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Pulsed-dose rate brachytherapy in prostate cancer

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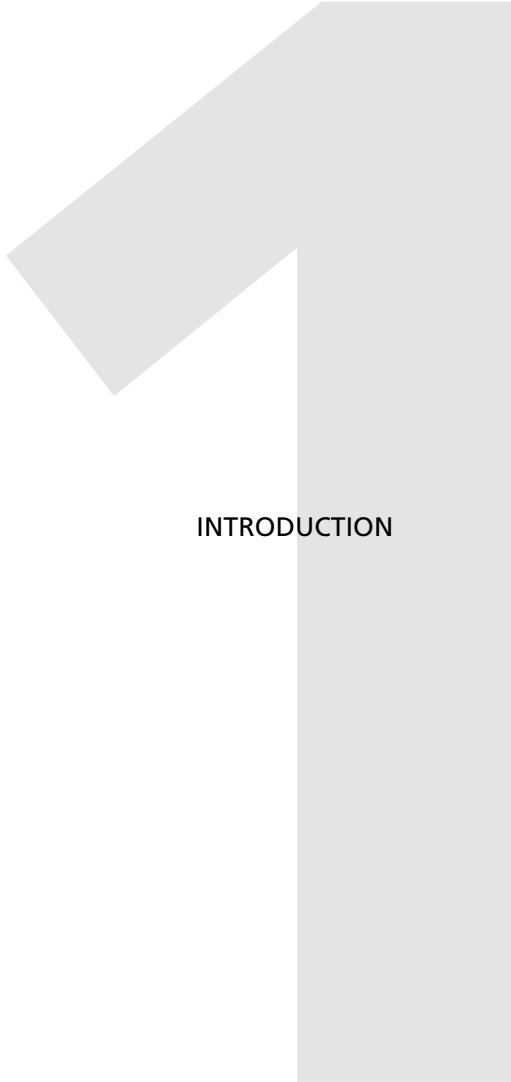
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INTRODUCTION

INTRODUCTION

In the Netherlands prostate cancer is the malignant tumor with the highest incidence in men (www.ikcnet.nl). The incidence of prostate cancer has recently surpassed the incidence of lung cancer, mainly because of Prostate-Specific Antigen (PSA) screening in the community. PSA is a protease that is mainly produced by epithelial cells and secreted into the lumen of prostate ducts. PSA can reach the serum by diffusion from luminal cells to capillaries. An elevation of serum PSA value can be indicative for prostate cancer. In 2007 prostate cancer has been diagnosed to 9588 men; in the same year 2425 men died due to prostate cancer in the Netherlands.

In general prostate cancer has a slow growth rate. For that reason some investigators advocate an active surveillance policy for low-risk prostate tumors at advanced age. The 10-year prostate cancer-specific mortality was found to be 3%-9% for patients with low-risk disease (T1-2, Gleason score ≤ 7 , PSA ≤ 15 ng/ml) [1, 2]. In a randomized clinical study of radical prostatectomy versus watchful waiting a 12-year absolute difference of 11% was found in prostate cancer-specific mortality for patients ≤ 65 years in favor of early treatment [3]. This study suggests that younger patients with localized prostate cancer will benefit from early treatment. Also patients with poorly differentiated prostate cancer are at a higher risk for prostate cancer mortality, as found in an active surveillance study, and can benefit from active treatment [2].

TREATMENT OF PROSTATE CANCER.

For active treatment of prostate cancer several therapies are available. Treatment options for localized prostate cancer are radical prostatectomy, external beam radiotherapy (EBRT) and brachytherapy. The value of cryotherapy and high-intensity focused ultrasound (HIFU) are under investigation.

Locally advanced prostate cancer is preferably treated by EBRT. According to the RTOG and EORTC studies it is evident that with the addition of long-term hormonal therapy overall survival is improved [4-7]. These studies have been conducted with a conventional EBRT dose of 65-70 Gy. Later, dose-escalating studies have shown an increase in biochemical control at higher radiation doses (≥ 74 Gy) [8-13]. It is still questionable if a higher dose on the prostate can replace hormonal therapy or that even better results will be obtained by combining dose-escalated radiotherapy with hormonal treatment.

One of the major drawbacks of dose-escalated EBRT was the increase in late toxicity. Gastrointestinal grade ≥ 2 and grade ≥ 3 late toxicity of 17-35% and 1-6%, has been reported for dose-escalated EBRT respectively [9-11, 14]. The reported incidence of genitourinary grade ≥ 2 and grade ≥ 3 late toxicity for dose-escalated EBRT was between 11-40% and 3-13%, respectively.

A high dose on the prostate gland can also be achieved with brachytherapy. One of the characteristics of brachytherapy is the high dose within the implant. For this reason,

brachytherapy is not only suitable for low-risk localized prostate cancer, but has also become of value for the treatment of intermediate- and high-risk prostate cancer.

Brachytherapy has the advantage that because of the steep dose gradient outside the implanted volume the dose to for example the rectum wall and the neurovascular bundle can be more limited than with 3-dimensional conformal EBRT. However, as the urethra is located within the implanted volume high doses are reached here and could influence urinary toxicity negatively. Modern EBRT techniques as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) are promising techniques for high precision therapy resulting in better tumor control and reduced toxicity [15-17]. The value of these modern EBRT techniques in relation to brachytherapy should be investigated in randomized prospective trials.

Proton therapy have been used in some centers for the treatment of prostate cancer with dose escalation [8, 10, 13]. Compared to proton therapy IMRT delivers low doses of radiation to a larger volume of tissue. On the other hand, the dose conformity of IMRT is higher than with proton therapy. With the lateral opposed beam proton therapy still high dose areas are found on the anterior rectal wall, which could hinder further dose escalation [18]. In addition to high dose areas in normal tissue close to the target volume seen with EBRT techniques, also large low dose areas occur. These low dose volumes are much more for IMRT and proton therapy compared to brachytherapy, as shown in a planning study for cervical cancer [19]. These relatively low dose volumes have been found to be associated with morbidity [20].

Dose distribution profiles very similar to high-dose rate (HDR) brachytherapy have been described for stereotactic body radiotherapy and can evolve as a new promising technique in competition to brachytherapy [21-23].

One disadvantage of brachytherapy for prostate cancer is that this treatment modality is not applicable for all prostate cancer patients treated with curative intent. If the prostate volume is too large technical problems caused by pubic arch interference can arise prohibiting an acceptable implant. Large prostate volume and severe lower urinary tract syndromes can cause serious urinary complaints after an implant. For these reasons patient selection for brachytherapy is necessary according to several guidelines [24-26].

HISTORY OF PROSTATE BRACHYTHERAPY

Pasteau and Degrais started in Paris with brachytherapy for prostate cancer in 1907 [27]. Brachytherapy was performed by placing a radium source in the urethra. Inspired by the French colleagues, Young introduced prostate brachytherapy in the U.S. at the John Hopkins Institute in Baltimore. He further developed the intracavitary technique by alternated placement of radium sources in not only the urethra, but also in the bladder and the rectum [28]. At the Memorial Hospital in New York radon sources were developed for medical treatment. Radon has a higher specific activity than radium; so

smaller sources for interstitial implants could be manufactured. Barringer was the first to describe a transperineal implantation technique. Needles bearing radon sources were left in place for 4 to 6 hours before being partially retracted and directed to the contralateral posterior lobe [29]. Subsequently radon-bearing glass capillary tubes were developed for permanent implants. High dose deposition of beta and low energy gamma rays led to painful necrosis in the vicinity of the sources. Gold-encapsulated seeds were developed for a more homogeneous dose distribution [30]. Often a combination of a transperineally and an open surgical suprapubic approach was used. Due to disappointing results, because of poor patient selection and poor dose distribution, prostate brachytherapy was largely abandoned in the forties of the last century. Also the development of radical prostatectomy techniques and the observation of tumor regression after castration have made brachytherapy less familiar.

In 1951 prostate brachytherapy gained new interest with the introduction of colloidal gold-198 (Au-198) injections in the prostate gland [31]. Flocks developed this technique further at the university of Iowa and introduced encapsulated Au-198 grains.

Whitmore et al. from the Memorial Sloan-Kettering Center in New York described in 1972 the open retropubic technique for permanent iodine-125 (I-125) prostate implantation. Needles containing I-125 sources were digitally guided with a finger in the rectum for positioning [32].

Holm et al. was the first to describe the transperineal I-125 seed implantation in prostatic cancer guided by transrectal ultrasonography at the Herlev Hospital in Copenhagen in 1983 [33]. The development of this technique laid the foundation of modern brachytherapy of the prostate.

The first transperineally ultrasound guided permanent prostate implant in The Netherlands was performed in the Academic Medical Center (AMC), Amsterdam by Blank in 1985 [34].

The first report on temporary prostate implants from L'Institut Gustave-Roussy in Villejuif was published in 1977 [35]. Flexible tubes were loaded with iridium-192 (Ir-192) for low-dose rate (LDR) brachytherapy.

At the Kiel University Bertermann and colleagues started with the development of HDR brachytherapy for prostate cancer in the eighties of the last century [36]. Together with permanent I-125 and palladium-103 (Pd-103) implants, HDR brachytherapy became very popular throughout the world.

The next development in temporary implants was treatment with pulsed-dose rate (PDR) brachytherapy. Blank and Pieters from the AMC started in June 2002 with this treatment modality by using an open template and self-anchoring catheters for the implantations [37].

TEMPORARY PROSTATE IMPLANTS

Brachytherapy for prostate cancer can be applied by permanent or temporary implants. Nowadays the most often used isotopes for permanent prostate implants are I-125 and Pd-103. Good treatment results have been reported resulting in a high acceptance as efficacious treatment modality worldwide [38-41]. Radioactive seeds are implanted directly into the prostate gland and remain there for the rest of patient's life. The effective dose is delivered during several weeks or months depending on the radioactive decay.

A different approach for brachytherapy is by temporary implants. Radioactive source(s) are placed into the prostate via needles or catheters. After the required dose has been applied, the source(s) and the needles/catheters are removed. The most developed and popular technique is with an HDR Ir-192 source [25]. Accurate positioning of the source is possible by placing first non-active needle/catheters. With an interactive treatment planning system a virtual dose distribution can be obtained which allows the possibility for needle/catheter position adjustments. Small imperfections of needle/catheter positioning can be adjusted with dwell time optimization techniques. An advantage of afterloading HDR brachytherapy is that there is no radiation exposure to medical personnel and other people. A disadvantage of HDR brachytherapy for prostate cancer compared to a permanent implant is the need for fractionated treatment. This means that a patient has to be hospitalized for several days or multiple implantation sessions should be planned.

PDR PROSTATE BRACHYTHERAPY

PDR prostate brachytherapy was introduced at the AMC in 2002 [37]. In contrast to the high source activity used for HDR (approximately 370 GBq), in PDR a source of 18.5 – 74 GBq is used. With PDR multiple small size fraction doses can be given in several hours or days. Because PDR brachytherapy uses the same stepping source technology as HDR, the same technical and physical features are applicable, such as virtual treatment planning, afterloading with no radiation exposure to other people, and dwell time optimization. However, different from HDR, the multifractionated dose delivery in PDR mimics a radiation course of LDR. The concept of PDR was proposed by Brenner and Hall to combine the features of a stepping source treatment with LDR treatment [42].

Cell survival after exposure to ionizing radiation can be described by the linear-quadratic formula [43]. Sensitivity to fractionation is dependent on the α/β -ratio of tissue. Tissues with a low α/β -ratio are more sensitive to fractionation than tissue with high α/β -ratio. Because the majority of malignant tumors have high α/β -ratio and normal tissue is characterized by low α/β -ratio the therapeutic window can be increased by fractionation or a protracted low-dose rate treatment. For prostate tumor cells a lower α/β -ratio than normal tissue has been suggested [44-47]. If the α/β -ratio for prostate cancer is indeed as low as 1.5 Gy a hypofractionated treatment with HDR is more beneficial. However, the value of the α/β -ratio is still under debate and also higher values have been proposed [48-50].

Also, biologic effect to high fraction doses of 5-10 Gy may be poorly predictable by the linear-quadratic model. Ongoing clinical trials (RTOG 0415 (NCT00331773), MD Anderson Cancer Center (NCT0066788), Fox Chase Cancer Center (NCT00062309), Ontario Clinical Oncology Group (ISRCTN43853433), Erasmus Medical Center (ISRCTN85138529), Royal Marsden NHS Trust (ISRCTN97182923)) will probably give more clarity on this matter.

Because there is still no clear evidence on the α/β -ratio for prostate cancer and excellent results have been found with conventional fractionated radiotherapy and low-dose rate permanent brachytherapy, the choice was made at the AMC to perform temporary implants with PDR. Liao et al. found in a radiobiological modeling study that for less responsive tumor cells to radiation there is hardly any difference in "complication-free tumor control probability" according to radiation schedule (conventional vs. hypofractionation) for an α/β -ratio for prostate cancer cells between 2.5-3.5 Gy. In this study complication-free tumor control probability was modeled as a combined parameter of tumor control probability (TCP) and normal tissue complication probability (NTCP) [51]. For responsive tumor cells the model predicts slightly better clinical results for hypofractionation.

COMBINATION OF EBRT AND BRACHYTHERAPY

As all other cancer diseases the presentation of prostate cancer is diverse. At diagnosis different stages of prostate cancer need a different treatment approach. But even for localized prostate cancer a subclassification is proposed according to risk profiles. Different risk profiles classifications are in use. All these classifications have in common a differentiation based on PSA-value, differentiation grade or Gleason score, and T-classification [24, 52, 53],[www.nccn.org]. The Gleason system is the most widely used grading system for prostate cancer. It is based on the architectural pattern of cells and is composed of the most prevalent pattern (Gleason pattern 1) and the second most prevalent pattern (Gleason pattern 2). The Gleason pattern is graded 1 to 5, with 1 being the most differentiated and 5 the most undifferentiated cells. The Gleason score is the sum of pattern 1 and 2. The T-classification describes the primary tumor extension, which is derived from the TNM-classification of the International Union Against Cancer (UICC) [54]. T1 is clinically inapparent tumor not palpable or visible by imaging, T2 is tumor confined within the prostate, T3 is tumor extending through the prostatic capsule, and T4 is tumor fixed to adjacent structures other than seminal vesicles. Some classifications also consider the amount of positive core biopsies as a prognostic factor [55]. The classification according to the American National Comprehensive Cancer Network (NCCN) is shown in table 1. The importance of subdivision into risk profiles is not only to assess the prognosis, but also to support in treatment choice [www.nccn.org, www.oncoline.nl].

Brachytherapy is characterized by high dose delivery near a radioactive source and a steep dose gradient resulting in a relatively low dose at some distance from the source [56]. For this reason selection of patients for brachytherapy is crucial. In general brachytherapy

is offered to patients with a circumscribed solitary lesion. Tumor size is often an important aspect in patient selection for brachytherapy.

The so-called low-risk prostate cancer (T1-T2a, PSA < 10 ng/ml, Gleason score \leq 6, www.nccn.org) can easily be treated with brachytherapy as monotherapy. The probability that the tumor is confined to the prostate is very high. There is a high probability that the tumor lesions within the prostate will be covered completely by the reference isodose if the whole prostate is treated. However, in the presence of adverse prognostic factors, such as \geq T2c, PSA > 10 ng/ml, Gleason score \geq 7, there is an increased risk of extraprostatic extension or distant metastases. So, for local radiation treatment it is recommended to enlarge the treated area by adding EBRT. Also hormonal therapy can be considered because of the risk for (micro)metastases [57].

Table 1. NCCN risk group classification for localized prostate cancer (Clinical practice guidelines in oncology v.1.2010)

Risk group	T classification	Gleason score	PSA (ng/ml)	Biopsy cores	PSA density (ng/ml/g)
Very low	T1c	\leq 6	< 10	Fewer than 3 biopsy cores positive, \leq 50% cancer in each core	< 0.15
Low	T1-2a	2-6	< 10		
Intermediate	T2b-T2c or	7 or	10-20		
High	T3a or	8-10 or	> 20		
Very high	T3b-T4				

AIMS AND OUTLINE OF THE THESIS

There is substantial data that with dose-escalated radiotherapy biochemical control for prostate cancer will improve. The major drawback for dose-escalated radiotherapy is that the probability for toxicity will also increase. There are several accepted techniques for dose escalation. One of these techniques is high dose EBRT with sophisticated treatment planning techniques, such as IMRT, and optimal position verification on the treatment machines with IGRT. EBRT can also be combined with brachytherapy to achieve a high dose. Brachytherapy is commonly applied with radioactive LDR seeds or with an HDR stepping source.

The aims of this work were to develop, to investigate the possibility to deliver, and to investigate the results of brachytherapy on the prostate by PDR in addition to EBRT.

In **chapter 2** a comparative study between concomitant boost IMRT, IMRT with HDR boost, and IMRT with PDR boost is presented. The 3-dimensional physical dose distribution was converted to linear quadratic dose at 2 Gy per fraction (EQD₂) for a useful comparison of the dose on the target volume and organs at risk (OAR). In external beam

radiation oncology treatment schedules are usually designed in 2 Gy per fraction. To make comparison of different external beam radiation schedules and different brachytherapy schedules easy understandable, these schedules should be converted to biologically equivalent doses as the EQD₂. In the appendix of chapter 2 the calculation of EQD₂ is explained.

A systematic review on observational studies was performed to compare clinical outcome of dose-escalated EBRT to EBRT with radioactive seeds boost and to EBRT with HDR boost. Comparison of combined survival curves was performed by metaregression analysis and described in **chapter 3**.

To perform brachytherapy for prostate cancer with PDR a different technique should be used than for radioactive seed implantation or HDR. A description of a novel technique with an open template and self-anchoring catheters for PDR brachytherapy is reported in **chapter 4**.

The first results of EBRT with a PDR boost are described in **chapter 5**. Patients were prospectively followed and data on tumor control and morbidity were collected and analyzed.

Assessment of toxicity can be done as a cumulative incidence as is presented in **chapter 5**. However, information on resolution of morbidity can be missed. For that reason in **chapter 6** a longitudinal analysis was performed to investigate the association of the development of late toxicity with time.

Brachytherapy is characterized by a heterogeneous dose distribution. Within the implant there are areas, that receive 20-40% more dose than the prescribed dose. With standard implantation of the prostate taking only the prostate volume as target organ these high dose areas do not necessarily coincide with tumor bearing areas. **Chapter 7** presents a method to visualize tumor lesions with contrast-enhanced ultrasound (CEUS) and to use this information for adaptation of the brachytherapy treatment plan.

In **chapter 8** a general discussion with future prospects is presented.

Chapter 9 provides a summary of this work in English, Dutch, and Papiamentu.

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