I-125 seed implants for prostate brachytherapy

Physical characteristics and relations with post-implant quality of life
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General introduction
1.1 Treatment of prostate cancer

1.1.1 Incidence rates and considerations for treatment

Incidence rates of prostate cancer have risen dramatically across Europe in the last 2 decades, placing it at the top of the list of diagnosed cancers [1-3]. In the 25 countries of the European Union plus Iceland and Norway the number of prostate cancer cases in 2006 was 301,500, being 24.1% of all cancer cases among the male population and 13.2% of all cancer cases among the total population. The number of deaths due to prostate cancer in the same year and region was 67,800, which accounted for 10.4% and 5.8% of all cancer deaths among male and total population, respectively [1].

The possibility of early detection by prostate-specific antigen (PSA) screening programs has led to an increase of diagnosed early stage prostate cancers. In the provinces Noord-Holland and Flevoland of the Netherlands for instance, the diagnosed stages T1 and T2 (TNM classification) as a percentage of all diagnosed prostate cancers increased from 47% in the period 1989-1991 to 56% in the period 1999-2001 [4]. The treatment of slow progressing localised prostate cancer is subject of large spread debate and controversy among urologists and radiation oncologists. These are based on the lack of clear and unambiguous relations between incidence rates, or rather early detection rates, and mortality rates. Two large randomised trials on PSA screening programs, an American and a European study, resulted in different conclusions regarding the effectiveness of early detection programs. The American study did not show any benefit of a regular screening program on mortality rates [5], the European study showed a 20% reduction of prostate cancer related death rate in a group of men undergoing regular PSA screening compared to a group of men that did not [6]. In the latter study, however, the risk of over-diagnosis and over-treatment due to screening was clearly recognised. The incidence rates of prostate cancer in the countries of the European Union vary largely due to variable use of PSA screening. This variability in incidence rates, however, does not reflect the same variability in mortality rates. Depending on the intensity of early detection programmes per country of the European Union, one out of 2.5-6 patients with diagnosed prostate cancer ultimately dies from the disease [3].

Because the risk of over-treatment is now recognised as a serious problem, so called “active surveillance” has become an accepted management strategy [3,7,8]. Choosing the best strategy, however, is a clear dilemma for both physician and
patient. Initiating immediate treatment after the diagnoses may result in overtreatment but active surveillance is not without risk. Erroneous staging of the cancer due to insufficient biopsy sampling and possible tumour differentiation over time are two important risk factors. And when to change from active surveillance to curative treatment in time? Ola Bratt strikingly called it “watching the face of Janus” [9]. Although all curative treatments are toxic to some extent, it does not mean that the quality of life of active surveillance is always better. The knowledge of having an untreated cancer can be a considerable psychological burden to some groups of patients [10].

1.1.2 Radical treatment
High incidence rates, risk of over-treatment and on the other hand increased survival due to treatment have increased the demand for effective but low toxic treatments. Several curative treatments for localised prostate cancer have been developed in the last few decades. Firstly, prostatectomy, which can be carried out as either an open radical technique or as a minimal invasive radical technique. Secondly, external beam radiotherapy, where patients receive fractionated radiation to a high total dose for a number of weeks by means of high-energy photon beams from a linear accelerator. And thirdly, brachytherapy, either as mono therapy or in combination with external beam therapy. These are the three well-established methods for radical treatment. Three other relatively new options, yet not very well established, are cryotherapy, photodynamic therapy and high intensity focused ultrasound (HIFU). These techniques still have to be proven to be as adequate as the more established techniques [11-13]. Although randomised trials are lacking, reported biochemical freedom from disease recurrence after prostatectomy, external beam therapy and brachytherapy are comparable [14].

1.1.3 Androgen deprivation therapy (ADT)
Of the non-radical treatments ADT should be mentioned because of its widespread use, both as primary therapy and as adjuvant therapy in conjunction with radical treatment. In the USA, between 2000 and 2002, 44.8% of all men with prostate cancer were exposed to ADT during the first year after diagnoses [15]. Because the efficacy of adjuvant ADT for low-risk prostate cancers has never been clearly demonstrated the use of ADT in these cases is controversial [16]. For more unfavourable risk cancers ADT, in conjunction with external beam radiotherapy and
brachytherapy, has been reported to increase PSA control and overall survival [17,18]. Concerning the duration of the ADT, benefits of long-term use should be weighted against adverse effects such as bone, muscle and cardiovascular complications [19].

1.2 Quality of life (QOL) after treatment

Since control rates can be considered to be comparable, other aspects of the three main radical treatment modalities will have to be considered by physicians and patients in order to make the best choice of treatment strategy. One important advantage of permanent brachytherapy with seeds is the limited burden of the implantation procedure. The minimal invasive procedure in the operation room (OR) takes 1½ - 2 hours. The total hospitalisation time is usually 1 day. Radical open prostatectomy requires approximately the same time in the OR but on average 6 days hospitalisation. Minimal invasive laparoscopic prostatectomy on the other hand requires a slightly longer time on the OR (2-3 hours) but only 2 days hospitalisation. External beam radiotherapy requires 25 to 35 daily fractions and the patient has to travel to the hospital for irradiation 5 times a week for 5 to 7 consecutive weeks.

Another very important aspect of the treatment of localised prostate cancer is the QOL after treatment. The burden of the treatment itself as well as the expected QOL after treatment will have to be taken into account to make the best choice of treatment but also to decide whether any active treatment is (yet) the best option. As mentioned before, there is an increasing number of patients diagnosed with early stage localised prostate cancer. For many of these men “active surveillance” could as well be an option as curative treatment. Although prostatectomy, external beam radiotherapy as well as brachytherapy are usually characterised as being "well tolerated" both acute and late toxic reactions due to these treatments are common. Decreased erectile function, genitourinary (GU) and gastrointestinal (GI) morbidity are associated with all three treatment modalities [20-23]. The QOL will be permanently or temporary affected to some degree by these post-treatment symptoms. It is difficult to favour out one of these treatment modalities in terms of post-treatment QOL because again, as for local control comparisons, randomised trials comparing post-treatment morbidities are lacking. The problem with the very few published retrospective comparisons is that subgroups of each treatment modality, in terms of different techniques or radiation doses, were not analysed
General introduction

separately or that specifications of treatments were not well defined within the investigated patient cohort [20,21,23]. Well founded conclusions can therefore not be drawn from these studies. However, side effects usually reported after brachytherapy of the prostate are obstructive and irritative urinary symptoms (chapter 4). Brachytherapy techniques could be further improved when the origin of these toxic reactions are known in more detail. Identifying predictors for urinary morbidity after brachytherapy is part of the research described in this thesis (chapter 5).

1.3 Brachytherapy: indications and PSA failure

1.3.1 Indications
One of the characteristics of brachytherapy with low energy photon-emitters such as Iodine-125 (I-125) or Paladium-103 (Pd-103) is a high local dose and a steep dose gradient immediately beyond the boundaries of the implant. This makes this treatment particularly suitable for localized prostate cancer, i.e. for patients with stage T1 or T2 disease. Within this group the outcome expressed in PSA relapse-free survival after monotherapy permanent seed implants will depend on tumour stage, Gleason score and pre-treatment PSA [24-27]. Not surprisingly, also the magnitude of the deposited radiation dose in the prostate influences outcome. Especially the minimal dose to 90% of the prostate (D90) has been reported to be a predictor for PSA relapse-free survival [27-29].

Results for low-risk cases (stage T1-T2a, Gleason score ≤ 6, PSA < 10 ng/ml) can be considered to be excellent but also the published results for intermediate-risk cases (stage T2b/c or Gleason score = 7 or PSA = 10-20 ng/ml) are very encouraging [30-32]. In combination with external beam radiotherapy and/or androgen deprivation therapy, brachytherapy has reported to result in excellent long-term PSA control rates for low-risk as well as for intermediate and high-risk cases [18,33,34]. Reported positive results for non low-risk cases may lead to less conservative indication strategies for brachytherapy while urologists and oncologists normally only consider low-risk patients eligible for brachytherapy.

1.3.2 PSA failure
It has to be noted that different definitions of biochemical failure exist. In literature mainly two definitions are used, the so called ASTRO definition [35] and the Phoenix definition [36]. The latter was defined after reported shortcomings of the
ASTRO definition. PSA failure according to the ASTRO definition is defined as three consecutive increases in PSA level, the date of failure midway between the dates of post irradiation nadir and the first rise. PSA failure according to the Phoenix definition occurs after a rise of at least 2 ng/ml above the nadir PSA, the date “at call” being the date of failure. In the publications referred to in this chapter one of these definitions has been used to define PSA failure. It should further be noted that both definitions are prone to false positive findings due to the phenomenon of PSA bouncing. Mitchell et al. [37] reported that 4 out of 23 PSA failures according to the ASTRO definition and 6 out of 28 according to the Phoenix definition were in fact PSA bounces.

1.4 Brachytherapy techniques

The combination of favourable physical properties of the radionuclide I-125 is one of the reasons for its widespread use for brachytherapy of the prostate. The radioactive material can be contained in thin walled titanium cylinders called "seeds" with a typical diameter of 0.8 mm and a length of 4.5 mm. These I-125 seeds are suitable for so called "permanent implantation". The seeds will be implanted in, and closely around the prostate and will not be removed. A half-value time of 59 days will result in a deposited dose after 59 days of 50% of the eventually total deposited dose, usually 145 Gy. The average energy of emitting photons is only 27 kV [38]. Consequently the penetration depth of the radiation is very small. With a sufficient high dose rate in the prostate, the dose rate at the skin surface of the patient seldomly exceeds 200 μSv/h shortly after implantation of the sources. At 1 m from the patient the dose rate will usually not exceed 2 μSv/h [39]. These low dose rates allow patients to leave the hospital without being a hazard to people in their close vicinity.

The radionuclide Pd-103 is also used for permanent prostate brachytherapy, although mainly in the USA. The average energy of the emitting photons of Pd-103 is even lower than that of I-125, (21 KeV). However, the most important difference is the lower half-value time of Pd-103, i.e. only 18 days [38]. This means that the dose is delivered faster, which was initially be expected to be beneficial for relatively fast growing tumours although this has not been confirmed by clinical studies [40]. The advantage of permanent implants over temporary implants is that the implantation needles will be removed after placement of the seeds. This means that the patient is mobile directly after the implantation of the seeds and that no
precautions have to be taken to prevent needles from displacing or being damaged. On the other hand, once the seeds are placed no corrections are possible.

The radionuclide Iridium-192 (Ir-192), commonly used for afterloading techniques, is not suitable for permanent implants. With an average photon-energy of 380 KeV the exit dose of the patient would be too high to safely interact with people in close vicinity. Ir-192 is used for brachytherapy of the prostate but for temporary implants only. The needles are placed transperineally, the same as the implant needles for permanent implantations, and one or several fractions are given while the needles are connected with a so called afterloader device. The afterloader mechanically transports a single Ir-192 source into the sequential needles where the source stops at pre-planned positions in the needles (dwell positions) for pre-planned times (dwell times). After the execution of the last fraction the needles will be removed. Temporary prostate brachytherapy usually is an additional treatment (boost treatment) after external beam therapy [41-43] and is seldomly reported to be used as a mono-treatment [44]. Permanent brachytherapy with I-125 or Pd-103 seeds can either be a boost treatment or a mono-treatment.

Since the introduction of permanent prostate brachytherapy with I-125 seeds in the early 1970s some significant improvements of the implantation technique have been introduced [45,46]. It started as an open laparotomy retropubic freehand implantation technique. This technique was rather invasive and the placement of the seeds was inaccurate. Soon it was replaced by minimal invasive implantation through the perineum with the patient in lithotomy position. This technique allows template guided needle implantation by means of transrectal ultrasound (TRUS) guidance. Then there was the introduction of application software for the determination of optimal dose distributions and corresponding implantation plans based on transversal TRUS-images of the prostate. The latest improvement of commercially available planning software is the possibility to correct planned seed locations based on “real” seed locations if visible on real-time TRUS-images. Accordingly, more accurate dose distributions can be determined and dose distributions are reported to have been improved significantly after the introduction of this modality [47].

The transperineal image guided implantation method is fast, accurate and minimally invasive. A drawback of this system is that the pubic bone can obstruct the implantation of ventral needles in case of large prostates. In general, a prostate
volume of 50 cm$^3$ is considered to be the upper limit for eligibility for transperineal implantation. This limit, however, is rather arbitrary and a prostate size greater than 50 cm$^3$ is not necessarily a contra-indication for brachytherapy or a reason to administer hormone therapy to down size the prostate volume prior to the implantation procedure [48].

1.5 Evaluation of brachytherapy seed implants

Although real-time TRUS-based dosimetry during the implantation of the seeds can be considered to be an improvement of the implantation process [47,49], still an accurate estimation of the final realised dose distribution solely based on this technique cannot be made [50]. The fact that this method is not real three dimensional (a single longitudinal plane is selected to trace the deposited seeds per needle) and poor visibility of the seeds on TRUS-images can contribute to inaccuracies in the dosimetry. Also organ motion and swelling during the implantation process and displacement of seeds in time are responsible for geometric and dosimetric uncertainties.

To be able to relate clinical outcome, i.e. tumour control and morbidity, to realised dose distributions, accurate dosimetry is mandatory. For the determination of 3D dose distributions in the prostate and organs at risk adequate imaging of these organs and of the seed implant is required. Computed tomography (CT) after implantation is recommended by the American Brachytherapy Society (ABS) [51] as image modality for this purpose. Nevertheless, CT is certainly not ideal for the delineation of the prostate contours. The visibility of the contours becomes even worse after implantation of the seeds. On the other hand, reconstruction of the seed implant from CT-images is very easy and accurate. The Probate Working Party of the GEC-ESTRO considers Magnetic Resonance Imaging (MRI) to be the best image modality for the delineation of the prostate [52]. MRI, however, is (still) expensive and time consuming and not all departments have easy access to such facility. Investigation of combined CT and TRUS imaging as an alternative for CT only, or in combination with MRI, is part of this thesis.

In case of low dose rate permanent implants with I-125 or Pd-103 seeds the irradiation dose will accumulate slowly. Commercially available planning systems determine the deposited dose after total physical decay of the radioactive sources. The geometry of implant and anatomy, however, is usually based on one single scan made at a particular moment after implantation. The question is whether the
time span between the implantation of the seeds and the execution of the CT scan (or other image modality) is critical and if any dose distribution based on a single scan can be representative for the total accumulated dose distribution. Also this has been investigated in detail as part of this thesis.

1.6 Objective of this thesis

The subjects of this thesis are all related to permanent brachytherapy of the prostate with I-125 seeds. The thesis can be divided into three main subjects. The first subject focuses on the determination of the dose distribution after the implantation of the seeds. As described in section 1.5, relations between clinical outcome and the dose distribution due to brachytherapy can only be determined when the prostate and the organs at risk can be accurately delineated. Also the seed implant has to be accurately reconstructed. The possibility to use both CT and TRUS images in order to join complementary features of both image modalities has been investigated. The technique and applicability of fused, simultaneous acquired CT and TRUS images is described in chapter 2. In clinical practise, the dose distribution after complete physical decay of the sources will be determined and will be based on one single image acquisition only. During physical decay of the sources, however, the geometry of organs and implant might change. A detailed analysis of changes in time and the influence on the dose distribution of prostate and organs at risk is described in chapter 3. The second subject is an investigation of possible relations between physical characteristics of the implant and post-implant urinary morbidity. Obstructive and irritative urinary symptoms are very common after brachytherapy of the prostate. Identifying possible causes of these symptoms are necessary for the development of less toxic techniques. The results of a comprehensive literature review regarding this subject is summarised in chapter 4. A search for possible relations in collected data from patients treated in the NKI-AVL is described in chapter 5. For this research, some dosimetrical parameters not previously mentioned in literature in relation to post-implant urinary morbidity are investigated. In literature, very little attention is paid to possible mechanical trauma due to insertion of implantation needles although this is very likely to contribute to post-implant toxic reactions. Studying possibilities to realize implants with fewer implantation needles without compromising adequate dose coverage of the prostate is the third subject of the thesis. Alternative, non-conventional seed
distribution patterns as well as the use of higher activity seeds are studied in order to reduce the number of implantation needles. The results of this study are described in chapter 6.
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Chapter 2

The applicability of simultaneous TRUS-CT imaging for the evaluation of prostate seed implants

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Abstract

To study dose-effect relations of prostate implants with I-125 seeds, accurate knowledge of the dose distribution in the prostate is essential. Commonly, a post-implant computed tomography (CT) scan is used to determine the geometry of the implant and to delineate the contours of the prostate. However, the delineation of the prostate on CT slices is very cumbersome due to poor contrast between the prostate capsule and surrounding tissues. Transrectal Ultrasound (TRUS) on the other hand offers good visualization of the prostate but poor visualization of the implanted seeds. The purpose of this study was to investigate the applicability of combining CT with three-dimensional (3D) TRUS by means of image fusion. The advantage of fused TRUS-CT imaging is that both prostate contours and implanted seeds will be well visible. In our clinic, post-implant imaging was realized by simultaneously acquiring a TRUS scan and a CT scan. The TRUS transducer was inserted while the patient was on the CT couch and the CT scan was made directly after the TRUS scan, with the probe still in situ. With the TRUS transducer being visible on both TRUS and CT images, the geometrical relationship between both image sets could be defined by registration on the transducer. Having proven the applicability of simultaneous imaging, the accuracy of this registration method was investigated by additional registration on visible seeds, after pre-registration on the transducer. In 4 out of 23 investigated cases an automatic grey value registration on seeds failed for each of the investigated cost functions, and in 2 cases for both cost functions, due to poor visibility of the seeds on the TRUS scan. The average deviations of the seed registration with respect to the transducer registration were negligible. However, in a few individual cases the deviations were significant and probably due to movement of the patient between TRUS and CT scan. In case of a registration on the transducer it is important to avoid patient movement in-between TRUS and CT scan and to keep the time in-between the scans as short as possible. It can be concluded that fusion of a CT scan and a simultaneously made TRUS scan by means of a 3D transducer is feasible and accurate when performing a registration on the transducer, if necessary, fine-tuned by a registration on seeds. These fused images are likely to be of great value for post-implant dose distribution evaluations.
2.1 Introduction

In order to study the dose-effect relations of prostate brachytherapy with I-125 seeds, an accurate determination of the dose distribution is essential. Commonly used is a post-implant CT scan to determine the geometry of the implant and to delineate the contours of the prostate and organs at risk, such as urethra, rectum and penile bulb. Although systems have been developed for real time or intermediate feedback of source placement during the implantation procedure [1-4], post-implant imaging remains important. It can be used to investigate the implantation and dosimetry accuracy of these new techniques and to study time-related factors influencing the dose distribution, like change of prostate volume and seed geometry.

The 3D reconstruction of the implant from CT images can be achieved easily and quickly when using an automatic seed finder. The accuracy of the reconstruction will be high if a sufficiently small CT slice thickness is used. The delineation of the prostate on CT slices, however, is very cumbersome due to poor contrast between the prostate capsule and surrounding tissues. It has been reported that prostate volumes delineated on CT images are, on average, 30-50% larger than on MRI or US images, due to poor contrast on CT images [5-8]. Also, streaking artefacts caused by the radio-opaque marker inside the seeds hamper an accurate delineation. Some studies report large inter- and intra-observer variations in the delineations of the prostate on CT images [9-11]. Consequently, uncertainties will be large in derived dosimetric parameters such as V100 (prostate volume contained within the 100% isodose surface) and D90 (isodose surface containing 90% of the prostate volume) [9,11,12]. Therefore, there is a need for an imaging modality more appropriate than CT for post-implant dose distribution evaluations. McLaughlin et al. suggested $T_2$-weighted MRI to be the optimal image modality for post-implant evaluations [7]. A MRI scan, however, is expensive and not accessible for all radiotherapy departments.

Although the use of TRUS for implant planning and image guidance is widespread, post-implant evaluations based on TRUS images are rare. The main reason is that, although the prostate contours are well visible, it is impossible or at least very difficult to locate all implanted seeds. Some seeds are visible due to a favorable reflection angle with respect to the TRUS transducer, others are not if US pulses do not reflect back to the transducer or are hidden behind calcifications. Movement of the prostate is another problem, originating from mechanical shifting of 2D TRUS
transducers from apex to base in a number of steps. Movement of the prostate makes it difficult to register the 2D TRUS images to a CT scan. The availability of a 3D TRUS transducer can possibly overcome this latter problem.

Our purpose in this study is to investigate the feasibility of a hybrid imaging technique offering sufficient contrast for both seeds and prostate, by acquiring simultaneously a 3D TRUS scan and a CT scan. After registering both scans, the implant geometry derived from the CT scan can be projected on the prostate contours derived from the TRUS scan. Subsequently, the dose distribution in the prostate can be determined.

2.2 Materials and methods

2.2.1 Scanning procedure and implant characteristics

One day and/or one month after implantation of the I-125 seeds a TRUS scan and simultaneously a CT scan were acquired. For US imaging a 3-D TRUS transducer with an internal scanning mechanism was used (GE/Kretz RRE6-10). A convex transversal array of 149° is scanned 135° in longitudinal direction, covering the whole prostate in a fraction of a second. The transducer was inserted while the patient was on the CT couch with the lower legs in a specially made support. Directly after the TRUS scan the CT scan was made with the transducer still in situ.

In this way, TRUS scan and CT scan were acquired almost simultaneously, that is to within 1 to 3 min. The CT scanner used in this study was a GE Hi-Speed single slice scanner. The CT scans consisted of 3 mm thick transversal slices with an increment of 3 mm. The software we use for dose calculations (Varian/Variseed V7.0) can detect seeds with a resolution of half the slice increment. The chosen parameters assure an accuracy of seed localization for dosimetry purposes better than 1.5 mm in the cranial-caudal direction, which is, in our opinion, sufficient.

The study involved 23 TRUS-CT scans of 18 patients. Of these combined scans, 8 were made one day after implantation and 15 one month after implantation. These 23 scans were not selected but consecutively realized after having started this imaging approach. The number of implanted seeds ranged from 55 to 98 (average 78), the prostate volume from 22 ml to 56 ml (average 37 ml). We used Amersham/Oncura stranded seeds, model 6711 with an average source strength of 0.57 U.

2.2.2 Image fusion
To be able to fuse TRUS and CT images, the geometrical relationship between both image sets has to be defined, expressed further as image registration. There are two possible options for TRUS–CT registration. The first is the registration on the implanted seeds. This is the most logical option since we want to know the seed positions within the prostate as accurately as possible in order to determine a reliable dose distribution within the organ. However, we found that both manual matching and automatic grey value matching on seeds was cumbersome and sometimes impossible due to the bad visibility of the seeds on the TRUS scan. For this reason we judged this method to be not appropriate for clinical practice. However, as later described in sec. 2.2.3, grey value registration was useful to fine-tune the registration after applying the second option described below. Judging the results of this fine-tuning to be the optimal fusion, the amount of fine-tuning could be taken as an accuracy parameter of the second method.

The second option is a registration on the TRUS transducer itself. The internal structures of the transducer are clearly visible on the CT scan (see Fig. 2.1a) which is of great value for the registration procedure. The spherical shape of the head of the transducer appears as a dark half-sphere on the TRUS scan (see Fig. 2.1b). Because the position of the transducer is obvious on both scans but the representation very different, a straightforward grey value registration is not possible. Instead, an indirect registration in three steps has to be performed, as described below and presented schematically in Fig. 2.2.

2.2.2.1. TRUS–CT registration in an experimental set-up ($M_{\text{ref}}$)

To determine the geometrical relation of the transducer image on TRUS and CT scan, a prostate phantom was scanned consecutively on both modalities. The TRUS probe was mounted on the CT couch and exactly aligned with the lasers of the CT. The structures within the phantom and the tips of two implant needles, all visible on both modalities, were used to manually fine-tune the registration. In Fig. 2.1a a fused US-CT image of the phantom is shown after this registration. The image combines the high-density structures, like needles and transducer, from the CT scan with the low-density structures, like the prostate, from the TRUS scan.

The calibration established, expressed in a transformation matrix $M_{\text{ref}}$ (see Fig. 2.2) was used in all subsequent patient procedures.
(a) Fused US-CT image of the phantom after registration. The image combines the high-density structures, like needles and transducer, from the CT scan with the low-density structures, like the prostate, from the TRUS scan. This is the result of transformation $M_{\text{ref}}$, the first step of the registration procedure on the TRUS transducer.

(b) The spherical appearance of the TRUS transducer on the patient and phantom TRUS scan are matched by a 3D translation. This is the result of transformation $M_{\text{us}}$.
Left: TRUS image of phantom, right: TRUS image of patient.

(c) The third step of the procedure is to match the image of the transducer of the phantom CT scan and the patient CT scan by means of a grey value registration (transformation $M_{\text{CT}}$).
Left: CT patient, right: CT phantom.
Figure 2.2 Schematical view of the registration process on the transducer. The reference scans of the phantom set-up are in the left column, the patient scans in the right column. Before starting the registration process, the TRUS scans have to be transformed to Cartesian coordinates in order to display these scans in the viewer of the registration program (indicated by single solid arrows). Before image fusion can take place, the CT scans have to be resampled to the US voxel size (indicated by the dotted single arrows). The double lined arrows indicate the indirect registration method on the transducer. The dotted double arrow indicates the result of the subsequent execution of the transformations indicated by the solid double arrows. $M_{\text{ref}}$ is determined once and can be used for all subsequent registrations; $M_{\text{US}}$ and $M_{\text{CT}}$ have to be determined for each individual case.

With this procedure, the geometrical relation between the transducer image on TRUS and CT has been determined for this experimental set-up. However, the position of the transducer in each Cartesian TRUS and CT scan will be different and therefore steps 2 and 3 have to be applied for each individual patient scan. The TRUS and CT scan of this experimental set-up are later referred to as the reference scans.

2.2.2.2 Patient TRUS scan to reference TRUS scan transformation ($M_{\text{US}}$)
Coordinate transformation of the original US scan (single lined solid arrows Fig. 2.2) is necessary because the viewer of our in-house-made registration software requires image data in Cartesian coordinates and the US device (GE/Kretz Voluson 730), by default, reconstructs image data in another coordinate system. After each TRUS volume scan a cubical region of interest for image data transformation in Cartesian coordinates has to be set manually. Because the origin of this region of interest is in one of the corners of the cube, the coordinates of the transducer position will depend on the size of the region of interest. The size setting has to be performed by mouse dragging and will therefore not be exactly the same from one scan to another. This means that a 3D translation is required to match the spherical appearance of the transducer of one TRUS scan onto another. The second step in the registration procedure was to perform this translation from the patient TRUS scan to the reference TRUS scan (see Fig. 2.1b). This translation, expressed in transformation matrix $M_{US}$ (see Fig. 2.2), was performed manually, supported by orthogonal viewing of the matched scans.

2.2.2.3. Reference CT scan to patient CT scan transformation ($M_{CT}$)
In the first two steps we established the registration of any TRUS scan to the reference CT scan. In the third and final step the reference CT has to be registered to the patient CT scan. In the set-up of a patient scan, the transducer is not aligned in any way and is positioned arbitrarily within the CT space. This step can be considered as a position determination of the transducer on the patient CT scan (see Fig. 2.1c).

The distinct internal structure of the transducer makes it easy to match its image on the reference CT scan with that on the patient CT scan. For this procedure, automatic grey value registration was used based on the root mean square of voxel wise grey value differences (Eq. 2.2). This registration is represented by transformation matrix $M_{CT}$ (see Fig. 2.2).

Registration of the TRUS scan to the CT scan of the patient is achieved by the subsequent execution of the three transformations mentioned above. The transformation matrices $M_{ref}$, $M_{US}$ and $M_{CT}$ are in homogeneous coordinates. These are 4x4 matrices of the form

$$
\begin{bmatrix}
R & t \\
0 & 0 & 0 & 1
\end{bmatrix}
$$
Simultaneous TRUS-CT, incorporating expressions for both rotation and translation. \( R \) is a 3x3 matrix for 3D rotation and \( t \) is a 3x1 matrix for 3D translation. The homogeneous coordinates of any point \( p = (x, y, z, 1) \).

The resulting transformation matrix patient TRUS scan to patient CT scan \( M_{\text{pat}} \) is calculated by:

\[
M_{\text{pat}} = M_{\text{CT}} \cdot M_{\text{ref}} \cdot M_{\text{US}} \tag{2.1}
\]

The registration of any point \( p \) of the TRUS reference frame to a corresponding point \( p' \) in the CT reference frame is now determined by \( x' = M_{\text{pat}} \cdot x \).

\( M_{\text{ref}} \) was determined once and could be used for all consecutive registrations. This means that a procedure in clinical practice involves two registration steps, namely the determination of \( M_{\text{US}} \) and \( M_{\text{CT}} \).

### 2.2.3 Accuracy of registration procedure

The registration on the transducer is an indirect method and inaccuracies in each of the steps will add up in the final result. Because the same \( M_{\text{ref}} \) is used in each registration procedure, an inaccuracy in its determination will result in a systematic error in \( M_{\text{pat}} \). The uncertainties in \( M_{\text{US}} \) and \( M_{\text{CT}} \) due to the registration procedures described above are expected to be small, but an unpredictable error in \( M_{\text{CT}} \) can occur due to patient and/or transducer movement in-between TRUS and CT scan. In this case the prostate might move with respect to the transducer and the geometry will not be the same during both scans. Consequently, the position determination of the transducer on the CT scan, expressed in \( M_{\text{CT}} \), will be disturbed by an error.

The choice of the registration procedure on the TRUS transducer was made because a grey value registration on visible seeds seemed to be unsuccessful in most cases due to the poor visibility of the seeds on the TRUS images. A registration on seeds only appeared to be possible if the TRUS and CT images were close to a perfect match. If not, the optimization process usually stopped in a local minimum far away from the optimal image match. Assuming the registration on the transducer matches registration on implanted seeds very closely, an automatic grey value registration on the seeds is likely to succeed when performed after a registration on the transducer. Successful registration means that all visible seed positions on the TRUS scan obviously coincide with seed positions on the CT
scan. It can be considered as a fine-tuning of the registration and can therefore be used to estimate the accuracy of the registration on the transducer. For this purpose a registration on visible seeds was performed after the registration on the transducer for 23 cases. Having tried a number of cost functions for the automatic grey value registration on seeds, two functions appeared to be successful in most cases, namely “root mean square on voxel wise grey value differences” (RMS) and “correlation ratio” (CR) [13]:

\[
\text{RMS} = \sqrt{\frac{1}{n} \sum_{i=1}^{n} (G_{US}(i) - G_{CT}(i))^2}
\]

(2.2)

\[
\text{CR} = \frac{E_g[\text{Var}(G_{US} | G_{CT}) = g]}{\text{Var}(G_{US})}
\]

(2.3)

where \(G_{US}(i)\) and \(G_{CT}(i)\) are the grey values of voxel \(i\) in the TRUS scan and the CT scan respectively. \text{Var} denotes the variance and \(g\) any grey value in the TRUS or CT scan. \(n\) is the number of voxels and \(E_g\) the expectation over all values of \(g\). In order to determine cost function values the CT scan was resampled to voxel sizes equal to those of the TRUS scan. In a downhill simplex optimisation process [14] both cost functions were minimized. The global minimum is expected to correspond with an optimal registration on the seeds. Before starting the optimization process the TRUS scan was clipped roughly to the borders of the prostate so that surrounding tissues were excluded.

2.2.4 Dose distribution evaluation

Commercially available software (Varian, Variseed V7.0) is used to determine the seed distribution from CT slices and to calculate the dose distribution. DICOM dose files are exported from the system and imported in an in-house made viewer. The prostate contours are manually delineated on transversal TRUS images and inspected on sagittal and coronal slices. After registration of the TRUS scan to the CT scan, the dose distribution can be overlaid on orthogonal TRUS slices and evaluated in a dose volume histogram.
2.3 Results

2.3.1 Registration success rate

In Fig. 2.3, a transversal slice through the centre of the prostate is presented of one of the 23 investigated cases. Shown in this figure are, at the upper left and right side panel the CT and the TRUS image, at the lower left and right side panel the fused TRUS-CT after registration on the transducer only and after subsequent fine-tuning on the seeds. There is a small but clearly visible mismatch between seed positions on TRUS and CT after registration on the transducer only. The seed positions that are clearly visible on TRUS are indicated with the open arrows, the corresponding positions on CT with the closed arrows. A registration on the transducer is robust in the sense that after this procedure, the image of the transducer on TRUS and CT will always coincide. However, it does not mean that it results in an optimal match of the seeds. After a consecutive registration on the seeds, seed images on both modalities coincide (Fig. 2.3, lower right).

Figure 2.3 An example of a transversal image through the center of the prostate before and after registration. Shown are on the upper left and right side the CT and the TRUS image and at the lower left and right side the fused TRUS-CT after registration on the transducer and after subsequent fine-tuning on the seeds. In this case there is a small but clearly visible mismatch between seed positions on TRUS and CT after registration on the transducer only. The seed positions that are clearly visible on TRUS are indicated with the open arrows, the corresponding positions on CT with the closed arrows.
Although the image match after registration on the transducer in the case presented in Fig. 2.3 was not optimal, a consecutive grey value registration on the seeds was successful. Being close to the optimum, the optimization procedure appeared less likely to be trapped in a local minimum not corresponding with the desired result. Without pre-registration, minimization of both the CR and RMS cost function mostly resulted in a local minimum that obviously did not match TRUS and CT images. Image registration on visible seeds as a fine tuning after registration on the TRUS transducer failed in 4 out of 23 cases for RMS and for the same number of cases for the CR cost function. Failure means that no minimum could be found that obviously seemed to be an optimal registration after visual inspection. In 2 cases both RMS and CR failed. It can be expected that failure of the grey value registration relates to a bad visibility of the seeds. Although several seeds on the TRUS scan of Fig. 2.3 are clearly visible, still only about half the number of seeds are visible compared to the corresponding CT image. Seed counting on TRUS is inaccurate because their image is sometimes so faint that they can easily be mistaken for natural prostate texture and the other way around, an assumed seed can appear to be part of the natural texture, after a comparison with the corresponding CT image. There are a few factors influencing the seed visibility on TRUS. First the image quality is important. For instance, artifacts due to calcifications or bad acoustic contact between the transducer and the rectal wall can hamper detection of seeds. Then the orientation of the seeds with respect to the transducer is critical. When the echo is not reflected back to the transducer, the seed will not be detected. Also seeds placed outside the prostate gland are difficult to detect due to the low contrast difference with respect to the surrounding tissue.

<table>
<thead>
<tr>
<th>Counted seeds</th>
<th>Number of scans</th>
<th>Failure CR</th>
<th>Failure RMS</th>
<th>Failure CR and RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 5</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>6 – 10</td>
<td>8</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>&gt;10</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Table 2.1* The number of counted seeds on the TRUS scans have been binned into three groups. In the second column, the number of TRUS scans related to the range in the first column is denoted. In the columns 3 and 4 the number of failed registrations on seeds after a pre-registration on the transducer is denoted for the cost functions “Correlation Ratio” (CR) and “Root Mean Square” (RMS). In column 5 the number of cases where both CR and RMS failed is denoted.
To investigate the relation between seed visibility and registration failure on each of the TRUS scans, the spots have been counted that lit up brightly and were unmistakable images of seeds. The number of clear seeds was binned from 0 to 5, 6 to 10 and more than 10. The number of implanted seeds ranged from 55 to 98 with an average of 77. In Table 2.1 the number of failures are denoted in relation to the number of counted seeds. Although there is an obvious relation between registration failure and the number of counted seeds, still a low seed count did not necessarily result in a failure, and a high seed count did not always result in a successful registration. Nevertheless, in case of a relatively good detection rate (>10), always at least one of the cost functions appeared to be successful. In both cases where both CR and RMS failed, the number of detected seeds was 10 or less.

Despite few visible seeds on TRUS, a successful registration could always be distinguished from a failure in the investigated cases. Registrations were considered successful if, after visual inspection, all perceptible seed positions on TRUS coincided, within visual discrimination limits, with seed positions on CT. Even in cases with a low number of bright seeds, there were enough faint spots that likely seemed to be seeds when positively matched with seeds on the CT scan.

### 2.3.2 Accuracy of registration procedure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$T_{LR}$ (mm)</th>
<th>$T_{CC}$ (mm)</th>
<th>$T_{AP}$ (mm)</th>
<th>$R_{LR}$ (°)</th>
<th>$R_{CC}$ (°)</th>
<th>$R_{AP}$ (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>RMS</td>
<td>CR</td>
<td>RMS</td>
<td>CR</td>
<td>RMS</td>
<td>CR</td>
</tr>
<tr>
<td>Average</td>
<td>0.4</td>
<td>0.4</td>
<td>-0.1</td>
<td>-0.2</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>1 SD</td>
<td>2.1</td>
<td>2.0</td>
<td>1.7</td>
<td>1.5</td>
<td>0.5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Table 2.2 Average deviation and 1 SD of grey value registration on seeds with respect to registration on the TRUS transducer (n=17). Used cost functions (CF) are “Root Mean Square” (RMS) and “Correlation Ratio” (CR). $T_{LR}$, $T_{CC}$ and $T_{VD}$ are translations in left-right (LR), cranial-caudal (CC) and anterior-posterior (AP) direction and $R_{LR}$, $R_{CC}$ and $R_{VD}$ are rotations over these axes with respect to the transducer.

In Table 2.2 the average deviations of the seed registration with respect to the transducer registration are denoted for those 17 cases where both cost functions CR and RMS were successful. $T_{LR}$, $T_{CC}$, and $T_{AP}$ are translations in the left-right (LR), cranial-caudal (CC) and anterior-posterior (AP) direction and $R_{LR}$, $R_{CC}$, and
$R_{\text{AP}}$ are rotations over these axes with respect to the transducer registration. The origin of the axes was chosen in the geometrical centre of the prostate. Obviously there is no significant difference between cost functions RMS and CR. The average deviations of the seed registration with respect to the transducer registration are very small. The largest difference occurs in $R_{\text{LR}}$, the rotation around the left-right axis. It seems systematic and is likely to be due to an inaccuracy of the calibration procedure in the experimental set-up described in Sec. 2.2.2.1. Since a rotation of $1.4^\circ$ results in a maximum error of 0.5 mm in the seed position, no significant influence on the calculated dose distribution is to be expected. Nevertheless, because this error is systematic, it can be compensated for in future procedures.

![Figure 2.4](image)

Figure 2.4 Seed registration with cost function “Correlation Ratio” (CR) relative to transducer registration. The registration failed for cases 3, 5, 14, and 18. Large deviations as in cases 4 and 15 are likely to be due to patient movement in-between TRUS and CT scan.

In the diagram of Fig. 2.4 the difference between the additional registration on seeds and registration on the TRUS transducer only, is shown for each individual case. Because the differences between CR and RMS were very small, only the results with CR are shown, except when CR failed (cases 3, 5, 14, and 18). Registrations failed in cases 6 and 12 using RMS, but were successful with CR and are therefore included in the graph. It should be noted that the standard deviation (1 SD) is rather large for $T_{\text{LR}}$ and $R_{\text{CC}}$ (see Table 2.2). These high SD’s are mainly
due to the large deviations of cases 4 and 15 (see Fig. 2.4). In these cases the patient probably moved in-between the TRUS and CT scan, causing a large discrepancy between registration on transducer and registration on seeds. Leaving out these outliers, the SD in $T_{LR}$ and $R_{CC}$ will be more than halved.

2.3.3 Image fusion and dose distribution evaluation

After registration, the fused US-CT images were examined on our in house made viewer. Fig. 2.5 shows an example of a transversal, a coronal and a sagittal fused image of the same patient. The high-density structures bone, transducer, bladder balloon, and seeds originate from the CT scan, the low-density contrast of the prostate originates from the TRUS scan. In this case, a relatively large number of seeds were placed just outside the prostate gland (Fig. 2.5a). The visibility of these seeds on TRUS images is usually worse than those placed inside the gland because of lower contrast differences between seeds and surrounding tissue. After the US-CT fusion, prostate contouring and dose distribution calculation, the dose distribution in the prostate volume is determined and visualized in orthogonal planes or in a dose-volume histogram. Fig. 2.6 shows an example of dose distribution evaluation in orthogonal planes. The prostate was delineated on transversal images with 3 mm slice spacing, which results in a slightly milled contour on the coronal and sagittal image.
Figure 2.5 Fused US-CT image of a patient one day after implantation of I-125 seeds. High-density structures seeds, transducer, foley balloon, and bones originate from the CT scan, low-density structures as the prostate originate from the TRUS scan.

a) Transversal image through the centre of the prostate. A=anterior, R=right. With arrows, points of interest are indicated. The artefact on the right side is caused by some air enclosed between transducer and rectal wall. A relative large number of seeds are placed just outside the prostate capsule, which makes these seeds particularly difficult to distinguish on TRUS images.

b) Coronal image through the centre of the prostate.

c) Sagittal image through the centre of the prostate. The visible seeds are stranded in an array of 4.
Figure 2.6 Dose distribution evaluation in a transversal, coronal, and sagittal plane. The white line is the contour of the prostate, the grey area represents a dose range between 80% and 120% of the reference dose. The dose in the areas enclosed by the grey areas is higher than 120%, the dose in the areas outside the grey areas is less than 80% of the reference dose.
2.4 Discussion

Although CT is the image modality most commonly used for the dose distribution determination after implantation of the prostate with I-125 seeds, there is no consensus on whether this modality is a reliable tool for this purpose [7,9-11,15]. However, it is inevitable that dose distributions, meant to be optimally conformal with the shape and volume of the prostate, will have dosimetric characteristics that depend largely on the accuracy of delineation. Due to poor contrast of the prostate with respect to surrounding tissues and the streaking artifacts of the seeds on CT images the accuracy of delineation is expected to be low. An important feature of post-implant dose distribution evaluation with combined TRUS/CT imaging is that the prostate can be delineated on TRUS images, while the implant can be automatically reconstructed from CT images. Delineation of the prostate is expected to be more accurate on TRUS images than on CT images and consistency is achieved with the implantation planning where the prostate is also delineated on TRUS images. The fact that the TRUS transducer is in situ during TRUS and CT scan, guarantees that the geometry of the prostate will not change due to removal or insertion of the transducer in-between scans. Moreover, the presence of the transducer during both scan modalities facilitates image registration.

Straightforward grey value registration of TRUS and CT scans appeared to be problematic. The mutual information on both scans, consisting of some seeds with a rather faint appearance on TRUS, was too little. The result was always an obvious mismatch, the optimization process somewhere trapped in a local minimum far away from an optimal registration. The registration on the transducer was more successful, in the sense that it always resulted somewhere close to a coincidence of matching seeds on both scans. However, because the transducer has a different appearance on CT and TRUS, an indirect method had to be used to register both scans. Visual inspection learned that the seeds not always coincided exactly after a registration on the transducer (see Fig. 2.3). Although a first registration on the transducer left small discrepancies in the position of visible seeds, its result was a sufficient start condition for a final match on grey values, resulting in an exact coincidence of visible seeds. Obviously because the optimum was close, a grey value registration after registration on the transducer mostly resulted in an exact coincidence of matching seeds on both scans. Consequently,
Simultaneous TRUS-CT

we could use this grey value fine tuning to investigate the accuracy of the registration procedure on the transducer. Out of 23 cases this grey value registration failed twice for both investigated cost functions. The reason was likely to be the low number of seeds clearly visible on the TRUS scans (see Table 2.1). In some cases, however, a relatively bad visibility of the seeds on the TRUS scan resulted in a successful seed registration while it also happened that a relatively good visibility resulted in a failure using one of the cost functions. A possible explanation could be the absents, or on the other hand the presence, of other apparent minima at some distance away from the optimal seed match, to where the optimization process could be diverted to.

A comparison of the 17 cases for which both cost functions were successful after pre-registration, revealed that the registration on the TRUS transducer differed, on average, very little from the registration on visible seeds (Table 2.2). Nevertheless, inaccurate results in case of transducer registration can occur (see outliers, Fig. 2.4), probably due to patient and/or transducer movement in-between the CT scan and the TRUS scan. Therefore the time in-between the TRUS and the CT scan has to be short and patients have to be instructed not to move during the procedure. Since increased attention was paid to these aspects, clear outliers in case of transducer registration were not observed (see Fig. 2.4, case 16 and further). The small remaining inaccuracies are likely to be due to the relatively small size of the transducer and the fact that a pixel size registration error can result in an error of several pixels at the location of the seeds a few cm away from the transducer. Visual inspection is recommended after a registration on the transducer and subsequently, if possible, a grey value registration on seeds should be performed to fine-tune.

The use of $T_2$-weighed MRI for post-implant evaluations has been proposed by McLaughlin et al [7]. They state that this modality provides superior prostate definition compared to CT and other MRI sequences. Like TRUS imaging, however, MRI $T_2$ offers very poor visualization of implanted seeds. A drawback is that a CT scan is required to reconstruct the geometry of the implant. Consequently, the TRUS or MRI scan has to be registered to the CT scan in order to determine the dose distribution in the prostate. An advantage of the poor visibility of seeds is that the contrast between prostate and surrounding tissues will
not be perturbed by the distinct contrasts of seeds, as is clearly the case on CT images.

To our knowledge, no studies have been published so far, comparing delineated volumes of the prostate on US images and $T_2$-weighted MRI after implantation. This topic will be the subject of investigation in our department in the near future. There are a number of practical advantages of TRUS over MRI that make it worthwhile to investigate whether TRUS is an acceptable alternative for $MRI-T_2$ for post-implant dosimetry. TRUS is less costly and a US device is transportable and easy to use at any time. TRUS can be performed in the CT room on the CT couch, making consecutive or simultaneous TRUS-CT imaging possible. Moreover, TRUS imaging is also used during pre-planning and therefore systematic differences between image modalities will be avoided. A disadvantage of TRUS is that calcifications in the prostate can disturb visibility of the prostate outline.

Recently, Reynier et al. published preliminary results of MRI/TRUS data fusion for improved implantation planning of the prostate [16]. They stated that MRI offers better visualization of the apex and base of the prostate. However, they used transversal, sagittal, and coronal slices for the segmentation of the prostate on MRI and just transversal slices for the segmentation on TRUS. They used a conventional 2D TRUS transducer and a mechanical stepper. A 3D TRUS in combination with a 3D viewer however, facilitates visualization of the prostate in orthogonal planes. Our experience is that the apex and the base of the prostate are better visible on coronal and sagittal slices than on transversal slices. For an optimal comparison of MRI and TRUS, equivalent visualization and segmentation facilities should be used. A comprehensive comparison of post-implant $T_2$-weighted MRI and 3D-TRUS has to give detailed information on the agreements and differences between these modalities in terms of prostate delineation after implantation.

Simultaneous TRUS/CT imaging, as presented in this paper, takes place in the CT room one day after implantation of the seeds, at earliest. When these images reveal a sub-optimal implant, a correction might be desirable. A correction, however, would require a second session in the operating room, which is demanding for the patient and medical staff. Replacing the imaging procedure to
the operating room would get us around this problem. Since there is no CT scanner in the operating room we will investigate the possibility of substituting CT by multi-angle fluoroscopy with a C-arm device. A number of groups have developed methods for the reconstruction of seed implants and/or dynamic dosimetry using multi-angle fluoroscopy images [1,17,18]. It is essential to find a fast and practical method that complies with the tight time schedules and the limited space of an operation room. A fast 3D TRUS scanner is likely to be useful. Multi-angle fluoroscopy might be more problematic, considering the limited space to rotate a C-arm around the patient and requires further investigation. Moreover, the inherent geometrical distortions of an image intensifier based C-arm will cause additional inaccuracies. However, the advent of C-arm systems with a flat-panel detector might solve this latter problem in the near future.

2.5 Conclusion

A 3D TRUS transducer is a new and useful tool allowing fast and easy visualization of the prostate without mechanical movement of the transducer in the rectum. A 3D TRUS scan made simultaneous with a CT scan is practically feasible and requires only 1 to 3 minutes scan time. A combined TRUS-CT scan offers both an optimal prostate and seed visibility. TRUS and CT images can be fused after registration. Because automatic grey value registration on the seeds was not successful due to the poor visibility of the seeds on the TRUS scans we developed a method to register on the transducer. Starting in a condition rather close to an optimal seed match, a grey value registration on the seeds appeared to be successful after having realized the transducer registration in 21 out of 23 cases.

A disadvantage of registration on the transducer is that it is an indirect method requiring a number of consecutive transformations. Although the average accuracy of this method over 23 cases was better than 0.5 mm/1.5°, relatively large inaccuracies occurred in a few individual cases probably due to movement of the patient in-between TRUS and CT scan. Optimally, after registration on the transducer, a grey value registration on seeds should be performed to fine tune. Having performed simultaneous TRUS-CT for 23 cases, we can conclude this to be a feasible method and that registration can be performed with adequate accuracy, provided a few practical conditions, like limited patient movement in-between
scans, are met. This method is likely to be of great value for post-implant dose distribution evaluations.
References

Chapter 3

The influence of geometrical changes on the dose distribution after I-125 seed implantation of the prostate

Marcel J. Steggerda, Luc M.F. Moonen, Henk G. van der Poel, Christoph J. Schneider.

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Abstract

Purpose
After prostate implantation, dose calculation is usually based on a single imaging session, assuming no geometrical changes occur during the months of dose accumulation. In this study the effect of changes in anatomy and implant geometry on the dose distribution was investigated.

Materials and methods
One day, one month and 3½ months after seed implantation, a combined TRUS-CT scan was made of thirteen patients. Based on these scans changes in dose rate distribution were determined in prostate, urethra and bladder and a 'geometry corrected' dose distribution was estimated.

Results
When based on the day-1 scan, parameters representing high dose volumes in prostate and urethra were largely underestimated: V150 of the prostate 18±10 % and V120 of the urethra 47±32 %. The dose to a 2 cm³ hotspot in the bladder wall (D2cc), however, was overestimated by 31±35 %. Parameters based on scans one month post-implant or later were all within ±5 % of geometry corrected values.

Conclusion
Values meant to indicate the adequacy of dose coverage of the prostate, V100 and D90, were not influenced by geometrical changes and independent of the post-implant scan date. Other parameters representing high dose volumes changed strongly within the first month after implantation.
3.1 Introduction

Implantation of the prostate with I-125 seeds is a well-established treatment for early-stage prostate cancer. This technique has some attractive characteristics: implanted seeds are, at least during short organ motion cycles, fixed to the prostate. This avoids moving of the prostate with respect to the 3D-dose distribution, which is a challenging problem in external beam RT. After the implantation of the seeds, dosimetric characteristics are determined indicating the adequacy of the dose coverage of the prostate and the dose burden to adjacent organs at risk. For that purpose a CT, or other image modality scan, is made at a certain time span after implantation. Commercially available software is available to determine the dose distribution based on the images of the CT scan. Because these implants are permanent, the dose is determined by integrating the dose rate from the time of implantation to infinity, taking into account the physical decay of the sources only. Of course, this method assumes that the geometry of implant and anatomy established at the date of scan is invariant over time.

This time invariance, however, might be questionable, since the prostate swells during implantation due to oedema and bleeding which will gradually resolve during the following weeks [1-4]. Obviously, the position of the seeds, and consequently the dose rate distribution, will change during this process. Therefore, a CT scan is often postponed to about 1 month after implantation assuming that the prostate volume will change very little afterwards. Although this might be a result of good physical intuition or even based on a mathematical model [5], it is no proof that the dose cumulated over time in the prostate and adjacent anatomical structures will be accurately estimated from the dose rate distribution based on images at this time.

On the other hand, there are some advantages in determining the dose distribution shortly after the implantation instead of waiting a month. With the urinary catheter still in situ, the urethra will be clearly visible on the CT-scan and the dose distribution in the organ can be determined. Feedback to the radiation oncologist or urologist is possible concerning the quality of the implant, while they can still remember the specific implantation procedure. Besides, the patient does not have to return to the hospital for an additional imaging session. The purpose of this study was to investigate the effect of geometrical changes of implant and prostate on the dose distribution.
3.2 Materials and methods

For this study we used fused images of 13 patients, i.e. simultaneously acquired CT and 3D transrectal ultrasound (TRUS) scans. The method and technical specifications have been previously described in detail [6]. Using the favourable characteristics of each image modality, the TRUS images were used for the delineation of the prostate, the CT images for the delineation of the bladder wall and the urethra and for the reconstruction of the seeds. The transversal slice increment and thickness of TRUS and CT scans were 3 mm. TRUS-CT scans were acquired 1 day, 1 month and 3½ month after implantation, referred to as Scan-1, Scan-2 and Scan-3, respectively. In Table 3.1 the average and standard deviation (1SD) of the number of days between implantation and scanning are denoted. Oncura stranded seeds model 6711 were used with a source strength of $0.57 \pm 0.02 \mu\text{Gy.h}^{-1}.\text{m}^{2}$ at the day of implantation. For the reconstruction of the seeds and the calculation of the dose distribution we used Varian-Variseed software version V7.1. In house made software was applied to delineate organs and to calculate dose-volume histograms (DVHs). All delineations were performed by the same experienced observer.

<table>
<thead>
<tr>
<th></th>
<th>Scan-1</th>
<th></th>
<th>Scan-2</th>
<th></th>
<th>Scan-3</th>
<th></th>
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<tr>
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<td>1SD</td>
</tr>
<tr>
<td>Days after implant</td>
<td>1</td>
<td>0</td>
<td>30.8</td>
<td>2.5</td>
<td>102.6</td>
<td>9.5</td>
</tr>
<tr>
<td>Number of seeds</td>
<td>80.8</td>
<td>10.0</td>
<td>79.6</td>
<td>10.0</td>
<td>77.8</td>
<td>10.4</td>
</tr>
<tr>
<td>Prostate volume (cm$^3$)</td>
<td>39.3</td>
<td>9.6</td>
<td>36.6</td>
<td>9.6</td>
<td>34.9</td>
<td>10.3</td>
</tr>
</tbody>
</table>

*Table 3.1* Characteristics of post-implant scans.

3.2.1 Imaging of the urethra

DVHs of the prostate are expected to relate to tumour control, those of the urethra and bladder wall to the frequently occurring post-implant urinary morbidity. Prostate and bladder wall were delineated on each post-implant scan, the urethra on Scan-1 only and this delineation was projected into Scan-2 and Scan-3. This approach was chosen because the urethra is only visible on CT or TRUS images with contrast filled catheter, as was the case during Scan-1. It was considered to be too demanding for the patients to have a urinary catheter placed before each scan. In order to estimate the dose burden to the urethra due to the dose distribution based on Scan-2 and Scan-3, Scan-1 with urethra delineation was registered to the
second and third scan. The seed positions on the second and third scan were found to have slightly moved towards the centre of implant with respect to the first scan, so no exact match was achievable. With chamfer matching on the seeds, however, the distribution pattern of the seeds, and therewith the central part of the implant could be matched well from one scan to the other. It was assumed that the position of the urethra was co-registered with the seeds.

3.2.2 Determination of dose distribution

Dose rate changes in time are due to the physical decay of I-125 and to geometrical changes of the implant. The dose rate at time interval $t$ can be determined by:

$$D_t = D_0 \cdot e^{-\mu t} \cdot f_{geo_t}$$  \hspace{1cm} (3.1)

Where $D_t$ and $D_0$ are dose rates at day $t$ and day 0 after implantation, $\mu$ is the physical decay factor of I-125 and $f_{geo_t}$ is a geometrical correction factor at time $t$.

The total accumulated dose over time was approximated in the following manner: After each scan the dose rate distribution at the day of the scan was determined for prostate, urethra and bladder wall and represented in cumulative dose rate-volume histograms (DRVHs). In steps of 10% volume increment, dose rate cut-off values were plotted against the number of days after implantation (1 day, 1 month and 3½ month) and a trend line was fitted through these points. The fitted functions were integrated from the day of implantation to the day Scan-3 was made (first term Eq. 3.2). It was assumed that from Scan-3 on, no further geometrical changes occurred that could significantly influence the total integrated dose and the dose rate was integrated up to infinity, taking into account the physical decay of I-125 only (second term Eq. 3.2). I.e., the dose $D_V$ to a volume $V$ of the cumulative dose-volume histogram taking into account geometry changes in time was calculated according to the formula

$$D_V = \int_0^{sc3} D_{Vt} \, dt + \int_{sc3}^{\infty} e^{-\mu t} \, dt$$  \hspace{1cm} (3.2)
where $\hat{D}_{V_t}$ is the fitted dose rate to volume $V$ at time $t$ and in fact an approximation of the dose rate according to Eq. 3.1. $\mu$ is the decay factor of I-125. $sc3$ is the time at which Scan-3 was made. Values determined with this formula will further be referred to as “geometry corrected values”.

3.2.3 Implant volume versus prostate volume

Waterman et al. [4] used the decrease in implant volume to quantify the volume reduction of the prostate. We verified the validity of this method by independent determination of prostate and implant volume reduction. The volume of the prostate was determined by delineation on TRUS images as described above. Changes in the volume of the implant were estimated by changes in the average length of all vectors spanning from the centre of the implant to the seeds. The implant volume ratio at day t2 and day t1 after implantation was therewith approximated by

$$\frac{V_{t2}}{V_{t1}} = \left(\frac{l_{t2}}{l_{t1}}\right)^3$$

where $l_{t1}$ and $l_{t2}$ are the average vector lengths from the centre of the implant to the seeds after time period $t_1$ and $t_2$ respectively.

We also investigated the relative shift of the implant in relation to the prostate gland by comparing the geometrical centres of implant and prostate at each of the three TRUS-CT scans.

3.3 Results

3.3.1 DVHs based on scans at different post-implant time intervals

From the anatomy and implant geometry based on a single scan, i.e. Scan-1, Scan-2 and Scan-3, DVHs were calculated by integration from the day of implantation to infinity, assuming geometrical invariance over time and applying no normalization of volume. A typical example depicting the different prostate DVHs, for one out of the thirteen cases, is presented in Fig. 3.1a. Clearly, the calculated DVH of the prostate strongly differs with the scan on which it is based due to decreases in prostate volume and increases in the volume receiving a high dose. The differences between the DVHs based on Scan-2 compared to Scan-1 are larger than those based on Scan-3 compared to Scan-2.
Influence of geometrical changes

Fig. 3.1 A typical example of dose / dose rate distribution of the prostate based on scans made 1 day (Scan-1), 1 month (Scan-2) and 3½ months (Scan-3) after implantation. a) Absolute DVHs of the prostate based on different scans made. With time the volume reduces due to oedema resolution while at the same time high dosed areas become larger. b) DRVHs are used to fit physical decay as well as geometry related dose rate distribution changes in time. Indicated with the dotted lines are dose rate values used for the fit of $D_{90_i}$.

3.3.2 Integration of dose rates
For the calculation of the dose distribution, taking into account geometrical changes over time, we used DRVHs (Fig. 3.1b). Volumes were normalized to the prostate volume of each scan. The dose rate values at a certain volume of each of the 3 DRVHs were plotted against the post-implant time interval and a best fit was made through these points in order to determine $D_{V_i}$ (Eq. 3.2).
3.3.3 DVHs based on a single scan compared to DVHs taking into account geometrical changes
Fig. 3.2 A typical example of dose distribution changes due to post-implant geometrical changes. Cumulative DVHs based on scans 1-3 are displayed as well as integrated values in time including geometrical changes (dark squares). a) DVHs of the prostate: increasing high dosed volume with time, stable volume value at 100% dose (V100) and stable dose at 90% volume (D90). The geometry corrected values, approximate curve of Scan-2 very closely. b) DVHs of the urethra: increasing high dose values with time. As with the prostate, the geometry corrected values approximate the curve of Scan-2 very closely. c) DVHs of the bladder wall: decreasing dose values with time. Again a good approximation of the geometry corrected values by the Scan-2 curve.

In Fig. 3.2a the DVHs of Fig. 3.1a are transformed to relative DVHs. Volumes were normalized to the prostate volume of each scan. The dose values were normalized to the prescribed dose, being 145 Gy. Additionally, at 10% volume intervals, $D_V$ values were calculated using Eq. 3.2, taking into account changes in geometry over time (square markers). For the low dose range up to 100% of the prescribed dose, little difference was found between the DVHs based on Scans 1-3, whereas these differed largely for high dose values. Very similar were the dose distribution changes in the urethra in this typical case (Fig. 3.2b); large increase of high dose between Scan-1 and Scan-2, small increase after Scan-2. In Fig. 3.2c DVHs of the bladder wall are shown. The volumes in this graph are given absolute (cm$^3$) because Hoogeman et al determined that absolute DVHs are more invariant under bladder filling than relative DVHs in case of partial irradiation of the bladder [7]. Contrary to the prostate and the urethra the estimated dose to the bladder wall decreased at Scan-2 compared to Scan-1, but again the differences between Scan-3 and Scan-2 were small. The geometry corrected values were not far off the values based on Scan-2 and Scan-3.

3.3.4 Time dependence of dose-volume parameters
For the quantification of dose distribution changes we took some generally used dose-volume characteristics, V100 and D90, and in addition some points of the DVHs of prostate, urethra and bladder that were expected to be relevant in relation to post-implant urinary morbidity. In Table 3.2 the investigated parameters are described, in Table 3.3 the results of the thirteen investigated cases are summarized.

The ratios of parameters derived from the geometry of Scan-1 and the geometry corrected values (Scan-1/Geom), deviated considerably from unity except for the D90 and V100 of the prostate. The average ratio for V120-ur was only 0.53. This high dose value of the DVH can change largely in time as illustrated in Fig. 3.2b.
None of the values based on Scan-2 or Scan-3 deviated more than 5% from the geometry corrected values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>V100-pr</td>
<td>Relative prostate volume receiving at least the reference dose (145 Gy)</td>
</tr>
<tr>
<td>D90-pr</td>
<td>Lowest relative dose value within the 90% of the prostate with the highest dose</td>
</tr>
<tr>
<td>V150-pr</td>
<td>Relative prostate volume receiving at least 1.5 times the reference dose</td>
</tr>
<tr>
<td>V120-ur</td>
<td>Relative urethra volume receiving at least 1.2 times the reference dose</td>
</tr>
<tr>
<td>D50-ur</td>
<td>Lowest relative dose value within the 50% of the urethra with the highest dose</td>
</tr>
<tr>
<td>D2cc-bl</td>
<td>Lowest relative dose value within the 2 cm³ of bladder wall with the highest dose</td>
</tr>
</tbody>
</table>

Table 3.2 Description of investigated dose-volume parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>1SD</th>
<th>Scan-1/Geom mean</th>
<th>Scan-2/Geom mean</th>
<th>Scan-3/Geom mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>V100-pr</td>
<td>91</td>
<td>3</td>
<td>1.01</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>D90-pr</td>
<td>103</td>
<td>9</td>
<td>1.01</td>
<td>0.98</td>
<td>1.00</td>
</tr>
<tr>
<td>V150-pr</td>
<td>63</td>
<td>8</td>
<td>0.82</td>
<td>0.99</td>
<td>1.02</td>
</tr>
<tr>
<td>V120-ur</td>
<td>62</td>
<td>12</td>
<td>0.53</td>
<td>0.96</td>
<td>1.02</td>
</tr>
<tr>
<td>D50-ur</td>
<td>135</td>
<td>18</td>
<td>0.87</td>
<td>0.98</td>
<td>1.03</td>
</tr>
<tr>
<td>D2cc-bl</td>
<td>58</td>
<td>12</td>
<td>1.31</td>
<td>0.98</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Table 3.3 Dose-volume characteristics.  
*Abbreviations: Geom = geometry corrected value in % of reference dose, based on Eq. 3.2  
  a ratio significantly different from unity (p<0.05)  
  b ratio highly significantly different from unity (p<0.0001)  

### 3.3.5 Physical characteristics of changes in prostate and implant geometry

In order to express volumetric changes, ratios of volumes were calculated. In Table 3.4 volumes of structures based on respectively Scan-2 and Scan-3 compared to Scan-1 are denoted along with the ratio of the prostate volume prior to implantation and during Scan-1. The implant volume ratios were calculated applying Eq. 3.3. All denoted ratios significantly differ from unity (p<0.05). The average reduction of the implant volume was much larger than the reduction in prostate volume. These differences were highly significant (p<0.0001). The prostate volumes during Scan-2 and Scans-3 were not significantly different from the pre-implantation volume.

The shrinkage of the implant resulted in a moderate reduction of the volume contained within the reference isodose surface (145 Gy) comparing dose distributions based on the geometry of Scan-2 and Scan-3 with that of Scan-1.
Contrarily, the high dose volumes within the 220 Gy and 290 Gy surfaces increased with time. The shrinkage of the implant volumes was anisotropical i.e. largest in cranio-caudal direction and smallest in left-right direction with respect to the dimensions during Scan-1. In Table 3.5 the mean values and standard deviations of 13 cases are denoted as well as (two tailed) t-test p values indicating the significance of the deviations from zero. Also in Table 3.5 the average shifts of the geometrical centre of the implant with respect to the prostate are denoted. For each scan the distance between the geometrical centres of the implant and the delineated prostate contours was measured in 3 directions and the change in this distance from one scan to another determined the shift. Positive values are shifts to the right, to posterior or to caudal.

<table>
<thead>
<tr>
<th>Structure</th>
<th>pre-implant/Scan1 mean</th>
<th>1SD</th>
<th>Scan2/Scan1 mean</th>
<th>1SD</th>
<th>Scan3/Scan1 mean</th>
<th>1SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>0.93</td>
<td>0.11</td>
<td>0.93</td>
<td>0.07</td>
<td>0.88</td>
<td>0.10</td>
</tr>
<tr>
<td>Implant</td>
<td>0.80</td>
<td>0.06</td>
<td>0.73</td>
<td>0.06</td>
<td>0.90</td>
<td>0.03</td>
</tr>
<tr>
<td>145 Gy</td>
<td>0.94</td>
<td>0.03</td>
<td>0.90</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>220 Gy</td>
<td>1.10</td>
<td>0.11</td>
<td>1.09</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>290 Gy</td>
<td>1.31</td>
<td>0.17</td>
<td>1.39</td>
<td>0.28</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.4 Volumes based on different scans compared to Scan-1.

<table>
<thead>
<tr>
<th>Motion Direction</th>
<th>Scan-2 mean</th>
<th>1SD</th>
<th>p</th>
<th>Scan-3 mean</th>
<th>1SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrinkage left - right</td>
<td>0.5</td>
<td>0.6</td>
<td>0.009</td>
<td>0.5</td>
<td>0.4</td>
<td>0.001</td>
</tr>
<tr>
<td>anterior - posterior</td>
<td>0.9</td>
<td>0.6</td>
<td>0.0002</td>
<td>1.2</td>
<td>0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>cranio - caudal</td>
<td>1.0</td>
<td>0.6</td>
<td>&lt;0.0001</td>
<td>1.8</td>
<td>0.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Shift left - right</td>
<td>0.0</td>
<td>0.9</td>
<td>0.9</td>
<td>0.2</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>anterior - posterior</td>
<td>1.0</td>
<td>0.9</td>
<td>0.001</td>
<td>0.3</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>cranio - caudal</td>
<td>0.6</td>
<td>2.1</td>
<td>0.3</td>
<td>2.2</td>
<td>1.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 3.5 Implant shrinkage and shift relative to Scan-1 (mm).

3.4 Discussion

3.4.1 Influence of post-implant scan date on dose-volume parameters of the prostate

Post-implant evaluations of permanent seed implants in the prostate using DVHs are common practice in many institutions. They are used to give the oncologist an
indication of the geometrical quality of individual implants or of an applied technique [8,9] and certain values from DVHs are used to investigate relations between dose distribution and clinical outcome [10]. Dose distributions with high V100 or D90 of the prostate are considered to be good implants. In our study neither V100 nor D90 did depend on the time span after implantation at which the TRUS-CT scan was acquired. This agrees well with findings of a recent publication by Taussky et al. [3] who used a MRI-CT instead of a TRUS-CT image combination and found only minor changes in these parameters at day 8 and day 30 compared to the day of implantation. The fact that the reduction of the prostate volume in time practically equalled the reduction of the volume contained within the reference isodose surface (145 Gy, Table 3.4) might explain the invariability in V100 and D90. On the other hand, a recent study by McLaughlin et al. [11] showed large individual changes in V100 and D90 for several cases, comparing MRI/CT scans 14 days after implantation with those made directly after implantation.

The observed increase of V150-pr with time was caused by an increased 150% isodose volume (approximately the 220 Gy of Table 3.4) within a reduced prostate volume. DVHs bases on a scan one month after implantation appeared to be a very close approximation of the DVHs taking into account geometry changes in time.

3.4.2 Dose to urinary system
A high dose to the urethra is expected to increase the risk of urinary morbidity. Consequently, it is advised to prevent this as much as possible. Although different groups reported to have found no or limited correlation between these complications and urethra dose [12-15], time trends in dose-volume parameters might be of some influence on investigated relations. The estimated dose to the urethra increases with time due to the contraction of the seeds towards the centre of the prostate where the urethra is located, as was also reported by Waterman et al. [16]. Analogous to the V150-pr, dosimetry based on a scan one day after implantation underestimates D50-ur, and largely underestimates V120-ur. Preliminary results of our own data show a correlation between urinary morbidity and the dose in the bladder wall. These findings and suggestions of Williams et al. in this direction [17] motivate recording of the dose to this organ as material for final conclusions at a later stage. From Fig. 3.2c and Table 3.3 it is obvious that the dose to the bladder wall decreases rather sharply during the first month after
implantation. This phenomenon could be the result of shrinkage and shift of the implant in caudal direction (Table 3.5). In addition the variable bladder filling will influence the dose distribution in the organ. However, the small volume in the neck of the bladder receiving a high dose (D2cc), is expected not to vary much with variable bladder filling.

3.4.3 Expected inaccuracies in geometry corrected dose-volume parameters
The calculation of the dose to a certain volume D_V of the “geometry corrected” DVH using Eq. 3.2 was based on two assumptions. Firstly it was assumed that the relative volume V contained the same organ cells during each of the scans. In other words, the volume cut-offs of the DRVHs (for example Fig. 3.1b ) contained exactly the same cells in each of the 3 curves. This might not always have been true because the implant shrinks and slightly drifts (see Table 3.5). As a consequence, especially the high dose sleeves around the seeds, might not always include the same cells. Strictly, dose not distributed in the exactly the same cells, cannot be accumulated. To cumulate dose correctly we have to register on organ cell level, which is, however, not possible. Therefore we used a simplified method of integrating dose rates to volumes of cumulative DRVHs, i.e. applying the above mentioned assumption. In case of large volume cut-offs like D90 the inaccuracies due to this assumption are expected to be negligible. In case of small volume cut-offs, such as D2cc, uncertainties are estimated to be a few percent. The second important assumption was that after Scan-3 the cumulated dose distribution was not influenced by geometrical changes. Between Scan-2 and Scan-3 DVH-values changed relatively little and it is reasonable to assume that the changes would be even less after Scan-3. Moreover, 3½ month after implantation as Scan-3 was made, about 70% of the dose was already deposited and remaining small changes in geometry will only affect 30% of the total deposited dose. Inaccuracies due to this second assumption were expected to be negligible.

3.4.4 Physical aspects of geometrical changes
The reduction of the implant volume after implantation was more than twice as high compared to the reduction of the prostate volume. This remarkable outcome could partially be explained by a non-uniform distribution of oedema over the prostate volume. Prostate swelling is due to oedema caused by needle insertions. If oedema distribute predominantly around the seeds, their resolution will have a
relatively large effect on the seed positions. As demonstrated in Table 3.5 the implant shrinkage was largest in cranio-caudal direction. After 1 month we determined an average shrinkage of 1 mm in this direction despite the fact that the encapsulating material of the strands was expected not to be dissolved yet. It seems unlikely that this reduction was caused by oedema resolution. Possibly seed strands extending far cranially were selectively forced in caudal direction, which explains the positive correlation between shrinkage and shift of the implant in cranio-caudal direction (one tailed p<0.05). Also loss of cranially placed (loose) seeds could be partially responsible for this phenomenon, although we did not find a significant correlation between caudal shift and seed loss.

The assumption by Waterman et al. [4] that the reduction of the implant volume equals the reduction of the prostate volume is not supported by the findings of this study. Consequently dynamic models based on the Waterman model [18,19] should be applied with care. However, the fact that we mainly used stranded seeds instead of loose seeds could be partially responsible for the discrepancy between prostate and implant shrinkage.

Apart from the fact that implants shrink they also shift with respect to the prostate. There was a small cranio-caudal shift (not significant) between Scan-2 and Scan-1 and a large (2.2 mm), highly significant, shift in this direction between Scan-3 and Scan1. A shift in cranio-caudal direction has also been reported by McLaughlin et al. [11]. They suggested that this shift is caused by contraction of the Levator Ani.

The rather modest reduction of the prostate volume compared to other studies [1,4,18] can possibly be explained by the fact that we delineated the prostate on TRUS images where others used CT. As mentioned by McLaughlin et al. [11], CT contouring is mostly “circling the seeds”. If so, volume changes will indeed be overestimated using CT images. Earlier McLaughlin et al. suggested that the degree of prostate swelling could be related to the image modality used [20]. They found modest swelling using MRI T2-weighted scans. Nevertheless Taussky et al. [3] found an average reduction of 25% at day 30 compared to day of implantation, using MRI T2-weighted images, which is much more than we found on US images between 1 month and 1 day after implantation. It should be noted, however, that their first scan was made at the day of implantation, where our first scan was made 1 day after implantation, which could at least partially explain the discrepancy. The prostate volume 3½ month after implantation was on average 5% smaller than the pre-implantation volume. Although the difference was not significant, a reduction
Influence of geometrical changes

below the pre-implantation volume could possibly be a result of radiation induced stromal fibrosis of the prostate tissue [21].

3.5 Conclusions

The unique features of simultaneously acquired 3D-TRUS and CT scans allowed accurate determination of volumetric and dosimetric changes over time of dose accumulation. For the cases investigated, the average shrinkage of seed implants in time was non-isotropical and largely exceeded the volume reduction of the prostate. Nevertheless, values indicating the adequacy of dose coverage of the prostate, such as V100 and D90 did not depend on the post-implantation date of the scan supplying the images for dosimetry. On the other hand, values of parameters possibly related to urinary morbidity, such as V120 of the urethra and D2cc of the bladder, strongly changed within the first month after implantation. This should be born in mind when reporting urinary morbidity in relation to dose-volume parameters. In general, DVHs based on scans made at least 1 month after implantation closely approximated DVHs including geometrical changes in time, regarding urethra, bladder as well as prostate.
References


Chapter 4

Predicting urinary morbidity after brachytherapy of localized prostate cancer

Marcel J. Steggerda, Luc M.F. Moonen, Henk G. van der Poel

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Abstract

Context
After implantation of the prostate with I-125 or Pd-103 seeds, the majority of patients develop lower urinary tract symptoms (LUTS). There is not yet general agreement among practitioners on how to predict or prevent these symptoms.

Objective
To examine agreements and disagreements in relevant publications regarding severity, resolution and methods to predict and reduce LUTS after brachytherapy of the prostate.

Evidence acquisition
The database of the U.S. National Library of Medicine (PubMed) was searched for the terms "quality of life" and "urinary morbidity" in combination with either "prostate brachtherapy" or "prostate seed implants". Also relevant references of retrieved publications were reviewed. Papers reporting severity and resolution of post-implant urinary symptoms as well as papers analysing correlations between these symptoms and physical characteristics of the brachytherapy treatment were selected for the study.

Evidence synthesis
Post-implant LUTS vary from increased urinary voiding frequency to acute urinary retention (AUR) and are usually temporal phenomena. Prophylactic use of α-blockers significantly reduces the severity and resolution time of LUTS. There is reasonable agreement on the relation between prostate size and AUR. For other obstructive and irritative urinary symptoms there is less agreement about the predictors. The possible relation between dose to the urethra and LUTS is often investigated but there is no unambiguous evidence that there is any relation between both. Recently, high dose to small volumes of the bladder wall was identified as a predictor for LUTS. In a limited number of cases (1%-5%) persisting extreme symptoms have to be managed by means of a trans-urethral resection of the prostate (TURP). TURP procedures after brachytherapy, however, carry significant risk of inducing urinary incontinence.

Conclusions
Prophylactic use of α-blockers is required to reduce post-implant LUTS. Patients with large prostates carry a higher risk to develop AUR. Access needle puncturing and seed placements in the bladder wall have to be avoided.
4.1 Introduction

Brachytherapy of the prostate with low energy γ-emitting Iodine-125 or Paladium-103 seeds has been a fast growing treatment modality for localized prostate cancer the last 10 to 20 years in the USA as well as in Europe. Its popularity is mainly due to the fast, minimal invasive and relatively uncomplicated treatment procedure. In the early 1980's the not very successful open laparotomy retropubic freehand implantation technique was rapidly replaced by closed transperineal template guided implantation under transrectal ultrasound guidance [1]. This latter procedure takes one to two hours in the operation theatre and required hospitalisation is in general not more than a day. Although the seeds are rather expensive, the facilities needed for accurate image guided implantation consist of little more than an ultrasound machine and a computer with dedicated software for implantation planning. The investment needed is rather modest. Although conclusive well-controlled randomized studies are lacking, reported biochemical freedom from disease recurrence for stage T1-T2 prostate cancer of brachytherapy, external beam therapy and radical prostatectomy are similar [2]. Brachytherapy is generally reported to be well tolerated but bowel symptoms, decreased erectile function and lower urinary tract symptoms (LUTS) do occur [3-16]. Bowel symptoms are usually minor and most patients do not have any bowel related problems [11]. Reduced sexual functioning is common, as for other treatment modalities, but little is known about the origin of the problems [5,7,13]. Most manifest of all side effects are LUTS. The majority of patients suffers from it to some degree during the first year after the implantation of the seeds. As stated by Potters et al. [2] "it is clear that brachytherapy is not the innocuous option that was touted in the early 1990's". Identifying factors that cause or predict side effects could help to reduce the symptoms or help to make the choice for the best treatment strategy. In this article the factors related to post-implant LUTS will be reviewed.

4.2 Irritative and obstructive symptoms

There are a number of urinary toxic reactions after implantation that negatively influence the quality of life of the majority of patients to some degree. High voiding frequency, urgency, nocturia, dysuria, decreased stream and retention are common symptoms. Acute urinary retention (AUR) requiring temporary catheterisation is the most significant symptom and will be discussed separately in
paragraph 4.3. A respectable number of data is published concerning the severity and resolution of the symptoms [3,4,10,15,17-22]. The modal situation is that these LUTS start a few days to a few weeks after implantation, reaching a maximum between 1 and 3 months and then gradually decrease, coming back to baseline as they were before treatment after about a year. The majority of studies made use of the International Prostate Symptom Score (IPSS) developed by the American Urological Association for the indexation of benign prostatic hyperplasia symptoms [23], which makes it easy to compare the results (Fig. 4.1). Despite little differences the tendency is clear: considerable increase of LUTS after implantation and slow resolution after a few months. Little change after one year, and symptoms almost back to pre-implant conditions (0 months in the graph).

**Fig. 4.1** IPSS as a function of post-implant time interval published by different authors [4,10,15,18,22]. * indicates a study with mean IPSS values, ** indicates a study with median IPSS values. 0 month represents the situation before treatment.

Part of the symptoms is of obstructive nature and has the same origin as urinary retention as will be described in the next paragraph, with the only difference that catheterisation is not required. This explains that, as for AUR, prostate volume is often reported to be a predictor for post-implant LUTS. Obstructive symptoms can also be the result of strictures of the bulbo-membranous urethra caused by implanted seeds in the peri-apical region [12]. These strictures are usually easily managed with dilation.
Irritative symptoms like frequent toilet visiting and high urge to urinate might have different origins. The cause of these symptoms is not well understood up till now. Mechanical damage or dose burden to the urethra is often thought to be an important cause of LUTS. Therefore, it is common practice to place the implantation needles as far away possible from the urethra, creating a so called
peripheral loading, where the needles and seeds are placed at the periphery of the gland (Fig. 4.2a). Mostly, no needles will be placed in the vertical urethral plane to avoid needle trauma of the urethra. This is an alternative for homogeneous loading where the seeds are distributed more or less evenly over the prostate (Fig. 4.2b). As a consequence, the dose to the urethra will be higher as well as the chance of puncturing the urethra. Despite the common effort to spare the urethra as much as possible there is no convincing evidence from the data published so far that there is any relation between urethra dose or urethra punctures and LUTS. The lack of registered correlations between urethra dose and LUTS, however, can be due the general effort to spare this organ as much as possible.

In Table 4.1 is denoted whether the different investigators found any significant relation between post-implant irritative and obstructive urinary symptoms, other than AUR and catheter dependency, and the denoted parameters. Only 3 out of 10 groups identified dose to the urethra as a predictor for any LUTS. While the vast majority of publications reported the prostate volume to be a predictor for AUR (par. 3), only 6 out of 13 publications found the prostate volume to be a predictor for either LUTS severity or resolution. Agreement exists about the correlation between LUTS after implantation and before implantation (IPSS-0). This however seems logical and does not say anything about the worsening of symptoms with respect to the situation before treatment. Contrarily to what could be concluded from these figures, Williams et al. [22] showed that higher pre-implant IPSS was likely to result in a smaller symptom worsening than a lower starting point. Recently, by our own group [24], high doses to small volumes (1 cm³) of the bladder neck and bladder base were found to significantly correlate with LUTS both at 3 months and at 6 month after implantation. Although not directly having determined the dose to the bladder, Williams et al. [22] reported far cranially placed seeds to correlate with LUTS, which could be a surrogate for high local bladder dose. An explanation for these correlations could be mechanical or irradiation induced irritation of the sensitive bladder neck or bladder trigone.
### Published predictors for urinary symptoms other than acute urinary retention

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*Tabel 4.1* Published predictors for urinary symptoms other than acute urinary retention

- Prost vol = prostate volume, TZ vol = transition zone volume, IPSS-0 = IPSS before treatment, AUR = acute urinary retention,
- ADT = androgen deprevation therapy, EBRT = additional external beam radiothrapy
- + Significant predictor for LUTS
- - No predictor for LUTS
- 0 Not assessed

1. only univariate analyses published.
2. no correlation with IPSS resolution, positive correlation with IPSS increase.
3. number of far cranially placed seeds as surrogate for bladder dose.
4.3 Acute urinary retention

The most significant acute symptom is urinary obstruction requiring catheterisation. Incident rates between 5-28% have been reported [4,10,17,18,20-22,25-28]. In most cases catheterisation is required only for a few days shortly after the procedure [17,20,22]. In a group of 1034 patients Gutman et al. reported catheter dependency of 1-4 days for 272 patients (26.3%) and prolonged dependency of 5 days or more for only 16 patients (1.5%). However, the need for longer catheterisation was reported by Henderson et al. [10]; a median duration of 4 weeks and in some cases prolonged self-catheterisation by choice of the patient in order to reduce nocturnal frequency. The policy of longer catheter use (6 weeks) was also considered good practice elsewhere [4]. Although very long catheter dependencies are seldom, periods of 3-18 months have been reported [18].

Because acute urinary retention (AUR) manifests directly after, or at most to several weeks after implantation, it is unlikely that it is related to the slowly accumulating radiation dose. Directly after the implantation procedure no dose, and after a few days only a small fraction of the total dose has been deposited. The seeds are implanted transperineally with 10 to 30 implantation needles and it is very likely that the insertion of these needles in the prostate and possibly the bladder neck causes trauma related AUR. This assumption has been more or less proven by a study of Buskirk et al. [29]. In a group of 157 patients undergoing transperineal ultrasound guided biopsies of the prostate, 18 (11.5%) patients developed urinary retention within 48 hours. This number is comparable with AUR rates in prostate brachytherapy patient groups. Predictors for AUR in the biopsy group of Buskirk et al. were prostate volume and the number of biopsy needles (range 12-26 needles). Also Lee et al. [30] found a correlation between AUR and the number of implantation needles.

Nearly all published studies reported the prostate volume prior to treatment as an important predictor for AUR [10,12,18-20,24,25,28,31]. Detailed segmentation of the internal anatomical structures of the prostate on MRI images by Thomas et al. [32] brought forward that the transition zone volume rather than the whole prostate volume is a predictor for AUR after brachytherapy. In an earlier study by Kaplan et al. [33] among 61 men with benign prostatic hyperplasia, a strong correlation was found between obstructive symptoms and the transition zone index. The transition zone index is the ratio between transition zone volume and prostate volume. The prostate volume and the transition zone volume were highly correlated in both
studies but the transition zone volume or the transition zone index was the best predictor for obstructive symptoms. In the study of Thomas et al. [32], after multivariate analyses, the prostate volume was eliminated and the transition zone volume remained the only significant predictor for AUR. This justifies the belief that AUR is caused by oedema within the benign prostatic hyperplasia of the transition zone as a result of needle insertions.

Unfortunately, very few groups investigated the possible relation between urinary flowmetry or residual bladder contents prior to treatment and AUR. Williams et al. [22] found that peak urinary flow rate prior to treatment was the only independent predictor for AUR in a group of 173 patients, whereof 34 developed AUR. Also Henderson et al. [10] found urodynamic status to be a predictor for AUR, Locke et al. [34] on the other hand did not. Earlier, Sonke et al. [35] reported that in a group of 1903 patients suffering from LUTS, prostate volume, peak urinary flow, voided volume and post void residual urine had substantial predictive value in relation to the outcome of pressure flow studies.

The use of the popular IPSS questionnaire [23] to identify patients at risk is common but few studies found a correlation between AUR and IPSS [10,18,25,34]. It should be noted however that this could be partially due to the fact that patients with high IPSS are often offered alternative treatment. Bucci et al. [25], having treated patients with high pre-treatment IPSS as well, found significant higher risk of catheterisation in patients with a baseline IPSS>15. Although a study over a small number of patients (62), Locke et al. [34] found a highly significant difference in AUR incidence in patients with pre-implant IPSS≥11 and those with IPSS≤10: 71% versus 15%. However, Sonke et al. [35] did not find any relation between IPSS and restricted flow rate and Williams et al. [22] reported that 71% of AUR events in their patient group had a pre-treatment IPSS≤6. These conflicting outcomes make pre-treatment IPSS as a predictor for AUR rather controversial. An explanation for these ambiguities can be that the IPSS questionnaire covers a spectrum of urinary symptoms. AUR, however, is a highly obstructive symptom and may be diluted by other scored symptoms. This is more or less confirmed by Kelly et al. [27] who reported that weak stream was the only symptom of the IPSS list that remained a significant predictor of catheterisation after logistic regression analysis.
4.4 Androgen deprivation therapy

Patients with large prostates often receive androgen deprivation therapy (ADT) for size reduction. Size reduction for large prostates is often necessary to avoid pubic arch interference during the implantation procedure. Prostate volumes exceeding 50 cm$^3$ or evidence of pubic arch interference are usually the criteria for ADT [18,25]. Expected benefits on tumour control can also be a reason to administer ADT [36]. Ambiguous data exists about the influence of ADT on urinary morbidity [6,8,18,20,21,25-27,36]. The reason is probably that on the one hand ADT is related to large prostates or transition zone volumes and on the other hand to the volume reduction of these organs. In a straightforward statistical analysis the net effect of the ADT may therefore be disguised. Hinerman-Mulroy et al. [26] did more detailed research on the effect of ADT and found a relation between catheter-dependency time and pre-hormonal therapy prostate volume, post-hormonal therapy transition zone volume and change in urethral position caused by transition zone shrinkage.

4.5 Transurethral resection and incontinence

Relieve of persistent obstructive urinary symptoms or retention will usually require transurethral resection of the prostate (TURP). TURP, however, is only required for a relative small amount of patients; percentages ranging from 1% to 5% are reported in literature [10,17,19-21,26,38]. Although TURP is an effective management tool, the risk of developing urinary incontinence after the procedure is significant. A detailed report concerning TURP and incontinence following TURP has been published by Kollmeier et al. [39]. Of a large group of 2050 brachytherapy patients 38 (2%) required one or more TURP procedures. The indications for TURP were retention in 17 cases, obstructive urinary symptoms in 17 cases and persistent hematuria in 4 cases. The total amount of tissue removed per procedure was 0.2 to 26 g (median 6g). Seven of these 38 patients (18%) developed urinary incontinence. The complaints varied from minimal leakage to requiring more than 5 pads per day. The most significant correlation with post-TURP incontinence was the timing of TURP; significant higher incidence when the TURP took place more than 2 years compared to less than 2 years after the seed implantation. This difference could be explained by the fact that late TURP procedures were mostly related to radiation-induced fibrosis, which carries more risk than early TURP procedures to manage urinary retention. The volume of tissue
resected at TURP did not correlate with incontinence, nor did prostate or urethral
dose or the addition of external beam radiotherapy. Other studies, however, did
find a relation between TURP and the dose to the urethra [20,21]. Other reported
predictors for TURP are catheter dependency after brachytherapy, androgen
depression-induced changes in prostate anatomy and maximum IPSS increase
[20,21,26].

History of TURP prior to brachytherapy has been associated with increased rates
of urinary morbidity and invasive procedures after brachytherapy [8]. Often, history
of TURP is considered to be a contra-indication for brachytherapy [25,32,39].
Moreover, extensive TURP can result in a rather large TURP cavity that may
hamper proper seed placement in the remnant peripheral zone containing the
cancer.

4.6 Radionuclide

For permanent seed implants of the prostate two radionuclides are available,
Iodine-125 (I-125) and Palladium-103 (Pd-103). The average photon energy of
these radioactive isotopes is 28 and 21 keV, respectively. These low photon
energies make both suitable for permanent implantation; nearly all irradiation
energy will be absorbed by the body of the patient. The very low radiation flux
leaving the body is of negligibly low risk to others and patients are only requested
to avoid close contact with small children and pregnant women the first months
after implantation of the sources. Contrary to the situation in the USA, the Pd-103
sources are not very popular in Europe where very few hospitals prefer them to I-
125 sources [37]. The main difference between both isotopes is the half value time,
60 days for I-125 against 17 days for Pd-103. This means that dose builds up much
faster with Pd-103 than with I-125 (Fig. 4.3). The expectation would be that
radiation induced LUTS would peak and resolve faster in patients implanted with
Pd-103 seeds. Of the few studies comparing side effects due to either isotope,
none concluded there to be any difference in LUTS intensity or post-implant peak
interval [17,19,21,38]. Allen et al. [17] and Wallner et al. [38] found a faster LUTS
resolution for Pd-103 patients, where Niehaus et al. [21] and Gelblum et al. [19] did
not. This could mean that the measurements were not sensitive enough to
distinguish between symptom peaks or that the peak is dominated by mechanical
trauma due to needle insertions. The longer resolution time for I-125 cases found
by Allen *et al.* and Wallner *et al.* could be the result of more dominant radiation effects at longer post-implant time intervals.

**Fig. 4.3** Dose build-up implant with I-125 sources and Pd-103 sources

Because of the shorter half value time of Pd-103 (17 days) compared to I-125 (60 days) the dose builds up much faster in prostates implanted with Pd-103. Consequently, the radiation dose is expected to resort effect earlier. Greater biological effectiveness requires less total dose when applying Pd-103 (usually 125 Gy) instead of I-125 (usually 145 Gy).

### 4.7 Use of α-blockers

Alpha-blockers are widely used to ameliorate brachythrapy related LUTS, either prophylactic or on therapeutic base. The difference between these approaches has been clearly demonstrated by Merrick *et al.* [40]. In a group of 234 consecutive patients, 142 patients received α-blockers starting 2 weeks before treatment and continuing until returning to baseline levels. 92 patients either did not receive an α-blocker or received an α-blocker after significant urinary symptoms. Although patients were not randomly appointed for either strategy (prophylactic approach in one hospital, therapeutic approach in another hospital) the differences in severity and resolution were rather convincing. In both cohorts the IPSS peaked at 1 month after implantation. Symptoms returned to baseline levels after a mean duration of 4 months and a median duration of 3 months in the prophylactic arm. In the therapeutic arm these figures were 10 and 6 month, respectively. The peak IPSS rise (one month after implantation), was on average 11 in the therapeutic arm and
only 4 in the prophylactic arm. However, prophylactic use of α-blockers had no impact on either urinary retention or the ultimately need for post-implant surgical intervention.

4.8 Long-term urinary quality of life

It is clear from Fig. 4.1 that enhanced urinary symptoms slowly resolve and that after about a year symptoms are back to baseline. Some groups reported longer resolution times. Caffo et al. [6] for example found that in their patient group urinary functions returned to pre-treatment level only after 3 years. The very few reports on late urinary symptoms do not exactly agree on whether there are late symptoms related to the brachytherapy. Merrick et al. [41] concluded after a median follow-up of 66 months that there was no significant difference in the overall long-term urinary quality of life when brachytherapy patients were compared with a group of newly diagnosed cancer patients of comparable demographics. On the other hand, after a median follow-up of 6.2 years, Miller et al. [13] found in there brachytherapy group a significantly lower urinary quality of life compared with a control group of prostate cancer free men. Vargas et al. [42] found 26% grade 2 (National Institute Common Toxicity Criteria 2.0) and 6.9% grade 3 toxicities after a median follow-up of 2.9 years after brachytherapy. This last patient group, however, was not compared with a control group.Remarkably, the number of needles and neo-adjuvant hormonal therapy were significant predictors for chronic urinary toxicity in their series. Interestingly, 2 studies reported what they call urinary symptom flare, that is recurrent symptoms occurring some time after resolution of initial post-implant symptoms. According to Cesaretti et al. [43], 35% of their patient group developed urinary flare of 5 or more IPSS points at a median post-implant time interval of 24 months (range 6-64 months). In 72% of the patients the flare subsided to baseline by the next follow-up visit, while in 25% of these patients flare symptoms occurred during their last visit. No predictors were found for these flare occurrences. Also Kelly et al. [27] reported temporary urinary symptom flare, but in only 15% of patients. Median follow-up of their series was 18 months (range 6-30 months). Neither did they find any explanation or predictor for this phenomenon.

4.9 Conclusions

Enhanced irritative and obstructive urinary symptoms are very common after seed implantation of the prostate. In the vast majority of cases symptoms return to base
line levels within a year. In a small number of cases (1-5%) a TURP procedure is required to manage persistent urinary complications. The prophylactic use of α-blockers during the first months after the procedure is proven to relax enhanced urinary symptoms.

Patients with large prostates, or more specifically large transition zones, are more likely to develop AUR. This is probably due to the fact that AUR is caused by oedema within the benign prostatic hyperplasia of the transition zone as a result of needle insertions. Nevertheless, large prostate size does not have to be a contraindication for brachytherapy per se, since AUR is only a temporary phenomenon, also for prostate larger than 50 cm$^3$ [44].

Although high pre-treatment IPSS predicts high post-plant IPSS, it does not seem to be a reliable predictor for IPSS rise or AUR due to brachytherapy. It is recommended to check the urodynamic status of patients with relatively high pre-treatment LUTS and/or large prostate size. Poor urodynamic status before treatment is a predictor for AUR after the implantation procedure.

Peripheral loading of seeds ensures low dose to the urethra and avoiding the column of the implantation grid coinciding with the "urethra-plane" is likely to limit dose and trauma related LUTS. Also, avoiding high hot spot doses and excessive needle puncturing of the bladder will reduce the chance of developing severe post-implant LUTS.
References


Chapter 5

An analysis of the relation between physical characteristics of prostate I-125 seed implants and lower urinary tract symptoms: bladder hotspot dose and prostate size are significant predictors

Marcel J. Steggerda, Henk G. van der Poel, Luc M.F. Moonen

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Abstract

Purpose
Lower urinary tract symptoms are frequently observed after I-125 seed implantation of the prostate. More knowledge about causes and predictors is necessary to be able to develop less toxic implantation techniques. The aim of this study was to identify implantation related factors that contribute to post-implant urinary morbidity.

Materials and methods
Analysed was a group of 72 patients that filled in a symptom score questionnaire before, 3 months and 6 months after implantation as well as a group of 15 patients that suffered from acute urinary retention. Several dose-volume parameters of prostate, urethra and bladder wall were determined based on a post-implant TRUS-CT scan.

Results
The dose to a 1 cm³ hotspot in the bladder wall (D1cc-bl) as well as the prostate volume were independently correlated with urinary morbidity symptom scores at 3 months (p=0.006 and p=0.005 respectively) and at 6 months (p=0.001 and p=0.015 respectively) after implantation. The number of implanted seeds and the D1cc-bl were significant discriminators (p<0.001 and p=0.015 respectively) for either mild or severe early urinary morbidity.

Conclusion
Bladder hotspot dose appears to be an important dosimetric predictor for urinary morbidity both at 3 months and at 6 months after implantation. Other predictors are prostate volume, or equivalently, the number of implanted seeds.
5.1 Introduction

Implantation of the prostate with I-125 seeds is a well-established treatment for early-stage prostate cancer. In general this brachytherapy treatment is relatively well tolerated [1-5]. Nevertheless, most patients experience lower urinary tract symptoms (LUTS) to some degree after implantation. The nature of the complaints are either irritative or obstructive, or a combination of both. They vary from frequent toilet visiting and nocturia to restricted urinary flow. These toxic symptoms usually disappear within a year [1,6-9] although longer recoveries and late symptom flare have also been reported [2,10].

There are two possible causes for post-implant LUTS. Firstly, the implantation procedure itself. Implantation needles are inserted through the perineum into the prostate, possibly causing trauma in the functional genitourinary anatomy. Secondly, the irradiation dose deposited by the I-125 sources. High doses to urethra and bladder could possibly cause or contribute to urinary morbidity. However, the dose accumulates rather slowly and only after 60 days half of the total dose will be delivered. It is therefore unlikely that dose related complications occur shortly after the implantation.

Although some studies showed correlations between dose and implant related parameters and LUTS, other studies did not, or found different predictors [1,3-9,11-17]. Most frequently reported predictor however is the prostate volume before implantation [7,8,11,14,15,18,19]. Many studies concentrated on the dose to the urethra but the dose to the bladder has been ignored so far. Probably the bladder is not regarded an organ at risk because it is not within the implanted area as are prostate and urethra. Nevertheless, the bladder wall and the bladder neck play an important role in the urinary flow regulation and although the average dose to the bladder is always very low, hot spots can occur close to cranially placed seeds. Only Williams et al. [9] reported a positive correlation between LUTS and the number of seeds implanted superior to the base of the prostate, suggesting that the dose to the bladder could be an important factor.

In order to remain an attractive treatment modality for localized prostate cancer in the future it is important to reduce side effects of seed implants like LUTS as much as possible. To be able to develop less toxic implantation techniques it is mandatory to identify the risk factors. The purpose of this study was to investigate possible correlations between LUTS recorded at two different time intervals after
implantation and implant related parameters with special attention to the dose to the bladder.

5.2 Materials and methods

5.2.1 Patients and implants
The study refers to 115 patients treated with permanent brachytherapy of the prostate in our department in the period June 2002 – June 2006. In all cases the specified dose was 145 Gy and no external beam radiotherapy was added. Clinical characteristics: tumour stage < T2c, PSA < 10, Gleason score < 7. Excluded from this treatment were patients with an IPSS > 12 and prostate volumes larger than 60 cm$^3$. Favourable patients with prostates larger than 55 cm$^3$ were pre-treated with androgen ablation. Between 50 and 100 I-125 seeds were implanted. All patients received 0.4 mg Tamsulosin (alpha blocker) once daily during the first 6 months after treatment. The seeds used were Oncura Rapid Strands model 6711 with a source strength of 0.55±0.02 μGy.h$^{-1}$.m$^2$.

Peripheral seed loading with additional seeds closer to the centre of the prostate was applied in order to achieve adequate dose coverage of the prostate, i.e. to aim at a minimal peripheral dose of 145 Gy. Seed positions were allowed up to 5 mm outside the prostate gland and were not allowed to be closer than 5 mm from the urethra. The average and 1SD of prostate volume, number of implanted seeds and implantation needles were 41±11 cm$^3$, 81±13 and 26±5, respectively.

5.2.2 Urinary symptom scores
For the scoring of LUTS experienced by patients after implantation of the prostate we used the International Prostate Symptom Score (IPSS) questionnaire [20]. It consists of 7 questions relating to irritative complaints and obstructive urinary flow. The score per question with increasing severity ranges from 0 to 5. I.e. in case of no complaints IPSS=0, in case of maximum severity IPSS=35. Questionnaires were filled in by 72 patients before implantation (IPSS-0) and at least once after implantation. 59 of these 72 patients filled in the questionnaire at 3 months (IPSS-3m) and 56 patients at 6 months (IPSS-6m) after implantation, i.e. 43 patients filled in the questionnaire both at 3 months and 6 months after implantation. The average and 1SD time span between implantation and IPSS-3m was 90±27 days and between implantation and IPSS-6m 180±26 days.
5.2.3 Early urinary symptom categories

Of the total group of 115 patients, 15 patients suffered from acute urinary retention (AUR) of more than 200 cm³. These patients depended on a urinary catheter for several days to several weeks after implantation. AUR and high IPSS-3m were both considered being early urinary symptoms. There were no patients with AUR included in the sub-group of 59 IPSS-3m measurements. In order to avoid double counting in the “early symptom category” and any influence of prolonged catheter dependency on the IPSS at 3 months, we excluded the available IPSS-3m scores of AUR patients from the analyses.

We joined the cases with registered AUR and IPSS-3m and stratified this combined group (n=59+15=74) in two categories. 1) Severe early LUTS (n=34): IPSS-3m ≥ 18 (high absolute score) and IPSS-3m – IPSS-0 ≥ 11 (high increase), or AUR. 2) Mild early LUTS (n=40): other patients within this group. The division between severe and mild was quite arbitrary but an IPSS-3m of at least 18 points is considered to be high by our physicians. 18 points is also just over half the maximum score (35 points). A rise of 11 points or more (IPSS-3m minus IPSS-0), the second requirement for severe symptom stratification was chosen because it was at least 1 point over the average rise.

Of 41 patients (115 minus 74) no or incomplete early symptom scores or post-implant dosimetric data were available and could therefore not be included in the early symptom group.

5.2.4 Imaging and dosimetry

One day after implantation a simultaneously acquired CT and 3D transrectal ultrasound (TRUS) scan were made. The method and technical specifications have been described in detail previously [21]. Using the favourable characteristics of these image modalities, the TRUS images were used for the delineation of the prostate, the CT images for the delineation of the bladder wall and the urethra and for the reconstruction of the seeds. The normally difficult to distinguish interface between the base of the prostate and the bladder neck was optimally determined by simultaneous viewing of registered CT and TRUS images. The urethra was made visible by a transurethral urinary catheter. Delineated was the urethra within the prostate boundaries.

In Table 5.1 the investigated parameters of prostate and implant characteristics in relation to LUTS are described. Previous research showed that the dose volume
parameters of the bladder wall based on a scan made 1 day after implantation differed from those based on a scan 1 month after implantation or later [22]. Therefore, we also determined dose volume parameters of the bladder wall based on a scan made 1 month after implantation. From the same study we know that urethra high dose values are underestimated when based on a day-1 scan. However, they do correlate very well with values based on a scan made 1 month after implantation. Therefore, we did not consider the rather demanding insertion of a urinary catheter, necessary for the discrimination of the urethra, during the scan at 1 month. Since the D90 of the prostate did not significantly change with scan date, we only used the day-1 value in the analyses. Because trauma sensitivity of the bladder neck was expected, the number of seeds within a radius of 15 mm from the ostium urethrae internum was counted on the CT made 1 day after implantation (Seeds-BN).

For the reconstruction of the seeds and the calculation of the dose distribution we used Varian-Variseed software version V7.1. In house made software was used to register and fuse TRUS and CT images, to delineate organs and to calculate dose-volume histograms.

5.2.5 Statistics
For the statistical analyses software package SPSS V15.0 was used. The entered parameters and endpoints are described in Table 5.1. In case of IPSS-3m and IPSS-6m, absolute levels rather than increase of symptoms were chosen as endpoints in order to investigate the influence of pre-treatment LUTS on post-implant LUTS. I.e. the IPSS before treatment (IPSS-0) was also entered in the analyses. When other factors than IPSS-0 appear to be predictors for post-implant IPSS, these factors can be considered to be responsible for the change in symptoms due to the brachytherapy. Univariate and multivariate (stepwise elimination) linear regression analyses were performed. Only parameters with a p<0.1 after univariate analysis were entered for the multivariate analysis. Parameters with a p<0.05 after multivariate analysis were considered to be significant independent predictors for the endpoint. The coefficient of determination, $R^2$, of the linear models has been determined to characterise its “goodness-of-fit".
Binary logistic regression analyses were performed to identify predictors for AUR and for severe early LUTS. The coefficient of determination of the logistic models was characterised by a pseudo R², the "Nagelkerke R²n".

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS-0</td>
<td>International Prostate Symptom score prior to brachytherapy</td>
</tr>
<tr>
<td>V-pr-0</td>
<td>Prostate volume before implantation</td>
</tr>
<tr>
<td>Horm ther</td>
<td>Hormonal therapy prior to implantation (yes or no)</td>
</tr>
<tr>
<td>D90-pr a</td>
<td>Dose to 90% of the prostate</td>
</tr>
<tr>
<td>D10-ur a</td>
<td>Dose to 10% of the urethra</td>
</tr>
<tr>
<td>D50-ur a</td>
<td>Dose to 50% of the urethra</td>
</tr>
<tr>
<td>D1cc-bl-1d a</td>
<td>Dose to 1 cm³ of bladder wall based on a scan made one day after implantation</td>
</tr>
<tr>
<td>D1cc-bl-1m a</td>
<td>As D1cc-bl-1d, but based on a scan made one month after implantation</td>
</tr>
<tr>
<td>Seeds-BN</td>
<td>Number of seeds within a radius of 15 mm from the ostium urethrae internum</td>
</tr>
<tr>
<td>Seeds</td>
<td>Number of implanted seeds</td>
</tr>
<tr>
<td>Needles</td>
<td>Number of implantation needles</td>
</tr>
<tr>
<td>Endpoint</td>
<td>Description</td>
</tr>
<tr>
<td>IPSS-3m</td>
<td>International Prostate Symptom score 3 months after implantation</td>
</tr>
<tr>
<td>IPSS-6m</td>
<td>International Prostate Symptom score 6 months after implantation</td>
</tr>
<tr>
<td>AUR</td>
<td>Acute Urinary Retention</td>
</tr>
<tr>
<td>Severe LUTS</td>
<td>IPSS-3m ≥ 18 and IPSS-3m minus IPSS-0 ≥ 11 or AUR</td>
</tr>
</tbody>
</table>

Table 5.1: Description of investigated parameters and endpoints.

* a Relates to the part of the organ receiving the highest dose. Within this part of the organ it is the lowest dose. I.e., this is the dose cut-off value of the stated volume of the cumulative dose-volume histogram.

5.3 Results

5.3.1 IPSS endpoints

In Table 5.2 the results of univariate and multivariate linear regression analysis of the different implant related parameters and the endpoints IPSS-3m and IPSS-6m are denoted. Mean value and 1SD of IPSS-0 was 5.5±3.6, of IPSS-3m 15.2±6.9, and of IPSS-6m 12.8±7.9. For endpoint IPSS-3m, V-pr-0, D1cc-bl-1d and IPSS-0 were significant predictors, for endpoint IPSS-6m, V-pr-0 and D1cc-bl-1m. The R² of the multivariate model of IPSS-3m was 0.31 and of IPSS-6m 0.25.

The correlation between the individual questions of the IPSS questionnaire and the most significant predictors of both IPSS-3m and IPSS-6m are presented in Table 5.3. Clearly, V-pr-0 correlates best with question 1 (sensation of not emptying the bladder after urinating), and D1cc-bl correlates best with question 2 (urinating again within 2 hours).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>IPSS-3m (N=59)</th>
<th>IPSS-6m (N=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td>IPSS-0</td>
<td>0.006</td>
<td>0.034</td>
</tr>
<tr>
<td>V-pr-0</td>
<td>0.014</td>
<td>0.005</td>
</tr>
<tr>
<td>Age</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>Horm ther</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td>D90-pr</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>D10-ur</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>D50-ur</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>D1cc-bl-1d</td>
<td>0.006</td>
<td>0.006</td>
</tr>
<tr>
<td>D1cc-bl-1m</td>
<td>0.074</td>
<td></td>
</tr>
<tr>
<td>Seeds-BN</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>Seeds</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Needles</td>
<td>0.89</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.2 Significance levels after univariate and multivariate regression analysis for IPSS endpoints.

*a* respectively, 17 of 59 and 14 of 56 patients were treated with hormones prior to brachytherapy.

For description of parameters and endpoints, see Table 5.1.
<table>
<thead>
<tr>
<th>Question number and subject</th>
<th>IPSS-3m (n=59)</th>
<th>IPSS-6m (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V-pr-0</td>
<td>D1cc-bl-1d</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>p</td>
</tr>
<tr>
<td>1. Sensation of not emptying the bladder after urinating</td>
<td>0.29</td>
<td>0.03</td>
</tr>
<tr>
<td>2. Urinate again less than 2 hours after urinating</td>
<td>0.15</td>
<td>0.3</td>
</tr>
<tr>
<td>3. Stop and start several times during urinating</td>
<td>0.16</td>
<td>0.2</td>
</tr>
<tr>
<td>4. Difficulty in postponing urination</td>
<td>0.23</td>
<td>0.08</td>
</tr>
<tr>
<td>5. Weak urinary stream</td>
<td>0.23</td>
<td>0.09</td>
</tr>
<tr>
<td>6. Push or strain to urinate</td>
<td>0.18</td>
<td>0.16</td>
</tr>
<tr>
<td>7. Frequently urinating during the night</td>
<td>0.25</td>
<td>0.05</td>
</tr>
<tr>
<td>1-7. Total score</td>
<td>0.32</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Table 5.3* Pearson correlation (R) and significance level (p) per question of the IPSS questionnaire.

For descriptions of parameters, see Table 5.1.
5.3.2 Urinary retention and early symptoms

After multivariate binary logistic regression analyses only the number of implanted seeds seemed a significant independent predictor for AUR (p=0.03). The predictive value of the model, however, was modest: Nagelkerke $R^2=0.21$.

For the early LUTS categories severe versus mild, the number of implanted seeds and D1cc-bl-1d were independent predictors after binary logistic regression analyses (Table 5.4). The predictive value was relatively high with a Nagelkerke $R^2=0.40$. The percentage correctly predicted early symptoms (either severe or mild) with the model would have been 80%.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± 1SD</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Severe (n=34)</td>
<td>Mild (n=40)</td>
</tr>
<tr>
<td>IPSS-0</td>
<td>6.6 ± 2.9</td>
<td>5.2 ± 3.8</td>
</tr>
<tr>
<td>V-pr-0$^a$</td>
<td>46 ± 10</td>
<td>38 ± 9</td>
</tr>
<tr>
<td>Horm ther$^b$</td>
<td>0.32 ± 0.48</td>
<td>0.28 ± 0.45</td>
</tr>
<tr>
<td>Age</td>
<td>67 ± 5</td>
<td>64 ± 5</td>
</tr>
<tr>
<td>D90-pr$^c$</td>
<td>138 ± 16</td>
<td>129 ± 21</td>
</tr>
<tr>
<td>D10-ur$^c$</td>
<td>195 ± 33</td>
<td>186 ± 28</td>
</tr>
<tr>
<td>D50-ur$^c$</td>
<td>169 ± 23</td>
<td>159 ± 21</td>
</tr>
<tr>
<td>D1cc-bl-1d$^c$</td>
<td>139 ± 46</td>
<td>114 ± 41</td>
</tr>
<tr>
<td>D1cc-bl-1m$^c$</td>
<td>109 ± 41</td>
<td>90 ± 31</td>
</tr>
<tr>
<td>Seeds-BN</td>
<td>3.4 ± 2.0</td>
<td>2.4 ± 2.1</td>
</tr>
<tr>
<td>Seeds</td>
<td>89 ± 11</td>
<td>77 ± 12</td>
</tr>
<tr>
<td>Needles</td>
<td>28 ± 5</td>
<td>26 ± 5</td>
</tr>
</tbody>
</table>

Table 5.4 Severe versus mild early lower urinary tract symptoms.

$^a$ cm$^3$.

$^b$ 22 of 74 patients were treated with hormones prior to treatment.

$^c$ Gy.

$^d$ All factors included in analysis.

$^e$ Only pre-treatment variables IPSS-0, V-pr-0, Horm ther and Age included in analysis.

For description of parameters and endpoints see Table 5.1.

The prostate volume and the number of implanted seeds were strongly correlated ($R=0.90$). It therefore made little difference for the predictive value when replacing Seeds for V-pr-0 (Nagelkerke $R^2$, 0.40 and 0.37, respectively). Knowing V-pr-0 before implantation, the maximum value of D1cc-bl-1d can be predicted to avoid severe early symptoms. In Fig. 5.1 D1cc-bl-1d is plotted against V-pr-0 for patients with either severe (n=34) or mild early LUTS. The solid line is the by the statistical model predicted dividing line between severe and mild LUTS:
Physical characteristics and urinary morbidity

\[ D_{1cc-bl-1d} = 358 - 5.45 \times V_{-pr-0} \]

Under the line the predicted symptoms are mild, above the line severe. Clearly, especially \( V_{-pr-0} \) is a strong predictor. Of 31 patients with a \( V_{-pr-0} > 44 \) cm\(^3\), 23 suffered from severe LUTS. Of 43 patients with \( V_{-pr-0} < 44 \) cm\(^3\), only 11 suffered from severe LUTS.

In the last column of Table 5.4 the p-values of significant pre-treatment parameters are denoted. Only IPSS-0, \( V_{-pr-0} \), Horm ther and Age were included in the multivariate analysis.

![Fig. 5.1 Relation between early urinary symptom stratification (severe versus mild) and the 2 predictors, initial prostate volume \( V_{-pr-0} \) and bladder hotspot dose \( D_{1cc-bl-1d} \). Acute urinary retention (AUR) is a sub-category of severe symptoms and these cases are separately indicated. The solid line is the predictive dividing line between mild and severe symptoms. The vertical dashed line is the second best dividing line, being \( V_{-pr-0} = 44 \) cm\(^3\). The horizontal dashed line is the line \( D_{1cc-bl-1d} = 118 \) Gy. The dashed lines divide the plot into 4 quadrants. The percentage severe symptoms per quadrant are: I) 79%, II) 44%, III) 5%, IV) 71%.](image)
5.4 Discussion

5.4.1 Bladder hotspot dose and urinary morbidity

An earlier study showed that the DVH of the bladder based on a scan made 1 month after implantation is a better approximation of the total accumulated dose distribution than a DVH based on a scan made 1 day after implantation [22]. Nevertheless, D1cc-bl-1d correlated better with IPSS-3m than D1cc-bl-1m (R=0.36 versus R=0.24). Possibly, high IPSS after 3 months is, at least partially, due to still existing trauma caused by needle punctures in the bladder wall and/or bladder neck during implantation of the seeds. In this case D1cc-bl could be a derivative of deeply inserted needles puncturing the bladder wall or bladder neck in order to place far cranially planned seeds. If this assumption is correct, indeed D1cc-bl-1d would be a better estimator than D1cc-bl-1m because it is a better reflection of the original seed positions.

By using a multi-modality imaging (CT and TRUS), the delineation uncertainty at the interface of prostate and bladder neck could be minimised. The bladder volume changes with time due to filling and voiding. However, a small bladder wall volume of 1 cm³ close to prostate and seeds is expected not to be much influenced by bladder filling. This expectation is supported by the findings of Pinkawa et al. [23] who found no correlation between bladder volume and bladder wall displacement near the bladder neck. The decrease of bladder hot spot dose with time is due to inferior seed migration [22]. This explains the difference between D1cc-bl-1d and D1cc-bl-1m.

The number of seeds in or near the bladder neck (Seeds-BN) was univariatly correlated with IPSS-3m but was eliminated after multivariate regression analysis and was therefore no independent predictor (Table 5.2).

After 6 months on the other hand, D1cc-bl-1m correlated better than D1cc-bl-1d with the IPSS (R=0.40 versus R=0.34). Since D1cc-bl-1m is the better estimator for the accumulated dose, this could be an indication that LUTS 6 months after implantation is mainly dose related.

In a comprehensive overview article by Merrick et al. [14] factors predicting LUTS after prostate brachytherapy found by leading professionals in the field are summarized. Factors like large prostatic transition zone index and large radiation dose to the urethra are mentioned but the dose to the bladder, however, seemed to have been overlooked. Also in the recently published supplement to the ESTRO/EAD/EORTC recommendations on prostate brachytherapy, the bladder is
not considered to be an organ at risk [24]. To our knowledge, only Williams et al. [9], and recently Pinkawa et al. [16], suggested a relation between bladder dose and LUTS. For external beam radiotherapy of the prostate recently Cheung et al. found a relation between bladder hot spots and late urinary toxicity [25]. The fact that Pinkawa et al. and Van Gellekom et al. [8] found a correlation between LUTS and D90 of the prostate might have been due to the fact that a high D90 often correlates with good covering of the base of the prostate and consequently with high dose to the bladder neck.

The organ at risk most often mentioned in relation to LUTS is the urethra. Nevertheless we didn’t find any relation between LUTS and dose to the urethra. D10-ur, recommended by the ESTRO/EAU/EORTC as the primary factor to report in connection with urinary morbidity [24], did not correlate with any of the investigated endpoints. Several groups investigated the relation between LUTS and the dose to the urethra, but their conclusions are not unambiguous [3,6-9,11,15,26]. The only dosimetric parameter in our study that appeared to have any relation with LUTS is the 1cm³ hotspot dose in the bladder wall. Despite the relatively small number of patients in the IPSS-3m and IPSS-6m group, the significance of correlations leaves little doubt about the influence of D1cc-bl (see Table 5.2). The choice of the cut-off volume of 1 cm³ was rather arbitrary, but our analyses showed that D1cc-bl correlated slightly better than D2cc-bl and considerably better than D5cc-bl with the endpoints. Replacing D1cc-bl by D2cc-bl would not have influenced the results significantly.

5.4.2 Predicting urinary morbidity
Probably, LUTS is caused by a combination of trauma and accumulated dose in the organs at risk. Acute symptoms are likely to be due to trauma caused by needle insertions as demonstrated by Buskirk et al. [27] and Eapen et al. [28]. Because dose accumulates very slowly (HVT=60 days) acute symptoms, such as AUR, are less likely to be dose related.

Our study and several other studies showed that large prostates, or more specifically large transition zones, increase the risk of LUTS [7,8,14,15,17,18,26,29]. The pre-treatment IPSS was a predictor for LUTS at 3 months, but remarkably not for LUTS at 6 months after implantation. The bladder hotspot dose was a predictor for LUTS both at 3 months and at 6 months but not for AUR.
In order to determine critical values for implantation parameters that can be useful as guidelines for physicians we stratified LUTS into a mild and a severe symptom group. High rise combined with a high absolute value of IPSS-3m as well as AUR were considered to be severe early LUTS. Combining the high IPSS-3m group and the AUR group in the same category might be debatable but the model had an acceptable predictive score and was only meant to make a crude division. In conjunction with outpatient check the IPSS questionnaire was filled in at 3 months intervals. Consequently, the IPSS was first available at 3 months after implantation. The IPSS has been reported to peak roughly between 1 month and 3 months after implantation [1,3,8,9,30]. Crook et al. [30] found an equal median IPSS at 1 and 3 months, so there is likely to be a stabilisation between both intervals. Therefore, we believe there is justification to still consider the IPSS at 3 months to be a quantification for early symptoms.

The predictive value of the number of implanted seeds and the initial prostate volume were highly significant in the univariate analyses. Because the correlation between both parameters was very high, obviously one was cancelled after stepwise logistic analyses. That the number of implanted seeds was slightly more significant could have been coincidence. Because the number of implanted seeds depends on the activity, determining a critical value for prostate volume seems more appropriate. Generalising the LUTS incidence of the investigated patient group we can posit that patients with prostate volumes smaller than 44 cm\(^3\) and with D1cc-bl-1d below 118 Gy have very little chance of developing severe early LUTS (5%). On the other hand, patients with prostate volumes larger than 44 cm\(^3\) have a considerable chance of developing severe early LUTS (75%).

Of the factors known before treatment, prostate volume and age were correlated with early LUTS.

5.4.3 Irritative and obstructive complaints

In this study, as in most other studies regarding urinary morbidity, no distinction has been made between irritative and obstructive complaints. Nevertheless it is possible that both symptoms have (partially) different origins. In the IPSS questionnaire questions relate to either symptom. From Table 5.3 we can learn that question 1, concerning sensation of incomplete emptying, correlates relatively strong with prostate size. Question 2, concerning the urinating frequency, correlates strongly with bladder hotspot dose, especially at 6 months post-implant.
Both can be considered to be irritative symptoms. Questions 5 and 6, relating to weak urinary stream and strain to void the bladder, typically relate to obstructive symptoms and correlated much less with prostate size and bladder hotspot dose than the questions 1 and 2. However, because the questionnaire is not validated to distinguish between irritative and obstructive symptoms we were reluctant to draw any conclusions about the correlation of implant characteristics to either symptom. For example, question 1 concerning sensation of incomplete emptying is an irritative symptom but could also be the result of an obstructive problem. It might be worthwhile to develop a method to better distinguish between the different symptoms of LUTS and determine predictors for each of them in a future study.

5.4.4 Implications for clinical practice

From this study follows that the bladder has to be considered an organ at risk in relation to post-implant urinary morbidity. Hot spot dose and probably also local trauma in the bladder wall at least partially determine the severity of LUTS. Large prostates are more at risk than small prostates. The technique of inserting implantation needles far cranially through the prostate capsule carries the risk of puncturing sensitive parts of the bladder, such as bladder neck and trigone, and inducing trauma related morbidity. Sparing the bladder, both mechanically and dosimetrically, will possibly result in under-dosage of the base of the prostate. Although transition zone tumour involvement is less common than peripheral zone involvement [31] an acceptable trade-off between prostate dose coverage at the base and minimising the dose to the bladder is likely to be case dependent. Using seeds with a higher activity could reduce the number of punctures in the bladder wall not only because fewer needles are needed but also because needles can be inserted less deep. Martin et al. recently reported excellent clinical results using high activity seeds (0.79-0.84 U) [19]. As part of a future study we will try to develop an implantation technique that is likely to be less toxic.

5.5 Conclusions

The 1 cm$^3$ hotspot dose to the bladder wall was the only dosimetric parameter correlating with LUTS at 3 months as well as at 6 months after implantation. The IPSS at 3 months correlated best with the bladder hotspot dose based on a CT-scan made one day after implantation whereas the IPSS at 6 months correlated
best with the bladder hotspot dose based on a scan made one month after implantation. A possible explanation is that morbidities at 3 months after implantation partially originated from trauma being induced during the implantation of the seeds. Of the other parameters investigated, the initial prostate volume, or almost equivalently, the number of implanted seeds was a strong predictor for LUTS. Of patients suffering from severe early LUTS, 2/3 had initial prostate volumes larger than 44 cm$^3$. 
References


Chapter 6

Minimizing the number of implantation needles for prostate I-125 brachytherapy; an investigation of possibilities and implications

Marcel J. Steggerda, Henk G. van der Poel, Luc M.F. Moonen

In press:
Brachytherapy, 2010
Abstract

Purpose
Reduction of the number of implantation needles for prostate brachytherapy will shorten the duration of implantation procedures and possibly reduce trauma-related morbidity. The purpose of this study was to investigate possibilities for the minimization of the number of needles and to investigate the consequences for the dose distribution.

Methods and materials
A planning study for 6 different prostate volumes was performed. The number of needles was minimized by changing fixed 1cm inter-seed spacing to free inter-seed spacing within the needles and by increasing the seed activity. Dose-volume parameters of prostate and organs at risk (OAR) bladder, rectum and urethra were determined. For plans with different needle and seed configurations the sensitivity for random seed placement inaccuracies was tested. Dose distributions of realized implants based on fixed (n=21) and free inter-seed spacing (n=21) were compared.

Results:
The average number of needles (±1SD) could be reduced from 18.8±3.6 to 12.7±2.9 (-33%) when changing from fixed inter-seed spacing to free inter-seed spacing and subsequently to 7.3±1.0 (-42%) by increasing the seed strength from 0.57U to 1.14U. These needle reductions resulted in increased dose inhomogeneity within the prostate and increased sensitivity of dose-volume parameters of the OAR for random geometrical inaccuracies. Introduction of free inter-seed spacing in our clinic resulted in very satisfactory dose-coverage of the prostate (D90=172±17 Gy), while the average number of needles was reduced by 30%.

Conclusion:
Substantial reduction of the number of implantation needles is possible without compromising adequate dose coverage of the prostate. However, the chance of an unpredicted high dose to the OAR increases as fewer needles are used.
6.1 Introduction

For the realization of a good implantation plan for brachytherapy of the prostate with I-125 seeds, a number of objectives have to be met. Adequate dose coverage of the prostate and limitation of the dose to organs at risk (OAR) is required. The plan has to be robust in the sense that common and unavoidable geometrical inaccuracies in the placement of the seeds will not result in unacceptable deviations from the planned dose distribution. Although practitioners might try to limit the number of implantation needles, a soundly based method to minimize the number of implantation needles is often lacking. Nevertheless, there are at least two reasons to minimize the number of implantation needles. In the first place, timesaving in the operating room (OR). Placement, loading and discharge of seeds takes a few minutes per needle. Consequently, the duration of an implantation procedure can be reduced substantially when an acceptable implantation plan with fewer needles will be realized. Secondly, the implantation needles will puncture organs and nerves at risk, such as penile bulb, neurovascular bundles, bladder neck and bladder trigone. Bowel symptoms, decreased erectile function and especially (temporary) lower urinary tract symptoms (LUTS) do occur after brachytherapy of the prostate [1-6]. Acute and very early toxic reactions after the implantation, such as acute urinary retention (AUR), are most likely to be due to the needle insertions since the delivered dose shortly after the procedure is probably too small to cause these symptoms. Several published papers suggest a relation between needle insertions and increased post-implant LUTS and erectile dysfunction [7-13]. Minimizing the number of implantation needles might be beneficial for the reduction of trauma related morbidity.

There are two possibilities to reduce the number of implantation needles. The first is to abandon the conventional fixed 10 mm inter-seed spacing technique and optimize the seed distribution within a needle track. The second is to increase the seed activity. Higher seed activity means fewer seeds and consequently fewer needles. The lower limit for the number of needles is determined by the required minimal dose within the prostate and the accepted maximum dose to the OAR.

The purpose of this study was to investigate how many needles can be saved by modifying needle loadings and seed activity. Also the consequences of needle minimization for the dose distribution and the sensitivity for random geometrical seed placement errors were investigated.
6.2 Methods and Materials

6.2.1 Inter-seed spacing
A drawback of conventional stranded seed systems is that the distance between seed centres within a needle track is fixed to 10 mm. The seeds have a length of 4.5 mm and in-between sequential seeds there is a non-active spacer with a length of 5.5 mm. Adding a seed in-between two sequential seeds is not possible and neither can seeds between the first and the last seed of the strand be left out when this would be beneficial for the dose distribution, i.e. optimization of seed positions within a needle track is not possible. The fixed, non-optimal, seed spacing of the seed strands necessitates the use of more needles than in case of optimized seed spacing. The use of loose seeds offers better possibilities to optimize the seed distribution within a needle track. Also stranded seed systems with customized inter-seed spacing became recently available. A recently introduced system of flexible strand assembling (ProLink, Bard Brachytherapy, Inc., Carol Stream, IL, USA) combines the advantages of conventional stranded seeds and loose seeds. The minimum distance between seed centers is 5 mm and the inter-seed spacing can be enlarged with 5 mm increments. The strands are to be assembled with a special apparatus in the OR according to the specifications of the implantation plan. This system, or equivalently a loose seed system, will be further referred to as the “free spacing system”, the conventional strand system as the “fixed spacing system”.

6.2.2 Implantation planning and objectives for optimization
For the study six previously planned cases were selected (see Table 6.1). Cases 1 (or 2), 3 (or 4), 5 and 6 have obvious different prostate volumes, cases 1 and 2 and cases 3 and 4 have equal volumes but different shapes. The prostate volumes were determined by delineation of transversal ultrasound images before implantation. For each of these cases five plans were made, starting of with conventional fixed seed spacing with a seed strength of 0.57 \( \mu \text{Gy.h}^{-1}.\text{m}^2 \) (U), then changing to free seed spacing and a sequential increase of the source strength in 3 steps (see Table 6.1). In all cases the reference dose was 145 Gy. No margin was added around the prostate in order to create a planning target volume (PTV). Instead, the minimal dose to 90% of the prostate (D90-pr) was chosen sufficiently high (>125%) to compensate for D90-pr decline due to seed placement errors and
other geometrical uncertainties. Seeds outside the prostate gland were allowed as long as at least one seed of the strand was within the gland. Seed positions were not allowed within 3 mm of the urethra, the bladder and the rectum. The objective was to make implantation plans with as few needles as possible, taking into consideration the following requirements for dose-volume histogram (DVH) parameters and total implanted activity:

1. The relative volume of the prostate receiving at least the reference dose (V100-pr) should be at least 99%.
2. D90-pr should be at least 125% of the reference dose.
3. The minimal dose to the highest dosed 10% of urethra (D10-ur) and the highest dosed 1 cm³ of the bladder wall (D1cc-bl) and the rectal wall (D1cc-re) should be minimized and not exceed 200%, 100% and 100% of the reference dose, respectively.
4. The total implanted activity for the free spacing plans should not exceed that of the conventional fixed spacing plan by more than 10%.

For this planning study commercially available software (Variseed V7.2, Varian Medical Systems, Charlottesville, VA, USA) was used. The selected source type for all cases was STM1251 (BrachySource, Bard Brachytherapy, Inc., Carol Stream, IL, USA). A standard transperineal implantation grid with a square arrangement of 5 mm spaced needle holes was used. Only the grid positions were allowed for needle positioning. The procedure was to manually determine a minimal amount of needle positions and use the automatic source placement module of the system to determine the seed positions within the needles, if necessary, followed by some manual adjustments. When the criteria were easily met the following step was to make a new plan with one needle less. When the criteria could not be met, not even after a rearrangement of the needles, a new plan was made with one needle more. This process was repeated until all criteria were met with as few needles as possible.
### Table 6.1 / part 1

Physical characteristics of the plans of the planning study, cases 1 - 3.

<table>
<thead>
<tr>
<th>Case/Prostate vol.</th>
<th>Seed spacing</th>
<th>Source strength (μGy.h⁻¹.m⁻²)</th>
<th>Seeds</th>
<th>Needles</th>
<th>Needles/cm³</th>
<th>D90-pr (%)</th>
<th>D10-ur (%)</th>
<th>V200-pr (%)</th>
<th>D1cc-bl (%)</th>
<th>D1cc-re (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 / 23 cm³</td>
<td>1cm seed-to-seed</td>
<td>0.57</td>
<td>46</td>
<td>13</td>
<td>0.560</td>
<td>127</td>
<td>18</td>
<td>169</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Free</td>
<td>0.57</td>
<td>47</td>
<td>8</td>
<td>0.345</td>
<td>126</td>
<td>29</td>
<td>176</td>
<td>72</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>Free</td>
<td>0.71</td>
<td>39</td>
<td>7</td>
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<td>32</td>
<td>177</td>
<td>82</td>
<td>81</td>
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<tr>
<td></td>
<td>Free</td>
<td>0.86</td>
<td>32</td>
<td>7</td>
<td>0.302</td>
<td>126</td>
<td>31</td>
<td>166</td>
<td>74</td>
<td>81</td>
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<tr>
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<td>Free</td>
<td>1.14</td>
<td>25</td>
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<td>0.259</td>
<td>126</td>
<td>28</td>
<td>180</td>
<td>79</td>
<td>82</td>
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<tr>
<td>2 / 24 cm³</td>
<td>1cm seed-to-seed</td>
<td>0.57</td>
<td>51</td>
<td>17</td>
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<td>164</td>
<td>98</td>
<td>72</td>
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<td>30</td>
<td>177</td>
<td>80</td>
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<td>0.71</td>
<td>42</td>
<td>10</td>
<td>0.418</td>
<td>126</td>
<td>28</td>
<td>163</td>
<td>89</td>
<td>77</td>
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<td></td>
<td>Free</td>
<td>0.86</td>
<td>34</td>
<td>9</td>
<td>0.377</td>
<td>128</td>
<td>39</td>
<td>178</td>
<td>89</td>
<td>71</td>
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<tr>
<td></td>
<td>Free</td>
<td>1.14</td>
<td>26</td>
<td>8</td>
<td>0.335</td>
<td>131</td>
<td>41</td>
<td>188</td>
<td>85</td>
<td>76</td>
</tr>
<tr>
<td>3 / 32 cm³</td>
<td>1cm seed-to-seed</td>
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<td>62</td>
<td>18</td>
<td>0.566</td>
<td>127</td>
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<td>148</td>
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<td>62</td>
<td>12</td>
<td>0.377</td>
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<td>173</td>
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<td>75</td>
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<td>10</td>
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<td>153</td>
<td>86</td>
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<td>34</td>
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<td>0.189</td>
<td>125</td>
<td>35</td>
<td>164</td>
<td>83</td>
<td>79</td>
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</tbody>
</table>

Abbreviations: 1cm seed-to-seed = distance between seed centres = 1 cm; Free = adjustable distance between seeds; D90-pr, D10-ur, D1cc-bl, D1cc-re = dose cut-off value (relative to 145 Gy) of cumulative dose-volume histogram at 90% of the prostate, 10% of the urethra, 1cc of the bladder and 1cc of the rectum, respectively; V200-pr = relative volume of the prostate receiving at least 200% of the reference dose.
Table 6.1 / part 2 Physical characteristics of the plans of the planning study, cases 4 - 6.

Abbreviations: 1cm seed-to-seed = distance between seed centers = 1 cm; Free = adjustable distance between seeds; D90-pr, D10-ur, D1cc-bl, D1cc-re = dose cut-off value (relative to 145 Gy) of cumulative dose-volume histogram at 90% of the prostate, 10% of the urethra, 1cc of the bladder and 1cc of the rectum, respectively; V200-pr = relative volume of the prostate receiving at least 200% of the reference dose.

<table>
<thead>
<tr>
<th>Case/Prostate vol.</th>
<th>Seed spacing</th>
<th>Source strength (μGy.h-1.m2)</th>
<th>Seeds</th>
<th>Needles/cm³</th>
<th>D90-pr (%)</th>
<th>V200-pr (%)</th>
<th>D10-ur (%)</th>
<th>D1cc-bl (%)</th>
<th>D1cc-re (%)</th>
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<tbody>
<tr>
<td>4 / 32 cm³</td>
<td>1cm seed-to-seed</td>
<td>0.57</td>
<td>61</td>
<td>21</td>
<td>0.656</td>
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<td>143</td>
<td>93</td>
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<td>0.86</td>
<td>42</td>
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<td>0.313</td>
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<td>30</td>
<td>146</td>
<td>91</td>
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<tr>
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<td>Free</td>
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<td>31</td>
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<td>0.250</td>
<td>126</td>
<td>31</td>
<td>157</td>
<td>77</td>
</tr>
<tr>
<td>5 / 39 cm³</td>
<td>1cm seed-to-seed</td>
<td>0.57</td>
<td>68</td>
<td>21</td>
<td>0.533</td>
<td>127</td>
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<td>159</td>
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<tr>
<td></td>
<td>Free</td>
<td>1.14</td>
<td>37</td>
<td>8</td>
<td>0.203</td>
<td>129</td>
<td>38</td>
<td>155</td>
<td>91</td>
</tr>
<tr>
<td>6 / 51 cm³</td>
<td>1cm seed-to-seed</td>
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<td>81</td>
<td>23</td>
<td>0.454</td>
<td>128</td>
<td>22</td>
<td>145</td>
<td>88</td>
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<td>143</td>
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<td>67</td>
<td>13</td>
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<td>125</td>
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<td>162</td>
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<td>0.86</td>
<td>57</td>
<td>10</td>
<td>0.197</td>
<td>130</td>
<td>33</td>
<td>177</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>Free</td>
<td>1.14</td>
<td>44</td>
<td>8</td>
<td>0.158</td>
<td>127</td>
<td>33</td>
<td>161</td>
<td>97</td>
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</tbody>
</table>
6.2.3 Sensitivity for random seed placement errors

The placement of seeds is subject to inaccuracies caused by needle diversions, organ deformation and displacement during insertion and retraction of needles, inaccurate needle depths and discharge of seeds from the needles. The question arises whether the influence of these displacements on the dose distribution depends on the geometry of the implant and/or the activity of the seeds. Since systematic errors will depend largely on the seed system, equipment used and the skills and experience of the team performing the procedure, it is impossible to perform a test which outcomes will be generally valid. Moreover, if we assume practitioners to be aware of systematic seed placement errors, adapting the implantation technique or planning can compensate for these errors. The focus of this test was on random geometrical errors for which, due to their unpredictable behaviour, no compensations are possible. Based on evaluations of realized implants, the real placement of the seed strands were estimated to be normally distributed around the planned position with a standard deviation (1SD) of 2 mm in left-right and posterior-anterior directions and 3 mm in caudal-cranial direction. Accordingly, 40 different implants for 3 plans of case 3 and 3 plans of case 4 (see Table 6.1) were "realized" using Monte Carlo simulation. The two cases were selected because they had equal volumes but different needle plans due to different shapes. The 3 plans were the plan with fixed spacing and 0.57 U seeds, the plan with free seed spacing and 0.57 U seeds and the plan with free spacing and 1.14 U seeds. All seeds within one strand or needle were assumed to have the same deviation from the planned position. For each simulation the seed positions were entered in the planning program and D90-pr, D1cc-bl, D1cc-re and D10-ur were calculated.

6.2.4 Comparison of clinical cases

Recently we changed from a fixed spacing system (Rapid Strands, Oncura, Arlington Heights, IL, USA) to the free spacing system described in the paragraph “Inter-seed spacing” (ProLink, Bard Brachytherapy, Inc., Carol Stream, IL, USA) in our department. The seed strength remained the same with the new system (0.57 U) but seed spacing optimizations within needle tracks were performed in order to reduce the number of needles. The team performing the implants remained unchanged after the introduction of the free spacing system. Part of the results of the planning study described above could now be tested in clinical practice. Before
and after the system change post-implant transrectal ultrasound (TRUS) and computed tomography (CT) scans were made of 21 cases of either technique, both at one day and at one month after implantation in order to compare the dosimetry of both systems. The TRUS and CT scans were registered and the combined modality was used to delineate the prostate, bladder and urethra. The method has been described in detail in a previous paper [14]. Since the urinary catheter, placed during the implantation procedure, was still present during the scans at one day after implantation, the urethra could be delineated at the images of these scans. During the scans at one month after implantation no urinary catheter was present and consequently the urethra could not be delineated. The presence of the TRUS-probe in the rectum during the scans made it impossible to accurately determine the rectal dose.

6.3 Results

6.3.1 Influence of needle reduction on the dose distribution

From Table 6.1 it is clear that for each case the number of needles could be reduced substantially when switching from fixed to free seed spacing. Further reduction could be achieved by increasing the source strength. The mean±1SD number of needles for the 5 plans were 18.8±3.6, 12.7±2.9, 10.7±2.3, 9.2±1.5 and 7.3±1.0, respectively. As a result of the constraints for optimization the V100-pr and the D90-pr differed very little from one plan to another. These needle reductions could only be achieved by having no constraints for the dose homogeneity within the prostate. Consequently, the overdosed volume V200-pr differed largely between subsequent plans. The number of needles per cm³ prostate volume (Needles/cm³ in column 6 of Table 1) depended on the needle loading but also on the prostate volume and the prostate shape. The number of needles/cm³ was smallest for case 6 (large volume) and highest for case 2 (small volume). The prostates of cases 1 and 2 and cases 3 and 4 had equal volumes but required different number of needles/cm³ due to different shapes. The shapes the prostates of cases 1 and 3 were convex without irregularities. The prostate of case 2 had a small extension at the base requiring more needles to meet the planning objectives than the prostate of case 1. The prostate of case 4 was rather concavely shaped and therefore required more needles to the meet the planning objectives than case 3.
The ratios of parameters of the subsequent free spacing plans and the conventional fixed spacing system with 0.57 U source strength are displayed in Fig. 6.1. The ratios are average values of the 6 investigated cases, the error bars are 1SD. V100-pr is not denoted in the figure because the value was by definition between 99% and 100% for all cases. Most substantial deviations from unity can be seen in the number of needles and in V200-pr. Since the standard deviations for the V200-pr ratios were very high and the number of averaged cases small, the mean ratio of plans with free seed spacing and 0.57 U did not differ significantly (p>0.05) from unity. Remarkably, none of the V150-pr ratios differed significantly from unity. The D10-ur increased slightly, but significantly, in 2 of the 4 ratios and slightly more activity was required in the high activity cases.

![Fig. 6.1](image)

**Fig. 6.1** Ratios of parameters for free seed spacing plans with various seed strengths and fixed seed spacing plans with 0.57 U seeds. The ratios are average values of 6 cases; the error bars are 1SD. Ratios significantly different (p<0.05) from unity are marked (*).

### 6.3.2 Sensitivity for random seed placement errors

The ratios of simulated and planned DVH values (N=40) were binned and denoted in the frequency distribution histograms of Fig. 6.2. In Fig. 6.2a it can be seen that D90-pr is very likely to decline due to random seed placement errors. The average ratios for the plans of cases 3 and 4 were all between 0.90 and 0.94. There were
more high D90-pr decreases (simulation/plan < 0.9) for the free spacing plans but there were no decreases lower than 0.8. For the 3 OAR only the average D10-ur ratio for both free spacing plans of case 3 was significantly higher than the average ratio for the fixed spacing plan. Despite few significant changes in average ratios for free spacing plans compared to fixed spacing plans, high ratios were more frequent in free spacing plans than in fixed spacing plans (Fig. 6.2b-d). This means that large deviations from planned DVH values were more likely to occur after execution of the free spacing plans with relatively few needles than in case of the fixed plans with relatively many needles. This effect was more extreme for the free spacing plans with 1.14 U seeds than with free spacing plan with 0.57 U. There were small differences in the sensitivity for random geometrical errors between case 3 and case 4. However, the global pattern was very much the same for both cases.
Case 3
D1cc-bl

Fixed 0.57U, 21 needles, mean=1.06 1SD=0.11
Free 0.57U, 14 needles, mean=1.02 1SD=0.16
Free 1.14U, 8 needles, mean=1.11 1SD=0.14

Case 4
D1cc-bl

Fixed 0.57U, 18 needles, mean=1.01 1SD=0.07
Free 0.57U, 12 needles, mean=0.99 1SD=0.09
Free 1.14U, 6 needles, mean=1.04 1SD=0.11

Case 3
D1cc-re

Fixed 0.57U, 18 needles, mean=1.00 1SD=0.09
Free 0.57U, 12 needles, mean=0.99 1SD=0.10
Free 1.14U, 6 needles, mean=1.02 1SD=0.13

Case 4
D1cc-re

Fixed 0.57U, 21 needles, mean=0.99 1SD=0.08
Free 0.57U, 14 needles, mean=1.02 1SD=0.09
Free 1.14U, 8 needles, mean=1.03 1SD=0.11
Minimizing number of needles

Fig. 6.2 Frequency distributions of 40 simulations of 3 different implantation plans for the cases 3 and 4 of the planning study (see Table 6.1). The values of D90-pr (a), D1cc-bl (b), D1cc-re (c) and D10-ur (d) after the simulation of random seed placement errors were divided by the value of the planning. These ratios were binned in order to visualize the frequency distributions in these histograms. Mean values and standard deviations (1SD) are denoted in the upper right of each histogram frame. Mean values for both free seed spacing plans that were significantly different (p<0.05) from that of the fixed spacing plan are marked (*).

6.3.3 Comparison of clinical cases

In Table 6.2 some physical parameters of the 21 fixed spacing cases and the 21 free spacing cases are denoted. The number of needles per cm$^3$ prostate volume was 30% lower for the free spacing cases than for the fixed spacing cases while the source strength U per cm$^3$ prostate volume was the same for both groups. The DVH values for the prostate, urethra and bladder were all higher for the free spacing group than for the fixed spacing group. Remarkably, the average D90-pr stability expressed in the ratio D90-pr realized/planned was substantially and significantly higher for the free spacing group. It should be noted that D10-ur was
based on a scan made one day after implantation. This means that the denoted values for this parameter are underestimations as was clearly demonstrated in a previous study [15]. However, for the comparison of both techniques, these values were still considered to be useful. The DVH values for the prostate and the bladder were based on scans made one month after the implantation and could therefore be considered a good representations for the realized dose distributions.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fixed spacing system(^1) (n=21)</th>
<th>Free spacing system(^2) (n=21)</th>
<th>T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean 1SD</td>
<td>Mean 1SD</td>
<td></td>
</tr>
<tr>
<td>Needles / prost vol (cm(^{-3}))</td>
<td>0.709 0.196</td>
<td>0.499 0.126</td>
<td>0.0003</td>
</tr>
<tr>
<td>Tot source str / prost vol (U.cm(^{-3}))</td>
<td>1.16 0.19</td>
<td>1.17 0.18</td>
<td>0.791</td>
</tr>
<tr>
<td>V100-pr (%)</td>
<td>88.5 6.5</td>
<td>92.5 6.7</td>
<td>0.046</td>
</tr>
<tr>
<td>V150-pr (%)</td>
<td>57.5 11.9</td>
<td>70.5 11.2</td>
<td>0.001</td>
</tr>
<tr>
<td>V200-pr (%)</td>
<td>31.3 11.9</td>
<td>36.9 11.8</td>
<td>0.148</td>
</tr>
<tr>
<td>D90-pr (%)</td>
<td>98.9 14.8</td>
<td>118.4 11.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>D90-pr realized/planned</td>
<td>0.771 0.110</td>
<td>0.903 0.101</td>
<td>0.0004</td>
</tr>
<tr>
<td>D10-ur (%)</td>
<td>134.6 24.9</td>
<td>147.7 28.0</td>
<td>0.117</td>
</tr>
<tr>
<td>D1cc-bl (%)</td>
<td>70.0 14.7</td>
<td>90.1 13.6</td>
<td>0.002</td>
</tr>
</tbody>
</table>

\(^1\) Oncura Rapid Strands; \(^2\) Bard Prolink Strands.

Table 6.2 Comparison physical characteristics of clinical cases

6.4 Discussion

6.4.1 Outcomes planning study

The conventional approach of loading implantation needles with seed strands with fixed inter-seed spacing and a moderate seed activity requires relatively many needles to adequately irradiate the prostate. The planning study shows that the number of needles can be reduced substantially by free seed spacing within the needles and by increasing the seed activity. There are a number of published studies demonstrating the effect of increasing seed activity [16-19] but to our knowledge this is the first study with the explicit purpose to minimize the number of implantation needles. We demonstrated that the number of needles could be
reduced without substantially increasing the dose to the OAR (Fig. 6.1). The total implanted activity was on average slightly higher for the free spacing plans compared to the fixed spacing plans but never exceeded 10% due to a constraint in the planning procedure. Since there is no convincing evidence from literature that increased dose inhomogeneity or high intraprostatic dose regions contribute to post-implant morbidity [20] we did not constrain the volume within the prostate receiving a high dose. Consequently, the overdosed volume V200-pr increased substantially after decreasing the number of needles, V150-pr, however, did not.

### 6.4.2 Geometrical uncertainties

The Monte-Carlo simulations were based on the assumption that random seed placement errors were normally distributed with a certain 1SD in each direction. This 1SD can be considered to be a rough estimation based on the evaluation of implants realized in our clinic. This estimation is probably not generally applicable for all systems and practitioners. However, the purpose of the simulations was to compare the effect of random seed placement errors on the dose distribution for alternative needle loadings (free seed spacing and higher source strength) and for conventional needle loadings (fixed seed spacing and low source strength). Although smaller or larger 1SD values certainly would have influenced the absolute values of the simulated DVH parameters, the relative effect on either needle configuration would not have been very different. Therefore the assumption was made that the magnitude of the chosen 1SD was not very critical for relative comparisons between the different needle/seed configurations. It seems impossible to model systematic seed placement errors that would be generally applicable for the enormous variation in technical details of implantation systems and skills of individual practitioners. However, one systematic error has to be mentioned because it influenced the dosimetry results of the investigated clinical cases. Seed strands tend to drift in inferior direction and as a consequence will influence the dose distribution [15,21]. The magnitude of these inferior displacements probably depends on the physical construction of the strands. Since there is not enough detailed knowledge about this phenomenon we do not know whether the magnitude of the effect on the dose distribution will depend on the number of needles used.

Three highly different plans of two cases of the planning study were subjected to random seed placement errors. For each plan 40 simulations were performed. As a
result of the placement errors the average D90-pr decreased for nearly all plans of both cases. For the OAR, bladder, rectum and urethra there were more high increases of DVH values (simulation/plan >1.2) in the free spacing plans compared to the fixed spacing plans. The latter effect was probably due to the relatively heavily loaded needles in the free spacing plans that can cause considerable dose increase when diverted towards the OAR.

6.4.3 Dose distribution of clinical cases
Filtering out the net effect of fewer needles on dose-volume parameters after switching from fixed to free seed spacing appeared to be difficult because other physical characteristics may have influenced the comparison between both systems. As mentioned previously, seed strands tend to displace in inferior direction. Our fixed spacing plans were realized with Oncura Rapid strands whereas the free spacing plans were realized with Bard ProLink strands. The inferior displacement with respect to the prostate is substantial for Rapid Strands. Moerland et al. [21] determined an average D90-pr decline of 39 Gy for these type of strands which is similar to what we found: 23% of 186 Gy = 43 Gy. The average D90-pr decline for the Prolink strands was only 10% (realized/planned = 0.90, Table 6.2). The difference might be explained by the different physical construction of both strands. The surface of a Rapid Strand is rather smooth and the diameter is practically the same over the whole length of the strand making it easy to move inside a tight canal. The seeds of a ProLink strand are connected with spacers having a larger diameter than the seeds. This might hamper movement, i.e. the difference in D90-pr decline was probably not caused by the difference in needle configurations but by differences in the mechanical properties of both types of strands. The low bladder dose (D1cc-bl) for the Rapid Strand implants can also be explained by the inferior displacement of the strands [15]. The average ratio realized/planned D90-pr of the free spacing ProLink implants was 0.90 and closely approaches the ratios simulated/planned D90-pr of the planning study (0.92 and 0.90 for cases 3 and 4 respectively). Assuming that the systematic errors for these type of implants were small, the average D90-pr was well predicted by the average value of the Monte Carlo simulations. The fact that the standard deviation of the (clinically) realized/planned D90-pr ratio (0.10) was larger than for the (Monte Carlo) simulated/planned D90-pr ratios (0.04 and 0.03 for cases 3 and respectively) can be due the fact that for the clinical cases the prostate had to be
delineated twice; once on the TRUS images on the OR and once on the TRUS images of the post-implant scan. The differences between both must have caused an additional uncertainty, which resulted in a higher 1SD.

Although the average V200-pr and D10-ur were higher in the free spacing group, the difference with the fixed spacing group was not significant. On the other hand V150-pr was significantly higher in the free spacing group. V150-pr was stronger correlated with D90pr than V200-pr, however, and the difference in V150-pr could, at least partially, have the same cause as the difference in D90-pr as described above.

Switching to the free spacing system resulted, as was predicted by the planning study, in a needle reduction of approximately 30%. The slightly higher average number of needles per cm³ prostate volume for the clinical cases compared to the cases of the planning study was caused by a less strict minimization procedure for the implantation plans of the clinical cases. Because a comprehensive morbidity evaluation of the recently introduced free spacing system would be premature at this stage this will be a subject for a future study.

6.4.4 Facts from literature

There is some evidence from literature that transperineal needle insertions can cause genitourinary (GU) morbidity. Buskirk et al. [7] proved that transperineal needle insertions after template-guided prostate biopsies cause AUR in a substantial number of patients. The recorded incidence (11.5%) was comparable with reported numbers in literature for AUR after brachytherapy of the prostate. This may lead to the conclusion that AUR after prostate brachytherapy is due rather to needle insertions than to irradiation dose. They also found that the number of needles was a predictor for AUR. A number of other studies found a relation between urinary toxicity and the number of needles [8,9,12,13]. An earlier study of our own group suggested a relation between needle punctures of the bladder wall and early urinary morbidity [11]. MacDonald et al. [10] found a significant relation between erectile dysfunction and the number of implantation needles. The reason that relatively few published studies found a relation between GU toxicity and the number of implantation needles can be the fact that the variation in the number of needles for a certain prostate volume was small within investigated patient groups. Since prostate volume itself is a strong predictor for
early toxic reactions such as AUR [5], the effect of number of needles might have been disguised.

A comprehensive study of the robustness of prostate seed implants was published by Beaulieu et al. [16]. Post-implant seed geometries were simulated with a Monte Carlo method. They found optimal V100-pr and D90-pr robustness with a seed activity of approximately 0.7 mCi (0.89 U). Their objectives for optimization did include minimization of hotspots and did not include minimization of the number of needles and were therefore different from our objectives. They registered a relative constant sensitivity for geometrical inaccuracies up to seed activities of 0.9 mCi (1.14 U). Their robustness qualification was based on average changes between pre-implant and post-implant dosimetric indices over 80 simulations. Unfortunately, no individual simulations were studied. However, although average changes can be small or non-existent, individual discrepancies can be substantial. Narayana et al. [18] concluded, based on a randomized trial, that implants with 0.76 U seeds resulted in significantly better post-implant V100-pr than implants with 0.4 U seeds. However, Moerland and Battermann pointed out that this could be the result of higher total implanted activity in the high activity arm [22].

6.5 Conclusions

From the planning study follows that the number of implantation needles could be reduced by more than 30% when switching from a conventional fixed 1 cm inter-seed spacing concept to a method that allows variable inter-seed spacing within a needle track. An additional reduction of the number of needles with approximately 40% could be achieved by increasing the source strength from 0.57 U to 1.14 U while maintaining sufficient V100-pr and D90-pr. The price paid was a substantial increase of V200-pr compared to fixed inter-seed spacing with 0.57U seeds. There was, however, no substantial difference in the dose to the OAR after optimizing the inter-seed spacing and increasing the source strength. The sensitivity of D90-pr for random geometrical seed placement errors was approximately the same for the investigated needle and seed spacing configurations. However, the chance of individual increases of more than 20% in DVH values of the OAR due to these errors increased as fewer needles were used. This means that dose burdens for OAR are less predictable for implants with a low number of heavily loaded needles. Evaluation of clinically realized implants before and after introduction of a free inter-seed spacing system showed significantly better prostate coverage in the free
spacing group compared to the fixed spacing group, while the average number of needles was reduced by 30%. This superior coverage was probably caused by favourable mechanical properties of the free spacing system. Minimization of the number of implantation needles is likely to reduce trauma related GU toxicity. Considering the outcome of this study, however, it is recommended to introduce needle reduction procedures in small steps while carefully evaluating post-implant dose distributions and monitoring acute and non-acute toxic reactions.
References


Chapter 7

General discussion
7.1 Multi-modality imaging of the prostate

For meaningful analysis of dose-effect relations, the dose distribution in the target volume and organs at risk (OAR) has to be determined accurately. High quality imaging, allowing accurate visualisation and reconstruction of the geometry of anatomical structures and radiation sources is mandatory for reliable dose distribution determination (dosimetry). In case of brachytherapy (BT) of the prostate, computed tomography (CT) is usually the image modality of choice for post-implant dosimetry. However, the delineation of the target volume - usually the whole prostate gland - on CT-images is cumbersome due to poor contrast between the organ and surrounding tissues [1,2]. Transrectal ultrasound (TRUS) offers better visualisation of the prostate boundaries but poor visualisation of the titanium encapsulated I-125 seeds (this thesis, chapter 2).

In chapter 2 a method has been described to combine TRUS and CT images in order to both delineate the prostate and reconstruct the seed implant with sufficient accuracy. An advantage of this method is that both image sets can be made simultaneously. This means that the anatomy during both acquisitions is the same and that the geometry of both sets will perfectly match after registration. Seppenwoolde et al. [3] recently demonstrated that there can be a serious mismatch when TRUS and CT are made at different moments in time and when the CT-images are acquired without TRUS transducer in the rectum. Another advantage of the method described in chapter 2 is that the base of the prostate is usually clearly visible on sagittal and coronal reconstructions of the 3D TRUS-scan. Accurate delineation of the base of the prostate makes it relatively easy to delineate the bladder neck on fused TRUS-CT images, which is usually cumbersome on CT-images alone. In chapter 5 we demonstrated that hotspot doses in the bladder are predictors for urinary morbidity. Accurate delineation of the bladder neck was an important condition for this study. Also the apex of the prostate is better visible on TRUS images than on CT images on which the plane between the prostate and the levator ani muscle can not be clearly distinguished.

Because of its superior soft tissue contrasts, Magnetic Resonance Imaging (MRI) is often recommended for organ delineation in the pelvic region [4,5]. MRI, however, has the same limitation as TRUS; the reconstruction of the seeds is very difficult. Consequently an X-ray facility or CT-scanner has to be used to make a 3D reconstruction of the seed implant [6,7]. On the MRI the patient will be scanned in a different position on a different couch than during the CT-scan. Because some time
will pass between both scans the bladder and rectum filling can change. These changes can result in a mismatch of the anatomy. This problem does not occur in case of simultaneous TRUS-CT scanning. Bloch et al. [8] investigated the possibility of post-implant dosimetry based on MRI alone. They found good results reconstructing the seeds from contrast enhanced T1-weighed MRI-images. In combination with T2-weighted images for the delineation of the prostate they suggested this to be a good alternative for combined MRI-CT imaging for post-implant dosimetry. This suggestion, however, was challenged by Beaulieu et al. [9] who stated that density information from CT is required for a reliable dosimetry. They based this conclusion on a Monte Carlo dosimetry study by Carrier et al. [10]. However, the fact that the generally accepted recommendations of Task Group 43 for brachytherapy dosimetry [11] are based on homogeneous watery tissue make their objections less relevant. More important is the fact that the time interval between both image acquisitions is short and that the patient remains in the same position. When basing the post-implant dosimetry on multi-modality imaging, simultaneity is an important condition for successful image registration. For the study presented in chapter 3, evaluation with combined TRUS-CT allowed a realistic comparison of the prostate volume before and after implantation of the seeds since the prostate was delineated on the same image modality (TRUS) during implantation planning in the operation room (OR) and the post-implant evaluations. Other studies concerning this subject use TRUS for implantation planning and CT and/or MRI for post-implant evaluations [12,13]. The latter method is likely to introduce a systematic error due to image modality depended interpretations of the prostate boundaries.

Except for the above mentioned favourable properties of the TRUS-CT based post-implant dosimetry there are also some inherent disadvantages. The rectal probe will slightly deform the dorsal side of the prostate and this will have some influence on the dose distribution. We tried to limit the pressure on the prostate as much as possible to minimize this effect but there is a trade-off with image quality, i.e. insufficient pressure will degrade the TRUS image quality. Another drawback is that the rectal dose can not be determined accurately with the TRUS probe in situ. The two mentioned limitations will also occur in case of MRI with rectal coil. TRUS has proven to be a very useful image modality for image guided BT in the OR. A reliable 3D evaluation of the seed distribution in the prostate, however, can be cumbersome using TRUS alone. Occasionally post-implant dosimetry reveals
an unexpected sub-optimal dose distribution. In our clinical practise (NKI-AVL) there were, based on post-implant dosimetry, 12 cases with an unintentional D90 < 145 Gy during the last 100 cases. Although this number was considerably lower than during the first 100 patients treated due to learning curve and improved techniques, these low values could have been avoided with the aid of adequate 3D imaging in the OR. Therefore, also in the OR we need a second modality to make a good 3D reconstruction of the seed implant in order to prevent patients to be dismissed from the OR with an inadequate dose coverage of the prostate. Ideally, the method prescribed in chapter 2 should be applicable in the OR as well. Unfortunately, a CT scanner in the OR is not very common. Recently, however, methods have been developed to combine TRUS and C-arm cone beam CT to check the dose distribution before patient dismissal from the OR [14,15]. An additional advantage of accurate dosimetry in the OR is that extra activity implanted to compensate for possible seed placement errors can be avoided which could result in reduced post-implant toxicity.

7.2 Post-implant seed kinetics and anatomy changes

The total deposited dose to the target volume and OAR, either by external beam radiotherapy (EBRT) or BT, is an accumulation of continuous changing geometrical properties of the anatomy in relation to the radiation sources. The challenge is to make a reliable estimation of the dose distribution after a series of fractioned dose deliveries by means of EBRT or high dose rate BT or after a long continuous dose accumulation by means of low dose rate BT. The estimated dose distribution is usually based on a single, or a limited number of image acquisitions before or during the process of dose deposition. In case of radiotherapy of the prostate, permanent seed implantations seem to have an important advantage over EBRT in the sense that the seeds are implanted in the prostate and thus the radiation sources move simultaneously with the target volume whereas the external beams have to be aimed at a target volume which can change from one day to another [16,17]. In chapter 3, however, we demonstrated that the geometry of the anatomy with respect to the seed implant changes over time. The prostate as well as the seed implant shrinks, while the seeds drift in caudal direction. The change in dose distribution is very large during the first month after the implantation and relatively small after one month. Our findings concerning implant shrinkage and caudal displacement of seeds were later confirmed by Pinkawa et al. [18] for the same
brand of stranded seeds (Rapid Strands, Oncura, Arlington Heights, IL, USA). After switching to another brand (ProLink, Bard Brachytherapy, Inc., Carol Stream, IL, USA), we found that the caudal shift of the seed implant reported in chapter 3 was rather a characteristic of the Rapid Strand system than of the ProLink system. The lower D90 decline and higher bladder dose of implants realised with ProLink strands compared to Rapid Strands is likely to result from smaller caudal drift of the ProLink strands. This phenomenon was discussed in chapter 6 where implants realised with both systems were compared. Moerland et al. [19] found a similar D90 decline of implants realised with Rapid Strands and also related this to caudal displacements of strands. Their hypothesis, however, was that especially seed strands placed caudally from the prostate apex were subject to caudal displacements whereas in chapter 3 and in the study of Pinkawa et al. far basally placed seed strands were thought to cause caudal implant displacements. It cannot be ruled out, however, that both hypotheses overlap. More detailed analysis has to bring more clarity to this phenomenon.

The question arises whether the conclusions of chapter 3 are generally applicable or that these are only valid for Rapid Strand implants. After changing to the ProLink seed system we again compared the dose distributions based on a scan made one day and one month after the implantation of the seeds (chapter 6). For the prostate the differences between Dose Volume Histograms (DVHs) based on either scan appeared to be larger for ProLink implants. In chapter 3 we concluded that the D90 of the prostate did not depend on the post-implant time interval of the scan it was based on. For the 21 investigated ProLink implants D90 based on the scan after one months was on average 9.7% higher than the D90 based on the scan after one day. This difference was highly significant (p<0.001). The pattern, small differences at low dose values and high differences at high dose values of the prostate DVHs, was the same for Rapid Strand and ProLink implants but the absolute differences were larger for the latter. We hypothesise that the D90 of the prostate has the tendency to increase during the first month after implantation due to oedema resolution but that in case of Rapid Strand implants this increase will be compensated by a decrease due to caudal drift of the seed strands. This caudal drift also resulted in lower bladder doses on one-month scans compared to one-day scans. In case of ProLink implants these differences in bladder dose were smaller. For both systems there was a reasonable correlation between the investigated DVH-values based on scans one day and one month after
implantation (Pearson correlation factors between 0.5 and 0.9). The conclusion of chapter 3 that high dose values of prostate and urethra will be underestimated whereas the high dose values of the bladder will be overestimated when based on a scan made one day after implantation is valid for both Rapid Strand and ProLink implants but the values presented do relate to Rapid Strand implants only. This implicates that after switching to seeds or strands of another vendor or after changing implantation techniques the validity of existing knowledge regarding seed kinetics and anatomy changes should be checked.

7.3 Relation between physical properties of seed implants and side effects

In chapters 4 and 5 we focussed on lower urinary tract symptoms (LUTS), being the most common complaint after BT of the prostate. Although decreased erectile functioning is also common after BT, as well as after EBRT and prostatectomy, this very complex phenomenon needs another series of well designed investigations in order to identify the most important predictor(s). The LUTS characteristics denoted in Fig. 1 of chapter 4 are typical for BT; increasing symptoms after implantation, peaking between 6 and 12 weeks, then slowly decreasing to (almost) baseline after one year. From table 1 of chapter 4 it is clear that the most investigated parameters in relation to LUTS are base line symptoms, prostate volume, prostate dose and urethra dose. Surprisingly, in existing literature very little or no attention was paid to possible relations between LUTS and dose to the bladder. Despite the small patient group, the investigation denoted in chapter 5 shows a significant positive relation between LUTS and dose "hotspots" in the bladder. After this study this relation was re-investigated in a later patient group implanted with a different brand of sources and a different needle loading technique (see chapter 6). The bladder hotspot dose D1cc-bl appeared to be a significant predictor for increased LUTS (rise of prostate international symptom score “IPSS”) during the first 3 months after implantation (p = 0.003, N= 89). It is therefore reasonable to assume that the positive correlation found in chapter 5 was no coincidence but that bladder dose is a predictor for increased LUTS after BT. To our knowledge no other studies from literature investigated the relation between bladder hotspot dose and post-brachytherapy LUTS. However, in a recent publication by Thomas et al. [20] results of investigated relations between the dose at different segments of the urethra and LUTS were presented. Only the dose to the part of the urethra closest to the base of the prostate appeared to correlate with LUTS. Unfortunately, they did not
determine the dose to the bladder neck as part of the study. Because the expected correlation between the dose to urethra at the base and the dose to the bladder neck it could very well be that they would have found a (stronger?) relation between the latter and LUTS.

The study presented in chapter 5 should be followed up by a study involving more patients and more detailed analyses of the relation between LUTS and bladder dose. It is very well possible that irritative symptoms originate from high doses at particular regions of the bladder neck or bladder trigone. This was not investigated in the present study.

Another aspect largely ignored from published studies concerning post-implant LUTS is mechanical trauma. As discussed in chapter 4, acute urinary retention (AUR) is likely to be the result from the needle insertions and has probably no relation with radiation dose. The fact that the incidence of AUR is higher for men with large prostates than for men with small prostates makes it also more likely that needle insertions are responsible. Men with a large prostate usually have a large transition zone. Swelling of a large transition zone after implantation may cause obstruction of the bladder outlet.

In the discussion of chapter 5 it was suggested that early LUTS could (partially) be due to needle puncturing of the bladder and that high hotspot doses in the bladder are indicators for deeply inserted needles. This suggestion, however, will be very difficult to prove. To prove that there is any relation between acute or early LUTS and needle insertions the variation in the number of needles has to be large which was not the case in our study. An additional assumption that has to be made is that the severity of mechanical trauma correlates with the number of implantation needles. Recently, in a study over 712 permanent BT cases by Keys et al. [21], acute urinary toxicity was related to the number of needles which makes this assumption plausible.

Because there is enough reason to believe that acute urinary symptoms such as AUR are related to the number of implantation needles, we investigated methods to reduce the number of needles. The results of this study are presented in chapter 6. One of the methods, allowing 'free inter-seed spacing', has been introduced in our clinic and resulted in a substantial reduction of the number of needles. After this substantial reduction in number of needles the incidence of AURs was reduced from 13% to 6%. This reduction, however, was only ‘borderline significant’ (Chi-square test p=0.07) possibly due to low patient numbers. Also other factors such
as increased skills by the physicians and another needle placement strategy may have influenced this difference.

More difficult than reducing trauma by less needle insertions is the reduction of the bladder dose. At least an effort should be made to avoid seed placement in the bladder. This, however, can be cumbersome when trying to adequately implant the prostate base. In cases where the dose to the prostate base is not of primary importance (no tumour present) hotspots in the bladder can easily be avoided.

7.4 The potentials and future developments of prostate brachytherapy

7.4.1 BT compared with advanced EBRT techniques

Modern EBRT techniques, such as intensity modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT), have greatly improved dose distributions for prostate cancer treatment with respect to more conventional EBRT techniques, allowing higher dose to the prostate while limiting the dose to the OAR [22]. Does this mean that BT will lose its position in treatment of localised prostate cancer in favour of EBRT? As discussed earlier in chapter 1 there are unfortunately no results based on randomised trials that could either prove (IMRT) EBRT or BT to be superior in terms of biochemical control, survival rate or treatment related morbidity. Nevertheless, there are rationales for the expectation that brachytherapy will remain an attractive alternative for EBRT despite important technological improvements for the latter.

In the first place, TRUS-guided BT is a far less complex technology than IMRT-IGRT. Although many Radiotherapy-departments will find state-of-the-art IMRT-IGRT a bridge too far there is no doubt that they will be able to implement TRUS-guided BT successfully. The method and the equipment required (ultrasound scanner and laptop with planning software) are well established. The most critical component of the seed placement procedure is the skill of the paramedical and medical staff involved to make an adequate implantation plan and to place the seeds as good as possible in accordance with this plan. Hospitalisation time including the implantation procedure on the OR for BT treatment takes 1 day only, whereas EBRT requires a daily hospital visit for several weeks in a row. This could be a second argument in favour of BT.
Fig. 7.1a-b Dose-Volume histograms of IMRT treatment plan and permanent brachytherapy I-125 treatment plan for low-risk prostate cancer case. The prescribed dose was 78 Gy for the IMRT plan and 145 Gy for the brachytherapy plan.
Fig. 7.1c-d Dose-Volume histograms of IMRT treatment plan and permanent brachytherapy I-125 treatment plan for low-risk prostate cancer case. The prescribed dose was 78 Gy for the IMRT plan and 145 Gy for the brachytherapy plan.
When comparing dose distributions of IMRT and BT with I-125 seeds some striking differences can be observed. In Fig. 7.1 DVHs of an IMRT-plan and a BT-plan are compared. The prostate volume was 32 cm$^3$, the anatomical features of the patient concerned were thought to be rather typical without extreme anatomical features. The IMRT-plan has the following specifications: 78 Gy (39 x 2 Gy) on prostate + 0 mm margin in dorsal direction and 5 mm margin in other directions; 72.2 Gy (39 x 1.85 Gy) on prostate + 7 mm margin in all directions; 5 multi-segment 10 MV IMRT beams. The brachytherapy plan has the following specifications: 59 I-125 seeds, seed strength = 0.57 U, V100 = 98%, D90 = 184 Gy. Both plans are realistic and representative for the clinical practice in the NKI-AVL (2008), concern the same patient and are based on the same CT-scan. The dose values of the DVHs are relative to the prescribed dose to the prostate, i.e. 78 Gy for the IMRT-plan and 145 Gy for the BT-plan. The dose distribution within the prostate is very heterogeneous for the BT implant compared to the IMRT plan (Fig. 7.1a). For the BT-plan 50% of the prostate receives a dose of at least 167% of the prescribed dose, for the IMRT-plan the overall maximum dose to the prostate is only 103% of the prescribed dose. On the other hand for the BT-plan 90% of the rectum, anus and bladder receives a dose less than 49%, 67% and 43% of the prescribed dose, respectively. For the IMRT-plan these numbers are 91%, 92% and 81%, respectively (Fig. 7.1b-d). Assuming that radiobiological factors will not completely compensate these large differences, the therapeutic window for the brachytherapy seems larger. The only concern for the BT-plan could be the high maximum doses in the OAR. These high doses, however, concern very small volumes. Of course this comparison has some limitations; it is just one example, there is not accounted for organ motion and implantation inaccuracies and, as mentioned, the comparison of biological effective dose could make some difference. This example, however, is only meant to make plausible that dose distribution of BT-implants are certainly not inferior to dose distributions of state-the-art IMRT-plans. This is in particular the case if we could manage to match the high dose areas of the BT-implant with dominant cancer lesions within the prostate.

A Combination EBRT and BT seems an attractive option for the treatment of intermediate and high-risk prostate cancer. Pieters et al. [23] concluded, by comparing biological equivalent doses of IMRT plans and IMRT plans in combination with brachytherapy, that the latter combination had several favourable characteristics over IMRT alone. Excellent biochemical control rates for patients...
with intermediate and high-risk disease treated with a combined EBRT – BT schedule (with or without adjuvant hormonal treatment) have been reported [24-27]. Ho et al., however, found the total biological equivalent dose to be predictive for biochemical control for intermediate-risk cancers, rather than brachytherapy alone or in combination with EBRT [28]. Unfortunately no QOL scores were reported in conjunction with these studies. From the literature the results of one randomised trial comparing EBRT and EBRT in combination with brachytherapy (HDR) are available [29]. The EBRT+BT arm showed better biochemical control rates, better QOL scores and less acute rectal toxicity compared to the EBRT arm. It should be noted, however, that the EBRT techniques were conventional (no IMRT) and that the biological equivalent dose to the prostate was lower than in the EBRT+BT arm. Future conclusions of the ongoing trial 0232 of the Radiotherapy Oncology Group (RTOG), comparing combined EBRT - BT and BT alone for the treatment of intermediate-risk prostate cancer, may result in better founded choice for either treatment strategy.

7.4.2 Implantation techniques
TRUS can be considered to be today’s image modality of choice for image guided brachytherapy. Its use is widespread and successful due to the fact that the apparatus is mobile and easy at hand in the OR and the exploitation costs are low. And above all, TRUS imaging is ‘real time’ allowing instantaneous visualisation of needle movements. This does not mean that TRUS is necessary the best available image modality to visualise the prostate and adjacent organs. MRI could well be superior in terms of image quality and soft tissue contrasts. New techniques are being developed to facilitate MRI-guided brachytherapy. These involve robotic devices for accurate automatic needle insertions in closed-bore MRI scanners with minimal image disturbance from the implantation materials used [30-32]. These techniques, however, are still in research phase and some technical difficulties yet have to be overcome before clinical implementation becomes possible.

The TRUS guided transperineal seed insertion technique by means of parallel template guided needles has hardly any competitors at present. Is parallel needle insertion indeed the best possible technique? Certainly, this technique optimally suits TRUS-imaging; sound waves interact at right angles with the needles making them well visible on the real-time images. In conjunction with the above mentioned experiments with robotic implantation devices for MRI-guided techniques, non-
parallel implantation methods have been investigated [33]. One finding was that pubic arch interference could be avoided when implanting with divergent needle trajectories. Pubic arch interference is a problem that often occurs when implanting ventral needles in a large prostate. For this reason a large prostate (> 50 cm³) can be a contra-indication for brachytherapy. Allowing non-parallel needle insertions could therefore relax restrictions for brachytherapy of large prostates or avoid patients being subjected to hormone therapy for prostate volume reduction. As mentioned before in this discussion, damage to organs and nerves by needle insertions could very well contribute to post-implant morbidity. Future research should investigate possibilities to optimally avoid puncturing rectum, urethra, bladder neck, penile bulb, corpus cavernosum and neurovascular bundles.

7.4.3 Dose differentiation within the prostate
The conventional approach for treatment of localised prostate cancer is to irradiate the prostate uniformly, i.e. to realise a dose distribution irrespective of the distribution of cancerous lesions within the prostate. As stated in chapter 1 the choice for radical treatment of low grade prostate cancer is often cumbersome because the chance of overtreatment is high and side effects as a result of the treatment can seriously affect the quality of life. Differentiation in dose specification between normal and cancerous areas within the prostate (dose painting) could improve the therapeutic ratio of the treatment. For instance the dose near the bladder, the rectum or one of the neurovascular bundles can be reduced substantially when locally reduced dose within the prostate is allowed due to the absence of cancerous lesions. On the other hand, dominant intra-prostatic malignant lesions can be boosted or treated solely to enlarge the therapeutic ratio. For unilateral (either left or right with respect to the urethra) located tumours, the contra-lateral side of the prostate could be spared in order to reduce morbidity. Mouraviev et al. identified 19.2% unilateral cancers among 1184 pathological investigated specimens (with exclusion of PSA ≥ 10, clinical stage ≥ T3, seminal vesicle invasion or lymph node involvement) [34]. Although the majority of prostate cancers appear to be multi-focal there is mostly one dominant lesion and additionally a few much smaller lesions. Extra-capsular extension mostly arises from the largest lesion and seldom from secondary lesions [35]. For a selective group of patients with low grade prostate cancer there could be a rational for focal therapy i.e. treating the dominant lesion(s) only. Focal
treatment is likely to cause less damage to adjacent organs and nerves at risk and side effects could therefore be minimised. Re-treatment or subsequent whole gland treatment after failure, without excess morbidity, could still be an option.

7.4.4 Future directions
Brachytherapy has great potentials regarding local or focal irradiation of the prostate. When the locations of dominant cancerous lesions are known the source distribution can be arranged so that these locations receive a high dose [35-38]. Crucial, of course, is accurate knowledge of these locations during implantation of the seeds. Advantages in functional imaging technology are likely to increase the applicability of dose differentiation in the near future. MRI combined with MRI-spectroscopy, dynamic contrast enhanced MRI, diffusion-weighted MRI and \(^{11}\)C-choline positron emission tomography (PET) in combination with CT are very promising localisers of cancerous lesions and can overcome the limitations of conventional sextant biopsy [1,39-46]. Also TRUS related techniques have been developed with promising sensitivity and specificity for detecting cancer lesions within the prostate [47-51]. These techniques could be appropriate for focal brachytherapy since the required equipment could easily be used in the OR for implantation planning and image guided seed implantation. Despite great apparent potentials for focal brachytherapy its effectiveness in terms of tumour control and morbidity reduction still has to be proven. This, however, might be difficult. When tumour control rates appear to be disappointing is the principle of focal treatment or the sensitivity of the imaging technique to blame?
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Chapter 1 (General introduction)

The incidence rate of prostate cancer has risen dramatically during the last decades mainly due to early detection by prostate-specific antigen (PSA) screening. Because these high increases in incidence rates do not result in equally high mortality rates immediate initiation of curative treatment for early stage prostate cancer might result in over-treatment. It is therefore important to develop effective but low toxic treatment modalities. Brachytherapy with Iodine-125 photon emitting sources, usually called I-125 seeds, is a well established treatment for localised prostate cancer. However, toxic reactions after this treatment, although mostly characterised as well tolerated, do occur. In particular irritative and obstructive urinary symptoms are common. To be able to reduce these adverse symptoms it is necessary to identify characteristics of I-125 implants that contribute to the side effects.

The purpose of this thesis was to firstly investigate physical properties of seed implants using adequate imaging techniques, secondly to discover relations between these physical properties and post-implant urinary morbidity and thirdly to investigate alternative implantation techniques that could possibly contribute to a reduction of toxic reactions after the implantation.

Chapter 2 (Simultaneous TRUS-CT)

In search of an appropriate image modality for the evaluation of prostate I-125 seed implants the applicability of combined computed tomography (CT) and 3D transrectal ultrasound (TRUS) imaging was investigated. Advantage of fused TRUS-CT imaging is that both prostate contours and implanted seeds will be well visible. A method was developed to match TRUS and CT image series. After insertion of the TRUS-transducer a CT and a TRUS scan have to be acquired (practically) simultaneously. After reconstruction of the transducer geometry on both image modalities, the geometrical relationship between both image sets could be defined by registration on the transducer. In order to investigate the accuracy of this registration method, for 23 cases a registration on visible seeds was performed after pre-registration on the transducer. In 2 out of 23 cases an automatic grey value registration on the seeds failed for both investigated cost functions due to poor visibility of the seeds on the TRUS scan. The average deviations of the seed registration with respect to the transducer registration were negligible. However, in a few individual cases the deviations were relatively large probably due to
movement of the patient between TRUS and CT scan. In case of a registration on the transducer it is important to avoid patient movement between TRUS and CT scan and to keep the time in-between the scans as short as possible. It can be concluded that fusion of a CT scan and a simultaneously made TRUS scan by means of a 3D transducer is feasible and accurate when performing a registration on the transducer, if necessary, fine-tuned by a registration on the seeds. These fused images will be of great value for post-implant dose distribution evaluations.

Chapter 3 (Dose distribution after prostate seed implantation)
After implantation of the prostate with I-125 seeds, dose calculation is usually based on a single imaging session, assuming no geometrical changes occur during the months of dose accumulation. In this study the effect of changes in anatomy and implant geometry on the dose distribution was investigated. One day, one month and 3½ months after seed implantation, a combined TRUS-CT scan was made in thirteen patients. Based on these scans changes in dose rate distribution were determined in prostate, urethra and bladder. A "geometry corrected" dose distribution was estimated representing the dose distribution after total decay of the I-125 sources. When based on the scan made one day after implantation, parameters representing high dose volumes in prostate and urethra were largely underestimated with respect to the geometry corrected values: the prostate volume receiving at least 150% of the stated dose (V150-pr) 18±10 % and the urethra V120-ur 47±32 %. The dose to a 2 cm³ hotspot in the bladder wall (D2cc-bl), however, was overestimated by 31±35 %. Values of dose-volume parameters based on scans one month post-implant or later were all within ±5% of geometry corrected values. Values meant to indicate the adequacy of dose coverage of the prostate, V100-pr and D90-pr, were not influenced by geometrical changes and independent of the post-implant scan date.

Chapter 4 (Predicting urinary morbidity, a literature review)
The majority of patients develop lower urinary tract symptoms (LUTS) to some degree after implantation of the prostate with I-125 or Pd-103 seeds. The symptoms vary from increased urinary voiding frequency to acute urinary retention (AUR) and are usually temporary phenomena. Prophylactic use of α-blockers significantly reduces the severity and resolution time of LUTS. During the last 10
years several studies have been published trying to identify predictors for these toxic reactions. There is reasonable agreement about the relation between prostate size and AUR. Some research, however, brought forward that a large prostatic transition zone rather than a large prostate volume is a predictor for AUR. Because transperineal biopting results in comparable AUR incidences there is reason to believe that AUR is the result of temporal transition zone enlargement due to the oedema caused by needle insertions. For other obstructive and irritative urinary symptoms there is less agreement about the predictors. The possible relation between dose to the urethra and LUTS has often been investigated but there is no unambiguous evidence that there is any relation between both. Recently, high dose to small volumes of the bladder was identified as a predictor for LUTS (see chapter 5). Additional studies are required to confirm this relation. In a limited number of cases (1%-5%) persisting extreme symptoms have to be managed by means of a trans-urethral resection of the prostate (TURP). TURP procedures, however, carry significant risk of inducing urinary incontinence.

Chapter 5 (Bladder dose and post-implant urinary morbidity)
More knowledge about causes and predictors of post-implant LUTS is necessary to be able to develop less toxic implantation techniques. The aim of this study was to identify implantation related factors that contribute to post-implant LUTS.
72 patients filled in an International Prostate Symptom Score (IPSS) questionnaire before, 3 months and 6 months after implantation. Values of dose-volume parameters of prostate, urethra and bladder wall were determined based on a TRUS-CT scan made one day after implantation. Values of dose-volume parameters of the bladder wall were also determined using a CT-scan made one month after implantation because previous research (chapter 3) demonstrated that the total deposited dose is this organ will be optimally estimated when based on a scan at this post-implant time interval.
The dose to a 1 cm³ hotspot in the bladder wall (D1cc-bl) as well as the prostate volume were independently correlated with the IPSS at 3 months (p=0.006 and p=0.005, respectively) and at 6 months (p=0.001 and p=0.015 respectively) after implantation. Remarkably, the symptoms at 3 month correlated best with D1cc-bl based on a scan made at 1 day (D1cc-bl-1d), whereas the symptoms at 6 months correlated best with D1cc-bl based on a scan made 1 month after implantation (D1cc-bl-1m).
Investigated dose-volume parameters of prostate and urethra did not correlate with urinary morbidity.

Chapter 6 (Minimising number of prostate implantation needles)
Reduction of the number of implantation needles for prostate brachytherapy will shorten the duration of implantation procedures and possibly reduce trauma-related morbidity. Possibilities to minimise the number of needles and the consequences for the dose distribution were investigated.

From a planning study followed that the average number of needles (±1SD) could be reduced from $18.8\pm3.6$ to $12.7\pm2.9$ (-33%) when changing from conventional fixed inter-seed spacing to optimised free inter-seed spacing and subsequently even further reduced to $7.3\pm1.0$ (-42%) by increasing the seed strength from 0.57 U to 1.14 U. These needle reductions, however, resulted in increased dose inhomogeneity within the prostate and increased sensitivity of dose-volume parameters of the OAR for random geometrical inaccuracies. Realised seed implants with free inter-seed spacing resulted in very satisfactory dose-coverage of the prostate while the average number of needles was reduced by 30% compared to implants realised with fixed inter-seed spacing.

It can be concluded that a substantial reduction of the number of implantation needles is possible without compromising adequate dose coverage of the prostate. However, the chance of an unpredicted high dose to the OAR increases as fewer needles are used.

Chapter 7 (General discussion)
An important advantage of combined TRUS-CT imaging for post-implant dosimetry over other multi-modality imaging, such as magnetic resonance imaging (MRI) in combination with CT, is that both TRUS and CT scan can be acquired simultaneously. A disadvantage is the presence of the transducer probe in the rectum which prevents accurate dose distribution determination of the rectum and slightly deforms the prostate.

The magnitude of seed displacements described in chapter 3 do relate to the brand of I-125 seed strands used for this investigation. Seeds or seed strands with different mechanical properties might have different kinetic characteristics. However, the conclusion that the dose to prostate and urethra is underestimated whereas the dose to the bladder is overestimated when the dosimetry is based on
a scan made one day after the seed implantation is likely to be valid for other seed brands as well.

An important finding described in chapter 5 was that hot spot doses in the bladder are predictive for post-implant LUTS. For early LUTS this finding has been confirmed by results from the youngest analyses concerning patients implanted with a slightly different technique.

Despite revolutionary technical and dosimetrical improvements of external beam radiotherapy, still brachytherapy of the prostate has not been surpassed in terms of optimal dose distributions and patient comfort. Brachytherapy has great potentials for focal therapy where only the dominant lesions within the prostate are to be irradiated in order to reduce adverse side effects from radiation as much as possible.
Samenvatting

I-125 zaadimplantaten voor brachytherapie van de prostaat; Fysische eigenschappen en relaties met kwaliteit van leven na implantatie.
Hoofdstuk 1 (Algemene introductie)
De incidentie van prostaatkanker is de laatste decennia sterk toegenomen voornamelijk doordat vroege detectie met behulp van prostaat specifiek antigeen (PSA) mogelijk werd. Omdat deze grote toename van het aantal incidenties niet heeft geleid tot een zelfde toename van sterftecijfers door prostaatkanker kan onverwijld ingezette curatieve therapie voor vroegstadia prostaatkanker mogelijk tot overbehandeling leiden. Het is daarom belangrijk om effectieve behandelmethoden te ontwikkelen die weinig belastende bijwerkingen voor de patiënt geven. Brachytherapie met radioactieve foton-emitterende Jodium-125 bronnen, meestal aangeduid als I-125 zaden, is een bewezen effectieve behandelingsmethode voor gelokaliseerde prostaatkanker. Ofschoon deze behandeling over het algemeen goed verdragen wordt, zijn bijwerkingen na deze behandeling vrij algemeen. Met name mictieklachten komen vaak voor. Om deze bijwerkingen te kunnen reduceren, is het noodzakelijk om vast te stellen welke eigenschappen van I-125 implantaties aanleiding geven tot deze klachten. Het doel van deze dissertatie was om in de eerste plaats fysische eigenschappen van I-125 implantaties te onderzoeken gebruikmakend van geschikte afbeeldingstechnieken om vervolgens relaties te onderzoeken tussen deze fysische eigenschappen en voorkomende mictieklachten. Ten slotte was ook het doel om alternatieve implantatiemethoden te ontwikkelen die zouden kunnen leiden tot een vermindering van de klachten na de behandeling.

Hoofdstuk 2 (Simultane TRUS-CT)
In de zoektocht naar een geschikte afbeeldingsmodaliteit voor de evaluatie van prostaat implantaties met I-125 zaden, werd de toepassing van gecombineerde “computed tomography” (CT) en 3D transrectale echo (TRUS) beelden onderzocht. Het voordeel van gecombineerde TRUS-CT beelden is dat zowel de prostaatcontouren als het implantaat duidelijk zichtbaar zijn. Een methode werd ontwikkeld om TRUS en CT beeldenseries geometrisch te “matchen”. Hiervoor moesten, na inbrengen van de TRUS-tranducer, simultaan een TRUS- en een CT-opname worden gemaakt. Na reconstructie van de transducer-geometrie op beide beeldmodaliteiten, konden geometrische relaties tussen TRUS en CT beeldensets worden vastgelegd. Om de nauwkeurigheid van deze methode te testen werd van 23 gevallen een automatische grijswaarde-match uitgevoerd na een match op de transducer. In 2 van de 23 gevallen kon er geen succesvolle grijswaarde match
worden uitgevoerd vanwege slechte zichtbaarheid van de zaadjes op de TRUS-scan. De gemiddelde afwijking van de grijswaarde match ten opzichte van de transducer match was te verwaarlozen. In een aantal gevallen echter, waren de afwijkingen relatief groot, waarschijnlijk door beweging van de patiënt tussen beide opnamen. Voor een succesvolle match op de transducer is het belangrijk om beweging van de patiënt te voorkomen en om de tijd tussen TRUS- en CT-scan zo kort mogelijk te houden. Er kan geconcludeerd worden dat een nauwkeurige fusie van TRUS- en CT-beelden mogelijk is na een match op de transducer, indien nodig, gevolgd door een verfijning door middel van een match op de zichtbare zaadjes van beide beeldensets. Deze gefuseerde beelden zijn zeer waardevol voor de evaluatie van dosisverdelingen na brachytherapy van de prostaat.

Hoofdstuk 3 (Dosisverdeling na implantatie van de prostaat)

Na implantatie van de prostaat met I-125 zaden wordt de dosisverdeling gewoonlijk bepaald met behulp van een serie beelden die gemaakt is op een bepaald tijdstip na de procedure. Er wordt dan verondersteld dat er geen geometrische veranderingen plaatsvinden gedurende de maanden van dosiscumulatie. In deze studie werd de invloed van geometrische veranderingen van anatomie en zaadimplant op de dosisverdeling onderzocht.

Een dag, een maand en 3½ maand na implantatie van de zaden werd een gecombineerde TRUS-CT beeldenset gemaakt bij 13 patiënten. Op basis van de 3 beeldensets werd de verandering van de dosistempoverdelingen bepaald in de prostaat, de urethra en de blaas. Op grond hiervan werd een "geometriegecorrigeerde" dosisverdeling bepaald die bij benadering representatief was voor de situatie na volledig verval van de I-125 bronnen.

Wanneer de dosisverdeling gebaseerd werd op de beeldenset gemaakt op de dag na de implantatie, dan werden volumina van hoge dosis binnen de prostaat en de urethra aanzienlijk onderschat: het prostaatvolume dat minstens 150% van de gespecificeerde dosis (V150-pr) ontvangt met 18±10 % en de urethra V120-ur met 47±32 % ten opzichte van de geometriegecorrigeerde waarde. De minimale dosis in een 2 cm³ hotspot van de blaaswand (D2cc-bl) werd echter overschat met 31±35 %. Waarden van dosis-volume parameters die gebaseerd werden op een beeldenset die minstens een maand na implantatie werd gemaakt, lagen allen binnen ±5 % van de geometriegecorrigeerde waarden. Waarden van parameters
die een maat zijn voor een adequate dosering van de prostaat, V100-pr en D90-pr, bleken onafhankelijk te zijn van de datum van de beeldenset.

Hoofdstuk 4 (Voorspellen van mictieklachten, literatuurstudie)
Na implantatie van de prostaat met I-125 of Pd-103 zaden krijgen veel patiënten in meer of mindere mate last van toxische reacties in de onderste urinewegen. De symptomen variëren van frequente aandrang om te urineren tot acute blokkade van de urinewegen en zijn meestal tijdelijk van aard. Profylactisch gebruik van α-blockers kunnen de duur en de hevigheid van de klachten aanzienlijk verminderen. Verschillende studies, met het doel om voorspellers voor mictieklachten te identificeren, zijn de afgelopen 10 jaar gepubliceerd. Er blijkt redelijke overeenstemming te bestaan over de relatie tussen prostaatvolume en acute urineretentie. Uit enkele studies kwam echter naar voren dat eerder een grote overgangszone dan een groot totaalvolume van de prostaat voorspellend is voor deze klacht. Omdat transperineaal biopteren van de prostaat tot vergelijkbare incidentie van urineretenties leidt, is er reden om aan te nemen dat dit fenomeen het gevolg is van een tijdelijke vergroting van de overgangszone door oedeemvocht dat ontstaat door naaldpuncties. Voor andere obstructieve en irritatieve klachten is er minder overeenstemming over de oorzaak van de klachten. De mogelijke relatie tussen de bestralingsbelasting van de urethra en mictieklachten is veelvuldig onderzocht maar een eenduidig verband is tot nu toe niet gevonden. Recentelijk werd een verband tussen mictieklachten en hoge lokale blaasdosis gevonden (zie hoofdstuk 5). Aanvullend onderzoek is echter nodig om deze bevindingen te bevestigen. In een beperkt aantal gevallen (1%–5%) moeten aanhoudende extreme klachten worden verholpen met een transuretrale resectie (TURP) om de urineweg vrij te maken. Een TURP procedure echter brengt een aanzienlijk risico op incontinentie met zich mee.

Hoofdstuk 5 (Blaasdosis en mictieklachten na implantatie)
Meer kennis van factoren die leiden tot mictieklachten na brachytherapy van de prostaat, is noodzakelijk om minder toxische implantietechnieken te kunnen ontwikkelen. Het doel van dit onderzoek was door uitgebreide analyse van fysische en dosimetrische variabelen, voorspellers voor mictieklachten te vinden. Een groep van 72 patiënten vulden voor, 3 maanden na, en 6 maanden na de implantatie van de I-125 zaden de vragenlijst “International Prostate Symptom
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Score” (IPSS) in. Waarden van dosis-volume parameters van de prostaat, de urethra en de blaas werden bepaald op basis van een TRUS-CT beeldenset gemaakt op de dag na implantatie. Bovendien werden de waarden voor de blaasparameters ook gebaseerd op een TRUS-CT beeldenset gemaakt 1 maand na implantatie, omdat uit eerder onderzoek (zie hoofdstuk 3) is gebleken dat deze een betere schatting opleveren van de totaal afgegeven dosis in het orgaan.

De dosis in een 1 cm³ “hotspot” in de blaaswand (D1cc-bl) en het prostaatvolume bleken onafhankelijk gecorreleerd met de IPSS 3 maanden (respectievelijk \( p=0.006 \) en \( p=0.005 \)) en 6 maanden (respectievelijk \( p=0.001 \) en \( p=0.015 \)) na implantatie. Opvallend was dat de klachten na 3 maanden het beste correleerden met D1cc-bl gebaseerd op de beeldenset gemaakt 1 dag na implantatie, terwijl de klachten na 6 maanden het beste correleerden met D1cc-bl gebaseerd op de beeldenset gemaakt 1 maand na implantatie van de zaden. Geen van de onderzochte dosis-volume parameters van de prostaat en de urethra correleerde met mictieklachten.

Hoofdstuk 6 (Minimalisering aantal prostaat implantatienaalden)

Verminderen van het aantal implantatienaalden voor brachytherapy van de prostaat verkort de procedure in de operatiekamer en zal mogelijk leiden tot minder traumagerelateerde morbiditeit. Onderzoek werd gedaan naar de mogelijkheden om het aantal naalden te minimaliseren en de invloed van het gebruik van minder naalden op de dosisverdeling.

Uit een planningstudie volgde dat het gemiddelde aantal naalden kon worden teruggebracht van 18.8±3.6 naar 12.7±2.9 (-33%) wanneer de vaste afstand van 10mm, die meestal tussen 2 opeenvolgende I-125 zaden binnen een naald wordt gehanteerd, wordt vervangen door een geoptimaliseerde naaldlading met flexibele afstanden tussen de opeenvolgende zaden. Een verdere reductie van het aantal naalden naar 7.3±1 (-42%) kon worden bewerkstelligd door de bronsterkte van de zaden te verhogen van 0.57U naar 1.14U. De vermindering van het aantal naalden, echter, resulteerde in een toegenomen dosisinhomogeniteit binnen de prostaat en verhoogde gevoeligheid van dosis-volume parameters van de omliggende “risico-organen” voor toevallige geometrische fouten. Klinisch gerealiseerde prostaatimplantaties met geoptimaliseerde afstanden tussen de zaden resulteerde in zeer goede dosisdekking van de prostaat terwijl het aantal
naalden werd gereduceerd met gemiddeld 30% ten opzichte van conventionele implantaten met gefixeerde afstanden tussen de zaden. Geconcludeerd kan worden dat het aantal implantatiernaalden aanzienlijk kan worden verminderd zonder verlies van dosisdekking van de prostaat. Echter, de kans op een onvoorspelbaar hoge dosis in de risico-organen wordt groter naarmate minder naalden worden gebruikt.

**Hoofdstuk 7 (Algemene discussie)**

Een belangrijk voordeel van gecombineerde TRUS-CT beeldvorming voor post-implantatie dosimetrie ten opzichte van andere meervoudige beeldvormende modaliteiten, zoals “magnetic resonance imaging” (MRI) in combinatie met CT, is dat TRUS en CT beelden simultaan kunnen worden opgenomen. Aanwezigheid van de echo-transducer in het rectum, echter, is een nadeel omdat de rectumdosis hierdoor niet goed kan worden bepaald en bovendien de prostaat lichtelijk vervormd wordt.

De grootte van de zaadverplaatsingen beschreven in hoofdstuk 3, zijn gerelateerd aan een bepaald type I-125 zaden. Zaden of systemen van “gelinkte zaden” met andere mechanische eigenschappen kunnen andere kinetische eigenschappen hebben. Echter, de conclusie dat de dosis in de prostaat en de urethra wordt onderschat en de dosis in de blaas wordt overschat wanneer de dosimetrie gebaseerd wordt op een beeldenset gemaakt op de dag na implantatie is waarschijnlijk ook geldig voor andere typen I-125 zaden.

Een belangrijke conclusie van hoofdstuk 5 was dat hotspot doses binnen de blaas voorspellend zijn voor mictieklachten na de behandeling. Deze conclusie werd later bevestigd voor vroege mictieklachten na implantaties met een iets gewijzigde techniek.

Ondanks revolutionaire technische en dosimetrische verbeteringen van radiotherapie met uitwendige bundels, is brachytherapie van de prostaat nog niet gepasseerd in termen van optimale dosisverdeling en patiëntcomfort. Brachytherapie heeft bovendien grote potenties voor focale behandeling van prostaatkanker, waarbij alleen dominante laesies binnen de prostaat worden bestraald om negatieve bijwerkingen van straling zoveel mogelijk te reduceren.
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Over de auteur


Naast zijn werk op het NKI-AVL volgde hij van 1999 tot 2002 een opleiding Bedrijfswiskunde aan de Hoge School van Amsterdam.