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## I-125 seed implants for prostate brachytherapy

Steggerda, M.J.

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## Summary

### *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 cm<sup>3</sup> 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  $\alpha$ -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 biotying 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 in this organ will be optimally estimated when based on a scan at this post-implant time interval.

The dose to a 1 cm<sup>3</sup> 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 months 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 ( $\pm 1SD$ ) could be reduced from  $18.8 \pm 3.6$  to  $12.7 \pm 2.9$  (-33%) when changing from conventional fixed inter-seed spacing to optimised free inter-seed spacing and subsequently even further reduced to  $7.3 \pm 1.0$  (-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.