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Pulsed-dose rate brachytherapy in prostate cancer

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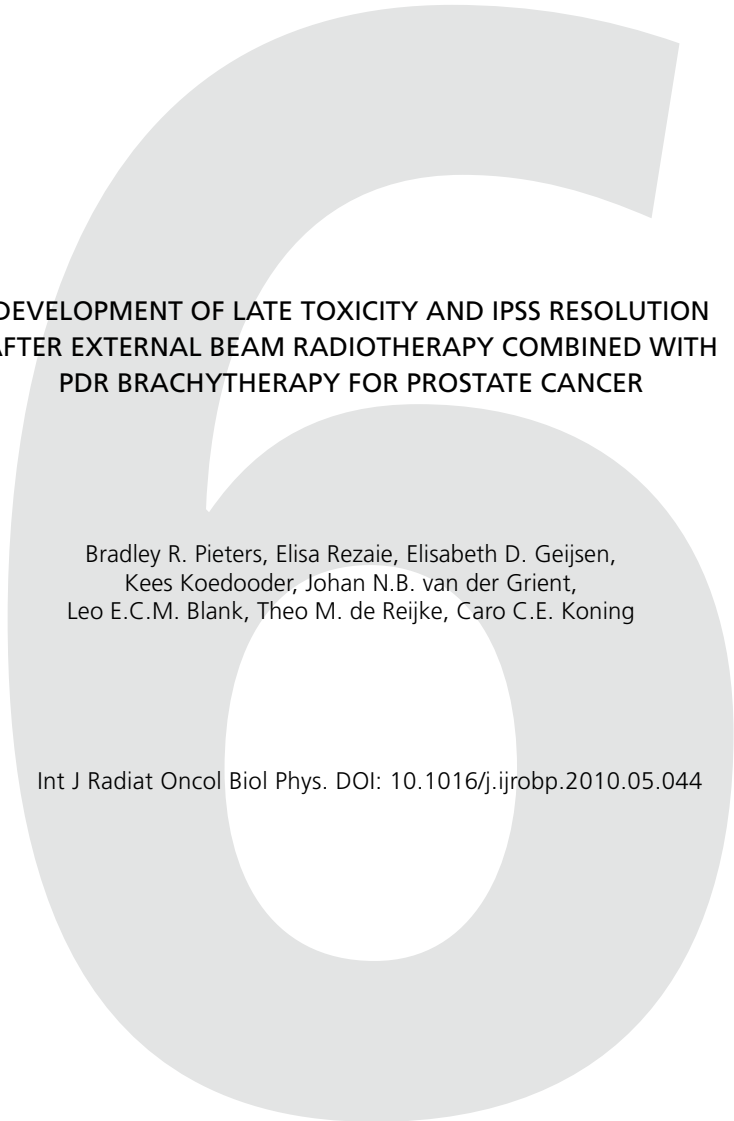
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**DEVELOPMENT OF LATE TOXICITY AND IPSS RESOLUTION
AFTER EXTERNAL BEAM RADIOTHERAPY COMBINED WITH
PDR BRACHYTHERAPY FOR PROSTATE CANCER**

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ABSTRACT

Purpose. To investigate the development of gastrointestinal (GI) toxicity, genitourinary (GU) toxicity, erectile dysfunction, and International Prostate Symptom Score (IPSS) resolution in a cohort of patients treated with external beam radiotherapy (EBRT) followed by a brachytherapy pulsed-dose rate (PDR) boost.

Methods and Materials. Between 2002 and 2008, 110 patients were treated with 46 Gy EBRT followed by PDR brachytherapy (24.96 Gy – 28.80 Gy). The investigated outcome variables, GI-, GU-toxicity, erectile dysfunction and IPSS were prospectively scored at several time-points in the follow-up. Association between time (as continuous and categorical variable) and the outcome variables was assessed using generalized linear models.

Results. No statistically significant association was found between time (continuous) and GI-toxicity (OR 0.97; 95% CI 0.89 to 1.06), GU-toxicity (OR 0.97; 95% CI 0.91 to 1.03), erectile dysfunction (OR 1.06; 95% CI 0.99 to 1.11), and IPSS (-0.11; 95% CI -0.41 to 0.20). Also, no statistically significant association was found between these variables and time as a categorical variable.

GU-toxicity was associated with IPSS resolution (OR 1.16, 95% CI: 1.09 to 1.24).

Post treatment IPSS was associated with pretreatment IPSS (0.52, 95% CI: 0.25 to 0.79).

Conclusions. No accumulation of high-grade toxicity over time could be established for a group of patients treated with EBRT and PDR brachytherapy for prostate cancer, probably because high-grade late toxicity resolves with time. Also, differences in IPSS-values between patients after treatment are smaller than before treatment.

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INTRODUCTION

Amongst all treatment modalities for prostate cancer brachytherapy is increasingly popular [1], either as monotherapy for low-risk disease tumors or combined with external beam radiotherapy or hormonal therapy for patients having one or more adverse prognostic factors. Brachytherapy is by some of its supporters not only propagated because of the high chance of tumor control, but also because of its relatively low toxicity profile [2-7].

At the Academic Medical Center (Amsterdam, The Netherlands) we started in 2002 with pulsed-dose rate (PDR) brachytherapy preceded by external beam radiotherapy for patients with intermediate- to high-risk prostate cancer. Since the data were prospectively collected, we investigated the development of toxicity and symptoms over time. This investigation will give additional information on the course of toxicity compared to a cross-sectional analysis, because for some patients symptoms tend to disappear with time, either spontaneously or after medical treatment. The principal question was: is the development of toxicity associated with time or other variables.

METHODS AND MATERIALS

Between April 2002 and June 2008, 110 patients were treated for prostate cancer at the AMC with external beam radiotherapy combined with PDR brachytherapy. Details of the treatment, procedures, and results were previously published [8, 9]. Briefly, treatment started with 3D-conformal external beam radiotherapy of 46 Gy in daily fractions of 2 Gy on a small part of the pelvis (upper border at the lower end of the sacro-iliac joints). If a pelvic lymph node dissection was done and showing no pathologic lymph nodes, the external beam treatment volume was restricted to the prostate and seminal vesicles. Within one week after external beam radiotherapy a temporary perineal implantation of the prostate was performed under ultrasound guidance. After implantation with self-anchoring flexible catheters a CT-scan was performed for definitive treatment planning. In this period the brachytherapy dose was step-wise increased from 24.96 Gy with pulse dose of 1.04 Gy and a period time of 2.2 hours to 28.8 Gy with pulse dose of 1.2 Gy and a time period of 2.0 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 the higher level.

Patients entered into the treatment protocol had one or more adverse prognostic factor(s) (cT2c or cT3a, PSA \geq 10 ng/ml, or Gleason score \geq 7). Other selection criteria were prostate volume \leq 55 ml and low urinary morbidity based on an International Prostate Symptom Score (IPSS) \leq 20 and maximum urinary flow (Qmax) \geq 15 ml/s.

Hormonal therapy was prescribed at discretion of the referring urologist or the radiation oncologist. As it became apparent from the literature that the benefit of the

addition of hormonal therapy to combined EBRT with brachytherapy was minimal or lacking, hormonal therapy was discouraged after these publications [10-12].

After treatment patients were followed every 3 months for the first year and biannually afterwards. After 5 years of follow-up with no evidence of disease visits were restricted to once a year.

Data on morbidity were prospectively collected at each visit. Late Gastrointestinal (GI) toxicity, late Genitourinary (GU) toxicity, and erectile dysfunction were 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. Severity of late urinary complaints was assessed and quantified by the IPSS.

Statistical analysis

Longitudinal relationship of all available longitudinal data was investigated by Generalized estimating equations (GEE). The association of late GI-toxicity, GU-toxicity, erectile dysfunction, and IPSS at consecutive time-points was investigated with time as the independent variable. Time points were taken in time intervals of 6 months, starting at 6-12 months after treatment and ending at 78-84 months.

For ordinal variables as GI-toxicity, GU-toxicity, and erectile dysfunction a multinomial distribution was assumed. The dependent variable was transformed by a cumulative logit link function. For IPSS a Normal distribution was assumed.

Association of prognostic variables at baseline with late GU-toxicity and IPSS resolution was investigated by a backward-analysis. Factors included into the model were age (continuous), voiding frequency (every 1 hour vs. 2 hours vs. 3hours vs. ≥ 4 hours), nocturia frequency (continuous), use of a selective $\alpha 1$ -receptor blocker (yes vs. no), prostate volume (continuous), maximum urinary flow (continuous), post-voiding residual bladder volume (continuous), pretreatment IPSS (continuous), hormonal therapy (yes vs. no), number of implanted catheters (continuous), brachytherapy dose (24.96 Gy vs. 26.40 Gy vs. 28.80 Gy), and time (continuous). In the model for late GU-toxicity IPSS at consecutive follow-up time-points was also included as an independent variable. The statistically least significant factors were stepwise removed from the model.

The same analysis was performed for erectile dysfunction with age, prostate volume, hormonal therapy, number of implanted catheters, brachytherapy dose (24.96 Gy vs. 26.40 Gy vs. 28.80 Gy), and time as independent variables. All analyses on erectile dysfunction were performed on those patients who reported to have erections prior to start of therapy.

In the models with time as a continuous variable a linear relationship is assumed with the dependent variable. Because the existence of a linear relationship is not certain, also models with time in categories were investigated. At later time-points there were few

Table 1. Patient characteristics.

Median age		64 years	(53-77)
Median pretreatment IPSS ¹		7	(0-23)
Mean Qmax ²		19.3 ml/s	(8.0-49.2)
Mean PVR ³		53 ml	(0-380)
Mean prostate volume		34.4 ml	(13.9-61.4)
Voiding frequency	Every 1 hour	3	2.7%
	Every 2 hours	19	17.3%
	Every 3 hours	33	30.0%
	Every 4 hours or more	49	44.5%
	Unknown	6	5.5%
Nocturia	0	30	27.2%
	1	52	47.3%
	2	21	19.1%
	3	3	2.7%
	4 or more	2	1.8%
	Unknown	2	1.8%
Use of selective α 1-rb ⁴	Yes	12	10.9%
	No	97	88.2%
	Unknown	1	0.9%
Erection	Yes	96	87.3%
	No	9	8.2%
	Unknown	5	4.5%
Use of hormonal therapy	Yes	19	17.3%
	No	91	82.7%
Mean PSA ⁵		9.9 ng/ml	(1.3-25.3)
Gleason score	≤ 6	74	67.3%
	7	32	29.1%
	≥ 8	3	2.7%
	Unknown	1	0.9%
Clinical T-classification	T1c	4	3.6%
	T2a	8	7.3%
	T2b	9	8.2%
	T2c	21	19.1%
	T3a	67	60.9%
	T3b	1	0.9%
Median number of catheters		12	(8-14)
Brachytherapy dose	≤ 24.96 Gy	48	43.6%
	26.40 Gy	23	20.9%
	28.80 Gy	39	35.5%

Number in parenthesis is the range.

¹IPSS = International Prostate Symptom Score.

²Qmax = maximum urinary flow.

³PVR = post voiding residual bladder volume

⁴Selective α 1-rb = selective α 1-receptor blocker

⁵PSA = Prostate Specific Antigen.

observations in the category grade > 0 (CTCAE). For that reason the time-points 37-48, 49-60, and 61-84 months were grouped together in 3 time categories.

Within one individual repeated observations are assumed to be correlated with each other, and therefore a correction has to be made for these within-subject correlations. An exchangeable working correlation structure was assumed within the GEE analysis.

Associations were expressed as odds ratio (OR) or regression coefficients (RC) with the 95% confidence intervals (95% CI). P-values ≤ 0.05 were considered statistically 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 presented in Table 1. Median age was 64 years, the mean prostate volume was 34.4 ml, the median IPSS before treatment was 7, and the mean Qmax was 19.3 ml/s. The majority of the patients were implanted with 12 catheters.

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.

Forty-two patients were treated to 24.96 Gy with brachytherapy, 23 patients to 26.40 Gy, and 39 patients to 28.80 Gy. Six patients did not complete brachytherapy due to conduct problems with the catheters. The remaining dose was completed by external beam radiotherapy (EBRT).

Median follow-up time was 31.9 months (range 6.9-79.7).

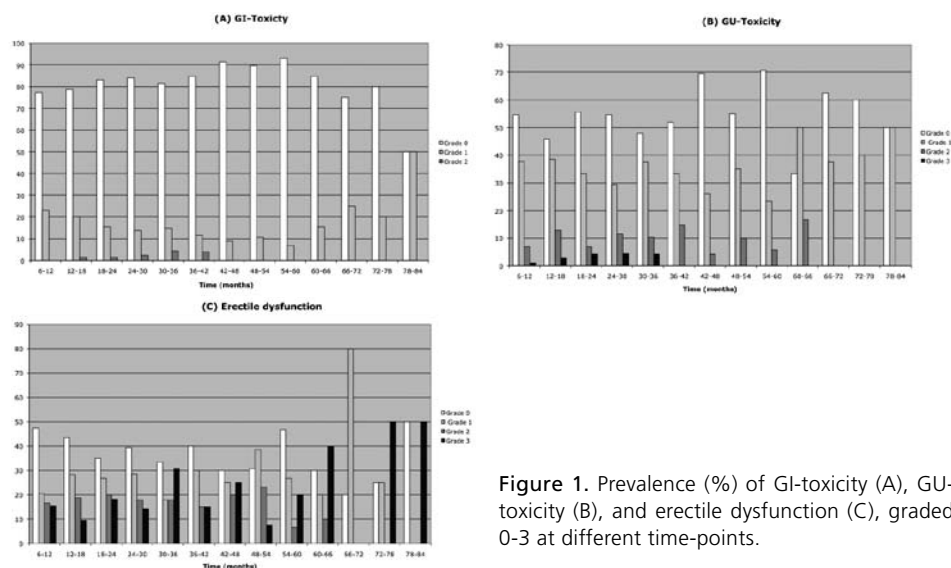


Figure 1. Prevalence (%) of GI-toxicity (A), GU-toxicity (B), and erectile dysfunction (C), graded 0-3 at different time-points.

Table 2. Association between time and four different independent variables. The effect size for the ordinal variables GI-toxicity, GU-toxicity, and erectile dysfunction is expressed as an odds ratio (OR). The effect size for the numerical variable IPSS is expressed as a regression coefficient (RC).

	Effect size	95% CI	P
Time as continuous variable			
GI-toxicity	OR 0.97	0.89 to 1.06	0.53
GU-toxicity	OR 0.97	0.91 to 1.03	0.33
Erectile dysfunction	OR 1.06	0.99 to 1.11	0.06
IPSS	RC -0.11	-0.41 to 0.20	0.49
Time as categorical variable			
GI-toxicity			0.86
GU-toxicity			0.76
Erectile dysfunction			0.25
IPSS			0.91

The OR with time as categorical variable is calculated for the variables at each time category with the situation at time-point 6-12 months as the reference. These OR's are not shown in this table.

The prevalence of toxicity at the several time-points is illustrated in Figure 1. The majority of patients had no GI-toxicity at several time-points with an increase of grade 1 GI-toxicity at the later time-points.

Grade 0 GU-toxicity remained stable over the years with an increase of grade 1 GU-toxicity at the later time-points. No grade 3 or higher GU-toxicity was seen after 36 months. Of the 5 patients with a grade 3 GU-toxicity, 2 underwent a bladder neck incision or transurethral resection of the prostate, 1 discontinued catheterization, 1 patient with incontinence died of gastric cancer, and the patient with cystitis did not reach 36 months follow-up.

An increase of grade 3 erectile dysfunction was seen over the years.

No statistically significant association was observed between time and the development of GI-, GU-toxicity, erectile dysfunction, or IPSS (Table 2).

With backward regression analysis GU-toxicity was significantly associated with the resolution of

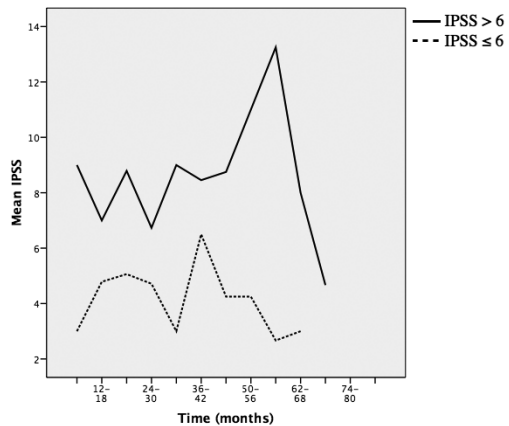


Figure 2. IPSS resolution separated for patients with pretreatment IPSS ≤ 6 and > 6.

IPSS (OR 1.16, 95% CI: 1.09 to 1.24) and the posttreatment IPSS was associated with pretreatment IPSS (RC 0.52, 95% CI: 0.25 to 0.79) (Figure 2). The OR and the RC values can be interpreted as a within-subject as well as a between-subject relationship. That means that if the IPSS within a subject increases by 1 point the odds to progress to a higher toxicity score increases by 16%. Also, the odds of being in a higher GU-toxicity group is 16% higher for a person with a 1 point higher IPSS than the other person. The interpretation of a 0.52 RC for IPSS is that if two persons differ by 1 point pretreatment IPSS their IPSS will differ by 0.52 points after treatment at the several time-points.

No factor was found to predict the development of erectile dysfunction.

DISCUSSION

Longitudinal data analyses are characterized by the fact that outcome variables are repeatedly measured over time within a subject. For the assessment of late toxicity a new dimension is introduced compared to survival analyses. In survival analyses after the occurrence of an event, the outcome variable is an irreversible endpoint. However, during longer observation, symptoms can still develop to a higher grade, or can improve spontaneously or after medical treatment. In longitudinal data analyses this development of symptoms after therapy can be followed and evaluated.

GI-toxicity

We found in this study no association between time and GI-toxicity. In fact no higher than grade 2 GI-toxicity was observed and the highest proportion of grade 2 GI-toxicity was 4.2% at 30-36 months posttreatment.

Merrick et al. analyzed rectal function after permanent interstitial implantation with or without EBRT for prostate cancer [13]. In their study analysis was done at three time points and a median follow-up of 9 years. Assessment was done with the Schiffler Cancer Center Rectal Function Assessment Score. Comparable to our study they found no change in global rectal function with time. Of all the investigated items only frequency of defecation and stool consistency improved with time. No patient developed ulcerations or fistulas.

Kälkner et al. reported on a cohort of prostate cancer patients treated with EBRT combined with HDR brachytherapy and neo-adjuvant hormonal treatment [6]. In their study an increase of RTOG grade 1-3 GI-toxicity was observed at 6 months post-therapy. Symptoms improved during the years that followed.

We have observed no grade 3 GI-toxicity that is in concordance to other HDR and low-dose rate (LDR) series. Yamada et al. found only 1 grade 3 rectal toxicity after EBRT with HDR brachytherapy [14]. In a similar treatment setting Åström et al. observed no severe rectal complications [15]. Phan et al. had 1 patient with a grade 4 rectal toxicity resulting in a colostomy [3]. In a large joint publication from the William Beaumont Hospital and the California Endocurietherapy Center almost no grade 3 GI-toxicity was reported for

monotherapy HDR [16]. Gelblum and Potters reported from a large series of 825 patients only 4 patients with a grade 3 rectal toxicity after a permanent implant [17]. With a median follow-up of 7 years Stone and Stock observed no ulcerations or fistulas and only 2.8% long-term rectal bleeding [18]. All these studies show the great ability to spare rectal mucosa with brachytherapy.

GU-toxicity and IPSS resolution

As in our analysis, Gutman et al. analyzed the resolution of IPSS in a cohort of patients treated with a permanent interstitial implant with or without EBRT [19]. Predictors of IPSS resolution were pretreatment IPSS, prostate volume, and catheter dependency. In contrast to our observation they found that patients with higher pretreatment IPSS showed a greater decline of IPSS after treatment. It should be mentioned that all patients in Gutman's study were prophylactically treated with a selective α 1-receptor blocker. In less than 6 months IPSS returned to baseline levels and no obvious further change in IPSS course was noticed afterwards, as was the case in our study. In this study no analysis was performed on GU-toxicity categories other than IPSS. We found a significant association between GU-toxicity and IPSS. The IPSS can be used as a fast screening tool in the follow-up of patients. If IPSS increases by 3 points, meaning a 56% increase in odds for a higher GU-toxicity category, special attention should be given if necessary with medical treatment for amelioration of symptoms. Niehaus et al. found in multivariate analysis preimplant IPSS, the addition of EBRT, and any need for catheterization after brachytherapy predictive for IPSS resolution in permanent prostate brachytherapy [20].

In the study of Van Gellekom et al. a slight decrease of IPSS was noted from 6 months to 2-years after permanent interstitial implantation (mean IPSS 15.2 to 10.4) [21]. This slight decrease of IPSS was in conjunction with a slight decrease of urinary problems according to the American Urological Association symptom index. We did not notice any decrease in IPSS or GU-toxicity with time, but the mean IPSS in our cohort was much lower than in Van Gellekom's study.

Kälkner et al. investigated RTOG-GU toxicity resolution in a cohort of patients treated with external beam radiotherapy combined with HDR brachytherapy and it was found that all grade toxicities decreased with time [6]. As in our observation the more severe toxicities (grade 3-4) were more often from the GU-tract than from the GI-tract.

With monotherapy HDR the most common GU-toxicity was due to increased voiding frequency and urgency that was usually graded as 1-2 [16]. We also observed the same predominance for increased voiding frequency [9]. Two patients in our cohort developed a urethra stricture which is relatively low compared to others [3, 15]. However, we have a limited follow-up and we have to pay special attention to the eventual development of this kind of complication.

Like the experience of others we found a low incidence of severe GU toxicity and no tendency for increase with time. Recently Keyes et al. reported the results on urinary

morbidity for one of the largest cohorts on permanent implants [7]. Five-year grade 2, 3, and 4 RTOG (Radiation Therapy Oncology Group) urinary toxicity was 24%, 6.2%, and 0.1%, respectively. They also reported the prevalence at 7 years, which was 7.4% and 0% for grade 2 and 3, respectively. In this study a decrease of grade ≥ 2 toxicity was seen after 6 months and stabilized after 12 months. As in our study there is no clear evidence of accumulation of severe toxicity over the years. Crook et al. found in their study on permanent prostate implants 6.4% of any urinary urgency or urge incontinence. These complaints resolved for the majority of patients after a median duration of 12 months [2]. In a large cohort of 351 patients Anderson et al. distinguished acute urinary side effects from late urinary effects. They found that short-term side effects were in general resolved by 8 months. The majority of late urinary effects were grade 1 and 2 and occurred within 3 years of the implantation [22].

Sexual functionality

We found no association between erectile dysfunction and time. When time was used as a continuous variable the association nearly reached significance ($P = 0.06$), but a non-significant association ($P = 0.25$) with time as categorical variable. In Figure 1 there is an impression for increase of grade 3 erectile dysfunction with time, which is partly explained by drop-outs. A second explanation for the variation in prevalence of erectile dysfunction is the inconsistent use of phosphodiesterase type 5 inhibitors. It cannot, however, be excluded that with longer follow-up or larger sample-size the increase in impotency rate would reach significance. Talcott et al. found an increase in sexual dysfunction after permanent interstitial implantation at 3-months post-therapy and little change afterwards [23]. Van Gellekom et al. found no change in sexual functioning, but a decrease in sexual activity most evident in the first four weeks after therapy [21].

Comparison of brachytherapy, external beam only and prostatectomy series by longitudinal data analysis shows that with prostatectomy the probability for incontinence and sexual dysfunction is greater. Radiotherapy more often leads to irritative urinary and bowel symptoms [23-26]. The majority of symptoms occurs in the first three months after treatment, with little change afterwards [23].

In this overview of published studies on the development of prostate brachytherapy related symptoms it is obvious that different patterns are observed. In general, the greatest changes are seen directly after treatment with little changes after 6 months to 1 year. In our study, the first to report on treatment related symptom development after PDR brachytherapy for prostate cancer, no changes in GI-toxicity, GU-toxicity, erectile dysfunction, and IPSS resolution are seen after 6 months in a selected group of patients with low pretreatment urinary or gastrointestinal problems. Pre-treatment IPSS is a strong predictor for post-treatment IPSS; however, the differences in post-treatment IPSS between patients are smaller than the pre-treatment values. The outcome of this study could have been different if patients with more pretreatment morbidity were allowed this treatment.

The selection was according to accepted guidelines for brachytherapy and our results confirm the recommendations of these guidelines [27]. A comparable comment can be placed on the results of erectile function, because the cohort was at a relative young age. The results of this study were adjusted for age. However, a trend to impaired erectile function was observed, which could be more obvious in an older cohort of patients.

CONCLUSION

The probability for severe late grade 3-4 toxicity after PDR brachytherapy combined with external beam radiotherapy in a selected group of patients with no or few symptoms at start of treatment is low. There is no evidence for an increase of late toxicity with time after 6 months post treatment. This observation is supported by the experience of others after permanent interstitial implantation or HDR brachytherapy for prostate cancer.

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