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### Pulsed-dose rate brachytherapy in prostate cancer

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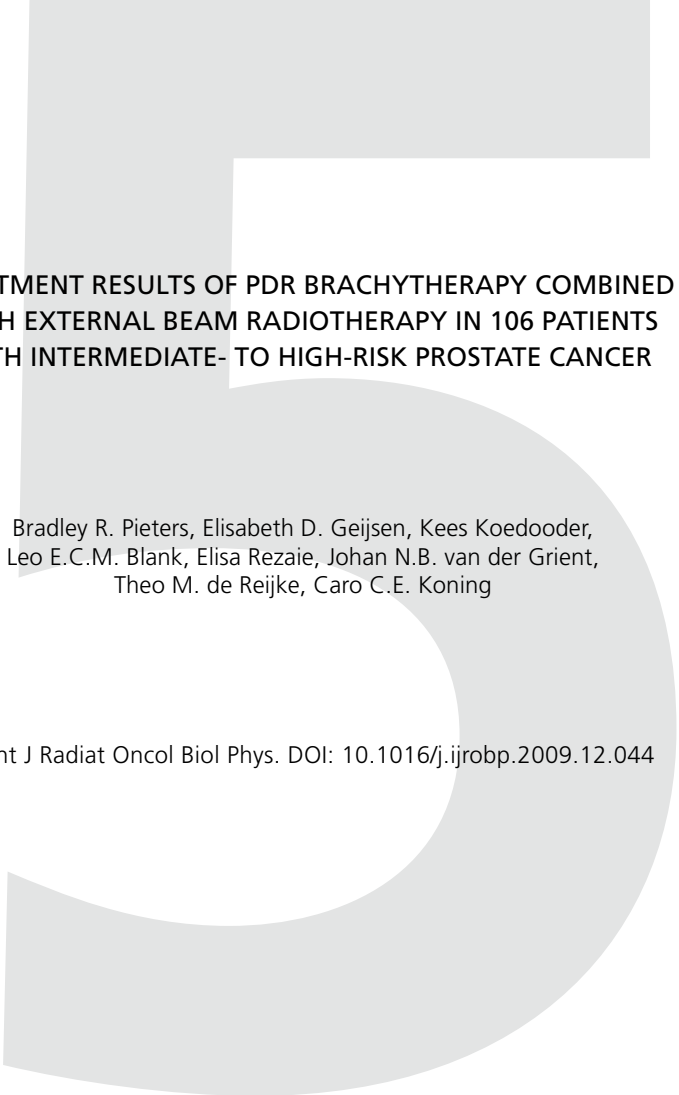
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**TREATMENT RESULTS OF PDR BRACHYTHERAPY COMBINED  
WITH EXTERNAL BEAM RADIOTHERAPY IN 106 PATIENTS  
WITH INTERMEDIATE- TO HIGH-RISK PROSTATE CANCER**

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## ABSTRACT

**Purpose:** To evaluate treatment outcome of Pulsed-dose rate brachytherapy (PDR) combined with external beam radiotherapy (EBRT) for the treatment of prostate cancer.

**Methods and Materials:** Between 2002 and 2007, 106 patients were treated by EBRT combined with PDR and prospectively followed. Two, 38, and 66 patients were classified as low-, intermediate-, and high-risk disease respectively according to the National Comprehensive Cancer Network criteria. EBRT dose was 46 Gy in 2.0 Gy fractions. PDR dose was increased stepwise from 24.96 Gy to 28.80 Gy.

Biochemical disease free survival and overall survival were determined by the Kaplan-Meier method. Cumulative incidence of late gastrointestinal (GI) and genitourinary (GU) toxicity were scored, according to the Common Terminology Criteria for Adverse Events.

**Results:** The 3- and 5-year biochemical non-evidence of disease (bNED) were 92.8% (95% CI: 87.1 to 98.5) and 89.5% (95% CI: 85.2 to 93.8), respectively. Overall survival at 3 and 5 years was 99% (95% CI: 96 to 100) and 96% (95% CI: 90 to 100), respectively.

The 3 and 5 year grade 2 GI toxicity was 5.3% (95% CI: 0 to 10.6) and 12.0 % (95% CI: 1.4 to 22.6), respectively. No grade 3 or higher GI toxicity was observed. The 3 and 5 year grade 2 or higher GU toxicity was 18.7% (95% CI: 10.3 to 27.1) and 26.9% (95% CI: 15.1 to 38.7), respectively.

**Conclusion:** Results on tumor control and late toxicity of EBRT combined with PDR are good and comparable to results obtained with EBRT combined with High-Dose Rate brachytherapy for the treatment of prostate cancer.

## INTRODUCTION

Randomized studies have shown that dose-escalated external beam radiotherapy is more beneficial to the conventional dose when treating prostate cancer because of better biochemical control [1-3]. A drawback of the higher dose seen in these studies is an increase in late toxicity. Another modality to achieve a high radiation dose within the prostate gland is by brachytherapy. Brachytherapy has the advantage of administering a high dose to the prostate and only a limited dose to particularly the rectum and is for this reason an attractive alternative. One randomized study has shown an improved biochemical outcome of external beam radiotherapy (EBRT) combined with high-dose rate (HDR)-brachytherapy above EBRT alone in patients with T1-3 disease [4].

If brachytherapy is applied for the treatment of intermediate- to high-risk prostate cancer, combination with EBRT is strongly advocated. Different definitions for risk-group classification exist. All these classifications recognize the adverse prognostic factors such as elevated initial Prostate Specific Antigen (PSA)-values ( $> 10$  ng/mL), high Gleason score ( $\geq 7$ ), and/or high clinical T-classification ( $\geq T2c$ ). Patients with these adverse prognostic factors have a higher probability of extra capsular extension, making brachytherapy alone a less attractive treatment option [5]. The reported 5-year biochemical control and overall survival in various studies with combined treatment is in the order of 80 to 90% and 85 to 95%, respectively [5-11]. In these studies brachytherapy was applied with low dose-rate radioactive seeds or a temporary HDR implant.

In our institute the possibility of treating prostate cancer with a temporary implant by means of pulsed-dose rate (PDR) brachytherapy as part of a combined radiation modality treatment was prospectively explored. In a previous study we described the technique with anchoring catheters to prevent movement of the catheters during treatment and ensuring proper dose delivery [12]. The aim of this study was to analyze the short-term biochemical progression free and overall survival results of this treatment, together with acute urinary complaints and late gastrointestinal (GI) and late genitourinary (GU) toxicity.

## METHODS AND MATERIALS

Between April 2002 and October 2007 106 prostate cancer patients were treated in our institute by EBRT and PDR brachytherapy and were prospectively followed. Patients with adverse prognostic factors, such as an initial PSA  $> 10$  ng/mL, Gleason score  $\geq 7$ , or T2c-T3a, were selected for this treatment. Categorization into risk groups was based on the National Comprehensive Cancer Network (NCCN) criteria ([www.nccn.org](http://www.nccn.org)). In case of very-high risk disease, such as initial PSA  $> 20$  ng/mL or T3b-T4, the preferred treatment modality was only EBRT with long-term hormonal treatment. The very high-risk patients were thus excluded from treatment with brachytherapy and were no part of this study. The prostate volume should be  $\leq 55$  mL to be admitted and no major urinary complaints should exist based on an IPSS  $\leq 20$  and a maximum urinary flow (Qmax) of  $\geq 15$  mL/s.

The technique of the procedure has been described previously [12]. Treatment started with EBRT on the pelvis by a conformal box technique to a dose of 46 Gy in daily fractions of 2 Gy. The irradiation volume was limited if a lymph node dissection had been performed and no pathologic lymph nodes were found. In these cases only the prostate and seminal vesicles were irradiated with 1-cm margin by a 3D-conformal technique.

Until 2006 a transrectal ultrasound (TRUS) based preplanning was done before implantation as an outpatient procedure. Based on this preplan, ultrasound-guided transperineal implantation of the catheters was performed under general or spinal anesthesia in the lithotomy position. Several anchoring needles were placed in the prostate up to the bladder and into the seminal vesicles. A final CT-based treatment plan (BPS 14.2 software, Nucletron B.V., Veenendaal, The Netherlands) was used for therapy. The clinical target volume was considered to be the prostate and base of the seminal vesicles. No margin was added for the planning target volume (PTV). From September 2006 onwards the preplan was performed intra-operatively with Oncentra Prostate planning system (Nucletron B.V., The Netherlands). The day before implantation antibiotics with ciprofloxacin was started and continued until 3 days after removal of the catheters.

At initiation of the protocol the prescribed dose with brachytherapy was 24 pulses of 1.04 Gy with a period time (time between start of two consecutive pulses) of 2.2 hours. Because at the start of this treatment there was no experience with PDR brachytherapy for prostate cancer we chose to begin with a relatively low dose, equivalent to our daily practice external beam dose. As it became apparent from the literature and our own experience that dose escalation to 75 Gy and above on the prostate was feasible we decided to increase the dose to this level. This dose was increased in June 2005 to 24 pulses of 1.1 Gy with a period time of 2.0 hours and since May 2006 to 24 pulses of 1.2 Gy with a period time of 2.0 hours. Treatment planning aimed at the prescribed dose covering 95% of the PTV.

Patients were followed 3, 6, and 12 weeks after brachytherapy. Further follow-up was every 3 months in the first year after treatment and biannually thereafter.

### Statistics

Severity of acute urinary complaints was assessed and quantified by the IPSS. Univariate analysis of covariance was performed by a linear regression model to investigate possible factors associated with increase of IPSS at 3 weeks post-brachytherapy. Factors investigated were voiding frequency, nocturia, initial IPSS, prostate volume, and maximal urinary flow. The condition for linear regression analysis was investigated by analysis of residuals.

Late toxicity was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Late toxicity was defined as any adverse event occurring 6 months after brachytherapy or later. The highest grade was used for the analysis.

The Cox proportional hazard analysis was used to investigate an association between predictive factors and the occurrence of grade 2 or higher GU toxicity. Factors included

Table 1. Patient characteristics.

<b>Median age</b>		64 years	(53-77)
<b>Median IPSS</b>		7	(0-23)
<b>Mean Qmax</b>		19.3 mL/s	(8.0-49.2)
<b>Mean prostate volume</b>		34.2 mL	(13.9-61.4)
<b>Voiding frequency</b>	Every 1 hour	3	2.8%
	Every 2 hours	17	16%
	Every 3 hours	32	30.2%
	Every 4 hours or more	48	45.3%
	Unknown	6	5.7%
<b>Nocturia</b>	0	28	26.4%
	1	50	47.2%
	2	21	19.8%
	3	3	2.8%
	4 or more	2	1.9%
	Unknown	2	1.9%
<b>Erection</b>	Yes	92	86.8%
	No	9	8.5%
	Unknown	5	4.7%
<b>Number of catheters</b>	8	5	4.7%
	10	17	16%
	11	2	1.9%
	12	75	70.8%
	13	6	5.7%
	14	1	0.9%
<b>Mean PSA</b>		9.9 ng/mL	(1.3-25.3)
<b>Median Gleason score</b>		6	(4-8)
<b>Clinical T-classification</b>	T1c	4	4.8%
	T2a	8	7.5%
	T2b	8	7.5%
	T2c	21	19.8%
	T3a	64	60.4%
	T3b	1	0.9%

Number in parenthesis is the range.  
 IPSS = International Prostate Symptom Score.  
 Qmax = maximum urinary flow.  
 PSA = Prostate Specific Antigen.

in the model were age (continuous), voiding frequency ( $\leq 2$  hours vs. 3 hours vs.  $\geq 4$  hours), nocturia frequency (continuous), use of alpha-blocker (yes vs. no), prostate volume (continuous), maximum urinary flow (continuous), post voiding residual volume (continuous), IPSS (continuous), and brachytherapy dose (24.96 Gy vs. 26.40 Gy vs. 28.80 Gy). For this investigation a backward analysis was performed by removing at each step the least significant factor.

Survival analysis was performed by the Kaplan-Meier method with 95% confidence intervals (95% CI). Biochemical recurrence was defined as a persistent PSA rise of the nadir plus 2 ng/mL [13]. Differences between groups were tested by log-rank test.

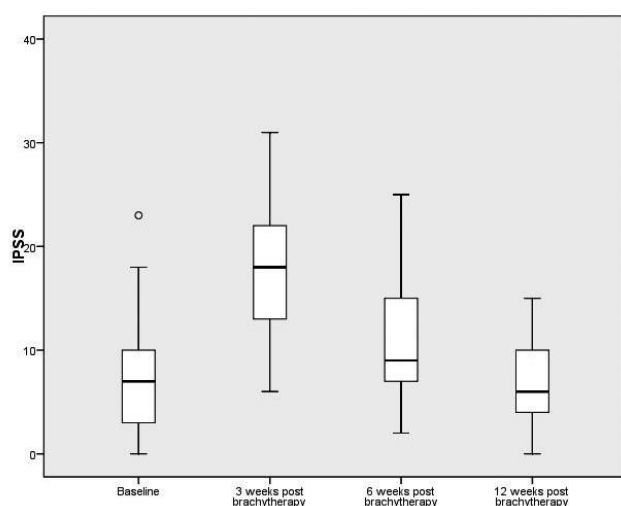
No patients were excluded from analyses.

All P-values were two-sided. P-values  $< 0.05$  were considered significant. Statistical analysis was performed with Statistical Package for the Social Sciences, version 16.0 for Mac OS X (SPSS, Chicago, IL, USA).

## RESULTS

Patient characteristics are given in Table 1. Median age was 64 years. The median IPSS was 7 and the mean Qmax was 19.3 mL/s.

According to the NCCN risk-group classification 2, 38, and 66 patients were considered to have low-, intermediate-, and high-risk disease, respectively. Nineteen patients received hormonal therapy of whom 6 an antiandrogen only and 13 with a luteinizing releasing hormone receptor analogue. Three patients used hormonal therapy for less than 3 months, 5 patients between 3 and 6 months, 10 patients for longer than 6 months and 1 patient for unknown duration.



**Figure1.** Boxplots of IPSS course at baseline and post brachytherapy.

Forty-two patients were treated to 24.96 Gy with brachytherapy, 23 patients to 26.40 Gy, and 35 patients to 28.80 Gy. Six patients did not complete brachytherapy due to guide problems with the catheters. The remaining dose was completed by EBRT.

Median follow-up time was 34.6 months (range 7.4-75.5).

The maximum IPSS was noticed at 3 weeks post-brachytherapy and gradually declined thereafter to baseline level at 12 weeks (Fig. 1). No significant association was found between any predictor variable and the maximum IPSS at 3 weeks (Table 2).

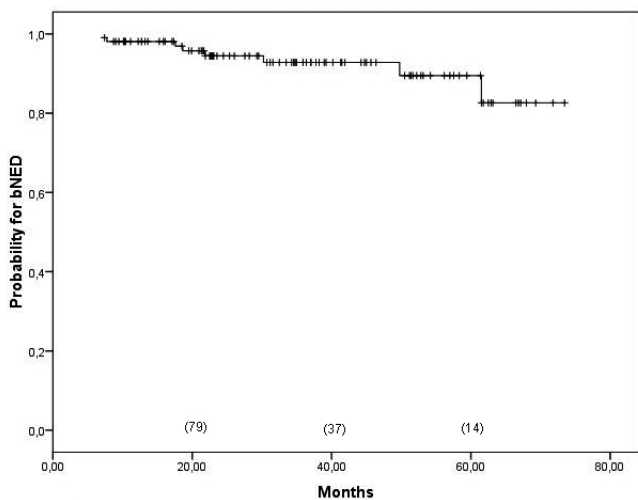
**Table 2.** Univariate analysis of the association between predictor variables and maximum IPSS at 3 weeks post brachytherapy.

	P-value
Voiding frequency	0.06
Nocturia	0.41
Initial IPSS	0.051
Qmax	0.34
Prostate volume	0.31

IPSS = International Prostate Symptom Score.  
Qmax = maximum urinary flow.

No grade 3 or higher GI toxicity was observed. The 3 and 5 year grade 2 GI toxicity was 5.3% (95% CI: 0 to 10.6) and 12.0% (95% CI: 1.4 to 22.6), respectively. The majority of grade 2 GI toxicity was due to fecal incontinence (3 patients) for which the patients needed daily use of pads. One grade 2 toxicity (fecal incontinence) resolved completely with time. Fourteen patients had rectal bleeding and in 2 cases medical intervention was necessary (argon plasma coagulation, beclometasone/mesalazine enema). Five patients had a complete resolution of rectal bleeding without medical intervention.

The 3 and 5 year grade 2 or higher GU toxicity was 18.7% (95% CI: 10.3 to 27.1) and 26.9% (95% CI: 15.1 to 38.7), respectively. The majority of grade 2 or higher GU toxicity was due to increased voiding frequency. Five patients with a grade 2 and one patient with



**Figure 2.** Survival probability for biochemical non-evidence of disease (bNED).

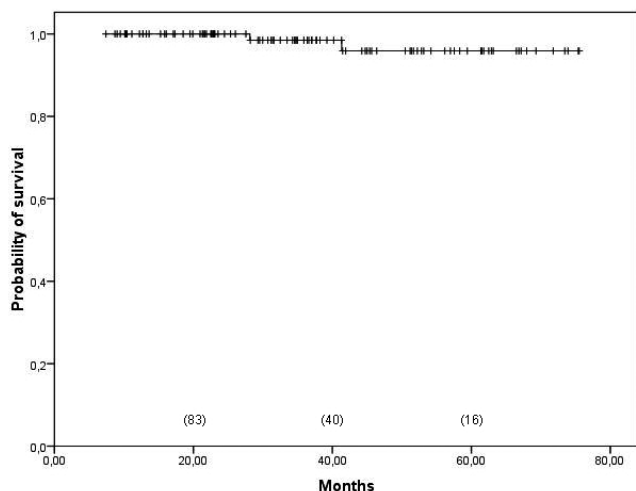


Figure 3. Survival probability for overall survival.

a grade 3 (increased voiding frequency) toxicity had a complete disappearance of the late effects. Five patients experienced a grade 3 GU toxicity yielding a 3 and 5 year GU toxicity rate of 4.8% (95% CI: 0.3 to 9.3) and 7.3% (95% CI: 0.6 to 14.0%), respectively. The observed late grade 3 GU toxicities were one with increased voiding frequency, one with cystitis, one with incontinence, and two with urethral obstruction. The patient with incontinence developed this symptom already during external beam treatment.

With Cox proportional hazard analysis no factor was found predictive for the occurrence of grade 2 or higher GU toxicity.

Of the 88 patients who reported to have sufficient erectile function before treatment and did not use hormonal therapy, 17% had diminished erectile function after treatment and 17% total disappearance of erectile function.

The 3- and 5-year biochemical non-evidence of disease (bNED) were 92.8% (95% CI: 87.1 to 98.5) and 89.5% (95% CI: 85.2 to 93.8), respectively (Fig. 2). No significant difference was found between the intermediate- and high-risk group ( $P=0.59$ ).

Overall survival at 3 and 5 years was 99% (95% CI: 96 to 100) and 96% (95% CI: 90 to 100), respectively (Fig. 3). The deaths of two patients, were due to a second malignancy.

## DISCUSSION

This is the first study to report results of PDR brachytherapy as part of the treatment of prostate cancer. Izard et al. also used a 37 GBq iridium-192 source of a PDR machine for prostate brachytherapy. However, dose delivery was at medium dose rate in 3 fractions of 6 Gy with at least 6 hours interval followed by 45 Gy EBRT [14].

In our study the results of treatment of patients treated with a PDR brachytherapy boost after a course of EBRT were analyzed. All patients were treated with a low dose per

pulse ( $\leq 1.2$  Gy) at short time intervals ( $\leq 2.2$  hours). These schedules correspond to what is accepted as PDR-schedules [15].

Previously, we published the technique for PDR prostate brachytherapy with self-anchoring catheters [12]. Use of these catheters is of importance because of the frequent displacement of standard catheters attached to a perineal template [16-19]. If not, it is practically impossible to check the catheter position every 1-2 hours.

We found the IPSS to attain its maximum at 3 weeks after brachytherapy due to acute urinary toxicity symptoms. At 12 weeks after brachytherapy IPSS returned to baseline level. In this selected group of patients with few pretreatment urinary complaints no association was found between any predictor variable and IPSS at 3 weeks.

Several observational studies have been published showing the results of treatment with EBRT combined with HDR brachytherapy. The median follow-up time in these studies is on average 50 months with some studies having a follow-up time of more than 5 years [20]. Several radiation schedules were used. The applied doses in these studies are approximately 60 to 110 Gy expressed as equivalent dose at 2 Gy per fraction ( $\text{EQD}_2$ ) for an  $\alpha/\beta$ -ratio of 3 Gy. However, because of the heterogeneous dose distribution of brachytherapy large areas in the prostate receive 20 to 50% more dose than the prescribed dose on the periphery of the prostate [21]. These high dose therapies have led to very acceptable results on tumor control.

Phan et al. treated 309 patients with 36 to 50.4 Gy combined with 15 to 26 Gy in 3 to 4 HDR fractions [10]. Five-year biochemical control and overall survival were 86% and 91%, respectively, while the group with high-risk disease had a 5-year biochemical control of 78%.

Another large cohort of 214 patients was published by Åström et al. [22]. The patients were treated up to a dose of 50 Gy EBRT combined with 2 fractions of 10 Gy HDR brachytherapy. Five-year biochemical control and overall survival were 82% and 89%, respectively. Biochemical control at 5 years for the high-risk disease group was 56%.

With PDR brachytherapy we found a 5-year biochemical control and overall survival of 90% and 96%, respectively. Biochemical control at 5 years in our high-risk group, with T3a clinical classification or Gleason score 8 or higher, was 87%. These results are comparable to the best results obtained with HDR brachytherapy [20]. We have excluded patients with a very high-risk disease. This makes comparison with other published series a little bit problematic. However, some studies reported the results for patients with only 1 risk factor, which is comparable to our high-risk cohort. Their results are similar to ours [7, 10, 11, 23].

In a model-study we have shown that when biologically equivalent PDR to HDR schedules are designed for an  $\alpha/\beta$ -ratio of 1.5 Gy small areas in the prostate receive a higher dose with HDR than with PDR [21]. However, with PDR, the minimal  $\text{EQD}_2$  to 50% volume of the prostate was only 2.5 Gy less than with HDR. So, also with PDR high dose schedules can be designed that result in high tumor control.

The results on late toxicity were acceptable. No grade 3 late GI toxicity was observed and the 5-year grade 2 late GI toxicity was 12.0%. This result illustrates the ability to spare rectal mucosa from high dose areas with brachytherapy [24]. One problem with the CTCAE classification is that fecal incontinence is also considered as a proctitis symptom interfering with activities of daily living (ADL) and classified as grade 3. Because three patients in our cohort had these symptoms but not interfering with ADL, we scored that as a grade 2.

More often and more severe toxicity was observed on the GU organs. The 5-year grade 2 and higher late GU toxicity were 26.9%. The late grade 3 GU toxicity was 7.3% at 5 years. These results are comparable to toxicity results published so far of EBRT with HDR brachytherapy [7, 10, 11, 22].

Severe late GI toxicity is seldom reported [10, 22, 25, 26]. The majority of late toxicity after combined EBRT and HDR brachytherapy concerns the GU tract. Chin et al. reported a crude 7.4% grade 3-4 late GU toxicity [25]. Urethral obstruction is an often observed GU toxicity [10, 22, 27]. Sullivan et al. found an actuarial 12% incidence at 6 years. Prior TURP, hypertension and dose appeared to be independent factors associated with the occurrence of late urethral obstruction [28]. In our cohort 2 patients experienced urethral obstruction for which treatment with bladder neck incision or transurethral resection of the prostate (TURP) was indicated. The most often seen late GU toxicity in our study was an increase in urinary frequency or nocturia up to two times normal, like in the study of Ghadjar et al. [29]. As was also noted by Kälkner et al. some of the symptoms that occurred, disappeared with time [11]. No factor was found predictive for occurrence of grade 2 or higher toxicity, probably because of the low incidence of toxicity or because of the selection of patients with low baseline urinary problems.

The results on potency preservation is in concordance with the results of other studies where HDR brachytherapy was used [10, 23, 30]. About 40-50% of the patients report a diminishing or disappearance of potency. However, the majority can be helped with medication.

When we started investigating the feasibility of PDR brachytherapy for the treatment of prostate cancer we decided to start with a relatively low dose, because of the lack of data for this modality of treatment. The combined PDR and EBRT prescription dose for the first cohort of patients was an EQD<sub>2</sub> of 68.8 Gy for an  $\alpha/\beta$ -ratio of 3 Gy. This dose was stepwise increased to 74.4 Gy. Because of the heterogeneous dose distribution in brachytherapy, large areas in the prostate received at least 20% more dose than the prescription dose, meaning an EQD<sub>2</sub> of 82.7 Gy for the latter cohort [31]. This dose is still less than the dose that has been reached in some other studies [7, 11]. Despite the low dose in our study, the tumor control rate is comparable to the best published HDR figures. Because of the low late complication rate till now, we consider further dose escalation for PDR worth investigating.

## CONCLUSION

For the treatment of intermediate- to high-risk prostate cancer good results regarding tumor control and late toxicity were achieved by treating patients with a combination of EBRT and PDR brachytherapy. The results are comparable to published data from EBRT combined with HDR brachytherapy studies. In our opinion, these results could only be obtained because a proper PDR technique was used with respect to the choice of fractionation regimen and with respect to positional stability of the implant during the complete course of PDR brachytherapy.

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