Stepping source prostate brachytherapy: From target definition to dose delivery
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Citation for published version (APA):
Dinkla, A. M. (2015). Stepping source prostate brachytherapy: From target definition to dose delivery

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Download date: 05 Dec 2018
Chapter 1
Introduction
1.1 External beam radiotherapy and brachytherapy

Radiation therapy is applied in the treatment of cancer, either as a single modality treatment or in combination with surgery. It can also be combined with systemic treatments such as hormonal or chemotherapy. It deploys ionizing radiation to kill cancerous tissue with a prescribed amount of radiation within the target volume, expressed as the radiation dose (Gy). Some tumours are more sensitive to radiation than normal, healthy tissue. Treatment of such tumours is associated with a wide therapeutic window, offering the possibility to irradiate and eradicate cancerous tissue while sparing normal tissue and surrounding organs at risk (OARs).

With external beam radiotherapy (EBRT), normally a high energy photon beam is aimed at the tumour, depositing part of the radiation dose along the way through the body by indirect ionization of the tissue. Ionizing radiation inflicts lethal damage to cancerous cells and sublethal damage, which the cell itself can still repair. By increasing the dose, a smaller fraction of the cells will survive. Already in 1911, professor Regaud (France) was one of the first to suggest the benefit of a fractionated treatment. His experiments with x-ray irradiation on the testes of rams showed that the scrotum could not be sterilized without substantial damage to the skin. If the same amount of dose was delivered in fractions during a longer period of time, the reaction of the skin tissue was less severe [1]. This demonstrated that side-effects can be reduced by delivering the radiation dose in fractions, instead of applying a single fraction of high dose.

During the last century, understanding of biological effects on ionizing radiation, i.e. radiobiology, has greatly developed. Many factors play a role in determining the tolerance of tissues to irradiation, among which that repair mechanisms in cancer cells are usually less efficient than in healthy tissue. Fractionating the dose can therefore further increase the therapeutic window, by giving healthy cells the opportunity to repair themselves in between fractions.

Originally applied to irradiate deep-seated tumours more efficiently [1], brachytherapy is a form of radiation therapy that irradiates the tumour cells from within the body. In contrast to EBRT, the sources of ionizing radiation are placed in the vicinity of or inside the tumour. In brachytherapy, radiation sources producing gamma rays are used to deposit the dose inside the target volume making it a very local treatment. The name brachytherapy stems from the Greek word for short-distance (βραχυς). An example of an external beam treatment and a brachytherapy treatment is shown in Figure 1.

1.2 History of brachytherapy

Shortly after the discovery of radium ($^{226}$Ra) by Marie and Pierre Curie (1898, Paris),
brachytherapy was successfully applied in the treatment of skin carcinoma in St. Petersburg (1903) by local application of a sealed radium source [2]. In France, brachytherapy is still referred to as curiéthérapie.

Radium therapy showed promising results in the treatment of skin cancer, but the outcome for less accessible tumour sites was not so conclusive [3]. Accurate positioning of large, rigid radium needles was difficult. Furthermore, personnel had to work quickly to avoid excessive exposure, since all sources were prepared and placed manually. Even though the principle of ‘afterloading’ had already been discussed in the beginning of the 20th century, the first remote afterloading device was introduced in the early 1960s [4,5]. With a remotely controlled afterloader, the radioactive source is transported from a shielded safe to its treatment position in the implanted catheters or applicators, reducing exposure to the personnel.

The use of brachytherapy had declined due to its impracticalities and progress in external therapy using high energetic (MeV) photon beams, generated with linear accelerators. After the invention of the cyclotron (1929) and the nuclear reactor (1932) artificial (radio-) isotopes started to become available, such as cesium-137, cobalt-60 en iridium-192. These sources of radioactivity have a high specific activity, i.e. activity per unit mass. Due to their relatively long half-life, replacement is necessary only once every few months ($^{192}$Ir) or only after years ($^{137}$Cs, $^{60}$Co). The gamma rays of $^{192}$Ir with a mean energy of 380 keV have a small penetration depth and can be shielded easily with 1-3 centimetres of lead. From 1958 onwards, iridium wires were widely used, at first often manually afterloaded inside needles or catheters. $^{192}$Ir is still the most commonly used radionuclide. These developments in sources and delivery led to a revival of brachytherapy. Furthermore, physicians, physicists and radiation biologists had gained much insight into the biological response to radiation. Better methods to calculate the deposited dose were developed. Most brachytherapy treatments nowadays use only one single, small, high-intensity, radioactive source that is directed into the target volume through an applicator device temporarily placed inside the body. The source is sent to pre-pro-

Figure 1: Cross-section of a prostate cancer patient showing a planned dose distribution on a CT scan (left) for two types of treatment: A 5-beam intensity-modulated radiation therapy (IMRT) dose distribution (middle) and a brachytherapy dose distribution (right). The color wash is scaled from 0% to 107% of the prescribed dose, since 107% is equal to the maximum dose in the EBRT plan.
grammed positions inside the applicator for a specified amount of time, hence the name ‘stepping-source’ brachytherapy.

We distinguish stepping source brachytherapy (or temporary implant brachytherapy) and permanent implant brachytherapy. Permanent brachytherapy involves placement of small radioactive iodine or palladium sources ($^{125}\text{I}$ or $^{103}\text{Pd}$), called seeds. Permanent implantation of $^{125}\text{I}$ seeds is commonly applied in the treatment of low-risk prostate cancer [6,7]. Composed of 40-100 seeds, the implant initially emits radiation at a dose rate of typically 7 cGy / h in the prostate. The intensity of the implant decreases over time, with a half-life of 60 days. Besides permanent implant prostate brachytherapy, this treatment is also often referred to as low-dose rate (LDR) prostate brachytherapy.

Brachytherapy is often categorized according to the location of the source placement. Interstitial brachytherapy refers to one or multiple sources placed inside the tumour volume via implanted needles or catheters (prostate, bladder, brain, head and neck). Intracavitary brachytherapy, on the other hand, refers to source placement inside a body cavity near the tumour volume, such as the vagina or cervix, using a specially designed applicator. Other types are surface (using moulds), intraluminal (trachea, oesophagus), and intravascular brachytherapy (in the treatment of e.g. coronary artery disease).

1.3 Stepping source brachytherapy

As stated above, in stepping source brachytherapy, a single, small (1 mm diameter), high-activity source that is attached to a steel wire, is directed from the afterloader into the implanted catheters. The source is remotely controlled by the afterloading device. It steps through the catheters to predefined positions (dwell positions) and remains in these dwell positions for a precalculated amount of time (dwell time). After delivery of the prescribed dose, the radioactive source is retracted back into the shielded safe.

In contrast to LDR brachytherapy, high-dose rate brachytherapy is always delivered using a single stepping source that is temporarily placed in or nearby the tumour. An important dosimetric advantage of a stepping source brachytherapy treatment is the possibility to optimize the dose distribution using different times in the dwell positions. High-dose rate (HDR) brachytherapy employs a high activity $^{192}\text{Ir}$ source (initial activity of around 10 Ci, or 370 GBq), allowing for much shorter treatment times. HDR brachytherapy can be delivered as a boost treatment after EBRT in a single ten minute session. If given as monotherapy, the treatment is delivered in 2-6 fractions. This allows for normal tissue repair between fractions, as is done in standard fractionated EBRT.

In pulsed-dose rate brachytherapy (PDR), the dose is delivered in a large number of small pulses, or fractions. The $^{192}\text{Ir}$ source has a lower activity than what is typically used for
HDR brachytherapy (0.5-2 Ci, or 18.5-74 GBq). A pulse is given every one or two hours, to deliver a dose of around 0.5-1 Gy per pulse to the tumour. This means that the total treatment can last up to several days. PDR brachytherapy was developed to mimic the radiobiological effectiveness of a continuous LDR treatment, while improving radiation safety and patient care, and increasing the flexibility for treatment planning [8-11].

At the Academic Medical Center in Amsterdam (AMC), PDR was introduced after years of experience using low-dose rate at other tumour sites [12-14]. With the availability of an afterloader, the choice of a pulsed dose schedule was based on radiobiological considerations. Continuous low-dose rate treatment could be simulated by low-dose fractions with a time interval of 1 or 2 hours [9-11,15,16]. The low-dose rate irradiation offers improved sparing of late reacting normal tissues by allowing for time for repair of sublethal damage.

1.4 Radiobiological considerations

In 1974, the unit gray (Gy = J/kg) was universally adopted to define the amount of radiation delivered in tissue, replacing the older unit rad. Dose-effect relationships were studied, showing that the relation between dose (in Gy) and effect (cell death, tumour control, complications to normal tissue) was non-linear. The relationships seemed to follow an S-shaped curve, in which at low doses, the effect was small, but steeply increased at a certain level of dose [17]. From the late 1970s onwards, it became clear that this effect originated from DNA damage inflicted by the irradiation, and the ability of cells to repair this damage [18]. This explained the fractionation effect. The relationship between (fractionated) dose and cell damage is usually described with the linear-quadratic (LQ) model. The basic formula in the LQ model gives the probability of cell survival after n amount of fractions with fractionation dose d and consists of a linear component and a quadratic component: Surviving fraction = exp-n(αd + βd²) [19]. The parameters of this model are the α (parameter in the linear component) and the β (parameter in the quadratic component). One possible mechanistic interpretation of these parameters is that cell deaths are caused by single track hits (corresponding to the linear component) and two track events (corresponding to the quadratic component) [20]. The values of α and β are different for all cell types. Knowing the values of α and β of a tumour can help to predict the survival fraction of a given fractionated treatment scheme.

Acquisition of the exact values of α and β is complicated. These values have to be obtained from in vitro experiments, in-vivo studies in mammals, and from large datasets of patient treatments and their outcome data. Besides the α- and β-values, other mechanisms influence sensitivity to irradiation and thus cell death as well. The most dominant mechanisms are referred to as the 4 Rs of radiobiology: cell repair, as discussed above, redistribution, repopulation and reoxygenation [20]. Redistribution of cells refers to the
ability to redistribute the cells into specific cell cycles during the interval between dose fractions. Repopulation restricts the overall treatment time and the number of fractions. In tumours that slowly proliferate or have a long onset time of repopulation, repopulation does not have major influence. Other tumours may show accelerated repopulation rates at the end of the irradiation scheme, which increases the rationale for accelerated (hypofractionated) treatments [21]. Cells inside solid tumours may become poorly oxygenated which results in less sensitivity to ionizing radiation. In between fractions, reoxygenation of the tumour can take place, improving the therapeutic effect of subsequent fractions. These effects are cell specific and depend on the dose rate of the irradiation [22,23], making it difficult to quantify them in a real-life treatment setting. The values for $\alpha$ and $\beta$ have been determined from large patient populations, by fitting dose-response curves and finding the best corresponding $\alpha$ and $\beta$ parameters.

The parameters $\alpha$ and $\beta$ are often combined to form the $\alpha/\beta$ ratio. Generally speaking, tissues with high $\alpha/\beta$ ratios are associated with early-responding tissue. These show mainly a linear response to fraction dose and are therefore not greatly influenced by fractionation. Low $\alpha/\beta$ ratios on the other hand represent late-responding tissue, with a relatively large quadratic part in the dose response. The dose-effect therefore depends greatly on the fractionation.

The value of the $\alpha/\beta$, as well as repopulation factors and dose rate effects all influence the efficacy and thus the choice of a particular treatment type and fractionation scheme. Low-dose rate irradiation can be applied to slowly proliferating tumours, possibly with an onset time of repopulation. With such a treatment, late-responding normal tissue benefits from a large amount of sublethal damage repair, reducing normal tissue damage and treatment complications [24]. For aggressive, fast proliferating tumours, a long treatment duration plays a detrimental role [25]. Permanent low-dose rate treatment might therefore be less suitable for treating tumours with short doubling times, especially when the repopulation onset time is also short. Most tumours are classified as early-responding tissue due to the higher $\alpha/\beta$ ratio. Presumably, many tumours also have shorter recovery half-lives. For these tumours, increasing the dose rate (or dose per fraction) will not improve tumour control without losing the sparing effect of low fraction doses [26]. Tumours with lower $\alpha/\beta$ ratios on the other hand, such as prostate cancer, might benefit from fractionation and higher dose rates [27,28], although LDR brachytherapy has been proven to be very effective as well.

1.5 Prostate cancer

Prostate cancer is the most common cancer in men in Europe, with approximately 382,000 new cases in 2008. In that same year, around 89,000 died of this disease, making it the third cause of death for men, after lung and colorectal cancer [29].
Netherlands, the incidence in 2011 was 11,421 new cases, with 2,500 deaths during that year [30].

The incidence of prostate cancer has increased notably during the last 20 years [31]. This increase can be explained by aging of the population, public awareness and the availability of the PSA (prostate specific antigen) as biomarker for the detection of prostate cancer [32]. Earlier detection of prostate cancer leads to a generally younger patient population with lower stage disease, which in turn improves treatment results in terms of disease free survival. A recent study demonstrated a substantial reduction in prostate cancer mortality attributable to PSA testing [33].

Several effective treatments have been established for prostate cancer. The treatment choice depends on patient characteristics and preferences. Treatments differ in terms of dosimetry, costs, logistics, and burden for the patient. Outcome in terms of local control and overall survival are generally comparable between existing treatments, but toxicity scores do vary. Different risk groups have been defined. Prostate cancer can be categorized as low, intermediate, high, or very high risk according to disease characteristics (clinical stage, Gleason score, PSA value) [34]. These risk stratifications are used to decide on the most appropriate treatment options [35].

For low-risk prostate cancer, radical prostatectomy is a common treatment, especially in patients younger than 50. In higher age groups, an increasingly large portion of patients receives permanent implantation of radioactive seeds [36]. Both treatments result in a recurrence free survival after 5 years of more than 90% [37]. Because of the slow progression rate of the tumour, active surveillance is also a viable option [38,39].

For intermediate-risk prostate cancer patients, the main treatment options are radiation therapy and radical prostatectomy. Both can be combined with androgen deprivation therapy (ADT), which is usually started before or at the start of radiation treatment. Radiation treatment can be delivered by EBRT, possibly combined with a brachytherapy boost, or by brachytherapy alone. In the Netherlands, more patients are treated with radiation therapy at higher age, as in the low-risk group [32,36,40]. For patients older than 75 or when life expectancy is short, an observational policy such as watchful waiting, is adopted more often.

High-risk patients receive radiation treatment (EBRT or EBRT+BT), which is most likely combined with ADT, or undergo a prostatectomy including pelvic lymph node dissection [34]. In the Netherlands, patients with high-risk disease underwent radiation therapy more often than surgery (45% vs 25%) [36].

For the treatment of intermediate- to high-risk prostate cancer, the addition of a brachytherapy boost has gained popularity in the last decade. Biochemical control in
prostate cancer has been shown to benefit from dose escalation [41-43]. The increase of total delivered dose without increasing morbidity can be done safely by delivering part of the total dose with a temporary or permanent implant brachytherapy boost [44-46]. The preliminary results of a multi-institutional phase-II trial, designed to test the safety of EBRT with an HDR boost, showed limited adverse events in the first 18 months [47]. A few randomised trials exist, which compare EBRT and HDR or PDR brachytherapy. A phase-III randomised trial compared EBRT and a combined treatment of EBRT plus an HDR boost for intermediate- and high-risk prostate cancer patients [48]. The results of this trial demonstrated improved biochemical control for the combined treatment without increasing early and late toxicity, proving that dose escalation for the prostate could safely be done with an HDR brachytherapy boost in a combined modality approach.

Prostate PDR Brachytherapy at the AMC
Since 2002, intermediate and high-risk prostate cancer patients treated at the AMC have the option to be treated with EBRT with a PDR brachytherapy boost [49-51]. This treatment consists of 23 x 2 Gy fractions of EBRT, followed by 24 pulses of 1.2 Gy PDR brachytherapy, delivered over 48 hours. The week after finishing 5 weeks of external beam radiotherapy, the implantation procedure is scheduled at the operating room. The patient receives full anaesthetics while the catheters are implanted into the prostate, under transrectal ultrasound (TRUS) guidance. After the implantation of around 12 to 14 needles, CT or MR images of the pelvic area are obtained that are used for catheter reconstruction and organ delineation.

Cranio-caudal displacement of the implanted catheters during the treatment or between HDR fractions is often reported and can have large effects on the dosimetry [52-54]. Strategies to deal with this issue are re-planning the dose distribution before starting the next fraction [53] or readjustment of the catheter positions using CT or Cone Beam CT [55-57]. For the 48 hour prostate PDR brachytherapy treatment at the AMC, special catheters were designed containing a self-anchoring mechanism [49]. This mechanism consists of an umbrella-like feature at the catheter tip that can be opened after the catheter is positioned correctly inside the prostate (Figure 2). An earlier study by Pieters et al. showed that the catheter tip displacement in cranio-caudal direction was indeed

Figure 2: Self-anchoring catheter [49]
minimal, proving their safety and feasibility [49].

The clinical outcome of this treatment of intermediate- to high-risk prostate cancer was reported in two studies [50,51]. With a 5 year biochemical non-evidence of disease (bNED) of 90% and overall survival of 96%, the results were comparable to what is being reported in the literature [58-60]. It was shown that the treatment was well tolerable in terms of complications. Similar toxicity data was reported by another group using PDR in a dose escalation phase-II trial [60]. In that trial, biochemical control was achieved in 88% of patients and they reported an overall survival of 86%.

1.6 Treatment planning

As explained, stepping source brachytherapy has the advantage of optimizing the dose distribution before the start of the treatment. Prior to optimization of a brachytherapy dose distribution, images of the patient with the catheters in place are acquired and loaded into a dedicated treatment planning system (TPS). In the treatment planning software, showing the 3-D representation of the patient, the user delineates the target volume with the surrounding organ volumes and reconstructs catheter positions, i.e. all items necessary for optimization. Calculation and optimization of the dose distribution, and evaluation of the treatment plan is also done in this system. To calculate the dose distribution from specified sources in a standardized way, a task group (TG-43) established the TG-43 formalism for dose calculation as international standard [61].

Imaging is a vital aspect in brachytherapy treatment planning. Where a dose distribution used to be based on orthogonal radiographs or even calculated by hand, nowadays the majority of brachytherapy dose calculations are based on 3-D imaging, showing both the implanted catheters or applicator and the tumour with surrounding OARs. Accurate catheter reconstruction and delineation of the PTV are the most important aspects. Catheter reconstruction is best performed using CT. For permanent implants, usually consisting of $^{125}$I seeds, CT is still the recommended modality [62-64], even though metallic seeds may cause streaking artefacts, obscuring the visibility of prostate boundaries.

The dose distribution is shaped according to the patient’s anatomy, and the geometry of the implanted catheters. Dose optimization starts by selecting the optimal dwell positions inside the catheters where the source should stop (dwell) and setting dwell times for these dwell positions. During the optimization process the dwell positions and their weights are adapted while evaluating the resulting dose distribution. The evaluation is done by visual inspection of isodose lines, or with dose-volume histograms (DVHs) and specific DVH-parameters that are extracted from them. After implantation and treatment planning, the optimized dwell times are sent to the afterloading device.
and the catheters are connected to the afterloader. The fraction or pulse consists of a
time-pattern of the source stepping through all the implanted catheters one by one. This
pattern generates the required distribution inside and around the implant. Treatment
plan optimization developed from geometry-based optimization to anatomy-based
optimization, in which the dose is optimized to meet the required dose value in every
voxel inside the regions of interest (ROIs).

Before the era of 3-D imaging, brachytherapists developed catheter templates and
standard applicators that were used to create known dose distributions. Dose prescrip-
tion was based on equivalent mass of radium. The first dosimetry systems were devel-
oped in the 1930s: the Quimby system and Manchester system [65,66]. These systems
included rules for source arrangement and dose specification that were applied to pre-
plan an implant. Both systems were based on the use of radium sources and contained
tables to calculate the amount of radium and the time needed to give a specific dose to
the surface of the implant.

The Quimby system for single plane, surface implants simply assumes an equally spaced
array of $^{226}$Ra sources of equal linear activity, which leads to a non-uniform dose distri-
bution. The Manchester system for planar implants was designed to deliver a uniform
dose within ~10% to a plane or volume. The uniform dose is then achieved in parallel
planes at 5 mm from the implant plane. In the 1960s, the Paris system was developed
in France for the flexible $^{192}$Ir wire implants that were then in use [67]. The implant rules
specified that the sources should be straight, parallel and equidistant, and preferably of
equal length and activity. The source separation itself depends on the thickness of the
implant. Specific reference points (basal dose points) were defined in the central plane
of the implant and were used to calculate the dose for the entire implant. Today, the
Paris system still forms the basis for single plane and multi-planar implants and is used
in breast, bladder and skin.

Specifically for gynaecological brachytherapy, another Manchester system was
designed, which was based on a single catheter in the uterus (the intra-uterine catheter)
and two vaginal catheters inside the ovoids. For these gynaecological applications spe-
cific loading rules were introduced. Intracavitary treatments were described in terms of
prescribed amount of radium (using the mg-hour concept), whereas external beam ther-
apy was described in terms of absorbed dose. A new approach was needed to describe
the combined treatment [68]. To be able to compare the dose between patients, the
reference points “A-left” and “A-right” were defined. These points “A” were located 2 cm
from the front side of the ovoids, at 2 cm left en right of the intra-uterine catheter, so
at a fixed distance from applicator, based on the cervical anatomy. Using this approach,
the treatment could be described in terms of dose to this point, regardless of applica-
tor and its loading. Prescribing the dose rate on points “A” translated into a dose that
was more or less reproducible from patient to patient. The principles of the Manchester
system are still applied in cervical treatments, to create standardized dose distributions and calculate and report the dose in points "A". The dose is currently mainly prescribed to points "A" or to a reference volume. With the introduction of 3-D imaging, more and more centres will prescribe to a target volume [23].

1.7 Dose optimization

Dose optimization is an essential part of treatment planning in radiotherapy in general thus also in brachytherapy. Currently, the most clinically used treatment planning methods for temporary implant prostate brachytherapy are graphical optimization, Inverse Planning Simulated Annealing (IPSA) and Hybrid Inverse Planning and Optimization (HIPO) [69,70]. Geometrical optimization (GO) is also still widely in use due to its ease and availability in many treatment planning systems [71,72].

Many institutes perform graphical optimization of the dose distribution. With graphical optimization the dose distribution is manually manipulated by performing multiple drag-and-drop actions on the isodose lines. Experience and time are required in this process [73,74]. Graphical optimization is used either as a full optimization method or to fine-tune the results of an inverse automatic method like IPSA or HIPO.

Schedules are usually tight in clinical practice, so automatic inverse optimization algorithms have been developed to speed up the dose optimization process [75-77]. In the last decade, several of these automated inverse optimization algorithms have become commercially available in treatment planning systems [72,73], and are increasingly used in clinical practice [74-76]. Brachytherapy treatment planning is a multi-objective optimization problem, since there are many conflicting objectives. Current commercially available inverse algorithms are based on an aggregated penalty function, optimizing all objectives at once. A (linear or quadratic) penalty is attributed to all dose points with doses outside the range as set by the user. Since planning objectives are often contradicting, the weights that are selected for each planning objective define the priority of the contradicting objectives. These are called a priori methods, because the set of dose objectives and their weights that will lead to the most clinically suitable plan is unknown beforehand. The optimization process often results in a trial-and-error procedure to find the desired dose distribution.

Furthermore, in IPSA and HIPO the objective function is composed of minimum and maximum dose levels for all organs involved, and does not contain planning objectives for dose-volume parameters. The DVH parameters that are used to evaluate and accept a treatment plan, are not linearly related to the minimum or maximum dose inside a volume. Therefore, in order to find the best dose distribution, the user often has to employ trial-and-error during the planning process. Every patient case is different.
regarding the anatomy, i.e. shape of the prostate and surrounding OARs. The implanted catheters are also patient specific, i.e. the location of potential dwell positions inside the prostate and with respect to the OARs. To reach a given dose level inside the prostate might be easy for one patient and extremely difficult for another, when one has to stay below maximum allowed doses for the OARs. To navigate efficiently through the possible solutions requires skill and experience. Of course efforts were undertaken to limit or mitigate this trial-and-error process. The amount of trial-and-error is limited by the development of one or more institute specific class solutions, which is a predefined, optimized set of parameters with dose constraints and penalty weights that form the objective function [73,78-81]. In practice, using this method is time saving (chapter 6), but will not result in the best possible dose distribution for all patients.

1.8 Plan evaluation

Evaluation of a treatment plan is performed by inspection of the isodose lines and DVHs. DVHs are calculated by the TPS and give the relation between volume and dose. This can be expressed in a differential DVH or cumulative DVH. Usually the cumulative DVH (cDVH) is evaluated. It represents for each dose level the amount of volume in an organ or ROI that receives at least this dose. In other words, it represents the volume inside an isodose surface. Several DVH parameters, like the volume receiving at least the prescribed dose, are extracted from the cDVH. Spatial information on the location of specific dose levels is not captured in the DVH. The various DVH parameters have different sensitivities to contouring. Furthermore, some DVH parameters are redundant due to their strong correlation with others [82,83]. Besides the DVH parameters that are widely used, other evaluation indices have been developed that quantify conformity to the target volume and homogeneity of the dose [84-87].

Dose reporting is important to derive relationships between dose parameters and clinical outcome parameters such as tumour control and adverse events. Furthermore, using the same set of parameters is useful to compare clinical practice between different institutions. To develop a common language for reporting based on existing concepts, the ICRU (International Commission on Radiation Units & Measurements) specified certain parameters to be reported, such as treatment volume, prescription dose, time-dose pattern, TRAK (total reference air kerma), minimum target dose, homogeneity index, high-dose regions, low dose regions, reference volume, irradiated volume [88,89]. Both the ABS (American Brachytherapy Society) [90] and the GEC-ESTRO (Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology) [91,92] have written recommendations on quality control parameters and reporting. The value of this comprehensive way of reporting is confirmed by the large number of studies on the correlation of dose-volume parameters and clinical outcome revealing relationships between dose to a volume and local control [93,94] and toxicity [95-98].
1.9 Objectives and outline of this thesis

MRI- versus CT-based treatment planning (chapter 2)
A prostate brachytherapy treatment plan is based on computed tomography (CT), magnetic resonance imaging (MRI) or transrectal ultrasound (TRUS). These 3D image acquisitions of the pelvic area are needed to define the tumour and surrounding organs. In the case of a prostate treatment, usually the entire prostate is defined on the scan by the radiation oncologist. The accuracy of the prostate contours depends on the resolutions and contrast in the scan. MRI scans have sub-millimetre resolution but usually thicker slices. CT and TRUS are more widely available and thus more generally applied than MRI. However, MRI has much better soft tissue contrast, improving the visualization of the prostate boundaries [99]. In chapter 2, the improvement in target dose coverage when using MRI-based delineations for treatment planning was studied, as compared to using CT-based delineations.

Anatomical variations and implant stability (chapters 3 and 4)
With treatment planning, or dose optimization, we assume stability of the catheters inside the tumour and stability of the organs’ position and shape. However, bowel movement and changes in bladder filling may change the location and shape of these OARs, with respect to the prostate [100,101]. Furthermore, the prostate may change shape, due to these external influences, or due to oedema caused by needle insertion [102-105]. The influence of changes in patient geometry during treatment on the dose distribution is analysed in chapter 3. The stability of the implant geometry, i.e. possible catheter deformation and accompanying changes in prostate volume, are studied in chapter 4.

Treatment plan optimization (chapters 5 and 6)
As a user-friendly alternative to graphical optimization, a new planning approach was developed and tested. This approach contains an enhanced version of the traditional geometrical optimization and an inverse treatment planning tool. Enhanced Geometrical Optimization (EGO) is used to create a dose distribution that is as homogeneous as possible. Subsequently, the user applies Interactive Inverse Planning (IIP) to shape the dose distribution to the patient specific anatomy. With intuitive, real-time user interaction, dose distributions are produced that are equally good or better than the dose distributions that are currently created in our clinical practice, using graphical optimization. In chapter 5, EGO and IIP are described. As a proof-of-principle, the results are presented of both an inexperienced and an experienced planner, who created prostate PDR brachytherapy treatment plans using these tools. In chapter 6, EGO-IIP, graphical optimization and two inverse algorithms (IPSA and HIPO) are compared to establish the optimal method for brachytherapy treatment planning.
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