MSc Thesis

Radiobiological models based evaluation of the consequences of potential systematic catheter shifts in the HDR brachytherapy of prostate cancer

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Abstract

**Purpose:** The purpose of this study is to investigate and analyze the influence of the possible errors eventually occurring in a 3D-US based HDR Brachytherapy of prostate cancer on the quality of dose delivery. The influence of modulation restriction tool on the plan quality and sensitivity is also investigated.

**Materials:** Twelve clinical implants for HDR Brachytherapy of prostate cancer have been selected out of the clinical routine. The range of the prostate volumes was 26-101 cm³. Due to the fact that the implanted needles are fixed on the template, the most probable error should be a systematic shift of the implanted catheters on the cranial-caudal direction caused by the movement of the patient relative to the template. The planning was done using HIPO which is implemented in the real time intraoperative planning system Oncentra Prostate (OcP). HIPO offers a unique modulation restriction option that limits the free modulation of dwell times. Firstly the reference plans, where no catheter shift has been simulated, the clinical with MR >0 and the theoretical with MR=0, for all 12 implants have been compared. Then for each of the 12 clinical implants, 10 systematic shifts of the implanted catheters in the range of [-5, +5] mm in step of 1mm were simulated. The influence of this systematic shift on DVH-, COIN, EI and radiobiological parameters of PTV and OARs is calculated and recorded. The analysis of the observed changes has been done firstly by addressing the quality of the implant. For this purpose the range of shift was estimated that the resulted 3D dose distributions keep fulfilling the clinical dosimetric protocol. Secondly, the focus was placed to the stability of the dose distribution. Here the range for the shift has been estimated which enables that the dosimetric, conformity and radiobiological parameters of the implant remain within ±5% or ±10% of the originally planned values.

**Results:** The use of modulation restriction (MR>0) results in plans with more conformal dose distribution (COIN, EI) but slightly lower D90 and V100, gEUD, EUD2,v and EUD2,s values. The quality analysis demonstrate that for the DVH based parameters values of prostate a maximal shift of ±1.0 mm can be tolerated, although in case of using the modulation restriction the sensitivity from the influence of the systematic shift is greater. Similar were the results for the DVH parameters for urethra, rectum and bladder. For the stability analysis in order to keep the dosimetric parameters within ±5% of the originally planned value for the prostate and OARs, a maximum shift of around ±0.5 mm can be tolerated and for the ±10% criterion this is -1.0/+0.5 mm. The same behavior applies for the radiobiological parameters. The analysis based on COIN considering only the target and also the OARs have shown a maximum shift range of ±1.5 mm. For the EI analysis this range is ±0.0 mm. For ±10% criterion this is ±2.5 mm and ±0.5 mm respectively.

**Conclusion:** Our study has demonstrated that high modulated, high conformal Brachytherapy dose distributions for prostate HDR implants are sensitive to
systematic catheter shift. The consequence of shift changes is not clear. We can generally speak about a required geometrical stability of the implant as high as ±1.0mm. Modulation restriction without improving this reduces significantly the total dwell time keeping the plan quality and increasing conformity (COIN, EI).
Tables of contents

Abstract ........................................................................................................................................... 2

1. Introduction .................................................................................................................................. 6
  1.1 Historical review ....................................................................................................................... 6
  1.2 Theoretical background ........................................................................................................... 7
    1.2.1 Radioactivity ....................................................................................................................... 7
      1.2.1.1 Decay Constant .............................................................................................................. 7
      1.2.1.2 Activity ........................................................................................................................ 8
    1.2.2 Energy Conversion ............................................................................................................. 8
      1.2.2.1 Kerma .......................................................................................................................... 8
      1.2.2.2 Kerma Rate .................................................................................................................... 9
    1.2.3 Deposition of Energy ......................................................................................................... 9
      1.2.3.1 Deposit of energy .......................................................................................................... 9
      1.2.3.2 Energy Imparted ........................................................................................................... 10
    1.2.3.3 Absorbed Dose .............................................................................................................. 10
      1.2.3.4 Absorbed Dose rate ..................................................................................................... 10
    1.2.4 Source Strength Specification ............................................................................................ 11
  1.3 Brachytherapy ......................................................................................................................... 12
    1.3.1. High Dose Rate (HDR) Brachytherapy ............................................................................ 14
    1.3.2 Iridium-192 ..................................................................................................................... 15
  1.4 Function and Equipment of MicroSelectron HDR Vs.3 afterloading system ....... 16
  1.5 Anatomy and Function of Prostate ......................................................................................... 19
    1.5.2 Prostate Cancer .................................................................................................................. 21
    1.5.3 Treatment of prostate cancer ........................................................................................... 23
  1.6 Treatment planning ................................................................................................................... 24
    1.6.1 Volume definition in brachytherapy .................................................................................. 24
    1.6.2 Dose Volume Histograms (DVH) ..................................................................................... 26
      1.6.2.1 Differential Dose-Volume Histogram ......................................................................... 27
      1.6.2.2 Cumulative Dose-Volume Histogram ......................................................................... 27
    1.6.3 DVH based parameters in brachytherapy ........................................................................... 28
      1.6.3.1 PTV-Oriented Parameters ........................................................................................... 28
      1.6.3.2 OAR-Oriented Parameters .......................................................................................... 29
  1.7 Brachytherapy of prostate in Strahlenklinik in Offenbach ............................................. 30
1.7.1 Infrastructure .................................................................................................................. 30
1.7.2 Work Flow ...................................................................................................................... 33
1.7.3 Clinical Protocols .......................................................................................................... 36
2. Methods and Materials .................................................................................................... 36
  2.1 METHODS ....................................................................................................................... 36
  2.2 Optimization .................................................................................................................... 36
  2.3 Conformity based indices .............................................................................................. 40
    2.3.1 Conformity Index (COIN) ......................................................................................... 40
    2.3.2 External Volume Index (EI) ..................................................................................... 42
  2.4 Radiobiological evaluation ............................................................................................. 42
    2.4.1 Radiobiological model: The Linear-Quadratic (LQ) model ....................................... 46
    2.4.2 Radiobiological indices ............................................................................................ 49
      2.4.2.1 gEUD (generalized Equivalent Uniform Dose) .................................................. 49
      2.4.2.2 EUD_{d,v} : Incorporation of fractionation ......................................................... 52
      2.4.2.3 gBED_{s} (generalized Biological Equivalent uniform Dose) .......................... 53
  2.5 Materials ........................................................................................................................ 56
3. Results and discussion ....................................................................................................... 59
  3.1 Influence of Modulation Restriction ............................................................................. 61
    3.1.1 Dosimetric Analysis ................................................................................................. 61
    3.1.2 Conformity Analysis ............................................................................................... 66
    3.1.3 Radiobiological Parameter Analysis ...................................................................... 68
    3.1.4 Dwell time analysis ............................................................................................... 71
  3.2 Shift analysis ................................................................................................................... 75
    3.2.1 Dosimetric analysis ............................................................................................... 75
    3.2.2 Conformity analysis ............................................................................................... 85
    3.2.3 Radiobiological analysis ....................................................................................... 88
4. Conclusion .......................................................................................................................... 92

Acknowledgements ............................................................................................................. 93

Literature ............................................................................................................................... 94
1. Introduction

1.1 Historical review

X-rays were first observed and documented by Wilhelm Conrad Roentgen, a German physicist who found them quite by accident while experimenting with vacuum tubes in 1895. One year later, the natural radioactivity was discovered by Becquerel after an accidental exposure of a photographic plate to uranium and two years later, in 1898, radium was isolated by the Curies. The prototypical X-ray generator, the Crookes tube, was inexpensive and readily available, and so diagnostic exposures were being made within months of Roentgen’s discovery. In 1896 the first cancer patient was treated with X-rays for nasopharyngeal cancer while after almost a decade we had the first successful radium brachytherapy treatment for cancer in 1903 where two patients were treated for facial basal cell carcinoma. Interstitial brachytherapy was first suggested in the USA by Alexander Graham Bell (1903), the inventor of the telephone, but was independently used in France and Germany at about the same time and therefore it is difficult to give priority to any one person. 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. After the First World War several different schools of brachytherapy were built such as the Radium Hemmet in Stockholm, the memorial hospital in New York and with Regaud and Lacassagne distribution the Radium Institute in Paris. The Stockholm and Paris methods for intracavitary radiation were described in 1914 and 1919 and during the 1930, the rules of Manchester System for interstitial radium therapy were published by Patterson and Parker and later by Meredith. In 1934, the artificial radioactivity induced by particle accelerators, was first reported by Curie and Joliot-Curie. However, quantities and forms of radioactivity useful for brachytherapy were not available until 1940s (Manhattan project 1946), when civilian applicators of nuclear reactors were encouraged. For the next years, radium was the isotope of choice for brachytherapy applications, finally yielding to reactor-produced nuclides such as cobalt, cesium and iridium with much shorter half-lives. In addition the digital computer made possible the calculation of isodose curves around individual brachytherapy treatments and improved afterloading which was first used in 1903. During the last two decades the development of remote
afterloading machines has allowed the complete radiation protection. Moreover the ability to vary source positions and the time that position (dwell time) has also improved the quality of treatment. Modern imaging facilities allow not only more accurate definition of target volume but also the localization of adjacent normal tissue and this can be used to guide afterloading and sources devices. This, combined with computerized dosimetry and better knowledge of the radiobiology involved, signified brachytherapy as more accurate and safe. (1; 2; 3; 4; 5)

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

\[
\lambda = \frac{dp}{dt}
\]  

(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)

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

$$A = \frac{dN}{dt}$$ (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

#### 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

$$K = \frac{dE_{tr}}{dm} = \frac{1}{\rho} \frac{dE_{tr}}{dV}$$ (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 $\dot{K}$ ($\text{J kg}^{-1} \text{s}^{-1}$) is the quotient of the kerma increment $\text{d}K$ occurring in the time interval $\text{d}t$ by the time interval $\text{d}t$:

$$\dot{K} = \frac{\text{d}K}{\text{d}t}$$  \hspace{1cm} (5)

If the special name gray is used, 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

$$\varepsilon_i = \varepsilon_{\text{in}} - \varepsilon_{\text{out}} + Q$$  \hspace{1cm} (6)

$\varepsilon_{\text{in}}$ is the energy of the ionizing particle before the interaction with its rest energy is excluded and $\varepsilon_{\text{out}}$ 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:

$$\varepsilon = \sum_i \varepsilon_i$$  \hspace{1cm} (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

$$\varepsilon = R_{in} - R_{out} + \sum Q$$  \hspace{1cm} (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 $d\bar{\varepsilon}$ is the mean energy imparted to matter in a volume $dV$ of mass $dm = \rho dV$ then the absorbed dose $D$ (J kg$^{-1}$) is defined as

$$D = \frac{d\bar{\varepsilon}}{dm} = \frac{1}{\rho} \frac{d\bar{\varepsilon}}{dV}$$  \hspace{1cm} (9)

The name of the SI unit for absorbed dose is gray (Gy): $1$ Gy $= 1$ J kg$^{-1}$ (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:

$$\dot{D} = \frac{dD}{dt}$$  \hspace{1cm} (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: \(1 \text{ Gy s}^{-1} = 1 \text{ J kg}^{-1} \text{ s}^{-1}\). (1)

### 1.2.4 Source Strength Specification

The currently recommended source strength specifications are:

**Reference air rate Kerma \(K_R\)**

The reference air kerma rate of a source is defined as the air kerma rate in air at a reference distance of 1 m 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 \(\text{mGy h}^{-1}\) at 1 m or \(\text{μGy h}^{-1}\) at 1 m.

**Air Kerma Strength \(S_K\)**

In 1987, the American Association of Physicists 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 along the perpendicular bisector, \(K_\alpha(r)\), and the square of the distance \(r\) (see Figure 1.1):

\[
S_K = K_\alpha(r)r^2 \quad (11)
\]

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 \(\text{μGy m}^2\text{h}^{-1}\) and has been denoted by the symbol \(U\):

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

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) (6)
Figure 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 $K_{\alpha}(r)$.

1.3 Brachytherapy

The word *brachytherapy* is derived from the Greek ancient word “*brachy*” meaning short distance and “*therapy*”, which means treatment. Brachytherapy has the advantage of delivering a high dose of radiation to a well-defined volume while sparing the surrounding normal tissues. Brachytherapy is delivered in short overall treatment duration that reduces the risk of tumor repopulation. (7; 3)

Brachytherapy is a cancer treatment modality where a source of radiation (in most cases a radioactive source) is brought very close to or into the tumor and for that reason the radionuclide is encapsulated within a cover in order to avoid any uptake of radioactivity into the body. The dose is delivered by one or several sealed sources where the most common emit photons. In a few specialized situations β or neutron emitting sources are used. The sources are placed in close proximity to the volume of interest and this is achieved, depending on the body site, using one of the several methods of brachytherapy. (6)

There exist different kinds of brachytherapy. The definition of them is characterized by the positioning of the sources, the duration of the irradiation, the method of source loading and by the dose rate resulted for treatment brachytherapy. (6; 3)
With refer to the positioning of the radionuclides, the first category is divided in two subcategories:

- Interstitial brachytherapy and in
- Contact brachytherapy

In interstitial brachytherapy the radioactive sources are implanted surgically, usually in the form of needles, seeds or wires, within the tumor tissue and this can directly treat the cancer with a rapid fall-off of the dose to the surrounding normal tissues and organs.

The contact brachytherapy is subdivided into four different methods: intracavitary, intraluminal, endovascular and surface brachytherapy. In intracavitary, sources are placed into the body cavities close to the tumor volume. In intraluminal the sources are placed in a lumen. In endovascular a single source is placed into small or large arteries and finally in the surface (mould), sources are placed over the tissue to be treated.

In the second categorization, with respect to the duration of the irradiation, there are two types of brachytherapy. Firstly, the permanent implants in which sources are definitely implanted and are left in the tumor tissue for gradually delivering the dose until the activity decays. The photon energy of the sources used in permanent implant is low in order to minimize demands on radiation protection. The most common radionuclides used for permanent implants are iodine, palladium and gold encapsulated in seeds. Secondly, we have the temporary implants (removable sources) were the sources are implanted for a short period of time. This approach requires that the source carriers remain in the patient until the treatment is finished. Their removal begins when the prescribed dose has been delivered. The majority of this kind of implants is performed with iridium cesium and cobalt sources.

In the method of source loading, which is the third categorization, we have firstly the hot loading where the applicator is preloaded and contain radioactive sources at the time of placement into the patient. Secondly we have the afterloading technique where the applicator is placed first into the target position and the radioactive sources are loaded after either manually or by a machine (automatic
remote afterloading or simply remote afterloading). The latter one is the method we will refer to in this project.

In the last categorization which is classified with respect to dose rate we have the Low Dose Rate (LDR), the Medium Dose Rate (MDR) and the High Dose Rate (HDR). In LDR the dose rate at the prescription dose is 0.4-2 Gyh⁻¹, in MDR is 2-12 Gyh⁻¹ and in HDR is >12 Gyh⁻¹(=0.2 Gymin⁻¹). MDR is not in common use and in those few cases that it has been used, the treatment results have been rather poor compared to LDR and HDR. In HDR treatments, the dose given is substantially higher than the one which is given by the lower limit of 0.2 Gymin⁻¹.

High Dose Rate brachytherapy (HDR) using temporary iridium-192 implants as a boost, in combination with external beam irradiation, was established in the 1990s as a conformal treatment technique for localized prostate cancer. (6; 3)

1.3.1. High Dose Rate (HDR) Brachytherapy

High-Dose-Rate (HDR) brachytherapy represents an alternative method of delivering brachytherapy and is applicable to virtually all stages of localized prostate and many other types of cancer as well. It is a modern radiation therapy modality where a high dose of radiation is delivered using a single source travelling in temporary implanted catheters. HDR has several potential advantages such as elimination of radiation exposure to the stuff, allows short treatment times and can be performed on an outpatient basis. It is an afterloading technique and the treatment plan is based on the actual geometry of the implant. In addition, the use of a single-stepping source allows optimization of dose distribution by varying the dwell time at each dwell position. (7; 8; 9; 10)

The most widely used radionuclide in HDR brachytherapy is ¹⁹²Ir. Its half-life of 73.81 days allows ¹⁹²Ir to be easily used for temporary implants where a decay correction of about 1% per day is possible. ¹⁹²Ir has a high specific activity which makes it practical to supply sources of a very wide spectrum of activities to hundreds of GBqs (370-500 GBq). This leads to very short treatment durations of typically 10-
20 minutes, resulting in a high level of comfort for the patients. Also a high number of treatments are in this way possible. (1)

The HDR brachytherapy is mainly used for the cure of gynecological tumors such as cervix, vagina and endometrial carcinoma of breast cancer, head and neck tumors, adenocarcinoma of prostate and sarcomas.

It may be given as the only treatment (called HDR Monotherapy) or it may be used in combination with external beam radiotherapy (brachytherapy as Boost). Monotherapy is an option for early stage of prostate cancer, or more specifically “low risk” prostate cancer. Intermediate or high risk prostate cancer is better treated with a more comprehensive treatment strategy, such as external beam radiation combined with HDR brachytherapy boost and temporary hormone therapy. (11; 12)

1.3.2 Iridium-192

In the past iridium-192 sources used to be fabricated in the form of thin flexible wires which could be cut to 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 (see Fig.1.2). These are of cylindrical shape. Iridium is a metal and has a mass density of 22.42 g cm^{-3}. It is produced by the neutron activation of iridium metal in nuclear reactors:

\[ ^{191}\text{Ir} (n,\gamma) ^{192}\text{Ir} \]

It decays mainly via \( \beta^- \), almost 95% of the time, and in the majority to the third and fourth excited states of \(^{192}\text{Pt}\).

\[ ^{192}_{77}\text{Ir} \rightarrow ^{192}_{78}\text{Pt} + ^{0}_{-1}\text{e} + \gamma \]

The second decay scheme of \(^{192}\text{Ir}\) is via Electron Capture (EC) which occurs 5% of the time into the fourth state of Osmium-192 (\(^{192}\text{Os}\)):

\[ ^{192}_{77}\text{Ir} \rightarrow ^{192}_{76}\text{Os} + \gamma \]
The de-excitation to the ground state of $^{192}$Pt occurs by almost 94% via gamma decay with emission of several $\gamma$-rays. The most frequent $\gamma$-rays which belong to the $\beta$-decay of $^{192}$Ir are 0.296 MeV (29%), 0.309 MeV (30%), 0.317 MeV (83%) and 0.468 MeV (48%) and those which belong to the EC decay are 0.206 MeV and 0.485 MeV with an intensity of about 3.3%. 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.

Due to its physical properties $^{192}$Ir is established as the preferred radionuclide for temporary and afterloading brachytherapy applications for virtually all tumor sites. The half-life of 73.81 days (1) and the low production costs implicates the storage of sources practical. (1; 14; 15)

1.4 Function and Equipment of MicroSelectron HDR Vs.3 afterloading system

One of the major advances in brachytherapy over the past 20 years has been the introduction of remote afterloading technology. In our days afterloading systems are using mainly $^{192}$Ir or $^{60}$Co HDR sources or $^{192}$Ir, PDR sources. (16)

The development of afterloading systems has as main purpose the reduction of the radiation exposure to all medical and support stuff (medical physicists,
oncologists, urologists, technicians, nurses, and perhaps some visitors) which are involved in the treatment. In remotely controlled afterloading systems, the sources return to safe, at the end of the treatment or whenever it is necessary. The sources are shielded in containers and they are computed control driven resulting in the minimization of irradiation to the personnel. Furthermore, all treatment data are logged and can be found at any time from the printed documents. (3; 17; 18; 19)

In Strahlenklinik Offenbach, the MicroSelectron HDR Vs 3\textsuperscript{1} Genius afterloading system with 30 hardware channels is used for the brachytherapy of prostate. The source is \textsuperscript{192}Ir with an initial activity of usually 370 GBq (10 Ci) (initial source strength of 40.82 KU). The Iridium source design of the MicroSelectron system is shown in Fig.1.3

Figure 1.3 The Iridium source design of the MicroSelectron system

The active core made by Iridium has a diameter of 0.65mm and a length of 3.6 mm. The outer diameter of the stainless steel encapsulated core is of 0.9mm, where the outer length is 4.5mm. The source is welded to the end of a metal wire, transferred to programmed locations in the applicators (dwell positions) and held in the place for programmed duration (dwell times), using a motor driving system.

\textsuperscript{1} Nucletron B.V., Veenendaal, The Netherlands
The MicroSelectron HDR Vs 3 Genius (Fig.1.4) consists of the following components (see also Fig.1.5):

(i) A shielding safe to store the source when the device is not being used.
(ii) A stepping-motor, which enables the user to position a radioactive source with great accuracy in an applicator inserted before in the target volume.
(iii) A system to move the source from the safe to the treatment position.
(iv) Several channels for source transport. In MicroSelectron HDR Vs 3 Genius 30 hardware channels are available. There is an indexer system to allow automatic transfer of the source among the different connected transfer tubes.
(v) Transfer tubes to connect the device to the applicators. The applicators which are used in interstitial brachytherapy for prostate in Strahlenklinik in Offenbach are rigid and made by stainless steel (metallic needles).
(vi) A safety system to ensure safe operation of the device. This system includes an automatic path-check of the applicator and a transfer tube with a check cable. A built in Geiger-Muller counter to check that the source has returned to the safe, and back up batteries to withdraw the source in the event of power failure and for saving treatment data.
(vii) Emergency systems that allow the source to be withdrawn into the safe if something goes wrong. Such a system must include a manual retraction mechanism.

(viii) A console to program the treatment and to control the different steps of the operation of the equipment. It is located outside the treatment room. (17; 20)

Figure 1.5 The guiding system for the check cable and the source cable of the Nucletron MicroSelectron HDR device. In the off-position, the source is located in the center of the tungsten safe.

From there, the source can be transported through the indexer ring to the source transfer tubes (not shown). (Courtesy Nucletron) (17)

1.5 Anatomy and Function of Prostate

Prostate is one of the important parts of a man’s reproductive system. Its development starts before birth and continues to grow until a man reaches adulthood. The prostate gland is about the size of a walnut and surrounds the neck of a man’s bladder, the organ that stores urine. It is located in front of the rectum and the urethra runs through the center of the prostate, letting urine flow out of the body (see Figure 1.6 and 1.7). Prostate is partly muscular and partly glandular, with ducts opening into
the prostatic portion of the urethra. The gland is covered by a membrane (called the prostate capsule) that produces Prostate-Specific-Antigen (PSA). PSA is used as a detector for prostate cancer.

**Figure 1.6 Anatomy of the prostate**

The prostate consists of three lobes, a right and a left lobe, and a central lobe located at the back beneath the neck of bladder. Additionally, is divided into three zones, the peripheral zone, the transition zone and the central zone. In the young adult prostate gland, the peripheral zone is composed of 65% of the glandular tissue, the transition zone 10% and the central zone 25%. Most cancer develop in the peripheral zone of the prostate gland.

**Figure 1.7 Anatomy of the prostate using 3D Ultrasound Imaging**
The primary function of the prostate gland is to produce a fluid. This fluid mixes with fluid from the seminal vesicles and sperm from the testicles to form semen. During ejaculation, semen travels through the urethra and out of the penis. Prostate health is closely linked to hormones (chemicals that carry messages throughout the body). Normal levels of hormones such as testosterone keep the prostate working properly.

There are three basic types of prostate illness. The prostatitis or inflection of the prostate, the adenoma or benign hypertrophy (BPH), which implies a non-cancerous tumor and causes enlargement of the prostate, and cancer which is malignant tumor of the prostate. (21; 22; 23; 24; 25; 26)

### 1.5.2 Prostate Cancer

Prostate cancer occurs when cells within the prostate grow uncontrollably, creating small tumors and usually grows slowly. It is the most common non-skin cancer in America, affecting 1 in 6 men. In fact a man is 35% more likely to be diagnosed with prostate cancer than a woman is to be diagnosed with breast cancer. In 2009, more than 192,000 men will be diagnosed with prostate cancer, and more than 27,000 men will die from the disease. It accounts of about 10% of cancer-related deaths in men. Around 300,000 new cases of prostate cancer are diagnosed in Europe each year. Worldwide, more than 670,000 men are diagnosed with prostate cancer each year. The highest rates are in the USA, Australia, New Zealand, Western and Northern Europe whilst the lowest rates are in East and South Central Asia. According to the most recent data, for all men, with prostate cancer, the relative 5-year survival rate is nearly 100% and the relative 10-year survival rate is 93%. The relative 5-year survival rate refers to the percentage of patients who live at least five years after their cancer is diagnosed. (27; 28; 29)

Prostate cancer typically is compromised of multiple very small, primary tumors within the prostate. At this stage, the disease is often curable (rates 90% or better) with standard interventions such as surgery or radiation that aim to remove or kill all cancerous cells in the prostate.
Prostate cancer is described by both grade and stage.

- **Grade** refers to how closely the tumor resembles normal glandular tissue of the prostate and it is described as low-, medium-, or high-grade cancer. One way of grading prostate cancer is the Gleason system which uses scores of 2 to 10. Another system uses G1 through G4.

- **Stage** refers to the extent of cancer. Early prostate cancer, stages I and II, is localized. It has not spread outside the gland. Stage III prostate cancer, extends outside the gland and may be in the seminal vesicles. Stage IV means the cancer has spread to lymph nodes and to other tissues and organs (see Figure 1.8).

![Figure 1.8 Stages of the prostate cancer](image)

Most of the time, prostate cancer does not initially cause symptoms. By the time symptoms do occur, the disease may have spread beyond the prostate. Early signs and symptoms of prostate can include urinary problems, difficulty in having an erection, blood in the urine and semen, and frequent pain in the lower back and hips. (30)
For most men, prostate cancer is first detected during a routine screening such as PSA test or a digital rectal exam (DRE). In DRE exam doctor feels the prostate through the rectum to find hard or lymph areas. PSA is a blood test that detects a substance made by the prostate called prostate-specific-antigen. Due to the widespread use of PSA testing, approximately 90% of all prostate cancer are currently diagnosed at an early stage and men are surviving longer after diagnosis. The patients who have prostate cancer are commonly categorized into low, intermediate and high risk categories. Three tumor related prognosis factors are normally used to stratify patient population, the clinical T-stage, the Gleason score and the pretreatment prostate-specific antigen (PSA) level. Commonly, low-risk is defined as T-stage<T2c, Gleason score<7, and PSA<10ng/ml. Patients with a high value in one of the three factors are stratified into the intermediate –risk group and the patients with at least two high values into the high-risk group. (30; 31; 32)

1.5.3 Treatment of prostate cancer

There is more than one way to treat prostate cancer and in some occasions a combination of treatments give a better result. Some treatment options are explained below:

(i) **Surgery**: A surgical approach toward the treatment of prostate cancer can be used to remove all or part of the prostate. It may be performed through a conventional surgical incision or with a robotic device that uses small scopes inserted through the abdominal wall (robotic prostatectomy). Surgery is completed in one session and provides valuable prognostic information. (7)

(ii) **External Beam Radiation Therapy (EBRT)**: The EBRT includes the delivery of radiation from outside the body into the prostate. CT scans and MRIs are used to map out the location of the tumor cells, and X-rays are targeted to those areas. Standard external beam linear accelerator therapy which historically is given with doses of 65-70 Gy, has limited success. With the computer-assisted three-dimensional treatment planning, made possible the delivery of higher doses to the rectal, resulting in more rectal complications. Intensity-Modulated radiation therapy (IMRT), allows the modulation and the change to the intensity of the doses and radiation beams to better target the radiation delivered to the prostate, while at the same time, give lower doses to
the bladder and rectum. Proton external beam radiation is another form of advanced external beam technology with precise targeting of the prostate cancer. (7; 33)

(iii) **Hormone therapy**: The purpose of hormone therapy is to reduce the level of the male hormones, called androgens, which are produced mostly in the testicles. Androgens, such as testosterone, help the prostate tumor grow. Hormone treatments are often used in patients with cancer that has already spread out beyond the prostate gland. (34)

(iv) **Chemotherapy**: This type of treatment uses chemicals that destroy rapidly growing cells. Chemotherapy can be quite effective in treating prostate cancer but cannot cure it. The drugs work in a variety of ways by stopping the growth and spread of the tumor. (35)

(v) **Brachytherapy**: Brachytherapy is an established treatment method for prostate cancer because it is a well-defined organ located between two important organs, the bladder and the rectum. With this treatment modality, most of the radiation dose is delivered to the target and not to the surrounding normal tissues and organs. Due to the inverse square law, the dose from a source of radiation within the prostate decreases rapidly, and results in low complication rates and high tumor control. Brachytherapy of prostate cancer can be delivered either as permanent seed implant or as temporary implant (HDR, PDR). (7)

### 1.6 Treatment planning

#### 1.6.1 Volume definition in brachytherapy

There have been several concepts and parameters defined and proposed for the evaluation of the 3D dose distribution in brachytherapy. The new developments provide the possibility to adapt the dose distribution much better to the Volume of Interest (VOI). Furthermore, remote afterloading with optimization of source dwell times enables a better dose homogeneity to be achieved. (3; 36)

Volume definition is necessary for meaningful 3D treatment planning and for accurate dose reporting. The definition of volume is reported according to recognized international classification and describes several target and critical structure volumes.
This helps in the treatment planning process and that provide a basis for comparison of treatment outcomes. The definition of volumes has the same significance in external beam planning as in brachytherapy planning. The following volumes have been defined as principal volumes in 3D treatment planning in brachytherapy. (6; 37)

- **GTV** (Gross Tumor Volume): The GTV is the gross palpable, visible or demonstrable extent and location of the malignant growth. It consists of the primary tumor volume (GTV primary), positive lymph nodes (GTV nodal) and distant metastasis (GTV-M). In brachytherapy the GTV is mainly the primary tumor and is essentially defined by clinical examination and imaging techniques.

- **CTV** (Clinical Target Volume): The CTV is the volume which contains the “gross” and “subclinical” disease. Clinically, it thus contains the GTV and a “safety margin” around the GTV (CTV-T) to take into account (probable) subclinical involvement. The CTV may also include other anatomical areas like regional lymph nodes (CTV-N) or other tissues with suspected or proven subclinical involvement (CTV-M). The implantation of a prostate is a procedure covering different targets and applying different target doses due to zonal anatomy related differences, possible tumor locations within the prostate gland and different implantation techniques and loading patterns used. Therefore, it is advisory to define different target areas within the gland and to record and report treatment parameters related to the overall prostate gland $CTV_1$, to the peripheral zone $CTV_2$, and to areas where gross disease is detectable $CTV_3$. The detectable tumor and the peripheral zone represent the regions with the highest tumor load, whereas the transitional zone and the central zone usually have a much lower tumor infiltration rate. These target definitions for prostate brachytherapy exists from the recommendations by GEC/ESTRO-EAU (38).

- **PTV** (Planning Target Volume): The PTV by definition includes GTV and CTV. The PTV is a geometrical concept used for treatment planning. The aim is to ensure that the prescribed dose is actually absorbed in the whole CTV, taking into account the net effect of all the possible variations of position of the CTV relative to the irradiation source. In brachytherapy the PTV is defined to select appropriate source arrangement, positioning and movement control.
Also in brachytherapy the PTV and CTV is considered to be identical. In Strahlenklinik Offenbach and for the Monotherapy the Planning Target Volume (PTV) is considered to be CTV1 (prostate gland).

- **Treated Volume**: this is encompassed by an isodose surface corresponding to the minimum target dose, the isodose ideally encompassing the CTV.
- **Irradiated Volume**: The Irradiated volume is the tissue volume, larger than the Treated volume, which receives a dose considered to be significant in relation to normal tissue tolerance.
- **Organs At Risk (OARs)**: OARs are normal structures and because of their radiosensitivity and their location close to the target volume, may significantly influence the treatment planning or the prescribed dose level. (36; 37; 6; 38)

Additionally ICRU report 58 (ICRU 1997) recommends to record the high-dose volume, defined as the volume encompassed by the isodose corresponding to 150% of the prescribed dose, and the low-dose volume, defined as the volume within the CTV, encompassed by the 90% isodose value. (36)

### 1.6.2 Dose Volume Histograms (DVH)

A plot of dose-volume frequency distribution, commonly known as DVH (dose-volume-histogram), graphically summarizes the simulated radiation distribution within a volume of interest of a patient which would result from a proposed radiation treatment plan. DVHs are used as tools for comparing rival treatment plans for a specific patient. Furthermore, the DVH has gained wide acceptance as a mechanism for reducing the voluminous data of a three-dimensional dose distribution into a two-dimensional graph. DVHs, however, do not provide any spatial information, such as the locations of the high- and low-dose regions (“hot” and “cold” spots) inside the Volume of Interest (VOI). DVH does not replace isodose distribution which provides the information for PTV coverage. Rather, it enhances the ability to choose an optimal plan and show the dose-volume relationships of the various Organs at Risk of interest. DVHs are usually displayed in the form of “per cent volume of total volume” on the ordinate against the dose on the abscissa. (39; 40; 41; 6)

There are two types of DVHs which are in use:
- Direct (or differential) DVH
- Cumulative (or integral) DVH

### 1.6.2.1 Differential Dose-Volume Histogram

To create differential DVH, the computer sums the number of voxels with an average dose within a given range and plots the resulting volume (more frequently as percentage of the total organ volume) as a function of dose. An example of the direct DVH is shown in Figure 1.9. 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. (6)

![Differential Dose Volume Histograms](image)

Figure 1.9 Differential Dose Volume Histograms for prostate treatment plan is shown in the left picture and in the right for urethra. The ideal target differential DVHs would be infinitely narrow peaks at the target dose for the PTV and at 0 Gy for the critical structure.

### 1.6.2.2 Cumulative Dose-Volume Histogram

A cumulative DVH (cDVH) is a plot in which each bin represents the volume, or percentage of volume (y-axis), that receives a dose equal to or greater than an indicated dose (x-axis). When calculating DVHs, the choice of voxel size is a compromise between computational speed (larger voxels) and accuracy (smaller voxels). In cumulative DVH 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 at the dose 0 Gy, since all of the volume receives dose $\geq 0$ Gy.
In the Fig.1.10 is shown the cumulative DVHs for the PTV (prostate) and the OARs. While displaying the percent volume versus dose is more popular, it is useful in some circumstances to plot the absolute volume versus dose. (6)

![Cumulative Dose Volume Histograms](image)

Figure 1.10 Cumulative Dose Volume Histograms for the same prostate and urethra which are used in the Fig.1.9. The ideal cumulative DVHs are shown in the right. Both volume and dose axes are given in % of VOI and prescription dose respectively.

1.6.3 DVH based parameters in brachytherapy

For the evaluation and documentation of the dose distribution DVH-based parameters have been proposed by GEC/ESTRO-EAU (38; 42).

1.6.3.1 PTV-Oriented Parameters

\( D_{100} \): The dose that covers 100% of the PTV volume which is exactly the MTD (Minimum Target Dose) proposed by ICRU report 58.

\( D_{90} \): 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 the PTV volume that has received at least the prescription dose, which is set to 100%.

\( V_{150} \): The volume, normally the PTV volume that has received at least 150% of the prescription dose. (36; 42; 43)

These parameters can be seen graphically in Figure 1.11.
Figure 1.11 Graphical demonstration of the definition of the $D_{100}$, $D_{90}$, $V_{100}$ and $V_{150}$ dosimetric parameters for an imaging-based 3D brachytherapy treatment planning based on the cumulative dose volume histogram of PTV.

1.6.3.2 OAR-Oriented Parameters

For the OARs there are not widely established dosimetric parameters. The dose to Organs at Risk (OARs) 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 by the GEC/ESTRO-EAU recommendations (38) to indicate the dose $D_{2cm^3}$ for the most exposed $2cm^3$ of rectum and bladder, and $D_{0.1cm^3}$ for the most exposed of $0.1 cm^3$ of the urethra or $D_1$ for $1\%$ of the contoured prostatic urethra. Furthermore, the $D_{10}$, which is defined at the highest dose covering $10\%$ of the OAR volume, is commonly used for the interstitial brachytherapy of prostate cancer for documenting the dose distribution in the related OARs urethra, rectum and bladder. Some of these parameters are shown in the Figure below (Fig.1.12) (38; 36)
Figure 1.12 Graphical demonstration of the definition of the $D_{10}$ and $D_{2cc}$ dosimetric parameters for an imaging-based 3D brachytherapy treatment planning based on the cumulative dose volume histogram of Urethra.

1.7 Brachytherapy of prostate in Strahlenklinik in Offenbach

1.7.1 Infrastructure

Since August 2001, the HDR Monotherapy is being used as a treatment for low risk prostate cancer in close cooperation with the Urology Clinic in Strahlenklinik in Offenbach. The clinical procedure is totally 3D Ultrasound based, using the real time intraoperative planning system Oncentra Prostate².

For the delivery of treatment for the prostate cancer there are two operation theatres (Figure 1.13) and one control room. Each operation theatre includes an operation table (Courtesy TRUMPF, MARS) where the patient is placed in lithotomy position after general or spinal anesthesia.

² OcP, Fa.Nucletron B.V., The Netherlands
Two different types of Ultrasounds are used in Strahlenklinik Offenbach. The first is an Ultrasound scanner B-K Medical Type Falcon 2101\(^3\) with frequency range 4-9 MHz and with scanning depth range 2.4-8.6 cm. The probe’s type is 8658. The second one is an ultrasound scanner ALOKA Prosound a10\(^4\) with frequency range 1-15 MHz and with scanning depth range 3-15 cm. The probe’s type is UST-678 (Figure 1.14).

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\(^3\) B-K Medical, Herlev, Denmark  
\(^4\) ALOKA CO., LTD., Tokyo, Japan
The Ultrasound devices, which are figured above, are used in combination with a stepper, an encoder and an immobilizer. The ultrasound probe (see Fig.1.15a) is placed on the stepper which helps the acquisition of imaging. The shifting of the stepper is 1mm (see Figure 1.15c). The encoder connects the stepper with the software and translates the movement of the stepper into signal. The stepper also provides an accessory to hold the template (see Fig.1.15b). The ultrasound is attached to a “cradle” device, the immobilizer, so there is no need to hold the ultrasound by keeping it stable during the procedure and allows to the user a free possibility of positioning the stepper unit in all directions. Additionally, a square template is attached to the ultrasound with a size of 74.50x71x20mm (HxLxT) This template is metal and it has holes every 0.5 cm through which needles will be placed (Figure 1.15d). The needles are 20 cm long with an outer diameter of 1.5 or 1.9 mm. Approximately 10-20 metal needles are being used depending on how large the prostate is. These are placed through the template and through the skin into the prostate gland. Usually the needles with 1.5mm diameter are preferred because of their flexibility and because they cause less trauma during insertion. Finally, for the clinical procedure, the Oncentra Prostate has been used.
**Oncentra Prostate (OcP)** (Nucletron Waardgelder1.Veenedaal, the Netherlands.): OcP is the real time treatment planning system for prostate brachytherapy. Direct 3D U-S imaging of the implant gives the possibility to update the treatment plan during insertion of the catheters in the prostate. The software provides the physician with anatomical and dosimetric information which is used to determine the positioning and loading of radioactive sources. Also, provides a variety of plan evaluation tools to assist in generating the most optimal dose distribution (e.g. dose verification at a point and dose volume histograms.

### 1.7.2 Work Flow

The whole treatment is divided in three fractions of 11.5 Gy per fraction (total dose 34.5 Gy). The interval between each fraction is two weeks and the patient must stay in the hospital three days after each treatment. One day before the implantation of the catheters the patient will take a bowel-preparation drink to empty out their bowels.

The procedure is described briefly below:

---

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

**Step 2**: Insertion of biplanar probe into the rectum.
Adjustment of implant 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 1.1)
**Step 6: Catheter Insertion**

(Implantation)

**Step 7: Live-plan**
- All needles are implanted
- Live acquisition, after definition of the base plane
- New contouring by radiation oncologist
- Catheter Reconstruction (catheters in green color)
- Generation and optimization of dose distribution through OcP utilizing HIPO

**Step 8: Irradiation**

with the MicroSelectron afterloader. The implanted catheters are connected via transfer tubes to the afterloader
1.7.3 Clinical Protocols

In Strahlenklinik Offenbach, the HDR Monotherapy is delivered in three implants separated by at least 2 weeks interval. In each implant a single fraction with a prescription dose of 11.5Gy is delivered resulting thus to a total Brachytherapy dose of 34.5Gy. As has been mentioned above the prostate gland (CTV1) is considered as PTV and urethra, bladder and rectum are used as OARs in the treatment planning. The whole procedure including dose delivery is realized intraoperatively utilizing 3D and 2D Ultrasound imaging. The dose-volume parameters of the dosimetric protocol are listed in Table 1.1

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

Table 1.1 Clinical protocol in Offenbach for HDR Monotherapy

2. Methods and Materials

2.1 METHODS

2.2 Optimization

Modern inverse optimization technology such as HIPO is implemented in OcP Vs. 3. HIPO is offering the possibility of anatomy based inverse optimization of a given implant (catheters in place) based on linear objective functions for targets and organs at risk (OAR) by adjusting the dwell times of all active source dwell positions (ASDPs) within the catheters. In addition HIPO can propose automatically a catheter placement and the corresponding dwell time pattern of the source movement within
the catheters that is best fulfilling all user defined objectives. In order to get restriction of the free modulation of dwell times allowing thus more smooth source movement and more smooth distribution of dwell time over dwell positions, HIPO offers the unique option of a modulation restriction (MR) parameter, the dwell time gradient restriction.

The dwell time gradient restriction considers the gradient of the dwell weights or times of the source within the separate catheters in form of a dedicated objective function. The MR parameter takes values in the range \([0.00, 1.00]\). A value of 0.00 will get the system to ignore this dwell time gradient objective, where a value of 1.00 results to the maximum consideration of it.

In the figure 2.1 all optimization related settings can be seen. Based on the defined Volumes of Interest (VOIs) and the preset values, the several objectives regarding PTV, GTV, Normal Tissue (NT) and OARs can be activated or deactivated and the corresponding low and high dose limit values and their importance factors (weights) can be accepted or changed. 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. Furthermore, the desirable value of modulation restriction can be changed (44).

![SOVHU optimization settings](image)

**Figure 2.1 Optimization settings** (OcP, Fa. Nucletron B.V., The Netherlands)

An example of the impact of the use of the Modulation Restriction is shown in the Figures of dwell times 2.2, 2.3.
In these figures 2.2 and 2.3 the significant change of dwell times in several dwell positions is marked. In the dwell positions, where the dwell time was extremely high, a redistribution of time among neighbors of that source dwell position is resulted when the modulation restriction is activated.

<table>
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<tr>
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Figure 2.2 The times of the respective dwell positions in each catheter without MR (MR=0)

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Figure 2.3 The times of the respective dwell positions in each catheter with MR (MR=0.20)

Figure 2.4 demonstrates a graphical comparison of the dwell time profiles of the two plans categories for that case. There is a total dwell time reduction when the
Modulation Restriction (MR=0.12) is used. Although, the time distribution within the catheter is lower this does not lead to significant changes in the DVH of the prostate as well as in the OARs (see Fig 2.5).

![Graph showing dwell time profiles with and without modulation]

**Figure 2.4** Comparison of the dwell time profiles for the two types of modulation (MR=0.20 and MR=0). The dwell times are listed in Fig. 2.2 and 2.3

![Graph showing DVHs with and without modulation]

**Figure 2.5** DVHs with and without Modulation Restriction
2.3 Conformity based indices

2.3.1 Conformity Index (COIN)

Baltas et al. (1998) has introduced a utility function as a measure of the implant quality, the conformal index (COIN), which has been later expanded to include OARs (MILICKOVIC et al. 2002). The COIN, which is also a measure for dose specification in brachytherapy, takes into account patient anatomy, both of the PTV, surrounding normal tissue (NT) and OARs. The ideal situation is that the prescription dose, $D_{ref}$, isodose 3D envelope is identical with the PTV and, outside the PTV, there is an extremely rapid fall-off of dose and, inside the PTV, there are no volumes with significantly higher doses (as defined by the clinician) than $D_{ref}$. Although in practice, such an ideal conformal treatment rarely occurs. This means that it is essential to have some quality index/figure of merit to distinguish between possible alternative 3D treatment plans, by taking into account the $D_{ref}$ volume ($V_{ref}$), the PTV, and significantly higher doses than $D_{ref}$, both inside and outside the PTV. This also should take into account critical organs and structures. (36; 45; 46)

The COIN for the reference dose value, $D_{ref}$ (prescription dose), is defined as

$$COIN = C_1 \cdot C_2$$  \hspace{1cm} (12)

$$C_1 = \frac{PTV_{ref}}{PTV} \hspace{1cm} (13) , \hspace{1cm} C_2 = \frac{PTV_{ref}}{V_{ref}} \hspace{1cm} (14)$$

where the coefficient $C_1$ is the fraction of PTV that is enclosed by $D_{ref}$ and is a measure of how accurately the PTV is covered by $D_{ref}$. The ideal situation is $C_1$=1. The coefficient $C_2$ is the fraction of $V_{ref}$ that is covered by PTV and is also a measure of how accurately the PTV is covered by $D_{ref}$. Additionally it is also a measure of how much normal tissue volume outside PTV is covered by $D_{ref}$. (45) The ideal situation is $C_2$=1 (see also Fig.2.6)
Equation 12 does not take into account the unwanted irradiation of parts of OARs and normal tissue. In this case, the algorithm of COIN must be modified by using a third coefficient $C_3$ which is defined below for several ($i=1, 2, 3,...$) critical structures. Then, the COIN including OARs is calculated by the following equation

$$COIN = C_1 \cdot C_2 \cdot C_3$$  \hspace{1cm} (15)

$$C_3 = \prod_{i=1}^{N_{OAR}} \frac{1-V_{OAR}^i(D>D_{crit}^i)}{V_{OAR}^i}$$  \hspace{1cm} (16)

$V_{OAR}^i$ is the volume of the $i_{th}$ OAR and $V_{OAR}^i(D>D_{crit}^i)$ is the volume of the $i_{th}$ OAR that receives a dose that exceeds the critical dose value $D_{crit}^i$ defined for that OAR. The product in the equation for $C_3$ is calculated for all $N_{OAR}$ OARs included in the treatment planning. The ideal situation is $COIN=C_1=C_2=C_3=1$. It should be noted that COIN can only take values between 0 and 1 and cannot be negative. (36; 45)

The COIN assumes in this form that the PTV, the OARs and the surrounding normal tissue are of the same importance. (36)
2.3.2 External Volume Index (EI)

One dosimetric parameter for the description of the quality of a brachytherapy application is the External Volume Index (EI). The External Index is the amount of normal tissue volume that receives a dose equal to or greater that the reference dose. The volume is expressed as a percentage of the target volume (47). In this project the EI is calculated from the following equation

\[
EI = \frac{C_1}{C_2} - C_1
\]  

(17)

where \( C_1 \) and \( C_2 \) are the coefficients described in the previous section.

2.4 Radiobiological evaluation

Radiobiology is a scientific field that concerns with the action of ionizing radiation on biological tissues and living organisms. It is also a combination of two disciplines, radiation physics and biology. When cells are exposed to ionizing radiation, standard physical effects occur between radiation and atoms or molecules of the cells and possible biological damage to cell functions follows. The biological effects of radiotherapy depend on dose distribution, treated volume, dose rate and treatment duration. However these various factors are of different importance in determining the outcome of external beam radiotherapy or brachytherapy (6; 48).

The process of inducing biological damage to human cells by ionizing irradiation can be divided into 3 consecutive steps (48; 49):

- A very short initial physical phase (about \(10^{-18} \text{s} \)), which is called energy deposition phase. During this phase photons interact with orbital e\(^-\), raising them to higher energy levels inside the atoms (excitation), or ejecting them from the atoms (ionization).
- The chemical phase in which the duration is again very short (about \(10^{-3} \text{s} \)). Ionized and excited atoms interact, leading to the breakage of chemical bonds
through a direct action or an indirect action, which involves the formation of free radicals. Free radicals are highly reactive and can induce chemical changes in biologically important molecules like DNA. Single-stand or double-stand break in DNA appear to be the basic types of damage, which lead to biological effects.

The **biological phase**, which lasts much longer than the other phases, includes all the subsequent processes. During this phase, the cells react to the inflicted chemical damage. The vast majority of lesions in DNA can be successfully repaired through specific enzymatic reactions. A few lesions though, may not be repaired and that may cause cell death. Cell death is not immediate and usually occurs during the next cell division. However, death due to a lethal lesion may be delayed for a limited number of mitotic divisions (up to 5 or 6).

The stem cells are the only cells that are divided in normal tissues, thus the earliest effect observed is related with a deficit in stem cells. The loss of the stem cells will lead to a deficit in differentiated cells, causing the observed clinical reactions. The early reactions are seen during the first days or weeks after irradiation. They are temporary because the cell deficit is compensated for the repopulation of stem cells and so from the differentiated cells. The so-called late reactions appear at longer times after the irradiation of normal tissues. They may be seen after months or years and 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.

A number of biological processes take place during irradiation and may modify radiation response. These processes are often described as the **4Rs of radiobiology** (49).

**Repair**: As evidenced by cellular recovery during the few hours after exposure.

**Reassortment**: Cell-cycle progression effects otherwise known as redistribution. The different phases of cell cycle are characterized by different radiosensitivities. Consequently, cells that survive a first dose of radiation will tend to be in a resistant phase of the cell cycle and within a few hours they may progress into a more sensitive phase. The cell cycle is divided in four consecutive stages: G₁, S, G₂ and M. G₁ is a
gap of apparent inactivity after a mitosis (M), before DNA synthesis (S-phase) resumes in view of the following cell division. G2 is a second gap of apparent inactivity between S-phase and M.

**Repopulation:** During a 5-7 week course of radiotherapy, tumor clonogenic cells that survive irradiation may proliferate and thus increase the number of cells that must be killed.

**Reoxygenation:** In a tumor, hypoxic cells are more radioresistant and tend to survive a first dose of radiation. However, after their oxygen supply their radiosensitivity may increase.

Two of these processes, repair and repopulation, will tend to make the tissues more resistant to a second dose of radiation. On the contrary, the other two processes, reassortment and reoxygenation, tend to make them more sensitive. These 4 factors may modify the response of a tissue to repeated doses of radiation and they are responsible for the slope of its iso-effect curve. The overall radiosensitivity of a tissue depends on a fifth “R”: Intrinsic radiosensitivity.

**Intrinsic Radiosensitivity** varies along the cell-cycle, S being the most resistant phase, and G2 and M the most sensitive. Therefore, cells which survive after an exposure are preferentially in a stage of low sensitivity (G1) i.e. synchronized in a resistant cell cycle phase. Then, they progress together to the S phase and then to the more sensitive G1 and M phases. A new radiation exposure at this time will have a larger biological effect (more cell killing).

Biological effects of radiation are also strongly dependent upon the rate of dose delivery. Repair, repopulation and reoxygenation, are the main factors determining the outcome of the treatment. They do not occur during the very short duration of irradiation (up to 10-15 minutes), but take place between consecutive fractions, provided the interval is adequate. HDR is generally given as fractionated treatments to decrease normal tissue toxicity. The ability to locate radioactive sources in or close to the tumor is a fundamental feature of the optimal conformal dose delivery system, which produces good dose distributions sparing early and late-responding normal tissues. Generally the optimal strategy for any radiotherapeutic regimen requires short
overall treatment times to limit tumor repopulation and long overall treatment times to reduce early normal-tissue reactions, especially to the skin and mucosa. In most radiotherapeutic situations there is a compromise between them in order to have minimization in tumor repopulation and to avoid unacceptable early complications. In brachytherapy, because of the very conformal dose distribution produced, there are very low early normal tissue damage rates which are associated with and much shorter treatment times. (48; 50; 51).

The effects of ionizing radiation on the various tissues of the body vary considerably, both in terms of the radiation dose required to produce a certain damage and the time required for the expression of that damage. Tissues are divided into two categories. The first one refers to the early-responding tissues which show the effects of radiation damage within a few weeks after radiotherapy. The second category refers to late-responding tissues which show their response to radiation damage over months to years after exposure. The damage to early-responding tissues tends to heal while the damage to late-responding tissues tends to be more permanent. The distinction between early and late-responding tissues has become more important because of the recognition that time-dose relationships are systematically different between them. Tumors normally respond as early-responding tissues (52).

**Cell survival curves:**

A cell survive curve describes the relationship between radiation dose and the portion of cells that survive. For cells growing in culture, the loss of the ability to continue the growth is termed reproductive death. The irradiated cells that are able to proliferate indefinitely are said to be clonogenic. The mean lethal dose for loss of reproductive capability is usually less than 2 Gy. Cell survival data are generally plotted with the surviving fraction on a logarithmic scale and the dose on a linear scale. The type of radiation influences the shape of the cell survival curves. At low doses, for sparsely ionizing radiations the survival curve starts out straight and then bends towards. At high doses the curve may straighten out again. Densely ionizing radiations exhibit a cell survival curve that is almost an exponential function of dose, shown by almost a straight line on the log-linear plot. The cell survival curves off early reacting normal tissues and tumors are less curved than those of late reacting normal tissues.
Several mathematical models of varying degrees of complexity have been developed to describe the shape of cell survival curves, all based on the concept of random nature of energy deposition by radiation (6; 48; 49; 53).

2.4.1 Radiobiological model: The Linear-Quadratic (LQ) model

Much effort has been and is being spent on developing quantitative models that attempt to predict the likely biological response of tumors or normal tissues to any arbitrary pattern of irradiation. The fundamental mechanism underlying some of these models is that of cell killing. The linear-quadratic (LQ) model is widely used in radiation therapy, because its low number of adjustable parameters can be used in order to explain cell killing. Due to this simplicity, the results of the LQ model are sensitive to its parameters. The selection of proper LQ parameters becomes important for using this model successfully. The LQ model is the best available for the quantitative assessment of clinical problems also because it allows distinction to be made between the fractionation and dose rate sensitivities of different tissue types (54; 55).

The main features of the LQ model may be summarized as follows. The fractional cell survival (S) following a radiation dose (D) is given by the equation (18) below (56; 6).

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

(18)

where \( S(D) \) is the fraction of cells surviving a dose \( D \), \( \alpha \) is the constant describing the initial slope of the cell survival curve and \( \beta \) is a smaller constant describing the quadratic component of cell killing. This is a continuously-bending survival curve with no straight portion at high radiation doses. This equation describes two distinct processes, each of which may lead to cell death. In the first process, two 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. In the second process, the 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, then the cell may consider to be sub-lethally damaged. The measures for the importance of each of the two processes are the \( \alpha \) and \( \beta \) parameters respectively with dimensions \( \alpha \text{ Gy}^{-1} \) and \( \beta \).
Gy$^{-2}$. The shape of a survival curve is determined by the ratio $\alpha/\beta$ ($G_y$). The initial slope of a cell survival curve ($\alpha$) represents the intrinsic radiosensitivity of the cell and is a non-repairable type of damage. The curvature of the cell survival curve ($\beta$) represents a repairable type of injury with time, and it is responsible for the dose-per-fraction and dose-rate variations in radiotherapy. The ratio $\alpha/\beta$ corresponds to the dose at which the linear contribution to damage ($\alpha D$ on the logarithmic scale) equals the quadratic contribution ($\beta D^2$) (49; 6; 56; 48).

$$\alpha D = \beta D^2 \quad \text{and} \quad D = \frac{\alpha}{\beta}$$

(19)

A large $\alpha/\beta$ corresponds to a small shoulder (small repair capacity) and a small $\alpha/\beta$ to a broad shoulder (large repair capacity).

The sensitivity to a change in fractionation can be quantified through the $\alpha/\beta$ ratio. Fractionation spares tissues with a low $\alpha/\beta$ ratio (late-responding tissues) more than it spares tissues with a high $\alpha/\beta$ ratio (early-responding tissues typical of most tumors). Most tumors have an $\alpha/\beta$ ratio which is in the range of 10-30Gy (Fowler 1989), while late responding tissues usually have lower values of around 3Gy. An important exception to this generalization about the tumor values is prostate adenocarcinoma for which the $\alpha/\beta$ ratio may be as low as around 1Gy (57; 58).

The $\alpha/\beta$ ratio and the tissue parameter $\mu$, which is known as the sub-lethal damage repair time constant, are the main parameters which influence tissue responses when the dose-rate is changed. The parameter $\mu$ is inversely proportional to the half-time for repair of sub-lethal damage and is a measure of the rate at which damage is repaired (55; 58)

$$\mu = \frac{0.693}{T_{1/2}}$$

(20)

The linear quadratic approach has also led to various ways of calculating isoeffect relationships for radiotherapy. Generally, the fraction of surviving cells
associated with an isoeffect in irradiated tissues is uniquely determined by the surviving fraction of target cells and is denoted as \( E \) (49).

\[
E = -\log_e(SF) = D(\alpha + \beta d)
\]

(21)

where \( D \) is the total dose, \( d \) is the dose per fraction and \( \alpha \) and \( \beta \) are the linear and quadratic terms of the tissue-specific survival curve, respectively. Dividing both sides of this equation by \( \alpha \), we get

\[
\frac{E}{\alpha} = D \left( 1 + \frac{d}{(\alpha/\beta)} \right) = D \times RE = \text{Biologically Effective Dose (BED)}
\]

(22)

where \( RE \) (Relative Effectiveness per unit Dose) is the relative effectiveness factor of the entire treatment and account for the biologically enhancing influence of dose rate, temporal pattern of radiation delivery and other parameters (59).

\[
RE = 1 + \frac{d}{\alpha}
\]

(23)

The \( \text{BED} \) is a measure of the biological dose delivered to a tumor or normal tissue and it is the theoretical total dose that would be required to produce a particular isoeffect using an infinitely large number of infinitesimally small dose fractions. \( \text{BED} \) is a measure of effect in units of \( \text{Gy}_x \) where the suffix \( x \) indicates the value \( \frac{\alpha}{\beta} \) assumed in the calculation (60).

For \( n \) fractions,

\[
E = n(\alpha d + \beta d^2) =
\]

\[
aD + \beta dD =
\]

\[
D \left( 1 + \frac{d}{\alpha/\beta} \right) = \text{Total Dose} \times RE
\]

(24)

where \( D = nd \) is the total dose. When the dose per fraction is reduced towards zero, \( \text{BED} \) becomes \( D \), i.e. the total radiation dose. \( \text{BED} \) is also the total dose required for \( \alpha \) single exposure at very low dose rate (49).
It should be noted that the above equations make no allowance for tumor repopulation during treatment. The incorporation of the repopulation effect is achieved through the use of a subtractive repopulation factor which takes into account the overall treatment time and repopulation rate. In HDR brachytherapy treatment for the prostate cancer, the factor of repopulation in prostate tumor cells is neglected. Prostate tumors are generally growing with an effective rate which is too small to be considered for tumor repopulation over the treatment time. The potential doubling time, which is the term that describes the proliferation rate, is 42 days. Such slow growth is typical for late-responding normal tissues. Furthermore, no repair occurs during an HDR fraction because it is delivered in a few minutes and has short treatment time. (60; 54; 61; 62)

The LQ model is in widespread use in radiotherapy and generally works well in describing responses to radiation in vivo and in vitro (49).

2.4.2 Radiobiological indices
2.4.2.1 gEUD (generalized Equivalent Uniform Dose)

Dose distributions are generally non-uniform, especially for normal structures. To quantitatively evaluate a treatment plan one needs to know the consequences of the applied dose distribution for all the structures of interest. Brachytherapy provides a high degree of conformity, but also results in a high degree of dose inhomogeneity in both target and normal tissues (63; 48).

A concept of Equivalent Uniform Dose (gEUD) for tumors, based on models of clonogen survival, has been developed and investigated in several clinical settings. The generalized EUD concept, which is a power-law function, applies to both tumors and normal tissues. For any dose distribution, the corresponding gEUD is the dose (in Gy), which, when distributed uniformly across the target volume, causes the survival of the same number of clonogens. For normal tissues, gEUD represents that uniform dose, which leads to the same probability of injury as the corresponding homogeneous dose distribution. The gEUD can be calculated easily because of its mathematical simplicity, and comparisons between multiple alternative treatment plans will be very
simple. One of the limitations of the gEUD is that it does not take into account the fractionation effects (63; 64).

Based on the analysis of outcomes for several clinical studies providing volumetric information for tumors and normal tissues, there is the proposal that gEUD for a structure of interest can be estimated as:

\[
gEUD = \left( \frac{1}{N} \sum_{i=1}^{N} D_i^a \right)^{1/a} \tag{25}
\]

using a cumulative dose-volume histogram or

\[
gEUD = \left( \sum_{i=1}^{N} v_i D_i^a \right)^{1/a} \tag{26}
\]

using a differential DVH, where N is the total number of voxels in the anatomic structure of interest, \( v_i \) and \( D_i \) are the fractional volume and the dose at that volume (bins of DVH), respectively, and \( a \) is the tissue-specific parameter that describes the dose-volume effect and can be obtained empirically from clinical outcome data (63; 65).

One advantage of this phenomenological model is that by adjusting the \( a \) parameter appropriately, the gEUD can be applied to tumors as well as to normal tissues. As expected from the property of the generalized mean, by varying the parameter \( a \), the most relevant part of the dose profile can be emphasized. For \( a = \infty \), the gEUD is equal to the maximum dose and for \( a = -\infty \), the gEUD is equal to the minimum dose. For \( a = 1 \), the gEUD is equal to the arithmetic mean, and for \( a = 0 \), gEUD is equal to the geometric mean. In tumors, for which cold spots are of greatest concern regarding tumor control probability (TCP), \( a \) takes on a “large” negative value. In normal tissues with serial functional subunit architecture, hot spot doses are emphasized with a very “large” positive value of “a”. For parallel normal tissues, such as the salivary glands, the mean dose is the most important factor in determining the normal tissue complication probability (NTCP). For these structures, the value of “a” is chosen to be 1. Another positive feature of the gEUD is that it can be applied to
normal tissues that are neither strictly serial nor parallel. The value of “a” will be positive for all normal tissues and negative for all tumors (65; 66; 67; 68; 69).

Determination of parameter “a”

The parameter “a” could analytically be related to partial dose-volume data. Under the assumption of uniform irradiation of partial organ volume, equations (25) and (26) can be reduced to

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

which states that the uniform dose to the entire volume of an organ has the same complication probability as the fractional volume \( V \) of an organ that receives a uniform dose of \( D \). The gEUD parameter “a” is related with the parameter \( n \) from the power law model for the volume effect used by Lyman (66) by

\[ a = \frac{1}{n} . \]  

Therefore, “a” approaches 1 for parallel normal tissues and positive infinity for serial normal tissues. The volume effect “n” is defined only for sensitive structures (65).

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, a characteristic for non-uniform irradiated normal tissue. An advantage of gEUD is that it can be applied to normal tissues that are neither strictly serial nor parallel. Because the ability to control tumors depends on the value of the dose at cold spots “a” can only have 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 quality 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 (65).
2.4.2.2 EUD\textsubscript{d,v}: Incorporation of fractionation

The concept of a biologically effective dose (BED) has already been mentioned in section 2.2.1. The BED is given from the equation

\[ BED = D(1 + \frac{d}{a/\beta}) \quad (29) \]

The BED has an advantage over the simple physical dose which is the ability to account for fractionation. Taking advantage of this feature of BED, the concept of EUD\textsubscript{d,v} can be defined as

\[ EUD_{d,v} = \left( \sum_{i=1}^{N} v_i BED_i \right) \frac{1}{C} \quad (30) \]

Where BED\textsubscript{i} is the BED for each sub-volume (bin) \( i \), \( C \) is the normalization factor for the reference dose per fraction \( d \), “a” as already mentioned is the tissue-specific parameter and \( d \) is the dose per fraction which in our case is 2 Gy.

The normalization factor \( C \) is inserted to correct for incorporating the BED and this makes the EUD\textsubscript{d,v} appear much greater than the gEUD. As an example, in the case of a sensitive structure with an \( a/\beta \) ratio of 3 Gy radiated at 2 Gy per fraction, the BED will be 1.67 times greater than the prescribed dose. According to this, a similar ratio between the EUD\textsubscript{d,v} and gEUD is expected without normalization. The clinicians’ experient intuition interferes with this increase of value. One easy way to solve this problem is to use a normalization factor similar to the one for the standard effective dose (SED).

\[ SED = \frac{nd(1 + \frac{d}{a/\beta})}{(1 + \frac{2}{a/\beta})} = \frac{BED}{(1 + \frac{2D_{EUD}}{a/\beta})} \quad (31) \]

The gEUD can be modified using the denominator of the standard effective dose (SED) as the normalization factor (65).
To incorporate different fractionation schemes the fraction size-specific \( EUD_{d,v} \) is given as

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

(32)

where

\[
C = 1 + \frac{d}{\alpha/\beta}
\]  

(33)

and \( d \) is the dose per fraction and for being able to compare different dose distributions based on a standard fractionation scheme the value of 2 Gy can be used.

One advantage of using the concept \( EUD_{d,v} \) is that 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 \( d=2 \text{ Gy} \), will yield the same clinical outcome as the inhomogeneous plan in question.

The \( EUD_{d,v} \), combining the gEUD with BED, preserves all advantages of the gEUD while reflecting the fractionation effects, as well as the linear and quadratic survival characteristics. It is important to mention that \( EUD_{d,v} \), is based on the power low volume effect as the gEUD does (Eq.26) (65).

2.4.2.3 gBED\(_s\) (generalized Biological Equivalent uniform Dose)

The BED formulae which were discussed in section 2.2.1 have assumed that the dose distribution is spatially uniform, which is not true in 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 tumor volume into small sub-volumes so that the dose rate distribution in each sub-volume can be considered as uniform (70).

The \( \text{BED}_i \) for a sub-volume \( i \) with initial dose rate of \( \dot{D}_i(0) \) can then be calculated using the equation (22). Mathematically the gBED\(_s\) for a clinical prostate implant can be calculated from the following procedure:

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.
The BED for the sub-volume $V_i$ is

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

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

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

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

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,

$$S = \frac{N_i}{\rho \cdot V} = \sum_{i=1}^{N} \frac{V_i}{V} \cdot e^{-\alpha \cdot BED_i} \Rightarrow$$

$$S = \sum_{i=1}^{N} V_i \cdot e^{-\alpha \cdot BED_i}$$

where $V_i$ is the fractional volume $V_i = \frac{V_i}{V} = \frac{V_i}{\sum_{i=1}^{N} V_i}$

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

$$gBED_s = -\frac{1}{\alpha} \ln (\sum v_i e^{-aBED_i}) \quad (34)$$
where $v_i$ is the fractional sub-volume receiving the dose rate $\tilde{D}_i(0)$ with $\sum v_i=1$ and N is the total number of bins in the differential DVH. The $\{v_i, \forall i\}$ is directly related to the differential dose (or initial dose rate) histogram of a permanent implant. The $g\text{BED}$ takes into account the spatial heterogeneity of dose rate distribution in prostate brachytherapy.

It is possible to calculate an equivalent uniform dose from Eq. (26) that corresponds to any desired dose delivery technique based on the total cell-kill.

The total $\text{BED}$ delivered to the prostate for combined modality treatments is the sum of the implant $\text{BED}$ and the $\text{BED}$ of the EBRT, which is given from the following equation

$$BED_{\text{EBRT}} = EUD_{d,s}(1 + \frac{\beta}{\alpha} d) \quad (35)$$

where $d$ is the daily fractionation dose so that over a total of $n$ fractions, the total dose is $D=nd$. The equivalent total uniform dose ($EUD_{d,s}$) of external beam radiation therapy delivered in $d$ Gy/fraction that would have the same radiobiological effect as that of the implant $\text{BED}$ may be found by equating the Eqs. (34) and (35) and solving for $EUD_{d,s}$ after setting the daily fractionation dose $d$ to a desired value, typically 1.8 or 2.0 Gy (in our case is $d=2$ Gy per fraction),

$$EUD_{d,s} = \frac{-\ln \left( \sum v_i e^{-g\text{BED}_i} \right)}{\alpha + \beta d} \quad (36)$$

$EUD_{d,s}$ is subscribed with $d$ because the calculated dose will depend on the daily fractionation dose chosen for comparison and with $s$ because it is based on the survival level considered.

In brachytherapy as in External Beam radiotherapy probabilistic models can be used as well (75)-(92).
2.5 Materials

Twelve clinical implants for HDR brachytherapy of prostate cancer, as monotherapy for low-risk cases have been selected out of the clinical routine in Strahlenklinik Offenbach. These twelve implants cover the whole range of prostate volumes with a full range of 26-101 cm³. The summary of characteristics of all twelve implants is listed in the Table 2.1 below.

<table>
<thead>
<tr>
<th>Case No</th>
<th>Prostate (PTV=CTV1) (cm³)</th>
<th>No Catheters</th>
<th>Catheter Type</th>
<th>Source Step (mm)</th>
<th>No ASDPs</th>
<th>ASDPs per cm³</th>
<th>MR values</th>
</tr>
</thead>
<tbody>
<tr>
<td># 1</td>
<td>26</td>
<td>16</td>
<td>metallic</td>
<td>2.5</td>
<td>217</td>
<td>8.3</td>
<td>0.15</td>
</tr>
<tr>
<td># 2</td>
<td>27</td>
<td>14</td>
<td>plastic</td>
<td>2.5</td>
<td>183</td>
<td>6.8</td>
<td>0.20</td>
</tr>
<tr>
<td># 3</td>
<td>36</td>
<td>14</td>
<td>metallic</td>
<td>2.5</td>
<td>197</td>
<td>5.5</td>
<td>0.10</td>
</tr>
<tr>
<td># 4</td>
<td>36</td>
<td>15</td>
<td>plastic</td>
<td>2.5</td>
<td>195</td>
<td>5.4</td>
<td>0.20</td>
</tr>
<tr>
<td># 5</td>
<td>38</td>
<td>14</td>
<td>plastic</td>
<td>2.5</td>
<td>188</td>
<td>4.9</td>
<td>0.10</td>
</tr>
<tr>
<td># 6</td>
<td>42</td>
<td>15</td>
<td>metallic</td>
<td>2.5</td>
<td>209</td>
<td>5.0</td>
<td>0.15</td>
</tr>
<tr>
<td># 7</td>
<td>48</td>
<td>14</td>
<td>plastic</td>
<td>2.5</td>
<td>239</td>
<td>5.0</td>
<td>0.12</td>
</tr>
<tr>
<td># 8</td>
<td>63</td>
<td>16</td>
<td>metallic</td>
<td>2.5</td>
<td>259</td>
<td>4.1</td>
<td>0.15</td>
</tr>
<tr>
<td># 9</td>
<td>64</td>
<td>18</td>
<td>plastic</td>
<td>2.5</td>
<td>309</td>
<td>4.8</td>
<td>0.12</td>
</tr>
<tr>
<td># 10</td>
<td>76</td>
<td>15</td>
<td>plastic</td>
<td>2.5</td>
<td>283</td>
<td>3.7</td>
<td>0.10</td>
</tr>
<tr>
<td># 11</td>
<td>80</td>
<td>18</td>
<td>metallic</td>
<td>2.5</td>
<td>313</td>
<td>3.9</td>
<td>0.10</td>
</tr>
<tr>
<td># 12</td>
<td>101</td>
<td>18</td>
<td>plastic</td>
<td>2.5</td>
<td>352</td>
<td>3.5</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Table 2.1 Summary of the characteristics of the 12 clinical implants of HDR brachytherapy of prostate. ASDP: Active Source Dwell Position. MR: Modulation Restriction

The clinical procedure is totally 3D ultrasound based using the real time intraoperative planning system Oncentra Prostate (OcP, Fa.Nucletron B.V., The Netherlands). The MicroSelectron HDR Vs 3 Genius is used (see section 1.4) and the HIPO inverse planning and optimization algorithm is implemented in OcP Vs 3. In Strahlenklinik Offenbach the prostate gland is considered to be the PTV (CTV1) and urethra, rectum and bladder are included as OARs. The dosimetric protocol can be seen in section 1.7.3 (Table 1.1)

For each of these twelve implants the clinically used implant was defined as the reference plan. All clinical implants have been inversely planned using HIPO with modulation restriction parameter (MR) parameter values as listed in Table 2.1. During the clinical procedure, the selections for the MR values were the maximum values resulting in plans that completely fulfill the dosimetric protocol. For each of these
twelve implants an additional plan without modulation restriction (MR=0) was produced for the purpose of this project.

In this study there is an investigation and analysis for the influence of possible errors that could eventually occur in HDR brachytherapy of prostate cancer. Because of an involuntary movement of the patient, errors can occur during treatment. Possible movements will result in displacement of the template relative to perineum and thus to systematic longitudinal displacement of all needles in relation to the prostate in cranio-caudal direction. The individual needles are fixed on the template as described in section 1.7.1

To investigate the influence of such systematic errors on the quality of treatment delivery an error simulation study was realized. For each reference plan (clinical with MR>0 and with MR=0) a total of 10 systematic shifts of all catheters has been simulated, ±1, ±2, ±3, ±4, ±5 mm, “+” indicates a shift in cranial direction and “−” indicates a shift in the opposite direction (caudal, see Fig.2.7-2.8). Thus a total of 11 plans using modulation restriction (MR>0) and a total of 11 plans with MR=0 for each one of the twelve cases in Table 2.1 have been analyzed. The total number for all 12 clinical implants considered in this study is 264.

![Figure 2.7 Catheters (yellow lines)-dwell position of the sources (the red balls) without shift of the twelve clinical implants](image)

Figure 2.7 Catheters (yellow lines)-dwell position of the sources (the red balls) without shift of the twelve clinical implants
For the treatment plan evaluation, DVHs for both plans, with (clinical) and without (MR=0, theoretical) modulation restriction were calculated. All the relevant dose-volume parameters, for the prostate and OARs (rectum, urethra and bladder) have been considered as dosimetric indices where all internationally recommended values are included (see Section 1.6.3). A summary of all dose volumes parameters is given in Table 2.2.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>$D_{90}$</td>
</tr>
<tr>
<td>Urethra</td>
<td>$D_{1}$</td>
</tr>
<tr>
<td>Rectum</td>
<td>$D_{10}$</td>
</tr>
<tr>
<td>Bladder</td>
<td>$D_{10}$</td>
</tr>
</tbody>
</table>

Table 2.2 Dose-volume parameters for prostate and OARs

In addition to these the conformal index (COIN) and the external volume index (EI) have been included in the comparison of different plans. Both of them are reported in detail in sections 2.3.1 and 2.3.2 respectively.

Radiobiological parameters were also considered in the evaluation of the plans for comparing the very inhomogeneous dose distributions of the HDR brachytherapy implants. These radiobiological indices are the gEUD, $EUD_{2,v}$ and $EUD_{2,s}$ as
described by the Eq. (26), (30) and (36) respectively. For the prostate cancer the value “a”=-10 (66; 71) has been used while for the rectum and bladder the value is the same “a”=6 (66). The most appropriate value for urethra seems to be “a”=4.

The LQ model parameters for prostate, which were used in this project, are shown in the Table 2.3 as recommended by AAPM\textsuperscript{5} and Wang et al (54). For the OARs a value of $\alpha/\beta$ is 3 Gy has been used (54; 72).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimated values</th>
<th>Standard Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$ (Gy\textsuperscript{-1})</td>
<td>0.15</td>
<td>± 0.04</td>
</tr>
<tr>
<td>$\alpha/\beta$ (Gy)</td>
<td>3.1</td>
<td>± 0.5</td>
</tr>
<tr>
<td>$T_r$ (minute)</td>
<td>16</td>
<td>[0, 90]</td>
</tr>
<tr>
<td>$K_1$ (clonogenic number)</td>
<td>$1.6 \times 10^6$</td>
<td>$[5.6 \times 10^4, 8.8 \times 10^7]$</td>
</tr>
<tr>
<td>$K_2$ (clonogenic number)</td>
<td>$3.0 \times 10^6$</td>
<td>$[1.0 \times 10^5, 2.1 \times 10^4]$</td>
</tr>
<tr>
<td>$K_3$ (clonogenic number)</td>
<td>$1.1 \times 10^7$</td>
<td>$[3.2 \times 10^5, 1.3 \times 10^9]$</td>
</tr>
<tr>
<td>$K$ (Gy/day)</td>
<td>0.11</td>
<td></td>
</tr>
</tbody>
</table>

Table 2.3 Estimated parameters for prostate cancer

In addition the reference plans (clinical MR>0 and theoretical MR=0) for all 12 cases have been compared utilizing the dosimetric indices in Table 2.2, COIN, EI, gEUD, EUD\textsubscript{2,v} and EUD\textsubscript{2,s}. Here the influence of the modulation restriction on plan quality was investigated. All comparisons have been based on the student two-sided t-test statistical method at the significance level of 0.05 (73).

3. Results and discussion

The analysis of our results is subdivided into three categories.

First the reference plans where no catheter shift has been simulated, the clinical with MR >0 and the theoretical with MR=0, for all 12 implants have been compared based on the DVHs and all the dose-volume, conformity indices and radiobiological parameters. This should illuminate the effect of the modulation restriction on the dose distribution and plan parameters such as dwell times of the source.

\textsuperscript{5} American Association of Physicists in Medicine (AAPM)
Secondly the shift simulation data, a total of 264 plans and 1056 DVH curves, have been analyzed considering similarly to above all the dosimetric, conformity and radiobiological indices and parameters.

Currently there are no data existing supporting the request for a specific level of stability of the dosimetry for the HDR prostate brachytherapy. This fact leads us to the following strategy. All simulation results have been analyzed based on two different criteria categories. In the first category it was examined if the plans still fulfill the clinical dosimetric protocol as listed in Table 1.1. This part of the shift simulation analysis is called *quality analysis*. In the second category it was examined if the dosimetric, conformity and radiobiological indices of the plans remain within ±5% and ±10% of the values of the corresponding reference plan (clinical or theoretical without any catheter shift simulated). This is called *stability analysis*.

For each of the included indices and parameters a statistical analysis of the results of the simulated plans for all 12 clinical implants is performed. With the help of Origin software\(^6\) these statistical results are demonstrated graphically, with a box-chart. With this visualization method all the important statistical parameters are presented: the smallest and the largest value, the average, the median, the low (25%) and the higher (75%) quartile (see Figure 3.1).

\[\text{Figure 3.1 Values represented in a box plot}\]

\(^6\) MicrocalSoftware, Inc., Microcal™, OriginVs.6.0
3.1 Influence of Modulation Restriction

3.1.1 Dosimetric Analysis

Figure 3.2 demonstrates the results for the dose volume indices for the prostate (PTV). Figures 3.3 to 3.5 show the results for the OARs, bladder rectum and urethra.

Figure 3.2 Dose-volume indices for prostate for the reference plans with (MR>0, clinical) and without (MR=0, theoretical) modulation restriction (a) for D$_{90}$ (b) for V$_{100}$ (c) V$_{150}$ and (d) V$_{200}$. Horizontal lines represent the corresponding values according to the clinical protocol (Table 1.1)
Figure 3.3 Dose-volume indices for bladder for the reference plans with (MR>0, clinical) and without (MR=0, theoretical) modulation restriction (a) for D_{10} (b) for D_{0.1cc} and (c)D_{2cc}. Horizontal lines represent the corresponding values according to the clinical protocol (Table 1.1)
Figure 3.4 Reference Dose-volume indices for rectum for the reference plans with (MR>0, clinical) and without (MR=0, theoretical) modulation restriction (a) for $D_{10}$ (b) for $D_{0.1cc}$ and (c)$D_{2cc}$. Horizontal lines represent the corresponding values according to the clinical protocol (Table 1.1).
The results of the statistical test of the observed differences for the different dosimetric indices for the prostate and OARs are listed in Table 3.1 to Table 3.2 respectively.

We observe that for the parameter $D_{90}$ of prostate the values are significantly lower (p<0.05) when the MR factor is used than without using the MR. The same behavior applies for the $V_{100}$ of prostate although the absolute difference of those values and for both $D_{90}$ and $V_{100}$ are always less than 1%. The opposite happens for the $V_{150}$ and the $V_{200}$ parameter of prostate where the values are greater when the MR is used (p=0.005 and p=0.409 respectively).

For urethra the parameters $D_{1}$, $D_{10}$ and $D_{0.1cc}$ are reduced when using MR and their difference is not significant. For bladder and rectum modulation restriction results to significant reduction of the $D_{10}$ parameter values with p=0.007 and p=0.0037 respectively. The observed differences in $D_{0.1cc}$ values are for both OARs not significant. The $D_{2cc}$ parameter value, for both rectum and bladder, results in significantly lower values when using the restriction option (p=0.039 and 0.009 respectively).
### Prostate(PTV)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIPO</th>
<th>Mean value (%)</th>
<th>Variance (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{90}$</td>
<td>w MR</td>
<td>102.48</td>
<td>2.25</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>103.05</td>
<td>3.18</td>
<td></td>
</tr>
<tr>
<td>$V_{100}$</td>
<td>w MR</td>
<td>92.17</td>
<td>1.54</td>
<td>0.010</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>92.70</td>
<td>2.11</td>
<td></td>
</tr>
<tr>
<td>$V_{150}$</td>
<td>w MR</td>
<td>30.43</td>
<td>4.32</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>29.20</td>
<td>5.39</td>
<td></td>
</tr>
<tr>
<td>$V_{200}$</td>
<td>w MR</td>
<td>8.70</td>
<td>1.3</td>
<td>0.409</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>8.60</td>
<td>1.4</td>
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</tbody>
</table>

Table 3.1 Mean values and variance of the different dose-volume parameters for the prostate (PTV) using HIPO with and w/o modulation restriction

### OARs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIPO</th>
<th>Mean value (%)</th>
<th>Variance (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethra</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_{1}$</td>
<td>w MR</td>
<td>117.35</td>
<td>3.21</td>
<td>0.074</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>118.13</td>
<td>2.33</td>
<td></td>
</tr>
<tr>
<td>$D_{10}$</td>
<td>w MR</td>
<td>112.31</td>
<td>2.91</td>
<td>0.226</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>112.53</td>
<td>3.58</td>
<td></td>
</tr>
<tr>
<td>$D_{0.1cc}$</td>
<td>w MR</td>
<td>114.30</td>
<td>2.79</td>
<td>0.079</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>114.64</td>
<td>3.13</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_{10}$</td>
<td>w MR</td>
<td>45.41</td>
<td>15.77</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>45.90</td>
<td>17.23</td>
<td></td>
</tr>
<tr>
<td>$D_{0.1cc}$</td>
<td>w MR</td>
<td>73.06</td>
<td>7.34</td>
<td>0.248</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>73.38</td>
<td>3.86</td>
<td></td>
</tr>
<tr>
<td>$D_{2cc}$</td>
<td>w MR</td>
<td>55.59</td>
<td>22.54</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>56.15</td>
<td>22.90</td>
<td></td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D_{10}$</td>
<td>w MR</td>
<td>62.59</td>
<td>26.62</td>
<td>0.037</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>62.76</td>
<td>25.60</td>
<td></td>
</tr>
<tr>
<td>$D_{0.1cc}$</td>
<td>w MR</td>
<td>76.62</td>
<td>2.05</td>
<td>0.072</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>76.40</td>
<td>1.62</td>
<td></td>
</tr>
<tr>
<td>$D_{2cc}$</td>
<td>w MR</td>
<td>62.70</td>
<td>18.27</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>62.89</td>
<td>17.25</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.2 Mean values and variance of the different dose-volume parameters for the OARs using HIPO with and w/o modulation restriction
3.1.2 Conformity Analysis

Figure 3.6 demonstrates the comparison of the results of COIN for the two different plan categories. In case of COIN, considering only the prostate (see also Eq.12), higher COIN values are observed when the modulation restriction is used and these differences are significant (p=0.003). This is also the case when OARs are considered in the calculation of COIN (see also Eq.15) with the plans using the modulation restriction resulting in higher COIN values. Figure 3.7 demonstrates the comparison of the results of C₁, C₂ and C₃ for the two different plan categories. In case of C₁ (see Eq.13) slightly higher C₁ values are observed when the modulation restriction is not used and these differences are significant (p=0.008). For C₂ higher values are observed when the modulation restriction is used and these differences are significant (p=0.0001). In case of C₃ slightly greater values are observed when the modulation restriction is used and these differences are not significant (p=0.182).

The results for External Index (EI) (see Figure 3.8) demonstrate that the plans using modulation restriction result in significant lower values. This means that the use of restriction leads to dose distributions with less extension of the reference isodose outside the target volume. This explains also the higher values for COIN for the reference plan using modulation restriction (clinical plans).
Figure 3.7 Comparison of the (a) $C_1$, (b) $C_2$ and (c) $C_3$ values for the clinical (MR>0) and the hypothetical (MR=0) reference plans for the 12 implants.

Figure 3.8 Comparison for the EI values for the reference plans with and without modulation restriction.
3.1.3 Radiobiological Parameter Analysis

Following is represented the analysis regarded to the influence of the systematic catheters displacement on the radiobiological parameters gEUD, EUD$^{2,v}$ for the prostate and OARs and EUD$^{2,s}$ only for the prostate (PTV).

Prostate (PTV)

The results for the gEUD, EUD$^{2,v}$ and EUD$^{2,s}$ parameter values are represented in Figure 3.9 where the statistical test results are listed in Table 3.3. As it can be seen from the graphs for all three cases the values when using the restriction option are lower than without using this option. Furthermore, these differences are significant with $p = 0.008$ for gEUD, $p = 0.001$ for EUD$^{2,v}$ and $p = 0.004$ for EUD$^{2,s}$ (Table 3.3). This is in agreement with the results presented for the dosimetric indices (Figure 3.2 and Table 3.1).
Figure 3.9 Comparison of the (a) gEUD, (b) EUD$_{2,v}$ and (c) EUD$_{2,s}$ parameters values for the prostate for the reference plans with and without modulation restriction

<table>
<thead>
<tr>
<th>Prostate (PTV)</th>
<th>Parameter</th>
<th>HIPO</th>
<th>Mean value (Gy)</th>
<th>Variance (Gy)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>gEUD</td>
<td>w MR</td>
<td>12.51</td>
<td>0.03</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>12.61</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EUD$_{2,v}$</td>
<td>w MR</td>
<td>32.17</td>
<td>1.33</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>33.11</td>
<td>1.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EUD$_{2,s}$</td>
<td>w MR</td>
<td>35.88</td>
<td>0.52</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>36.37</td>
<td>0.82</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.3 Mean values and variances of the different radiobiological parameters for the prostate (PTV)

OARs

Figures 3.10-3.12 demonstrate the results for the OARs where the Table 3.4 summarizes the significant tests for the radiobiological parameters.

For the urethra, gEUD when modulation restriction is used, has lower values than without using this restriction and their observed difference is significant (p=0.047). For EUD$_{2,v}$ the same behavior is observed although the observed differences are not significant (p =0.171). Exceptions are only cases 4 and 11 where the parameter values when the modulation restriction is used are slightly higher.
For rectum the values for gEUD using modulation restriction are significant lower than those without using modulation restriction ($p=0.017$). For EUD$_{2,v}$ the observed differences (lower values for modulation restriction) are not significant ($p=0.562$).

For bladder all parameters values are reduced when using modulation restriction is used. The observed differences are for both gEUD and EUD$_{2,v}$ significant, $p=0.004$ and $p=0.017$ respectively. These results are in agreement with the findings for the dose-volume parameters (Figure 3.3).

Figure 3.10 Comparison of the a) gEUD and b) EUD$_{2,v}$ parameters of the urethra for the reference plans with and without modulation restriction

Figure 3.11 Comparison of the (a) gEUD and (b) EUD$_{2,v}$ parameters of the rectum for the reference plans with and without modulation restriction
### OARs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HIPO</th>
<th>Mean value (Gy)</th>
<th>Variance (Gy)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urethra</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gEUD</td>
<td>w MR</td>
<td>11.42</td>
<td>0.11</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>11.49</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>EUD(_{2,v})</td>
<td>w MR</td>
<td>34.36</td>
<td>2.22</td>
<td>0.171</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>34.59</td>
<td>2.39</td>
<td></td>
</tr>
<tr>
<td><strong>Rectum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gEUD</td>
<td>w MR</td>
<td>5.82</td>
<td>0.20</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>5.84</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>EUD(_{2,v})</td>
<td>w MR</td>
<td>12.07</td>
<td>1.17</td>
<td>0.562</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>12.08</td>
<td>1.11</td>
<td></td>
</tr>
<tr>
<td><strong>Bladder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gEUD</td>
<td>w MR</td>
<td>4.54</td>
<td>0.05</td>
<td>0.004</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>4.58</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>EUD(_{2,v})</td>
<td>w MR</td>
<td>9.03</td>
<td>0.24</td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td>w/o MR</td>
<td>9.15</td>
<td>0.22</td>
<td></td>
</tr>
</tbody>
</table>

Table 3.4 Mean values and variances of the different radiobiological parameters for the OARs with and without modulation restriction

#### 3.1.4 Dwell time analysis

The effect of the modulation restriction is already mentioned in section 2.2.

The following Figure 3.13 shows a comparison of dwell time profiles of the two plan categories for all 12 implants listed in Table 2.1. It is clearly demonstrated that when the modulation restriction is used then a more smooth distribution of dwell time over dwell positions in the catheters is achieved. These results demonstrate that there is a total dwell time reduction of 1.4 % when the modulation restriction is used (see Table 3.5 & Figure 3.14). This is statistically significant (p=0.002). The mean dwell time for each implant is significantly lower for the plans with MR>0(p<0.001).
This also the case for the variance of dwell times in each plan (p<0.001) (see Table 3.6).
Figure 3.13 Comparison of dwell time profiles for the reference plans (clinical plans) using modulation restriction and without modulation restriction for the 12 implants of Table 2.1. The value of the modulation restriction parameter MR is given in each figure.
Table 3.5 Total dwell times for the 12 clinical cases and for the reference plans using and without considering modulation restriction (MR=0)

<table>
<thead>
<tr>
<th>Case No</th>
<th>MR value</th>
<th>Total dwell time (s) w MR</th>
<th>Total dwell time (s) w/o MR</th>
<th>Diff (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td># 1</td>
<td>0.15</td>
<td>248.22</td>
<td>249.86</td>
<td>0.66</td>
</tr>
<tr>
<td># 2</td>
<td>0.20</td>
<td>246.54</td>
<td>250.56</td>
<td>1.60</td>
</tr>
<tr>
<td># 3</td>
<td>0.10</td>
<td>303.24</td>
<td>307.43</td>
<td>1.36</td>
</tr>
<tr>
<td># 4</td>
<td>0.20</td>
<td>302.48</td>
<td>306.17</td>
<td>1.21</td>
</tr>
<tr>
<td># 5</td>
<td>0.10</td>
<td>316.54</td>
<td>323.51</td>
<td>1.23</td>
</tr>
<tr>
<td># 6</td>
<td>0.15</td>
<td>337.92</td>
<td>337.67</td>
<td>-0.07</td>
</tr>
<tr>
<td># 7</td>
<td>0.12</td>
<td>372.19</td>
<td>379.09</td>
<td>1.82</td>
</tr>
<tr>
<td># 8</td>
<td>0.15</td>
<td>430.99</td>
<td>439.49</td>
<td>1.93</td>
</tr>
<tr>
<td># 9</td>
<td>0.12</td>
<td>446.11</td>
<td>446.80</td>
<td>0.15</td>
</tr>
<tr>
<td># 10</td>
<td>0.10</td>
<td>482.55</td>
<td>499.76</td>
<td>3.44</td>
</tr>
<tr>
<td># 11</td>
<td>0.10</td>
<td>496.85</td>
<td>505.42</td>
<td>1.70</td>
</tr>
<tr>
<td># 12</td>
<td>0.20</td>
<td>601.73</td>
<td>607.53</td>
<td>0.95</td>
</tr>
<tr>
<td>Mean value</td>
<td>0.14</td>
<td></td>
<td></td>
<td>1.43</td>
</tr>
</tbody>
</table>

Figure 3.14 Total dwell time for each one of the 12 clinical cases for the reference plans using and w/o using modulation restriction
<table>
<thead>
<tr>
<th>Case</th>
<th>Mean value (s)</th>
<th>Variance (s)</th>
<th>S.D. (s)</th>
<th>S.D.(%)</th>
<th>Mean value (s)</th>
<th>Variance (s)</th>
<th>S.D. (s)</th>
<th>S.D.(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td># 1</td>
<td>1.14</td>
<td>0.71</td>
<td>0.84</td>
<td>73.57</td>
<td>1.15</td>
<td>2.78</td>
<td>1.67</td>
<td>144.85</td>
</tr>
<tr>
<td># 2</td>
<td>1.35</td>
<td>0.78</td>
<td>0.89</td>
<td>65.44</td>
<td>1.37</td>
<td>5.01</td>
<td>2.24</td>
<td>163.57</td>
</tr>
<tr>
<td># 3</td>
<td>1.54</td>
<td>1.26</td>
<td>1.12</td>
<td>73.04</td>
<td>1.56</td>
<td>7.39</td>
<td>2.72</td>
<td>174.28</td>
</tr>
<tr>
<td># 4</td>
<td>1.55</td>
<td>1.04</td>
<td>1.02</td>
<td>65.82</td>
<td>1.57</td>
<td>5.10</td>
<td>2.26</td>
<td>143.88</td>
</tr>
<tr>
<td># 5</td>
<td>1.70</td>
<td>1.83</td>
<td>1.35</td>
<td>79.68</td>
<td>1.72</td>
<td>6.30</td>
<td>2.51</td>
<td>145.91</td>
</tr>
<tr>
<td># 6</td>
<td>1.62</td>
<td>1.10</td>
<td>1.05</td>
<td>64.97</td>
<td>1.62</td>
<td>4.61</td>
<td>2.15</td>
<td>132.84</td>
</tr>
<tr>
<td># 7</td>
<td>1.56</td>
<td>1.39</td>
<td>1.18</td>
<td>75.84</td>
<td>1.59</td>
<td>8.15</td>
<td>2.85</td>
<td>179.97</td>
</tr>
<tr>
<td># 8</td>
<td>1.66</td>
<td>1.65</td>
<td>1.29</td>
<td>77.23</td>
<td>1.70</td>
<td>7.92</td>
<td>2.82</td>
<td>165.90</td>
</tr>
<tr>
<td># 9</td>
<td>1.42</td>
<td>1.68</td>
<td>1.29</td>
<td>91.18</td>
<td>1.44</td>
<td>9.37</td>
<td>3.06</td>
<td>213.18</td>
</tr>
<tr>
<td># 10</td>
<td>1.71</td>
<td>1.35</td>
<td>1.16</td>
<td>68.24</td>
<td>1.77</td>
<td>10.91</td>
<td>3.30</td>
<td>187.10</td>
</tr>
<tr>
<td># 11</td>
<td>1.59</td>
<td>1.67</td>
<td>1.29</td>
<td>81.43</td>
<td>1.62</td>
<td>8.68</td>
<td>2.95</td>
<td>182.51</td>
</tr>
<tr>
<td># 12</td>
<td>1.71</td>
<td>1.79</td>
<td>1.34</td>
<td>78.43</td>
<td>1.72</td>
<td>13.13</td>
<td>3.62</td>
<td>210.56</td>
</tr>
</tbody>
</table>

Table 3.6 Mean dwell times for the 12 clinical cases and for the reference plans using and without considering modulation restriction (MR=0)

### 3.2 Shift analysis

#### 3.2.1 Dosimetric analysis

**Quality analysis**

**Prostate (PTV)**

Figure 3.15 summarizes the results of the prostate (PTV). For the parameter $D_{90}$ without using the restriction option, a maximum systematic catheter shift of $\pm1$ mm is allowed in order to keep fulfill the clinical protocol ($D_{90} \geq 100\%$). When the MR is used this interval is $[-1.0, +0.5]$ mm. For the parameter $V_{100}$ the protocol requires a minimum value of 90% and this is still satisfied for a systematic shift in the interval $[-1.5, +1.0]$ mm without using the MR while for using the MR option this is $[-1.5, +0.5]$ mm. Figure 3.15(c) shows that the parameter $V_{150}$ is insensitive to systematic shift of the catheter for with and without using the modulation restriction. The protocol ($V_{150} \leq 35\%$) is fulfilled in systematic shifts up to $\pm5$ mm. This is expected since the maximum dose in the volume depends on the relative position of the catheter. The values of the parameter $V_{150}$ are reduced and this reduction is symmetric in both directions because of the parallel arrangement of the catheters with the main axis of the prostate (base, apex). The fall of the value of $V_{150}$ is expected because for a
systematic catheter shift larger than 1mm, parts of high dose will remain outside the prostate.

Figure 3.15 Simulated plans with and without modulation restriction for the dosimetric indices (a) \(D_{90}\) (b) \(V_{100}\) and (c) \(V_{150}\) for prostate (PTV). Horizontal lines represent the corresponding values of the clinical protocol (Table 1.1)

**OARs**

Figures 3.16, 3.17 and 3.19 summarize the results of the quality analysis for the OARs.

For the **urethra** (Figure 3.16), the \(D_{10}\) parameter without using the MR and for a systematic shift more than ±1.0 mm will no longer satisfy the limits of the protocol (\(D_{10} \leq 115%\)). When using the MR the interval in order to not exceed the limits of the protocol is \([-2.5, +2.0]\) mm. Contrary the parameter \(D_{0.1cc}\) is insensitive to systematic shifts in both situations (with and without MR). For all simulations of ±5 mm of all 12 clinical implants, the limits of the protocol are completely fulfilled.
However, an increase in the dispersion of individual values while increasing the value of the systematic shift, above the value of +2.0 mm, can be observed for both methods.

![Graph](image)

**Figure 3.16** The simulated plans with an without modulation restriction for the dosimetric indices (a) $D_{10}$ and (b) $D_{0.1cc}$ for urethra. Horizontal lines represent the corresponding values of the clinical protocol (Table 1.1)

For **rectum** and for the $D_{10}$ parameter values with and without using the modulation restriction are shown in Figure 3.17. It can be seen that the values of $D_{10}$ parameter for the whole simulation area ($\pm 5.0$ mm) stay below the required maximum value of 75% for both situations. This may be due to the parallel arrangement of the catheters with respect to the anterior rectum wall except from the direction of the apex where the volume of the prostate reduces while the volume of the rectum increases (see Figure 3.18). An important observation is that the dispersion of individual values increases with the increase of the catheter shift. In contrast, for the $D_{0.1cc}$ parameter shifting values greater than 2.00 mm in the caudal direction in case of without using the MR and greater than 1.00 mm in case of using the MR are not consistent with the requirements of the protocol ($D_{0.1cc}\leq80\%$). According to figure 3.17 (b), when the MR is not used, a threshold of -1.5 mm may be considered. For catheter shift in cranial direction the $D_{0.1cc}$ seems to be insensitive for both situations (with MR and without MR) and remains below the threshold of 80% ($D_{0.1cc}\leq80\%$). This may be because of the parallel arrangement of the catheters with the anterior rectum wall as already mentioned (see Figure 3.18). It is generally found only for the situation of using the MR, that while the catheter shift increases (caudal (-) to cranial (+) direction), the $D_{0.1cc}$ decreases and the dispersion of individual values increases.
Figure 3.17 The simulated plans with an without modulation restriction for the dosimetric indices (a) $D_{10}$ and (b) $D_{0.1cc}$ for rectum. Horizontal lines represent the corresponding values of the clinical protocol (Table 1.1).

Figure 3.18 Presentation of prostate and OARs in sagittal view. Base and apex are defined. An implanted catheter and source dwell positions are also displayed.

Exactly the opposite is observed, as expected, for the bladder (see Figure 3.19). The values of the parameter $D_{10}$ are on the rise with the increase of the systematic catheter shift up to +5.0 mm in order to remain below the protocol limit of 75%. For the $D_{0.1cc}$ parameter a similar behavior is noticed. The dispersion increases
steadily with increasing the catheter shift. When using the modulation restriction the range of the systematic shift in order to retain the limits of the protocol ($D_{0.1cc} \leq 80\%$) is 0.5 mm in cranial direction and this applies also for the case of not using the modulation restriction. This behavior may be explained by the position of the bladder and of the catheters. During the insertion of the catheters there is a displacement of the prostate which is adjacent to the bladder. In order to have an adequate coverage of the basic region of the prostate the $D_{90}$ should be more than 100% but the bladder should receive no more than 80% in order that the protocol be fulfilled.

Thus it is expected that a small cranial displacement of the catheter may cause an increase in the dose that the bladder will receive.

Table 3.7 summarizes all the above discussed results.

![Graphs of Bladder D10 and D0.1cc](image)

**Figure 3.19** The simulated plans with an without modulation restriction for the dosimetric indices (a) $D_{10}$ and (b) $D_{0.1cc}$ for bladder. Horizontal lines represent the corresponding values of the clinical protocol (Table 1.1)

<table>
<thead>
<tr>
<th>VOI</th>
<th>$D_{90}$</th>
<th>$V_{100}$</th>
<th>$V_{150}$</th>
<th>$D_{10}$</th>
<th>$D_{0.1cc}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>-1.0/+1.0</td>
<td>-1.5/+1.0</td>
<td>-5.0/+5.0</td>
<td>-1.0/0.5</td>
<td>-5.0/+5.0</td>
</tr>
<tr>
<td>Urethra</td>
<td>-1.0/+0.5</td>
<td>-1.0/+0.5</td>
<td>-5.0/+5.0</td>
<td>-2.5/+2.0</td>
<td>-5.0/+5.0</td>
</tr>
<tr>
<td>Rectum</td>
<td>-5.0/+5.0</td>
<td>-1.0/+5.0</td>
<td>-5.0/+5.0</td>
<td>-5.0/+5.0</td>
<td>-5.0/+5.0</td>
</tr>
<tr>
<td>Bladder</td>
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<td>-5.0/+5.0</td>
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</tr>
</tbody>
</table>

Table 3.7 Summary of the limits in mm for the systematic catheter shift so that the clinical protocol is kept fulfilled (w/o MR, w MR)
**Stability analysis**

Following is represented the statistical analysis regarded to the influence of the systematic catheters displacement on the dosimetric indices. The results of these evaluations are presented in the following Figures 3.20-3.23. All DVH based parameters of the simulated plans of an implant are normalized to the corresponding value of the reference plan for this implant. The limits for the acceptance or rejection of a plan are ±5% or ±10%.

**Prostate analysis**

D₉₀ parameter for prostate (PTV) shows a remarkable sensitivity to systematic catheter shift for both cases of with and without using the restriction option (see Figure 3.20). Also, a relatively symmetric behaviour for shifting in cranial (+) and in caudal (-) direction is observed. For the D₉₀ the maximum systematic shift for the preservation of the limits within ±5% seems to be ±2.5 mm for both categories of plans, the MR and without the MR option. This becomes -2.0/+3.5 mm for ±10% criterion when the MR is used and -3.5/+4.0 when the MR is not used. Furthermore, an increase in the dispersion of individual values while increasing catheter shift is observed regardless of the direction. The values of the V₁₀₀, V₁₅₀ and V₂₀₀ parameters are reduced as the shift increases in cranial or caudal direction for both situations (with and without MR). The explanation for the decrease is that the isodoses follow the catheters. As far as these move outside the target the isodoses follow this and V₁₀₀ and V₁₅₀ are reduced. Additionally, when the modulation restriction is not used shifts in the interval [-2.5, +2.5] mm keep the parameter values within the ±5% of the corresponding reference plan. For plans using MR this interval is [-3.0, +2.5] mm and [-2.5, +2.5] mm for V₁₀₀ and V₁₅₀ respectively. For V₂₀₀ when the MR is used this interval is -1.5/+2.5 mm and -2.5/+2.0 when the MR is not used. This becomes ±4.0 mm for ±10% criterion for the V₁₀₀ parameter and for both plan categories. For V₁₅₀ this interval is -4.0/+3.5 when the restriction option is not used and -4.5/+3.5 when the MR is used. For V₂₀₀ the ±10% criterion is -2.5/+2.0 without the MR factor and -1.5/+2.5 when the modulation restriction is used.
Figure 3.20 Results of the catheter shift simulation study with and without using the modulation restriction for (a) $D_{90}$, (b) $V_{100}$, (c) $V_{150}$ and (d) $V_{200}$.

**OARs analysis**

For the OARs the results are demonstrated in Figures 3.21-3.23. Figure 3.21 shows the results for the urethra. All values of $D_1$, $D_{10}$ and $D_{0.1cc}$ parameters, for the entire range of shift ($\pm 5.0$ mm), remain within the limits of $\pm 5\%$ showing to be unchangeable to shifts. This becomes $\pm 5.0$ mm for $\pm 10\%$ criterion also.
Figure 3.21 Results of the catheter shift simulation study with and without using the modulation restriction for (a) D_{10}, (b) D_1 and (c) D_{0.1cc} for the urethra

For the rectum (see Figure 3.22) and for the D_{10}, D_{2cc} parameter for both situations the shift interval that fulfils the stability criterion of ±5% is [-2.5, +3.0] mm while for the D_{0.1cc} the interval is [-2.0, +3.0] mm. For all parameters appears a dispersion of individual values for the 12 implants as the shifting increases in both directions. For ±10% criterion this becomes ± 5.0 mm for D_{10} and D_{2cc} when the modulation restriction is not used and -4.5/+5.0 mm, -4.0/+5.0 respectively when the MR is not used. For D_{0.1cc} the interval for ±10% criterion is -3.5/+5.0 when the restriction option is used and -4.0/+5.0 when the MR is not used.
Figure 3.22 Results of the catheter shift simulation study with and without using the modulation restriction for (a) D$_{10}$, (b) D$_{0.1cc}$ and (c) D$_{2cc}$ for the rectum.

On the other hand, bladder (Figure 3.23) shows a significant greater sensitivity to systematic catheter shift. For D$_{10}$, D$_{2cc}$ and D$_{0.1cc}$ the interval in which the values of all 12 implants will remain within ±5% of the reference plan is 0.5 mm. This becomes ±1.0 mm for ±10% criterion for the D$_{10}$ and D$_{2cc}$ and for D$_{0.1cc}$ this interval is -1.0/+0.5 mm for both plan categories. The following tables Table 3.8 and 3.9 summarize the implant stability expressed as cranio-caudal systematic catheter shift, required for keeping the resulted 3D dose distribution within ±5% and ±10% of the reference one (w/o MR, w MR).
Figure 3.23 Results of the catheter shift simulation study with and without using the modulation restriction for (a) $D_{10}$, (b) $D_{0.1cc}$, and (c) $D_{2cc}$ for the bladder.

<table>
<thead>
<tr>
<th>VOI</th>
<th>Parameter</th>
<th>$D_{0}$</th>
<th>$V_{100}$</th>
<th>$V_{150}$</th>
<th>$V_{200}$</th>
<th>$D_1$</th>
<th>$D_{10}$</th>
<th>$D_{0.1cc}$</th>
<th>$D_{2cc}$</th>
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<td>Prostate</td>
<td></td>
<td>-2.5/+2.5</td>
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<td>-2.5/+2.5</td>
<td>-2.5/+2.5</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>-2.5/+2.5</td>
<td>-3.0/+2.5</td>
<td>-2.5/+2.5</td>
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<td></td>
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<tr>
<td>Urethra</td>
<td></td>
<td>±5.0</td>
<td>-5.0/+5.0</td>
<td>-5.0/+5.0</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>±5.0</td>
<td>-5.0/+5.0</td>
<td>-5.0/+5.0</td>
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</tr>
<tr>
<td>Rectum</td>
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<td>-2.5/+3.0</td>
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<td>-2.5/+3.0</td>
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<tr>
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<td>-2.5/+3.0</td>
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<tr>
<td>Bladder</td>
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<td>±0.5</td>
<td>±0.5</td>
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<td>±0.5</td>
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</table>

Table 3.8 Summary of the limits in mm for the systematic catheter shift so that values will remain within ±5% of the reference plan (w/o MR, w MR).
<table>
<thead>
<tr>
<th>VOI</th>
<th>Parameter</th>
<th>( D_{90} )</th>
<th>( V_{100} )</th>
<th>( V_{150} )</th>
<th>( V_{200} )</th>
<th>( D_1 )</th>
<th>( D_{10} )</th>
<th>( D_{0.1cc} )</th>
<th>( D_{2cc} )</th>
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<tbody>
<tr>
<td>Prostate</td>
<td></td>
<td>-3.5/+4.0</td>
<td>-4.0/+4.0</td>
<td>-4.0/+3.5</td>
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</tr>
<tr>
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<td></td>
<td>-2.0/+3.5</td>
<td>-4.0/+4.0</td>
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<td>±5.0</td>
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</tr>
<tr>
<td>Urethra</td>
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<td></td>
<td></td>
<td></td>
<td>±5.0</td>
<td>±5.0</td>
<td>±5.0</td>
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<td>Rectum</td>
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<td>±5.0</td>
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<tr>
<td>Bladder</td>
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<td>±5.0</td>
<td>±5.0</td>
<td>±5.0</td>
<td>±5.0</td>
</tr>
</tbody>
</table>

Table 3.9 Summary of the limits in mm for the systematic catheter shift so that values will remain within ±10% of the reference plan (w/o MR, w MR).

### 3.2.2 Conformity analysis

The changes of COIN and EI with regard to catheter movement are shown in the following Figures 3.24-3.28.

![Figure 3.24](image_url)

**Figure 3.24** Changes of COIN values based only on PTV (Eq.12) with regard to systematic catheter shift (a) absolute values and (b) values normalized to the COIN value of the corresponding reference plan.
Figure 3.25 Changes of COIN values including OARs (Eq.15) with regard to systematic catheter shift (a) absolute values and (b) values normalized to the COIN value of the corresponding reference plan.

The absolute COIN values in both figures (3.24, 3.25) are higher in the case modulation restriction is used in the plans than when MR=0. Regarding the ±5% and ±10% stability requirement the corresponding catheter shift range is ±1.5 mm and ±2.5 mm respectively (see also Table 3.10). There are no differences here regarding the modulation restriction influence.

EI values for plans using modulation restriction are lower in the whole range of catheter shift (Figure 3.28 a) due to the dependence of the coefficients $C_1$ and $C_2$ (see Eq.17 & Figures 3.26 and 3.27). EI demonstrates an extremely high sensitivity with respect to catheter shift. The ±5% stability criterion required practically 0 mm changes in the catheter position, where for the ±10% criterion this value is ±0.5 mm (see also Table 3.10).

Figure 3.26 Changes of $C_1$ values (Eq.13) with regard to systematic catheter shift (a) absolute values and (b) values normalized to the EI value of the corresponding reference plan.
Figure 3.27 Changes of $C_2$ values (Eq.14) with regard to systematic catheter shift (a) absolute values and (b) values normalized to the $EI$ value of the corresponding reference plan.

Figure 3.28 Changes of $EI$ values (Eq.12) with regard to systematic catheter shift (a) absolute values and (b) values normalized to the $EI$ value of the corresponding reference plan.
3.2.3 Radiobiological analysis

Prostate analysis

The results of the systematic shift analysis for the radiobiological parameters gEUD, EUD_{2,v} and EUD_{2,s} for the prostate are shown in the Figure 3.29. The change of the parameter values in dependence on systematic shift follow the same pattern, being more or less symmetrical in the cranial (+) and caudal (-) direction. This behavior corresponds exactly to that observed for the dosimetric indices D_{90} and V_{100} in section 3.2.1. The limits for the displacement of the systematic catheter shift in order to the values of the radiobiological parameters remain within ±5% of the values of the reference plan are ±1.0 mm for gEUD, -1.0 mm / + 0.5 mm for EUD_{2,s} and ±0.5 for EUD_{2,v}. For the ±10% stability criterion these limits are ±2.0 mm, -2.0 mm/ +1.5 mm and ±1.0 mm respectively (see also Table 3.10). These limits are common for both categories of plans, with and without modulation restriction.

![Diagram](a)

![Diagram](b)
Figure 3.29 Change of (a) gEUD, (b) EUD$_{2,v}$, and (c) EUD$_{2,s}$ values for the prostate in dependence on the systematic catheter shift. All values are normalized to the value of the corresponding reference plan.

Figures 3.30 demonstrate our results for the gEUD and EUD$_{2,v}$ for the urethra. For the gEUD parameter the differences between the two different plan categories are not significant. In plans where the modulation restriction is used, the EUD$_{2,v}$ values are slightly greater than in those without using the modulation restriction. Although gEUD and EUD$_{2,v}$ are power law depended, the latter gives higher values due to the $\alpha$, $\beta$ parameters which give weight to the dose. The limits in order to remain within the $\pm$5% of the reference plan are for the both parameters $\pm$0.5 mm, where for $\pm$10% the limits are for -5.0/ +2.5 mm and $\pm$1.0 mm for the gEUD and EUD$_{2,v}$ respectively independently of the usage or not of modulation restriction.
Figure 3.30 Change of (a) gEUD, and (b) EUD$_{2,v}$ values for the urethra in dependence on the systematic catheter shift. All values are normalized to the value of the corresponding reference plan.

Figure 3.31 shows that the gEUD parameter for the rectum has almost exact the same behavior in both categories of plans. For the EUD$_{2,v}$ there is a small reduction in values when the modulation restriction is used for caudal shift of catheters. The required limits for the catheter shift so that gEUD and EUD$_{2,v}$ remain within ±5% of the originally planned values is ±0.5 mm independently of modulation restriction. This limit becomes ±1.0 mm for gEUD and ±0.5 mm for the EUD$_{2,v}$ for the ±10% stability criterion.
Figure 3.31 Change of (a) gEUD, and (b) EUD\textsubscript{2\%,v} values for the rectum in dependence on the systematic catheter shift. All values are normalized to the value of the corresponding reference plan.

The results for the bladder are demonstrated in Figures 3.32. An increase in the dispersion of individual values while increasing the value of the systematic shift, above the value of +2.0 mm, can be observed for both categories of plans. For bladder, like rectum and urethra the limit for keeping a ±5% stability of the planned values is ±0.5 mm. This limit becomes ±0.5 mm for gEUD and EUD\textsubscript{2\%,v} for the ±10% stability criterion also. The radiobiological parameters demonstrate the same extreme sensitivity to catheter shifts as the corresponding dosimetric indices (see also Figure 3.19).
Table 3.10 summarizes all the above discussed results for the Conformity indices and the radiobiological parameters.

<table>
<thead>
<tr>
<th>VOI</th>
<th>Parameter</th>
<th>EI</th>
<th>COIN (OARs)</th>
<th>gEUD</th>
<th>EUD$_{2,s}$</th>
<th>EUD$_{2,v}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td></td>
<td>±0.0</td>
<td>±1.5</td>
<td>±0.5</td>
<td>±1.0</td>
<td>±1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>±0.5</td>
<td>±2.5</td>
<td>±2.5</td>
<td>±2.0</td>
<td>±2.0</td>
</tr>
<tr>
<td>Urethra</td>
<td></td>
<td>±0.5</td>
<td>±1.5</td>
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<tr>
<td></td>
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<td>±2.5</td>
<td>-5.0/2.5</td>
<td>±0.5</td>
<td>±1.0</td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
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<tr>
<td>Bladder</td>
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<td>±0.5</td>
</tr>
</tbody>
</table>

Table 3.10 Summary of the limits in mm for the systematic catheter shift so that values will remain within ±5% and ±10% of the reference plan.

4. Conclusion

Our study has demonstrated that high modulated, high conformal Brachytherapy dose distributions for prostate HDR implants are sensitive to systematic catheter shift. The consequence of shift changes is not clear. We can generally speak about a required geometrical stability of the implant as high as ±1.0mm. Modulation restriction without improving this, reduces significantly the total dwell time keeping the plan quality and increasing conformity (COIN, EI).
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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
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