NEW TECHNIQUES AND METHODS FOR DECREASING HEALTHY TISSUE DOSE IN PROSTATE CANCER RADIOTHERAPY, WITH SPECIAL REFERENCE TO RECTAL DOSES

Vesa-Pekka Heikkilä
NEW TECHNIQUES AND METHODS FOR DECREASING HEALTHY TISSUE DOSE IN PROSTATE CANCER RADIOTHERAPY, WITH SPECIAL REFERENCE TO RECTAL DOSES

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University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center Oulu; Oulu University Hospital 

Abstract

Prostate cancer is the most common cancer among men in Western industrialized countries. Approximately 60% of prostate cancer patients receive radiotherapy at some phase of the disease, a treatment based on the use of ionizing radiation to kill or control malignant cells. Unfortunately, adjoining healthy tissues are also affected by exposure to ionization, potentially leading to the emergence of adverse side effects, even several years later. The main radiation treatment modalities are external radiotherapy and low dose rate (LDR) or high dose rate (HDR) brachytherapy. Different techniques and methods are used to decrease the dose to healthy tissues, thus limiting the possibility of adverse effects.

In this thesis a novel technique and associated equipment were developed whereby brachytherapy can be performed by inserting all needles simultaneously. This reduces the implantation time, thus minimizing the impairing effect on seed positioning accuracy resulting from prostate swelling. A phantom model was also constructed for testing and training purposes.

DuraSeal® was investigated as a spacer material between the prostate and rectum, and its effect on rectal dose was evaluated during brachytherapy and external radiotherapy. DuraSeal® is resorbed over one to six months, thus altering rectal doses compared with the original dose plan. In brachytherapy, the resorption effect on rectal doses was calculated along with an evaluation of the potential of using different isotopes. In external radiotherapy, the resorption effect on rectal dose-volume histograms (DVHs) was calculated and the need for adaptive planning considered.

DuraSeal®, as a spacer gel, clearly has favorable effects on rectal and anterior rectal wall DVHs in brachytherapy and external radiotherapy, and has the potential to decrease adverse effects. It is especially beneficial in hypofractionated treatments and external radiotherapy and brachytherapy combination treatment. In LDR brachytherapy using permanent seeds, dose planning is recommended prior to gel injection to prevent excessive rectal tolerance doses in situations where gel is rapidly resorbed. In external radiotherapy, the use of adaptive planning with a spacer gel improves rectal DVH, but is not necessary according to this thesis.

Keywords: adverse effects, brachytherapy, needle implantation, prostate, radiotherapy, spacer gel
Heikkilä, Vesa-Pekka, Uusia tekniiikoita ja menetelmiä tervekudostojen, erityisesti rektumannosten pienentämiseksi eturauhasen syövän sädehoidossa. Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä


Tässä väitöskirjassa kehitettiin uusi menetelmä ja laitteisto, joiden avulla voidaan brakyterapiassa asettaa kaikki neulat samanaikaisesti eturauhasen. Menetelmä nopeuttaa implantointivaihetta, jolloin eturauhasen turpoaminen ei ehdi vaikuttaa jyvien asettelutarkkuutta heikentävästi. Samassa yhteydessä rakennettiin myös fantomi laadunvalvontaa ja harjoittelua varten.

Työssä tutkittiin ja arvioitiin myös DuraSeal® geelin käyttöä välikemateriaalina eturauhasen ja peräsuolen välissä sekä geelin vaikutusta peräsuoliannoksiin. DuraSeal® resorboituu kuuden kuukauden aikana muuttavan alikuperäisen annossuunnitelman mukaista peräsuoliannosta. Brakyterapiassa tutkittiin ja laskettiin resorption vaikutusta sekä arvioitiin eri isotoppien käyttöä. Ulkoisessa sädehoidossa laskettiin resorption vaikutusta peräsuolen tilavuushistogrammeihin ja tutkittiin mahdollisen adaptiivisen suunnitelun käyttöä.

DuraSeal® geelin käyttöä välikemateriaalina pienentää selkeästi peräsuoliannoksia ja siten myös mahdollisesti tervekudosten haittavaikutuksia sekä ulkoisessa sädehoidossa että brakyterapiassa. Geelin käyttö on erityisen hyödyllistä hypofraktiohoidossa sekä ulkoisen sädehoidon ja brakyterapiapain kombinoidussa käytössä. Matala-annosnopeuksissa brakyterapiassa (jyvähoitoissa) annossuunnitelma suositellaan tehtäväksi ennen geelin ruiskutusta, jotta peräsuolen toere-annosennoksi voi liittetävä vaikka geeli resorboituisikin nopeasti. Ulkoisessa sädehoidossa adaptiivinen suunnitteluvälikegeeli kannaa tuo lisäävää pientä haittaa edelleen peräsuoliannoksia, mutta ei ole välttämätöntä.

Asiasanat: brakyterapia, eturauhanen, haittavaikutus, ulkoinen sädehoito, välikegeeli
To my family
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My very best wishes go to our UFO (urologi, fyysikko, onkologi) team members Markku Vaarala and Merja Korpela M.D., with whom I have been working for several years on prostate radiotherapy treatments, especially brachytherapy. The conversations, ideas and collaboration have been a driving force in this thesis.

With pleasure, I thank the personnel of the Department of Radiotherapy for a pleasant and inspiring working environment. It has never been difficult to wake up in the morning and go to work, as it has been a true team work place. Special thanks go to Pertti Henttu Tech. Lic., whose supportive ideas for progressing this project have, although not all practical, been extremely exhilarating and have lightened the way.

I wish to thank my parents, my late father Osmo and my mother Kerttu, for supporting whatever I have been endeavored to do. I hope I can pass on to my children at least some part of my father’s advice and my mother’s joy of life – she went, for the very first time in her life, to see an AS Rome football match in Rome to mark her 85th birthday.

Finally, I wish to express my warmest thanks to my family, my better half and wife Riikka, and our children Venla and Aapo, without whom this work would
probably been completed a decade ago, but without whom this all would mean nothing. I have had a wonderful journey with Riikka, watching and being part of our children’s growth to become fine young adults. You are the most precious things in my life.

This thesis has taken a considerable length of time to complete, and acknowledgment of all the people involved in the process is not possible. However, if you read this, you are most certainly a person somehow part of this process, and entitled to acknowledgment. Thank you.

Haukipudas, April 2016

Vesa-Pekka Heikkilä
### Abbreviations

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<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>3DCRT</td>
<td>3 dimensional conformal radiotherapy</td>
</tr>
<tr>
<td>AAPM</td>
<td>American Association of Physicists in Medicine</td>
</tr>
<tr>
<td>AP</td>
<td>anteroposterior</td>
</tr>
<tr>
<td>BED</td>
<td>biologically effective dose</td>
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<tr>
<td>CBCT</td>
<td>cone beam computed tomography</td>
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<tr>
<td>CLE</td>
<td>consequential late effect</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>CTV</td>
<td>clinical target volume</td>
</tr>
<tr>
<td>EAR</td>
<td>excess absolute risk</td>
</tr>
<tr>
<td>eBT</td>
<td>electronic brachytherapy</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
</tr>
<tr>
<td>ERB</td>
<td>endorectal balloon</td>
</tr>
<tr>
<td>ESTRO</td>
<td>European Society for Radiotherapy and Oncology</td>
</tr>
<tr>
<td>EUD</td>
<td>equivalent uniform dose</td>
</tr>
<tr>
<td>FF</td>
<td>flattening filter</td>
</tr>
<tr>
<td>FFF</td>
<td>flattening filter free</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GPU</td>
<td>graphics processing unit</td>
</tr>
<tr>
<td>GU</td>
<td>genitourinary</td>
</tr>
<tr>
<td>Gy</td>
<td>gray (J/kg)</td>
</tr>
<tr>
<td>HA</td>
<td>hyalourasil (a spacer gel)</td>
</tr>
<tr>
<td>HRS</td>
<td>hyper-radiosensitivity</td>
</tr>
<tr>
<td>HDR</td>
<td>high dose rate</td>
</tr>
<tr>
<td>IDRE</td>
<td>inverse dose rate effect</td>
</tr>
<tr>
<td>IGRT</td>
<td>image guided radiotherapy</td>
</tr>
<tr>
<td>IMRT</td>
<td>intensity modulated radiotherapy</td>
</tr>
<tr>
<td>LDR</td>
<td>low dose rate</td>
</tr>
<tr>
<td>LINAC</td>
<td>linear accelerator</td>
</tr>
<tr>
<td>MEBXS</td>
<td>miniature electronic brachytherapy x-ray sources</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NISE</td>
<td>needle insertion by simultaneous execution</td>
</tr>
<tr>
<td>NTCP</td>
<td>normal tissue complication probability</td>
</tr>
<tr>
<td>OAR</td>
<td>organ at risk</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>OER</td>
<td>oxygen enhancement ratio</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethylene glycol (a spacer gel)</td>
</tr>
<tr>
<td>PTV</td>
<td>planning target volume</td>
</tr>
<tr>
<td>PZ</td>
<td>peripheral zone</td>
</tr>
<tr>
<td>RBE</td>
<td>relative biological effectiveness</td>
</tr>
<tr>
<td>RTOG</td>
<td>Radiation Therapy and Oncology Group</td>
</tr>
<tr>
<td>SABR</td>
<td>stereotactic ablative radiotherapy</td>
</tr>
<tr>
<td>SEER</td>
<td>surveillance, epidemiology, and end results</td>
</tr>
<tr>
<td>TD5</td>
<td>tissue tolerance dose, 5% risk of severe complications within 5 years after irradiation</td>
</tr>
<tr>
<td>TD50</td>
<td>tissue tolerance dose, 50% risk of severe complications within 5 years after irradiation</td>
</tr>
<tr>
<td>THI</td>
<td>tissue harmonic ultrasound imaging</td>
</tr>
<tr>
<td>TRUS</td>
<td>transrectal ultrasound</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>XRT</td>
<td>external radiotherapy</td>
</tr>
</tbody>
</table>
List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


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1 Introduction

Prostate cancer is most common cancer among men in Western industrialized countries (Ferlay et al. 2015). In Finland, 5,124 new cases were diagnosed in 2013, equivalent to 30.9% of all cancers in males (Suomen Syöpärekisteri 2015). The predicted incidence in Finland in 2020 is 6,371 new cases (35.7% of all cancers in males) (Ferlay et al. 2015) indicating steady growth. Commonly used treatment options with radical intent include radical prostatectomy and external or internal radiation therapy. It is estimated that 60% of prostate cancer patients receive radiotherapy at some phase of their disease (Delaney et al. 2005). In terms of survival or side effects, treatment outcomes are comparable for surgery or radiotherapy alone (Klein et al. 2009). Radiotherapy as a treatment modality is based on the use of ionizing radiation to kill or control malignant cells. This is achieved primarily by damaging the DNA of cancer cells. Unfortunately, healthy cells are also affected by the radiation although they are considered more capable of repairing sub-lethal damage. The success of radiotherapy requires the absorption of a sufficiently high dose to the prostate (Cozzarini et al. 2014, Zelefsky et al. 1998). An increase in prescribed dose (70 Gy to 78 Gy in external radiotherapy) results in a significant improvement in freedom from failure but also increases gastrointestinal and genitourinary reactions (Pollack et al. 2002, Kuban et al. 2008). In brachytherapy, the rectal dose (D2cc, the maximum dose that covers 2 cm³) correlates significantly with the incidence of adverse events (Van Gellekom et al. 2005). The majority of cancer foci (74%) are found in biopsies taken from the peripheral zone (PZ) (Chen et al. 2000), which is typically located beside the rectum. The vicinity of the rectum and other organs such as the bladder, urethra, bowel and femoral heads makes external radiotherapy and brachytherapy challenging because of undesired but unavoidable healthy tissue doses. These doses can cause adverse side events which might not emerge for several years.

Acute, late, and consequential late effects

Side effects include radiation-induced normal tissue responses over a time scale of weeks to years after exposure. Joiner and van der Kogel defined acute reactions as those expressed < 90 days after the onset of radiotherapy and having a radiobiological α/β ratio > 6, and late reactions as starting after 90 days with α/β < 5 (Joiner & van der Kogel 2009). A linear quadratic–model assumes that acute
and late effects are independent of each other, but evidence suggests that the late effects can originate in part from severe acute effects. The damage that arises from these effects is referred to as consequential late effect (CLE) and is mainly observed in the urinary and intestinal system, of particular significance after radiotherapy for prostate cancer. (Heemsbergen et al. 2006, Dörr & Hendry 2001, Pinkawa et al. 2010). Tables 1 and 2 present possible acute and late toxicity side effects in prostate cancer radiotherapy (Mohammed et al. 2012).

### Table 1. Acute toxicity side effects in prostate cancer radiotherapy.

<table>
<thead>
<tr>
<th>Genitourinary (GU)</th>
<th>Gastointestinal (GI)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>dysuria</td>
<td>diarrhea</td>
<td>pruritis (cutaneous)</td>
</tr>
<tr>
<td>retention</td>
<td>tenesmus</td>
<td>rash (cutaneous)</td>
</tr>
<tr>
<td>urinary frequency</td>
<td>acute proctitis</td>
<td>fatigue</td>
</tr>
<tr>
<td>incontinence</td>
<td>bleeding</td>
<td></td>
</tr>
<tr>
<td>hematuria</td>
<td>nausea</td>
<td></td>
</tr>
<tr>
<td>pain, burning on urination</td>
<td>vomiting</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Late toxicity side effects in prostate cancer radiotherapy.

<table>
<thead>
<tr>
<th>Genitourinary (GU)</th>
<th>Gastointestinal (GI)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>dysuria</td>
<td>bleeding</td>
<td>erectile dysfunction</td>
</tr>
<tr>
<td>urinary frequency/urgency retention</td>
<td>frequency, loose stool proctitis</td>
<td>femoral head/neck fractionation secondary cancer</td>
</tr>
<tr>
<td>hematuria</td>
<td>rectal incontinence</td>
<td></td>
</tr>
<tr>
<td>incontinence</td>
<td>nausea</td>
<td></td>
</tr>
<tr>
<td>urethral stenosis</td>
<td>ulceration</td>
<td></td>
</tr>
<tr>
<td>urethral stricture</td>
<td>stricture</td>
<td></td>
</tr>
</tbody>
</table>

**Side effects grade classification: RTOG / CTCAE / WHO**

Side effects are typically classified into five grades, referring to the severity of the adverse event. Different classification systems exist, such as RTOG/EORTC, CTCAE (NCI) and WHO, all of which essentially comparable (EORTC 2009, NIH & NCI 2009). Grades 1 and 2 consist of mild and moderate symptoms which do not require invasive intervention. Grades 3 and 4 are more severe, and grade 5 refers to death related to an adverse event. Zhu et al. performed a meta-analysis for external radiation therapy modalities in prostate cancer and found that 26% of treated patients suffered acute gastrointestinal (GI) side effects and 25% acute genitourinary (GU) side effects of grade ≥ 2. Corresponding late effects included
GI 18% and GU 17%. (Zhu et al. 2014). Radiation therapy is associated with an increased risk of grade 3 or 4 side effects that persist beyond 5 years (Kim et al. 2011).

Radiotherapy treatment modalities

Radiotherapy modalities for prostate cancer include external radiotherapy (XRT) and internal radiotherapy, commonly referred to as brachytherapy. External radiotherapy typically uses photons, but particle therapy with protons, helium and carbon ions is also possible with the advantages of radiobiological effectiveness and high conformity (Rucinski et al. 2013). The treatment technique used in XRT is generally intensity-modulated radiotherapy (IMRT) and, more often, volumetric arc therapy (VMAT) with image guidance (IGRT) using fiducial or rf-markers. Conventional fractionation is 38–39 × 2.0 Gy, but hypofractionation is gaining in popularity; schedules such as 5 × 7.0 Gy or 20 × 3.0 Gy deliver biologically equivalent or superior doses to the prostate compared with conventional fractionation, according to recent studies (Tree et al. 2013, Fowler et al. 2003). Hypofractionation is an attractive option from an economic and resource basis, although questions remain regarding its side effects. In brachytherapy, both low dose rate (LDR) and high dose rate (HDR) treatments are used, and can be combined with external radiotherapy.

The purpose of this thesis was to study and develop methods and techniques to decrease healthy tissue doses and adverse events in prostate cancer radiotherapy. For brachytherapy treatments, a device was developed for inserting implantation needles simultaneously in order to decrease implantation time and swelling effects during the procedure, thus increasing accuracy. A novel ultrasound phantom for implantation training was also developed, and dosimetry evaluation using DuraSeal® as a spacer gel between the prostate and rectum was carried out (specifically on the gel resorption effect on rectal doses). In external treatments, the need for adaptive planning when using a spacer gel was evaluated using simulated dose plans. In brachytherapy, the resorption and isotope selection effect on rectal doses was analyzed in actual patients.
2 Review of the literature

2.1 Radiobiological aspects

When ionizing radiation passes through cells, the energy it dissipates causes ionization and excitation reactions which break molecular bonds to form highly reactive unstable molecules. These free radicals are either inactivated or fixated, leading to stable chemical changes in biologically important molecules. The majority of the molecular lesions are successfully repaired, but some fail, eventually leading to cell death. The time-scale for these processes to emerge from irradiation ranges from 10–18 seconds to years (Fig. 1). The processes are usually divided into three phases: physical, chemical and biological, and when selecting an endpoint for a certain radiation response effect, the all phases of the process should be given consideration (Joiner & van der Kogel 2009).

![Fig. 1. Time-scale of radiation effects on biological systems (Joiner & van der Kogel 2009).](image-url)

Different mathematical models have been used to describe the shape of cell survival curves. The most popular at present is the linear-quadratic (LQ) formula, which was proposed in the 1940s (Lea & Cathcheside 1942) but gained popularity after its application to fractionated radiotherapy by Douglas and Fowler (Douglas & Fowler 1976) and later developed further by various authors (Barendsen 1982, Withers et al. 1982, Thames et al. 1982, Fowler 1989). The formula describes the
surviving fraction (SF) of target cells after a dose per fraction (d) assuming each fraction is equally effective:

$$SF = e^{-ad - \beta d^2}$$  \hspace{1cm} (1)

When the treatment is fractionated to n fractions, the effect E is:

$$E = -\ln(SF)^n = n(ad + \beta d^2)$$  \hspace{1cm} (2)

From equation (2), the concept of biologically effective dose (BED) was formulated:

$$BED = \frac{E}{\alpha} = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$  \hspace{1cm} (3)

If the radiation lasts more than a few minutes, intracellular repair (g) must be taken into account:

$$BED = nd\left(1 + g\frac{d}{\alpha/\beta}\right)$$  \hspace{1cm} (3a)

$$g = \frac{\mu - 1 + e^{-\mu t}}{\mu t^2}$$  \hspace{1cm} (3b)

Where $\mu = 0.693/t_{\beta}$ ($t_{\beta}$ = repair half time, often taken as 1.5 h) and $t$ = duration of irradiation (h).

During the overall course of treatment time (T), repopulation of irradiated cells must be taken into account:

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \ln2 \left(\frac{T>T_k}{aT_p}\right)$$  \hspace{1cm} (4)

Where: $T_k$ = days after repopulation starts (kick-off) and $T_p$ = cell doubling time.

The formulas detailed above are applicable to external radiotherapy. When treating with exponentially decreasing LDR brachytherapy at an initial dose rate ($R_0$), BED is calculated according to Dale:

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Where $\lambda = 0.693/(\text{T}_{1/2})_c$, an overall rate constant describing the loss of activity, and $(\text{T}_{1/2})_c = \text{effective clearance half-life}$. (Dale 2004).

The most common biophysical explanation for LQ model is that it represents two types of DNA damage. In type A, the double strand break happens in a single ionizing event and is not repairable, while in type B, separate ionizing events break each strand. If the first break is repaired before the second event, there is no lethality observed. In the LQ cell survival curve, $\alpha$ is the initial slope of the line (representing type A damage) and $\beta$ is a measure of the downward curvature (presenting type B damage) (Dale 2004). $\alpha$ is also described as intrinsic radiosensitivity and $\beta$ represents the repairable component. The $\alpha/\beta$ value is the dose at which type A and type B damages are equal, and each tissue and tumor has a specific $\alpha/\beta$ value. A low $\alpha/\beta$ value (0.5–6 Gy) is characteristic of late-responding normal tissues, and higher $\alpha/\beta$ values (7–20 Gy) are typical of early-responding normal tissues and many tumors. (Joiner & van der Kogel 2009). The LQ model is applicable to both tumor and normal tissues when evaluating the likelihood that the therapeutic index (tumor cure vs. healthy tissue complications) might change by altering radiation delivery. The model also provides information on acute and late responses.

In prostate cancer radiotherapy, the LQ model has played an important role in developing treatment strategies. The prostate $\alpha/\beta$ value is defined either in vivo, from clinical data, or in vitro, using cultured prostate cancer cell lines. Prostate cancer is highly heterogeneous, not only between individuals but also within the same patient with different tumor subgroups (Boyd et al. 2012). Furthermore, both $\alpha$ and $\beta$ values vary according to phase in the cell-cycle (Ling et al. 2013). Defining the $\alpha/\beta$ value is therefore challenging in either method, and is more or less either a representative mean value (in vivo) or a measured value for particular cell line (in vitro), from which the various clinical interactions are absent. In Nahum’s study, the average $\alpha/\beta$ value was 8.3 as calculated from different in vitro studies using different cell lines (Nahum et al. 2003). However, the variation was extremely high, even for the same cell lines among different laboratories, demonstrating that the microenvironment has a major impact on radiation response.
In *in vivo* studies the $\alpha/\beta$ value ($< 2$) has been shown to be lower than the $\alpha/\beta$ value for late complications in rectal tissue (Brenner & Hall 1999, Fowler *et al.* 2001, Brenner *et al.* 2002, Dasu & Toma-Dasu 2012). This observation suggests that the treatment dose per fraction could be increased in XRT (hypofractionation) without increasing the incidence of late complications. Furthermore, XRT with a brachytherapy boost could produce greater biological tumor effects with acceptable late complications compared with conventional daily 2 Gy (Fowler 2009).

Carlson *et al.* found that the *in vivo* and *in vitro* data are consistent with prostate cancer cells having an $\alpha/\beta$ value less than about 3 or 4 Gy, when the larger confidence level of *in vitro* studies is taken into consideration (Carlson *et al.* 2004).

At present low prostate $\alpha/\beta$ value is clinically widely accepted and hypofractionation is gaining more popularity. Table 3 presents organs at risk, their $\alpha/\beta$ values, and possible endpoints in prostate cancer radiotherapy taken from literature (Kehwar 2005, Emami 2013). Unfortunately, the $\alpha/\beta$ values tend to vary according to reference source. The common $\alpha/\beta$ value used for late reactions is 3.

**Table 3. Organs at risk, possible endpoint, late reaction $\alpha/\beta$ values.**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Endpoint</th>
<th>$\alpha/\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>rectum</td>
<td>severe proctitis, necrosis, stenosis, fistula</td>
<td>3.9</td>
</tr>
<tr>
<td>small bowel</td>
<td>obstruction, perforation</td>
<td>6.0–8.3</td>
</tr>
<tr>
<td>bladder</td>
<td>symptomatic bladder</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>contracture and volume loss</td>
<td>3.4–4.5</td>
</tr>
<tr>
<td>penile bulb</td>
<td>erectile dysfunction</td>
<td>-</td>
</tr>
<tr>
<td>femoral head &amp; neck</td>
<td>necrosis</td>
<td>0.8</td>
</tr>
<tr>
<td>skin</td>
<td>necrosis, ulceration</td>
<td>1.9–2.3</td>
</tr>
</tbody>
</table>

**Bystander effect**

Cells that are exposed to ionizing radiation can release signals that induce similar effects in non-targeted neighboring cells, causing a decrease in survival of non-irradiated bystander cells. Sometimes, low dose-irradiated cells can increase the survival of cells irradiated to a higher dose, indicating that the signaling appears to be mutual (Rzeszowska-Wolny *et al.* 2009). The ‘bystander effect’ can thus cause collateral damage in normal tissue, even if that tissue has not been irradiated. An advantage of using IMRT is a reduction both in dose and in risk of
complications in normal tissue. IMRT benefits may, however, be complicated; because of the greater volume irradiated to low doses, the system burden of bystander factors may be increased (Marín et al. 2015).

Abscopal effect

The abscopal effect has been defined as a ‘distant bystander’ effect (Kaminski et al. 2005). Radiotherapy is typically and somewhat dogmatically proclaimed a local treatment which lacks systemic effects. However, there is evidence that long-distance signaling also exists; interestingly, even from one whole multicellular organism to another (from irradiated fish to non-irradiated fish, for example) in appropriate circumstances (MotherSill & Seymour 2011).

2.1.1. Fractionation and dose rate

Radiation delivered at high dose rates is biologically more effective than the same dose delivered at a low dose rate. Early reacting tissues (with high $\alpha/\beta$ values) have a smaller dose rate effect than late reacting tissues (low $\alpha/\beta$ values) (Dale 1996, Kuperman & Spradlin 2013). This suggests that prostate cancer should theoretically be treated with a high dose rate, causing a greater impact to the prostate and lower effects on surrounding healthy tissues.

If the treatment fraction time in XRT is prolonged, as is typically in the case with static IMRT delivery compared with conventional XRT, cell killing can be significantly decreased. A study by Wang concluded that, in tumors with low $\alpha/\beta$ ratios and short repair half-times such as prostate cancer, a treatment fraction time in the range of 15–45 minutes may significantly impair the treatment outcome. The equivalent uniform dose (EUD) decreased from 78 Gy to 69 Gy for a prescribed 81 Gy (1.8 Gy fraction) IMRT with a fraction delivery time of 30 min. (Wang et al. 2003).

Flattening Filter Free (FFF) treatments

Modern linear accelerators (LINACS) are capable of delivering increased dose rates of up to 24 Gy/min by removing the flattening filter (FF) thus theoretically increasing the biological effectiveness in prostate cancer radiotherapy. This FFF approach is also useful in shortening the treatment fraction time in hypofractionated and stereotactic treatments (including those targeting the
prostate). The achieved dose rate effect on cell killing remain somewhat controversial. Studies show that FFF beams with higher doses per pulse are more efficient in reducing cell survival compared to FF beams (Lohse et al. 2011), but that no difference in clinical outcome is observed between FFF and FF treatments (King et al. 2013). However, the reduced fraction treatment time decreases for the likelihood of prostate movement and deformation during the fraction, thus ensuring delivery of the correct dose to the prostate and without overdosing adjacent healthy tissues.

**Inverse dose rate effect – IDRE**

The general rule in clinical practice is that cellular sensitivity decreases with decreasing dose rate. However, if the dose rate is very low or the absorbed dose is below 0.01 Gy, cells may show hyper-radiosensitivity (HRS) causing more cell killing than the LQ-model predicts (Marples & Joiner 1993). This phenomenon is called the inverse dose rate effect (IDRE). Leonard and Lucas presented a dose response factor of 2.0 to >5.0 when comparing IDRE with non-IDRE normal behavior, thus influencing the cell killing by factors of 8–100 (Leonard & Lucas 2009). It has been suggested that the BED calculation should involve multiple BED evaluations using multiple parameters (Jones, et al. 2001). Leonard and Lucas described IDRE excess cell killing effect on BED by using the following dose rate-sparing BED formula:

$$BED = k \left[ \left(1 - e^{-\lambda T}\right) \frac{(dD/dt)_b}{\lambda} \left(1 + \frac{2\lambda(dD/dt)_b}{\sigma_b^2}\left[\frac{1}{1-e^{-\lambda T}}\left[1+\frac{1}{(\mu_0 + \lambda)(1-e^{-\lambda T})}\right]\right]\right) \right]$$

Where $\mu = repair\ rate\ constant, \lambda = decay\ constant, T = time\ after\ the\ IDRE\ threshold\ dose\ rate\ appears, K = excess\ cell\ kill\ factor, and (dD/dt)_b = initial\ dose\ rate (Leonard & Lucas 2009).

The exposure time (T), for the implant source to decay from the initial dose rate to the threshold dose rate, is calculated initially. Using achieved time T, the dose (BED) without the IDRE is then calculated using equation (6) and K=1. The BED is calculated again with an excess cell kill factor (for example K=10), using the present time and a new initial dose rate in which IDRE exists. Following the IDRE transition, the BED is calculated once more, again using a new time, initial dose rate and K=1. Thus the obtained BED values are summed together to result in the final BED.

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LDR brachytherapy with permanent seeds is one treatment mode where IDRE can potentially have an influence, especially in adjoining tissues and organs of the prostate. Leonard and Lucas estimated that 50–80% of adjoining tissues experience IDRE causing possible excess cell killing. They also presented a hypothesis that HDR brachytherapy or LDR brachytherapy without permanent seeds may reduce post-therapy complications. (Leonard & Lucas 2009).

### 2.1.1 Radiation-induced secondary malignancies

Radiation is a well-known carcinogen. Therefore, it is fair to assume that radiotherapy can cause the emergence of second cancers, years and even decades later. Two different biological mechanisms with different relationships to radiation dose are known to cause second cancers following prostate cancer radiotherapy. One mechanism is related to radiation damage to the rectum, bladder and skin, caused by acute, chronic and consequential damage after high radiation dose. Reducing the absorbed dose and chronic radiation damage to healthy tissues will also reduce the risk of second cancers caused by this mechanism. The other mechanism is related to low-dose regions, such as in the lung. Here, the dose-risk relationship is unlikely to follow a simple mathematical function, and the International Commission of Radiological Protection (ICRP) effective dose method for radiation protection purposes should not be used in estimating secondary cancer risk; instead, epidemiological data from radiotherapy patients should be evaluated (Joiner & van der Kogel 2009, ICRP 2007).

In a large cohort study (122,123 patients), the risk of radiation-induced second cancer from prostate cancer radiotherapy was 0.3%. Of these cancers, bladder and lung cancer each represented 39.5%, rectal cancer 12%, and leukemia 9%. The treatments took place between 1973–1993, using very different techniques from current IMRT approaches. (Brenner et al. 2000). Another cohort study in Canada (1984–2000) reported an overall increase in second cancer risk of 0.45% in radiotherapy-treated prostate cancer patients (Pickles & Phillips 2002).

Liauw et al. studied the incidence of bladder and colorectal cancers after prostate brachytherapy compared with brachytherapy combined with XRT and found no difference. The absolute maximum risk for bladder cancer was found to be 35 cancers per 10,000 patients. The authors suspected, however, that this outcome could be related to more vigilant screening and thorough workup as a result of radiation side effects. (Liauw et al. 2006). In Surveillance, Epidemiology, and End Results (SEER) analysis (1973–2002), no significant
differences were found between the radiotherapy groups of brachytherapy, XRT, or combined brachytherapy and XRT (Abdel-Wahab et al. 2008).

2.2 Defining target

The most important aspect of treatment planning is the definition of the correct target. If the target is poorly defined, the treatment will miss the true target and possibly cause adverse effects on surrounding healthy tissues, regardless of the quality of positioning or equipment and techniques. ICRU 50, 62 and 83 (ICRU 1993, ICRU 1999, ICRU 2010) give recommendations and instructions on prescribing, recording and reporting photon beam therapies. These reports also contain guidelines on defining target and other objects. In order to derive the correct planning target volume (PTV) from the clinical target volume (CTV), one must know the geometrical uncertainties of tumor position during the treatment. Typical error estimation is performed by calculating the sum of different errors in quadrature. This requires that the errors are independent of each other and are treated as Gaussian:

$$ \Delta f = \sqrt{\delta x^2 + \delta y^2 + \cdots + \delta z^2} $$  \hspace{1cm} (7)

It has been suggested that systematic and random errors often result in different margins and should be studied separately, particularly when based on biological effects. This can be achieved using data collected from groups of similar patients and treatments. From this data, systematic and random deviations for translations and rotations are defined in all directions and the resulting parameters are used in calculating the margins around a CTV. Adequate margins appear to be approximately:

$$ 2 \cdot \Sigma + 0.7 \cdot \sigma $$  \hspace{1cm} (8)

Where $\Sigma$ is standard deviation for systematic errors and $\sigma$ is standard deviation for stochastic errors. (Stroom et al. 1999).

There are numerous methods and algorithms for calculating PTV margins. A thorough review of these formulas has been performed by van Herk (van Herk 2004). In prostate cancer radiotherapy, the margin size of 6 mm is related to the treatment dose and technique so that the normal tissue complication probability (NTCP) value for the rectum is smaller than 10% with 74 Gy 3DCRT and 78 Gy IMRT (Kukolowicz et al. 2015).
Soft tissue contrast and therefore target delineation are superior in MR imaging. In radiotherapy MR images are often registered with CT images, which are geometrically accurate and considered necessary for electron density data on dose calculation. However, the image registration features errors which can affect improved target delineation. To avoid these registration errors, the use of MR images alone in treatment planning with conversion from MRI intensity to HU values, has been shown to be a feasible method. (Kapanen et al. 2013, Korhonen et al. 2014).

2.3 Patient setup position effect

In external beam prostate cancer radiotherapy, patients can be treated either in the supine or in the prone position. The latter may be favored because, when a patient is in the supine position, the prostate rests on the rectum and increased rectal doses can result. The prone position has also been shown to lead to superior target coverage interfractionally, when using alignment based on bony structures (Liu et al. 2008). Intrafractional motion of the prostate, however, has been shown to be less frequent in the supine position during external radiotherapy (Kitamura et al. 2002) and has a greater impact on target coverage, demanding a larger PTV margin in prone position compared to supine position (Olsen et al. 2012). This motion includes respiratory induced prostate movement which is substantial in the prone position and reduced in the supine position (Dawson et al. 2000). The PTV margin can be decreased if respiration-induced motion is accounted for in treatment planning (Shah et al. 2011, Kitamura et al. 2002), rendering a simple technique more complex. In a study by Wilders, no position-related significant difference was observed in anteroposterior (AP) and superoinferior prostate motion, and patients reported greater comfortable in the supine position (Wilders et al. 2010).

In brachytherapy, the patient is in a lithotomy position for both LDR and HDR treatments (Ash et al. 2000, Kovács et al. 2005) in order to make the procedure easier for staff to carry out; the fixation is done to the prostate itself.

2.4 Patient immobilization devices

Typical patient immobilization devices in XRT are thermoplastic shells and various cushions. In prostate cancer radiotherapy, the effectiveness of using shells around the pelvis is limited and can even cause additional intrafractional
respiratory-induced movement in the prostate itself. This observation is explained
by intra-abdominal pressure and constraint induced by the shell, causing
abdominal content to move in a cranio-caudal direction instead of an anterior-
posterior direction (Malone et al. 2000).

In brachytherapy, the procedure is normally performed under general or
spinal anesthesia (Hoskin et al. 2013) although local anesthesia is also used,
mainly because of the need for process efficiency (Pellizzon 2008). The use of
general anesthesia ensures that, during the treatment procedure, no voluntary or
involuntary movements can cause movements of the needles and distortion of the
dose distribution.

2.5 Prostate immobilization devices

The prostate itself can be immobilized, although the techniques used are invasive
and can be uncomfortable to the patient. An endorectal balloon (ERB) can be used
to reduce both intrafraction motion of the prostate and rectal doses in external
beam radiotherapy. An ERB is inserted in the rectum and inflated using air, water
or contrast agent, thus stabilizing the prostate. Improved stabilization ensures that
the treatment targets the PTV, decreasing the CTV-PTV margin and thus the
healthy tissue dose. Regarding prostate setup, Smeenk et al. found that ERB
significantly reduces intrafraction prostate motion, but not interfraction variation,
and that the use of ERB is particularly beneficial in treatment sessions lasting
longer than 150 s (Smeenk et al. 2012). From a dosimetric viewpoint, the
reduction in the posterior and lateral rectal wall dose is apparent because of the
increased distance from high-dose regions (Smeenk et al. 2011). The anterior
rectal wall is pressed tightly against the prostate, exposing it to higher doses and
possible adverse effects. Evidence suggest that, when the ERB is filled with air, it
can reduce the anterior rectal wall dose because of the build-up effect (Teh et al.
2002, Teh et al. 2005). However, an air-filled balloon was found to produce more
under dosage in the PTV and overlap region, and to increase dose inhomogeneity
compared with water or contrast-filled balloons, which are therefore preferred
(Srivastava et al. 2013). ERB-induced errors are typically related to positioning
and balloon size, which can cause prostate deformation and dosimetric changes
(Jones et al. 2013). Gas and stool adjacent to the balloon in the rectum can also
cause large random interfraction prostate displacements (van Lin et al. 2005). In a
review article by Both et al., acute GI toxicities were shown to be reduced when
using an ERB (Both et al. 2012). ERB and late effects have been studied in
relatively few articles. van Lin et al. examined rectal wall late effects, with or without ERB, by periodic (3 months, 6 months, 1 year, and 2 years) endoscopic assessment and found that ERB increased tolerance for late rectal wall damage (van Lin et al. 2007). Teh et al. used RTOG late effect scale systems and found that the rectal toxicity profile was very favorable at a median follow up of 31.3 months (Teh et al. 2005).

**Anchor needles**

In brachytherapy treatments, the prostate can be immobilized using stabilization needles (Hoskin et al. 2013, Ash et al. 2000). The use of anchor needles prevents a rocking motion in the prostate when anterior needles are inserted, thus improving LDR treatment accuracy of seed placement (Feygelman et al. 1996). Hooked or regular needles in angulated configurations are shown to produce a more stabilized prostate (Sherman et al. 2006). Taschereau et al. found no difference between the use of parallel stabilization needles versus non-stabilization needles in seed misplacement, and concluded that seed misplacement is caused by friction between prostatic tissues and implantation needles (Taschereau et al. 2000).

**2.6 Spacers**

One way to decrease the dose to nearby organs at risk (OAR) is to increase the distance between the target and OAR. In prostate cancer treatments, this implies the distance between the rectum and prostate, and can be used both in brachytherapy and external radiotherapy. In brachytherapy, the benefit comes mainly from the inverse square law, while in external radiotherapy, it comes from field positioning and optimization; a greater portion of fields bypasses the rectum. A Dutch cost-effective study on gel spacers in XRT showed that quality-adjusted life years (QALYs) were higher following IMRT with spacers against IMRT with no spacers, producing 0.028 QALYs. This results in an incremental cost-effectiveness ratio (ICER) of €55,800 per QALY gained. (Vanneste et al. 2015). The spacer cost in Vanneste’s study was €1,300 (total €1,700), but use of the same parameters with cheaper spacer materials such as DuraSeal® (€300) and no extra charge (study II in this thesis), results in an ICER of €5,000 per QALY gained.
2.6.1 Prostate water displacement kit

In HDR brachytherapy treatment, a transrectal ultrasound (TRUS) probe is used for imaging the prostate. It is covered by a sheath which can be filled with water to elevate the prostate anteriorly. Following elevation, the dose plan is completed and needles are implanted. The water is then removed, causing the anterior wall of the rectum to collapse towards the rectal probe while the prostate is immobilized by the needles. This increases the distance between the prostate and rectum. This technique has been shown to reduce the rectum inner wall dose by 20%. (Kälkner et al. 2006).

2.6.2 Biodegradable balloon

To increase the distance between the prostate and rectum, a biodegradable implant can be placed between the two. A rolled biodegradable balloon is inserted transperineally using a catheter, filled with isotonic saline solution to increase the distance by approximately 9 mm, and sealed in situ with a compatible polymeric plug (Levy, et al., 2009). A multi-center study of different external radiotherapy techniques (IMRT, conf-3D, total doses 70–78 Gy) showed that the average prostate-rectum distance increased 2.2 cm after balloon implantation and did not reduce significantly during XRT. The balloon degraded completely after 6 months. Dosimetry analysis showed a significant reduction in V50, V60, D50, D70, D80, D90 and D100 rectal dosimetry values in DVHs compared before and after implantation. No severe adverse events were reported. (Gez et al. 2013). In Wolf’s study, use of a balloon showed superior rectal dose reduction compared with spacer gel, but the volume loss of the balloon was > 50% while the gel remained relatively constant during the XRT course (Wolf et al. 2015).

2.6.3 HA and PEG gel

Two types of gel can be used as spacer material, hyaluronic acid (HA) and synthetic polyethylene glycol (PEG) based hydrogels. Both are biocompatible materials which are absorbed and metabolized over a period of months. HA is a polysaccharide found in human tissues as a component of connective tissue. It normally degrades in a short time, but can be stabilized for up to one year when modified. HA was originally used in osteoarthritis treatment but its usage has been extended to prostate cancer radiotherapy (Prada et al. 2007, Chapet et al.)
2013, Wilder et al. 2011). As a downside, HA is reported to experience degrading effects from radiation—in particular, 6 MV radiotherapy doses—which reduce viscosity (Daar et al. 2010). PEG is a hydrogel which is widely used in skull surgeries. It is composed of two liquid solutions which polymerize in situ to form a gel when mixed. PEG is degraded by the hydrolysis of ester bonds and is excreted renally. Its clearance time varies from one to six months (Augmenix 2015, Covidien 2015). PEG gel is used in brachytherapy and XRT treatments and has also been tested for particle therapy (Susil et al. 2010, Strom et al. 2014, Uhl et al. 2014, Rucincki et al. 2013).

2.6.4 Collagen

Collagen is the most abundant protein in the human body and has been demonstrated as well tolerated when injected into the perineum to modulate exposure to high doses of radiation. It is reported to be 50% absorbed after 6 months, and completely absorbed at 12 months. Unfortunately, the availability of collagen is variable and can be affected by demand from the black market (Noyes et al. 2012, Mok et al. 2014).

2.7 Image guided radiotherapy (IGRT)

Image-guided radiotherapy refers broadly to treatment delivery using modern imaging methods in target and non-target structures. It increases the precision and accuracy of radiation delivery, reducing toxicity with the potential for dose escalation and improved tumor control (Image-Guided Radiotherapy Committee Key Members 2001). In prostate cancer radiotherapy, IGRT is associated with an improvement in biochemical tumor control in high risk patients and a lower rate of late urinary toxicity compared with high dose IMRT (Zelefsky et al. 2012).

2.7.1 Fiducial markers

Fiducial markers in radiotherapy are materials that are used as a reference points on, or implanted in, the body. Used as landmarks to help localize the target and position the patient and treatment fields, they can minimize the dose to the surrounding healthy tissue whilst ensuring high therapeutic doses to the target. The use of fiducials in the prostate gland is ideal and has been shown to be
necessary. In Chen’s study on XRT using fiducials, over 90% of the treatments required shifts $\geq 3$ mm. (Crook et al. 1995, Chen, et al., 2007, Ng et al. 2014).

**Passive markers**

Typical “passive” markers are made of gold, which can be designed in different shapes to minimize migration, with some containing steel, for example, to allow easier visualization with MRI. Recent developments have focused on polymer based fiducials, which are visible in MRI and CT and produce minimal artifacts. The number of fiducials is recommended to be at least three, in order to allow triangulation and measurement of position in different planes (Ng et al. 2014), although two fiducials implanted in the apex and base are reported to be sufficient (Kudchadker et al. 2009). The use of additional fiducials allows for the possibility of migration or fiducial loss.

**Active markers**

Fiducials can also be “active”, sending real-time position information to a receiver which can be integrated to LINAC. These types of markers typically use radiofrequency signals and include wireless Calypso® (Calypso Medical Technologies, Seattle, USA) and wired RayPilot® (Micropos Medical AB, Gothenburg, Sweden) technology. Magnetic implants with magnetic field sensors have also been developed and tested (Lennernäs 1997).

**2.7.2 Ultrasound**

Ultrasound (US) is the primary imaging mode in prostate brachytherapy during the implantation process, but can also be used in XRT for image guidance.

**US and brachytherapy**

Transrectal ultrasound guidance in prostate brachytherapy is the most commonly used and recommended image guidance method in LDR (permanent seed implantation) and HDR-treatments (Davis et al. 2012, Yamada et al. 2012). In brachytherapy, the absorbed doses can be very high, especially near seeds or source wire dwelling positions. During implantation, it is crucial to distinguish the urethra inside the prostate for treatment planning in order to avoid overdose
and possible adverse effects to the urethra. One way to achieve this is the use of aerated gel as a contrast agent inside a catheter located in the urethra. Another approach is the use of tissue harmonic ultrasound imaging (THI), which has been proved to be superior to brightness (B) mode imaging when delineating the prostatic urethra and rectal wall (Sandhu et al. 2014).

**US and XRT**

US features high soft tissue contrast, real-time capability, low acquisition costs, and the absence of ionizing radiation, which decreases excess radiation dose from imaging, especially to healthy tissues. These properties make it particularly suited for intrafractional motion tracking (Jenne & Schwaab 2015). Robotically-controlled US probe manipulators incorporating image guidance hardware and radiotherapy treatment plan have been shown to have accuracy less than 1 mm in each direction (Lachaine & Falco 2013, Western et al. 2015). Ultrasound guidance using fiducial markers has also been demonstrated. The markers were satisfactorily visible and reduced the subjectivity involved in interpreting the soft tissue image (Vavassori et al. 2009).

### 2.8 Intensity modulation radiotherapy

#### 2.8.1 IMRT in external radiotherapy

IMRT is based on increasing the intensity of the beam to the target and reducing the intensity of beams that cross sensitive structures. Inhomogeneities in dose distribution are compensated for by cold and hot spots coming from other directions (Newhauser & Durante 2011). Although IMRT/VMAT is a very popular treatment mode in external radiotherapy, enabling higher treatment dose, it has some drawbacks. Although it produces attractive dose distributions in treatment planning systems, possible error sources can be overshadowed by the sophisticated technology it presents. Modulating the radiation intensity often uses very complex MLC patterns; small patient movements (affecting the prostate or OAR) can disturb the actual dose distribution. It has been suggested that conventional conformal beams with on-line adaptive planning would be a better approach (Rouzaud, 2013). From a radiobiological point of view, IMRT decreases high doses to the OAR but at the same time increases the healthy tissue volume
that receives low doses. This is because of an increased number of fields directly affected by the radiated volume, but also because of the greater number of monitor units used which in turn increases accelerator leakage radiation. The result is an increase in the computational risk of second primary cancers (Hall 2009, Hall & Wuu 2003). In prostate treatments, the interest is mainly in rectal and bladder cancers, and pelvic bone and soft tissue sarcomas. Murray et al. evaluated four different techniques for prostate IMRT: conventional IMRT, VMAT, FFF, and stereotactic ablative radiotherapy (SABR), and found that excess absolute risk (EAR) was low in all techniques. Theoretically, relative second primary cancer risk improved with SABR and FFF techniques, although the absolute differences between techniques and absolute risk itself were small (Murray et al. 2015). IMRT related out-of-field low doses to the whole body following prostate treatment has been shown to cause inflammation through viral and immune responses and delayed or missing DNA repair mechanisms (El-Saghire et al. 2014). Intensity-modulated particle therapy has been suggested to lead to lower risks than X-ray techniques, mainly because of lower doses to healthy tissues. Particle therapy-related neutron exposure can be decreased using a spot-scanning delivery method (Newhauser & Durante 2011). Although several theoretical computational risk assessment studies have been performed on radiation-induced second primary cancers after prostate cancer radiotherapy, the number of real clinical patient data studies is scarce. From the SEER database, Abdel-Wahab et al. calculated a 0.16% increased risk (Abdel-Wahab et al. 2008), and Murray et al. concluded in a review article that the risk was small, in the range of 1 in 290 to 1 in 220 (0.34–0.45%), over all durations of follow-up. The risk was also found to increase to 1 in 70 patients (1.4%) followed up for more than 10 years, but these patients were treated with older techniques such as non-conformal and large field methods. (Murray et al. 2014).

### 2.8.2 Intensity modulated brachytherapy

Brachytherapy, in common practice, utilizes radioactive sources such as Ir-192, Cs-137, I-125, Pd-103, and Sr-90. In HDR treatments, dose modulation is based mostly on time; the longer the dwelling time, the bigger the dose. Brachytherapy has been described as “original intensity-modulated radiotherapy” (Thomadsen, et al. 2012), because of its ability to modify the dose. Even though the dose can be modulated relatively easily, dose distribution is typically radially symmetrical. To also modulate the radiation direction, directional sources based on partial
shielding (Song et al. 2012) (Petrokokkinos et al. 2011) or rotating asymmetric sources (Ebert 2006) can be used. Adams et al. developed a Gd-153 source with a dual needle system, where the outer needle allows insertion of the shielded catheter in which the source will be inserted. By rotating the shielded catheter, one can modify dose distribution. This approach was shown to lower the urethral dose in prostate brachytherapy relative to conventional HDR by 29–44% (Adams et al. 2014).

Directional shielding can also be used in LDR treatment. Lin et al. presented a I-125 source with gold shielding in breast brachytherapy (Lin et al. 2008). Using lower energy sources reduces the shield thickness so that the final source diameter is not overly thick. The tenth value layer (TVL) for Ir-192 is 8 mm of lead, which is not feasible in interstitial treatments. For I-125, the TVL is 0.08 mm and for Pd-103, 0.025 mm of lead, making integration of an internal shield within interstitial brachytherapy sources reasonable. (Lin et al. 2008). A substantially easier approach to intensity modulation in prostate seed implantation LDR treatment is to use different source activities; higher activity sources are implanted in regions where bigger doses are required, and vice versa. By implanting lower activity sources in the posterior part of the prostate or in the vicinity of the urethra, one can thus reduce rectal and urethral doses and possible adverse effects. Another possibility is the use of multi-species seed configuration, different isotopes with different energies. Chaswal et al. compared single seed (I-125) against a combination of two seed types (I-125 and Ir-192) in dose plans for three different prostate volumes. The activity of the I-125 seeds was constantly 14.8 MBq, but the Ir-192 seeds varied from either 4.44 MBq to 9.25 MBq. All methods produced sufficient target coverage, although the multi-species configuration required fewer seeds and needles and exhibited better dose uniformity. Furthermore, improved urethral sparing was achieved with the multi-species configuration. Rectal doses increased with higher Ir-192 activity seeds because of a lower dose drop-off rate, but rectal doses were of the same magnitude as I-125 seeds with lower activity. (Chaswal et al. 2007). A limitation of using multi-species or different activity seeds lies in post planning. To calculate the dose, one needs to identify different sources from CT-images, which can prove quite challenging.

A novel approach to intensity-modulated brachytherapy is electronic brachytherapy (eBT), utilizing X-rays as the radiation source. Intraoperative radiotherapy, which has a long history of use, falls into this category but is relatively unknown and rarely used. In eBT, the dose rate and penetration can be
adjusted using variable currents and voltages, allowing the source to mimic several isotopes. Theoretically, the use of lower energies and higher dose rates would radiobiologically raise relative biological effectiveness (RBE) (Nath et al. 2005) and reduce doses to healthy tissues. This approach also has the advantage of increased radiation safety to personnel administering the radiotherapy. The concept of eBT remains somewhat unclear, since it is excluded from current regulations of brachytherapy sources. Some reports discussing the issue exists, however (Park et al. 2010, Thomadsen et al. 2009). Safigholi et al. studied the design of miniature electronic brachytherapy X-ray sources (MEBXS) based on TG-43U1 dosimetric data and Monte Carlo simulations. Optimal results were achieved using a tungsten conical-hemisphere target shape with an apex angle of 60 degrees, and a 0.9 mm radius of uniform cylinder as a cathode. (Safigholi et al. 2012). eBT in prostate treatment is not yet feasible because of the relatively large diameter of the applicator (approximately 5.4 mm). The source itself is 2.5 mm, surrounding water cooling is required.

2.9 Adaptive radiotherapy

Adaptive radiotherapy can be defined as a closed-loop radiation treatment process which uses a systematic feedback of measurements to modify the treatment plan (Yan et al. 1997). By using adaptive planning, PTV margins can be modified in each fraction. Adaptive radiotherapy is based on offline or online procedures. In the offline procedure, the original dose plan is modified by the data received from CT or cone beam computed tomography (CBCT) images, acquired from first fractions and used in the rest of the treatment course (Nuver et al. 2007). In the online procedure, the dose plan is modified in every fraction using the particular fraction’s CT or CBCT images to re-optimizing the plan. Methods such as segment aperture morphing and segment weight optimization have been presented (Ahunbay et al. 2010). A limitation of online procedures is the time typically required to perform the re-optimization (11 minutes in Ahunbays’s work). The treatment process may be slowed and the gained benefit of the adaptive plan missed when the prostate position is changed due to patient or rectal movement during the planning stage. Use of a direct aperture optimization algorithm and a fast graphics processing unit card (GPU) has shortened the optimization time to under 4 seconds (Men et al. 2010).
2.10 Particle therapy

Particle therapy, also called as hadron therapy, has been used in radiotherapy with charged particles such as protons, carbon, helium and other ions, and pions (Jermann, 2015). This approach has physical properties that confer significant benefits on radiotherapy. Large amounts of energy can be accurately deposited into tumors at various depths, while surrounding healthy tissue, particularly behind the tumor, receives less dose. This is achieved as a result of Bragg peak. Hadron therapy also has radiobiological advantages such as higher relative biological effectiveness (RBE) and lower oxygen enhancement ratio (OER) compared with X-rays. These features are especially beneficial when using carbon ions, which have smaller penumbras (Allen et al. 2011). Although theoretically beneficial in terms of treatment, an efficacy and cost-effectiveness study comparing hadron therapy with photon therapy in prostate cancer radiotherapy was unable to draw definitive conclusions (Lodge et al. 2007).

2.11 Watchful waiting

A watchful waiting approach is recommended for patients with early stage prostate cancer. Active treatments (and thus side effects) are postponed, increasing the quality of life during the waiting period (Kasperzyk et al. 2011). The downside of watchful waiting is that patients can experience a significant burden on mental health compared with patients treated with prostatectomy or radiotherapy (Ravi et al. 2014). Another limitation is the difficulty in identifying patients who will benefit from watchful waiting and that, ultimately, watchful waiting does not erase the original problem of side effects.

2.12 Side-effects in different techniques

In dose escalation to 80 Gy using IMRT, the acute and maximal late grade 2 GI toxicity were 3% and 8% respectively, and late grade 2 GI toxicity fell to 0% at the end of follow up (median 29 months). No late grade 3 GI was observed. Acute and maximal late grade 2 GU toxicity were 56% and 28% when pre-treatment values were 20% and 5%. At the end of follow up, late grade 2 GU toxicity decreased to 15%. Grade 3 GU toxicity was 8% and 3% respectively. (Ghadjar et al. 2008).
In a health-related quality of life study, urinary incontinence and rectal discomfort were most pronounced at 6 months after external radiotherapy (IMRT or 3DCRT). Both decreased over time, but rectal discomfort increased again 2 years after radiotherapy. (Schaake et al. 2014).

Kim et al. studied late GI toxicities in different radiotherapy modalities: 3D-conformal, IMRT, brachytherapy and proton therapy. IMRT and brachytherapy as monotherapy were associated with relatively low rates of late grade 3/4 GI toxicities. The authors found, somewhat surprisingly, that proton therapy had the highest GI toxicity, although toxicity values decreased significantly in treatments administered after 2004. The overall risk continued over five years. (Kim et al. 2011).

Sutani et al. also studied different radiotherapy modalities: conventional radiotherapy, IMRT, LDR-brachytherapy alone, and LDR brachytherapy combined with external radiotherapy, and their effects on GU and GI toxicity. They concluded that differences in toxicity could not be explained by treatment modality, but instead depended on total dose to the GU/GI tract. (Sutani et al. 2015).

Hypofractionated radiotherapy is gaining in popularity because of the decreased number of fractions required and the associated lower departmental costs and improved logistical convenience. Increasing treatment dose, however, increases the risk of side effects. Cozzarini found an increased risk of severe urinary toxicities (grade 3–4) in postprostatectomy patients receiving hypofractionated radiotherapy (Cozzarini et al. 2014). However, hypofractionated IMRT, compared with conventional IMRT, has been shown to be equally well tolerated at 2 years (Dearmaley et al. 2012). Using a SABR technique in hypofractionation was been shown to be well tolerated (Loblaw et al. 2013). If the hypothesis of consequential and late damage emerging from acute effects is true, the hypofractionated radiation scheme with 2 or 3 fractions per week (instead of 5) would not only limit acute toxicity, but also late toxicity (Heemsbergen et al. 2006).

In a study by Grills, prostate brachytherapy HDR treatment (Ir-192, 4 × 9.5 Gy) was compared with LDR (Pd-103 seeds, 120 Gy) monotherapy and resulted in similar biochemical control. However, HDR compared with LDR was associated with decreased rates of acute Grade 1–3 dysuria (33% vs 64%), urinary frequency (8% vs 46%), rectal pain (80% vs 90%), long term urinary complications (32% vs 50%) and 3-year impotency (15% vs. 45%). (Grills et al. 2004).
Combining brachytherapy and external radiotherapy yielded significantly less acute urinary side effects compared with implantation only, but late grade 2 rectal and urinary toxicities were more common (Zelefsky et al. 2008).


**Aims of the study**

The aim of this thesis was to study and develop techniques and methods to decrease healthy tissue doses and thus adverse effects in prostate cancer radiotherapy. The specific objectives were:

1. To develop and construct a brachytherapy system and equipment for inserting all implantable needles simultaneously into the prostate, in order to prevent prostate rotation and to decrease the impairing swelling effect on seed accuracy during the implantation process.

2. To study the feasibility of using the DuraSeal® PEG spacer gel and its resorption effect on rectal doses in LDR brachytherapy.

3. To dosimetrically evaluate an adaptive versus a single plan with a PEG spacer gel in external radiotherapy.
3 Materials and methods

3.1 Materials

This study was carried out in the Department of Radiotherapy at Oulu University Hospital. A new concept (and equipment) for implanting all needles simultaneously was developed and constructed together with a testing phantom (study I). Dosimetric studies using a spacer gel in brachytherapy and XRT (studies II and II) were performed using routine planning equipment and software available in the department.

3.1.1 Needle Insertion by Simultaneous Execution (NISE)

The basic concept was to develop and construct equipment to reduce brachytherapy implantation time in order to decrease the swelling effect and its impairing effects on seed positioning accuracy. Due to swelling, the prostate anatomy, especially the base and posterior edge, can be more difficult to visualize (Grimm et al. 2004), which may give rise to set up errors. Also, solitary needle insertion can cause gland motion and deformation (Wan et al. 2005, Lagerburg et al. 2005, Stone et al. 2002). To address these limitations, a technique and equipment for inserting needles simultaneously was developed. It was originally designed for use with LDR treatment, but can also be used in HDR. The system consists of two similar templates, connected by sliding rails, through which the needles are set. The rear template is moveable and has a locking mechanism for the needles. The system is connected to a stepper and a TRUS transducer.
Fig. 2. Needle Insertion by Simultaneous Execution (NISE) equipment (published by permission of IOP publications).

The needles are set through the templates according to dose plan coordinates without penetrating the patient’s skin. In LDR treatments, the tips of the needles are set relative to each other (cranio-caudal, the direction of the prostate) and locked to the rear template. In HDR treatment, the needles are set to the same level. After needle presetting, the rear template is pushed forward through the patient’s perineum using US guidance until the chosen depth is reached. In LDR treatment, the lock is then released and the seeds are implanted in the prostate, needle by needle, with empty needles pulled away. In HDR treatment, the after-loading system transfer tubes are connected to the needles and source wire driven in to them. The needles are locked to the rear template during the procedure to prevent movement and are released when the treatment is over. In both techniques, the position of the needles is verified after insertion using US, and necessary adjustments can be made either to the needle position (LDR) or dose plan (HDR).
Testing phantom

A testing phantom was constructed (study I), primarily to test the feasibility of the developed needle implantation equipment but also to act as a learning phantom for the procedure itself—“to see is to understand”. The phantom consisted of an open-top persplex case featuring a front wall opening with bolus material through which the needles are set, a plastic tube for the US transducer, and a replaceable prostate model made of gelatin. The prostate model was fixed to the case using rubber bands, allowing slight rotation and movement of the model to imitate prostate movement in a real patient. The case was filled with water.

![Fig. 3. Testing phantom for needle implantation (published by permission of IOP publications).](image)

The prostate model (Fig 4.) and testing phantom (Fig 3.) were manufactured transparent so that implantation could be visually checked at any time during the procedure.
3.1.2 Patients

Ten voluntary patients, consecutively receiving LDR brachytherapy treatment, were enrolled in study II following approval by the local ethics committee. Written informed consent was obtained from each patient. PEG spacer gel was injected transperineally between the prostate and rectum after the normal implantation procedure to ensure that rectal tolerance doses were not exceeded, even if the gel was cleared immediately. Four CT imaging sessions were performed; one preoperatively, the day before the actual implantation in order to obtain reference images, and three post planning series over the following three months. One MR imaging session was undertaken on the same day as one of the post planning CT imaging series. The same patients and their image series were used in simulated XRT dose plans in study III.
3.1.3 Treatment planning systems

In LDR brachytherapy (study II), a VariSeed 8.0 (Varian, Palo Alto, USA) treatment planning system was used together with an ultrasound B&K ProFocus machine and transducer 8848. The CT and MR image series were captured with GE HiSpeed CT and 3.0 T Siemens Skyra.

In study III, the treatment planning system used was Eclipse 11.0 (Varian, Palo Alto, USA). The image series used was the same image series as in study II. The calculation algorithm was DVO/AAA 11.0.31.

3.1.4 Spacer gel

DuraSeal® (Covidien, Mansfield, USA) was chosen as a spacer gel (study II and III). It contains water soluble PEG with reactive linkages. When mixed with trilysine, the combination crosslinks instantaneously to form an absorbable hydrogel. Dilution was used to delay the polymerization by a few seconds (Susil et al. 2010). DuraSeal® is essentially the same material as spaceOAR® gel, used commercially for prostate treatment. DuraSeal® was selected based on economic reasons; the price of DuraSeal® is approximately €300 while spaceOAR® costs €1500. In addition to this, DuraSeal® is widely used in skull surgeries, easy to use, and forms a more rigid spacer compared with hyaluronic acid. The PEG clearance time varies from one to three months, a somewhat short period (especially in the context of LDR treatments) but one which can also have an effect in XRT treatments; therefore, the clearance time and effects on dose distribution were analyzed in both studies.

3.2 Methods

3.2.1 NISE phantom materials

The needle-skin resistance 6.28 N in the prostate and 8.87 N in the perineum using 18 G needle and corresponding values of 8.42 N and 15.57 N when using a 17 G needle were obtained from the literature (Podder et al. 2006), and measured during an actual implantation procedure using a specially-constructed power gauge. A force-calibrated spring was attached to the piston and the force was read when the physician inserted the needle during implantation. The readings
obtained were used as reference values when choosing the materials for the phantom model.

### 3.2.2 Beveling effect

A possible beveling effect (Fichtinger et al. 2006), caused by chisel-type needle tips, was studied in the standard “single grid” system and the developed NISE system using two types of needle sets (IsoCord® needle 18 G (pink), and Accuneedle® 18G (green)). A frame with millimeter paper was set 5.5 cm from the implantation grid so that the skin model (15 mm) plus prostate model (40 mm) would fit in the second phase. Twenty-two needles were set according to the dose plan and pushed against the millimeter paper. The resulting holes were marked as reference holes. The needles were then pushed through the bolus and prostate model against the stationary millimeter paper. The distance and direction between the reference holes from the first push and the new holes caused by beveling were measured. The chisel effect (needle beveling to the direction of the long end of the needle tip) was evaluated by placing the long sides of the needles either all facing upward or placed randomly within both grid systems.

The mean beveling values with standard deviations were calculated. The beveling effect on the dose distribution was studied on five randomly chosen dose plans from actual implantations. The dose plans were recalculated with parallel posterior needle shifts of 1 mm, 3 mm and 5 mm, and in a randomized direction with a randomized shift of 1–3 mm, producing four new plans for each original plan. The DVH parameters, V140 on the prostate and D1 on the urethra, were calculated and compared.

### 3.2.3 Imaging

The brachytherapy treatments and phantom simulations (studies I and II) were performed using transversal and sagittal US images. CT-image series (studies II and III) were taken at intervals of 1 day pre-implantation, 1 day post-implantation, 1 month post-implantation, 2 months post-implantation, and 3 months post-implantation. MR imaging was performed once on the same day as one of the post-implantation CT series. The purpose of this was to help delineate the gel in CT images. The MR imaging sequence used was T2 turbo spin echo. In dose calculations, the CT images were chosen because of superior seed visibility
(study II) and the existing electron density information for inhomogeneity corrections (study III).

![Fig. 5. PEG spacer gel in US (post1d), CT (post1mth) and MR (post2mths) images. Gel marked with arrows (published by permission of Elsevier).](image)

### 3.2.4 Treatment planning

**Brachytherapy**

In LDR seed implantation, the dose plan was executed normally using US images without the spacer gel. After seed implantation, the spacer gel was injected transperineally into the perirectal space between Denonvilliers’ fascia and the rectal wall (Fig. 6). The needle was positioned using sagittal US guidance and the correct location was ensured by injecting approximately 10 mL of saline into the space. A maximum of 10 mL diluted DuraSeal® was then injected between the prostate and rectum. A new US image series was taken to measure gel volume and for use in dose calculations. The gel was injected after the seed implantation to ensure that, even if the gel was absorbed immediately, the rectal tolerance dose would not be exceeded. This method also provided the opportunity to compare dose distributions, with and without the gel, in the same patient. From the CT images, the volume of the prostate and gel was measured as a function of time and dose, and dose calculations were performed. The actual dose plan was done using I-125 IsoCord S06 seeds (Bebig, Germany).
Fig. 6. Sagittal MR image from pelvis; arrow indicates the location where the spacer gel is injected.

The gel effect on rectal doses was studied using two models, with and without the gel. The former model was further divided into calculations performed with and without the gel clearance effect. In case of no clearance, the dose was calculated from the images taken right after gel injection, taking into account only the isotope’s decay factor. In cases where clearance could be measured as a function of time, the final dose was calculated by measuring the dose from the particular image series and multiplying it by the ratio of the total treatment time in order to calculate the received doses (Eq. 9). The clearance effect was the remainder of these doses.

\[
D_{2cc} = \sum_{i=1}^{n} D_{2cc,i} \left[ (1 - e^{-ln^2 t_1/T_{1/2}}) - (1 - e^{-ln^2 t_{i-1}/T_{1/2}}) \right] \quad (9)
\]

Where \( t_i \) = time examined, \( T_{1/2} \) = isotope half-life.
The target dose was chosen as $D_{2cc}$, according to European Society for Radiotherapy and Oncology (ESTRO) and American Association of Physicists in Medicine (AAPM) recommendations (Salembier et al. 2007, Nath et al. 2009). Prescribed dose was 145 Gy using seed activity of 17.46 MBq (0.472 mCi).

Dose planning, with and without the gel, was done also using Pd-103 seeds to determine the gel effect on rectal doses compared with I-125 seeds. The smaller isotope half-life is theoretically superior, as gel clearance has a smaller effect on total dose as a function of time. Pd-103 has a half-life of 16.99 days, compared with 59.4 days for I-125. The prescribed dose using Pd-103 was 125 Gy, using seed activity of 55.5 MBq (1.5 mCi). The prescribed doses for I-125 and Pd-103 were chosen according to a AAPM TG 64 report (Yu et al. 1999).

**XRT – dose optimization**

Planning was conducted on image series received from study II using simulated dose plans. IMRT treatment plans with dynamic multileaf collimator leaves were prepared. Planning target volume (PTV) was defined from clinical target volume (CTV) using a 0.5 cm margin. The CTV was taken as the visible prostate. The spacer gel was not separated from the PTV. The rectum was segmented, 1 cm longer from both ends compared with PTV, in the craniocaudal direction and included the rectal content. The anterior rectal wall was defined from the rectum by creating a contour asymmetric inner margin 3 mm in an anteroposterior direction. Thus, the received contour was subtracted from the original rectum contour, resulting in the anterior rectal wall. The prescribed dose was 76 Gy in 38 fractions, with a primary reference point PTV and no normalization used. The plan consisted of seven fields and gantry angles: 215/268/303/0/62/95/135. The dose constraints to PTV were: upper 0%, 77 Gy, and lower 100%, 76 Gy, both with a weight factor of 80. Rectal upper dose constraints were used according to the Fox Chase Center (Feigenberg et al. 2005) and were 5% 75 Gy; 15% 70 Gy; 25% 65 Gy; 35% 60 Gy; and 45% 50 Gy, each with a weight factor of 50. Bladder upper dose constraints were 5% 75 Gy; 25% 60 Gy; and 50% 50 Gy. Normal tissue objective weight factor was 150. Optimization was continued until the progression plateau was reached.
XRT – plan comparison

The reference dose plan was made using CT image series taken before gel implantation. To study the effect of gel on rectal doses, two different planning methods were compared: (1) dose optimization and planning using each image series (1 day post-implantation, 1 month post-implantation, and 2 months post-implantation) separately, and (2) dose optimization and planning using the 1 day post image series which was then fused to the other image series. The first method represented adaptive planning—all varying parameters influencing the dose plan were included. The second method represented the situation where a single dose plan is used during the whole treatment course. The image fusion in method 2 was aligned using the prostate posterior edge with the help of brachyseeds. This was implemented in order to reduce the influence of prostate swelling from brachytherapy seed implantation in the original images. Rigid registration was performed and leaf motion and monitor units were kept intact, but the final calculation was performed to determine the actual dose distribution. The rectal DVH values were normalized to absolute volumes (post 1 day) to account for the gel resorption effect.

XRT – elimination of swelling effect

The swelling effect seen in all post-image series, caused by seed implantation and its impact on dose distribution, was studied using regression analysis. In each patient case, the edema magnitude was compared with rectal DVH values to determine whether any correlation existed.

3.2.5 Statistical methods

In study I, the beveling effect was studied by measuring the mean values and standard deviations for needle positions and their effects on target and urethra isodoses.

In study II, the means and standard errors of the variables were calculated and significance-tested using related samples and a Wilcoxon signed-rank test to compare D2cc doses, with or without PEG gel.

In study III, the swelling effect on doses was studied by regression analysis in each case. The correlations in edema volume and DVH dose pairs were calculated to determine whether edema had an impact on DVH values. The fusion and
adaptive plan DVH values were compared using a Wilcoxon signed-rank test. The significance level was $p<0.05$. 

4 Results

4.1 Beveling effect and NISE

The mean needle resistance force measured with an 18 G needle during actual implantation was 8 N, and the mean force when penetrating the skin was 11 N. Different materials were evaluated to determine which gave similar resistance values. A 15 mm-thick bolus material (Superflab, Mick Radio-Nuclear Instrument Inc.) was chosen for the skin model along with 20% gelatin for the prostate model.

The beveling of needles appeared in both techniques (single and NISE grid), although to a relatively small degree (Table 4.).

<table>
<thead>
<tr>
<th>Grid / Needle type</th>
<th>Needle tip orientation</th>
<th>mean offset (mm)</th>
<th>STDEV (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B&amp;K / IsoCord®</td>
<td>upward</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>mixed</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>B&amp;K / Accuneedle®</td>
<td>upward</td>
<td>1.7</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>mixed</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td>NISE / IsoCord®</td>
<td>upward</td>
<td>1.5</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>mixed</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>NISE / Accuneedle®</td>
<td>upward</td>
<td>1.8</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>mixed</td>
<td>1.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

The beveling effect on target isodoses and DVHs was relatively small. The maximum mean dose decrease in target volume that received 140 Gy (V140) was 5.8%. However, the beveling effect caused mean urethra max dose (D1) to increase by 54 Gy (Table 5.).
Table 5. Beveling effect on isodoses (published by permission of IOP publishing).

<table>
<thead>
<tr>
<th>Needle shift</th>
<th>$V_{140Gy}$ (%)</th>
<th>SD</th>
<th>Urethra max $D_{1%}$ (Gy)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean original</td>
<td>99.7</td>
<td>0.2</td>
<td>207.0</td>
<td>6.7</td>
</tr>
<tr>
<td>1 mm parallel shift, mean difference</td>
<td>-0.1</td>
<td>0.2</td>
<td>0</td>
<td>11.4</td>
</tr>
<tr>
<td>3 mm parallel shift, mean difference</td>
<td>-1.8</td>
<td>0.6</td>
<td>18.0</td>
<td>27.7</td>
</tr>
<tr>
<td>5 mm parallel shift, mean difference</td>
<td>-5.8</td>
<td>0.8</td>
<td>54.0</td>
<td>36.0</td>
</tr>
<tr>
<td>Mixed shift (1–3 mm), mean difference</td>
<td>-0.1</td>
<td>1.1</td>
<td>37.0</td>
<td>32.6</td>
</tr>
</tbody>
</table>

4.2 PEG spacer gel and rectal doses in brachytherapy

No severe adverse events were observed. One patient reported a sensation of pressure in the rectum at follow-up. Another patient felt a sudden need for defecation. Neither patient required treatment for these adverse events. The side effects were observed one month after the operation and were resolved by three months.

DuraSeal® resorption

The DuraSeal® gel was visualized by US, CT or MR (Fig. 5). Gel clearance rate as a function of change in volume and change in separation distance is shown in Fig. 7. Although the volume decreases rapidly, the separation between the prostate and rectum does not. This observation becomes apparent in the volume calculation; volume increases/decreases approximately proportional to the radius cubed. The gel volume clearance half-life was 47 days, but the separation half-life was 110 days. Separation thus has a clear effect on rectal dose, and should be used when estimating the effect of the gel as a function of time.
Fig. 7. Change in magnitude of prostate mean volume due to treatment-induced edema (a), mean distance between the prostate and rectum (b), and mean gel volume change (c) as a function of time, measured from CT-images (published by permission of Elsevier).

Gel effect on rectal doses

The actual plan and implantation were made using I-125 isotope. For comparison purposes, rectal doses were also calculated using Pd-103 isotope. The half-life of Pd-103 (16.9 d) compared to I-125 (59.4 d) gives, respectively, 99% vs. 72% of the total dose in 110 days (the half-life of separation in this study). This observation favors the use of the Pd-103 isotope as the clearance effect would be negligible. However, increased tumor cell survival resulting from the prostate swelling effect appears to be more pronounced for Pd-103 than I-125 because of the shorter half-life (Yue et al. 2002). The clearance effect was calculated using equation (9) for I-125. Mean rectal dose $D_{2cc}$ dropped significantly after gel injection with both isotopes (Table 6).

<table>
<thead>
<tr>
<th>Isotope</th>
<th>$D_{2cc}$ pre US</th>
<th>$D_{2cc}$ post US</th>
<th>p value</th>
<th>Reduction (no clearance)</th>
<th>Reduction (clearance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-125</td>
<td>95 ± 13 Gy</td>
<td>64 ± 13 Gy</td>
<td>0.005</td>
<td>31 ± 13 Gy</td>
<td>22 ± 12 Gy</td>
</tr>
<tr>
<td>Pd-103</td>
<td>58 ± 13 Gy</td>
<td>33 ± 10 Gy</td>
<td>0.005</td>
<td>25 ± 8 Gy</td>
<td>Not measured</td>
</tr>
</tbody>
</table>
4.3 PEG spacer gel and rectal doses in external radiotherapy

The use of a spacer gel distinctly reduces rectal DVH values. The difference was clear during the entire treatment course using both methods (adaptive and single plan), although it lessens towards the end of the treatment course. The mean reduction in rectal absolute volume DVH values in adaptive plans during the treatment course was 6.6 cc (2.5–10.2 cc) and was 5.2 cc (2.0–7.1 cc) in single plans. The mean relative reduction in adaptive plans was 54 % (22.8–85.7 %) and 40.6% (13.1–59.2 %) in single plans. Non-normalized and normalized mean rectal DVH values as a function of time, for single plan and adaptive plan approaches, are presented in Figures 8 and 9.

Fig. 8. Single plan (fusion, method 2) rectal DVH as a function of time: (2) without volume normalization and (b) with volume normalization (published by permission of BIR publications).

Fig. 9. Adaptive planning rectal DVH as a function of time: (a) without volume normalization and (b) with volume normalization (published by permission of BIR publications).
Adaptive vs. single plan

Adaptive planning confers some benefits compared with a single plan when used throughout the whole treatment course. The values obtained were significantly different (p = 0.043). Fig. 10 shows mean rectal DVH, although the differences and significance values remain the same when comparing patients separately.

![Fig. 10. Adaptive vs. single plan (fusion) rectal DVH: (a) without volume normalization and (b) with volume normalization (published by permission of BIR publications).](image)

Sagittal images showing 45 Gy isodose lines for post 1 day plan, post 2 month fusion plan, and post 2 month adaptive plan are shown in Fig. 11. Gel resorption can also be seen.

![Fig. 11. 45 Gy isodose line in (a) original post-implantation plan on 1-day, (b) post 2-month fusion plan, (c) post 2-month adaptive plan. Rectum, gel and 45-Gy isodose lines are delineated. Arrows show the regions of interest (published by permission of BIR publications).](image)

Swelling effect

The swelling effect on rectal doses was studied by regression analysis in each patient case. No correlation between edema volume and DVH dose pair was
found ($R = 0.0006–0.07$). Thus, the swelling effect on rectal doses was not significant.

**Anterior rectal wall**

The use of a spacer gel reduces anterior rectal wall DVH values compared with plans without the use of the gel, and the gel resorption effect on DVH values can be seen. However, adaptive planning did not improve DVH values, most likely because the anterior rectal wall was not used in optimization constraints.

**Fig. 12.** Anterior rectal wall DVH with (a) single plan (fusion) and (b) adaptive planning. (published by permission of BIR publications).
5 Discussion

Radiotherapy modalities in prostate cancer include external radiotherapy and brachytherapy. The treatment effect is based on ionizing radiation and its ability to kill cancer cells or prevent cell division. The ionizing radiation also harms the healthy tissue adjacent to the prostate and can cause adverse effects to emerge immediately or years later. To mitigate for adverse effects, the healthy tissue doses must be decreased and controlled. In this thesis, different methods and techniques are presented. DuraSeal® and its usability as a spacer gel was studied in brachytherapy and external radiotherapy. The main objectives were to determine 1) the dosimetric benefit on rectal doses of using gel, 2) the extent of gel clearance and its effect on rectal doses during the treatment course, and 3) whether compensating actions like adaptive planning are necessary when using a spacer gel.

In prostate brachytherapy, the needles are normally implanted one by one. During implantation, the prostate starts swelling, thus changing the original dose planning parameters and causing possible inaccuracies in seed placement (using LDR) and subsequently in dose distribution. A novel technique and equipment were developed and constructed to shorten the duration of the needle implantation procedure in order to decrease the swelling effect during seed positioning and ensure the accuracy and correctness of the planned dose distribution. A testing and training phantom model was also developed.

5.1 NISE

The NISE system was evaluated in the phantom and found to work well. The beveling effect appeared to be of the same magnitude in the NISE double grid as in the commonly used single grid. The effect on target doses was negligible, but urethra doses clearly increased. However, urethra dose values are partly artificial and merely computational; during a real implantation procedure, the operator will verify the urethra dose and perform necessary adjustments to the needles. Prostate model rotation during implantation using the NISE system was negligible. The prostate tended to be somewhat pushed forward, but this can be easily compensated for by checking the new base level. Stabilization needles were not considered necessary. The equipment and method are unique and not presented earlier.
The developed testing phantom was found to be effective, not only as a quality assurance tool, but also as training equipment. The whole implantation procedure, US imaging, planning, needle insertion and seed implantation with realistic resistance, could be performed using the phantom and the results could be visually checked during any stage of the treatment procedure. The mean needle implantation resistance forces were of the same values as in the literature. The phantom materials are inexpensive and prostate models easy to manufacture in different shapes, sizes and concentrations (for resistance), making the model reusable, unlike many commercially-available US phantoms.

5.2 PEG spacer gel in brachytherapy

The use of a spacer gel significantly reduces maximum rectal doses in prostate brachytherapy. When using HDR brachytherapy, the treatment itself lasts only minutes and is either given immediately or over two weeks. As a spacer material, DuraSeal® is not absorbed during this time and the benefits of its use are clear. In LDR brachytherapy with I-125 seeds, the treatment lasts longer and gel clearance happens during the treatment course, altering the original planned dose distribution. I-125 has a half-life of 59.4 d, so approximately 90% of the dose is received in 200 days. Because of the clearance effect the maximum rectal dose \( D_{2cc} \), which is strongly related to adverse events, eventually becomes higher than the dose in the actual dose plan made with the spacer gel. This has to be taken into account, especially if the treatment dose plan is made after the gel injection. If the treatment dose plan is made before the gel injection, the rectal \( D_{2cc} \) tolerance dose won’t be exceeded even though the gel would be resorbed quickly.

Seed isotope Pd-103 has a half-life of 16.9 d and an energy of 21 keV compared with 29 keV for I-125, theoretically producing a higher dose gradient. The increased distance between prostate and rectum decreases the rectal dose more quickly with Pd-103; furthermore, the gel clearance effect is negligible during the treatment. Unfortunately, target dose weakening because of prostate swelling is more pronounced in Pd-103, thus mitigating the decrease in rectal dose benefit when using the gel and the isotope with the shorter half-life.

5.3 PEG spacer gel in external radiotherapy

In external radiotherapy, the use of spacer gel shows a clear improvement in rectal and anterior rectal wall DVH compared with treatment without gel. The mean
NTCP value for rectal TD5 decreased from 66.4% without gel to 43.4% with gel, using an equivalent uniform dose (EUD)-based NTCP calculation (Gay & Niemierko 2007). TD50 was already low without the use of gel, because of the optimization constraints. Using the same patient data and increasing the total treatment dose to 82 Gy for better local control would yield an NTCP (TD50) value reduction from 8.3% without gel to 3.8% with gel. The use of gel gives more margin to dose planning and the opportunity to increase the prostate total dose, without exceeding rectum DVH tolerances and increasing possible adverse effects. The change in rectal volume shifts the DVH to the right when volume decreases and to the left when volume increases. In this thesis, the effect was minimized using rectal volume normalization, leaving the gel resorption effect as a primary factor in rectal DVH changes.

The use of spacer gel and adaptive planning gave better results on rectal DVH but not on anterior rectal wall DVH. This was likely because dose-planning optimization was performed using only rectum constraints. Using anterior rectal wall constraints would probably improve DVH. Gel resorption happens during the treatment course, and its effect can be seen in DVH. Although adaptive planning decreases the gel resorption effect and improves rectal DVH during the treatment course, the effect is minor at the doses used here. Adaptive planning is laborious, requiring multiple CT image series and dose plans in the planning phase; in the treatment process, choosing the appropriate dose plan can be difficult, requiring cone beam CT and, preferably, one or two explicit measurements. The benefit of adaptive planning with the use of the spacer gel comes with higher doses.
6 Conclusions

This thesis investigated and developed methods and techniques to decrease healthy tissue doses and possible adverse effects in prostate cancer radiotherapy. Specific equipment for inserting all needles simultaneously in brachytherapy was developed, and the feasibility of using DuraSeal® as a spacer gel and its dosimetric effects on rectal doses were evaluated in brachytherapy and external radiotherapy. The main conclusions from the thesis are summarized as follows:

1. The developed NISE system for inserting all needles simultaneously in brachytherapy worked well in phantom tests. The actual implantation time can be reduced from 30–45 minutes to 5 minutes. However, more testing is required before it can be used clinically.

2. The developed testing phantom for the NISE system can be used as a quality assurance tool, but also proved to be a very good training phantom for physicians and physicists in all steps of the treatment procedure; “to see is to understand”.

3. DuraSeal® as a spacer gel in prostate cancer radiotherapy is clearly favorable in rectal and anterior rectal wall DVHs in brachytherapy and external radiotherapy, and has potential for decreasing adverse effects. The material is relatively easy to use, quite unnoticeable and harmless to the patient, and provides more margin for dose planning and the possibility to increase the prescribed treatment dose. In hypofractionated treatments and the combination of external radiotherapy and brachytherapy, it is especially useful.

4. Gel resorption occurs during the course of radiotherapy treatment, both in brachytherapy and in external radiotherapy, increasing the planned rectal dose. In LDR brachytherapy with permanent seeds, dose planning is recommended prior to the gel injection to prevent possible excess in rectal tolerance doses in situations where the gel is resorbed quickly.

5. In external radiotherapy, using adaptive planning with spacer gel improves rectal DVH, but was deemed not necessary according to this thesis.
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