MSc Thesis

RADIOBIOLOGICAL MODELS BASED EVALUATION OF THE CONSEQUENCES OF POSSIBLE CHANGES IN THE IMPLANT GEOMETRY AND ANATOMY IN THE HDR BRACHYTHERAPY OF PROSTATE CANCER

KATSILIERI ZAIRA - CHRISTIANA

Examination Committee:
Nikiforidis G., Professor, Panagiotakis G., Professor, member, Kagkadis G., Professor, member

Supervisor:
Nikiforidis G., Professor, Mavroidis Panayiotis, Associate Professor, Karolinska Institutet & Stockholm University, Sweden

Local Supervisor:
Baltas Dimos, Professor, Strahlenklinik Offenbach, Germany

Patras, September 2009, Greece
ABSTRACT

Radiobiological models based evaluation of the consequences of possible changes in the implant geometry and anatomy in the HDR Brachytherapy of prostate cancer (4D-Planning)

Purpose: The purpose of this work is to investigate the influence of possible patient movement and anatomy alteration on the quality of delivered prostate US based HDR-brachytherapy. The effect of patient movement and anatomy change (after the needle implantation and 3D image set acquisition) on catheter and organ dislocation and the consequences that this generated on the DVHs, conformity index and on radiobiological parameters.

Materials and methods: This work is based on 3D image sets and treatment plans of 48 patients obtained right after the needle implantation (clinical plan is based on this 3D image set) and before and after the irradiation. In our institution the 3D-US based pre-planning, the transperineal implantation of needles using template and the intraoperative planning and irradiation is realized using the real-time dynamic planning system Oncentra Prostate\(^1\). All pre-plans and all the inverse optimization of clinical plans were based on HIPO\(^2\) using the modulation restriction option. The patient body/OARs/catheters movement are generated from the clinical, pre- and post-irradiation plans and its influence on DVH-, COIN and radiobiological parameters of PTV and OARs are calculated and presented.

Results: It is observed a slight decrease of treatment plan quality with increase of time between the clinical image set acquisition and the patient irradiation. Also, we show that the patient body movement/anatomy alteration and/or catheters dislocation results in decreased plan quality; change of values of the COIN, DVH- and radiobiological parameters.

Conclusion: The measured mean shift of anatomy and needles (beams) is as low as 1.0mm that is lower by an order of magnitude to values known from external beam irradiation. For high modulated plans as those in HDR Brachytherapy such small shifts result in dosimetric changes which are in general lower than 5%. Our results demonstrate that quality assurance procedures have to be clinically implemented to guarantee anatomy and implant stability of the order of 1mm. This can only be realized without any manipulation of the implant and anatomy as done, for instance in the case of removing the US-probe before treatment delivery or moving the patient from one bed to another for the irradiation purposes.

---

\(^1\) OcP, Fa. Nuclertron B.V, The Netherlands

# Table of Contents

1. **GENERAL ASPECTS** ............................................................... 4
   
   1.1 HISTORY - THE BEGINNING OF BRACHYTHERAPY .......................... 4
   1.2 THEORETICAL BACKGROUND ................................................. 5
     
     1.2.1 Radioactivity .............................................................. 5
     1.2.2 Energy Conversion ...................................................... 6
     1.2.3 Deposition of Energy .................................................. 7
     1.2.4 Source Strength Specification ....................................... 9
   1.3 BRACHYTHERAPY .................................................................... 10
     
     1.3.1 High Dose Rate Brachytherapy ......................................... 12
     1.3.2 Iridium-192 ................................................................. 12
   1.4 AFTERLOADING TECHNIQUE AND AFTERLOADING EQUIPMENT ............ 13
   1.5 PROSTATE CANCER ............................................................... 17
     
     1.5.1 Anatomical Topography of Prostate ..................................... 17
     1.5.2 Detection of Prostate Cancer ........................................... 19
     1.5.3 Pathology – Staging of Prostate Cancer ............................... 20
     1.5.4 Treatments of Prostate Cancer .......................................... 21
   1.6 TREATMENT PLANNING .......................................................... 23
     
     1.6.1 Volume Definitions in Brachytherapy ................................... 23
     1.6.2 Dose Volume Histograms ................................................ 24
     1.6.3 DVH based parameters in Brachytherapy ............................... 26
   1.7 HDR BRACHYTHERAPY IN STRAHLENKLINIK OFFENBACH .................... 28
     
     1.7.1 Infrastructure ............................................................... 29
     1.7.2 Work flow ..................................................................... 32
     1.7.3 Clinical Protocols .......................................................... 35

2. **METHODS AND MATERIALS** .................................................. 35
   
   2.1 METHODS ............................................................................. 35
     
     2.1.1 Conformal Index (COIN) .................................................. 35
     2.1.2 Radiobiological Evaluation .............................................. 37
     2.1.3 Radiobiological Indices .................................................... 40
   2.2 MATERIALS ............................................................................ 46

3. **RESULTS & DISCUSSION** .................................................... 51

4. **CONCLUSION** ....................................................................... 79

LITERATURE ................................................................................. 81
1. General Aspects

1.1 History - The Beginning of Brachytherapy

Although the discovery of X – Rays by Roentgen in 1895 and of activity by Becquerel discovery in 1896 were closely, their clinical application was separated by a decade. The Crookes tube was inexpensive and readily available, and so the diagnostic exposures were being made within months of Roentgen’s discovery. The discovery of activity in 1896 led to the discovery of radium by Maria and Pierre Curie in 1898 (1; 2). Implanting radioactive sources directly into a tumour was an idea first suggested by Alexander Graham Bell (1903), the inventor of the telephone. The development of brachytherapy was owing initially to the purification of radium by Marie and Pierre Curie and later to the construction of platinum needles to contain the radium sulfate (3). After the discovery of radium, the biological results were observed and exploited, with most applications involving brachytherapy or short distance therapy (4). The first successful radium brachytherapy treatment for cancer was in 1903 in St. Petersburg (1). Until the late 1920s there was the opinion that a uniform distribution of sources on a surface applicator or for a single planar interstitial implant would produce a uniform dose distribution. During the 1930s it was shown that a non uniform distribution of sources produce a uniform dose distribution thus the rules of Manchester System for interstitial radium therapy were published by Patterson and Parker and later by Meredith. In 1934, Irene Curie (Pierre and Marie Currie’s daughter) and her husband Frederick Joliot discovered artificial radioactivity by particles accelerators. However, quantities and forms of radioactivity useful for brachytherapy were not available until 1940s, when civilian applicators of nuclear reactors were encouraged. In the US, reactor – produces teletherapy and brachytherapy source development was coordinated by the Medical Division of the Oak Ridge Institute for Nuclear studies, which was created by the US Atomic Energy Commission. Barshall Brucer, along with developing one of the first cobalt teletherapy devices, his group collaborated in the design, production or dissemination of virtual all of the radium-substitute sources investigated in the US during the 1950-1965 period. In Canada and UK, the Chalk River and Harwell (1952) reactor sites made important contributions to medical use of artificial radionuclides. (5) For local and systemic applications, $^{32}$P, $^{131}$I and $^{198}$Au were used, but these applications as well
as some of the radionuclides have been discarded. Of the early developments sources still in use are $^{131}$I solution for Thyroid, $^{125}$I as seeds and $^{192}$Ir as wire or seeds, and $^{137}$Cs as tubes. Radium is no longer used because of radiation protection concerns. The Paris System which was developed much later by Pierquin, Chassagne and Dutreix established new rules for interstitial brachytherapy of iridium wire sources. $^{192}$Ir is the standard brachytherapy source today in the form of miniature sealed sources for use in high dose rate (HDR) afterloading systems (3; 1). With the development of remote afterloading machines, the last two decades, it has been allowed complete radiation protection. The ability to vary source positions and the time that a source is in that position (dwell time) has improved the quality of the treatment. Modern imaging allows more accurate definition of target volume and the localization of normal tissues and can also be used to guide afterloading and sources devices. These together with the knowledge of computerized dosimetry and of the radiobiology involved have made brachytherapy much more accurate and safe (6).

1.2 Theoretical Background

1.2.1 Radioactivity

A nuclide is a species of atoms that have a specific number of protons (atomic number $Z$) and a specific number of neutrons ($N$) in their nucleus. The property of several nuclides (unstable nuclides) spontaneously, without any external influence such as temperature or pressure, and under emission of irradiation to be transformed (disintegrated) in other stable nuclides is described as radioactivity. In this process, the whole atom (nuclei and orbital electrons) is involved. The unstable nuclides are called radionuclides. Radioactivity is a stochastic process. Its values follow a specific probability distribution. In a number of nuclei of a specific radionuclide it is not possible to predict which of them will undergo a spontaneous nuclear transformation (i.e., will decay) and when. Any nucleus may decay in any given interval with a certain probability. (1)
1.2.1.1 Decay Constant

If $dp$ is the probability that a given nucleus of a radionuclide in a particular energy state undergoes a spontaneous nuclear transformation from that energy state in the time interval $dt$, the decay constant $\lambda$ (s$^{-1}$) is defined as

$$\lambda = \frac{dp}{dt} \quad (1.1)$$

According to this the half-life $T_{1/2}$ (s) of a radionuclide is defined as $T_{1/2} = \ln(2)/\lambda$. $T_{1/2}$ is the time increment required for the number of radionuclides in the particular energy state to be reduced to one half of this number.

Another quantity of great practical importance is the mean life $\tau$ of a radionuclide. It is defined as the inverse of the decay constant and represents the mean lifetime of an individual nucleus. (1)

$$T = \frac{1}{\lambda} = \frac{T_{1/2}}{\ln(2)} \quad (1.2)$$

1.2.1.2 Activity

In order to describe quantitatively the time rhythm of the occurrence of spontaneous nuclear transformation (decays) of an amount of a specific radionuclide, the activity $A$ (s$^{-1}$) is defined as

$$A = \frac{dN}{dt} \quad (1.3)$$

where $dN$ is the number of decays observed during the time interval $dt$. The special name for the unit of activity is Becquerel (Bq). Until recently, the unit used to describe activity has been the Curie (Ci): 1Ci = $3.7 \times 10^{10}$ Bq. (1)

1.2.2 Energy Conversion

A number of quantities and units have been defined for describing the radiation beam and the most commonly used dosimetric quantities and their units are defined below. (1)
1.2.2.1 Kerma

The quantity kerma (from the kinetic energy released per unit mass) refers to the kinetic energy of charged particles, e.g., electrons and positrons that have been liberated by uncharged particles such as photons. Kerma does not include the energy that has been expended against the binding energies of these charged particles, even if this is usually a relatively small component.

If $dE_{tr}$ is the sum of the initial kinetic energies of all charged particles liberated by uncharged particles within a volume element $dV$ of a material containing a mass $dm=\rho dV$ of that material, the kerma $K$ (J kg$^{-1}$) is given by

$$K = \frac{dE_{tr}}{dm} = \frac{1}{\rho} \frac{dE_{tr}}{dV}$$

(1.4)

The name of the SI unit for kerma is gray (Gy): $1\text{Gy}=1\text{ J Kg}^{-1}$. (1)

1.2.2.2 Kerma rate

The kerma rate $\dot{K}$ (J Kg$^{-1}$s$^{-1}$) is the quotient of the kerma increment $dK$ occurring in the time interval $dt$ by the time interval $dt$:

$$\dot{K} = \frac{dK}{dt}$$

(1.5)

the unit of kerma rate is gray per second: $1\text{ Gy s}^{-1}= 1\text{ J kg}^{-1}\text{ s}^{-1}$. As with the case of kerma, kerma rate can be defined for a specific material at a point inside a different material (medium). (1)

1.2.3 Deposition of Energy

The energy deposition in matter is a stochastic process and the quantities discussed in the following for describing this are stochastic: their values are not unique but they follow a probability distribution.
1.2.3.1 Deposit of Energy

Let us consider an ionizing particle that undergoes a single interaction $i$ in matter. The energy deposited by this particle in this single interaction is called energy deposit $\varepsilon_i$ (J) and is defined according to

$$\varepsilon_i = \varepsilon_{in} - \varepsilon_{out} + Q \quad (1.6)$$

$\varepsilon_{in}$ is the energy of the ionizing particle before the interaction with its rest energy is excluded and $\varepsilon_{out}$ is the sum of the energies of all ionizing particles leaving this interaction where their rest energies are again excluded. $Q$ is the change occurring in the rest energies (masses) of the nucleus and of all particles that are involved in the interaction. If there is a decrease of rest energy, $Q$ has a positive value; otherwise $Q$ has a negative value. (1)

1.2.3.2 Energy Imparted

If we consider now all energy deposits $\varepsilon_i$ that take place within a given volume in matter, the energy imparted $\varepsilon$ (J) is defined as the total energy deposited in that volume expressed as the sum of all these energy deposits:

$$\varepsilon = \sum_i \varepsilon_i \quad (1.7)$$

Given that the energy deposit is the result of a single interaction of an ionizing particle at some transfer point within the volume under consideration, we can express the mean energy imparted $\bar{\varepsilon}$ to that volume in matter in terms of radiant energy as

$$\varepsilon = R_{in} - R_{out} + \sum Q \quad (1.8)$$

where $R_{in}$ is the radiant energy of all ionizing particles entering the volume and $R_{out}$ is the radiant energy of all ionizing particles leaving that volume. The summation term in the above equation extends over all changes $Q$ of the rest energy of nuclei and particles occurring in the volume. (1)
1.2.3.3 Absorbed Dose

If $d\bar{E}$ is the mean energy imparted to matter in a volume $dV$ of mass $dm = \rho dV$ then the absorbed dose $G$ (J Kg$^{-1}$) is defined as

$$D = \frac{dD}{dt}$$

(1.9)

As in the case of kerma rate, if the special name gray is used, the unit of absorbed dose rate is gray per second: $1$ Gy s$^{-1} = 1$ J kg$^{-1}$ s$^{-1}$. (1)

1.2.3.4 Absorbed Dose Rate

The absorbed dose rate $\dot{D}$ (J kg$^{-1}$ s$^{-1}$) is the quotient of the increment of absorbed dose $dD$ observed in the time interval $dt$ by this time interval:

$$\dot{D} = \frac{dD}{dt}$$

(1.10)

As in the case of kerma rate, if the special name gray is used, the unit of absorbed dose rate is gray per second: $1$ Gy s$^{-1} = 1$ J kg$^{-1}$ s$^{-1}$. (1)

1.2.4 Source Strength Specification

The currently recommended source strength specifications are:

*Reference air rate Kerma $\dot{K}_R$*

The reference air kerma rate of a source is defined as the air kerma rate in air at a reference distance of 1m from the center of the source corrected for attenuation and scattering in air. The ICRU Report 58 proposed that the reference air kerma rate should be expressed either in mGyh$^{-1}$ at 1 m or $\mu$Gyh$^{-1}$ at 1 m.

*Air Kerma Strength $S_K$*

In 1987, the American Association of Physisits in Medicine, in their report No21 by the AAPM Task Group No32 introduced the idea for the specification of brachytherapy sources in terms of strength. That is, the air kerma strength, $S_K$, defined
as the product of the air kerma rate in free space at a measurement distance \( r \) from the source center alone the perpendicular bisector, \( \dot{K}_a(r) \), and the square of the distance \( r \) (see Figure 1.1):

\[
S_K = \dot{K}_a(r) r^2
\]  

(1.11)

The distance \( r \) must be chosen to be large enough so that the source can be treated as a point source and so that the finite dimensions of the detector used for the measurement have no influence on the result.

The recommended unit for air kerma strength is \( \mu \text{Gy} \text{ m}^2 \text{ h}^{-1} \) and has been denoted by the symbol \( U \):

\[
1U = 1 \mu \text{Gy} \text{ m}^2 \text{ h}^{-1} = \text{cGy cm}^2\text{ h}^{-1}
\]

Although the air kerma strength \( S_K \) and the reference air kerma rate \( K_R \) are dimensionally different, the numerical values should be equal within the achievable dosimetric accuracy. (1)

---

**Figure 1.1** Schematic representation of the geometry as defined in AAPM Report 21 of the AAPM task group 32. This report is for the source strength specification using the air kerma strength, \( S_K \), concept for a cylindrical source. \( L_a \) is the length of the active part of the sealed source (active core) and \( r \) is the used radial distance for the measurement of air kerma rate in free space \( \dot{K}_a(r) \). (1)

### 1.3 Brachytherapy

Brachytherapy (from the Greek word “brachy”, meaning short), is a term used to describe the short distance treatment of cancer with radiation from small encapsulated radionuclide sources. One of the advantages compared to external beam radiotherapy, is that it provides localized radiation around the tumour with minimal doses to the
surrounding normal tissue (7; 8; 9). Different kinds of brachytherapy treatments have been defined with regard to the positioning of the radionuclide, duration of implant and dose rate which are summarized below.

a) Types of the positioning of the radionuclide (6; 7; 8; 10)
   - Interstitial, in which the sources are inside the tumour.
   - Contact brachytherapy, in which radioactive sources are close to the tumour.
     Contact brachytherapy is divided into four different kinds of brachytherapy:
     - Intracavitary, in which the radioactive source is placed in an applicator that has been positioned in a body cavity, i.e. the uterus, vagina etc.
     - Intraluminal, in which sources are placed in a lumen
     - Intravascular, in which a single source is placed into small or large arteries
     - Surface, in which sources are placed over the tissue to be treated.

b) Treatments Classified with respect to treatment duration
   - Temporary: The sources are implanted for a specific time of duration. Most of the implants in this type are using $^{192}$Ir, $^{137}$Cs or $^{60}$Co. Most of these implants can be performed with remote afterloading machines.
   - Permanent: The sources are implanted permanently into the tumour tissue until a complete decay. The most common permanent implants are using $^{125}$I, $^{198}$Au and $^{103}$Pd encapsulated seeds.

Intracavitary implants are always temporary; while interstitial can be temporary or permanent.

c) Treatment classified with respect to source loading
   - Hot loading: The applicator is preloaded and contains radioactive source at the time of placement into the patient
   - Afterloading: The applicator is placed first into the target position and the radioactive sources are loaded later, either by hand (manual afterloading) or by a machine (automatic remote afterloading).

d) Treatment classified with respect to dose rate (1)
- Low Dose Rate (LDR) the dose rate at the reference is 0.4-2.0 Gy h\(^{-1}\)
- Medium Dose Rate (MDR) the dose rate at the reference is 2-12 Gy h\(^{-1}\)
- High Dose Rate (HDR) the dose rate at the reference is >0.2 Gy min\(^{-1}\)

### 1.3.1 High Dose Rate Brachytherapy

In the past brachytherapy was mainly performed as LDR using Radium. According to modern radiation standards Ra and Rn are no longer used. The majority of interstitial brachytherapy implants are being performed as a HDR temporary brachytherapy implant and \(^{226}\)Ra has been replaced by Iridium \(^{192}\)Ir. HDR brachytherapy is one of the effective approaches for safely delivering greater doses to the target. The advantages of HDR treatment include (11; 12; 13; 14; 15):

- Short course compared to other type of radiation treatment
- Delivers high radiation dose, within a well defined volume, with a rapid falloff of the dose outside the implanted volume and at the same time sparing the normal tissues.
- Dose delivery is not affected by interfraction or intrafraction organ motion.
- There are no radioactive seeds left in the body after the procedure is over as in the case of permanent implants.
- No radiation exposure to medical staff.

### 1.3.2 Iridium-192

The most popular radionuclide in HDR-brachytherapy is Iridium-192 \((^{192}\text{Ir})\). It is produced by when stable \(^{191}\)Ir absorbs a neutron. Its half time is 73.81 days (1) and it decays mainly via \(\beta^-\), to several excited states of \(^{192}\)Pt (95 % of the time) and via EC (Electron Capture) to Osmium \((^{192}\text{Os})\) (5% of the time). On average 2.3 photons are emitted by both decay processes resulting in an average energy of the emitted photons of 0.355 MeV where the average energy of only the emitted \(\gamma\)- rays is 0.372 MeV.

\[
^{192}\text{Ir} \rightarrow ^{192}\text{Pt} + 0^1_e + \gamma
\]
In the past $^{192}$Ir it was fabricated in the form of thin flexible wires which can be cut in desired lengths. These wires could then be manually or automatically afterloaded in the implanted catheters.

In our days the most common Iridium sources are of HDR or PDR type. These are of cylindrical shape. The cylindrical active core is encapsulated in a thin titanium or stainless steel capsule to allow smoother handling in HDR afterloading equipment and to guarantee avoidance of leakage due to friction of source with applicator and connector parts. These sources are welded in a drive cable that is used for driving the sources in the afterloaders.

Because of the lower energy, $^{192}$Ir sources require significantly less shielding than for Radium, $^{137}$Cs or $^{60}$Co. Due to its relatively long (almost 2 months) half life it can be use for temporary implants by making decay corrections of approximately 1% per day. (8; 1; 16)

![Image](image_url)

**Figure 1.2:** The $^{192}$Ir source, placed in a stainless steel, capsule and laser welded to the end of a flexible steel wire. (1)

### 1.4 Afterloading technique and Afterloading equipment

When a radioactive source is positioned in the patient after the surgical procedures, i.e. after the insertion of the applicators, the technique is called “afterloading”. There are two types of afterloading:
Manual afterloading systems: plastic tubes, guide gutters, hypodermic and guide needles, plastic needles for interstitial brachytherapy; applicators for intracavitary or surface brachytherapy; catheters for intraluminal applications.

Remote afterloading systems: these can be used with interstitial as well as with contact brachytherapy. Afterloading equipment is connected to various types of applicators and catheters. Remote afterloading is mandatory for MDR, HDR and PDR brachytherapy for reasons of radiation protection.

Since the present work carried out in Strahlenklinik Offenbach we will analyze the remote afterloader that it is used here.

In Strahlenklinik Offenbach the remote afterloading machine which is used is MicroSelectron – HDR Vs.3 Genius\(^3\) (Figure 1.3) with a single \(^{192}\)Ir source, with initial activity of usually 370 GBq (10Ci) and thus of an initial source strength of 40.82 KU. Technically sources for HDR afterloading are realized by a core of pure \(^{192}\)Ir, with 4-5 mm length and 0.6-1.1 mm outer diameter, which is encapsulated in stainless steel or Ti/Ni mixture at the end of a metal wire. The dimensions of the sources vary with different commercial models and manufacturers. The source is welded to the end of a drive cable, transferred to programmed locations in the applicators (dwell positions), and held in the place for programmed duration (dwell time), using a motor-driven system.

\(^3\) Nucletron B.V., Veenendaal, The Netherlands
The Microselectron HDR Vs.3 Genius (Figure 1.3):

- Shielded safe to hold the source when it is not used in the head of the machine. The safe also contains a check cable which identical in appearance with the source, but not radioactive.
- A stepper motor for the source and a stepper motor for the check cable (Figure 1.5). When the appropriate stepper motor rotates then, the source or the check cable is advanced into the treatment channel and can be positioned with an accuracy of ±1mm.
- Several channels for source transport. Within each treatment channel the source can occupy up to 48 dwell positions with spacing of 2.5 mm, 5mm or 10mm. In MicroSelectron – HDR V3 Genius are 30 hardware channels available.
- The front face of the machine called the “indexer” has a series of numbered outputs ports to which the transfer tubes can be connected (Figure 1.4).
- Transfer tubes to connect the device to the applicators. The applicators which are used in interstitial brachytherapy of prostate in Strahlenklinik Offenbach are rigid stainless steel.
- Safety system to ensure safe operation of the device including:
  a) Automatic path – check of the applicator and transfer tube with a check cable. When the treatment starts the check cable in and out to the first
channel to check connectivity and for obstructions. If there is any problem then the treatment stops, else the source is driven to the first channel and stays in the dwell positions as it is programmed. The source retracts back to the safe and then the check cable and then the source can be driven out into the next channel and so on until all the required channels and dwell positions have been exposed as it is programmed.

b) Means of sensing the source position and timing of its motion.

c) Backup batteries to withdraw the source in the event of power failure and for saving treatment data

- Emergency system that allows the source to be withdrawn onto the safe if something goes wrong. Such a system must include a manual retraction mechanism.

A control console which operates the afterloader system is located outside the treatment room and shows the source position.

Due to the fact that these machines can use radioactive sources of high activity, gives the possibility of reducing the treatment times, thus improving the comfort of the patient. Due to the ability of adjusting the dwell time of the sources at the different dwell positions, the 3D dose distribution can be very fine shaped to cover the target volume and to avoid organs at risk. Moreover, because the source it is computed driven in the absence of the staff members (radiation oncologists, physicists, attending physicians, source curators, nurses) and after the completion of the irradiation the source returns to the safe thus we do not have any irradiation of the staff. (18; 19; 20; 21; 22).

Figure 1.4: Indexer, face of microSelectron HDR which guides the source into one of 30 channels. (17)
1.5 Prostate Cancer

1.5.1 Anatomical Topography of Prostate

The prostate (Figure 1.6 a & b) is a firm, partly glandular and partly muscular body, which is placed immediately below the internal urethral orifice and around the commencement of the urethra. It is situated in the pelvic cavity, below the lower part of the symphysis pubis, above the superior fascia of the urogenital diaphragm, and in front of the rectum, through which it may be distinctly felt, especially when enlarged. It is about the size of a chestnut and somewhat conical in shape, and presents for examination a base, an apex, an anterior, a posterior and two lateral surfaces. The base (basis prostate) is directed upward, and is applied to the inferior surface of the bladder. The greater part of this surface is directly continuous with the bladder wall; the urethra penetrates it nearer its anterior than its posterior border. The apex (apex prostate) is directed downward, and is in contact with the superior fascia of the urogenital diaphragm. The prostate is separated into a right and a left lateral lobe: these form the main mass of the gland and are directly continuous with each other behind the urethra. (23)
Figure 1.6: (a) Prostate anatomy b) Prostate with seminal vesicles and seminal ducts, viewed from in front and above.

In Figure 1.7 it can be seen the position of the prostate, the base and the apex of the prostate and its surrounding organs, under Ultrasound imaging. The red line shows the contour of the prostate and urethra, bladder and rectum are delineated with yellow, blue and green respectively.

Figure 1.7: Position of the prostate and its surrounding organs, under Ultrasound imaging. Left: axial view, Right: Sagittal view, Low: 3D view of the Prostate, urethra and Bladder.
Its major function is to produce seminal fluid or semen which is then stored in a small gland called the seminal vesicle until the time of ejaculation. As the prostate is at the junction of the urinary and reproductive systems for men, this means that any change in the prostate or enlargement can cause trouble passing urine.

The prostate is divided into the peripheral zone, transition zone, central zone, and anterior fibromuscular stroma. The peripheral zone constitutes 70% of the prostate gland and is readily palpated through the rectal wall. The central zone contains 20% to 25% of the prostate glandular tissue. The anterior fibromuscular stroma contains very little glandular tissue. Approximately 75% of prostate malignancies originate in the peripheral zone, 20% in the transition zone, and 5% in the central zone. The major routes of disease spread are direct extension, lymphatic drainage, and hematogenous spread (24; 25).

### 1.5.2 Detection of Prostate Cancer

Prostate cancer is one of the most common forms of cancer for men, mainly affecting men over the age of 65. As men get older, the likelihood of developing prostate cancer increases, therefore, physicians usually recommend that prostate cancer screening begin at age 50. For men with a family history of prostate cancer, physicians recommend screening beginning at age 40.

The uses of the PSA assay on the clinic, refinements in TRUS (transrectal ultrasonography), digital rectal exam (DRE) and directed biopsy of the prostate have vastly improved the ability to detect prostate cancer. PSA is a measurement of the amount of prostate-specific antigen in the blood. PSA is released into a man’s blood by his prostate gland. Serum PSA level also has been roughly correlated with prostate tumor volume. A serum PSA of more than 4 ng/ml is considered abnormal. The DRE is a traditional diagnostic tool for the detection of prostate cancer and is sometimes given during regular “physicals.” The doctor feels the prostate through the rectum, checking for irregularities that could indicate the presence of a tumor. Increasingly, doctors use the DRE in conjunction with the PSA test to diagnose prostate cancer. (26)
1.5.3 Pathology – Staging of Prostate Cancer

The degree of the differentiation is described by the Gleason scoring system, which is the most commonly used grading system for adenocarcinomas of the prostate, although more than 30 other systems have been described. Biopsy material (core biopsy or operative specimens) is required to be able to assess the Gleason score; cytological preparations cannot be used. The system describes a score between 2 and 10, with 2 being the least aggressive and 10 the most aggressive. This score is the sum of the two most common patterns (grades 1-5) of tumour growth found. (27; 28; 24).

CLASSIFICATION

The 2002 TNM (Tumour Node Metastasis) classification for CaP is shown in Table 1.1.

Table 1.1: Tumour Node Metastasis (TNM) Classification of CaP (29)

<table>
<thead>
<tr>
<th>PRIMARY TUMOR, CLINICAL (T)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
</tr>
<tr>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
</tr>
<tr>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1   Clinically inapparent tumor not palpable or visible by imaging</td>
</tr>
<tr>
<td>T1a  Tumor incidental histologic finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b  Tumor incidental finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c  Tumor identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level)</td>
</tr>
<tr>
<td>T2   Tumor confined within prostate*</td>
</tr>
<tr>
<td>T2a  Tumor involves one half of one lobe or less</td>
</tr>
<tr>
<td>T2b  Tumor involves more than half of one lobe, but not both lobes</td>
</tr>
<tr>
<td>T2c  Tumor involves both lobes</td>
</tr>
<tr>
<td>T3   Tumor extends through the prostate capsule**</td>
</tr>
<tr>
<td>T3a  Extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T3b  Tumor invades seminal vesicle(s)</td>
</tr>
<tr>
<td>T4   Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall</td>
</tr>
</tbody>
</table>
REGIONAL LYMPH NODES † (N)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional Lymph Node(s) cannot be assessed (e.g. previously removed)</td>
</tr>
<tr>
<td>NO</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in regional lymph node or nodes</td>
</tr>
</tbody>
</table>

DISTANT METASTASIS ‡ (M)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Nonregional lymph node(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone(s)</td>
</tr>
<tr>
<td>M1c</td>
<td>Other sites</td>
</tr>
</tbody>
</table>

* Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c.

** Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

† Metastasis no larger than 0.2 cm can be designated pN1

‡ When more than one site of metastasis is present, the most advanced category should be used.

RISK GROUP CRITERIA

Table 1.2: Risk Group Criteria (30)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk Group</td>
<td>T1-T2a and Gleason score 2-6 and PSA&lt;10 ng/mL</td>
</tr>
<tr>
<td>Intermediate Risk Group</td>
<td>T2b-T2c or Gleason score 7 or PSA 10-20 ng/mL</td>
</tr>
<tr>
<td>High Risk Group</td>
<td>T3a or Gleason score 8-10 or PSA&gt;20 ng/mL</td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>Very High: T3b-T4</td>
</tr>
</tbody>
</table>

1.5.4 Treatments of Prostate Cancer

Depending on the stage of the disease, of the Gleason score and of the PSA value there are three risk groups that characterised the prostate cancer, low, intermediate and high risk which lead to the selection of the appropriate treatment. Below they are described the alternative treatments for prostate cancer.
**Surgery:** Radical prostatectomy is the most common procedure which is usually done with early stage prostate cancer. In radical prostatectomy the entire prostate and the seminal vesicles are removed. Surgery is associated with urinary incontinence and erectile dysfunction.

**External Beam Radiotherapy (EBRT):** EBRT uses high energy rays. Radiotherapy can be used in all high risk groups of prostate cancer. The introduction of the three-dimensional conformal radiation therapy (3DCRT) resulted in excellent treatment results for clinically localized prostate cancer (T1 and T2). It is possible to deliver higher and more effective doses to the target (75-78 Gy), but higher doses to the rectal, consequently higher rectal complications. Also, with Intensity Modulated Radiation Therapy (IMRT), it is possible to improve control of the target and deliver higher doses to the prostate and lower to the normal tissues. In EBRT it is required the patient to come in the treatment center 5 days/week for 6-8 weeks.

**Chemotherapy,** which is the use of any one or combination of anti-cancer drugs and it is prescribed by medical oncologists. The drugs are given intravenously. It is given in advanced cancer stages that are no longer responsive to hormonal therapy.

**Hormonal Therapy:** One possible treatment in prostate cancer is by removing androgens from the body and making the cancer shrink and then grow slowly. The ways of removing androgens are: 1) orchiectomy, in which the testicles are removed and 2) by drugs which block the production of androgens. Hormone therapy can be used in conjunction with EBRT and brachytherapy in the case of intermediate and high risk groups.

**Brachytherapy:** As it has been described in Section 1.3 & 1.3.1, in brachytherapy because of the steep dose gradient between the target and the adjacent critical organs, allows the surrounding organs to be spared despite the delivery of high doses to the prostate cancer. Prostate brachytherapy can be done either with $^{125}$I or $^{103}$Pd as permanent implants, either with $^{192}$Ir as temporary implants using high dose rate. In the case of low risk group, HDR-Brachytherapy can be used as monotherapy while in intermediate risk group it can be used in combination with EBRT called Boost. (31; 32; 33)
1.6 Treatment Planning

1.6.1 Volume Definitions in Brachytherapy

To report a treatment correctly, the definition of the volumes is of utmost importance in brachytherapy as it is for external beam radiation. ICRU Report 58 (1997) introduced volume definitions for interstitial brachytherapy, as already known in external beam radiotherapy:

The *Gross Tumour Volume* (GTV) is the gross palpable, visible or clinically demonstrable extent and location of the malignant growth. The GTV may consist of the primary GTV (GTV-T), the metastatic lymphadenopathy (GTV-N) or distant metastases (GTV-M). In brachytherapy applications, the GTV is mainly the primary tumour, thus GTV-T.

The *Clinical Target Volume* (CTV) is the volume which contains the “gross” and “subclinical” malignant disease. Clinically, it thus contains the GTV and a “safety margin” around the GTV (GTV-T) to take into account probable subclinical involvement.

In implantation of a prostate is a procedure covering different targets and applying different target doses due to zonal anatomy related differences, possible tumour locations within the prostate gland and different implantation techniques and loading patterns used. Specifically for the target definition for the prostate brachytherapy there exists a recommendation by GEC/ESTRO-EAU which defines different target areas within the gland to record and report treatment parameters as outlined above related to the overall prostate CTV1, to the peripheral zone CTV2 and to areas where gross disease is detectable CTV3. (34)

The *Planning Target Volume* (PTV) is a geometrical concept used for treatment planning. In brachytherapy it is lower importance, compared to EBRT, because the radioactive source and the target volume are fixed to each other and does not need to deal with the problem of day to day treatment set up variations. Therefore, in brachytherapy, the PTV is often considered to be identical to the CTV.
In Strahlenklinik Offenbach and for the monotherapy the planning target volume is considered to be CTV1.

The Treated Volume (TV) is thus encompassed by an isodose surface corresponding to that dose level, which is the Minimum Target Dose (MTD).

The Organs at risk (OARs) (“critical normal structures”) are normal structures that, because of their radiosensitivity and/or their location close to the target volume, may significantly influence the treatment planning and/or the prescribed dose level.

ICRU Report 58 (ICRU 1997) also recommended using the Minimum Target Dose (MTD), which is related to the source arrangement and is the dose delivered to the periphery of CTV and the Mean Central Dose (MCD) which is the arithmetic mean of the local minimum doses between sources in the central plane. Finally, the high-dose region should be defined as that encompassed by the isodose corresponding to 150% of the MCD and the low-dose region is defined as a region, within the CTV, which is encompassed by the 90% isodose value. (35; 36)

1.6.2 Dose Volume Histograms

To represent the dose distribution over a 3D matrix of points over the patient’s anatomy it is needed a mechanism that reduces the voluminous data of a 3D dimensional distribution into a two – dimensional graph. The most common data reduction techniques is the dose volume histogram commonly referred to by the acronym DVH. Plots of DVHs summarize the information contained in the 3D dose distribution within a volume of interest (VOI) and are extremely powerful tools for quantitative evaluation of treatment plans. On this graph the physician can quickly see how the dose is distributed over a particular structure. DVHs are usually displayed in the form of “per cent volume of total volume” on the ordinate against the dose on the abscissa.

Two forms of DVH are commonly used in treatment planning, the differential DVH and the cumulative DVH. Which of these kinds of presentation should be used depends on the situation being analyzed. If one is interested in comparing the overall behavior of a number of different structures for one particular treatment plan, the cumulative histogram of each of these structures as for example PTV and normal
tissues, may be the most useful. If, on the other hand, one wants to try to understand in detail the shape of the histogram then the differential DVH is more relevant. (37; 38; 39)

- Direct (or differential) DVH

To create a differential DVH, the computer sums the number of voxels with an average dose within a given range and plots the resulting volume (or more frequently the percentage of the total organ volume) as a function of dose. An example of a differential DVH for a target is shown in Figure 1.8 (a). The ideal DVH for a target volume would be a single column indicating that 100% of the volume receives the prescribed dose. For a critical structure, the DVH may contain several peaks indicating that different parts of the organ receive different doses. An example of dDVH of critical structure can be seen in Figure 1.8 (b).

- Cumulative (or integral) DVH

Differential DVH do not give us information about how much of the volume (either relative or absolute) of the critical structure in question received a given dose, thus it would be necessary to determine the area under the curve for all dose levels above the prescription dose. For this reason, cumulative DVH displays are more popular.
The computer calculates the volume of the target (or critical structure) that receives at least the given dose and plots this volume (or percentage volume) versus dose. All cumulative DVH plots start at 100% of the volume for 0 Gy, since all of the volume receives at least no dose. In Figure 1.9 it can be seen the cumulative DVH for the same structures as in Figure 1.8. While displaying the percent volume versus dose is more popular, it is useful in some circumstances to plot the absolute volume versus dose. Furthermore, in the case of some critical structures, tolerances are known for irradiation of fixed volumes specified in cm³.

![Cumulative dose volume histograms](image)

**Figure 1.9**: Cumulative dose volume histograms for the same prostate brachytherapy treatment plan used in Figure 1.8. The ideal cumulative DVHs for the target and for OARs are shown on the right. Both volume and dose axes are given in % of VOI and prescription dose respectively.

DVHs, however, do not provide spatial information, such as the locations of the high- and low-dose regions (“hot” and “cold” spots) inside the volume of interest (VOI). (38; 37)

### 1.6.3 DVH based parameters in Brachytherapy

For the evaluation and documentation of the dose distribution GEC/ESTRO-EAU proposed DVH-based parameters which are described below (40; 41; 34; 35; 42).

**PTV – Oriented Parameters**

**D<sub>100</sub>**: The dose that covers 100% of the PTV volume, which is the strict definition of MTD.
**D_{90}**: The dose that covers 90% of the PTV volume. A D_{90} value of greater than or equal to the prescription dose is a measure of a good implant quality.

**V_{100}**: The percentage of prostate volume (PTV) that has received at least the prescription dose (100% = prescribed dose).

**V_{150}**: The volume that has received 50% more than the prescribed dose (150% of the prescription dose).

The definitions of the above parameters are shown graphically in Figure 1.10.

**OAR- Oriented Parameters**

The dose should be related to fixed points and/or fixed volumes, even if there is no general agreement on certain points or fixed volumes at present. There are suggestions to use the maximum doses for the OARs, where the maximum doses are considered to be (34; 42):

**D_{2cc}**: the dose for the most exposed 2 cm$^3$ of rectum or bladder,
**D_{0.1cc}**: the dose for the most exposed 0.1cm³ of the urethra

**D_{10}**: the highest dose covering 10% of the OAR volume (rectum, bladder, urethra)

The definitions of the above parameters are shown graphically in Figure 1.11.

![Graphical demonstration of the definition of the D_{10}, D_{2cc} dosimetric parameters for an imaging-based 3D brachytherapy treatment planning based on the cumulative dose volume histogram of Urethra](image)

**1.7 HDR Brachytherapy in Strahlenklinik Offenbach**

Since 1996 in Strahlenklinik Offenbach with cooperation with the Urologic clinic, is carried out the HDR Brachytherapy with $^{192}$Ir in combination with EBRT and since 2001 is carried out HDR Brachytherapy with $^{192}$Ir as monotherapy for low risk prostate cancer. Below are described the infrastructure, the workflow and the clinical protocols that the clinic uses.
1.7.1 Infrastructure

For the Brachytherapy of prostate cancer, Strahlenklinik Offenbach provides two operating rooms (Figure 1.12) with two operating theatre tables. The equipment which is used for the treatment procedure is the following:

![Figure 1.12: One of the two operating theatres.](image)

![Ultrasound units: (a) Aloka Type a10, (b) B-K Medical, Falcon Type 2101](image)

(a) 
(b)

*Figure 1.13: Ultrasound units: (a) Aloka Type a10, (b) B-K Medical, Falcon Type 2101*
Two Ultrasound units:

a) Ultrasound scanner Aloka Prosound a10⁴, with a biplanar probe UST-678. Figure 1.13 (a)

b) Ultrasound scanner BK-Medical Falcon Type 2101⁵, with a biplanar probe 8658T. Figure 1.13 (b)

The biplanar probes UST-678 by ALOKA (see Figure 1.14) can be operated in a frequency range of 1-15 MHz and for the 8658 Type B-K Probe in a range of 4-9 MHz.

![Figure 1.14: Ultrasound biplanar probe Aloka UST-678](image)

Each US device is equipped with a stepper encoder system (see Figure 1.15) which allows the acquisition of images with 1mm shifting. The transrectal probe is mounted on the stepper, in order to prevent movement. The encoder is mounted to the stepper device which allows the detection of the probe movement based on a reference position.

---

⁴ ALOLA CO., LTD., Tokyo, Japan
⁵ BK-MEDICAL, Herlev, Denmark
Figure 1.15: Stepper for (a) Aloka US probe and (b) B-K Medical US probe equipped with encoders for the digitization and tracking of the z-movement.

Also an immobilizer allows to the user a free possibility of positioning the stepper unit in all directions and keeps it stable during the duration of the procedure.

The stepper also provides an accessory (see Figure 1.16 (a)) to hold the template, which is used for the stabilization and precise placement of the needles. The template is metallic, with size 74.50x71x20 mm, also it is equipped with a matrix of holes with a space of 5mm between them (Figure 1.16 b).

Figure 1.16: (a) Accessory which holds the template (b) Template for HDR treatment

The needles (Figure 1.17) which are used are metal with a diameter of 1.5 or 1.9mm and a length of 200mm. Usually the 1.5mm are used since they are more flexible and cause less trauma during insertion.
For the clinical procedure it is used the real time intraoperative planning system Oncentra Prostate (OcP, Fa. Nucletron B.V, The Netherlands). The software provides the physician with anatomical and dosimetric information of radioactive sources and with a variety of plan evaluation tools to assist in generating the most optimal dose distribution.

1.7.2 Work flow

The procedure of brachytherapy of prostate in Strahlenklinik Offenbach is represented in the following schematic diagram. Stages 1-2 and 3 are used for the purpose of this project (see Section 2.2 Materials).

Step 1: The patient is placed in a lithotomy position after general or spinal anaesthesia

Step 2: Insertion of biplanar probe into the rectum.
Adjustment of image quality
Step 3: Immobilization of the prostate with two fixation needles. Definition of base plane (z=0). 3D acquisition by moving continuously the probe from cranial to caudal direction. Definition of apex and reference plane

Step 4: Contouring by the oncologist

Step 5: Pre-Plan
With the help of the OcP software, virtual catheters are created (blue catheters). This can be done either automatically (HIPO) or manually by the user. The resulting 3D dose distribution fulfills the clinical protocol (Table 1.3)
Step 6: Catheter Insertion (Implantation)

Step 7: Live – plan
- All needles are implanted
- Live acquisition, after definition of the base plane. (**STAGE -1**)
- New contouring by the radiation oncology
- Catheter Reconstruction (Green Catheters)
- Generation and optimization of dose distribution through OcP utility HIPO

**STAGE-2: Acquisition just before beginning the patient irradiation**

Step 8: Irradiation with the MicroSelectron afterloader. The implanted catheters are connected via transfer tubes to the afterloader.

**STAGE-3: Acquisition after the completion of patient irradiation**
1.7.3 Clinical Protocols

In Strahlenklinik Offenbach as already mentioned in Section 1.6.1 the PTV is considered to be the CTV1 (the prostate gland) and urethra, rectum and bladder are considered as OARs. The dosimetric protocol for monotherapy treatment is listed in the following table.

Table 1.3: Clinical Protocol in Strahlenklinik Offenbach for HDR monotherapy

<table>
<thead>
<tr>
<th>Organs</th>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prescribed Dose</td>
<td>11.5 Gy (=100%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>$D_{90}$</td>
<td>$\geq 100% $ (=11.5 Gy)</td>
</tr>
<tr>
<td></td>
<td>$V_{100}$</td>
<td>$\geq 90%$</td>
</tr>
<tr>
<td></td>
<td>$V_{150}$</td>
<td>$\leq 35%$</td>
</tr>
<tr>
<td>Urethra</td>
<td>$D_{10}$</td>
<td>$\leq 115%$ (=13.2 Gy)</td>
</tr>
<tr>
<td></td>
<td>$D_{0.1cm}^{3}$</td>
<td>$\leq 120%$ (=13.8 Gy)</td>
</tr>
<tr>
<td>Rectum</td>
<td>$D_{10}$</td>
<td>$\leq 75%$ (=8.6 Gy)</td>
</tr>
<tr>
<td></td>
<td>$D_{0.1cm}^{3}$</td>
<td>$\leq 80%$ (=9.2 Gy)</td>
</tr>
<tr>
<td>Bladder</td>
<td>$D_{10}$</td>
<td>$\leq 75%$ (=8.6 Gy)</td>
</tr>
<tr>
<td></td>
<td>$D_{0.1cm}^{3}$</td>
<td>$\leq 80%$ (=9.2 Gy)</td>
</tr>
</tbody>
</table>

A total of 3x fractions in 3 implants (1x fraction per implant) separated by ca. 2 weeks, are delivered for the monotherapy of low risk prostate cancer.

2. Methods and Materials

2.1 Methods

2.1.1 Conformal Index (COIN)

Baltas et al (43) has introduced a utility function as a measure of the implant quality and dose specification in brachytherapy, the conformal index (COIN), which has been later expanded to include OARs (44). The COIN takes into account patient anatomy, both of the PTV, surrounding NT and OARs. COIN for a specific dose value $D$ ($D_{ref}$) is defined as

$$COIN = c_1 \cdot c_2$$  \hspace{1cm} (2.1)

$$c_1 = \frac{PTV_{ref}}{PTV} \quad c_2 = \frac{PTV_{ref}}{V_{ref}}$$  \hspace{1cm} (2.2)
Where the coefficient $c_1$ is the fraction of the PTV ($PTV_{ref}$) that receives dose values of at least $D_{ref}$ and is a measure of how accurately the PTV is enclosed by $D_{ref}$. The coefficient $c_2$ is the fraction of the calculated (body) volume with dose values of at least $D_{ref}$ ($V_{ref}$) that is covered by the PTV. It is also a measure of how much of NT outside the PTV is covered by $D_{ref}$. The ideal situation is $c_1=c_2=1$ (see also Figure 2.1).

Normal tissue (NT) is considered to be a thin layer of tissue surrounding the PTV where no other VOIs are defined by the user. NT is utilized for avoiding the uncontrolled expansion of the dose outside the PTV in areas where no OARs are defined.

However Eq. 2.1 does not take into account the unwanted irradiation of parts of all critical structures. In this case the algorithm for COIN must be modified by using a third term, $c_3$, which is defined below for several ($i=1,2,3,\ldots$) critical structures.

$$c_3 = \prod_{i=1}^{N_{OAR}} \left(1 - \frac{V_{OAR}^{i}(D>D_{crit}^{i})}{V_{OAR}^{i}}\right)$$

(2.3)

and the COIN including OARs is calculated by the following equation

$$COIN = c_1 \cdot c_2 \cdot c_3$$

(2.4)

Figure 2.1 Volumes necessary for computation of the conformal index COIN

$V_{OAR}^{i}$ is the volume of the $i$th OAR and $V_{OAR}^{i}(D>D_{crit}^{i})$ is the volume of the OAR that receives a dose that exceeds the critical dose $D_{crit}^{i}$. The product in the equation for $c_3$ is calculated for all N_{OAR} OARs included in the treatment planning. In
the case where an OAR receives a dose $D$ above the critical value defined for a that structure, the conformity index will be reduced by a fraction that is proportional to the volume that exceeds this limit. The ideal situation is $\text{COIN} = c_1 = c_2 = c_3 = 1$. The COIN assumes in this form that the PTV, the OARs and the surrounding NT are of the same importance. (35; 43; 44)

2.1.2 Radiobiological Evaluation

2.1.2.1 Introduction

Radiobiology is a science that deals with the action of ionizing radiation on biological tissues and living organs. Radiobiology identifies mechanisms which are responsible for the response of tumours and normal tissues to irradiation. It describes the impact of observed phenomena like hypoxia, reoxygenation, cell repopulation and mechanisms of repair of DNA. Finally it is important for selecting appropriate treatment, schedules in clinical radiotherapy and promotes the development of new approaches in radiotherapy.

The biological effects of radiotherapy depend on dose distribution, treated volume, dose rate, fractionation and treatment duration. These various factors are of different importance in determining the outcome of external beam radiotherapy or brachytherapy. In brachytherapy the prescribed dose refers to an isodose line encircling the small target volume and it is very heterogeneous due to the rapid fall off in the vicinity of the sources. Nowadays, improved control source placement and dwell times can enhance the degree of conformity and with modern afterloading equipment, the control of source position and dwell times is allowed in CLDR, HDR and PDR brachytherapy. The above features require an understanding of the physical and radio biological interactions in order to achieve the best therapeutic result. The radiobiological mechanisms that take place during irradiation are described below. (45; 46)

2.1.2.2 Radiobiological Mechanisms

The absorption of ionizing radiation by matter is followed by events, of which depend on absorbed dose, the chemical and physicochemical composition of the irradiated material. Various stages can be recognized in the development of radiation
effects. A very short initial physical phase involves the interaction between charged particles and atoms comprising the tissue. A high speed e- takes about $10^{18}$ seconds to transverse DNA molecule and about $10^{14}$ sec to pass across a mammalian cell. The interactions that take place are ionization or excitation. A chemical phase which is very short $\sim 10^3$ sec during which the damaged atoms and molecules interact leading to the breakage of chemical bonds and the formation of free radicals. These are highly reactive and can lead to stable chemical changes in DNA. The biological phase can last from seconds to years. In this phase specific repair enzymes can successfully repair the vast majority of lesion in DNA. Some rare lesions fail to repair and these eventually lead to cell death, which may not be immediate. After small doses of irradiation the heavily damaged cells may undergo a number of mitotic divisions before dying. The early manifestations of normal tissue damage are caused by the killing of stem cells and the subsequent loss of cells. The early reactions are seen during the first days or weeks after irradiation (for example diarrhea or acute mucositis). Late reactions due to damage to the late reacting tissues, for example blood vessel damage, fibrosis etc, may be seen after months or years. Damage to these late reacting normal tissues is poorly repaired and is responsible for most severe complications of radiotherapy. The sparing of these tissues is an important constraint for radiation therapy. (45; 46)

2.1.2.3 The 4Rs of Radiobiology

A number of biological processes take place during irradiation and may modify radiation response. These processes are described as the 4Rs of radiobiology: 1) Repair 2) Reassortment 3) Repopulation 4) Reoxygenation. However biological effects also depend upon the rate of dose delivery.

The radiobiological processes involved in high dose brachytherapy are similar to those involved in fractionated EBRT. Repair, repopulation and reoxygenation are the main factors determining the treatment outcome. They do not occur during very short duration of irradiation (up to 10-15 minutes), but take place between consecutive fractions, provided the time interval is adequate. Repopulation does not occur in late responding normal tissue during the course of a 6-7 weeks irradiation schedule, but plays a role in early reactions and tumour cell killing. Proliferation has a little effect in tumours for treatment times shorter than 3-4 weeks. (45; 46)
2.1.2.4 Cell survival curves

A cell survival curve is a plot of surviving fraction against dose. They are plotted on a logarithmic scale of survival. At low doses for sparsely ionizing radiations (low LET) the survival curve starts out straight and the bends downward. At high doses the curve may straighten out again. For high LET, the survival curve is almost a straight line from the origin. (45)

2.1.2.5 Linear Quadratic (LQ) model

Models are now regarded as a natural part of a scientific method. In radiobiology research they are necessary for predicting the radiation response of biological systems. The biological effects of radiotherapy depend on dose distribution, treated volume, dose rate, fractionation and overall treatment duration.

The assumption of an underlying dose response curve corresponding to a cell survival curve, to calculate the log cell kill from multiple fractions is basic. The dependence of tissue effect on dose rate and fractionation schedule using HDR brachytherapy treatment can satisfactorily be described by the LQ model.

Cell survival after irradiation depends on dose in a linear quadratic manner when plotted as the logarithm of survival fraction versus dose. Using this model the survival fraction of cells irradiated with a single dose \( D \), is described by the following Poisson statistics based equation:

\[
SF = e^{-(\alpha D + \beta D^2)} \tag{2.5}
\]

It is useful to consider equation (2.5) as describing two processes, which may lead to cell death. In the first process, two critical sites (targets) within the cell are simultaneously damaged (hit) in a single radiation event. Such hits in adjacent targets lead to the death of the cell. The induction of a single lethal damage events is proportional to dose. This is the linear component \( \exp(-\alpha D) \). In the second process the cells targets are damaged in separate radiation events after which the damaged sites may cooperate to produce cell death. When only one of the target doublets is hit, we may consider the cell to be sublethally damaged. The probability of inducing two independent sublethal damage events, which will be closed enough to interact, is proportional to the square of dose. This is the quadratic component \( \exp(-\beta D^2) \) of
equation (2.5). Lethal damage events are not influenced by fractionation or dose rate, whereas more sublethal damage could be repaired when radiation exposure time is extended. Thus, the α and β parameters measure the amount of the two processes. The α and β parameters are the cell radiosensitivity coefficients and are expressed in units of Gy\(^{-1}\) and Gy\(^{-2}\) respectively. Therefore the ratio \(\alpha/\beta\) is expressed in units of Gy and is of prime significance.

In a logarithmic representation the survival curve shows an initial linear decrease at low doses followed by shoulder for which the bending is determined by the \(\alpha/\beta\) ratio. The α parameter determines the initial slope of this curve, whereas, parameter β determines the degree of curvature. Thus a lower \(\alpha/\beta\) value means a more bendy curve.

The \(\alpha/\beta\) ratios provide an indication of the sensitivity of a given tumour or organ to changes in dose-rate as well as to changes in dose per fraction. The ratio for early normal tissues is high, whereas for late normal tissues is low. When dose per fraction decreases, the tissues being characterized by low values of \(\alpha/\beta\) are preferentially spared relative to those with higher \(\alpha/\beta\) values. The difference in fractionation sensitivity between early and late reacting tissues is interpreted as reflection of their differences in DNA damage repair capacity. (47; 48; 49; 46; 50; 51; 52)

For tumours \(\alpha/\beta\) ratio is generally high, it is reported to be in the range of 5-25 Gy. An important exception to this generalization about the tumour is prostate adenocarcinoma for which the \(\alpha/\beta\) ratio may vary in the range 1.5-3.0 Gy. (47; 53; 54)

2.1.3 Radiobiological Indices

2.1.3.1 Biological Equivalent Uniform Dose (BED)

We may consider that biological effect (E) in irradiated tissues is uniquely determined by the surviving fraction of cells. The level of effect is related to the survival curve by:
Effect of a single dose $E = -\ln(SF)$ \hfill (2.6)

Using (2.5) we have:

$$E = \alpha D + \beta D^2 \hfill (2.7)$$

Since we usually know from the clinical trials the value of the $\alpha/\beta$ ratio with a higher accuracy than the values of the $\alpha$ or $\beta$ parameters individually, we divide both parts of the previous equation by $\alpha$ to obtain the ratio $\alpha/\beta$, thus:

$$BED = \frac{E}{\alpha} = \frac{-\ln(SF)}{\alpha} = D + \left(\frac{\beta}{\alpha}\right) D^2 \hfill (2.8)$$

The term $E/\alpha$, is called the Biologically Effective Dose, BED and it is a measure of the biological dose delivered to a tumour or organ. BED is a measure of effect in units of Gy$_x$, where the suffix $x$ indicated the value of $\alpha/\beta$ assumed in the calculation. It is the theoretical total dose that would be required to produce a particular isoeffect using an infinitely large number of infinitesimally small fractions.

For $n$ equal fractions of $d$ each, the survival fraction will be $e^{-n(\alpha d + \beta d^2)}$, thus the equation (2.7) becomes:

$$E = \frac{n}{\alpha} = nd + n \left(\frac{\beta}{\alpha}\right) d^2 \Rightarrow$$

$$BED = \frac{E}{\alpha} = nd \left(1 + \left(\frac{\beta}{\alpha}\right) d\right) \hfill (2.9)$$

Equation (2.9) can be described as

$$BED = \text{Total dose} \times \left(1 + \frac{d}{\alpha/\beta}\right) \Rightarrow BED = D \times RE \hfill (2.10)$$

The term in the brackets is called the relative effectiveness, RE. RE depends only upon dose per fraction and type of tissue ($\alpha/\beta$).

$$RE = 1 + \frac{d}{\alpha/\beta} \hfill (2.11)$$

Since in this work high dose rate brachytherapy of prostate is investigated, corrections for repair and for tumour repopulation are not included. Repair does not occur during irradiation, because the exposure times are short (~15min). Furthermore, DNA repair occurs only between successive fractions and provided that the gaps
between fractions are long enough to ensure complete repair, the repair rate is irrelevant. Also, prostate behaves as a late responding tissue with a very low repopulation rate, T\text{pot} \sim 42 \text{ days}, which is almost the same as the length of the entire treatment for HDR brachytherapy (55). (56; 57; 58; 52; 46; 59; 60; 61)

2.1.3.2 Generalized Equivalent Uniform Dose (gEUD)

Although cumulative DVHs and differential DVHs have become indispensable tools in modern 3-D treatment planning, their usage for dose specification and reporting is typically limited to selecting a point on a DVH plot to which the prescription dose is defined.

Brachytherapy provides a high degree of conformity, but also results in a high degree of dose inhomogeneity, in target and normal structures. To quantitatively evaluate a treatment plan one needs to know the consequences of dose inhomogeneity for all the involved structures of interest (62). Niemerko introduced the concept of generalized equivalent uniform dose (gEUD) that applies both on normal tissues and tumours.

In principle the gEUD uses the entire dose distribution and it is defined as the radiation dose which, if given uniformly to the target volume or normal tissue, would result in the same biological effect as the applied heterogeneous dose distribution, which is described by the DVH (63). gEUD is a phenomenologic model based on the power law dependence of the dose response of a tissue in dependence on the irradiated tissue volume.

The value of gEUD for a structure can be calculated from its voxel based dose distribution as:

$$g\text{EUD} = \left( \frac{1}{N} \sum_{i=1}^{N} D_i^a \right)^{1/a},$$

or using its differential DVH as:

$$g\text{EUD} = \left( \sum_{i=1}^{N} v_i D_i^a \right)^{1/a}$$

(2.12)

Where N is the total number of “bins”, the subvolumes used in the DVH, \{v_i,D_i\}is the fractional volume and the dose at that volume form the differential DVH.
respectively. “a” is the tissue specific parameter that describes the dose-volume effect and can be obtained empirically from clinical outcome data. For \( a = +\infty \), the gEUD is equal to the maximum dose and for \( a = -\infty \) it is equal to the minimum dose of the dose distribution. For \( a = \pm 1 \), the value of gEUD is equal to the arithmetic mean of the dose distribution and for \( a = 0 \) it is equal to the geometric mean. (64)

**Determination of parameter “a”**

Parameter a can be related analytically to the partial organ dose-volume data. Under the assumption of applying a uniform irradiation to partial organ volume, equation (2.12) can be reduced to:

\[
gEUD = V^{1/a} D(V)
\]  

(2.13)

The expression has the same form as the power law model used by Lyman to represent the volume effect. Parameter “a” and the Lyman parameter n are related to \( a = \frac{1}{n} \). (65) The volume effect “n” approaches 1 for parallel tissues and 0 for serial tissues. Thus, the gEUD parameter “a” approaches 1 for parallel normal tissue and positive infinity for serial normal tissues.

From this reciprocal relationship we can see that the range of “a” for normal tissues should be 1 to positive infinity. For large positive values of “a”, the gEUD tends to be near the maximum dose, which is characteristic for non-uniform irradiated normal tissues. An advantage of gEUD is that it can be applied to normal structures that are not strictly serial or parallel. On the other hand, since tumor control depends on the value of the dose at cold spots, “a”, can only have a negative value. gEUD drops quickly if only a small part of the tumor is significantly underdosed. This means that when gEUD is used as a measure of the effectiveness of the target dose distribution, the presence of a hot spot will have an insignificant advantage but underdosing will reduce the quality of a plan significantly. (64; 66; 67; 63; 68; 69)

**2.1.3.3 Incorporation of fractionation-EUD\(_{2,v}\)**

The concept of biologically effective dose, BED (Section 2.1.3.1) has an advantage over the simple physical dose since it is able to account the fractionation effects. By incorporating this advantage of this it is defined the :
\[
EUD_{D,v} = \left( \sum_{i=1}^{N} v_i \text{BED}_i \right)^{\frac{1}{C}}
\]

Where \( \text{BED}_i \) is the BED for each subvolume (bin) \( i \) and \( C = 1 + \frac{D}{a/\beta} \) is the normalization factor for the reference dose per fraction \( D \).

The normalization factor is inserted to correct for incorporating the BED, which makes the \( EUD_{D,v} \), appear much larger than the gEUD. For example, in the case of a “typical” sensitive structure with an \( a/\beta \) ratio of 3 Gy radiated at \( D = 2 \) Gy/fraction, the BED will be 1.67 times greater than the prescribed dose. Accordingly, a similar ratio between the \( EUD_{D,v} \) and gEUD without normalization should be expected. The easiest way to remedy this problem is by using a normalization factor similar to the one for the standard effective dose.

\[
\text{SED} = \frac{nD \left( 1 + \frac{D}{a/\beta} \right)}{(1 + \frac{D}{a/\beta})} = \frac{\text{BED}}{(1 + \frac{D}{a/\beta})}
\]

The gEUD can be modified using the denominator of the standard effective dose as the normalization factor. Thus in our case of \( D = 2 \) Gy/fraction

\[
EUD_{2,v} = \left( \sum_{i=1}^{N} v_i \text{BED}_i \right)^{\frac{1}{C}}, \quad C = 1 + \frac{2}{a/\beta}
\]

One advantage of using the concept \( EUD_{D,v} \) is that the reporting of a plan can be simplified to a single number for each structure of interest. Each number can be interpreted as the uniform radiation dose that, if delivered in fractions of \( D = 2 \) Gy, will yield the same clinical outcome as the inhomogeneous plan in question.

The \( EUD_{2,v} \), combining the gEUD with the BED, preserves all advantages of the gEUD while reflecting the fractionation effects, as well as the linear and quadratic survival characteristics (66). It is important to mention that \( EUD_{D,v} \), is based on the power law volume effect as the gEUD does (Eq.2.12)

### 2.1.3.4 Generalized Biological equivalent dose gBEDs

The BED formulae discussed in Section 2.1.3.1 have assumed that the dose rate distribution is spatially uniform, which is not true for a real implant. The dose rate distribution inside a prostate implant is highly non-uniform. The BED for such an implant can be calculated by partitioning the tumour volume into small sub-volumes so that the rate distribution in each sub-volume can be considered as uniform. The
BED$_i$ for a sub-volume $i$ can be calculated using the eq2.9 in Section 2.1.3.1. Mathematically the gBED$_i$ for a clinical prostate implant can be calculated as follows:

A tumor volume is partitioned into small sub-volumes $V_i$, where $N_i=\rho V_i$ is the number of clonogenic cells in $V_i$ and $\rho$ (N/cm$^3$) is the tumor clonogenic cell density.

![Diagram of tumor volume partitioned into sub-volumes](image)

The BED for the sub-volume $V_i$ is

$$BED_i = -\frac{\ln S_i}{\alpha} \implies$$

$$-\ln S_i = \alpha \cdot BED_i$$

$$\ln S_i = -\alpha \cdot BED_i \implies$$

$$S_i = e^{-\alpha \cdot BED_i}$$

where $S_i$ is the survival fraction in volume $V_i$.

The survived number of clonogenic cells in $V_i$ is

$$N_{S_i} = N_i \cdot S_i = \rho \cdot V_i \cdot e^{-\alpha \cdot BED_i}$$

The total number of survived clonogenic cells in $V$ is

$$N_S = \sum_i N_{S_i} = \rho \cdot \sum_i V_i \cdot e^{-\alpha \cdot BED_i}$$

The total number of clonogenic cells in $V = \sum_i V_i$ is $N = \rho \cdot V$ thus,

$$S = \frac{N_S}{\rho \cdot V} = \sum_{i=1}^N \left(\frac{V_i}{V}\right) \cdot e^{-\alpha \cdot BED_i} \implies$$

$$S = \sum_{i=1}^N V_i \cdot e^{-\alpha \cdot BED_i}$$
where $V_i$ is the fractional volume $V_i = \frac{V_i}{V} = \frac{V_i}{\sum_{i=1}^{N} V_i}$

$$gBED_s = -\frac{\ln S}{\alpha}$$

$$gBED_s = -\frac{1}{\alpha} \ln \left( \sum_{i=1}^{N} v_i e^{-\alpha \cdot BED_i} \right)$$  \hspace{1cm} (2.17)$$

Where $v_i$ is the fractional volume and $N$ is the total number of bins in the differential DVH. The $\{v_i, \forall i\}$ is directly related to the differential dose volume histogram of the implant. Equation 2.13 takes into account the spatial heterogeneity of dose distribution in prostate brachytherapy. The equivalent total uniform dose $EUD_{D,s}$ of external beam therapy delivered in $D$ Gy/fraction that would have the same radiobiological effects as the implant BED may be found by equating (70):

$$BED_{EBRT} = EUD_{D,s} \left( 1 + \frac{D}{\beta} \right) = -\frac{1}{\alpha} \ln \left( \sum_{i=1}^{N} v_i e^{-\alpha \cdot BED_i} \right)$$

By solving for $EUD_{D,s}$ after setting the daily fractionation dose $D$ to a desired value, we get the following expression.

$$EUD_{D,s} = -\frac{1}{\alpha} \ln \left( \sum_{i=1}^{N} v_i e^{-\alpha \cdot BED_i} \right)$$  \hspace{1cm} (2.18)$$

where $C = 1 + \frac{D}{\alpha/\beta}$

In our case where $D=2$ Gy/fraction we have

$$EUD_{2,s} = -\frac{1}{\alpha} \ln \left( \sum_{i=1}^{N} v_i e^{-\alpha \cdot BED_i} \right), \quad C = 1 + \frac{2 \text{ Gy}}{\alpha/\beta}$$  \hspace{1cm} (2.19)$$

In brachytherapy as in external beam radiotherapy probabilistic models can be used as well. (81)-(99)

### 2.2 Materials

Our study is based on data of 48 prostate cancer patients who received 3D-US based HDR brachytherapy treatment. The patients were treated as monotherapy for low-risk or boost therapy in combination with external beam for intermediate risk.
cases. For the 38 of 48 patients the treatment was made under spinal anesthesia, the 8 of them under caudal block and the rest 2 of them under general anesthesia.

In Section 1.7.2 it can be seen the schematic diagram of the procedure of HDR brachytherapy of prostate in Strahlenklinik Offenbach. After the needle implantation a new 3D US image set is acquired. Following this, new contouring of the prostate PTV and OARs is done by the radiation oncologist. The catheter reconstruction and the preparation of the plan are done by the medical physicist. In our procedure this is the “clinical plan stage-1”

Just before the patient irradiation new 3D image sets were acquired, on which the “pre-irradiation plan stage-2” (used in our study), was prepared. The “post-irradiation stage-3” plan was based on 3D image acquisition obtained after the completion of patient irradiation. We have to mention here that for the 48 patients we acquired post-irradiation image sets and only for the 25 patients we acquired pre-irradiation image sets.

Based on the 3D-US acquisitions of stage-2 and stage-3 first the adjustment of contours for all, target and OARs, is realized and then the catheters reconstruction is fine tuned. Oncentra Prostate enables the automatic transfer of the contoured anatomy and dwell times to any new 3D-US acquisition, so that the repeated planning process for each patient is significantly simplified.

After finalizing the catheter reconstruction (adjustment) for the pre- and post-treatment image set, the catheter loading (source dwell positions and dwell times) from the original clinical plan is transferred into the actual one using the plan load option in OcP. The resulted dose distribution and DVHs correspond in this way to what should happen at that stage if the clinical plan is delivered. For each of the clinical, pre- and post- irradiation acquisition the free length of each catheter is measured. Our procedure requires that the US-probe, which is positioned with the transversal detector at the base plane, remains unchanged within the rectum after acquisition and until the irradiation has finished.

In Strahlenklinik Offenbach the real- time dynamic planning system Oncentra Prostate is used for the 3D-US pre-planning, the transperineal implantation of the needles using template, the intraoperative planning and irradiation. All pre-plans and
all the inverse optimization of clinical plans were based on HIPO using the modulation restriction (MR) parameter. The modulation restriction option limits the free modulation of dwell times. The range of MR values used among the 48 patients was [0.0-0.1].

The 48 cases covered a representative area of prostate volumes 17-60 cm³ with a mean prostate volume (PTV) of 35.0 cm³. The average time spent between the clinical and the pre-irradiation acquisition was (50.4±9.0) min, and between pre-irradiation and post-irradiation was (18.8±2.2) min. The relative long time gap between stage-1 and stage-2 can be explained, that in our clinic regularly new resident physicians have to be trained for the brachytherapy of prostate.

In Strahlenklinik Offenbach as explained previously (see Section 1.6.1) the prostate is considered as the PTV (CTV1) and the urethra, rectum and bladder as OARs. The dosimetric protocol is listed in Table 1.3 in Section 1.7.3.

The PTV movement was estimated by measuring its shifting between the clinical and pre-irradiation; and clinical and post-irradiation plans and pre- and post-irradiation plans. For all plans this measurement is made on the reference plane (the reference plane is the middle plane between the base plane and apex). After the check we made before each new acquisition, the base plane and the apex remained as by the clinical acquisition. From this, the prostate movement in the Z direction was equal to 0mm for each of our acquisitions. The movement in X and Y direction was measured compared to the prostate contour central point on the reference plane, see Figure 2.2.

The shift of urethra was measured between the clinical and pre-; and clinical and post-irradiation plan. For all plans these measurements were made on the base, reference and apex plane: the shift on each of these three planes was measured compared to the urethra contour central point on that plane. As expected and presented later on in the chapter with Results the urethra showed the largest displacement.
The shifts of the catheters on base, reference and apex plane is measured between the clinical and pre-irradiation; clinical and post-irradiation and pre- and post-irradiation plan.

**Plan evaluation**

For the evaluation of the influence of possible catheter shifts and of the PTV and OAR movements to the plans, the dose volume histogram (DVH) for each plan was exported in an excel file together with all relevant dose-volume parameters for the prostate and for all OARs (urethra, rectum and bladder), which have been considered as dosimetric indices (see Table 2.1). These parameters were compared for the clinical, pre-irradiation and post-irradiation plans.

**Table 2.1: DVH parameters used for evaluation and comparison of the dose distributions which are also included in the clinical protocol (see Table 1.3)**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>D_{90}</td>
</tr>
<tr>
<td></td>
<td>V_{100}</td>
</tr>
<tr>
<td></td>
<td>V_{150}</td>
</tr>
<tr>
<td>Urethra</td>
<td>D_{10}</td>
</tr>
<tr>
<td></td>
<td>D_{0.1cm}^{3}</td>
</tr>
<tr>
<td>Rectum</td>
<td>D_{10}</td>
</tr>
<tr>
<td></td>
<td>D_{0.1cm}^{3}</td>
</tr>
<tr>
<td>Bladder</td>
<td>D_{10}</td>
</tr>
<tr>
<td></td>
<td>D_{0.1cm}^{3}</td>
</tr>
</tbody>
</table>
The dosimetric parameters listed in Table 2.1 are internationally recommended parameters for dose evaluation and documentation (see Section 1.6.3) and have been considered as the indicators of the influence of potential patient movement and anatomy changes on the quality of treatment plan and patient treatment.

In addition to these the conformal index, COIN (Baltas et al) has been included for comparing the plans. In our study we have compared COINs including OARs (see Section 2.1.1), for the reference dose D_{ref}.

As radiobiological parameters for comparing the three sets of treatment we considered gEUD, EUD_{2,v}, and EUD_{2,s}, for the target volume and gEUD and EUD_{2,v} for the OARs which can be calculated from equations 2.12, 2.16, 2.19 respectively.

The exponent “a” in the equations for gEUD (Eq.2.12) and EUD_{2,v} (Eq.2.16) is a structure specific parameter which is generally negative for tumours and positive for normal tissue and OARs. In our study for prostate cancer “a” value of -10 has been used in gEUD and EUD_{2,v} analysis (71; 68). For rectum and bladder the value of a=6 (68) and for urethra a=4 have been used. The LQ parameters for prostate tissue are according to Wang et al. (54) and AAPM they are listed in Table 2.2. For all OARs and late effects a value for α/β ratio of 3.0 is used.

Table 2.2: Estimated parameters for prostate cancer

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimated values</th>
<th>Standard Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>α (Gy-1)</td>
<td>0.15</td>
<td>±0.04</td>
</tr>
<tr>
<td>α/β (Gy)</td>
<td>3.1</td>
<td>±0.5</td>
</tr>
<tr>
<td>Tr (minute)</td>
<td>16 [0,90]</td>
<td>[5.6×10^4,8.8×10^7]</td>
</tr>
<tr>
<td>K1 (clonogenic number)</td>
<td>1.6×10^6</td>
<td>[1.0×10^5,2.1×10^8]</td>
</tr>
<tr>
<td>K2 (clonogenic number)</td>
<td>3.0×10^6</td>
<td>[3.2×10^5,1.3×10^9]</td>
</tr>
<tr>
<td>K3 (clonogenic number)</td>
<td>1.1×10^7</td>
<td></td>
</tr>
<tr>
<td>K (Gy / day)</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

The significance test for the observed differences is always done using the student paired t-test, two sided statistical method (72).

---

6 American Association of Physicists in Medicine
3. Results & Discussion

Results are represented graphically using the Microcal Origin[^7] software and its “box-chart” presentation method. Given statistical parameters are shown in Figure 3.1.

![Box-Plot Diagram](image)

**Figure 3.1: Values represented in a box plot presentation method**

**PTV and OAR movements**

Patient movement and anatomical alteration can cause PTV and OARs movement. Following, we discuss and graphically present these movements.

For prostate (PTV in our case) the average shift was measured on the reference plane between the acquisitions in stages 1-2, stages 1-3 and stages 2-3, in X and Y directions. There was no noticed PTV dislocation in the Z direction (cranio-caudal). Between the acquisitions in stages 1 and 2, movement in X direction (horizontally) was (0.1±0.2)mm and in Y direction (vertically) (0.4±0.6)mm.

Between the stages 1 and 3 the movement in X direction was (0.1±0.3)mm and in Y (0.4±0.7)mm. Between the acquisitions taken just before and immediately after the irradiation, this movement is negligible with values (0.0±0.0)mm and (0.1±0.3)mm for X and Y directions respectively.

Presented movement values are summarized in the following Table 3.1:

[^7]: Microcal Software, Inc. Microcal™ Origin Vs 6.0
Table 3.1: Average shifts of Prostate in X and Y direction

<table>
<thead>
<tr>
<th>Stages</th>
<th>X direction (mm)</th>
<th>Y direction (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- 2</td>
<td>0.1±0.2</td>
<td>0.4±0.6</td>
</tr>
<tr>
<td>1- 3</td>
<td>0.1±0.3</td>
<td>0.4±0.7</td>
</tr>
<tr>
<td>2- 3</td>
<td>0.0±0.0</td>
<td>0.1±0.3</td>
</tr>
</tbody>
</table>

Graphical presentation of the prostate movements between the acquisitions in stages 1-2 and 1-3 in X and Y direction is shown in Figure 3.2.

![Graphical representation of prostate movements](image)

Figure 3.2: Absolute values of prostate shift on reference plane for the 25 cases having all three plan categories

From our results we can see that the largest displacement is taking place along the Y direction according the DICOM coordinate system. The largest movement that occurred was 3.6 mm in Y direction and is measured at one case between the acquisitions in stages 1 and 3.
These displacements can generally be caused by the movement of patient or by the rectums alteration. Also from Table 3.1 we can see that the displacement between pre- and post acquisition is negligible as the time which is spent between the acquisitions in stages 2 and 3 (duration of irradiation) is much less than the time between the acquisitions in stages 1-3.

As expected, the largest displacement is observed for urethra. The dislocation of urethra was measured at the base, reference and apex plane between the clinical and pre- and clinical and post- acquisitions. The mean values of the displacements on the base, reference and apex plane are given in Table 3.2.

Table 3.2: Mean values of the dislocation in mm of urethra on the base, reference and apex plane

<table>
<thead>
<tr>
<th>Stages</th>
<th>Base</th>
<th>Reference</th>
<th>Apex</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–2</td>
<td>0.6±0.7</td>
<td>0.6±0.7</td>
<td>0.6±0.8</td>
</tr>
<tr>
<td>1–3</td>
<td>0.7±1.1</td>
<td>0.7±0.9</td>
<td>0.7±1.0</td>
</tr>
</tbody>
</table>

Figure 3.3 shows the urethra shifts in all three mentioned planes for all cases and patients. The paired t tests shows that the displacement on the apex and reference planes between the stages 1-2 and 1-3 was not significant (p=0.204 and p=0.125 respectively). However the displacement on the base plane was significant (p=0.020).

The maximum observed values on the base, reference and apex planes between the acquisitions on stages 1-3 were (5.1, 3.7 and 3.7) mm respectively.
Catheter Displacement

Needles are reconstructed for each image set. The needle dislocation was measured on base, reference and apex plane between acquisitions on stages: 1-2 and 1-3 and 2-3 presented in Figure 3.4.

The maximum dislocation is observed for one patient between the acquisitions stages 1 and 3 at the reference plane with the values of (3.6, 3.6 and 2.6) mm on the base, reference and apex plane respectively. For all other cases the needle movement was less than 1.5 mm.

Next, the catheter free length (this is the length of the catheter in front of the template, the visible part of the catheter) was measured and compared between the mentioned acquisitions. Our results show displacement under 0.6 mm.
**Needle Shift: Free length, Base, Reference and Apex plane between clinical(1)-pre (2)-clinical-post-(3) and pre-post- irradiation plans**

Figure 3.4: Catheter Dislocation for the 25 cases having all 3 plan categories

---

**Dose Volume Histograms**

The 3D dose distribution and DVHs for Prostate (PTV), urethra, bladder and rectum (OARs), were calculated and analyzed.

Next, the results of our analysis regarding the influence of patient movement and anatomy changes on the DVHs are represented. This analysis includes all the dosimetric parameters that are listed in Table 1.3 in Section 1.7.3.

**DVH parameters of Prostate**

Figure 3.5 summarizes the results for (a) $D_{90}$, (b) $V_{100}$ and (c) $V_{150}$, of the prostate (PTV).
Figure 3.5: Comparison of (a) $D_{90}$ (b) $V_{100}$ (c) $V_{150}$ values of prostate for clinical, pre- and post- irradiation treatment plans for the 25 cases having all 3 plan categories.
For the parameter $D_{90}$, as well as for $V_{100}$ and $V_{150}$ the changes between clinical and pre- and clinical and post- irradiation plan are significant, while the changes between pre- and post- irradiation plan are not significant. For the paired t-tests the significance level was 0.05. From these results, the influence of time on the quality of the final therapy is obvious.

The mean values for $D_{90}$, $V_{100}$ and $V_{150}$ of prostate for the clinical, pre- and post- irradiation plan are presented in the following table:

Table 3.3: Mean values for the $D_{90}$, $V_{100}$, and $V_{150}$ of prostate given in % of the prescribed dose.

<table>
<thead>
<tr>
<th>DVH-parameters</th>
<th>Clinical</th>
<th>Pre-irradiation</th>
<th>Post-irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{90}$ (%)</td>
<td>103.7±1.9</td>
<td>102.2±2.1</td>
<td>101.6±2.7</td>
</tr>
<tr>
<td>$V_{100}$ (%)</td>
<td>92.8±1.4</td>
<td>91.8±1.7</td>
<td>91.2±2.3</td>
</tr>
<tr>
<td>$V_{150}$ (%)</td>
<td>31.6±2.9</td>
<td>31.4±3.1</td>
<td>29.5±3.6</td>
</tr>
</tbody>
</table>

For the pre-irradiation plans, there are only 3 cases (of 25 patients) that did not fulfill our protocol where the $D_{90}$ parameter should be larger than 100%. These three values are: 96, 98, 98%.

For the post- irradiation plans, there are ten cases (of 48 patients) with values of $D_{90}$ below of 100%. The minimum value of these was 95.5% and the maximum one 99.2%. All the observed changes of $D_{90}$ are less than 5%, thus all plans are considered to be clinically acceptable.

For the parameter $V_{100}$ and for the pre-irradiation plan we observed the values only for 3 cases: 88.2, 88.3, 88.3 % which did not fulfill our protocol (less than 90%). For the post- irradiation plan there are ten cases (the same as in $D_{90}$) with value less than 90%, within the range (83.1, 83.9).

For the parameter $V_{150}$ and for the pre- irradiation plan we observed one case (of 25) that did not fulfill our protocol (over 35%) with value 39%. For the post-irradiation plan there are two cases (of 48) with values larger than 35%: 37.4 and 37.6%.
As expected, larger differences between the DVH parameters of the post- and pre-irradiation plans according to the clinical plan are noticed than between the pre- and post-irradiation plan.

From the results we presented till now, we found out that there is much more sense in observing the influence of the relative shift of catheters according to prostate on the DVH and also radiobiological parameters (that we discuss later) than the influence of absolute dislocation of needles and/or OARs separately. The cases that showed a large absolute prostate and catheter displacements, but small relative displacement according one-to-another don’t correspond to any of the above cases that didn’t fulfill our protocol for D$_{90}$.

Dislocation of catheters according to prostate remains within a range of (0.1 - 1.3) mm with an average of (0.6±0.3)mm.

Figure 3.6 demonstrates the dependence of prostate D$_{90}$ on the relative shift of catheters according to prostate between the clinical and post- treatment acquisition.

![Figure 3.6: Dependence of prostate D$_{90}$ on relative displacement of catheters](image-url)
DVH parameters of Urethra

Figure 3.7 summarizes the results for DVH parameters $D_{10}$ and $D_{0.1cm}^3$ for the urethra.

The mean values for $D_{10}$ and for $D_{0.1cm}^3$ of urethra for the clinical, pre- and post- irradiation plan are presented in the following table:
Table 3.4: Mean values for the $D_{10}$ and $D_{0.1cm}^3$ of urethra given in % of the prescribed dose

<table>
<thead>
<tr>
<th>DVH parameter</th>
<th>Clinical</th>
<th>Pre-irradiation</th>
<th>Post-irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{10}$ (%)</td>
<td>113.4±2.0</td>
<td>111.2±3.4</td>
<td>111.7±3.8</td>
</tr>
<tr>
<td>$D_{0.1cm}^3$ (%)</td>
<td>114.7±1.9</td>
<td>112.4±3.2</td>
<td>113.1±4.0</td>
</tr>
</tbody>
</table>

For the parameter $D_{10}$ and for the post-irradiation plan there are 8 cases (of 48) that exceed our protocol defined value of 115% and are within the range of (115.5, 120.9)%.

For two cases (of 25) in pre–irradiation plan the value of $D_{10}$ exceeds the 115% limit with maximum observed value 117.6%.

For the pre-irradiation plans (25 cases) $D_{0.1cm}^3$ remains for all cases under the limit of 120% and in two (of 48) post-irradiation plans exceed the limit of 120% with values (122 and 124.9)%.

For the parameter $D_{10}$ as well as for $D_{0.1cm}^3$ the differences between clinical and pre-; and clinical and post- irradiation plans are significant and the changes between pre- and post- irradiation plan are not significant. For the paired t-tests the significance level was 0.05. These results are following our expectations.

**DVH parameters for Rectum**

Figure 3.8 summarizes the results for DVH parameters $D_{10}$ and $D_{0.1cm}^3$ for the rectum.
Figure 3.8: Comparison of (a) $D_{10}$ and (b) $D_{0.1cm^3}$ values of rectum for clinical, pre- and post- irradiation Plan for 25 cases having all 3 plan categories

For the parameter $D_{10}$ as well as for $D_{0.1cm^3}$, the changes between clinical, pre- and post-irradiation plan are not significant. For the paired t-tests the significance level was 0.05.

The mean values for $D_{10}$ and for $D_{0.1cm^3}$ of rectum for the clinical, pre- and post- irradiation plan are presented in the following table:

Table 3.5: Mean values for the $D_{10}$ and $D_{0.1cm^3}$ of rectum given in % of the prescribed dose

<table>
<thead>
<tr>
<th>DVH parameter</th>
<th>Clinical</th>
<th>Pre-irradiation</th>
<th>Post-irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{10}$ (%)</td>
<td>53.7±5.5</td>
<td>56.5±6.3</td>
<td>54.3±5.4</td>
</tr>
<tr>
<td>$D_{0.1cm^3}$ (%)</td>
<td>75.4±3.6</td>
<td>76.0±3.7</td>
<td>75.8±3.7</td>
</tr>
</tbody>
</table>

For the parameter $D_{10}$ of pre-irradiation plans only one case (of 25) exceeded the limit of 75% having a value of 76.6%. For the post-irradiation plan all cases were under 75%. For 3 cases (of 25) of pre-irradiation plans, and for 3 cases (of 48) of post-irradiation plans the value of $D_{0.1cm^3}$ exceeded the limit of 80%. The highest observed values were 83.3% and 86.7% respectively. The highest observed value of
86.7% corresponds to a patient that showed a large catheter and prostate displacement.

Generally we observed an increase of the mean value for both parameters between the stages 1-2 and 1-3, which remains insignificant as confirmed by the paired t tests and it is always below the limits with a few exceptions mentioned above.

**DVH parameters of Bladder**

In Figure 3.9 the results for $D_{10}$ and $D_{0.1cm}^3$ for the bladder are summarized.

![DVH parameters of Bladder](image)

Figure 3.9: Comparison of (a)$D_{10}$ and (b)$D_{0.1cm}^3$ values of bladder for clinical, pre- and post- irradiation Plan for 25 cases having all 3 plan categories
For bladder and for all cases, the DVH parameters of all plans fulfill our protocol values.

COIN

Our results for the COIN including OARs are summarized in Figure 3.10. The COIN values of the clinical plans are all larger than the 80% limit.

The COIN values for all pre-irradiation plans remain above 0.8. For 2 (of 48) post-irradiation plans the COIN drops below 0.8 with values 0.78 and 0.79.

As expected, the observed differences between clinical and pre-; and clinical and post-irradiation plans were significant and the differences between pre- and post-irradiation plans were not significant. Although the mean value of COIN drops between the clinical and post-irradiation plans, the plans are considered to be acceptable, see Figure 3.10.
Radiobiological Evaluation

After the presentation of results of the influence of patient movement and anatomy changes on the DVH parameters, we show and discuss this influence on the radiobiological parameters $g\text{EUD}$, $\text{EUD}_{2,v}$ for prostate (PTV) and OARs and $\text{EUD}_{2,s}$ for prostate.

From the 48 clinical implants for HDR prostate brachytherapy, the 26 of them were treated as monotherapy and the 22 were treated in combination with external beam radiotherapy. The prescribed dose for monotherapy and for combined therapy (Brachytherapy as a Boost) was 11.5 Gy and 10.5 Gy respectively.

Next the radiobiological parameters for the prostate are presented.

Radiobiological Parameters of the Prostate

Figures 3.11, 3.12 show the comparison of $g\text{EUD}$, $\text{EUD}_{2,v}$, $\text{EUD}_{2,s}$ values of prostate monotherapy and Boost therapy respectively. In Tables 3.6 and 3.7 the mean values for the parameters and their differences between the plans in stages 1, 2 and 3 are given.
Figure 3.11: Comparison of (a) gEUD (b) EUD\textsubscript{2,v} and (c) EUD\textsubscript{2,s} values of prostate for the 15 (of 26) monotherapy implants for clinical, pre- and post-irradiation plans.
Clinical (1), pre(2)-and post (3) treatment plan

<table>
<thead>
<tr>
<th>gEUD   (Gy)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>9.5</th>
<th>10.0</th>
<th>10.5</th>
<th>11.0</th>
<th>11.5</th>
<th>12.0</th>
<th>12.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>p12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.511</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3.12: Comparison of (a) gEUD, (b) EUD$_{2,v}$ and (c) EUD$_{2,s}$ values of prostate for the 10 (of 22) implants (combined therapy, brachytherapy as a boost) clinical, pre- and post- irradiation plan
Table 3.6: Mean values of gEUD, EUD\(_{2,v}\), and EUD\(_{2,s}\) for prostate monotherapy and Boost for clinical (stage 1), pre- (stage-2) and post- (stage-3) irradiation plans.

<table>
<thead>
<tr>
<th>Prostate</th>
<th>Monotherapy (1x11.5 Gy)</th>
<th>Boost (1x10.5 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test parameters</td>
<td>gEUD (Gy)</td>
<td>EUD(_{2,v}) (Gy)</td>
</tr>
<tr>
<td>Stage-1</td>
<td>12.45±0.53</td>
<td>31.50±3.46</td>
</tr>
<tr>
<td>Stage-2</td>
<td>12.29±0.44</td>
<td>30.71±2.93</td>
</tr>
<tr>
<td>Stage-3</td>
<td>12.17±0.60</td>
<td>30.20±3.52</td>
</tr>
</tbody>
</table>

The following discussion is based on the results for the post- irradiation plan, as the largest differences according to the clinical plan are noticed there.

The lowest values that are observed from the prostate monotherapy cases are for one patient (10.51, 20.08, 30.52) Gy for gEUD, EUD\(_{2,v}\) and EUD\(_{2,s}\) respectively. For the boost treatment the lowest values are (9.90, 19.01 and 27.89) Gy for gEUD, EUD\(_{2,v}\) and EUD\(_{2,s}\) respectively.

Table 3.7: P values for prostate monotherapy and combined therapy.

<table>
<thead>
<tr>
<th>Prostate</th>
<th>Monotherapy</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test parameters:</td>
<td>gEUD</td>
<td>EUD(_{2,v})</td>
</tr>
<tr>
<td>Stages 1-2</td>
<td>0.021</td>
<td>0.043</td>
</tr>
<tr>
<td>Stages 1-3</td>
<td>0.025</td>
<td>0.105</td>
</tr>
<tr>
<td>Stages 2-3</td>
<td>0.731</td>
<td>0.910</td>
</tr>
</tbody>
</table>

For prostate monotherapy we observe that the values of gEUD, EUD\(_{2,v}\) and EUD\(_{2,s}\) decrease between the clinical, pre- and post irradiation plan; see Figure 3.11 and Table 3.8. The paired t–tests results presented in Table 3.7, show that the differences between stages 1-2 and 1-3 were significant and between stages 1-3 insignificant as it was expected. It is important to mention that the maximum observed reduction in the mean value of gEUD, EUD\(_{2,v}\), EUD\(_{2,s}\) (see Table 3.6) is 4.57% with a range of 1.28%-4.57%.
For the patients that were treated with combined therapy similar results were observed for gEUD, EUD\textsubscript{2,v} and EUD\textsubscript{2,s}. From the decrease of values of radiobiological parameters it is observed that there is a dependence on treatment time as we already concluded by analyzing the DVH parameters.

We have to mention here that the values for EUD\textsubscript{2,v} are much higher than the gEUD although they are both based on the power law method. The reason is that the EUD\textsubscript{2,v} is much more sensitive as it includes the $\alpha$, $\beta$ values which give more emphasis to dose, see Section 2.1.3.3.

The radiobiological parameters depend on the dose distribution within the volume. The decreased values of gEUD and EUD\textsubscript{2,v} may be explained with the small underdosed regions within the prostate caused by patient/organ/catheters shifts. This supports also results that we got from the analysis of DVH-parameters.

Following we represent and discuss our results for the radiobiological analysis of the OARs.

**Radiobiological Parameters of the Urethra**

Figures 3.13, 3.14 show the comparison of gEUD, EUD\textsubscript{2,v} values of urethra for monotherapy and combination therapy respectively. Mean values of these parameters and their differences between the acquisitions in stages 1, 2 and 3 are given in Tables 3.8 and 3.9.
Figure 3.13: Comparison of (a) gEUD, (b) EUD_{2\nu}, values of urethra for the 15 (of 26) implants (monotherapy) clinical, pre- and post- irradiation plans.
By monotherapy and post-irradiation plans (48 cases) the highest observed value of both gEUD, EUD$_{2,v}$ for urethra is (11.74, 36.48)Gy respectively. For the Boost therapy the largest observed values are (11.34, 33.34)Gy for gEUD, EUD$_{2,v}$ respectively.

Figure 3.14: Comparison of (a) gEUD, (b) EUD$_{2,v}$ values of urethra for the 10 (of 22) implants (combination therapy, Brachytherapy as a Boost) clinical, pre- and post- irradiation plans.
Table 3.8: Mean values of urethra gEUD, EUD<sub>2,v</sub>- monotherapy and Boost for clinical (Stage-1), pre- (Stage 2) and post- (Stage 3) irradiation plans

<table>
<thead>
<tr>
<th>Test parameters [Gy]</th>
<th>Monotherapy</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>gEUD</td>
<td>EUD&lt;sub&gt;2,v&lt;/sub&gt;</td>
<td>gEUD</td>
</tr>
<tr>
<td>Stage-1</td>
<td></td>
<td>11.35±0.32</td>
</tr>
<tr>
<td>Stage-2</td>
<td></td>
<td>11.15±0.34</td>
</tr>
<tr>
<td>Stage-3</td>
<td></td>
<td>11.09±0.36</td>
</tr>
</tbody>
</table>

Table 3.9: P values between treatment plans for urethra monotherapy and combined therapy.

<table>
<thead>
<tr>
<th>P-value</th>
<th>Urethra:</th>
<th>Monotherapy</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test parameters</td>
<td>gEUD</td>
<td>EUD&lt;sub&gt;2,v&lt;/sub&gt;</td>
<td>gEUD</td>
</tr>
<tr>
<td>Clinical-pre treatment plan</td>
<td>0.006</td>
<td>0.007</td>
<td>0.003</td>
</tr>
<tr>
<td>Clinical-post treatment plan</td>
<td>0.016</td>
<td>0.010</td>
<td>0.009</td>
</tr>
<tr>
<td>Pre-Post treatment plan</td>
<td>0.763</td>
<td>0.734</td>
<td>0.618</td>
</tr>
</tbody>
</table>

Results of analysis of radiobiological parameters of urethra for both: mono- and combined therapy arts are following our expectations. The differences between parameters by clinical and post – treatment plan are significant, and between pre- and post- treatment plan are not.

Radiobiological parameters for Rectum

Following figures presents the results of the radiobiological parameters for the clinical, pre- and post- irradiation treatment plan.
Figure 3.15: Comparison of (a) gEUD, (b) EUD$_{2,v}$ values of rectum for the 15 (of 26) implants (monotherapy cases) clinical, pre- and post- irradiation plans.
Figure 3.16: Comparison of (a) gEUD, (b) EUD$_{2,v}$ values of rectum for the 10 (of 22) implants (combined therapy) for clinical, pre- and post-irradiation plans.

The mean values of gEUD and EUD$_{2,v}$ parameters of rectum for the case of mono- and combined therapy for the clinical, pre- and post- irradiation plans are presented in the following table:
Table 3.10: Mean values of gEUD, EUD$_{2,v}$ of rectum for mono- and Boost therapy clinical, pre- and post-irradiation plans.

<table>
<thead>
<tr>
<th>Rectum:</th>
<th>Test parameters [Gy]</th>
<th>Monotherapy</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gEUD</td>
<td>EUD$_{2,v}$</td>
<td>gEUD</td>
</tr>
<tr>
<td>Stage-1</td>
<td>5.13±0.47</td>
<td>10.47±1.25</td>
<td>4.68±0.36</td>
</tr>
<tr>
<td>Stage-2</td>
<td>5.34±0.45</td>
<td>10.94±1.09</td>
<td>4.77±0.27</td>
</tr>
<tr>
<td>Stage-3</td>
<td>5.21±0.48</td>
<td>10.75±1.29</td>
<td>4.69±0.34</td>
</tr>
</tbody>
</table>

In the case of monotherapy the highest observed values of parameters gEUD, EUD$_{2,v}$ for rectum are (6.39 and 13.66)Gy respectively. The largest value of EUD$_{2,v}$ corresponds to the plan of the patient that had the largest value for D$_{0.1cm^3}$ of the rectum. It is important to mention that the maximum observed increase in the mean value of gEUD, EUD$_{2,v}$ (see Table 3.10) is 4.49% with a range of 0%-4.49%.

For combined therapy the highest values are (5.38 and 10.3) Gy for gEUD, EUD$_{2,v}$ respectively.

Table 3.11: P values between the gEUD and EUD$_{2,v}$ for rectum between stages 1, 2 and 3 for the case of mono- and Boost therapy.

<table>
<thead>
<tr>
<th>Rectum:</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test parameters:</td>
<td>gEUD</td>
</tr>
<tr>
<td>Clinical-pre treatment plan</td>
<td>0.989</td>
</tr>
<tr>
<td>Clinical-post treatment plan</td>
<td>0.296</td>
</tr>
<tr>
<td>Pre-Post treatment plan</td>
<td>0.067</td>
</tr>
</tbody>
</table>

From Figures 3.15 and 3.16 and Table 3.10, we can see that the gEUD, EUD$_{2,v}$ are slightly increasing for both types of treatment. However, this change is for all cases insignificant; see Table 3.11. This was expected as in the case of D$_{10}$ and D$_{0.1cm^3}$ we had the same behavior.
Radiobiological parameters for Bladder

![Diagram](image)

Figure 3.17: Comparison of (a) gEUD, (b) EUD$_{2,v}$, values of bladder for the 15 (of 26) monotherapy implants between the clinical, pre- and post-irradiation plans.
Figure 3.18: Comparison for (a) gEUD, (b) EUD$_{2,v}$ values of bladder for the 10 (of 22) implants (combined therapy, Brachytherapy as a Boost) between the clinical, pre- and post- irradiation plans.
The mean values for parameters $g_{\text{EUD}}$ and $\text{EUD}_{2,v}$ of bladder for the cases of mono- and combined therapy and their differences between the clinical (Stage-1), pre- (Stage-2) and post- irradiation (Stage-3) plans are presented in the following tables:

Table 3.12: Mean values of bladder $g_{\text{EUD}}$, $\text{EUD}_{2,v}$ – for the case of mono- and Boost therapy for clinical, pre- and post- irradiation plan

<table>
<thead>
<tr>
<th>Bladder</th>
<th>Monotherapy</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test parameters [Gy]</td>
<td>$g_{\text{EUD}}$</td>
<td>$\text{EUD}_{2,v}$</td>
</tr>
<tr>
<td>Stage-1</td>
<td>4.78±0.61</td>
<td>9.24±1.89</td>
</tr>
<tr>
<td>Stage-2</td>
<td>4.94±0.77</td>
<td>9.41±2.45</td>
</tr>
<tr>
<td>Stage-3</td>
<td>4.88±0.72</td>
<td>9.35±2.19</td>
</tr>
</tbody>
</table>

Table 3.13: P values between treatment plans for the radiobiological parameters $g_{\text{EUD}}$ and $\text{EUD}_{2,v}$ of bladder for the case of mono-and combined therapy.

<table>
<thead>
<tr>
<th>P-value</th>
<th>Bladder:</th>
<th>Monotherapy</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test parameters:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical-pre treatment plan</td>
<td>$g_{\text{EUD}}$</td>
<td>0.115</td>
<td>0.195</td>
</tr>
<tr>
<td>Clinical-post treatment plan</td>
<td>$\text{EUD}_{2,v}$</td>
<td>0.203</td>
<td>0.451</td>
</tr>
<tr>
<td>Pre-Post treatment plan</td>
<td>$g_{\text{EUD}}$</td>
<td>0.152</td>
<td>0.344</td>
</tr>
<tr>
<td></td>
<td>$\text{EUD}_{2,v}$</td>
<td>0.363</td>
<td>0.878</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.644</td>
<td>0.307</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.838</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.443</td>
</tr>
</tbody>
</table>

Figures 3.17 and 3.18 and Table 3.12 show that the $g_{\text{EUD}}$ and $\text{EUD}_{2,v}$ are slightly increasing for both treatment types. However, this change is insignificant for all cases; see Table 3.13. It is important to mention that the maximum observed increase in the mean value of $g_{\text{EUD}}$, $\text{EUD}_{2,v}$ (see Table 3.12) is 4.48% with a range of 0.51%-4.48%.
Furthermore, we show the relation between the dosimetric and the radiobiological parameters. Results of this analysis for the case of prostate for mono- and combined therapy is given in following Figures.

![Figure 3.19: Relation of radiobiological parameters $D_{90}$ of prostate for the case of mono- (a-c-e) and combined (b-d-e) therapy art](attachment:Figure3.19.png)
As expected, our results demonstrate that there is the same behavior between the dosimetric and the radiobiological parameters. It is observed that the radiobiological parameters tend to increase as the $D_{90}$ increases and vice versa.

4. Conclusion

The measured mean shift of anatomy and needles (beams) is as low as 1.0mm that is lower by an order of magnitude to values known from external beam irradiation (73; 74; 75; 76). For high modulated plans as those in HDR Brachytherapy such small shifts result in dosimetric changes which are in general lower than 5%.

We have to keep in mind that the reproducibility of contouring process was here not investigated. Considering this as a source of inaccuracy, part of observed dosimetric differences are probable the result of this error source. Thus the presented values for the changes can be considered as the upper limits. The true changes are expected to be lower than these values.

Our results demonstrate that quality assurance procedures have to be clinically implemented to guarantee anatomy and implant stability of the order of 1mm. This can only be realized without any manipulation of the implant and anatomy as done, for instance in the case of removing the US-probe before treatment delivery or moving the patient from one bed to another for the irradiation purposes. The whole procedure should be attempted to be as short as possible.
Acknowledgments

First of all, I wish to express my sincere gratitude to my supervisor Prof. Dimos Baltas, for the opportunity he gave to me to participate in this research, his help and for his advices in the scientific part of this work, his guidance and his friendly support.

I would like to thank especially Associate Professor (Docent) Panayiotis Mavroidis for the great supervision, his scientific advises and his friendly support and for the opportunity he offered me to do part of my studies in Germany.

Dr. Natasa Milickovic for the opportunity she gave me to participate in this project by spending much of her time guiding me and helping me to understand the clinical part of this subject, supporting and offering me her friendship.

Sokrates Papaioannou, for his cooperation, for our discussions that helped me to understand theoretical and practical parts of this procedure and for his valuable friendship.

My examination committee, Professor Georgios Nikiforidis, Assistant Professor Georgios Sakellaropoulos from the Department of Medical physics of Patras University.

The entire staff of the medical radiation Physics Department in Strahlenklinik Offenbach.

My friend and colleague, Vasiliki Kefala, for helping me and supporting me to finish this project and for keeping me the best company during my staying in Germany.

My colleagues from the master of Medical Radiation Physics, University of Patras for their warm friendship.

My Family and friends who support me all these years.
Literature


72. [Online]
http://www.gla.ac.uk/sums/users/jdbmcdonald/PrePost_TTest/pairedt1.html.


82. **al-Abany, Massoud.** Towards Elimination of Anal-sphincter and Rectal Dysfunction after Radiation Therapy for Prostate Cancer,Phd thesis in Clinical Cancer Epidemiology and Medical Radiation Physics, Department of Oncology-
Pathology. Karolinska Institutet, Radiumhemmet, Karolinska, University Hospital, S-171 76. Stockholm, Sweden : s.n.


Part of the presented results have been submitted and accepted for oral presentation in the World Congress in Medical Physics and Biomedical Engineering:


Note: The dosimetric material for the clinical cases presented in this thesis has been provided by Dr. Milickovic