4-2 were again utilised for these experiments. The phantom was aligned using the room lasers, the film was wrapped around the Rectafix® and the anterior section marked, the sleeve was then pushed over the Rectafix® and then inserted into the CIRS phantom. The Rectafix® was aligned using the room lasers, and then its position was verified using a pre-treatment megavoltage (MV) CT scan by the TomoTherapy® unit at approximately 3.5 MV\textsuperscript{80}. The fiducials can be seen and are used as a verification tool in the process.

Figure 6-1 TomoTherapy® plan view with isodose lines obtained from TomoTherapy® planning station.

The first two passes were measured using the film at the rectal wall interface, and then the set up was shifted 2mm in an anterior direction into the high dose region, and then another measurement was taken using film.

The film was then analysed using the protocol outlined in Section 2.8.
A line profile was extracted from the most anterior section, in the superior-inferior direction of the Rectafix® device by making use of the markings on the film placed prior to irradiation. The PV obtained was then converted to OD and then to dose, by making use of the calibration equation 3-2. The red channel calibration curve was utilised as the dose range most suited to the dose measured by the measurements.

A 5\textsuperscript{th} order median filter was then applied to each curve twice, using Matlab, to reduce any noise and small scratches and smooth the curves.

A line profile was then extracted using the TomoTherapy\textsuperscript{®} TPS at the anterior edge of the Rectafix\textsuperscript{®}, in a superior-inferior direction. A profile 2 mm anterior to the Rectafix\textsuperscript{®} was also extracted in the superior-anterior direction.

The measured and calculated profiles at the anterior edge of the Rectafix\textsuperscript{®} were then superimposed. The dose profiles measured and calculated 2mm anterior to the Rectafix\textsuperscript{®} were also superimposed. The measured dose profile of the first pass at the rectal wall and the 2mm anterior shift was also compared. The measured profiles and calculated profile doses were then calculated at 1mm increments to determine the dose of each profile at the same distance.

This information was then used to carry out a gamma analysis of each point using MATLAB; this analysis was carried out with the same gamma parameters used previously, 3%/3mm, 3%/1mm, 2%/1mm and 1%/1mm, where $\gamma < 1$ was accepted as a pass and $\gamma \geq 1$ was taken to be a fail.
6.3 Results and Discussion

The measured film results were compared to TPS data, as shown in Figure 6-2.

Figure 6-2 TomoTherapy® Film and TPS profiles.

The film results and TPS were compared by again utilising the gamma analysis. A further gamma analysis was carried out utilising acceptance criteria 3%/3mm, 3%/1mm, 2%/1mm and 1%/1mm, as shown in Figures 6-2, 6-3, 6-4, and 6-6 respectively.

The pass rate for the gamma analysis for 3%/3mm acceptance criteria are 100%, and this is shown in Figure 6-3.
Figure 6-3 3%/3mm gamma analysis of Figure 6-2 TomoTherapy® delivery Pass rate: 100%

The criteria were tightened again to 3%/1mm. Figure 6-4 shows that gamma analysis failed at ~6.1 cm along the profile which corresponds to a “bump” in Figure 6-2, most likely indicating damage or stain on the film at this location which altered the PV obtained. The gamma analysis also failed ~7.8 cm to 8 cm along the film profile.
The same pattern can be seen in the acceptance criteria 2%/1mm with more points failing, dropping the pass rate to 97.3%. The gamma analysis failed at ~6.1 cm along the profile and ~7.8 cm to 8 cm along the film profile. There is also a new point which failed at ~4.9 cm along the profile. In Figure 6-2 this section can be visually seen to correspond to another “bump” on the profile, which may indicate damage or stain on the film at this particular location.
Figure 6-5 2%/1mm gamma analysis of figure 6-2 TomoTherapy® delivery Pass rate: 97.3%

The pass rate here fell below the 95% acceptance level at 1%/1mm acceptance criteria, with added points at the start of the profile of ~3.2 cm, 3.6 cm to 3.9, 4cm, 4.9cm, 5.1 cm, 5.3 cm, 5.5 cm, 6.1 cm and 7.8 cm to 8 cm.
Figure 6-6 1%/1mm gamma analysis of figure 6-2 TomoTherapy® delivery Pass rate: 85.0%

The TomoTherapy® plan measurement was then repeated and the same gamma analysis carried out. The film measurement repeated against the calculated TPS profiles can be compared in Figure 6-7.

Figure 6-7 TomoTherapy® repeat film measurement against TPS profile.
Figure 6-8 3%/3mm gamma analysis of Figure 6-7 TomoTherapy® delivery Pass rate: 100%

Figure 6-9 shows that a 3%/1mm acceptance criteria produced a pass rate of 100%, but when compared to the measurement seen previously in Figure 6-4 with a pass rate of 98.5%, the repeat measurement is noticeably more accurate. In Figure 6-7, the same number of “bumps” on the film measurement is also not apparent, as seen in Figure 6-2; this may be due to an increased efficiency and skill in the use of film at this point, leading to less human error when handling the film.
Figure 6-9 3%/1mm gamma analysis of Figure 6-7 TomoTherapy® delivery Pass rate: 100%

The gamma analysis shown in Figure 6-9 is a 100% pass for 2%/1mm acceptance criteria, which indicates a better match than Figure 6-5 which has a pass rate of 97.3%; this may also be due to increased skill in the phantom set up and handling film while carrying out this experiment.
Figure 6-10 2%/1mm gamma analysis of Figure 6-7 TomoTherapy® delivery Pass rate: 100%

The 1%/1mm gamma analysis shown in Figure 6-10 has a pass rate of 91.00% with the majority of gamma points failing ~3cm along the profile. The measured profile deviates to a slightly lower dose than the TPS, possibly due to error when analysing the film, or damage and stain that may have affected the PV obtained in that section.
Figure 6-11 1%/1mm gamma analysis of Figure 6-7 TomoTherapy® delivery Pass rate: 91.0%

To compare the two TomoTherapy® measurements obtained, both the profiles were plotted together as shown in Figure 6-12.
A 2%/1mm gamma analysis was then carried out, as shown by Figure 6-12, and produced a pass rate of 99.8%

Figure 6-13 2%/1mm gamma analysis between the TomoTherapy® profile and the TomoTherapy® profile repeat. Pass rate: 99.8%
When the measured profiles are compared to each other, a miss match is visible at the end of the profiles ~7.9 cm along the profile.

Since this dose was delivered in one out of three passes for the single fraction, the dose delivered to the rectal wall will the six times that shown on the extracted profiles shown in Figure 6-12.

The objective of the treatment plan is to limit the dose to the rectum to 14-16 Gy, with the maximum dose occurring in the overlap region between the rectum and PTV because the PTV adjacent to the rectal volume may receive a minimum dose of 16 Gy.

The maximum dose delivered to any single point on the rectal wall will be 16.04 Gy, as indicated at the location 2.6 cm along the profile; this is within the dose objectives set for the treatment plan.

A measurement was obtained 2 mm anterior to the rectal wall and then compared to the TPS, as shown in Figure 6-14.

Figure 6-14 TomoTherapy® 2mm anterior shifted film and TPS profiles.
A gamma analysis was carried out with 3%/3mm acceptance criteria and it revealed a 100% gamma pass rate. This indicates that as long as the position of the film is known, the relevant profile can be extracted from the TPS and matched with the measurement obtained by utilising film.

![Gamma Analysis Graph](image)

Figure 6-15 3%/3mm gamma analysis of Figure 6-14. Pass rate: 100%.

Comparing the film dose measured at 2mm anterior shifted position to the TPS at the rectal wall, as shown in Figure 6-16, indicates that the initial build-up of dose matches, but the measured profile gives a larger dose to a larger area. This will probably increase rectal toxicity and may cause the complications discussed previously in the NTCP model.
Figure 6-16 TomoTherapy® measured profile at rectal wall against 2 mm anterior shifted measurement.

6.4 Conclusion

Successfully measuring the dose profile at the anterior rectal wall in a prostate boost high precision TomoTherapy™ plan has proven that the method is successful and in this pilot phantom study, 2mm shifts were detected with a dose difference of 1%.
7 Discussion

The measured profiles were only extracted from the anterior edge of the Rectafix® in the superior-inferior direction because this is the area of most interest in studying the dose received by the rectal wall, being the closest to the PTV and hence the area of rectal wall where most of the dose is deposited.

Due to the nature of the film, the edges near the border suggested not to be used for measurements due to damage by cutting, a dose map of the full rectum could not be obtained, but a large portion was easy to obtain.

That the film covers a wide area of the rectal wall opens up the possibility of measuring a dose at any point, profile, or plane covered by the film.

The method used to obtain the profiles in section 2.8 can be used to obtain multiple parallel points along the film and around the Rectafix® on the TPS; this to obtain the full 2D dose coverage of the rectal wall in line with the film.

The gamma analysis was for a 2D profile, while the plan delivered is for a 3D patient; this eliminates a spherical check of the DTA factor and limits it to the 2D plane instead; this also removes some of the power of the gamma analysis.

When the gamma acceptance criteria of 3%/3mm was used no points failed, which indicated that the chosen parameters could not detect any significant difference in the compared profiles.
As the acceptance criteria became tighter it became apparent that although the same measurements were repeated, the gamma analysis showed some difference between them. The most suitable criteria for a high precision boost treatment was 2%/1mm, and this is some of the tolerance suggested from the literature. All the films were above the minimum pass rate of 95%.

The 1%/1mm acceptance criteria produced an underwhelming pass rate. The pass rate for complex fields of 88% suggested by Basran et. al. was only reached on one of the two runs for each VMAT and TomoTherapy® deliveries. This level of precision is at the current limit of accuracy for this delivery.

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Table 7-1 Summary of gamma pass rates obtained

The dose delivered by VMAT will exceed the limit of the prescribed dose to the rectal wall, although this method successfully detected a 2 mm shift. This affords an opportunity to make necessary adjustments before treatment is continued and in turn avoids any unwanted rectal toxicity.

The TomoTherapy® plan was within the dose limit prescribed to the rectal wall, so in this case the treatment is safe and the second fraction can be delivered with confidence because it could detect a 2 mm shift.
8 Conclusion and Recommendation

We can now go back to answer some of the research questions set previously:

i. *Can EBT3 film be positioned on Rectafix® device such that it simulates a dose at the rectal prostate interface?*

It was found that positioning film around a Rectafix® device is a viable way of measuring the dose to the rectal wall in VMAT and TomoTherapy® high precision prostate boost treatments. Indeed it is evident that comparing the dose at the rectal wall obtained from TPS to the measured dose utilising film deployed on the Rectafix® device showed that this method successfully simulated the dose at the rectal wall interface.

ii. *Can EBT3 film be calibrated and used at high dose per fraction doses (typically 8Gy)?*

In this thesis film was successfully analysed and calibrated for the red channel for doses up to 2 Gy, and up to 14.84 Gy for the green channel, and measurements in a high dose setting of up to 11.95 Gy, with high dose gradients were carried out with a high degree of accuracy.

iii. *What is the accuracy and reproducibility of the EBT3 film measurements?*

The data obtained was analysed by utilising a gamma analysis with suggested acceptance criteria of 2%/1mm with a minimum pass rate of 95%; all the
measurements met this criterion. The measured film data was then used to successfully and accurately predict dose in the high dose, high dose gradient setting in which it was used.

Film measurement is not reproducible because each scan of the film, each scanner temperature, as well as the film variation inter sheet and inter batch render film are not a reproducible dose measurement modality. This has also been discussed by Huet et al. 69

iv. How do the pre in-vivo EBT3 film measurements compare with radiotherapy treatment planning dose estimates for simple fields and for volumetric modulated arc (VMAT) dose delivery?

Pre-in vivo measurements utilising simple fields and modulated arc beams have met the data extracted from TPS.

VMAT delivery measurements were observed to be a good match with the TPS, as were the VMAT measurements which can be predicted to an accuracy of 2%/1mm acceptance criteria with pass rates of 98.76% and 98.23%.

v. How do the in phantom EBT3 measurements compare with radiotherapy treatment planning dose calculations for TomoTherapy® delivery?

TomoTherapy® delivery measurements have been successful in the setting they were analysed in when compared to the TPS, indeed they were accurate to 2%/1mm acceptance criteria with a pass rate of 97.26% and 100%.

The method used in this thesis is a viable quality assurance method that can be used in-vivo during high precision prostate boost treatment, as long as a Rectafix® or other spacer devices are utilised.
9 Future Work

For future studies the Rectafix® will need to be modified to accommodate film within itself so that it can be used in-vivo during patient treatment. The proposed model will have the following structure:

Figure 9-1 Modified Rectafix® device model

The entire enclosed casing will have the same dimensions as a Rectafix® device.

As seen in the study, handling the film and keeping it free from stain or damage is crucial for obtaining good results. The screw in the top cover that encases the film will keep it in a known and fixed position within the Rectafix® device.

Fiducial markers are a great tool for imaging the Rectafix® within a patient pre-treatment, and therefore should be included in the design. This is discussed further in Appendix A.

With the Rectafix® in position, the film will be able to measure the dose received by the rectal wall retrospectively, and once the results are analysed ~24hrs post
irradiation, the dose can be measured and the plan can be modified if there is a risk of the rectal wall being over-irradiated due to the current plan set up.

Conformal high precision boost treatments at close proximity to critical structures require great precision because small errors can have a huge impact, as has been shown in this thesis. This has the possibility of improving patient outcomes and increasing confidence in the plan being delivered. The collected data can also be used to develop a protocol and set limits according to the patient outcomes observed with the method employed.

One drawback to this method will be an increase in department workload and it will take some time to complete; therefore a clinical trial is needed to justify the routine use of this method during prostate boost Radiotherapy.
APPENDIX A - FIDUCIAL IMAGES

The fiducials markers were scanned using CT imaging inside the CIRS phantom to review the clarity of the fiducial markers and obtain a CT image of the CIRS phantom and Rectafix® set up to import onto the TPS and overlay patient plans, as required.

Figure A-2 Coronal, lateral and sagittal view of CT image of fiducials placed on the anterior edge of the Rectafix®
As a side experiment, it was expected that future studies may involve MRI so the fiducial markers were also tested in MRI. A Rectafix® device with the attached fiducials was placed inside a cylindrical body of water to provide the required hydrogen molecules needed to image the Rectafix® and fiducial markers.

Two scans were taken, one using the ultrashort echo-time (UTE) value of 0.07 ms and another in a normal sequence MRI with a TE value of 4.6 ms. UTE MRI allows for components to be imaged where a normal sequence MRI may show the artefacts, or not show them at all. 81
Figure A-4 Image on the left shows MRI image taken with UTE, image on right shows MRI image taken using normal TE.
Here, the fiducials markers appear as a hole caused by an artefact in the phantom next to the fiducial markers, where in fact there is none because the fiducials themselves are not imaged.

This apparent hole is much more prominent in the MR image taken with UTE, where it appears to be visible but with more precision, and with less artefacts and better quality images. This is recommended as the modality of choice while using these markers.
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