Amit Ben Antony Bennan

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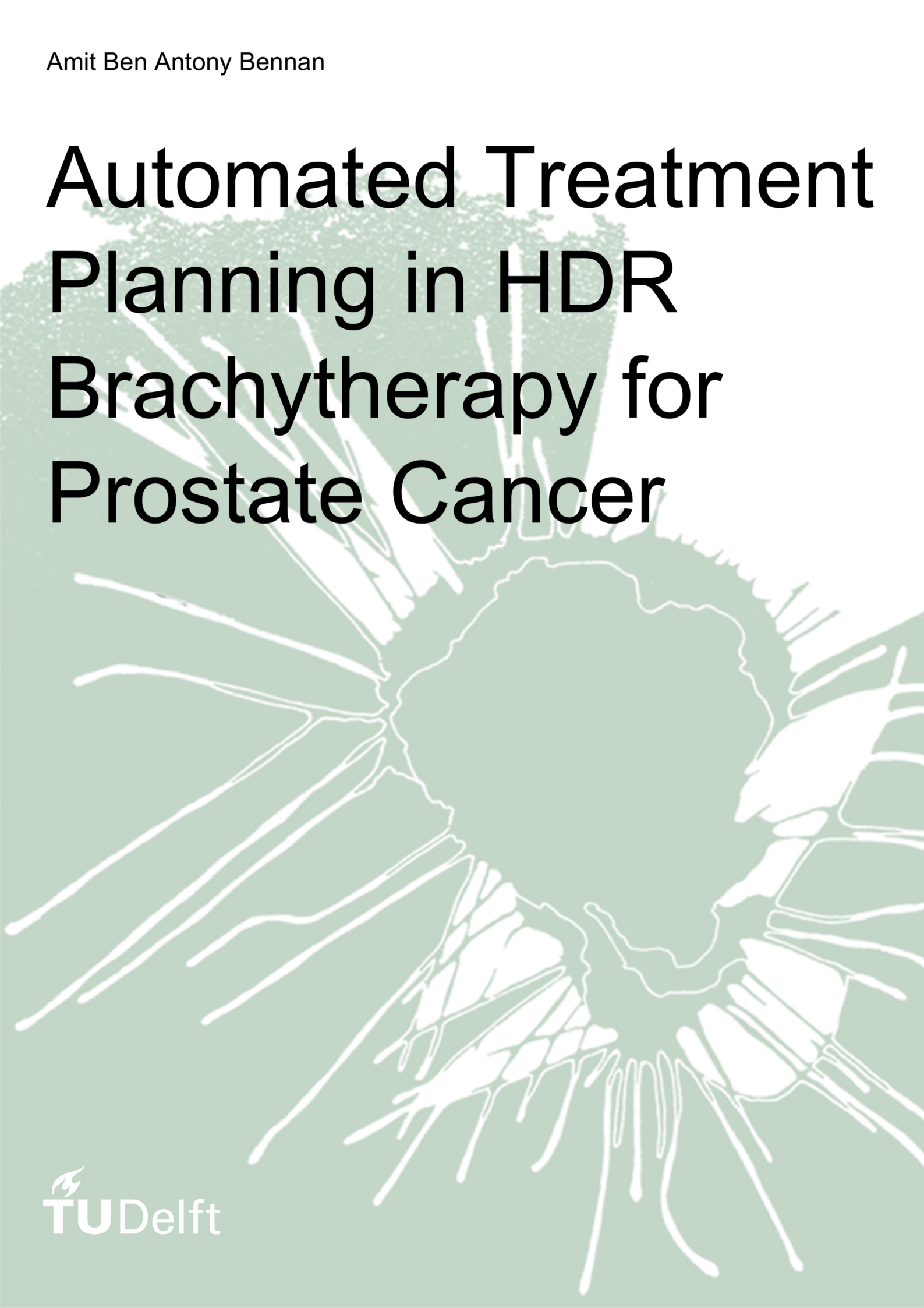

TU Delft

Automated Treatment Planning in HDR Brachytherapy for Prostate Cancer

By

Amit Ben Antony Bennan

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Supervisor:	Prof. Dr. ir. D.R. Schaart, TU Delft
Thesis committee:	Prof. Dr. B.J.M. Heijman, Erasmus MC
	Dr. ir. S. Breedveld, Erasmus MC
	Dr. ir. I.K.K. Kolkman-Deurloo, Erasmus MC
	Dr. ir. D. Lathouwers, TU Delft
	Dr. ir, M.C. Goorden, TU Delft

TU Delft

ABSTRACT

Introduction: High Dose Rate (HDR) Brachytherapy is a radiotherapy modality that involves temporarily introducing a highly radioactive source into the target volume with the use of an applicator. With respect to HDR brachytherapy for prostate cancer, an ^{192}Iridium source is driven into the target volume through catheters implanted into the prostate. The dose delivered to a point in the prostate depends on the time the source dwells at a given position. Treatment planning for brachytherapy involve the optimization of dwell times and dwell positions. The aim of the treatment plan is to deliver the prescribed dose to the target volume, the prostate, while minimizing the dose to the organs at risk (OAR), namely the urethra, bladder and rectum. In current clinical practice, the process of treatment planning involves the manual manipulation of the parameters of an optimizer until the desired dose distribution is achieved. This implies that the plan quality depends on the experience of the planner, and there is variation in plan quality between planners. The aim of this project was to develop an automated treatment planning system that would able to generate clinically acceptable plans with minimal human intervention. The brachytherapy treatment planning module is named B-iCycle and may be integrated in the future with the treatment planning software suite, called Erasmus-iCycle, developed at the Erasmus MC.

Materials and methods: At the core of the treatment planning system (TPS) is a precise and fast dose engine that is able to simulate the dose to be delivered. In this project, we employ the TG-43 dose calculation formalism as it is the most widely implemented method in dose engines for brachytherapy treatment planning systems. The dose engine is then verified against the dose engine of the clinical treatment planning system. B-iCycle uses the 2-phase ϵ-constraint (2pϵc) algorithm to optimize the dwell times and positions. The 2pϵc algorithm requires a 'wish-list', which encapsulates the treatment protocol as goals and constraints for each critical structure. For this project three treatment protocols were chosen, four fractions of 9.5 Gy, single fraction of 19 Gy and single fraction of 20 Gy, and wish-lists were generated for each protocol. Three patient groups with different catheter geometries were selected. Treatment plans were generated for each patient and compared against the plans that were generated, for the same patients, in the clinic. The treatment plans that were generated in B-iCycle were then exported to the clinical treatment planning system (Oncentra from Elekta) to obtain the dose characteristics. The plans were compared based on the dose characteristics and the Conformity Index (COIN). The plans were also verified by a radiation oncologist.

Results: The TG-43 dose engine was successfully verified against the clinical dose engine. The Gamma analysis showed that only 0.68% of the voxels failed the gamma analysis and these voxels were located within the catheters therefore they can be ignored as no tissue lies at these positions. With regard to plans that were generated, the physician confirmed that the clinically acceptable B-iCycle plans are very comparable to the clinical plans. The B-iCycle plans are better at minimizing the dose to the urethra. When comparing B-iCycle plans to the clinical plans using COIN, B-iCycle was found to be better than the clinical procedure. B-iCycle can generate a treatment plan in approximately 10 seconds, which is much faster than the clinical procedure, which averages at 10 minutes. It is also able to avoid the issue of treatment planner variability and is able to generate consistent, high quality treatment plans.

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Contents

LIST OF ABBREVIATIONS AND SYMBOLS

IMRT	Intensity Modulated Radiotherapy
TPS	Treatment Planning System
EBRT	External Beam Radiotherapy
PSA	Prostate Specific Antigen
TRUS	Transrectal Ultrasound
MRI	Magnetic Resonance Imaging
LDR	Low Dost Rate
HDR	High Dose Rate
CPE	Charged particle equilibrium
μ_{tr}	Energy transfer coefficient
E	Energy of the photon
$\vec{r}$	Position vector
$\Phi(E,\vec{r},t)$	Energy distribution of fluence rate
PDF	Probability density functions
LBTE	Linear Boltzmann Transport Equation
GBBS	Grid Based Boltzmann equation Solvers
$\Psi(\vec{r},E,\hat{\Omega})$	Angular flux
$\sigma_t(\vec{r},E)$	Macroscopic cross section or probability of interaction
$Q^{scat}(\vec{r},E,\hat{\Omega})$	Scattering source
$Q^{ex}(\vec{r},E,\hat{\Omega})$	Brachytherapy source (extraneous source)
$\sigma_s(\vec{r},E'\rightarrow E,\hat{\Omega}.\hat{\Omega}')$	Macroscopic differential scatter cross-section
DOM	Discrete Ordinates method
OAR	Organs at Risk
AAPM	American Association of Physicists in Medicine
MCO	Multicriteria optimization
IPSA	Inverse Planning Simulated Annealing
HIPO	Hybrid Inverse Planning Optimizer
$\dot{D}(r,\theta)$	Dose rate at any point in the system
RAKR	Reference Air Kerma Rate
S_K	Air kerma strength in vacuo

Λ	Dose rate constant in water
MC	Monte Carlo
$G_L(r,\theta)$	Geometry function
β	Angle subtended by the point (r, θ) to the two ends of the source
L	Length of the source in cm
$g_L(r)$	Radial dose function
F (r, θ)	2D anisotropy function
ESTRO	European Society for Radiotherapy and Oncology
DTA	Distance to agreement
x_m	Spatial location of reference point for Gamma analysis
x_c	Relative spatial location of the calculated dose distribution
$D_m (x_m)$	Reference dose
$D_c (x_c)$	Calculated dose
Δd_M	DTA criterion
ΔD_M	Dose difference criterion
$\gamma(x_m)$	Gamma index
2pεc	2 phase ϵ-constraint
LTCP	Logarithmic Tumour Complication Probability
GU	Genitourinary
GI	Gastrointestinal
COIN	Conformity index
GVH	Gamma Volume Histogram
DVH	Dose volume histograms
D_{max}	Maximum dose to the urethra

1. Introduction

Prostate cancer is the fourth most prevalent type of cancer in the world according to the World Cancer Research Fund. In radiotherapy, the various modalities of treatment offered include Intensity Modulated Radiotherapy (IMRT), three-dimensional Conformal Radiotherapy, proton therapy and brachytherapy. In this project, we delve into the automation of the treatment planning process in brachytherapy, concentrating on prostate cancer.

High Dose Rate Brachytherapy is a form of internal radiation therapy where a high activity source (^{192}Ir) is introduced into the tumour with the help of catheters. Brachytherapy shows high tumour control and lower toxicity rates compared to other treatment modalities as it is possible to deliver higher doses with better precision and conformity to the target.

At the Erasmus MC, the treatment planning procedure starts with the acquisition of a post-implant CT, where the target volume is identified and the implanted catheters are segmented. The treatment planning is done on the Oncentra Treatment Planning System (TPS) from Elekta, which offers tools for each step of the treatment planning stage. Once the catheters have been segmented and the feasible dwell positions are identified. The time spent at each dwell position (dwell time) is optimized using a semi-automated optimizer. The Oncentra system offers two optimizers, the Inverse Planning Simulated Annealing (IPSA) optimizer and the Hybrid Inverse Planning and Optimization (HIPO) tool. The technician manually tweaks the parameters of the optimizer iteratively, until the desired dose distribution is achieved. Therefore, the quality of the plan would depend on the experience of the planner and the plan quality would vary between planners. This points to a need for an automated treatment planning system that would consistently ensure the best plan quality for all patients.

Erasmus-iCycle is a treatment planning software suite, developed at the Erasmus MC, for various radiotherapy modalities such as External Beam Radiotherapy (EBRT), Cyberknife etc. In this project, a module will be added to Erasmus-iCycle to extend its reach to treatment planning for brachytherapy.

2. Project Overview

2.1. Prostate Cancer Epidemiology

The prostate is an exocrine gland of the male reproductive system that is located below the bladder and in front of the rectum. It is almost continuous with the bladder and the urethra runs through the prostate on the ventral part of the prostate.

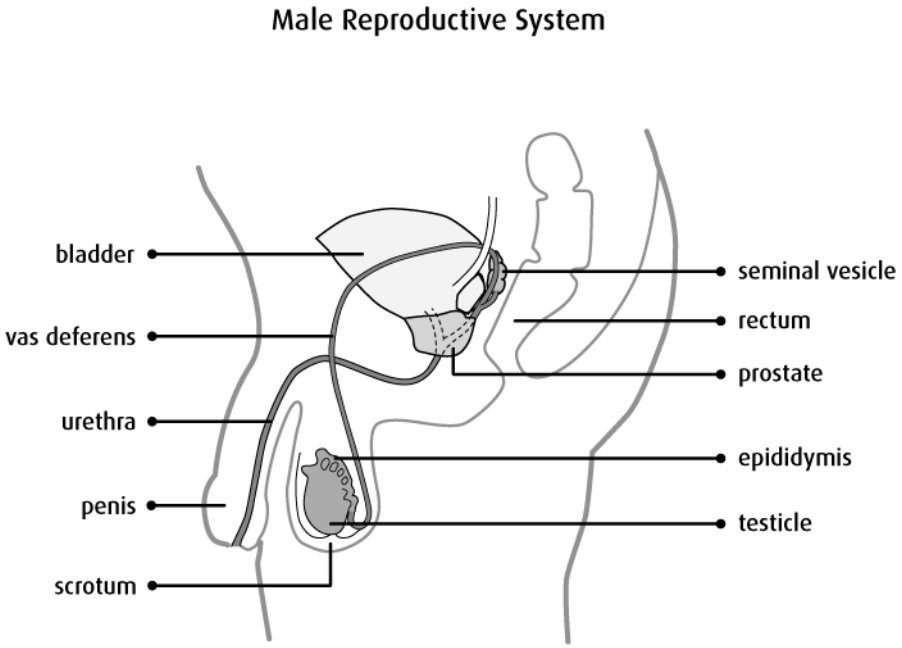

FIGURE 1. MALE REPRODUCTIVE SYSTEM

Estimates of global cancer incidences show that prostate cancer has become the third most prevalent cancer in men with half a million new cases each year. It constitutes almost 10% of all cancers in men. Showing higher incidences in countries with a higher aging population, and accounts for almost 15% of cancers in men in developed countries and 4% in developing countries [2]. The incidence rates have been on the rise with many populations that have age distributions shifting to the elderly. This rise in incidence has also been attributed to the advent of newer faster screening procedures. There are a few risk factors that have been identified for example, age, family history, race and other lifestyle factors [3]. The progression of prostate cancer may be unpredictable due to a larger proportion of slowly developing smaller tumours that do not give rise to symptoms and stay as latent tumours [4]. The relationship between zones of origin and probability of cancer was estimated to be 68% in the peripheral zone (outer layer of the prostate), 24% in the transition region and 8% in the central region of the prostate [5].

The initial clinical screening is done by a digital rectal examination and the measurement of Prostate Specific Antigen (PSA). The use of the PSA test has led to an increase in the

proportion of patients who present with an early stage of the disease. These initial tests may underestimate the local stage of the cancer in 40-60% of cases [6].

2.2. Screening and Diagnosis

Most prostate cancer cases are identified in the screening stage with a Digital Rectal Exam (DRE) or a Prostate Specific Antigen (PSA) blood test. These screening procedures generally identify symptoms presented by advanced cancers. The PSA test gives an indication of the chance of having prostate cancer. Imaging techniques like Transrectal Ultrasound (TRUS) and Magnetic Resonance Imaging (MRI) are also used in the staging and screening of Prostate Cancer. But ultrasound guided biopsy under local anaesthesia is considered as the gold standard method for diagnosis (Gleason Score) [7]. This system scores prostate cancer based on the similarity of the cancer to the normal prostate tissue. Higher the Gleason score, the more likely it is that the cancer will grow and spread. The treatment choices may vary from active surveillance to radical radiotherapy to prostatectomy based on this diagnosis.

2.3. Introduction to Brachytherapy

Brachytherapy is a form of radiotherapy in which a radioactive source is brought into close proximity to the target site. The dose delivered depends on the extent of time for which the source is held in that position. The first clinical use is recorded by Danlos and Bloch (1901) in Paris [8]. Initially the only radionuclide that was used for brachytherapy was Radium-226. After the discovery of artificial radioactivity, the use of newer radionuclides like ^{60}Co, ^{137}Cs, ^{182}Ta and ^{198}Au was attempted. Currently ^{192}Ir is the most widely used source in brachytherapy. Another important milestone in the development of brachytherapy was the introduction of the remote afterloading systems in 1962. These machines use cables attached to the radioactive seeds, to control the movement of the sources through surgically implanted applicators. This reduced the exposure of health care personnel to the radioactive sources. Later advances in remote after loader technologies allows precise step control of the sources and the modulation of the dwell times within the applicator, allowing users to control the dose distribution. This improvement in safety and control stimulated the growth of High Dose Rate (HDR) treatment schedules in the field of brachytherapy.

Due to the inherent characteristics of brachytherapy and the advances in the supporting fields, it has a few advantages over other forms of radiotherapy [8].

Firstly, as the sources are in the tissue and generally in the target volume, brachytherapy is unaffected by the effects of movement of the target volume. Therefore, it has the least in-patient variation during the treatment.

Secondly, brachytherapy has the ability to deliver a relatively high dose to the target volume. The dose falloff follows the inverse square law and ensures that the dose to surrounding organs at risk and normal tissues is very low. Coupled with dwell time modulation, it is possible to deliver highly conformal dose distributions.

These characteristics make brachytherapy an important treatment modality for a wide range of sites like the head and neck region, breast, prostate etc.

2.4. Low Dose Rate (LDR) versus High Dose Rate (HDR) Brachytherapy

Brachytherapy is comprised of two treatment modalities Low Dost Rate (LDR) and High Dose Rate (HDR) brachytherapy. LDR brachytherapy involves permanent implantation of ^{125}I or ^{103}Pd seeds into the target. The dose rates vary between 0.4 to 2 Gy h^{-1} [9]. It has the advantage of being a onetime procedure and used to be a common radiotherapy procedure. A drawback being that it may have a limited capability for tumour coverage due to anatomic restrictions and that the patient is radioactive for some time after the procedure.

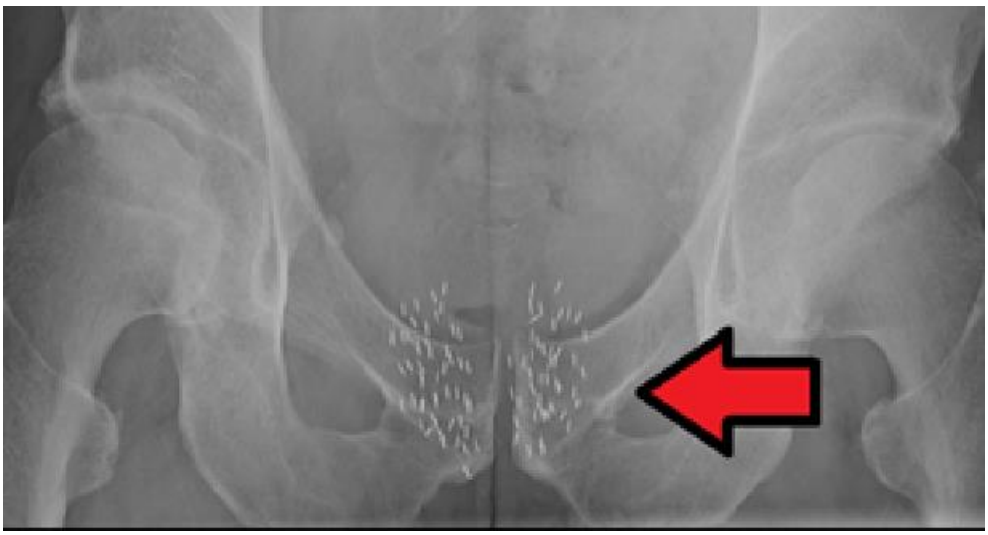

FIGURE 2 LDR BRACHYTHERAPY SEEDS USED TO TREAT PROSTATE CANCER. ARROW MARKS BEADS. (COURTESY: JAMES HEILMAN, MD, CC BY-SA 4.0)

HDR brachytherapy uses ^{192}Ir sources with dose rates greater than 12 Gyh^{-1}. It is an invasive procedure where catheters are implanted into the target and the radioactive sources are passed through the catheters. One possible source of error for HDR brachytherapy may be inter-fraction catheter displacement [10]. HDR brachytherapy allows for greater control of the post implant dose distribution with the manipulation of dwell times and dwell positions.

Although LDR and HDR brachytherapy have comparable biochemical control, HDR brachytherapy presents decreased rates of genitourinary toxicity and gastrointestinal toxicity compared to LDR [11]. Radiobiological models suggest that dose escalation treatment schemes may increase biologically effective doses and hence better outcomes. If the prostate does have a higher sensitivity to dose fractionation (low α/β ratio) then this would point to greater advantage of HDR brachytherapy. HDR also reduces the cost of treatment as the same radioactive sources can be used across patients.

2.5. Radionuclides in Brachytherapy

In brachytherapy, it is favourable to have high energy photons in the spectrum as this allows for a high dose at the central part of the tumour but also a relatively high dose to regions a few centimetres away. The sources must satisfy a few criteria to be used as a source for brachytherapy. The soft particle radiation (β^- (1.46 Mev) for ^{192}Ir) generated must be either absent or absorbable in the thin casing materials like stainless steel. The radionuclide should have a sufficiently high half-life, so that it logistically feasible to use one source for multiple procedures. No toxic gases must be produced as decay products. The radionuclide must have a high specific activity such that it is possible to produce sources that are small enough with the required dose rate. The ELEKTA Flexitron machine used at Erasmus MC uses a single cylindrical ^{192}Ir source of diameter 0.5 mm and length 3.5 mm, with activity in the range of 370 GBq (10 Ci). The radionuclide must be used in state that is non-soluble and not biologically toxic in case of leakage of the material and must maintain physical integrity, therefore not in a powder or dust form. Practically, the radionuclide must be pliable so as to be shaped into sources of different shapes and sizes, and the source must be able to withstand the common sterilization techniques.

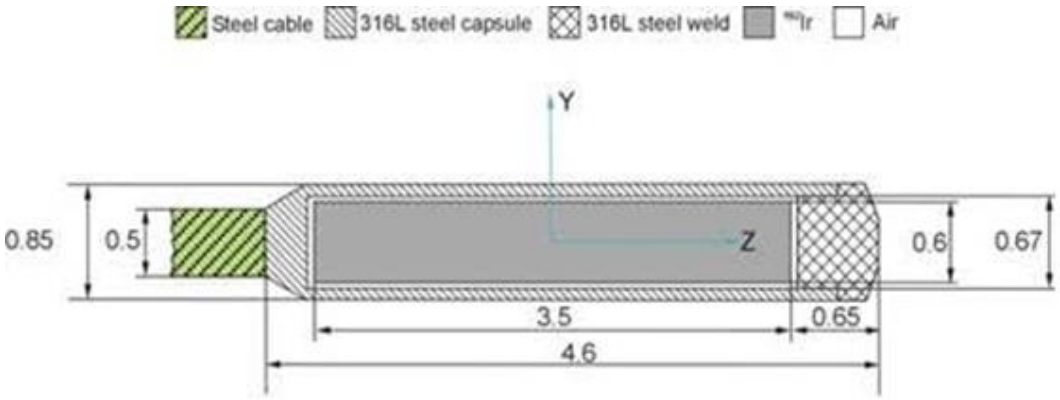

FIGURE 3 NUCLETRON HDR IR-192 MODEL 'FLEXISOURCE' [11]

2.6. Catheters and Implantation procedure

The sources are driven into the patient by the remote after loaders through catheters that have been implanted into the prostate. The patients are implanted with roughly 15 to 20 catheters depending on the size of the prostate. Each catheter is inserted through the skin in the perineum (the area between the base of the scrotum and the anus) with the help of continuous trans-rectal ultrasound (TRUS). At Erasmus MC, the catheters are placed using the template shown in Figure 4.

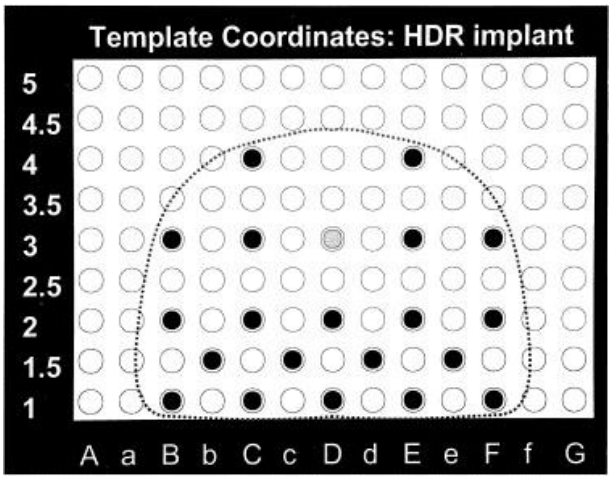

FIGURE 4 TEMPLATE FOR PROSTATE IMPLANTATION (COURTESY: MATE ET AL, 1998)

The plastic template is sutured to the perineum and used as a guide to implant the catheters and to hold the catheters in place during the procedure. Once the positions of the catheters have been confirmed a planning CT is taken, as seen in Figure 5. The number and size of the catheters has, over the years, reduced, to lessen the trauma to the patient. Catheters of diameter 2 mm are currently used (6 Fr). The downside to using thinner flexible catheters is the tendency of catheters to bend and deflect due to the anatomy of the patient. This results in a suboptimal catheter placement which, in turn, affects the quality of the dose distribution. The quality of treatment for brachytherapy is heavily dependent on the catheter geometry. Therefore, we must accept the idea that it may not be possible to obtain the desired dose distribution without good catheter placement.

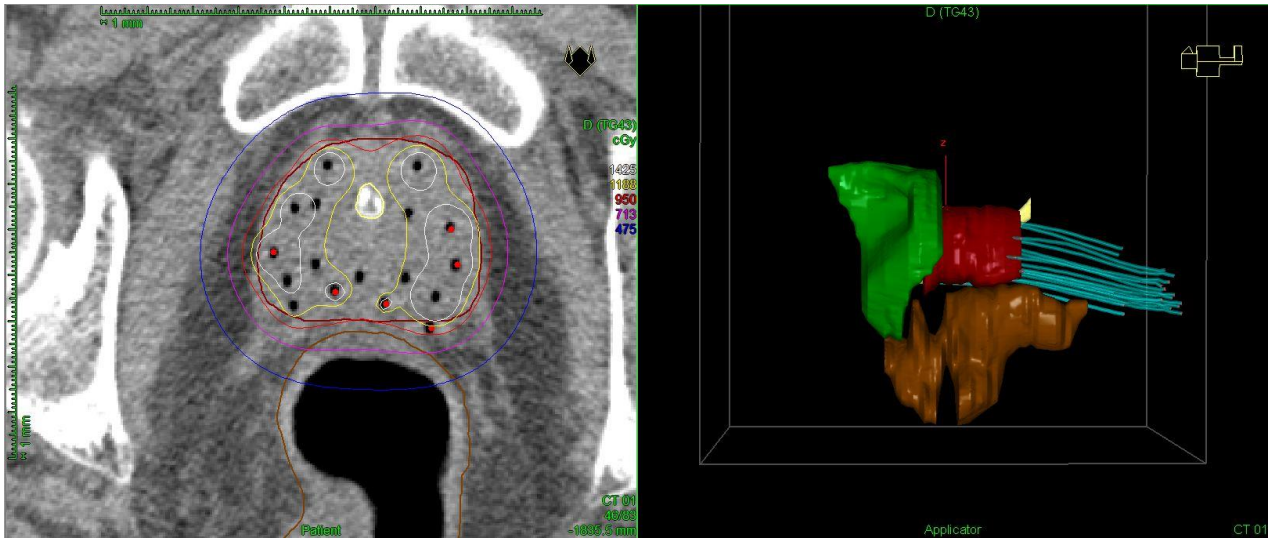

FIGURE 5 LEFT: AXIAL VIEW ON THE CT OF THE PROSTATE SHOWING THE DELINEATED PROSTATE (THICK RED LINE), URETHRA (THICK YELLOW LINE). THE BLACK SPOTS SEEN WITHIN THE PROSTATE ARE THE IMPLANTED CATHETERS. RIGHT: RECONSTRUCTION OF THE IMPLANTED PROSTATE AND THE OAR

2.7. Treatment Planning

2.7.1. The Basics of computational brachytherapy dosimetry

Computational dosimetry is one of the core components of any treatment planning system. It is the use of computational techniques to recreate the dose distribution around a brachytherapy source. Given the physical properties of the source the dose distribution can be estimated in a homogenous water geometry. Focussing on brachytherapy there are a few assumptions to be considered first. Majority of the brachytherapy sources are assumed to be low energy photon emitters, and due to this the range for the generation of secondary electrons is considered negligible. Another assumption is that there exists a charged particle equilibrium (CPE) at every point in the water geometry. The radiative energy loss from the secondary electrons can be considered to be negligible in the energy range of brachytherapy in water, energy transferred (energy transfer coefficient μ_{tr}) can be assumed to equal to the energy absorbed (energy absorption coefficient μ_{en}).

$$\acute{D}(\vec{r}) \equiv \acute{K}(\vec{r}) = \int \Phi(E,\vec{r},t)E\left[\frac{\mu_{en}(E)}{\rho}\right]dE \qquad (1)$$

Where, E is the energy of the photon, $\vec{r}$ is the position of the point being considered and t is the time of exposure. The $\Phi(E,\vec{r},t)$ represents the energy distribution of fluence rate in $MeVcm^{-2}s^{-1}$. In knowing the fluence rate at every point in the water geometry we know the dose rate distribution.

The above given assumption ignores several factors. For instance, the spatial distribution of activity inside the source, the scatter of radiation within the source and its shell, the attenuation of photons within the source and the photon attenuation in the water medium around the source. Equation 1, can also be given as

$$\acute{D}(r) = \frac{1}{4\pi r^2}AE\left[\frac{\mu_{en}(E)}{\rho}\right]_{water} \qquad (2)$$

Where A is the source activity, and $\acute{D}(r)$ is the dose rate to a small volume of water at distance r from the source. However, activity is not an appropriate quantity to define the source strength. The Air-kerma strength, S_k, is a much more practical quantity, is defined a

$$S_k = AE\left[\frac{\mu_{en}(E)}{\rho}\right]_{air} \qquad (3)$$

Also, to be taken into consideration, is the attenuation of the photon fluence in water. Therefore, the dose is defined as

$$\acute{D}(r) = \frac{1}{r^2}S_k\left[\frac{\mu_{en}(E)}{\rho}\right]_{air}^{water} e^{-\mu(E)r} \qquad (4)$$

The scattered photon fluence build up seen due to the interaction of photons with water is not analytically calculated as it adds much more complexity to the problem, because of the dispersion of photon tracks and multiple scattering. Although the dose rate can be considered to be a stochastic quantity, due to the probabilistic nature of the interactions, its expected value is given as Equation 4.

With brachytherapy sources, we can assume them to be linear sources and correction for the distribution of radioactivity in the source can be taken into account using a geometric factor.

The question of computing dose for brachy therapy can be approached from three directions: firstly, semi empirical methods, which brings together simpler dose calculation concepts with empirical data. Secondly, stochastic methods like Monte Carlo simulations that simulate the tracks of the radiation. Finally, deterministic methods (solving the linear Boltzmann equation).

2.7.1.1. STOCHASTIC DOSE CALCULATION

The Monte Carlo simulation is a stochastic method of dose calculation that depends on random sampling to produce observations. The statistical study of these observations gives an “empirical” dose calculation that is based on the central limit theorem.

The system is modelled as a series of probability density functions (PDF), where events are sampled randomly from these PDFs, and a tally of these events gives the dose, inferential statistics. For a random variable with a known probability distribution, the arithmetic mean of sufficient number of randomly sampled values will estimate the “unknown central limit”. The precision will depend on the sample size and the variance.

For brachytherapy, for a fluence rate that is known for all points in space, possible trajectories of the photons are randomly sampled. The challenge being, that it is not possible to sample every possible trajectory and therefore the solution is to create a Markov chain process. A core idea of the Monte Carlo simulation is the random traversal of the Markov chain. This requires a method to randomly sample events from the probability distributions [12].

To briefly illustrate this concept, consider a mono-energetic photon source in a water phantom. The emission is spherically isotropic and the probability for emission in a solid angle Ω can be given as dΩ/4π. After randomly selecting the direction of the emission, a site for the first interaction must be chosen randomly. The type of interaction is decided using a discrete random variable. Assume that the event is a scattering event, the new energy and direction must be randomly sampled. After which, the next interaction site and type would be randomly sampled, so on and so forth, until the photon is completely absorbed or it escapes the defined space. The types of interactions considered for brachytherapy are: photo-electric effect, coherent and incoherent scattering and characteristic X-ray production. Other input that would be required includes the interactions cross sections, linear attenuation coefficients and incoherent scattering factors.

The Monte Carlo simulations are considered to be the gold standard for dose calculations. Although such calculations are analytically not as challenging as deterministic methods of dose calculations, it requires many parameters to be defined to accurately describe interactions, and it is computationally demanding to simulate so many experiments.

2.7.1.2. DETERMINISTIC DOSE CALCULATION METHODS

One of the methods of computational dosimetry is the explicit dose calculation by solving the differential Linear Boltzmann Transport Equation (LBTE). The deterministic methods calculate the average particle’s behaviour. The LBTE is too complex to be solved using any analytical method, therefore it is solved by limiting the system to a geometrically simpler space by discretizing spatial, angular and energy variables. Such methods are called Grid Based Boltzmann equation Solvers (GBBS).

GBBS solves the 3D LBTE for radiation transport. In brachytherapy, this is given by,

$$\hat{\Omega}.\vec{\Psi}(\vec{r},E,\hat{\Omega}) + \sigma_t(\vec{r},E)\Psi(\vec{r},E,\hat{\Omega}) = Q^{scat}(\vec{r},E,\hat{\Omega}) + Q^{ex}(\vec{r},E,\hat{\Omega}), \vec{r}\epsilon V \quad (5)$$

$$\Psi(\vec{r},E,\hat{\Omega}) = 0, \vec{r}\epsilon\delta V, \hat{\Omega}.\vec{n} < 0 \quad (6)$$

For volume V with surface δV, here $\Psi(\vec{r}, E, \hat{\Omega})$ is the angular flux at position $\vec{r}$, with Energy E, direction $\hat{\Omega}$ and $\vec{n}$ is the normal vector to the surface δV. Here, $\sigma_t(\vec{r}, E)$ is the macroscopic cross section or probability of interaction. The first term on the left-hand side of equation 5 is the streaming operator that represents the flux. The second term on the left-hand side is known as the collision operator. The right-hand side describes the source terms, describing the scattering source, $Q^{scat}(\vec{r}, E, \hat{\Omega})$ and the brachytherapy source (extraneous source), $Q^{ex}(\vec{r}, E, \hat{\Omega})$. The scattering source is described as

$$\mathrm{Q^{scat}}(\vec{\mathrm{r}}, \mathrm{E}, \widehat{\Omega}) = \int_0^{\infty} \mathrm{dE'} \int_0^{4\pi} \sigma_{\mathrm{s}}(\vec{\mathrm{r}}, \mathrm{E'} \rightarrow \mathrm{E}, \widehat{\Omega}.\widehat{\Omega}')\Psi(\vec{\mathrm{r}}, \mathrm{E'}, \widehat{\Omega}')\mathrm{d}\widehat{\Omega}' \qquad (7)$$

Where $\sigma_s(\vec{r}, E' \rightarrow E, \hat{\Omega}.\hat{\Omega}')$ is the macroscopic differential scatter cross-section.

Steps in energy and angular discretization are then taken to make the problem computationally manageable. By evaluating the scattering source integral in a finite number of directions it is able to resolve the issues of anisotropic scattering. This is generally called the Discrete Ordinates method (DOM). For discretization of energies, the range from the minimum energy of photons to the maximum energy of photons emitted by the source is divided into groups, and an LBTE is constructed for each energy group in each direction. Space is also discretized into volume elements. Such deterministic methods are non-stochastic; therefore, the only possible errors are systematic errors in the setup of the calculation. It provides a solution for the entire space.

2.7.1.3. TG-43 FORMALISM

The TG-43 formalism is the international standard for brachytherapy dose computations. It was first presented by the American Association of Physicists in Medicine (AAPM) Task Group 43 in 1995 [13]. It is based on dose rate at a reference point in water with respect to the actual source geometry. It then corrects for attenuation in water with a radial dose function and an anisotropy function. The TG-43 formalism was created with the aim of accuracy and consistency without needless complication and specification of various terms that are required for the other models. The initial draft of TG-43 was updated in 2004 [1], which will be presented in detail in section 3.6.1. We have chosen to use the TG-43 as the dose engine for this project as it is the most widely used dose calculation method used for TPS's in brachytherapy.

2.7.2. *iCYCLE* MULTICRITERIA OPTIMIZATION

iCycle is a multicriteria optimization (MCO) algorithm that was developed at the Erasmus MC, Rotterdam. It was developed for optimizing beam intensity profiles and beam angles for IMRT. As will be in section 3.3.3, treatment goals are defined as objectives that must be optimized subject to constraints that must never be violated. Typically, the objective is maximal coverage of the target volume with the prescribed dose while managing the dose to the Organs at Risk (OAR) within certain limits. The method used by iCycle is called the 2-phase ϵ-constraint (2pϵc) algorithm [14], that was repurposed for optimizing the dwell times for brachytherapy. An overview of the algorithm is presented in section 3.3.

2.8. Remote After Loaders

Remote after loaders are devices that allow the operators to remotely introduce the source into the needles or applicators hence minimize the dose to the medical staff. The HDR source is capable of delivering around 700 cGy per minute at 1 cm. During treatment, this source is moved from a lead lined safe into the needle applicator in the patient and then back into the safe. At the Erasmus MC, the Flexitron® treatment delivery system from ELEKTA is in use. It has 40 channels, i.e. possible catheter connections. The indexer is the part of the remote after loader that diverts the source cable to the corresponding channel (exit port). And the exit port is connected to the applicator (catheter) using transfer tubes that smoothen the transition.

The source driver controls the speed of the source motion within the catheter. The speed of transfer of the source, especially from the safe to the starting dwell position would affect the source transfer dose to the healthy tissue, which may be significant for high activity sources. The travel speeds vary between 300 and 600 mm/s for different machines. Before the actual source is deployed into the catheter, a dummy source is driven into the catheters to verify the catheter connections and to ensure that there are no blockages in the catheters.

As remote after loaders are complex mechanical systems with highly radioactive sources, they are equipped with a number of safety features to prevent accidents. Emergency switches allow the operator to quickly stop the treatment and retract the source to the safe in case of an emergency. Emergency cranks are also used to retract the source in case of failure of the motor and the emergency motor.

2.9. Current workflow for Prostate Brachytherapy at Erasmus MC

The current workflow for brachytherapy starts with a CT and/or MRI to study the anatomical structure of the patient and to plan the implantation procedure. The implantation procedure itself is done by the physician with the assistance of a Transrectal Ultrasound (TRUS). Post implantation a planning CT is acquired. The target volume and OAR are delineated on the planning CT. The catheters are reconstructed on the clinical TPS (Oncentra TPS, ELEKTA) using an automatic catheter reconstruction tool. Once this is acquired the dwell time activation tool selects the feasible dwell positions and activates them, as there are a few dwell positions that may be too close to the urethra or outside the target volume that must be deactivated. After this is done the clinical technician will generate a treatment plan using a treatment planning optimizer in the treatment planning system. The Oncentra system offers two optimizers the Inverse Planning Simulated Annealing (IPSA) and Hybrid Inverse Planning Optimizer (HIPO). The manual planning procedure involves the manipulation of the weights of the optimizers to get the best possible treatment plan. The final tweaking of the plan may be done by a manual manipulation of the dwell times using a drag and drop tool on the isodose lines. The time take to generate a clinically acceptable plan is 5 -10 minutes. The generated plan is then analysed, verified and approved by the medical physicist and the radiation oncologist. After which the plan is uploaded to the remote after loader, and the patient receives the treatment.

2.10. Research Question

As described above the treatment planning that is performed in the clinic depends on a significant amount of human intervention. This means that the quality of the treatment plan depends on the planner's experience, and is subject to human variability. The aim of this project is to develop an automated treatment planning system for HDR brachytherapy focussing on prostate cancer with the intent of producing high quality clinically acceptable plans while overcoming limitations in planning efficiency, human variability and consistency of plan quality. This project is intended to be incorporated with the treatment planning software suite, iCycle, that was developed at Erasmus MC. This brachytherapy module is coined B-iCycle.

2.11. Previous work

There have been several studies into automated treatment planning for seed implantation in LDR Brachytherapy, but research into automated treatment planning for HDR brachytherapy has only recently begun in literature. Zhou et al ([15], [16]), have created an automated HDR brachytherapy treatment planning suite for a single channel vaginal cylinder applicator, named AutoBrachy. An interface for automatic registration of the applicator position and orientation, treatment plan optimization and export the plan to a treatment planning system. The AutoBrachy uses an iterative quadratic optimization technique to compute the dwell times.

Gorissen et al. [17] propose a mixed integer programming approach to find possible catheter positions and optimize dwell times within these catheters. For a given template used to guide the implantation procedure, the mixed integer programming was used to select positions of the catheters in the template and to optimize on the dwell times with a linear dose based model and a quadratic dose based model, with the aim of maximizing the target coverage. This study showed that the linear dose model, as used in current standard practice, is a stable solution to finding clinically acceptable plans and that the combination with the mixed integer programming allows for a strong system that can solve the HDR brachy therapy planning problem to optimality.

3. Materials and Methods

3.1. Dose Calculation

3.1.1. 2D Dose Calculation Formalism

The TG-43 system assumes that, for high energy photons, the attenuation in tissue is equal to the attenuation in water. All points in the system are defined by a polar coordinate system as shown in Figure 6.

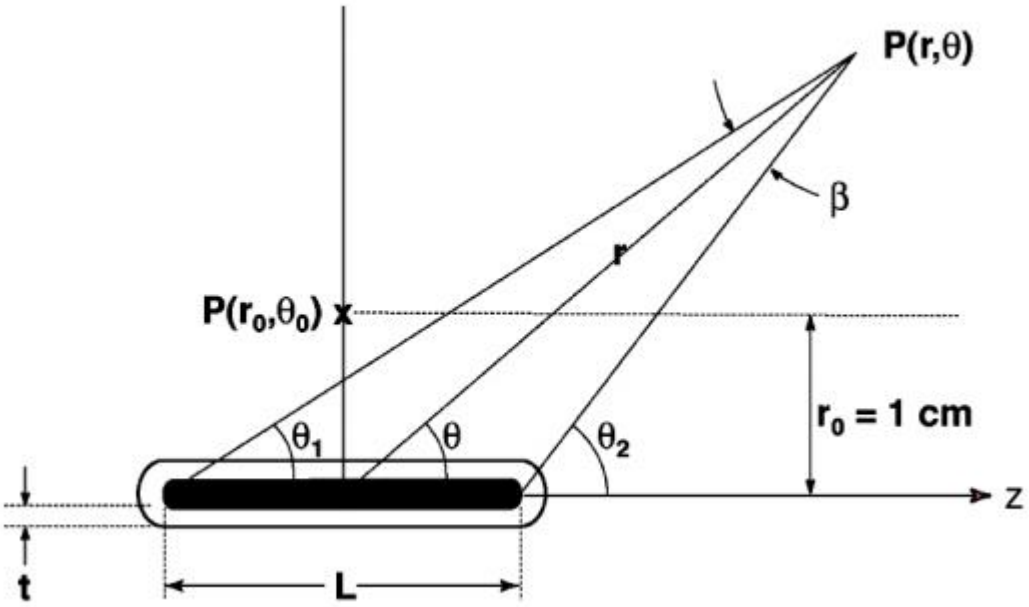

Figure 6 Coordinate system for brachytherapy dosimetry calculations.

For a photon emitting brachytherapy source dose rate at any point $\dot{D}(r,\theta)$ is given by

$$\dot{D}(r,\theta) = S_K . \Lambda . \frac{G_L(r,\theta)}{G_L(r_0,\theta_0)} . g_L(r) . F(r,\theta) \quad (8)$$

Where,

S_K is the brachytherapy source air kerma strength in vacuo. It is measured in the source calibration stage on the source transverse plane, and is defined with the unit *U* (1 U = 1 cGy cm^2 h^{-1}). In Europe, the Reference Air Kerma Rate (RAKR) is used to define the source strength. RAKR is defined as the Air Kerma Rate at a reference point that is 1 cm on the transverse plane of the source.

Λ is the dose rate constant in water. It is the ratio of the dose at the reference point (r=1 cm, θ=90°) and S_K, and has units of cGy $h^{-1}U^{-1}$.

$$\Lambda = \frac{\dot{D}(r_0, \theta_0)}{S_K} \tag{9}$$

It can be identified using measurements during source calibration or Monte Carlo (MC) simulations.

$G_L(r, \theta)$ is the geometry function defined for a point at (r, θ). It is a line source approximation of the distribution of activity in the source; an inverse square law correction. It is given as,

$$G_L(r, \theta) = \frac{\beta}{Lr \sin\theta} \tag{10}$$

Here β is the angle subtended by the point (r, θ) to the two ends of the source, as shown in Figure 6. And L is the length of the source in cm. Along the axis,

$$G_L(r, 0) = \frac{1}{r^2 - \left(\frac{L}{2}\right)^2} \tag{11}$$

For much larger distances (r>>L) the geometric function can be approximated as the point source inverse square law.

The geometry function is used to improve the accuracy of interpolating doses calculated at discrete points. It does not take into account scattering or attenuation. The TG-43 states that this simplistic approximation is sufficiently accurate for treatment planning purposes.

$g_L(r)$ is the radial dose function. It describes the radial dose falloff, on the source transverse plane, from photon scattering and attenuation. The function takes a value of unity at r_0. It is the ratio of dose rate falloff, relative to the dose rate at the reference position.

$$g_L(r) = \frac{G_L(r_0, \theta_0)\, \dot{D}(r, \theta_0)}{G_L(r, \theta_0)\, \dot{D}(r_0, \theta_0)} \tag{12}$$

Although $g_L(r)$ can be represented as a fifth order polynomial, it is usually specified in a high-resolution lookup table.

F(r, θ) is the 2D anisotropy function that is defined as

$$F(r, \theta) = \frac{G_L(r, \theta_0)\, \dot{D}(r, \theta)}{G_L(r, \theta)\, \dot{D}(r, \theta_0)} \tag{13}$$

The anisotropy function describes the variation in dose as a function of polar angle relative to the transverse plane due to self-absorption and attenuation effects of encased source. It is dependent on the thickness of the casing and the photon energy. It tends to decrease with the decrease in r and for angles closer to 0° or 180°. Therefore, it is essential to know the orientation of the source at each dwell position to calculate the dose $\dot{D}(r, \theta)$.

3.1.2. PRACTICAL CONSIDERATIONS

The values of dose rate constant in water (Λ), radial dose function ($g_L(r)$) and the 2D anisotropy function ($F(r,\theta)$) are obtained from a repository of consensus dosimetry data maintained by the European Society for Radiotherapy and Oncology (ESTRO) [18]. The TG-43 recommends a linear-log interpolation for the radial dose function and linear-linear interpolation for the 2D Anisotropy function, for locations not included in the dosimetric data.

The RAKR is set to the calibrated air kerma rate which can be scaled to the current RAKR given the time of treatment.

The total dose is the superimposition of the dose "sphere" for each dwell position. In this project, the dose is limited to a sphere of 10 cm around each dwell position. The dose can be considered to be negligible at regions outside this sphere due to the sharp dose fall-off due to the inverse square law.

The dose is theoretically infinite for voxels inside the source for a dwell position and very high for voxels around the dwell position. Therefore, the dose for these voxels may be explicitly set to a finite high value.

3.2. Validating the Dose engine

The dose engine is at the heart of any treatment planning system so it is very important to verify the dose computation. It will determine the integrity of the steps that are to follow. The optimizer uses the dose engine for a dependable feedback. At the end of the optimization, the dose engine represents the result of the planning, therefore it must be the most accurate representation of the dose. For this project, we have chosen to verify our dose calculation against the dose distribution generated by the clinical TPS, Oncentra TPS.

Firstly, a single source was chosen and assigned a dwell time and the dose distribution was computed on the B-iCycle dose engine and the Oncentra dose engine. The transverse dose profile through the source was used to compare the two dose engines.

Finally, the dose distribution for a complete treatment plan is recomputed using the B-iCycle Dose engine and is compared to the Oncentra dose distribution using the gamma analysis.

3.2.1. GAMMA ANALYSIS

The Gamma analysis is a method used to compare two dose distributions as presented by Low et al., 1998. Here we consider a dose distribution generated by Oncentra to be a reference plan. The dwell positions and dwell times were used from this reference plan to re-compute the dose distribution using the B-iCycle dose engine. This forward calculated plan is validated by comparison against the reference plan. The simple dose difference is a good tool to compare dose differences in low dose gradient regions but is not as useful in high dose gradient regions as a small spatial shift would result in a large dose difference. On the other hand, the distance to agreement (DTA) performs well in matching high dose gradient regions and poorly in the low dose gradient regions. The Gamma analysis combines the use of these two complimentary methods to compare doses. The dose difference is compared to a threshold value, ΔD_m. Likewise, the DTA criterion is given by Δd_m. For this project criterion values for dose difference and DTA of 3% and 1.5mm were chosen respectively.

Figure 7 is a 1-dimensional representation of the gamma analysis.

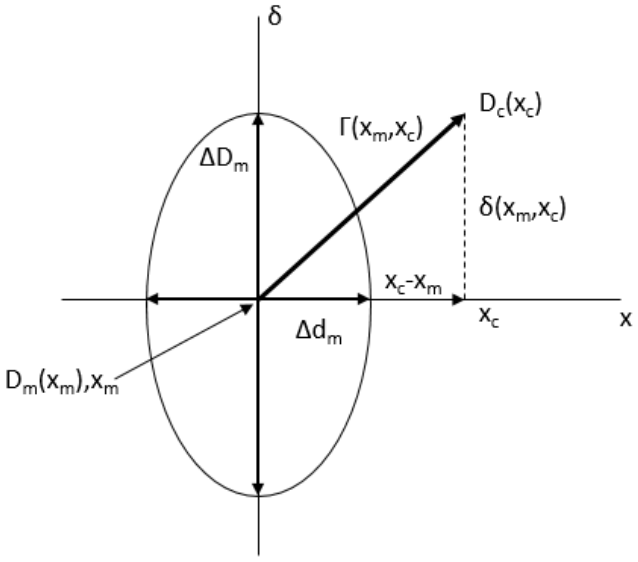

FIGURE 7 ONE-DIMENSIONAL REPRESENTATION OF THE DOSE DISTRIBUTION EVALUATION CRITERIA USING THE COMBINED ELLIPSOIDAL DOSE DIFFERENCE AND DISTANCE-TO-AGREEMENT TESTS

x_m is a single point, at the origin, at which the Gamma index is calculated. The x axis depicts the relative spatial location, x_c, of the calculated dose distribution. The y axis (δ) represents the difference between the reference dose [$D_m(x_m)$] and the calculated dose [$D_c(x_c)$]. The DTA criterion is described in the image as Δd_M. if the calculated dose point $D_c(x_c)$ intersects the x axis at a point $x_c < \Delta d_M$, then the calculated dose distribution can be said to have passed the DTA test at this point. If the difference in dose between the calculated and the reference dose is less than the dose difference criterion, i.e. $| D_c(x_m) - D_m(x_m) | \leq \Delta D_M$, the calculated dose is said to have passed the dose difference test. These two tests can be combined into a single acceptance criterion in the form of an ellipsoid, given by a surface

$$1 = \sqrt{\frac{r^2(x_m, x_c)}{\Delta d_M^2} + \frac{\delta^2(x_m, x_c)}{\Delta D_M^2}} \tag{14}$$

Where

$$r(x_m, x) = |x - x_m| \tag{15}$$

$$\delta(r_m, r) = D(r) - D_m(r_m) \tag{16}$$

If the calculated dose $D_c(x_c)$ intersects the ellipsoid at any point, it can be said that $D_c(x_c)$ has passed the test at point x_m.

Therefore, the gamma index can be defined as

$$\gamma(x_m) = min\{\Gamma(x_m, x_c)\} \forall \{x_c\} \tag{17}$$

Where,

$$\Gamma(x_m, x_c) = \sqrt{\frac{r^2(x_m, x_c)}{\Delta d_M^2} + \frac{\delta^2(x_m, x_c)}{\Delta D_M^2}} \tag{18}$$

The pass and fail criteria would therefore be presented as

$$\gamma(x_m) \leq 1, the\ calculation\ passes$$
$$\gamma(x_m) > 1, the\ calculation\ fails \quad (19)$$

The gamma test of the two distributions can be summarized by Gamma histograms to quantitatively analyse the results [19]. 3D gamma analysis was done using an in-house developed tool (Erasmus MC - RTStudio).

3.3. Treatment Plan Optimization

3.3.1. 2PϵC ALGORITHM FOR MULTICRITERIA OPTIMIZATION OF DWELL TIMES

The 2pϵc algorithm, presented by Breedveld et al. [14], is based on the ϵ-constraint method proposed by Haimes [20]. The ϵ-constraint method optimizes one constraint at a time while holding the other objectives as constraints. This implies that each objective is optimized once, the drawback being that it could result in a plan that is Pareto optimal but not necessarily the optimal plan.

The treatment objectives and constraints have goals and priorities assigned for each, and is organized in what is known as a *wish-list*. The optimization problem is given as

$$\begin{aligned} &minimize f_1(x) \\ &subject\ to\ g(x) \leq 0 \end{aligned} \quad (20)$$

Where f_1 is the objective with the highest priority and g is the list of constraints. The 2pϵc method extends this to a second iteration using the solution, x^*, of the first, to define a new constraint. The new constraint is given by

$$\epsilon_i = f(x) = \begin{cases} b_i, & f_i(x^*)\delta < b_i \\ f_i(x^*)\delta, & f_i(x^*)\delta \geq b_i \end{cases} \quad (21)$$

Where, b_i is the goal and ϵ_i is the new constraint for the i^{th} objective. $f_i(x^*)$ is the value obtained for the i^{th} objective. δ is a relaxation value used to "relax" the solution to achieve a more favourable trade-off for the lower prioritized objectives.

The second iteration is given as

$$\begin{aligned} &minimize\ f_2(x) \\ &subject\ to \quad g(x) \leq 0 \\ &f_1(x) \leq \epsilon_1 \end{aligned} \quad (22)$$

Where f_1 *and* f_2 are the first and second objective functions respectively, ϵ_1 is the new bound that was introduced from the first iteration result, and g is the vector of constraints.

The second iteration of the 2pϵc method makes it possible to minimize the objectives, of a possibly lower priority, that meet the set goals while holding the other objectives as constraints.

3.3.2. PREOPTIMIZATION PROTOCOL

For the brachytherapy protocols used in the Erasmus MC, the aim is to deliver the prescribed dose to 95% of the tumour volume. The remaining freedom in the dose delivery is then used to minimize the dose to the urethra. Coverage is a non-convex objective, and cannot be optimized on directly in Erasmus-iCycle. We have therefore implemented a preoptimization

approach. The dose to the tumour is represented by an LTCP cost-function (as will be described in section 3.3.3). The dose to the urethra is then iteratively minimized until the requested 95% coverage for the tumour is obtained. The found parameters are then set as constraints. After this preoptimization procedure, the wish-list is processed according to the 2pϵc algorithm.

3.3.3. WISH-LIST

The 2pϵc optimizer generates treatment plans according to the clinical protocol. In the wish-list, the treatment protocol is defined as a combination of objectives and constraints. An *objective* has a goal assigned, that has to be met as well as possible, before continuing to lower prioritized objectives. The *constraints* are absolutely inviolable, and its limits are predefined by the planner.

To define the wish-list, plans are generated for a *training set* of patients, the objectives and constraints are tweaked iteratively to obtain the best possible plans. The quality of the plans is verified by a Radiation Oncologist to ensure that the plans are clinically acceptable. The definition of the wish-list is very important to the success of the optimizer, ill-defined objectives result in a suboptimal plan. Two competing constraints will not allow the optimizer to reach a feasible solution.

For the wish-lists that were generated, the objectives and constraints are defined in terms of dosimetric linear maximum, dosimetric linear minimum and an LTCP (Logarithmic Tumour Complication Probability). The LTCP objective function as presented by Alber and Reemtsen, [21], is given as

$$LTCP = \frac{1}{m}\sum_{i=1}^{m} e^{-\alpha(d_i - D^p)} \tag{23}$$

Where, m is the number of voxels of the target volume, α is a constant related to the cell survival characteristics, d_i is the dose at voxel *i* and D^p is the prescribed dose. The LTCP objective imposes an exponential penalty on the differences in dose between d_i and D^p. The α constant determines the number of voxels that may be under-dosed for the target. The LTCP constraint is also used to define near maximum dose limits for the OAR which is done by setting the α to a negative value.

The minimum target coverage for the preoptimization step is defined as a volume percentage that receives the prescribed dose. A shell is defined at 7mm from the prostate and a linear constraint is imposed on it. this is done to ensure dose conformity and also prevents the possibility of having a very high dwell time at a position. The wish-lists were created with the intention of generating treatment plans that are clinically acceptable as defined in section 3.6.

The wish-list for 9.5 Gy treatment protocol (as shown in

Table 2) is created by training the wish-list on 5 patients from the patient group for four fractions of 9.5 Gy. Training of the wish-list involves iteratively tweaking the wish-list to generate plans that are clinically acceptable and compliant to the physician's specifications. The wish-list for the single fraction 19 Gy is trained on the PROGRESS patient group and the wish-list for the single fraction 20 Gy was trained on the PROBACH Patient Group.

TABLE 1 THE WISH-LIST USED TO GENERATE FOUR FRACTIONS OF 9.5 GY PLANS.

Priority	Structure	Type	Goal	Parameters
Constraint	Urethra	Linear	11.4 Gy	
Constraint	Prostate	Vol (%) with dose >Dref	95.8%	D^P=9.5 Gy
Constraint	Prostate	LTCP	0.4	D^P=9.5 Gy, α=0.4
Constraint	Rectum	LTCP	0.1	D^P=7.6 Gy, α=-0.6
Constraint	Bladder	LTCP	0.1	D^P=7.6 Gy, α=-0.6
1	Urethra	Linear	11.4 Gy	
2	Prostate Shell 7mm	Linear	20 Gy	

TABLE 2 THE WISH-LIST USED TO GENERATE SINGLE FRACTION 19 GY PLANS.

Priority	Structure	Type	Goal	Parameters
Constraint	Urethra	Linear	20.65 Gy	
Constraint	Prostate	Vol (%) with dose >Dref	95.5%	D^P =19 Gy
Constraint	Prostate	LTCP	0.4	D^P=19 Gy, α=0.4
Constraint	Rectum	LTCP	0.1	D^P=14.7 Gy, α=-0.6
Constraint	Bladder	LTCP	0.2	D^P=15 Gy, α=-0.7
1	Urethra	Linear	21 Gy	
2	Prostate Shell 7mm	Linear	30 Gy	

TABLE 3 THE WISH-LIST USED TO GENERATE SINGLE FRACTION 20 GY PLANS.

Priority	Structure	Type	Goal	Parameters
Constraint	Urethra	Linear	20.7 Gy	
Constraint	Prostate	Vol (%) with dose >Dref	95.8%	D^P= 20 Gy
Constraint	Prostate	LTCP	0.4	D^P= 20 Gy, α=0.4
Constraint	Rectum	LTCP	0.1	D^P=15.3 Gy, α=-0.6
Constraint	Bladder	LTCP	0.14	D^P=15 Gy, α=-0.5
1	Urethra	Linear	21 Gy	
2	Prostate Shell 7mm	Linear	30 Gy	

3.4. Patient Data

For this project, three patient groups were used. The treatment plans were generated on the delineated post implant CT's as described in chapter 2.4. The groups differ by catheter geometry.

4x9.5 Gy Group: 22 patients with low-intermediate risk prostate cancer. The patients were treated with four fractions of 9.5 Gy HDR brachytherapy.

PROBACH Group: The patients were treated with 1x13 Gy HDR brachytherapy boost and External Beam Radio Therapy (EBRT). For this project, data from 9 patients of the PROBACH study were used to generate single fraction 19 Gy and 20 Gy plans. The PROBACH catheter geometry is interesting as it has additional catheters on the dorsal region of the prostate where the bulk of the dose is delivered.

PROGRESS Group: The PROGRESS study is a dose escalation study that prescribes 1x19 Gy for low-intermediate risk. Plans were generated for 5 patients from the PROGRESS study. The catheter geometry for the PROGRESS study has extra catheters in the lateral and dorsal regions of the prostate to cover for cold spots predicted by the physician.

3.5. Study Setup

For this project, the plans generated in B-iCycle are compared against the plans generated by the clinical technicians on Oncentra. B-iCycle optimizes on the dwell times using the catheter positions and dwell positions of the corresponding Oncentra plan that have been extracted from the RTPlan. This is done to compare the B-iCycle optimization to the optimizer used in the clinic.

For each treatment protocol, a wish-list is generated by iteratively tweaking the wish-list parameters on a smaller subset of patients. The plans are for the complete patient group are generated using these wish-lists. The generated plans in B-iCycle are then exported into Oncentra to obtain the dose characteristics, which are then compared against the dose characteristics of plans generated by the clinicians, which are presented in this report.

There exists a small difference between the dose characteristics seen in the B-iCycle and in Oncentra, this is because of a slight difference in the volumes calculated for the delineated structures and we can expect a difference in the dose characteristics projected by the B-iCycle system and the Oncentra system.

3.6. Treatment Protocols

The treatment protocol contains the dosimetric goals (prescribed dose) and limits set by the physician. In this project plans were generated for 3 treatment protocols. A wish-list was compiled for each of these treatment protocols using a training set of 5 patients, as shown in section 3.3.3.

3.6.1. 4x9.5 Gy treatment protocol

The 4x9.5 Gy treatment protocol is clinically used for low-intermediate risk prostate cancer patients. This treatment scheme prescribes 38 Gy in four fractions of 9.5 Gy [22]. The protocol

specifies a minimum target coverage of 95% i.e. $V_{PD}\% \geq 95\%$. Dose to 1 cc of the rectum and bladder is restricted to 80% of the prescribed dose. For the urethra, dose to 1% of the volume is limited to 120% of the prescribed dose. The treatment plan must satisfy these constraints to be *clinically acceptable*. Any excessive dose to any of the organs at risk strongly increases the probability of Genitourinary (GU) and Gastrointestinal (GI) toxicity ([22], [23]). Limiting the dose to the organs at risk is considered to be of higher priority than target coverage. The radiation oncologist placed sparing of the urethra as a higher priority over the target coverage (provided minimum target coverage is achieved).

3.6.2. SINGLE FRACTION TREATMENT PROTOCOLS

The Erasmus MC-Cancer Institute is currently undertaking a dose escalation study. The prostate is widely accepted to have a low α/β which indicates better tumour control with hypofractionation of the prescribed dose [24]–[26]. The dose escalation study initially investigates the effect of delivering 19 Gy in a single fraction to the prostate. If the toxicity from the treatment is within clinical constraints, the prescribed dose is raised to 20 Gy. Since all the dose is delivered in one fraction, the patient is treated within a few hours on a single day, discomfort is greatly reduced and the effects of intrafraction catheter displacement can be avoided [10].

TABLE 4 DOSIMETRIC CONSTRAINTS FOR 1X19 GY AND 1X20 GY TREATMENT PROTOCOLS

Prostate	D_{95}	≥	100% PD
	V_{100}	≥	95%
Rectum	D_{1cc}	≤	15.5 Gy
	D_{2cc}	≤	14.5 Gy
Bladder	D_{1cc}	≤	16 Gy
	D_{2cc}	≤	15.5 Gy
Urethra	$D_{0.1cc}$	≤	21 Gy
	$D_{10\%}$	≤	20.5 Gy
	$V_{120\%}$	=	0 cc

A smaller set of acceptable plans lie between the limits of the high dose coverage and maximum dose to the organs at risk hence it is more difficult to generate clinically acceptable plans for these protocols. In this project plans are generated for the prescribed doses of 19 Gy in a single fraction and 20 Gy in a single fraction. Due to the fact that all the dose is delivered in a single fraction, the radiation oncologist preferred to maximize the target coverage while maintaining the 21 Gy isodose line outside the urethra.

3.7. Types of Plans

In this project, we have considered three treatment protocols (we focus on the single fraction protocols) and three patient groups.

TABLE 5 SUMMARY OF THE PLANS THAT WERE GENERATED.

Patient Data \ Treatment Protocol	4 x 9.5 Gy	1 x 19 Gy	1 x 20 Gy
4 Fraction Patients	i. Comparison of Clinical Plans and B-iCycle Plans	----	ii. Comparison of plans generated by a technician and B-iCycle Plan
PROBACH Patients	----	iii. B-iCycle dose characteristics of B-iCycle Plans	iv. Comparison of plans generated by a technician and B-iCycle Plans
PROGRESS Patients	----	v. Comparison of Clinical Plans and B-iCycle Plans	----

There were seven experiments carried out for the three patient groups using the three wish-lists:

i) 4 x 9.5 Gy plans for the four-fraction patient group were generated using B-iCycle and compared against their respective clinical plans using dose characteristics extracted from the Oncentra TPS.

ii) Plans for the single fraction 20 Gy protocol were generated for the four fraction patients group using B-iCycle. The dose characteristics for the B-iCycle plans are logged from the Oncentra TPS and compared against the dosimetric characteristics from a study conducted by the clinical technicians. The catheter geometry for the four-fraction patient group is not designed the kind of dose distribution required for the single fraction protocols therefore a lower number of clinically acceptable plans would be expected. The plans are crated for this patient group to test whether it is possible to generate single fraction plans for the patient group.

iii) Single fraction 19 Gy plans were generated for the PROBACH patients using B-iCycle. The dose characteristics of the plans are recorded from the B-iCycle dose statistics function. The aim of the experiment is to test whether it is possible to generate plans for this protocol and patient group.

iv) Single fraction 20 Gy plans were generated for the PROBACH patients using B-iCycle. The dose characteristics for the B-iCycle plans are logged from the Oncentra TPS and compared against the dosimetric characteristics from a study conducted by the clinical technicians.

v) Single fraction 19 Gy plans were generated for the PROGRESS patients using B-iCycle. The dose characteristics for the B-iCycle plans are logged from the Oncentra TPS and compared against the clinical plans.

3.8. Plan Evaluation

Once we have generated the treatment plans, the plans must be evaluated dosimetrically and evaluated by a physician (Clinical evaluation). We shall evaluate the B-iCycle plans with respect to the clinical plans and the plans generated by the clinical staff. The plans will be dosimetrically evaluated using the COIN in the next section.

3.8.1. CONFORMITY INDEX (COIN)

The conformity index as defined by Baltas et al[27] , is a Dose volume histogram (DVH) based plan evaluation metric. It allows for a combined study of target coverage, dose to Normal tissues and dose to the organs at risk.

c1

The *c1* coefficient is the target coverage and is the fraction of the target volume that receives the prescribed dose to the total target volume.

$$c1 = \frac{PTV_{PD}}{PTV} \tag{24}$$

Where, PTV_{PD} is the volume of the PTV that receives the prescribed dose. Ideally, complete coverage of the target, hence c1 = 1.

c2

The coefficient *c2* is the fraction of the target volume to the total volume that receives the prescribed dose (V_{PD}). Using this coefficient, we can infer the volume of Normal tissues and critical structures that receive the prescribed dose. For a dose distribution that is perfectly conformal, *c2* = 1.

$$c2 = \frac{PTV_{PD}}{V_{PD}} \tag{25}$$

c3'

Among the COIN coefficients suggested by Baltas et al., the c3 coefficient is a product of the fractions of the volume critical structures, that receive a dose less than the prescribed dose, to the volume of the critical structures. One of the advantages of brachytherapy is that it is highly conformal and that the volumes of the critical structures that receive the prescribed dose are very small. For the 4x9.5 Gy treatment protocol, the dose constraints on the Rectum and the Bladder is 80% of the prescribed dose. The Urethra has a dose limit of 120% of the prescribed dose. Therefore, the c3 coefficient would always be misrepresentation of the dose to the organs at risk, with respect to the treatment protocol, hence a new c3' is proposed. The c3' is a measure that would represent the conformity of the dose received by the critical structures, to the dose constraints defined by the protocol. In the ideal case *c3'*=1.

$$c3' = \prod_{i=1}^{N_{CS}} \left\{ 1 - \frac{V_{DC_{CS,i}}}{V_{CS,i}} \right\} \tag{26}$$

Where, N_{CS} is the number of critical structures, $V_{DC\,CS,\,i}$ is the volume of the i^{th} critical structure that receives, at least, the maximum permissible Dose (Dose Constraint). $V_{CS,i}$ is the volume of the i^{th} critical structure. Such that:

$$COIN' = c1 * c2 * c3' \tag{27}$$

The *COIN'* value would be a score that would describe the conformity of the dose to the PTV, and the sparing of the OARs with respect to their individual dose limits, weighted by the target coverage, in the ideal case *COIN'=1*.

4. Results

4.1. Dose Distributions

B-iCycle uses a TG-43 dose engine to generate the dose distributions. Typically, dose distributions for brachytherapy are characterized by a very high dose within the prostate and a sharp dose fall-off outside the prostate. Figure 8, Figure 9 and Figure 10 show the dose distribution for one patient as seen on the iCycle patient viewing tool. The red regions show the areas that receive a high dose and the blue regions show areas that receive a low dose.

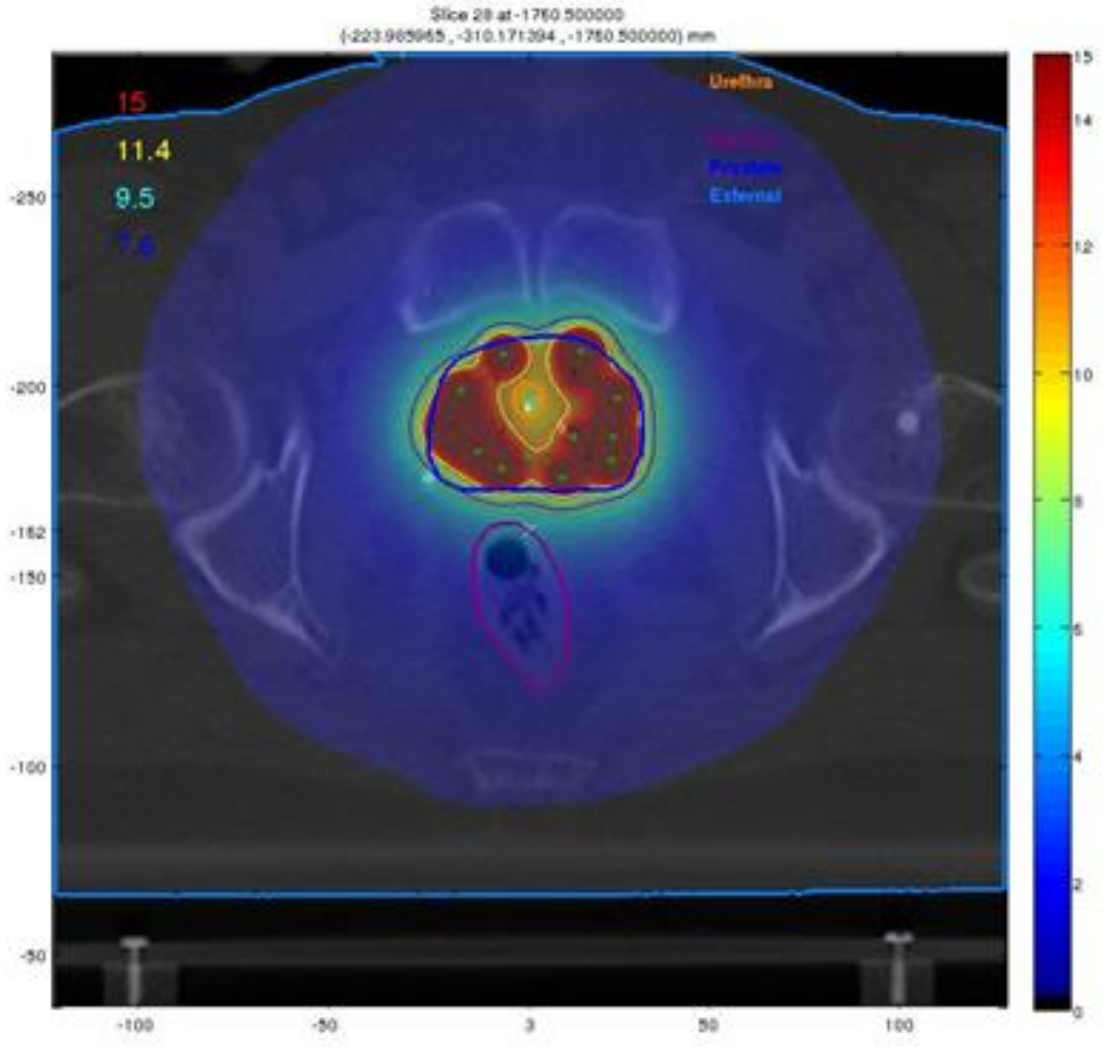

FIGURE 8 AXIAL VIEW OF THE DOSE DISTRIBUTION. RED AREAS REPRESENT HIGH DOSE REGIONS AND BLUE AREAS REPRESENT LOW DOSE REGIONS.

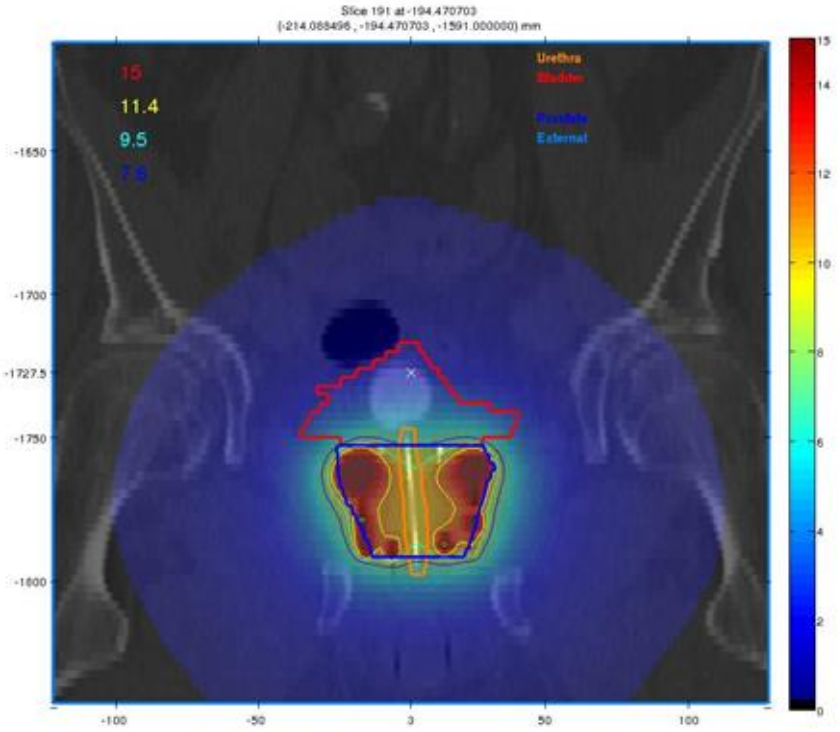

FIGURE 9 CORONAL VIEW OF THE DOSE DISTRIBUTION. RED AREAS REPRESENT HIGH DOSE REGIONS AND BLUE AREAS REPRESENT LOW DOSE REGIONS

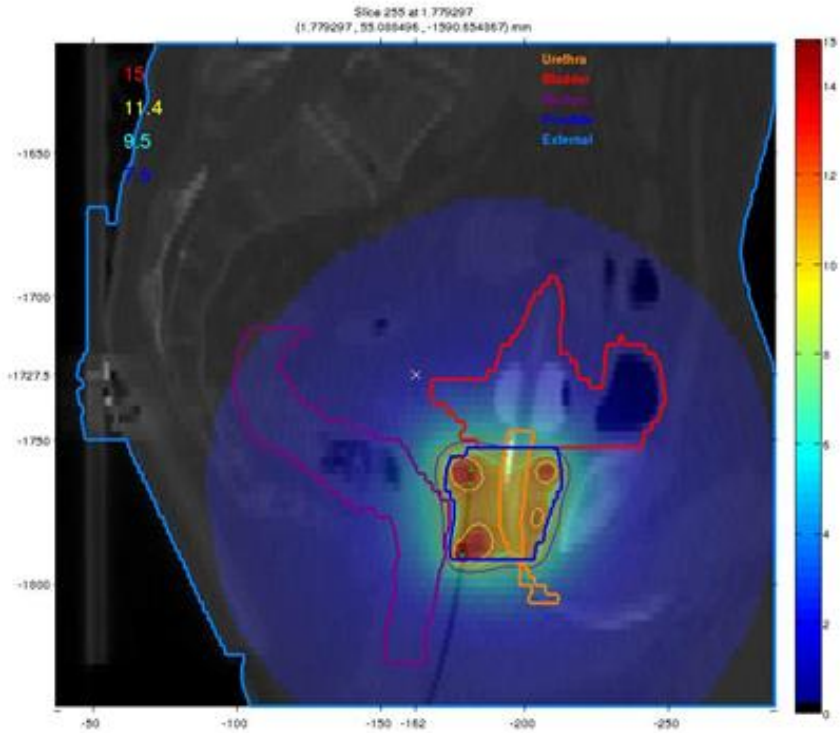

FIGURE 10 SAGITTAL VIEW OF THE DOSE DISTRIBUTION. RED AREAS REPRESENT HIGH DOSE REGIONS AND BLUE AREAS REPRESENTING LOW DOSE REGIONS

4.2. Validation of the dose engine

Comparing the dose profiles of a single source, one exported dose distribution from Oncentra and the other is the forward calculated dose. The forward calculated dose is the dose distribution calculated by the B-iCycle dose engine, using the dwell positions and Dwell times of the clinical plan. Catheters used in brachytherapy have a diameter of 2 mm. the largest differences in dose are seen within the catheter (can be ignored as there is no tissue there) and voxels right next to the catheter as shown in Figure 11.

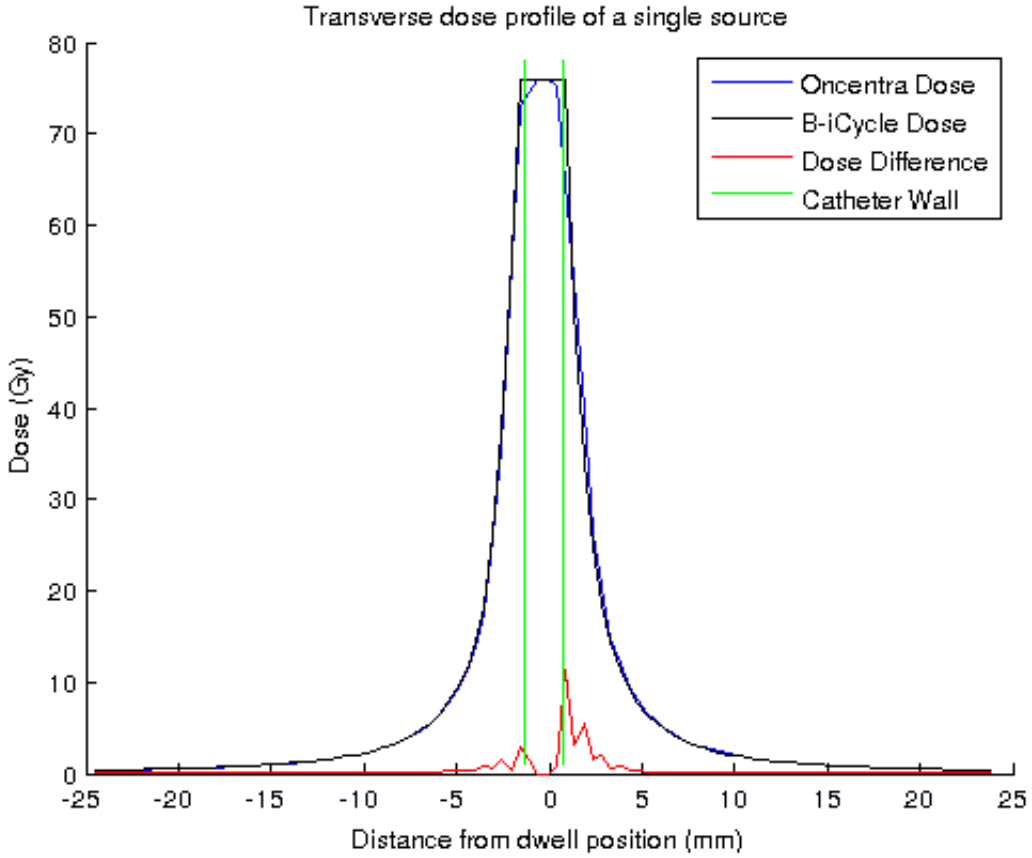

FIGURE 11 TRANSVERSE DOSE PROFILE FOR A SINGLE SOURCE. RED LINE: DIFFERENCE IN DOSE BETWEEN ONCENTRA DOSE PROFILE AND B-ICYCLE DOSE PROFILE. GREEN LINE: WALLS OF THE CATHETER.

Comparing the dose distribution from the Oncentra dose engine and the B-iCycle dose engine of a complete treatment plan, the Gamma Volume Histogram (GVH) in Figure 12 shows that the percentage volume of prostate that has a gamma value greater than 1 was 0.67%, i.e. failing the gamma analysis test. The points where gamma is greater than 1, are located inside and around the dwell positions, as seen in Figure 13.

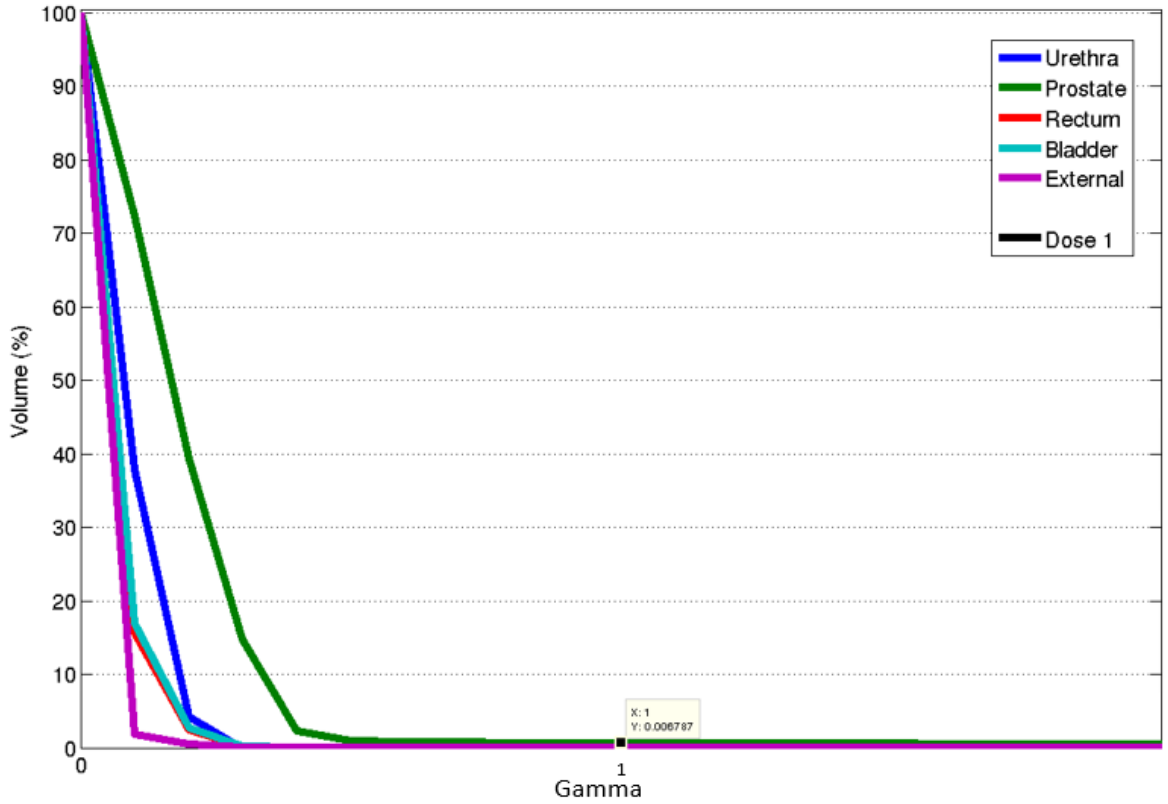

FIGURE 12 GAMMA VOLUME HISTOGRAM COMPARING A CLINICAL TREATMENT PLAN AND FORWARD CALCULATED PLAN

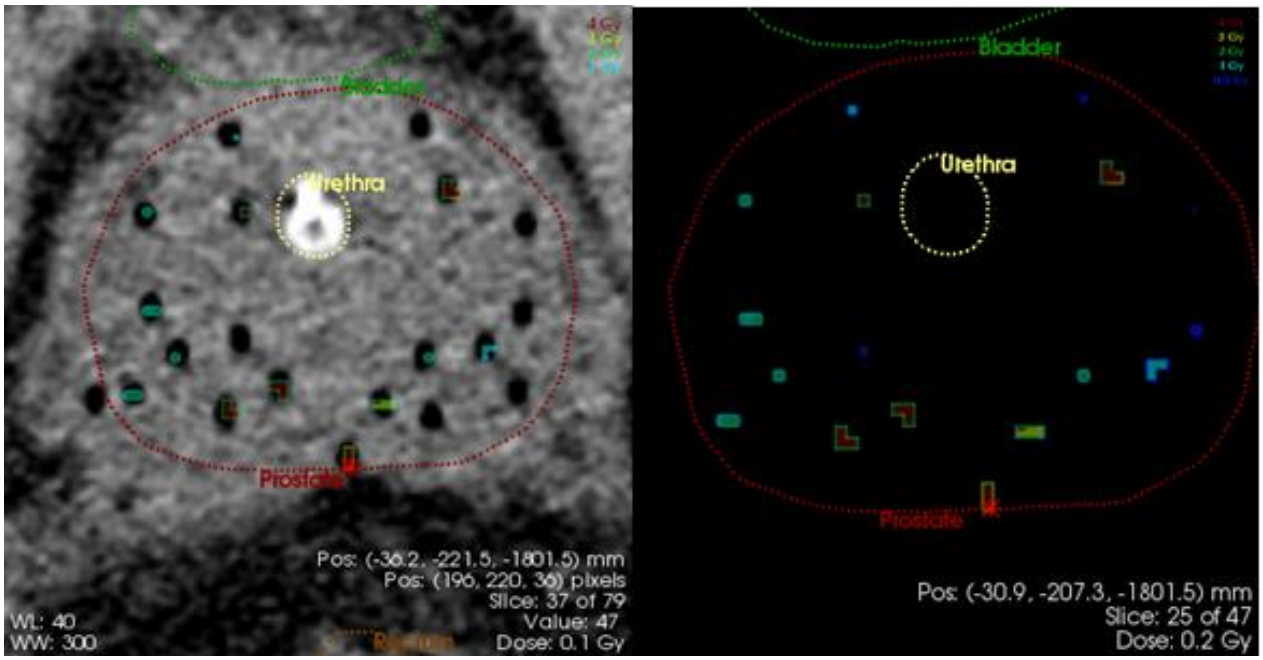

FIGURE 13 SLICE OF THE THREE-DIMENSIONAL GAMMA ANALYSIS WHERE THE COLOURED VOXELS ARE VOXELS WITH A GAMMA VALUE >1 (RIGHT). THE CT OVERLAY (LEFT) SHOWS THE VOXELS WITH GAMMA> 1 ARE LOCATED IN THE CATHETERS.

4.3. Planning stage

The plans were generated using the wish-list as specified in section 3.3.3. The dose distribution for the plan can be seen in Figures 8-10.

The B-iCycle optimizer takes approximately 10 seconds to find the optimal dwell times for each patient. Figure 14 shows the dose volume histograms (DVH) of a clinical plan that was used to treat a patient and a plan generated using B-iCycle. The solid line depicts the dose volume characteristics of the B-iCycle Plan and the dashed line represents the clinical plan as generated by the iCycle DVH tool. For this patient, the clinical plan shows a slightly higher coverage at 9.5 Gy and a higher maximum dose to the urethra (D_{max}). However, the B-iCycle plan covers 95% of the prostate volume according to the clinical protocol.

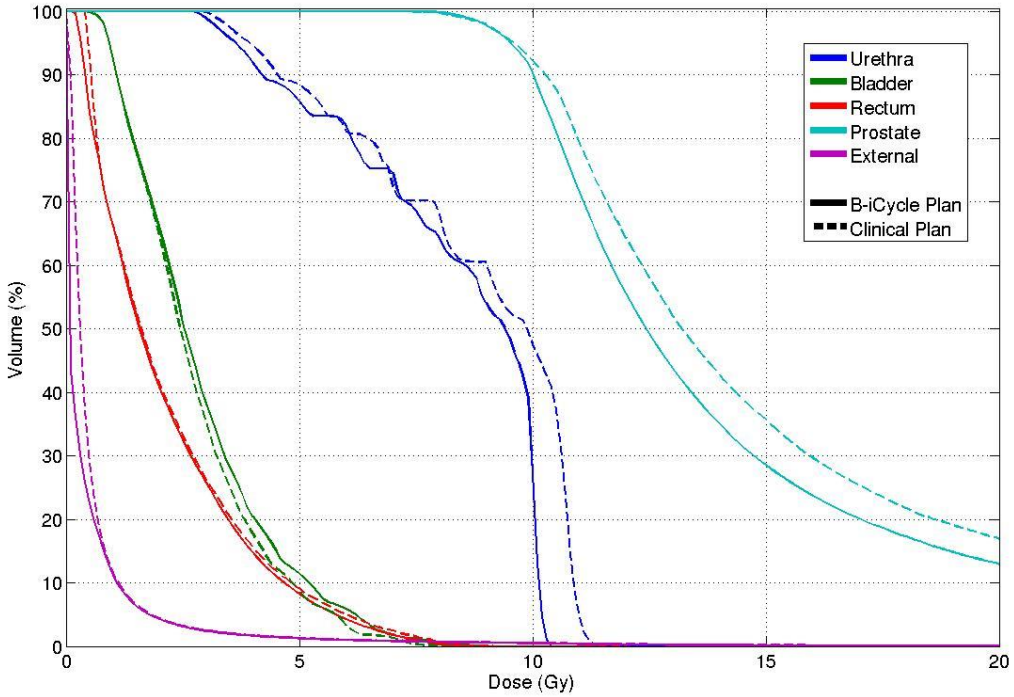

FIGURE 14 DVH COMPARISON OF DOSE DISTRIBUTION OF CLINICAL PLAN (DOTTED LINE) AND B-ICYCLE PLAN (SOLID LINE).

4.4. Plan Evaluation

4.4.1. Clinical Evaluation

All the plans that were generated in this study on the training data were evaluated by the physician. The plans were evaluated dosimetrically to ensure the dose distribution was within the treatment protocol. And the dose distributions were visually analysed for isodose line characteristics.

The radiation oncologist verified that the B-iCycle plans are equal to the clinical plans in terms of plan quality and tend to perform better for difficult cases.

4.4.2. Dosimetric evaluation

4 X 9.5 GY PLANS FOR THE FOUR FRACTION PATIENTS

4 x 9.5 Gy plans were generated for 22 patients of the four-fraction patient group, out of which B-iCycle was able to generate 18 clinically acceptable plans. The comparison of dose characteristics of clinical plans and B-iCycle plans can be seen in Figure 15. In this figure, the points placed above the diagonal line show that the B-iCycle plans perform better than the clinical plans for the respective dose characteristic. Here, it can be observed that B-iCycle maintains an almost consistent target coverage around 95.5%. Clinical plans have greater average target coverage of 96.4%, although the protocol does not favour coverage above 95%. The urethra dose, which is placed at the highest priority, shows a significantly larger number of plans in favour of B-iCycle. The clinical plans have an average urethral $D_{1\%}$ of 11.2 Gy (min = 11 Gy, max = 11.4 Gy, SD = 0.1 Gy) whereas B-iCycle plans have an average urethral $D_{1\%}$ of 10.6 Gy (min = 10 Gy, max = 11.4 Gy, SD = 0.4 Gy). The trade-off for the lower urethra dose is a slightly higher dose (within dose constraints) to the rectum and the bladder. The dose characteristics are presented in Appendix A

Figure 16 shows a comparison of the COIN coefficients for B-iCycle plans versus Clinical plans for the four-fraction patient group. In this figure, the points placed above the diagonal line shows that the B-iCycle plans perform better than the clinical plan for the respective COIN coefficient. C1 coefficient describes the target coverage, and as seen above, B-iCycle has limited target coverage to 95.5%. The C2 coefficient indicates a greater number of plans in favour of B-iCycle. The C3 coefficient shows a greater number of plans in favour of the Clinical plans. The COIN coefficient data is presented in Appendix B. The two tailed Wilcoxon signed-rank test suggests that the B-iCycle plans have a higher COIN index compared to the clinical plans.

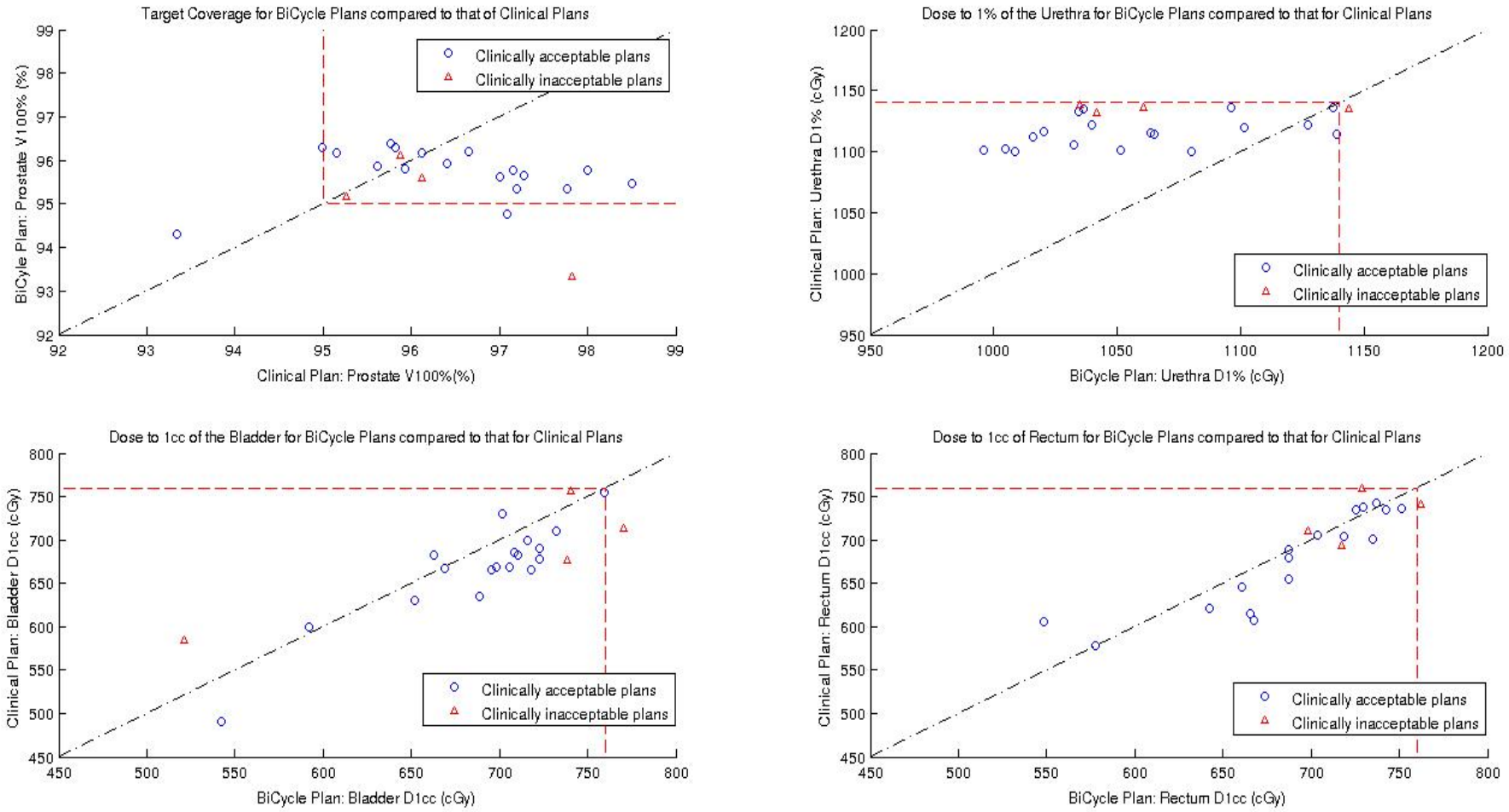

FIGURE 15 COMPARISON OF DOSE CHARACTERISTICS OF 4 X 9.5 GY PLANS FOR THE FOUR FRACTION PATIENT GROUP. (RED DASHED LINE: MAXIMUM DOSE LIMIT FOR OAR / MINIMUM TARGET COVERAGE)

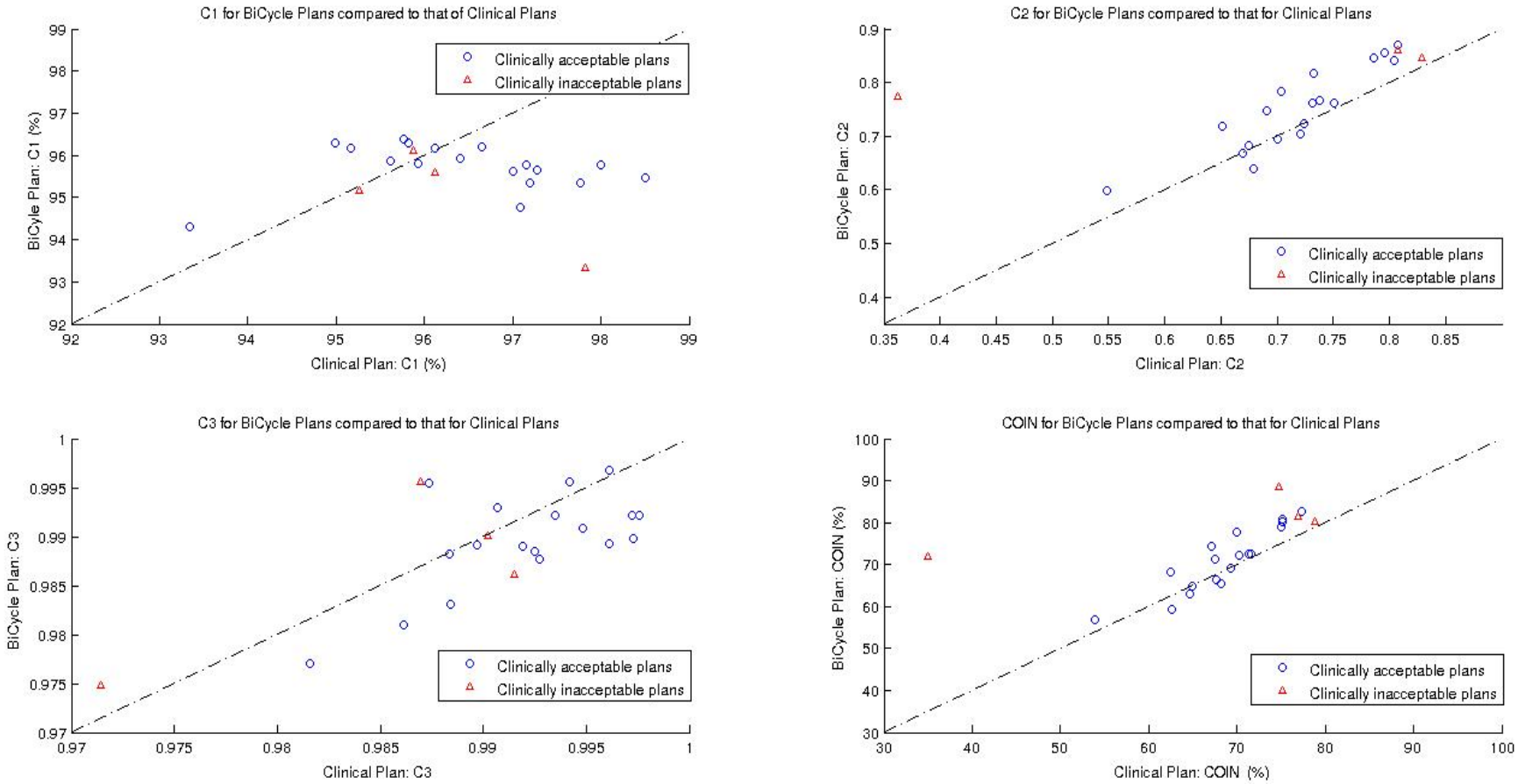

FIGURE 16 COIN COEFFICIENTS COMPARING B-ICYCLE PLANS AND CLINICAL PLANS FOR THE FOUR FRACTION PATIENT GROUP

SINGLE FRACTION 20 GY PLANS FOR THE FOUR FRACTION PATIENT GROUP

The single fraction for 20 Gy is a protocol for which it is difficult to achieve a clinically acceptable treatment plan. Out of the 22 patients in the four-fraction patient group, with the clinical procedure it is only possible to create 5 clinically acceptable plans and B-iCycle is able to generate 4 clinically acceptable plans. The main challenge with planning for the single fraction 20 Gy is the difficulty in achieving the minimum target coverage of 95% due to the catheter geometry. The dose characteristics data is presented in Appendix C.

TABLE 6 SUMMARY OF THE PLANS GENERATED FOR SINGLE FRACTION 20 GY TREATMENT PROTOCOL FOR THE FOUR FRACTION PATIENT GROUP

	Acceptable B-iCycle Plans	Inacceptable B-iCycle Plans
Acceptable Clinical Plans	3	2
Inacceptable Clinical Plans	1	16

SINGLE FRACTION 20 GY PLANS FOR PROBACH PATIENT GROUP

Out of the nine patients in the PROBACH patient group there were four patients for whom both, the clinical plans and the B-iCycle plans, satisfied the treatment constraints. For two of the patients, clinical plans and B-iCycle plans were both inacceptable. This was because the catheter geometry for these specific patients were bad due to deflections in the catheters. For two of patients, clinical plans were acceptable but B-iCycle was unable to generate clinically acceptable plans. For patient 2 in Table 8, the clinical plan was unacceptable as the $D_{0.1cc}$ violated the constraint, this case is managed by B-iCycle better as it yields a better target coverage and OAR sparing.

TABLE 7 SUMMARY OF THE PLANS GENERATED FOR SINGLE FRACTION 20 GY TREATMENT PROTOCOL FOR PROBACH GROUP

	Acceptable B-iCycle Plans	Inacceptable B-iCycle Plans
Acceptable Clinical Plans	4	2
Inacceptable Clinical Plans	1	2

In Figure 17, among the clinically acceptable plans, B-iCycle proved better at sparing the urethra in all five cases (mean = 20.4 Gy, SD = 0.06 Gy). For the two cases where B-iCycle plans were unacceptable, the plans had exceeded the dose threshold for the urethra. B-iCycle plans fared better in terms of minimizing dose to the bladder compared to clinical plans. It is interesting to note that for the two cases where 95% coverage was not achievable, 94% coverage was deemed sufficient by the physician, B-iCycle was able to maximize the coverage and manage dose to the urethra better than the clinical plans.

TABLE 8 DOSE CHARACTERISTICS OF CLINICAL PLANS AND B-ICYCLE PLANS IN SINGLE FRACTION 20 GY PROTOCOL FOR PROBACH PATIENTS (RED ID NUMBER: UNACCEPTABLE PLAN)

Clinical Plans

	Prostate	Bladder		Rectum		Urethra	
	V100% (%)	D1cc (cGy)	D2cc (cGy)	D1cc (cGy)	D2cc (cGy)	D0.1cc (cGy)	D10% (cGy)
1	94.0	1402	1251	1460	1334	2076	2048
2	94.0	1578	1406	1218	1031	2103	2049
3	92.6	1598	1427	1548	1433	2071	2046
4	96.3	1588	1459	1532	1384	2075	2048
5	96.6	1558	1419	1518	1402	2069	2037
6	96.6	1595	1428	1525	1355	2083	2047
7	96.1	1593	1442	1546	1401	2066	2047
8	95.1	1569	1455	1502	1360	2070	2041
9	91.6	1593	1481	1474	1338	2081	2050

B-iCycle Plans

	Prostate	Bladder		Rectum		Urethra	
	V100% (%)	D1cc (cGy)	D2cc (cGy)	D1cc (cGy)	D2cc (cGy)	D0.1cc (cGy)	D10% (cGy)
1	94.7	1195	1053	1458	1324	2066	2038
2	94.6	1194	1068	1306	1099	2079	2042
3	93.5	1443	1319	1569	1451	2072	2048
4	95.2	1446	1324	1487	1335	2052	2029
5	95.2	1454	1322	1541	1415	2061	2032
6	94.9	1456	1315	1449	1292	2075	2035
7	94.9	1498	1369	1475	1347	2068	2051
8	95.1	1495	1385	1541	1397	2080	2063
9	92.5	1552	1442	1510	1385	2092	2062

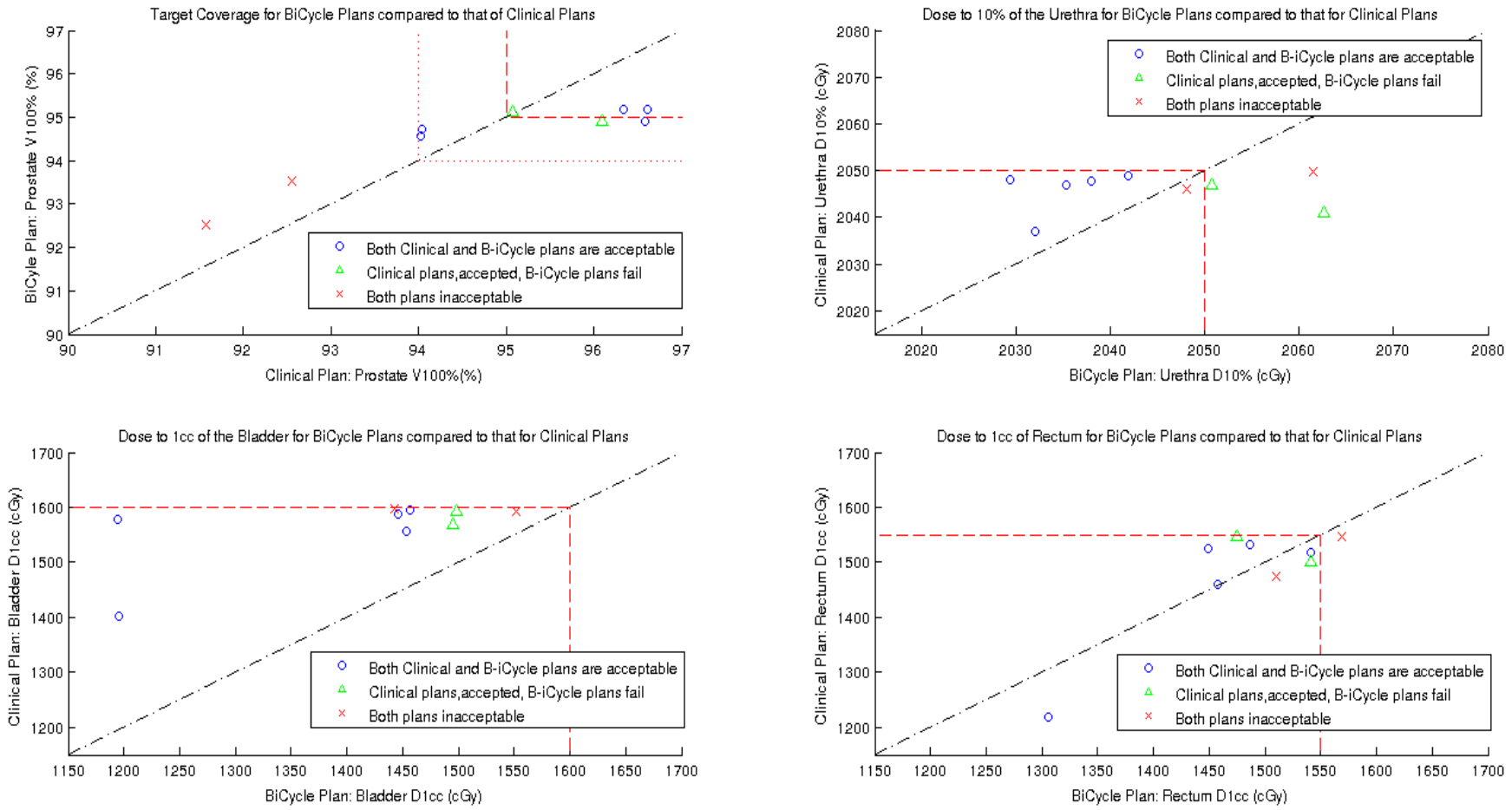

FIGURE 17 COMPARISON OF DOSE CHARACTERISTICS OF 1 X 20 GY PLANS FOR THE PROBACH PATIENT GROUP. (RED DASHED LINE: MAXIMUM DOSE LIMIT FOR OAR / MINIMUM TARGET COVERAGE, RED DOTTED LINE: MINIMUM COVERAGE THAT MAY BE ACCEPTABLE)

SINGLE FRACTION 19 GY PLANS FOR THE PROBACH PATIENT GROUP

B-iCycle was able to generate five clinically acceptable plans. Of the four plans that were deemed clinically inacceptable, three of the treatment protocol violations were due to an excess dose delivered to the rectum. B-iCycle is able to maintain a low dose to the urethra (mean = 1940 Gy, SD = 0.3 Gy). The dose characteristics extracted from the B-iCycle dose statistics function, for the plans generated with B-iCycle, are presented in Appendix D.

SINGLE FRACTION 19 GY PLANS FOR THE PROGRESS PATIENT GROUP

Out of the five patients in the PROGRESS patient group, B-iCycle was able to generate clinically acceptable plans for four cases. B-iCycle was unable to generate a clinically acceptable plan for patient 3 and shown in Figure 18, by an overshoot in the dose to the bladder. The dose characteristics seen in the B-iCycle software, for this patient, fulfils all constraints and is clinically acceptable. On further inspection, the bladder volume differs as 329 cc B-iCycle and 327 cc for Oncentra. For this group, both, clinical plans and the B-iCycle plans maintain a relatively equal and low dose to the urethra, while delivering a target coverage of 95%.

Figure 19 shows the comparison between COIN coefficients of clinical plans and B-iCycle plans. Considering c1 and c3 individually, clinical plans and B-iCycle plans are almost equal in terms of target coverage and dose to the organs at risk. The c2 coefficient results more plans in favour of B-iCycle compared to clinical plans. The COIN coefficients are presented in Appendix E. The overall COIN index suggest that B-iCycle plans are better that clinical plans.

TABLE 9 DOSE CHARACTERISTICS OF CLINICAL PLANS AND B-ICYCLE IN A SINGLE FRACTION 19 GY PROTOCOL FOR PROGRESS PATIENTS (RED ID NUMBER: UNACCEPTABLE PLAN)

Clinical Plans

	Prostate	Bladder		Rectum		Urethra
	V100% (%)	D1cc (cGy)	D2cc (cGy)	D1cc (cGy)	D2cc (cGy)	D10% (cGy)
1	95.6	1422	1318	1435	1299	1961
2	95.0	1484	1363	1274	1111	1953
3	95.1	1484	1370	1312	1141	2049
4	95.4	1310	1159	1458	1313	1953
5	95.0	1383	1249	1389	1191	2025

B-iCycle Plans

	Prostate	Bladder		Rectum		Urethra
	V100% (%)	D1cc (cGy)	D2cc (cGy)	D1cc cGy)	D2cc (cGy)	D10% (cGy)
1	95.1	1498	1329	1373	1237	1948
2	95.1	1549	1403	1211	1055	1962
3	95.6	1631	1491	1352	1161	2037
4	94.5	1380	1210	1468	1315	1928
5	95.5	1536	1386	1401	1195	2035

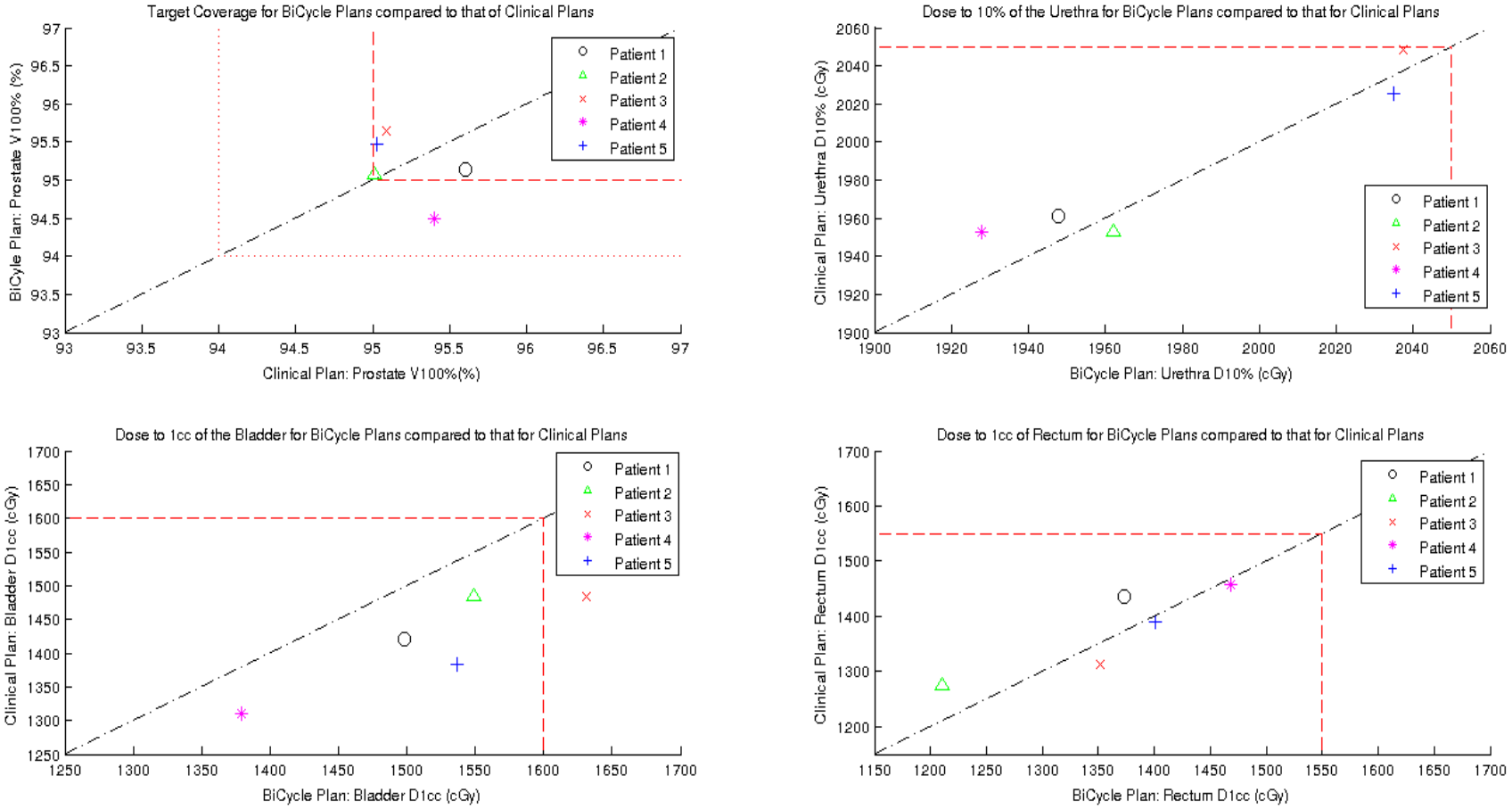

FIGURE 18 COMPARISON OF DOSE CHARACTERISTICS OF 1 X 19 GY PLANS FOR THE PROGRESS PATIENT GROUP. (RED DASHED LINE: MAXIMUM DOSE LIMIT FOR OAR / MINIMUM TARGET COVERAGE, RED DOTTED LINE: MINIMUM COVERAGE THAT MAY BE ACCEPTABLE

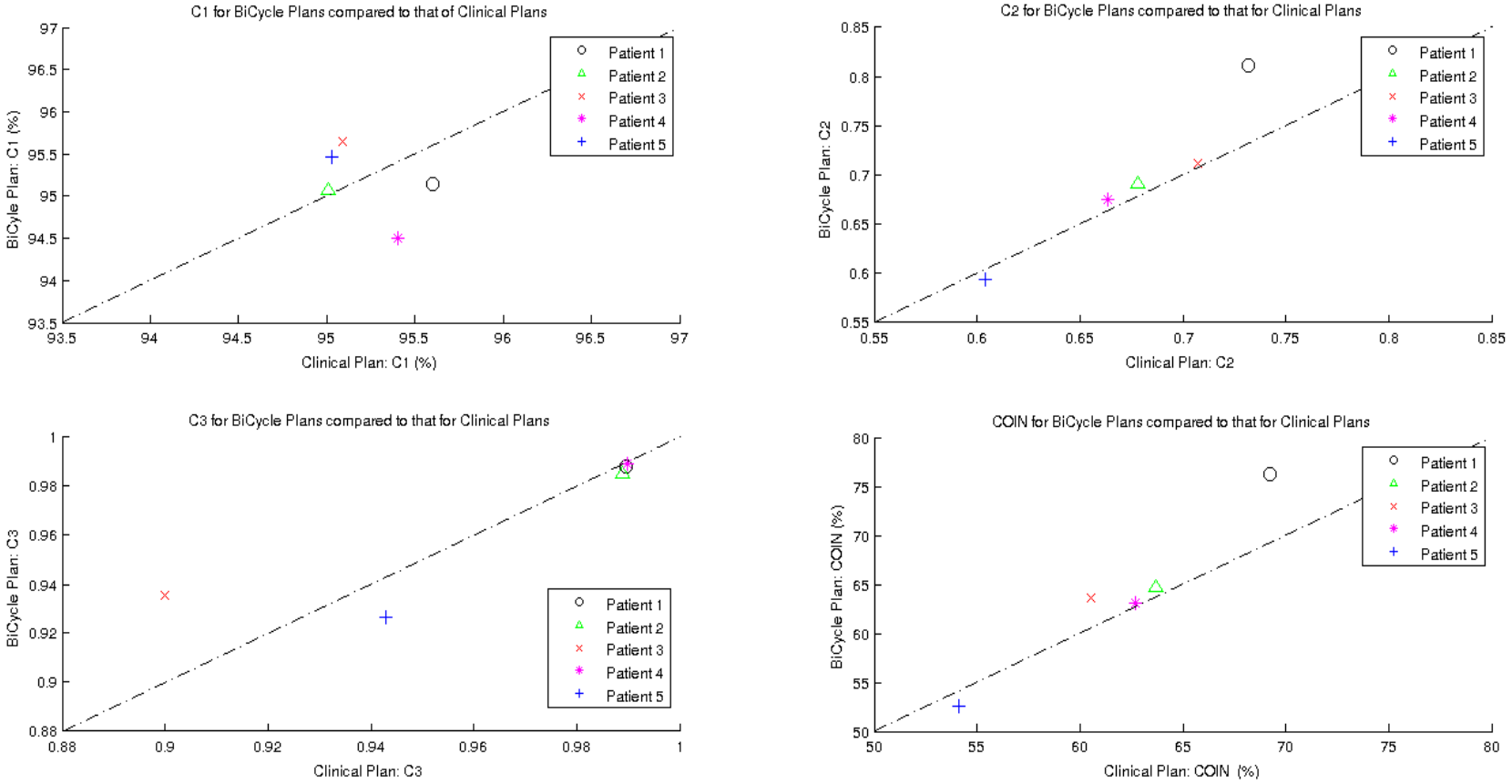

FIGURE 19 COIN COEFFICIENTS COMPARING 1 X 19 GY PLANS, B-ICYCLE PLANS AND CLINICAL PLANS, FOR THE PROGRESS PATIENT GROUP

5. Discussion

With respect to the current workflow for brachytherapy, it is a trial-and-error approach to treatment planning where the planner must iteratively tweak the optimizer parameters to find the acceptable plan, this may be a time-consuming process. The target coverage is a non-convex problem, subject to constraints on the dose to the OAR. B-iCycle is an answer to this challenge.

From the plans generated for the protocol of four fractions of 9.5 Gy, we can see that B-iCycle can generate quality, clinically acceptable plans that are comparable to the plans that are generated manually. The consistent plan quality of B-iCycle circumvents the issue of varying plan quality between planners. B-iCycle, with a well-designed wish-list, will always converge to the optimal plan, ensuring the best possible treatment for the patient.

The single fraction protocols for the prescribed doses of 19 Gy and 20 Gy are even more challenging to plan for manually, and take an average of 10-15 minutes to plan. B-iCycle is able to generate plans of equal, if not better, quality in a fraction of that time (10 seconds).

B-iCycle also uses a dose conformity constraint in the wish-list and can therefore limit the dose to the normal tissue better than the clinical planning system. This reduces the damage to the normal tissue and reduces the chance of radiotherapy induced cancers in the tissue.

For many of the plans seen in the results where the target coverage of 95% is achieved but the dose to one of the OAR violates the constraint by a small margin, these plans may have been clinically acceptable on the B-iCycle dose characteristics. On exporting these plans from the B-iCycle system to the Oncentra TPS, there may be a slight change in these dose characteristics that results in one of the dose constraints being violated, therefore clinically inacceptable. This difference arises from the difference in the method of calculating volumes of the organs from delineated CTs.

To ensure consistent plan quality, one possible additional step that can be taken is, the rescaling of the dose to the exact requirement of the treatment protocol. The target coverage can be rescaled to 95%, which is a matter of rescaling the dwell times. This would standardize the coverage and for the plans which were flagged as clinically unacceptable after import of the plan into the Oncentra, the rescaling would reduce the dose to the OAR to a value that may be acceptable to the treatment protocol.

Other automated treatment planning systems in literature such as the one presented by Gorissen et al. [17], consider maximization of the target coverage as the aim of treatment planning, B-iCycle on the other hand is more flexible. It allows for the selection of a plan that may not have the highest target coverage but is able to reduce the dose to the OAR, which may be clinically more favourable.

6. Conclusion

In this thesis project, an automated treatment planning system for HDR brachytherapy called B-iCycle was created. The TPS has a TG-43 protocol based dose engine. The dose engine was successfully verified by comparison with the dose engine of the clinical TPS (Oncentra). The 2pεc optimizer is used by the TPS to optimize on the dwell times for pre- segmented and selected dwell positions. Wish-lists were created for three treatment protocols and the plans generated with these wish-lists were compared to clinically generated plans. B-iCycle was able to generate clinically acceptable plans with equal, if not better, quality compared to the plans that were generated with the clinical work-flow. B-iCycle treatment planning is also much faster than the clinical workflow.

B-iCycle can be developed into the complete brachytherapy treatment planning tool by adding the ability to suggest and therefore improve catheter placements for a catheter implantation template. B-iCycle may be a tool that, in the future, may enable an on-the-go brachytherapy solution. Where the patient, once implanted with the catheters, can be imaged and planned for in the operating room, in a matter of minutes. This would greatly reduce the procedure time and improve patient comfort without compromising on treatment quality.

The B-iCycle module may be, in the future, incorporated into the Erasmus-iCycle treatment planning software suite that is in use at Erasmus MC.

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8. Appendix

APPENDIX A

TABLE 10 DOSE CHARACTERISTICS OF CLINCIAL PLANS AND B-ICYCLE PLANS IN FOUR FRACTIONS OF 9.5 GY FOR THE FOUR FRACTION PATIENTS. (RED ID NUMBER: CLINICALLY INACCEPTABLE PLANS)

	Clinical Plans				B-iCycle Plans				
	Prostate	Bladder	Rectum	Urethra		Prostate	Bladder	Rectum	Urethra
	V100% (%)	D1cc (cGy)	D1cc (cGy)	D1% (cGy)		V100% (%)	D1cc (cGy)	D1cc (cGy)	D1% (cGy)
1	97.82	585	710	1139	1	93.32	521	698	1035
2	98.5	630	654	1101	2	95.46	652	688	996
3	97.09	599	615	1133	3	94.77	592	666	1034
4	93.34	682	688	1114	4	94.31	663	687	1139
5	97.15	490	608	1114	5	95.77	542	667	1065
6	95.15	666	738	1122	6	96.16	695	730	1127
7	98	668	579	1122	7	95.77	669	578	1040
8	95.82	678	646	1100	8	96.31	723	661	1080
9	97.2	731	605	1135	9	95.36	702	549	1036
10	97.77	636	655	1102	10	95.36	688	687	1005
11	95.77	669	621	1119	11	96.38	706	643	1102
12	95.93	668	734	1101	12	95.82	698	726	1051
13	96.41	711	705	1117	13	95.92	732	719	1020
14	97.28	665	706	1101	14	95.64	718	704	1009
15	96.12	686	680	1105	15	96.18	709	687	1032
16	96.12	714	694	1136	16	95.59	770	717	1061
17	97	691	742	1112	17	95.62	722	737	1016
18	95.26	756	760	1135	18	95.16	740	729	1144
19	94.99	755	736	1136	19	96.3	759	751	1138
20	96.65	682	735	1115	20	96.2	711	742	1063
21	95.62	699	701	1136	21	95.86	716	735	1096
22	95.87	677	742	1131	22	96.11	739	762	1042

APPENDIX B

TABLE 11 COIN RESULTS FOR 4 X 9.5 GY PLANS FOR THE FOUR FRACTION PATIENT GROUP

Clinical Plans

ID	c1	c2	c3	COIN (%)
1	97.82	0.3620	0.9869	34.9498
2	98.5	0.5489	0.9972	53.9131
3	97.09	0.6695	0.9942	64.6248
4	93.34	0.6791	0.9884	62.6590
5	97.15	0.6747	0.9907	64.9375
6	95.16	0.7207	0.9862	67.6363
7	98	0.6913	0.9961	67.4836
8	95.82	0.7243	0.9976	69.2326
9	97.2	0.6512	0.9873	62.4927
10	97.77	0.7001	0.9973	68.2679
11	95.77	0.7509	0.9961	71.6327
12	95.93	0.7042	0.9935	67.1130
13	96.41	0.7856	0.9927	75.1841
14	97.28	0.7383	0.9925	71.2830
15	96.12	0.7323	0.9948	70.0267
16	96.12	0.8077	0.9902	76.8726
17	97	0.7314	0.9897	70.2120
18	95.26	0.8083	0.9715	74.7981
19	94.99	0.8044	0.9816	75.0088
20	96.65	0.8070	0.9919	77.3631
21	95.62	0.7953	0.9883	75.1554
22	95.87	0.8287	0.9915	78.7707

B-iCycle Plans

ID	c1	c2	c3	COIN (%)
1	93.32	0.7739	0.9956	71.9001
2	95.46	0.5988	0.9921	56.7107
3	94.77	0.6691	0.9956	63.1276
4	94.31	0.6397	0.9831	59.3065
5	95.77	0.6826	0.9929	64.9091
6	96.16	0.7036	0.9810	66.3763
7	95.77	0.7474	0.9968	71.3478
8	96.31	0.7227	0.9921	69.0504
9	95.36	0.7179	0.9955	68.1473
10	95.36	0.6943	0.9898	65.5393
12	96.38	0.7612	0.9892	72.5744
13	95.82	0.7827	0.9922	74.4130
14	95.92	0.8471	0.9877	80.2580
15	95.64	0.7662	0.9885	72.4382
16	96.18	0.8163	0.9909	77.7983
17	95.59	0.8600	0.9901	81.3959
18	95.62	0.7625	0.9891	72.1138
19	95.16	0.9523	0.9748	88.3338
21	96.3	0.8403	0.9771	79.0687
22	96.21	0.8700	0.9890	82.7808
23	95.86	0.8545	0.9882	80.9493
25	96.11	0.8457	0.9861	80.1560

APPENDIX C

TABLE 12 DOSE CHARACTERISTICS OF CLINICAL PLANS IN SINGLE FRACTION 20 GY PROTOCOL FOR FOUR FRACTION PATIENTS (RED ID NUMBER: CLINICALLY INACCEPTABLE PLANS)

Clinical Plans

	Prostate	Bladder		Rectum		Urethra
	V100% (%)	D1cc (cGy)	D2cc (cGy)	D1cc (cGy)	D2cc (cGy)	D10% (cGy)
1	93.35	1297	1119	1442	1284	2047
2	96.30	1468	1294	1450	1270	2049
3	93.31	1408	1223	1379	1189	2050
4	85.39	1543	1348	1423	1214	2049
5	91.65	1039	839	1492	1310	2049
6	89.45	1591	1423	1543	1424	2049
7	93.66	1511	1366	1253	1102	2049
8	92.88	1588	1464	1498	1317	2049
9	96.56	1600	1443	1550	1437	2049
10	96.31	1586	1462	1473	1307	2049
11	90.42	1598	1445	1329	1163	2049
12	93.80	1596	1481	1545	1386	2049
13	95.23	1594	1484	1548	1426	2049
14	96.23	1599	1451	1550	1398	2047
15	95.77	1601	1473	1546	1400	2048
16	91.36	1591	1477	1532	1378	2049
17	95.33	1586	1455	1545	1431	2050
18	87.21	1598	1466	1549	1423	2048
19	90.02	1599	1494	1539	1449	2049
20	92.74	1597	1482	1549	1429	2049
21	91.65	1596	1491	1552	1411	2049
22	91.87	1599	1486	1514	1450	2049

TABLE 13 DOSE CHARACTERISTICS OF B-ICYCLE PLANS IN SINGLE FRACTION 20 GY PROTOCOL FOR FOUR FRACTION PATIENTS. (RED ID NUMBER: CLINICALLY INACCEPTABLE PLANS)

B-iCycle Plans

	Prostate	Bladder		Rectum		Urethra
	V100% (%)	D1cc (cGy)	D2cc (cGy)	D1cc (cGy)	D2cc (cGy)	D10% (cGy)
1	92.58	1256	1103	1464	1280	2037
2	95.05	1428	1279	1410	1236	1993
3	91.62	1234	1112	1398	1219	2031
4	84.98	1382	1197	1426	1233	2028
5	91.80	1104	940	1394	1212	2049
6	88.89	1484	1342	1529	1417	2042
7	93.45	1465	1364	1234	1087	2041
8	90.73	1593	1474	1447	1276	2023
9	93.26	1544	1435	1193	1033	2037
10	95.15	1457	1360	1438	1270	2043
11	91.31	1543	1402	1357	1199	2048
12	94.24	1572	1443	1558	1380	2045
13	95.67	1618	1508	1511	1396	2049
14	95.45	1613	1434	1471	1330	2050
15	95.35	1544	1445	1450	1320	2048
16	93.28	1698	1557	1516	1363	2055
17	95.15	1567	1429	1549	1429	2049
18	88.14	1626	1506	1519	1395	2041
19	91.40	1642	1561	1586	1486	2049
20	93.19	1611	1500	1567	1439	2050
21	93.36	1580	1457	1544	1406	2056
22	94.80	1613	1513	1592	1520	2055

APPENDIX D

TABLE 14 B-ICYCLE DOSE CHARACTERISTICS OF B-ICYCLE PLANS IN THE 19 GY PROTOCOL FOR THE PROBACH PATIENT GROUP. (RED ID NUMBER: INACCEPTABLE PLANS)

	B-iCycle Plans						
	Prostate	Bladder		Rectum		Urethra	
	V100% (%)	D1cc (cGy)	D2cc (cGy)	D1cc (cGy)	D2cc (cGy)	D0.1cc (cGy)	D10% (cGy)
1	94.70	1130.89	1016.96	1500.13	1355.70	1881.86	1922.63
2	94.71	1111.30	1007.36	1204.53	1014.36	1878.29	1946.22
3	95.43	1460.54	1321.11	1658.01	1523.73	1932.28	1973.21
4	94.84	1407.92	1287.61	1447.39	1293.73	1826.63	1913.43
5	95.34	1499.72	1353.89	1615.60	1477.74	1868.12	1916.47
6	94.93	1485.12	1337.08	1430.48	1265.96	1885.56	1923.28
7	95.09	1584.09	1415.26	1475.56	1330.57	1879.21	1929.52
8	95.38	1531.90	1413.32	1628.43	1472.29	1805.24	1927.11
9	95.14	1621.62	1481.99	1497.78	1356.96	1965.06	2006.43

APPENDIX E

TABLE 15 COIN RESULTS FOR 1 X 19 GY PLANS FOR THE PROGRESS PATIENT GROUP

Clinical Plans

ID	c1	c2	c3	COIN (%)
1	95.6	0.7319	0.9896	69.2427
2	95.01	0.6779	0.9888	63.6926
3	95.09	0.7074	0.9001	60.5475
4	95.4	0.6637	0.9898	62.6771
5	95.03	0.6040	0.9429	54.1191

B-iCycle Plans

ID	c1	c2	c3	COIN (%)
1	95.14	0.8113	0.9882	76.2749
2	95.07	0.6909	0.9852	64.7118
3	95.64	0.7115	0.9355	63.6629
4	94.5	0.6747	0.9890	63.0582
5	95.47	0.5940	0.9267	52.5475