Internal report

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Prostate brachytherapy: Pre-plan and real-time transperineal ultrasound guided Iodine-125 permanent seed implants at Södersjukhuset, Karolinska University Hospital

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Thesis for Master of Science in Medical Radiation Physics
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List of abbreviations
ABS American Brachytherapy Society
EAU European Association of Urology
EORTC European Organisation for the Research and Treatment of Cancer.
ESTRO European Society for Therapeutic Radiology and Oncology
TRUS Transrectal Ultrasound
US Ultrasound
cc cm³

dosimetric parameters for prostate:
D(100), D(90), D(80) [Gy] Dose that covers 100%, 90%, 80% of the prostate.
D90 [%] Fraction of the dose that covers 90% of the prostate and prescribed dose.
V(80), V(90), V(100), V(150), V(200) [%] The percentage of prostate volume receiving 80%, 90%, 100%, 150%, 200% respectively of prescribed dose.
CI Conformal Index: Fraction of V(100) whole prostate volume and V(100) prostate, this reflects the unwanted irradiated tissue outside the prostate.
HI Homogeneity Index: Fraction of volume within the prostate receiving 100% to 150% of the prescribed dose and the prostate volume.
NDR Natural Dose Rate: Fraction of the prescription dose and the natural prescription dose from the DVH, this reflects the overdose or under dose of prostate.

dosimetric parameters for urethra:
UrD30, UrD10, UrD5 [Gy] Dose that covers 30%, 10%, 5% of the urethra.
UrD30, UrD10, UrD5 [%] Fraction of dose that covers 30%, 10%, 5% respectively of the urethra and prescribed dose.

dosimetric parameters for rectum:
RD2cc, RD0.1cc [Gy] The highest dose to a rectum volume of 2 cc, 0.1 cc.
RV100, RV150 [cc] Volumes of rectum receiving 100%, 150% of the prescribed dose.
RD(30)[Gy], RD(10)[Gy] Dose that covers 30%, 10% of rectum.
1 INTRODUCTION

1.1 PROSTATE BRACHYTHERAPY

1.1.1 Prostate Cancer
Prostate cancer is the most common cancer disease among men and mostly older men are affected (Cancerfonden 2005). There are several treatment options such as radical prostatectomy, external radiation therapy, temporary and permanent brachytherapy, cryotherapy, hormonal therapy and watchful waiting. PSA testing which became available in the late 1980s led to an increased detection of early stage disease, where brachytherapy is a suitable treatment option (DeVita et al 2001). Cancer of the prostate usually presents itself as a slow growing tumour which is relatively radioresistant. Therefore a good theoretical rationale for treating selected patients who have no metastases with a high localized dose of radiation exists. This can be done with conformal external beam radiation therapy (CEBRT) and brachytherapy. Brachytherapy offers several advantages over CEBRT for early located prostate cancer. Rapid dose fall gives the possibility to deliver high dose to the target with low dose to the surrounding tissue.

1.1.2 Development of prostate brachytherapy
Pasteau and Degrais did the first implant in Prostate Brachytherapy history in 1910 by using radium delivered through the urethra (Baxter et al 2006). Prostate Brachytherapy was also attempted in 1930 by using radioactive gold. The technique of open retro-pubic Iodine-125 seed implant was developed by Whitmore et al in New York in the early 1970s. The seed placement of open retro-pubic technique was however difficult to perform and early techniques for distribution and dose determination were crude (Ash et al 1998).

Prostate brachytherapy, with transperineal ultrasound guided $^{125}$I permanent seed implants was first introduced in the early 1980s by Holm and colleagues in Denmark. Holm and Gammelgaard first developed a technique for guided needle biopsy with ultrasound (Holm and Gammelgaard 1981). Shortly after Holm et al published another
article describing a similar technique that could be used to guide the I-125 accurately in the prostate (Holm et al 1983). In the 1980s Holm’s initial work was subsequently further developed by Blasko and associates who described an ultrasound-guided transperineal technique incorporating an extensive planning method (Glegg et al 2004).

At Södersjukhuset, Karolinska University Hospital (SÖS), there are today two forms of curative treatments with brachytherapy for prostate cancer patients, Low dose rate (LDR) permanent implants and high dose rate (HDR) temporary implants combined with external radiation therapy. With HDR treatments a high activity source is used to deliver a pulse of radiation to the prostate, using an after-loading technique. In this thesis LDR treatment alone with permanent seed implant will be studied.

1.2 PERMANENT SEED IMPLANT AT SÖDERSJUKHUSET, KAROLINSKA UNIVERSITY HOSPITAL

1.2.1 Treatment selection criteria

Patients suitable for prostate brachytherapy with permanent seed implants are those who comply with the following criteria:

- PSA < 10 ng/ml
- Gleason score ≤ 6
- Prostate volume < 50 cc.
- Early stage disease, Stage T1-T1c (TNM-system)
- No metastases
- Expected survival > 10 years
- No transurethral resection of the prostate, TURP.
- Low International Prostate Symptom score (IPPS)

The selection criteria are further discussed in the Appendix.
1.2.2 The seed

At Södersjukhuset, Karolinska University Hospital, the radionuclide Iodine-125 is used for prostate brachytherapy treatments. Palladium-103 is an alternative nuclide for the treatment but only I-125 is used in Sweden today. The main reason for the selection of Iodine-125 seeds is the longer half-life of the isotope which is more appropriate for clinical use (Table 1).

<table>
<thead>
<tr>
<th></th>
<th>Iodine-125</th>
<th>Paladium-103</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half life [days]</strong></td>
<td>59.4</td>
<td>17.0</td>
</tr>
<tr>
<td><strong>Energy range [keV]</strong></td>
<td>27-36</td>
<td>20-23</td>
</tr>
</tbody>
</table>

Table 1: Half life and energy range of emitted photons for the two radionuclides used for brachytherapy.

The I-125 seed which is used at Södersjukhuset is a 6711 model, supplied by Oncura, with the seeds placed in Rapid Strands with interlocking seeds and spacers as seen in Figure 1a. The Rapid Strands contain ten seeds each. Before the treatment the Rapid Strands are cut to the required length. The dimensions of the seed can be seen in Figure 1b. The seeds are encased in thin titanium-walled tubing welded at both ends.

Iodine-125 is adsorbed on a silver rod and decays by electron capture with the emission of characteristic photons and internal conversion electrons. The titanium...
wall absorbs the electrons so that only photons are emitted from the seeds. It is important to note that this model also emits 22.1 keV and 25.2 keV fluorescent X-rays resulting from the interaction of the Iodine-125 photons with the silver rod. Each seed has an activity of 15.4 MBq, range 13.4-16.7 MBq (0.415 mCi, range 0.361-0.450 mCi) and a corresponding air kerma strength value of 0.527 μGy/h (range 0.458-0.572 μGy/h).

1.2.3 Treatment description
The treatment at Södersjukhuset entails two visits for the patient, the first for a volume study for the pre-plan and the second for the actual seed implant.

Volume study:
The volume study is necessary to assess the right amount of seeds and to do a pre-plan. The patient is placed in the treatment position, a dorsal lithotomy position and a urinary catheter with contrast is inserted to outline the bladder and urethra. No anaesthetic is used during the volume study. To align the patient correctly lasers are used. The ultrasound probe is very stable, adherent in a cradle that is fixed to the table (Figure 2). On the ultrasound screen there is an electronic grid which corresponds precisely to the template grid, that will be used at the time of the implant. The prostate is studied trough the rectum, both in the axial and the longitudinal directions. An appropriate amount of water is inserted in a “balloon” attached to the probe, in order to lift the prostate to the first grid. The cradle has a system that allows the probe to move in and out of the rectum so that 7-12 axial pictures are taken from the base of the gland to the apex at 5 mm intervals. The images are transferred during the study to a treatment planning software. A physician outlines the target volume, prostate

**Figure 2:** The cradle in which the ultrasound and template grid are attached.
gland and the target at risks, rectum and urethra, for each slice section. A physicist pre-
plans the seeds positions and the dose distribution with information from the ultrasound
images and the template co-ordinates that appear on each section. Based on the pre-plan
the right amount of sources can be ordered.

Seed implant:
A team composed of an urologist, a radiation oncologist, an anaesthetist, a physicist
and nurses work together during the implant procedure. The patient is positioned in the
same position as in the volume study and a urinary catheter is inserted. The patient is
furthermore given general anaesthesia. The prostate is studied with TRUS, transrectal
ultrasound, as in the volume study (Figure 3). A template grid with coordinates
according to the electronic grid is placed at the cradle between the rectum and the
scrotum.

Figure 3: The prostate is studied with ultrasound trough the rectum. The needles with seeds are guided
within the prostate with the template coordinates. Organs at risks, urethra, rectum and the bladder can
be seen in the picture. (The picture to the left is from the home page of the Lund University hospital in

In every section it is checked with ultrasound to ensure that the patient is in exactly the
same position as in the volume study. If not a new outlining of the prostate and dose
computation is made (as intraoperative planning). Once the set up is considered optimal
two stabilising needles are inserted before the sources to keep the prostate in place. The
needles with the seeds are inserted one by one through the template and perineum along
the periphery of the prostate according to the plan, guided by ultrasound (Figure 3 and
Figure 4). When a needle reaches the right depth a double echo appears in the ultrasound image and the seeds can be deposited. This is also controlled by fluoroscopy. If the seed does not fall exactly to the right position as planned, the physicist can re-plan the position and dose distribution online, from the ultrasound (Interactive planning) constantly updating the dose distribution. Once the seeds have been inserted and approved by the physicist and urologist a fluoroscopic image is taken. This image and the ultrasound image are compared with the plan of the implant. If needed, extra seeds can be supplemented during the procedure in order to improve the dose distribution. Parameters from both the pre-plan and the treatment plan are saved for reference.

*Restrictions to treated patients:*
The patient does not have to stay isolated after treatment for radiation protection reasons as $^{125}$I only emits low gamma energy that can penetrate only to a very small degree outside the body. Prolonged close contact with children and pregnant women is however not recommended. It is also advised that children shouldn’t sit in the patient’s lap, for the first six month after the treatment. The patient may sleep in the same bed as his partner providing the partner is not pregnant. However it is advised to not have sexual intercourse for two weeks after the treatment and the patient should wear a condom or masturbate for the first ejaculations, in order to prevent the passage of a seed into the partner (Nag et al 1999).
1.3 AIM OF THE THESIS

Several studies have been published in this area, but since there has not been a uniform method of defining and calculating the dose, it is very difficult to compare values reported by different authors. The aim of this thesis is to study the European (ESTRO/EAU/EORTC) and American (ABS) guidelines on how to report the permanent seed implant and the most significant dosimetric parameters. The thesis will also report on the permanent seed implant procedure at Södersjukhuset, Karolinska University Hospital according to the guidelines. The reporting differences will also be discussed. Another part of the study is to investigate how morbidity correlates with the dose. The results in this report will give an overview of the treated patients and hopefully will make it easier to compare data in the future.

The dose parameters are obtained from a single record of the cumulative Dose Volume Histogram, DVH. Explanations of the different dosimetric parameters are stated in the List of abbreviations.

1.3.1 European ESTRO/EAU/EORTC guidelines

ESTRO/EAU/EORTC (Ash et al 2000) have made recommendations for permanent I-125 seed implant for localised prostate cancer. The suggested parameters to report for post-implant are:

- Prostate volume implanted [cc]
- Number of needles
- Number of seeds
- Prescribed dose
- Total activity implanted [mCi]
- The dosimetric parameters D(90), V(100), V(150).

Recently a supplement to ESTRO/EAU/EORTC (Ash et al 2000) has been released (Salembier et al 2007). This article defined stricter recommendations when defining the target and organs at risk and also the dosimetric parameters. ESTRO/EAU/EORTC recommendations of the prescription doses for pre-implant dosimetry for the clinical
target volume (CTV) can be seen in Table 2 (Salembier et al 2007). These are until now the only recommendations from ESTRO/EAU/EORTC for pre-implant dosimetry.

<table>
<thead>
<tr>
<th>Dose Parameter</th>
<th>ESTRO/EAU/EORTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate:</strong></td>
<td></td>
</tr>
<tr>
<td>D(90) [%]</td>
<td>≥ 100%</td>
</tr>
<tr>
<td>V(100) [%]</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>V(150) [%]</td>
<td>≤ 50%</td>
</tr>
<tr>
<td><strong>Urethra:</strong></td>
<td></td>
</tr>
<tr>
<td>UrD(10) [%]</td>
<td>&lt; 150%</td>
</tr>
<tr>
<td>UrD(30) [%]</td>
<td>&lt; 130%</td>
</tr>
<tr>
<td><strong>Rectum:</strong></td>
<td></td>
</tr>
<tr>
<td>RD_{2cc} [Gy]</td>
<td>≤ 145 Gy</td>
</tr>
<tr>
<td>RD_{0.1cc} (D_{max}) [Gy]</td>
<td>&lt; 200 Gy</td>
</tr>
</tbody>
</table>

**Table 2:** ESTRO/EAU/EORTC recommendations of the prescription doses for pre-implant dosimetry. (Salembier et al 2007).

The ESTRO/EAU/EORTC recommend CT-imaging for post-implant evaluation. The dosimetric parameters to report according to ESTRO/EAU/EORTC for CT post-implant are stated in Table 3. Secondary parameters are recommended even if their value in relation to outcome remain to be proven (Salembier et al 2007).

<table>
<thead>
<tr>
<th>Primary parameters</th>
<th>Secondary parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate:</strong></td>
<td></td>
</tr>
<tr>
<td>D(90) [%]</td>
<td>D(100)</td>
</tr>
<tr>
<td>V(100) [%]</td>
<td>V(200) [%]</td>
</tr>
<tr>
<td>V(150) [%]</td>
<td>NDR (Natural Dose Rate)</td>
</tr>
<tr>
<td></td>
<td>HI (Homogeneity Index)</td>
</tr>
<tr>
<td></td>
<td>CI (Conformal Index)</td>
</tr>
<tr>
<td><strong>Urethra:</strong></td>
<td></td>
</tr>
<tr>
<td>UrD(10) [Gy]</td>
<td>UrD(30) [Gy]</td>
</tr>
<tr>
<td></td>
<td>UrD(5) [Gy]</td>
</tr>
<tr>
<td><strong>Rectum:</strong></td>
<td></td>
</tr>
<tr>
<td>RD_{2cc} [Gy]</td>
<td>RD_{0.1cc} (D_{max}) [Gy]</td>
</tr>
<tr>
<td></td>
<td>RV(100) [cc]</td>
</tr>
<tr>
<td></td>
<td>RV(150) [cc]</td>
</tr>
</tbody>
</table>

**Table 3:** The CT post-implant dosimetric parameters to report according to ESTRO/EAU/EORTC (Salembier et al 2007).
1.3.2 American (ABS) guidelines

The American Brachytherapy Society, ABS, has also provided recommendations for seed implants. The recommendations for dosimetric parameters for pre-plan and implant to report are $D(100)$, $D(90)$, $V(100)$ and to minimize the length of urethra receiving 200% of the prescribed dose (Nag et al 1999).

The ABS also recommends CT-imaging for post-implant evaluation (Nag et al 2000). Dosimetric parameters for CT post-implant evaluation are:

- $D(100)$, $D(90)$, $D(80)$, $V(200)$.
- $V(150)$, $V(100)$, $V(90)$, $V(80)$.
- Urethra and rectal doses.
- Post-implant prostate volume [cc].
- Number of days between implant and the date of imaging study.

The reporting recommendations that differ from ESTRO/EAU/EORTC including both CT-based evaluation and implant are that ABS adds $D(80)$, $V(90)$, $V(80)$ but does not include CI, HI and NDR. ABS also recommends minimizing the length of urethra receiving 200% of the prescribed dose. Other recommendations for organs at risks were not mentioned by Ash et al (2000) or Nag et al (1999, 2000). Recommended dosimetric parameters which describe the dose to the urethra and rectum are stated in Salembier et al (2007). These recommendations do not include the length of urethra receiving a certain dose, but only volume parameters.

2 MATERIALS AND METHODS

2.1 PATIENT DATA

2.1.1 Patient characteristics

On the 10th of March 2004 the first patient was treated with permanent transperial ultrasound guided $^{125}$I seed implant brachytherapy at Södersjukhuset, Karolinska University Hospital in Sweden. By the middle of October 2007, 198 patients have
received implants. The median age of treated patients was 65 years, (range 48 – 77 years). Patient characteristics can be seen below in Table 4. As can be seen a few of the patients did not fully comply with the treatment criteria. One treated patient had a prostate volume greater than 50cc, two patients had T2 disease, nine patients had Gleason score 7 and eight patients had a pre-PSA value greater than 10.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Category</th>
<th>n</th>
<th>[%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-stage:</td>
<td>T1</td>
<td>196</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Gleason score:</td>
<td>≤5</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>172</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Pre-treatment PSA: [ng/ml]</td>
<td>&lt;5</td>
<td>70</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>5-10</td>
<td>120</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Neoadjuvant androgen deprivation:</td>
<td>Yes</td>
<td>77</td>
<td>39</td>
</tr>
<tr>
<td>Prostate volume: [cc]</td>
<td>&lt;20</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>20-50</td>
<td>186</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
<td>1</td>
<td>0,5</td>
</tr>
</tbody>
</table>

Table 4: Characteristics of 198 patients which have undergone permanent I-125 implants. n=number of patients.

Both of the T2 staged patients were among the 30 first patients in 2004. At that time T2 stage patients were accepted for implant treatment which is not the case at present. One patient had stage T2a and for the other the T2 stage is not specified. All the T1 patients were T1c with the exception of one individual that was T1a. Seven of the nine patients that had a Gleason score of 7 were among the 30 first patients and two of these patients had a Gleason score of 4+3. Retrospectively these patients shouldn’t have been included in the group for permanent seed implants. The highest pre-treatment PSA was 18 ng/ml. Apart from this value, five of the patients had a PSA value between 10-11 ng/ml, one had PSA value of 12 ng/ml and one a PSA value of 14 ng/ml.

Table 5 shows the median values with range of the prostate volume, number of needles, number of seeds, seeds/cc and the total activity of the 198 patients treated with permanent seed implants at Södersjukhuset, Karolinska University Hospital.
<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate volume [cc]</td>
<td>30</td>
<td>14-58</td>
</tr>
<tr>
<td>Number of needles</td>
<td>23</td>
<td>15-30</td>
</tr>
<tr>
<td>Number of seeds</td>
<td>61</td>
<td>42-90</td>
</tr>
<tr>
<td>Number of seeds/cc</td>
<td>2.0</td>
<td>1.5-3.3</td>
</tr>
<tr>
<td>Total activity [MBq] (mCi)</td>
<td>936 (25.3)</td>
<td>644-1354 (17.4-36.6)</td>
</tr>
<tr>
<td>Total Air kerma rate [μGy/h]</td>
<td>32.1</td>
<td>22.1-46.5</td>
</tr>
</tbody>
</table>

Table 5: Prostate volume, number of needles, number of seeds, seeds/cc and total activity.

2.1.2 Morbidity

Iodine-125 implant has a steep dose gradient which helps to minimize the dose to the organs at risk. But even with a rapid fall in dose and when the seeds are placed in the periphery of the prostate, parts of rectum and urethra will receive a certain dose. This can lead to complications for the patient depending on the amount of dose to the organ and the individual radiosensitivity of the patient. The morbidity rates were obtained from Dr Jesper Rosvall from the Department of Urology at Södersjukhuset, Stockholm.

Relapse:
- Three patients (1.5%) have had a relapse in their cancer disease.

Serious radiation related side effects:
- Lung embolism and acute renal failure n = 1 (0.5%)
- Urinary retention n = 10 (5%)

Milder radiation-related side effects:
- Mild proctitis n = 2 (1%)
- Urethra stricture n = 3 (1.5%)
- Urethritis n = 2 (1%)
2.2 DOSE PLANNING DATA

2.2.1 Dose planning

The treatment planning software that was used to perform real-time dose computation at Södersjukhuset, Karolinska University Hospital was VariSeed 7.1, with online connection to the ultrasound system which also contains screen volume calculations. The prescribed dose to the prostate is 145 Gy (Yu Y et al 1999), using dosimetry based on AAPM TG-43 recommendations (Nath et al 1995, Rivard et al 2004). This is the minimum peripheral dose to the margin of the target volume. General directions for the dose planning are that large areas with high doses should be avoided, moderate dose to urethra and as low dose as possible to the membrane of rectum, not more than the prescribed dose. As few seeds as possible outside the prostate and loose seeds only in exceptional cases. Dose limits are shown in Table 6.

<table>
<thead>
<tr>
<th>Dose Parameter</th>
<th>Dose limits (SÖS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prostate:</strong></td>
<td></td>
</tr>
<tr>
<td>V(100) [%]</td>
<td>&gt; 99%</td>
</tr>
<tr>
<td>V(150) [%]</td>
<td>&lt; 60%</td>
</tr>
<tr>
<td>V(200) [%]</td>
<td>&lt; 25%</td>
</tr>
<tr>
<td><strong>Urethra:</strong></td>
<td></td>
</tr>
<tr>
<td>UrD(10) [%]</td>
<td>&lt; 130%</td>
</tr>
<tr>
<td>UrD(30) [%]</td>
<td>&lt; 125%</td>
</tr>
</tbody>
</table>

Table 6: Dose limits at Södersjukhuset, Karolinska University Hospital (SÖS).

By using online in vivo 3-D dosimetry and real-time verification mechanisms and stabilization needles and as an extra control fluoroscopy, the variation in the position of the prostate during implant can be minimized. Oedema directly after implant is only temporary. By being able to change the seed position and re-plan the dose distribution online combined with the ultrasound during the treatment also reduces the uncertainties in seed placement (Salembier et al 2007). As a result of these no margins are planned around prostate and the planning target volume (PTV) is the same as the clinical target volume (CTV). This also minimizes the risk that seeds will be placed outside the prostate. In ESTRO/EAU/EORTC recommendations it is stated that there is no need for a margin around the prostate when using real-time intraoperative 3D technique with additional fluoroscopy (Salembier et al 2007).
2.2.2 CT Post-implant evaluation
The first 100 patients had a CT scan 1-2 months after the procedure. Due to difficulties in outlining the prostate plus critical organs and to define the seed positions in the CT-image as well as lack of time, the doses and volumes could not be fully reconstructed. This led to poorly evaluated dosimetry. By using real-time verification, the variations in seed placement during implant are already corrected for. Post-CT evaluation from Södersjukhuset, Karolinska University Hospital will not be included in this report.

2.2.3 Rectum definitions
To be able to examine and compare rectum doses, rectum has to be defined in the same way for every patient. ESTRO/EAU/EORTC recommendations are to outline both the inner and the outer wall of the rectum (Salembier et al 2007). In this thesis 55 patients were randomly chosen for study. One of the reasons that not all patients were outlined was due to the fact that both ESTRO/EAU/EORTC and ABS recommend CT. With the help of expertise the restrictions followed to outline rectum were defined as follows:
The inner rectum wall was defined by the “balloon” attached to the probe. The outer rectum wall was defined by Fascia Denonvillier that is a thin layer of connective tissue which separates the prostate and the seminal vesicles from rectum, appearing as a white structure in the ultrasound-image. Sometimes between Fascia Denonvillier and the rectum-wall fat tissue appears black in the image. This fat was not included in the outer wall of the rectum. If the rectum wall was difficult to define, the treatment planning software interpolated between the slices. The rectum wall is outlined in all slices that show seeds or a prostate contour. The rectum contour together with the prostate and the urethra contours are shown in Figure 5. The rectal doses and volumes will be presented in the results of this thesis.
3 RESULTS

3.1 IMPLANT DATA FROM SÖDERSJUKHUSET, KAROLINSA UNIVERSITY HOSPITAL

3.1.1 Prostate

The median dose values received by the prostate at Södersjukhuset, Karolinska University hospital are shown in Table 7 with their corresponding ranges.

<table>
<thead>
<tr>
<th>Prostate:</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>D(90) [Gy]</td>
<td>174 (120%)</td>
<td>153-194 (105-134%)</td>
</tr>
<tr>
<td>V(100) [%]</td>
<td>99</td>
<td>93-100</td>
</tr>
<tr>
<td>V(150) [%]</td>
<td>57</td>
<td>40-74</td>
</tr>
</tbody>
</table>

Table 7: The prostate median dose values, received from cumulative DVH’s.
3.1.2 Organs at risk: urethra and rectum

**Urethra:**
The doses to the urethra and the volume of urethra from the permanent implants at Södersjukhuset, Karolinska University hospital are given in Table 8. UrD(10) refers to the maximum urethra dose.

<table>
<thead>
<tr>
<th>Urethra:</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>UrD(10) [Gy]</td>
<td>188</td>
<td>162-213 (112-147%)</td>
</tr>
<tr>
<td>UrD(30) [Gy]</td>
<td>180</td>
<td>156-206 (107-142%)</td>
</tr>
<tr>
<td>Volume [cc]</td>
<td>0.6</td>
<td>0.3-1.6</td>
</tr>
</tbody>
</table>

Table 8: The doses to the urethra and the volume.

**Rectum:**
The doses to the rectum and the volume of the rectum from the permanent implants at Södersjukhuset, Karolinska University hospital are given in Table 9.

<table>
<thead>
<tr>
<th>Rectum:</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>RD_{3cc} [Gy]</td>
<td>98</td>
<td>73-128</td>
</tr>
<tr>
<td>RD_{0.1cc} [Gy]</td>
<td>164</td>
<td>119-240</td>
</tr>
<tr>
<td>RV(100) [cc]</td>
<td>0.3</td>
<td>0.0-1.3</td>
</tr>
<tr>
<td>RV(150) [cc]</td>
<td>0.0</td>
<td>0.0-0.2</td>
</tr>
<tr>
<td>Volume [cc]</td>
<td>4.0</td>
<td>2.6-7.9</td>
</tr>
</tbody>
</table>

Table 9: The doses to the rectum and the volume.

3.2 MORBIDITY

3.2.1 Relapse

The three patients that have had a relapse of their cancer disease are described in Table 10.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-PSA [ng/ml]</th>
<th>Gleason</th>
<th>Stage</th>
<th>P volume [cc]</th>
<th>D(90) [Gy]</th>
<th>V(100) [%]</th>
<th>V(150) [%]</th>
<th>Year of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>P 1</td>
<td>9</td>
<td>3+3=6</td>
<td>T1c</td>
<td>38.0</td>
<td>176</td>
<td>99</td>
<td>52</td>
<td>2005</td>
</tr>
<tr>
<td>P 2</td>
<td>9.5</td>
<td>3+4=7</td>
<td>T1c</td>
<td>37.6</td>
<td>158</td>
<td>96</td>
<td>43</td>
<td>2004</td>
</tr>
<tr>
<td>P 3</td>
<td>8.4</td>
<td>4+3=7</td>
<td>T1c</td>
<td>14.2</td>
<td>170</td>
<td>99</td>
<td>55</td>
<td>2004</td>
</tr>
</tbody>
</table>

Table 10: Patient characteristics and the prostate parameters for patient that got a relapse of their cancer disease.
3.2.2 Urinary problems

The implant values of the ten patients with urinary retention are shown in Table 11, the two patients with urethritis in Table 12 and the three patients with urethra stricture in Table 13.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Urinary retention</th>
<th>UrD(10) [Gy]</th>
<th>UrD(30) [Gy]</th>
<th>Urethra volume [cc]</th>
<th>D(90) [Gy]</th>
<th>V(100) [%]</th>
<th>Year of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ur 1</td>
<td>194 (134%)</td>
<td>181 (125%)</td>
<td>0.5</td>
<td>176</td>
<td>99</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Ur 2</td>
<td>184 (127%)</td>
<td>178 (123%)</td>
<td>0.8</td>
<td>173</td>
<td>99</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Ur 3</td>
<td>187 (129%)</td>
<td>181 (125%)</td>
<td>0.5</td>
<td>174</td>
<td>99</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Ur 4</td>
<td>188 (129%)</td>
<td>180 (124%)</td>
<td>0.4</td>
<td>173</td>
<td>99</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Ur 5</td>
<td>190 (131%)</td>
<td>184 (127%)</td>
<td>0.4</td>
<td>175</td>
<td>99</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Ur 6</td>
<td>194 (134%)</td>
<td>186 (129%)</td>
<td>1.4</td>
<td>175</td>
<td>99</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Ur 7</td>
<td>187 (129%)</td>
<td>179 (124%)</td>
<td>1.1</td>
<td>174</td>
<td>99</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Ur 8</td>
<td>188 (130%)</td>
<td>181 (125%)</td>
<td>0.4</td>
<td>174</td>
<td>100</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Ur 9</td>
<td>192 (132%)</td>
<td>186 (128%)</td>
<td>0.7</td>
<td>182</td>
<td>99</td>
<td>2006</td>
<td></td>
</tr>
<tr>
<td>Ur 10</td>
<td>184 (127%)</td>
<td>176 (121%)</td>
<td>1.2</td>
<td>173</td>
<td>99</td>
<td>2004</td>
<td></td>
</tr>
</tbody>
</table>

Table 11: Dosimetric parameters for patients that obtain urinary retention.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Urethritis</th>
<th>UrD(10) [Gy]</th>
<th>UrD(30) [Gy]</th>
<th>Urethra volume [cc]</th>
<th>D(90) [Gy]</th>
<th>V(100) [%]</th>
<th>Year of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ur 11</td>
<td>203 (140%)</td>
<td>190 (131%)</td>
<td>0.5</td>
<td>177</td>
<td>99</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Ur 12</td>
<td>182 (125%)</td>
<td>172 (119%)</td>
<td>0.8</td>
<td>171</td>
<td>99</td>
<td>2005</td>
<td></td>
</tr>
</tbody>
</table>

Table 12: Dosimetric parameters for patients that obtain urethritis.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Urethra stricture</th>
<th>UrD(10) [Gy]</th>
<th>UrD(30) [Gy]</th>
<th>Urethra volume [cc]</th>
<th>D(90) [Gy]</th>
<th>V(100) [%]</th>
<th>Year of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ur 13</td>
<td>181 (125%)</td>
<td>177 (122%)</td>
<td>0.5</td>
<td>169</td>
<td>98</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Ur 14</td>
<td>196 (135%)</td>
<td>192 (133%)</td>
<td>0.7</td>
<td>175</td>
<td>99</td>
<td>2005</td>
<td></td>
</tr>
<tr>
<td>Ur 15</td>
<td>197 (136%)</td>
<td>185 (128%)</td>
<td>0.7</td>
<td>181</td>
<td>100</td>
<td>2005</td>
<td></td>
</tr>
</tbody>
</table>

Table 13: Dosimetric parameters for patients that obtain urethra stricture.
3.2.3 Rectal complications

The implant parameters for the two patients that had mild proctitis are shown in Table 14.

<table>
<thead>
<tr>
<th>Patient</th>
<th>RD$_{2cc}$ [Gy]</th>
<th>RD$_{0.1cc}$ [Gy]</th>
<th>RV(100) [cc]</th>
<th>RV(100) [Gy]</th>
<th>R volume [cc]</th>
<th>Year of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>R 1</td>
<td>128</td>
<td>240</td>
<td>1.34</td>
<td>0.17</td>
<td>5.3</td>
<td>2005</td>
</tr>
<tr>
<td>R 2</td>
<td>105</td>
<td>187</td>
<td>0.57</td>
<td>0.03</td>
<td>6.0</td>
<td>2005</td>
</tr>
</tbody>
</table>

Table 14: The intraoperative values for the two patients that got mild proctitis.

Patient R 1 and patient Ur 11 are one and the same patient and had both mild proctitis and uretheris. Both the rectum and the urethra doses were very high, RD0.1cc = 240Gy and UrD(10)=203Gy.

4 DISCUSSION

4.1 CLINICAL DATA RESULT COMPARISON

4.1.1 Data comparison with ESTRO/EAU/EORTC recommendations

Data comparison of our obtained values with European (ESTRO/EAU/EORTC) recommendations is shown in Table 15.

<table>
<thead>
<tr>
<th>Dose Parameter</th>
<th>SÖS Median values</th>
<th>SÖS Dose limits</th>
<th>European recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D(90) [%]</td>
<td>120% (range 105-134)</td>
<td>-</td>
<td>≥ 100%</td>
</tr>
<tr>
<td>V(100) [%]</td>
<td>99% (range 93-100)</td>
<td>&gt; 99%</td>
<td>≥ 95%</td>
</tr>
<tr>
<td>V(150) [%]</td>
<td>57% (range 40-74)</td>
<td>&lt; 60%</td>
<td>≤ 50%</td>
</tr>
<tr>
<td>Urethra:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UrD(10) [%]</td>
<td>130% (range 112-147)</td>
<td>&lt; 130%</td>
<td>&lt; 150 %</td>
</tr>
<tr>
<td>UrD(30) [%]</td>
<td>124% (range 107-142)</td>
<td>&lt; 125%</td>
<td>&lt; 130 %</td>
</tr>
<tr>
<td>Rectum:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD$_{2cc}$ [Gy]</td>
<td>98Gy (range 73-128)</td>
<td>-</td>
<td>≤ 145 Gy</td>
</tr>
<tr>
<td>RD$<em>{0.1cc}$ (D$</em>{max}$)[Gy]</td>
<td>164Gy (range 119-240)</td>
<td>-</td>
<td>&lt; 200 Gy</td>
</tr>
</tbody>
</table>

Table 15: Data comparison of Södersjukhuset, Karolinska University Hospital (SÖS) dosimetric dose values and limits with European = ESTRO/EAU/EORTC recommendations (Salembier et al 2007).
As seen in Table 15 the data from Södersjukhuset, Karolinska University Hospital (SÖS) dosimetric values are in good agreement with the recommended values. The $V(150)$ is the only parameter that exceeds the recommended value. $V(150)$ reflects the hot spots in the prostate, that get 150% of the prescribed dose. When $V(100)$ exceeds the dose limit of 99% it will affect $V(150)$. Due to this, if one prefers a lower $V(150)$ it is presumably necessary to lower $V(100)$. The recommended value for $V(100)$ should only exceed 95%. The reason that the constraint of $V(100)$ is set to 99% is because there is no margin around the prostate.

Some patients did not achieve the dose limits for the dosimetric parameters. How many patients that did not agree with the dose limits at Södersjukhuset, Karolinska University Hospital (SÖS) and the European (ESTRO/EAU/EORTIC) recommendations in percents are stated in Table 16.

<table>
<thead>
<tr>
<th>Dose Parameter</th>
<th>SÖS Dose limits</th>
<th>Percent of patients that did not agree with the SÖS limits</th>
<th>European Recommendations</th>
<th>Number of patients that did not agree with the European Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D(90)$ [%]</td>
<td>-</td>
<td>-</td>
<td>≥100%</td>
<td>0%</td>
</tr>
<tr>
<td>$V(100)$ [%]</td>
<td>&gt; 99%</td>
<td>48%</td>
<td>≥ 95%</td>
<td>0,5%</td>
</tr>
<tr>
<td>$V(150)$ [%]</td>
<td>&lt; 60%</td>
<td>30%</td>
<td>≤ 50%</td>
<td>60%</td>
</tr>
<tr>
<td>Urethra:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ur$D(10)$ [%]</td>
<td>&lt; 130%</td>
<td>43%</td>
<td>&lt; 150 %</td>
<td>0%</td>
</tr>
<tr>
<td>Ur$D(30)$ [%]</td>
<td>&lt; 125%</td>
<td>40%</td>
<td>&lt; 130 %</td>
<td>4,5%</td>
</tr>
<tr>
<td>Rectum:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RD$_{2cc}$ [Gy]</td>
<td>-</td>
<td>-</td>
<td>≤ 145 Gy</td>
<td>0%</td>
</tr>
<tr>
<td>RD$<em>{0.1cc}$ (D$</em>{max}$) [Gy]</td>
<td>-</td>
<td>-</td>
<td>&lt; 200 Gy</td>
<td>1,5%</td>
</tr>
</tbody>
</table>

Table 16: Number of patients in percentages that did not agree with the European Recommendations = ESTRO/EAU/EORTIC limits (Salembier et al 2007) and Södersjukhuset, Karolinska University Hospital (SÖS) limits.

As seen in Table 16 the SÖS implanted dose values correspond to the ESTRO/EAU/EORTIC recommendations for the pre-planning parameters except from $V(150)$ as described above. The obtained implanted dose values have a broad range as seen in Table 15. It has been noticed that these values are from intraoperative planning with a dynamic dose calculation. In reality during the implant
procedure it is not always possible to follow the restrictions set by possible normal
tissue complications. The seeds cannot always be placed in the exact position as in
the pre-plan, the seed is then dragged to the right seed position and a new dose
volume histogram is computed. This can explain why many patients did not agree
with the SÖS limits. Especially for V(100)>99%, that almost only the half of the
patients achieve. If this means that the dose limit V(100)>99% is too high or
necessary to reach have to be further investigated.

4.1.2 Data comparison with other authors
Comparison of data with those from other clinics is very difficult at present, due to the
absence of a uniform method of defining and calculating the dose to the target and the
organs at risk. The target volume and organs at risk are evaluated differently in
different places. There are also differences in the planned margins around the prostate.
Furthermore, sometimes it also differs within one clinic when different physicians use
different methods of outlining the volumes of target and organs at risk. The prescribed
radiation dose varies, nowadays mostly 145 Gy for Europe and 144 Gy for the United
States. There are also different methods for evaluating the treatment, the most common
being CT-based, but MRI-based methods also exist. Two different radionuclides are
used for implants, I-125 and Pa-103, either as loose seeds or in Rapid Strands.
Differences in implanting methods appear as not all centres are doing a pre-plan for
implant, intraoperative planning with dynamic dose calculation and interactive
planning. Also different software is in use.

Hoskin and Venselaar (2007) have published an overview of 57 centres in Europe
practicing permanent seed implant. The clinical target volume (CTV) was defined by
the prostate contour at all the centres. However an important observation was the
variation in the definition of the planning target volume, PTV. The margin of the
prostate varied from 0 to 10 mm. All except two centres were using I-125 with a
standard prescribed dose of 145 Gy. As ESTRO recommended all of the centres
undertook post plan evaluation, the majority using CT. The dosimetric parameters used
for prostate volume included D(90), V(100) and V(150) for all centres. Some of the
centres (10%) had no constraints for the rectum and some (9%) had no constraints for the urethra.

D(90) and V(100) values with various authors are compared in Table 17. Doses to organs at risks like the urethra and the rectum are difficult to compare with other clinics when there has not existed a uniform method of defining and calculating the dose.

<table>
<thead>
<tr>
<th>Authors</th>
<th>D(90) [Gy]</th>
<th>V(100) [%]</th>
<th>Prescribed dose [Gy]</th>
<th>Prostate volume [cc]</th>
<th>Number of patients</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>SÖS, Sweden, 2007</td>
<td>174</td>
<td>99</td>
<td>145</td>
<td>30</td>
<td>198</td>
<td>US-based, no margin, VariSeed software</td>
</tr>
<tr>
<td>Zelefsky et al 2007</td>
<td>166</td>
<td>96</td>
<td>144</td>
<td>36</td>
<td>555</td>
<td>CT-scan 3h after implant</td>
</tr>
<tr>
<td>Chauveinc et al 2004</td>
<td>183</td>
<td>99.7</td>
<td>145</td>
<td>35</td>
<td>450</td>
<td>US-based, VariSeed software, loose seeds</td>
</tr>
<tr>
<td>Potters et al 2003</td>
<td>161</td>
<td>96</td>
<td>144</td>
<td>44</td>
<td>26</td>
<td>US-based, VariSeed software, 2mm margin</td>
</tr>
</tbody>
</table>

Table 17: D(90) and V(100) values compared with various authors using the real-time technique. SÖS=Södersjukhuset, Karolinska University Hospital.

Zelefsky et al 2007:
The values from Zelefsky et al (2007) are from CT scans 3 hours after implant and are therefore not really comparable with our values. The CT-scan dosimetry provides different values of the dosimetric parameters for a number of reasons, including differences in the contouring of the volume and that oedema or bleeding occurs after treatment. The prescribed dose was 144 Gy. Zelefsky has since 1998 used the real-time method for permanent seed implant. The constraints used at dose planning are V(100) ≥ 95%, UrD(10) ≤ 120% (173 Gy), average rectal dose < 80%. Earlier the urethra constraints were less strict UrD(10) ≤ 150%. The dosimetric data reported by Zelefsky et al in their study was V(100)[%], V(150)[%], V(200)[%], D(90)[Gy], UrD(30)[Gy], UrD(10)[Gy], RD(30)[Gy], RD(10)[Gy] and mean rectal and urethra doses. The maximal doses to the urethra and the rectum were defined in this report as UrD(10) [Gy], RD(10) [Gy]. It should be noticed that the rectum parameters here are reported differently and that the mean urethra dose are added to urethra parameters. Prostate dosimetric parameters are reported as recommended.
**Potters et al 2003:**

Potters et al (2003) use a real-time implantation approach. They also use the same dose planning software, VariSeed with an online connection to the ultrasound. Their D(90) =161 Gy are low compared to the D(90) =174Gy at SÖS. (The difference between mean and median values are minimal according to the SÖS values.) Potters et al (2003) are using a 2mm margin around prostate and their prescribed dose is 144 Gy. It has to be mentioned that the reported value in Potters et al (2003) for D(90)[%] is112%, and that gives D(90)[Gy] = 1.12 \times 144 = 161Gy. Dosimetric data that Potters et al (2003) reported in their article were D(90)[%], V(100)[%], V(150)[%].

**Chauveinc et al 2004:**

Chauveinc et al (2004) are also using a real-time implantation approach. The prescribed dose is 145 Gy, loose seeds are used with VariSeed as a dose planning software. Their dosimetric values of D(90) and V(100) are the highest. Their constraints during implant were D(90) =175Gy and V(100) >99.95%. The dosimetric data reported were D(90) and V(100).

### 4.2 DOSIMETRIC PARAMETERS TO REPORT

#### 4.2.1 Dosimetric parameters to report for the prostate

The most common significant post-implant dosimetric parameters worldwide for reporting prostate are D(90)[Gy], V(100)[%], V(150)[%]. There are also some secondary parameters that are recommended for reporting even if their value in relation to outcome is not proven. These parameters are D(100), V(200), NDR, HI and CI (Salembier et al 2007). ABS also recommends D(80), V(90), V(80) (Nag et al 2000). The most recently article of Zelefsky et al (2007) reported V(100)[%], V(150)[%], V(200)[%], D(90)[Gy].

Yu et al (1996) showed that D(90) is a more realistic parameter for dose specification than D(100).
4.2.2 Dosimetric parameters to report for organs at risk

The primary dose parameters to report for implant are UrD(10)[Gy] for urethra and RD2cc[Gy] for rectum according to ESTRO/EAU/EORTIC. There are also secondary parameters for the organs at risk that are recommended for reporting such as UrD(30)[Gy], UrD(5)[Gy], RD0.1cc[Gy], RV(100) [cc], RV(150) [cc] (Salembier et al 2007).

In this study there does not appear to be any clear relationships between UrD(10), UrD(30) and urinary morbidity. It can be discussed if there are other dosimetric parameters that may show a better correlation between dose and morbidity and which should be reported. ABS recommended minimizing the length of urethra receiving 200% of the prescribed dose (Nag et al 1999). The effect of this warrants further investigation.

Crook et al (2005) published their recommendations on how to define the organs at risk. They recommended that the urethra dose should be reported as UrD(5)[Gy], UrD(30) [Gy], and UrV(150) [cc]. The urethra should be contoured on each slice in which seeds can be seen. For the rectum, both inner and outer rectum walls should be contoured on all slices where seeds are visible and RV(100)[cc] and RV(150)[cc] should be reported. These parameters are recommended as a minimum requirement to report. Due to lack of consistent reporting no dose constraints for the organs at risk are stated in this article.

Zelefsky et al (2007) chose to report rectum doses in RD(10) (maximum dose to urethra) and RD(30) and mean rectal dose and have added the mean urethra dose to the urethra parameters.
More data and further investigations on the data from Södersjukhuset, Karolinska University Hospital are needed for conclusions regarding which dosimetric parameters show the best correlation with clinical outcome.

4.3 CT-BASED EVALUATION FOR POST-IMPLANT

Both ABS and ESTRO/EAU/EORTC indicate that postoperative dosimetry should be performed on each patient and CT-based evaluation is recommended (Nag et al 1999, Ash et al 2000, Salembier et al 2007). Without this information it is impossible to confirm the actual dose delivered to the prostate and the organs at risk. It is recommended to perform a CT scan approximately 4 weeks after the implant procedure due to the enlargement of the prostate secondary to oedema directly after the implant (Nag et al 1999). Additional information regarding the recommended CT technique can be found in Nag et al (2000). This recommendation is for earlier implant techniques and further studies are needed to determine if it includes the real-time implantation which will be discussed below.

Potters et al (2003) have compared their CT study with the intraoperative US-study when doing a real-time implantation using the dose planning software VariSeed 7.0. The root-mean-square error was 4.6 mm, with an average of 2.5 mm in a single plane. It is difficult to determine whether this error is significant and additional studies are needed. The article also states that it is difficult to outline the organs on the CT-image and that large differences in interpretations have sometimes appeared between physicians when examining the same CT image. In an article by Al-Qaisieh (2002) the influence of different observers is investigated in relation to how to contour the prostate volume on CT-based post-implant images. It was clear that the prostate volume varies between different observers and this has an effect on the post-implant dosimetry, in particularly D(90).
Chauvenic et al (2004) also compared the real-time US-based dosimetry with CT-based dosimetry. The results showed an agreement between these two evaluation methods. The main difference between Chauvenic et al and the implantation at Södersjukhuset, Karolinska University Hospital is that they outlined a new prostate contour with the implanted needles. Another difference is that they were using loose seeds. The dose planning software used was VariSeed 6.7 an earlier version of our VariSeed 7.1.

Further studies are needed to determine whether a postimplant CT-study is really necessary for real-time implantation, as there is not enough published evidence. A new system, Bard, has been recently introduced at Södersjukhuset, Karolinska University Hospital, but it was not included in this report. After the insertion of the periphery needles the contour of the prostate is re-outlined if there are any changes in the structure, and a new dose-plan is made before seed implantation as Chauvenic et al (2004). An upgrade in the dose-planning system to VarisSeeds 7.2 has also been made. It should be pointed out that V(150) has decreased in use of this new system.

CT post-planning has restarted at Karolinska but there still are some problems evaluating data due to difficulties outlining the organs and localizing the seeds.

4.4 MORBIDITY

4.4.1 Relapse

Relapse:
Longer time is needed, ca 10-15 years for a correct follow up since prostate cancer is a relatively slow growing disease (Nag et al 1999). The three patients that had a relapse in their cancer disease probably had their staging misjudged, as shortly after the treatment metastases were found. As seen in Table 10, two of the patients that got relapse had Gleason score 7 when starting the treatment. The third patient had a small prostate volume, 14.2 cc.
4.4.2 Urinary problems

Urinary problem is the most commonly reported side effect following permanent seed implants. The patients that got urinary problems had a wide range of dose levels to the urethra. The patient with the highest D(10) and D(30) values did not get any urethra complications, while patients with significant lower doses did get complications. In this study there are not shown any relationships between UrD(10), UrD(30) and urinary morbidity. But it also has to be further investigated if the contouring of the urethra is uniformly outlined. It should be pointed out that principally all patients with urinary retention were treated during 2006-2007. If there has been a change in treatment or if it is coincidentally needs to be further investigated. As seen in Table 11,12,13 the patients with urinary problem have a median urethra volume 0.7 cc. The median urethra volume for all 198 patients is 0.6 cc. This difference is too small to make any conclusions if the urinary problems correlates with larger urethra volume. It should be noted that the median implant value of D(90) [Gy] is 174 Gy and by looking at the D(90) values in Table 11,12,13 for the patients with urinary problem, the median value is 174 Gy. This means that there are no correlations between the D(90) value and urinary complications. With the exception of one patient all patients with urinary problems received V(100)>99 %. However, if this indicates that our dose limits for V(100) are too high is unclear and will have to be further investigated. The main reason for this form of treatment is to cure the cancer without serious morbidity. Due to this aim before lowering the dose it has to be investigated if there are other methods to reduce the urinary problems. A step forward would be to investigate which urethra dosimetric parameters correspond best to the outcome.

It has also been shown in earlier studies that prostate volumes greater than 50cc increase the risk of acute urinary retention (Baxter et al 2006). There was one patient whose volume exceeded 50 cc but he was not among the ones with urethra problems.

4.4.3 Rectal complications

There have been no constraints to outline the rectum, and mostly only the inner wall of rectum has been outlined, the membrane of rectum was not included in the organ of risks, but the physicist pays special attention during the intraoperative doseplanning.
This can be one of the reasons why the side effects of the irradiation of the rectum are small. One of the patients that had mild proctitis also had the highest $R_{D0,1cc}$ value (240Gy) as seen in Table 14. It is difficult to say if this indicates that there is a threshold dose for rectum complications and more patient data are needed to draw a definitive conclusion. As seen in Table 14, the other patient, R2 that had mild proctitis had no significant high dose $R_{D0,1cc}=187Gy$, and the intrinsic radiosensitivity could have contributed.

5 CONCLUSIONS

Comparison of data between clinics is very difficult at present. A uniform method of defining the target and the organs at risk, to decide which dosimetric parameters to be given is needed. A necessary prerequisite is a uniform method of keeping patient data records.

I suggest to follow the latest update of the ESTRO/EAU/EORTC recommendations (Salembier et al 2007). In the ESTRO/EAU/EORTC recommendations, the most significant parameters to report for the prostate are $D_{90}[Gy]$, $V(100)[\%]$ and $V(150)[\%]$. The urethra parameters are $UrD10[Gy]$, $UrD30[Gy]$. The rectum parameters are $D_{2cc}[Gy]$ and $D_{0,1cc}[Gy]$. There are some secondary parameters, as shown in Table 3 that are recommended to report even if their value in relation to outcome is not demonstrated. ABS also recommended minimizing the length of urethra receiving 200% of the prescribed dose (Nag et al 1999).

In this study there has not been shown any relationship between $UrD(10)$, $UrD(30)$ and urinary morbidity. It can be discussed if there are other dosimetric parameters that show better correlation between dose and morbidity and which should also be reported. It also has to be investigated if the contouring of the urethra is uniformly outlined, Crook et al (2005) as recommended that the urethra should be contoured on each slice in which seeds can be seen.
Regarding rectum, further studies on D_{0.1cc} and D_{2cc} have to be carried out in order to establish a possible correlation with morbidity.

The values at Södersjukhuset, Karolinska University Hospital correspond with the values recommended for pre-implant dosimetry. It has to be discussed if the limit for V(100) should be lower than 99%, in order to spare urethra and to minimize V(150). Also because 48 percentage of the patients did not achieved this limit. As the main reason for this form of treatment is to cure the cancer without serious morbidity, before lowering the dose limits it has to be investigated if there are other methods for lowering the urethra complications. A step forward to that would be to investigate which dosimetric parameters relevant for the urethra correspond best to the outcome.

According to the recommendations every patient should undergo CT-based evaluation. It has to be further investigated if a post-implant CT-study is really necessary for real-time implantation, as there is not enough published data that shows the benefit of this investigation.

Hoskin and Venselaar (2007) have observed that there is a noticeable variation in the definition of planning target volume, PTV. In ESTRO/EAU/EORTC recommendations it is stated that there is no need for a margin around the prostate when using real-time, intraoperative 3D, technique with additional fluoroscopy (Salembier et al 2007).

Rectum outline constraints have to be developed at Södersjukhuset, Karolinska University Hospital. ESTRO/EAU/EORTC recommends outlining both inner and outer rectum wall (Salembier et al 2007). The rectum should also be outlined in all slices where seeds are visible (Crook et al 2005).

This report has given an overview of the dosimetric parameters for the seeds implants at Södersjukhuset. Longer observation time is needed for a correct reporting of morbidity since prostate cancer is a relatively slow growing disease.
ACKNOWLEDGEMENTS

Primarily, I would like to thank my supervisor Anna-Karin Ågren Cronqvist, hospital physicist at Södersjukhuset who has guided me and Åsa Johansson, hospital physicist at Södersjukhuset, who has answered a lot of my questions and showed me the treatment technique.

A special thank to Younes Mejaddam plus Massoud Al-Abany for their support and Svante Söderström for helping me finding articles. Of course, I also would like to thank the rest of the physics department at Södersjukhuset, Karolinska University Hospital.

I want to thank the Brachytherapy physicians Dr Ulf Norming and Dr Rolf Zimmerman and Dr Jesper Rosvall for answering my questions and of course Dr Jesper Rosvall that have provide the morbidity rates.

A thank to the Brachytherapy nurses Martina Gustavsson, Ann Wigren, Kristina Sjödin, Anne-Mari Stenberg, Ingela Lindblad and Jane Hägglund for their support and interest in my work.

I would like to thank Dr Rolf Lundh for reading my thesis carefully.

Also special thanks to Professor Lennart Andersson, who has helped me define the anatomy of rectum and the prostate.

Finally I want to thank my teacher Bo Nilsson for introducing me to the world of medical radiation physics also for being kind, helpful and understanding.
APPENDIX

PSA, prostate specific antigen, is a protein that forms in the prostate. In case of cancer more PSA is created than in normal prostate tissue. PSA goes into the blood and an abnormally high level of PSA in the blood is therefore a good mark for diagnosing prostate cancer (Cancerfonden 2005).

With a biopsy of the prostate the Gleason score can be determined. This is a method of grading the prostate cancer tissue. It is a good mark when decisions regarding options for therapy are made. Gleason score is a sum of two numbers; the primary grade and a secondary grade of different glandular patterns. The primary grade represents the predominant pattern and secondary grade the next most predominant pattern. Each of these is ranging from 1 to 5, which means that the sum, the Gleason score, will be ranging from 2 to 10. The higher the sum is, the more aggressive the tumour probably is (O’Dowd et al 2001).

The major reason that measured prostate gland volumes more than 50cc are excluded is that they are technically more difficult to treat. The public arch interference and the gland need a lot more seeds to give the prostate the required dose (Nag et al 1999).

TNM (Tumour Node Metastasis) is a system that describes the stage of the tumour. T combined with a number states how large and widespread the tumour is. N and M combined with numbers state that the tumour is spread to lymph nodes or other organs in the body. To perform brachytherapy the patient has to have a small volume, localized disease with a small risk of extra-capsular spread, that is T1-T1c (Ash et al 2000 and DeVita et al 2001).

TURP, transurethral resection of the prostate, could lead to loss of seeds that can have significant effects on the dose distribution. Urethral necrosis, stricture and urinary incontinence are more common for patients who have undergone TURP (Nag et al 1999).
IPSS (International Prostate Symptom Score) indicates the likelihood of urinary complications and functional outcome after treatment. Those with less urinary problems from the beginning have a low risk of acute retention and prolonged urinary problems after treatment (Ash et al 2000).
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