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### Pulsed-dose rate brachytherapy in prostate cancer

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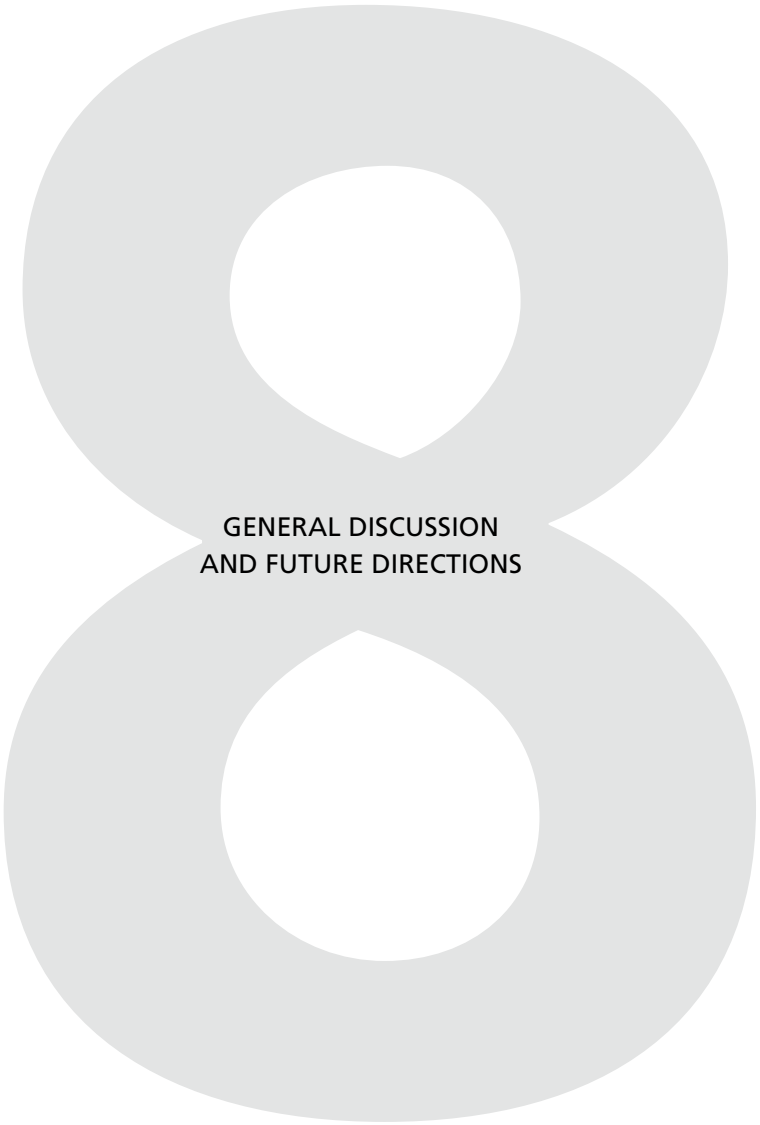
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**GENERAL DISCUSSION  
AND FUTURE DIRECTIONS**

## GENERAL DISCUSSION AND FUTURE DIRECTIONS

The aims of this thesis were threefold. Firstly, to describe a method to perform pulsed-dose rate (PDR) brachytherapy for prostate cancer. There is worldwide more experience with temporary implants for high-dose rate (HDR) prostate brachytherapy. However, the precision of dose delivery is negatively influenced by needle/catheter displacements. For this reason needle/catheter displacement must be corrected before each fraction. In the case of highly fractionated PDR brachytherapy a new technique had to be developed for fixation of needle positions because needle/catheter repositioning before each pulse would be too labor intensive and so impracticable.

Secondly, to investigate the feasibility and conditions to perform PDR brachytherapy for intermediate- and high-risk prostate cancer in addition to external beam radiotherapy (EBRT). The Academic Medical Center (AMC) in Amsterdam is the first center to perform PDR brachytherapy for prostate cancer. Studies were conducted to assess the feasibility of this novel treatment.

Thirdly, to investigate the results of this treatment modality. Patients were prospectively followed for biochemical tumor recurrence, survival, side effects and complications. These results were compared to the results of EBRT and EBRT combined with HDR brachytherapy from the literature.

For the future the addition of extra imaging techniques to gray scale ultrasound can help in optimizing brachytherapy treatment planning by defining tumor areas within the prostate. The addition of contrast-enhanced ultrasound was investigated.

### CHOICE FOR PDR

The department of Radiotherapy at the AMC has a longstanding tradition to perform brachytherapy at low-dose rate (LDR). Because in general tumor cells have a high  $\alpha/\beta$ -ratio (in the linear-quadratic formula to describe a cell survival curve to radiation) and normal tissue a low  $\alpha/\beta$ -ratio, the therapeutic window is increased with continuous LDR brachytherapy compared to hypofractionated HDR brachytherapy [1]. PDR mimics the dose delivery of LDR because multiple small dose fractions are given separated by 1-2 hours. The advantage of PDR brachytherapy above LDR is that because PDR is given by one single stepping source the possibilities for dose distribution optimization are increased. Also, because between treatment fractions (pulses) the source is kept within a source container, radiation exposure to medical personnel and relatives is absent, making it a more patient-friendly approach. Between pulses the patient can receive visits from relatives and friends and is not continuously locked in a room, as is the case with LDR. Also medical and nursing personnel can spend more time for the needed care. Because of the radiobiologic similarity of PDR to LDR and the physical advantages of PDR, introduction into the clinic began in 1995.

For the treatment of prostate cancer the choice for PDR brachytherapy is questionable. Some investigators suggested a low  $\alpha/\beta$ -ratio for prostate cancer cells, even lower than the  $\alpha/\beta$ -ratio for normal tissue. If this hypothesis is true, the preferred method for radiotherapy to prostate cancer would be hypofractionation. HDR brachytherapy would be more advantageous than PDR. However, the true value of the  $\alpha/\beta$ -ratio for prostate cancer is still under debate. Other investigators have argued that the  $\alpha/\beta$ -ratio is not as low as 1.5 Gy, but probably in the range of 3-5 Gy, similar to normal tissue. The discriminative biologic effect of radiation schedules disappears when tumor cells and normal tissue  $\alpha/\beta$ -ratio values are close to each other.

Clinical arguments to support a conventional or protracted treatment for prostate cancer are the good results reported so far with radioactive seeds implants. Radiation with radioactive seeds is characterized by a very LDR. The reported 8-10-year biochemical control for low risk prostate cancer is more than 90% [2-4]. Also, the reported grade 3-4 toxicity is low [5-8]. Considering the acceptable clinical results for very LDR and the ongoing debate on the  $\alpha/\beta$ -ratio for prostate cancer we found it challenging to start investigating the feasibility of PDR brachytherapy for prostate cancer.

## TECHNIQUE PDR BRACHYTHERAPY FOR PROSTATE CANCER

The common technique to perform a prostate implant is via the transperineal route. In case of a temporary implant needles or catheters are left in place. This technique was developed in the eighties of last century for HDR brachytherapy [9, 10]. For HDR brachytherapy several large dose fractions are applied either with multiple implants separated by several days or a single implant with multiple fractions. When one single implant is used, careful judgment of needle positioning is necessary before each treatment. Numerous studies have shown interfractional displacement of needles [11-15]. Displacement of up to 4 cm has been reported. Displacement of needles is caused by prostate edema and/or subcutaneous edema and/or skin retraction. For needle repositioning a Computed Tomography (CT)- or Magnetic Resonance Imaging (MRI)-scan of the prostate with needles in situ can be performed or repositioning of the needles relative to fiducial markers on fluoroscopy.

In case of PDR brachytherapy pulses are given every 1-2 hours. It is almost impracticable to assess needle positions at each pulse. Therefore, we preferred to develop such a system that flexible catheters were anchored into the prostate gland. At the tip of the catheter an "umbrella-like" mechanism can be unfolded to anchor the catheter. The catheter can be removed at the end of the treatment by folding the anchor in. By using this catheter frequent assessment of catheter position appeared unnecessary. The minimal displacement of few millimeters had little influence on dose-volume parameters [16]. This novel technique particularly suitable for PDR brachytherapy is described in **chapter 4**. The self-anchoring catheter is not only usable for PDR brachytherapy, but also for fractionated HDR brachytherapy.

Besides developing a new catheter for PDR prostate brachytherapy we also developed an open template for needle/catheter guidance. In general prostate brachytherapy templates have a closed hole for needle guidance. Needles are brought in and out these holes. In case of a permanent implant the template is removed after the implantation. In case of a temporary implant the template is sutured on the skin with the needles inside. We preferred a system to remove the template immediately after the implantation for better patient comfort. More importantly, we feared frequent kinking of flexible catheters obstructing the passage of the iridium-192 source.

The removable template was designed in such a way that an adjustable arm could be positioned on every location for guidance of a needle/catheter. Because this guidance arm was not completely closed, it could be removed from the needles/catheters. Despite this technique without fixed template during treatment in bed we still observed disturbances during treatment in 12.1% of all pulses given [17]. In a cohort of 106 patients brachytherapy was abandoned in 6 cases and the treatment was continued with a supplemental external beam dose [18]. These problems were particularly observed in the early period. This had led to further improvement of the technique. At first the vendor of the catheters was asked to provide us with more rigid catheters less prone to kink. Also, the mattresses on which the patients lay were adapted with a hole caudal of the perineum resulting in more space for the catheters. The last precaution was to take extra care on placement of the catheters and the connecting transfer tubes to avoid high friction and resistance during passage of the (dummy) source wire. Since then the frequency of enduring errors were markedly reduced.

A drawback in prostate PDR brachytherapy treatment planning is the more or less unreliable plans based on ultrasound. After the pre- and intraoperative treatment planning with the following implantation, the ultrasound probe is removed. This will cause a modification of the shape of the prostate and the distance between prostate and rectum. For this reason a definitive treatment plan based on CT-scan or MRI should be done. For the future it can be considered to incorporate the information of the situation without a rectal probe in the pre- and intraoperative treatment planning. For this purpose techniques for preferably deformable fusion of ultrasound and MRI should be developed. By doing that the intraoperative treatment plan can be used as definitive plan for better accuracy and gain of time.

## **TREATMENT OF INTERMEDIATE- AND HIGH-RISK PROSTATE CANCER WITH BRACHYTHERAPY.**

The radiation treatment strategy differs according to the risk profile according to which a patient is classified in. This differentiation is also true for brachytherapy. Several risk profile classifications are in use [19-21],[[www.nccn.org](http://www.nccn.org)]. They have all in common a differentiation based on adverse prognostic factors, such as a high clinical T-stage, a Gleason score > 6,

and a PSA-value > 10 ng/ml. The so-called intermediate- and high-risk prostate cancers have a high probability of extracapsular extension. Treatment by brachytherapy alone can lead to geographical misses hampering local tumor control. Stone et al. found in a multicenter analysis that the addition of EBRT to a seed implant for Gleason score 7-10 prostate tumors was associated with an improved biochemical control [22]. The addition of EBRT not only enlarged the treated volume, but also increased the dose on the target volume. From this study it is not very clear which factors (treated volume, dose, or both) had the greatest contribution to the good results on tumor control. Biochemical control at 5 years for an EQD2 of  $\leq 100$  Gy, 100-110 Gy, and  $> 110$  Gy was 76.4%, 83.5%, and 88.3%, respectively. The majority of patients receiving only brachytherapy fell in the low dose group (EQD2  $\leq 100$  Gy). Even an impact on overall survival was noticed for patients with a Gleason score 8-10. Compared to the highest dose group of Stone's study our patients were treated to a rather low dose. Along the years the total peripheral dose was increased from EQD2 68 Gy to 74 Gy ( $\alpha/\beta$ -ratio = 2 Gy, T1/2 = 1 hour, according to Stock for comparison [23]). One should realize that the reported EQD2 of Stone et al. were derived from the D90s and no correction for tumor cell repopulation was included in the calculations. In the AMC we have chosen to start with a low dose, because there was no experience with PDR for prostate brachytherapy. Considering the acceptable results we have on tumor control and toxicity a further dose escalation is worthwhile investigating.

A point of ongoing discussion is the need to add EBRT to patients with an intermediate-risk disease. Hinnen et al. found in one of the largest cohort of I-125 monotherapy a 5-year and 10-year actuarial biochemical control for intermediate-risk prostate cancer of 87% and 61%, respectively [3]. In our cohort with a much shorter follow-up the 3-year biochemical control rate was 96% for the intermediate-risk group (chapter 5) using the same risk profile classification as Hinnen et al. To have a better understanding of the need for supplemental EBRT in the intermediate-risk group, studies should be reported with uniform risk group classification and endpoint for biochemical recurrence.

We preferred the addition of EBRT to PDR brachytherapy because the majority of our patients (63%) had a T3-disease, corresponding to extraprostatic extension. If brachytherapy is part of the treatment we consider external beam radiation important for adequate disease coverage. Other means for improving tumor control is by adding hormonal therapy. In our cohort 18% (19 of 106) of patients used hormonal therapy of whom 8 for less than 6 months. We excluded patients with a very high-risk disease, such as a PSA-value > 20 ng/ml or a combination of T3 with Gleason score 8-10. Particularly for this category hormonal therapy can be of important value. Martinez et al. did not find any benefit of short-course hormonal therapy in addition to EBRT and HDR brachytherapy [24, 25]. On the contrary Stone et al. found hormonal therapy to be an independent factor for biochemical control [22]. The value of hormonal therapy deserves further investigation, as does the length of hormonal treatment.

## COMPARISON EBRT ALONE VERSUS COMBINED EBRT WITH BRACHYTHERAPY

Brachytherapy is characterized by a heterogeneous dose distribution. For that reason dose prescription without specification has little meaning. It is also possible that different implant geometries have identical target volume coverage (e.g. V100 and D90), but large differences in high-dose areas. We use a mean of 12 catheters for prostate PDR implants resulting in large areas receiving 20% to 40% more dose than prescribed on the periphery of the prostate [26]. Studies reporting on combined EBRT with brachytherapy are treating at a higher biologic dose than EBRT alone [27]. We have shown in **chapter 3** with a systematic review the superiority of combined EBRT with HDR brachytherapy above dose-escalated EBRT alone [27]. The combination with HDR showed also better biochemical control and overall survival than the combination with radioactive seed implants. This study has of course its limitations, such as unknown confounding factors, non-uniform biochemical recurrence endpoints, and lack of long-term data. However, preliminary results of a randomized study has also shown the superiority of combined EBRT with HDR brachytherapy [28].

Brachytherapy is also characterized by a sharp dose falloff. In general no treatment planning margins are taken beyond a clinical target volume because set-up and organ motion uncertainties play a limited role in brachytherapy. For these reasons the dose in adjacent organs at risk can be more limited than with EBRT. In **chapter 2** it was illustrated that with intensity modulated radiotherapy (IMRT) combined with brachytherapy a substantial dose reduction could be achieved on rectum and bladder compared with IMRT only [29]. The reduction of the D2ml for the rectum and bladder were for both organs between 8 and 12 Gy EQD<sub>2</sub>. No obvious sparing of the urethra was noticed, but that could be improved with placement of more catheters. By placement of more catheters the isodose distribution can be optimized by reduction of the urethra dose without compromising the target volume coverage.

Clinical studies of dose-escalated EBRT have reported an increased risk for late gastrointestinal (GI) and genitourinary toxicity (GU). Reported grade  $\geq 2$  and grade  $\geq 3$  GI late toxicity for dose-escalated EBRT ranged between 17-35% and 1-6%, respectively [30-34]. In **chapter 5** we found no grade 3 GI toxicity and a 5-year probability of grade 2 GI toxicity of 12% [18]. These figures compare favorable to dose-escalated EBRT, with the remark that our study has a short follow-up. The low GI toxicity seen in our study is in concordance with the ability to reduce the dose on the rectal wall with brachytherapy. Longer follow-up is necessary to confirm these results.

The reported incidence of grade  $\geq 2$  and grade  $\geq 3$  GU late toxicity for dose-escalated EBRT was between 11-40% and 3-13% respectively [30-34]. Our results on GU toxicity were within the range of the results of dose-escalated EBRT studies. Five year grade  $\geq 2$  and grade  $\geq 3$  GU toxicity were 26.9% and 7.3% and described in **chapter 5** [18]. The higher incidence of GU toxicity compared to GI toxicity is explained by the high dose on the urethra.

The urethra is located within the implant and usually received a dose between 120% to 140% of the prescribed dose for brachytherapy. Fortunately, as described in **chapters 5 and 6** late toxicity was often self-limiting or could be resolved by medical therapy. We could not find an association of the development of late GI and GU toxicity with time. Although not statistically significant, we could not exclude a worsening of erectile function with time.

For the future, modern techniques in EBRT, such as IMRT, image guided radiotherapy, proton therapy, and stereotactic body radiotherapy will be in competition to brachytherapy concerning methods to limit toxicity [32, 35-42]. However, in the proximity of source dwell positions very high radiation dose is reached and the dose decreases rapidly outside the implant because of the physics inverse square law. This particular dose distribution can practicably not be simulated by external beam modalities. Randomized trials are necessary to prove the value of each of the modalities.

## FUTURE DIRECTIONS

One of the most striking developments in radiotherapy is the incorporation of improved spatial imaging techniques and functional imaging techniques for proper treatment planning, dose delivery, and dose reporting. Nowadays CT-, MRI-, and Positron emission tomography-scans are routinely used for target volume and organs at risk delineation and treatment planning. These imaging techniques can also be used for the verification of adequate dose delivery, such as cone-beam CT-scans in EBRT or repeated CT- and MRI-scans in brachytherapy. Modern prostate brachytherapy is carried out with ultrasound guidance. New developments are underway for MRI-assisted implantations [43-46]. In **chapter 7** we investigated a method to optimize brachytherapy with the aid of contrast-enhanced ultrasound. With the evolving technology of imaging techniques better identification of tumor lesions in the prostate will be possible. This will give the possibility to indicate areas of high risk that probably need a higher dose than the areas without tumor. It would be even possible to de-escalate the dose in non-tumor bearing areas. We saw a marked improvement of the coverage of intraprostatic lesions by the 140% isodose (mean 66.0% to 92.5% and 67.7% to 95.7% for the largest and smallest intraprostatic lesions, respectively) without an increase in rectum and urethra dose. Adaptation of the geometry of an implant to risk areas within the prostate for improving local control and reducing toxicity can be one of the goals for the future. Other important question still is the eventual difference in outcome between EBRT and EBRT combined with brachytherapy, particularly for intermediate- and high-risk prostate cancer. Does the higher dose on the prostate with brachytherapy translate into better local control? Does the limited dose on the rectum, bladder, neurovascular bundle, and penile bulb with brachytherapy translate into less late effects? These questions should be answered in randomized studies of modern EBRT techniques and brachytherapy for which techniques as radioactive seed implantations, HDR brachytherapy, and PDR brachytherapy are available.

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