Prediction of acute urinary retention after I-125 prostate brachytherapy

Quality of life matters

Ellen Maria Aleida Roeloffzen

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Prediction of acute urinary retention after I-125 prostate brachytherapy

Het voorspellen van acute urine retentie na jodium-125 prostaat brachytherapie
(met een samenvatting in het Nederlands)

Proefschrift

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Aan mijn ouders

Contents

List of abbreviations

AUR	acute urinary retention
CI	confidence interval
CT	computer tomography
D_{10}	the minimum dose (Gy) in 10% of the corresponding volume
D_{50}	the minimum dose (Gy) in 50% of the corresponding volume
D_{90}	the minimum dose (Gy) in 90% of the corresponding volume
EBRT	external beam radiotherapy
EORTC	european organization for research and treatment of cancer
Gy	gray
HRQOL	health related quality of life
HT	hormonal treatment
I-125	iodine-125
IMRT	intensity-modulated radiotherapy
iPSA	initial (at diagnosis) prostate specific antigen
IPSS	international prostate symptom score
MVA	multivariate analysis
MRI	magnetic resonance imaging
NHT	neo-adjuvant hormonal treatment
OR	odds ratio
PSA	prostate specific antigen
QOL	quality of life
SD	standard deviation
SPOT	sonographic planning of oncology treatment
TRUS	transrectal ultrasound
TURP	transurethral resection of the prostate
UVA	univariate analysis
V_{100}	percentage of the corresponding volume, receiving 100% of the prescribed dose
V_{150}	percentage of the corresponding volume, receiving 150% of the prescribed dose
V_{200}	percentage of the corresponding volume, receiving 200% of the prescribed dose

Chapter 1

General introduction and aims of the thesis

Background

Nowadays, prostate cancer is the most frequently diagnosed type of cancer and the second most common cause of cancer death in the western world (1). In the Netherlands, 9600 new cases of prostate cancer are diagnosed each year, and one out of 35 patients will die from prostate cancer (2). The recorded incidence of prostate cancer has substantially increased in the past two decades, probably because of the introduction of screening with prostate-specific antigen (PSA) (3), the use of improved biopsy and imaging techniques for diagnosis, and increased public awareness (4). As our population ages, we are likely to see a continuing increase in the prevalence of prostate cancer (5). Therefore, the social impact of prostate cancer will further rise in the future.

Treatment of prostate cancer

PSA screening methods have led to stage migration to lower tumor stages (3;5). For localized prostate cancer ($T_{1\text{-}2}N_0M_0$) (*Figure 1*), different treatment options with curative intent are available. The most commonly used are radical prostatectomy (open, laparoscopic, or robotic), external beam radiotherapy (EBRT) and brachytherapy. Other treatment options, still under investigation, are high intensity focused ultrasound (HIFU), cryotherapy, radiofrequency ablation, or treatment with nano-particles. Furthermore, focal treatment of prostate tumors is a promising procedure, however, long-term outcomes have to be confirmed in future prospective clinical trials (6).

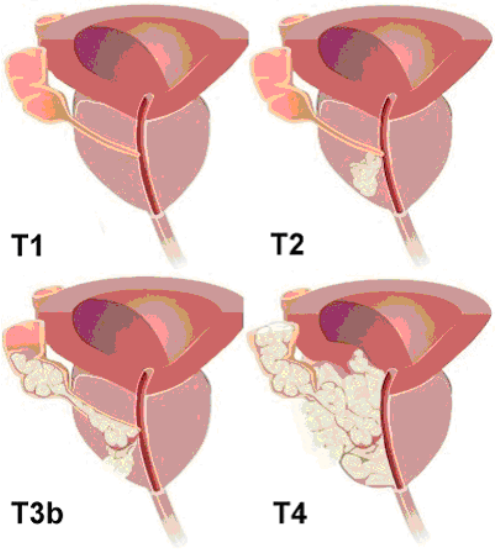

Figure 1 Tumor stage classification according to TNM criteria.

T1 = Tumor assessed by needle biopsy, but not palpable or visible by imaging
T2 = Tumor palpable, confined to the prostate
T3 = Tumor extends through the prostatic capsule or invades seminal vesicles
T4 = Tumor invades adjacent structures

Because only few patients will die from low-risk prostate cancer, the question rises whether treatment is necessary for all patients. In the last few years, strategies of active surveillance have emerged (7). The purpose of active follow-up is to recommend potentially curative management to men whose cancer progresses and to avoid the side effects and cost of treatment, at least temporarily, in men whose cancer does not progress (8). Active surveillance is considered a reasonable option for highly selected patients with low-risk prostate cancer (7). Recent studies suggest that outcomes after direct treatment or active surveillance combined with delayed treatment are similar, however, long-term follow-up is still needed (7;9). A disadvantage of active surveillance is the possible anxiety and distress for patients of withholding radical treatment (10).

In Iodine-125 (I-125) prostate brachytherapy small radioactive iodine sources are permanently brought into the prostate in order to kill the tumor cells (*Figure 2*). It has been shown to be an effective treatment in T1-T2 prostate tumors (*Figure 1*). The most important advantage of brachytherapy compared to external beam radiotherapy, is the rapid fall off of dose around the radioactive sources (*Figure 3*) and thereby sparing the surrounding normal tissues. I-125 seed implantation involves only a one-day stay in the hospital. Several large studies on outcome after I-125 prostate brachytherapy for localized prostate cancer have been published. Reported 10-year biochemical no evidence of disease (bNED) rates vary from 74-89% for low risk and 61-78% for intermediate risk patients (11-15). Ten-year disease specific survival rates up to 96% have been described (11;14;15). It has been shown that optimal implant quality as

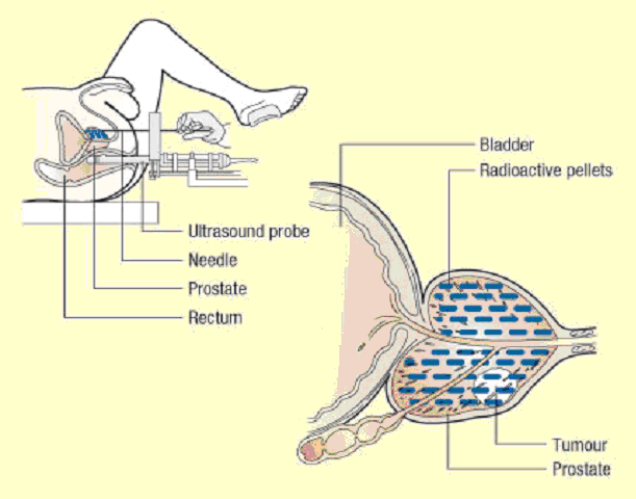

Figure 2 I-125 prostate brachytherapy procedure (www.prostateuk.org).

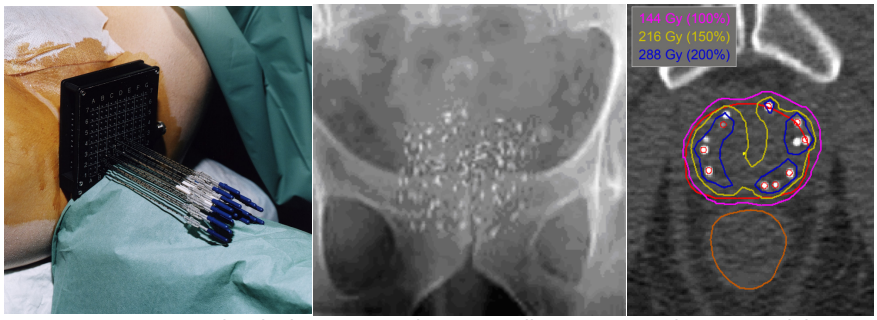

Figure 3 I-125 prostate brachytherapy procedure. a) needle insertions with patient in lithotomy position; b) X-ray after implantation for seed localization; c) typical dose distribution on CT imaging.

expressed by the D_{90} (minimal dose received by 90% of the prostate) is the most important controllable factor for long-term outcome (12;13;16). For patients who experience biochemical failure, PSA doubling time is a sensitive predictor of survival (11).

To date, no significant differences in outcome have been shown in retrospective studies between radical prostatectomy, EBRT, and brachytherapy (17-20). Random assignment to the different treatment modalities in clinical trials turned out to be difficult. The only randomized trial comparing radical prostatectomy and brachytherapy (SPIRIT trial, ACOSOG Z0070) stopped due to poor accrual (21). Compellingly, after extensive education sessions the majority of patients (60%) chose brachytherapy instead of prostatectomy (21). For patients with favorable tumor characteristics (i.e. well-differentiated tumor with a low initial PSA level and low tumor stage), treatment outcome is generally good. Kupelian *et al.* (18) reported 5-year bNED rates for radical prostatectomy, EBRT >72 Gy and I-125 prostate brachytherapy of 81%, 81% and 83%, respectively. In a review of Peschel *et al.* (19), 5-year bNED rates according to clinical group were 80–94%, 66-82%, and 34-65% for favorable, intermediate and poor risk patients, respectively. Again, no significant difference between the treatments was shown. A well-designed retrospective matched case-control study, however, showed significantly better 5- and 7-year bNED rates for brachytherapy compared to EBRT (95% versus 85%; and 95% versus 75%, respectively) (22). For all treatment options improved outcomes are observed for patients treated after 2000, which might be due to stage migration, better surgery and implant techniques, optimum use of hormone therapy, and new technologies such as three-dimensional conformal radiotherapy and intensity-modulated radiotherapy (IMRT).

Because tumor control and survival rates for low-risk prostate cancer are excellent and comparable between the different treatment modalities,

additional outcome measures are required for treatment selection and patient counseling. Toxicity and quality of life are considered important endpoints that should be taken into account. The balance between treatment outcome and quality of life is currently gaining lots of interest, but still needs further investigation.

Toxicity

The type and rate of toxicity differs between the various treatment options (23-26). Toxicity is also related to characteristics of the individual patient (e.g., age, comorbidity, previous disturbances, prostate volume, addition of hormonal therapy), and the use of modern surgical or radiation techniques (e.g., nerve-sparing surgery, IMRT) (26). According to the common terminology criteria for adverse events (CTC AE score), possible adverse events after treatment for prostate cancer include: dysuria, urinary incontinence, urinary retention, frequent voiding, hematuria, erectile impotence, diarrhea, rectal pain and rectal bleeding.

When comparing the toxicity profiles of the three most common treatments, it is evident that erectile dysfunction and urinary incontinence are more common after radical prostatectomy, while bowel problems are more common after radiotherapy treatment (27;28). Erectile dysfunction rates vary from 20-100% after radical prostatectomy, 10-85% after EBRT (4;28), (29;30), and 14-66% after brachytherapy (31;32). Noteworthy, the pre-treatment rate of erectile dysfunction in this patient group is already approximately 30-40% (28). Urinary incontinence was observed in 39-49% after radical prostatectomy and in 6-7% after radiation therapy (27). Also, recovery of urinary control to baseline values is more likely after radiotherapy treatment than after radical prostatectomy (33). At two years after radical prostatectomy or radiation therapy, complete incontinence was seen in 10% and 4%, respectively (34). However, the rate of bowel problems was more common after radiotherapy (30-35%) compared to prostatectomy (6-7%) (27).

For prostate brachytherapy, toxicity rates are generally lower than for external beam radiotherapy (35), which is directly related to the surrounding normal tissue sparing effect. Although symptoms after prostate brachytherapy are often mild, some severe (CTC grade ≥ 3) adverse events may occur. Late grade 3 toxicity comprises urethral strictures (in 2-12% of patients) (32;36;37), and fistula (in 1-2.4% of patients) (31). The most common severe acute toxicity after prostate brachytherapy is *acute urinary retention* (AUR), occurring in 6-34% of patients (31;38-43)

Acute urinary retention

According to Trotti *et al.*, AUR is defined as: 'any need for urinary catheterization within three months after implantation' (44). AUR is often of limited duration, however, some patients require prolonged catheterization or even a transurethral resection of the prostate (TURP) to relieve obstruction. Since these interventions may lead to an increased risk of urethral strictures, urinary incontinence and long-term morbidity (45), AUR might have a long-lasting impact for patients.

The exact pathophysiologic mechanism of AUR is still unknown. In the literature, several attempts to identify risk factors for AUR have been made. The most frequently reported independent predictors are prostate volume (41;43;46), International Prostate Symptom Score (IPSS) (38;40;43), and hormonal treatment (38;41). However, inconsistent results exist as well, especially regarding the influence of radiation dose (39-41;43;46-50). It is important to identify any risk factor that predispose to the development of AUR, because these factors can aid in selecting patients at high risk of AUR. Furthermore, for men with a relatively long life expectancy (low risk prostate cancer), the risk of serious but immediate side effects from treatment with curative intent should be weighed against the low risks of progression of the cancer to metastases or death.

Health-related quality of life

Nowadays, in the Western world, the importance of health-related quality of life (HRQOL) is increasingly recognized. HRQOL is more than toxicity alone. HRQOL comprises not only somatic functioning, but also the patient's perception of his social and psychological functioning and well-being (51;52). Since life expectancy is generally good after treatment for localized prostate cancer (11-15), an acceptable HRQOL after treatment is of great value for patients. Furthermore, it has been shown that changes in HRQOL after treatment influence satisfaction with treatment outcomes among patients and their spouses or partners (26). Therefore, accurate reporting of HRQOL after treatment is crucial.

Since the appraisal of physical and psychosocial complications after prostate cancer treatment can differ when evaluated by patients or physicians (53), HRQOL assessments should be performed using internationally validated questionnaires (54). Different validated HRQOL questionnaires are available, including cancer specific and prostate specific questionnaires; however the interpretation of HRQOL scores remains difficult. A statistically significant difference in HRQOL is not always clinically relevant for the patient. According to published data concerning the interpretation of HRQOL data, a change of ≥

10 points on a 100-point scale is considered clinically relevant (55).
Most authors who stated to report on HRQOL after prostate brachytherapy in their studies, only showed IPSS or other toxicity scores. Furthermore, although many studies reported some kind of HRQOL measurements after prostate brachytherapy (12;23;24;56-62), most are limited by being cross-sectional, by having a short follow-up, or by lacking extended and validated HRQOL questionnaires. As long-term side effects may occur more than three years after treatment (25), long-term follow-up of HRQOL is required.

Aims and scope of the thesis

As described above, I-125 brachytherapy for localized prostate cancer shows excellent tumor control and survival rates (11;13;63;64). Results are equivalent to those achieved by radical prostatectomy or external beam radiotherapy (19). Hence toxicity and HRQOL are considered important endpoints that should be taken into account in the decision of a treatment modality. The overall aim of this thesis is to evaluate long-term HRQOL after prostate brachytherapy, and to identify risk factors for AUR in order to improve patient selection and patient counseling.
The first three chapters of this thesis focus on long-term HRQOL after I-125 prostate brachytherapy. In *chapter 2* we prospectively assess HRQOL up to six years after treatment and in *chapter 3* we analyze depression scores up to eight years after treatement. Furthermore, we hypothesize that the occurrence of AUR (the most common adverse event after I-125 prostate brachytherapy) may have a negative impact on the patient's HRQOL. This hypothesis is studied in *chapter 4*. We also evaluate whether pretreatment HRQOL questionnaires have additional value in the prediction of AUR.
The next chapters concern the prediction of AUR after I-125 prostate brachytherapy. We identify several risk factors and assess their predictive values. In particular, we aim to extensively explore the relation between dose and AUR. In *chapter 5* we assess the influence of radiation dose on the risk of AUR in 714 patients treated at our center, using magnetic resonance imaging (MRI) for delineation of the prostate (65;66) (*Figure 4*). In *chapter 6* we study the influence of dose in different regions of the prostate on the risk of AUR. Furthermore, based on clinical experience, we hypothesize that variation in prostate anatomy may influence the risk of AUR. Therefore, we aim to assess the impact of different anatomic parameters (e.g. prostate protrusion into the bladder, bladder overlap, urethra angle and urethra-bladder angle) on the risk of AUR.

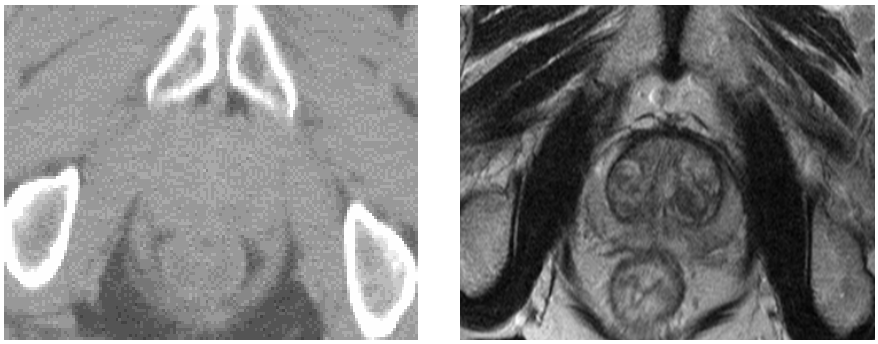

Figure 4 Differences in soft tissue contrast on a) computed tomography (CT) and b) magnetic resonance imaging (MRI) of the prostate.

Because AUR is a relatively common and often annoying adverse event, pre-operative prediction of AUR is required. Prediction of AUR might aid in selecting patients for prostate brachytherapy and facilitate patient counseling. At present, there is no prediction tool available to predict the risk of AUR prior to treatment. Therefore, the final aim of this thesis is to develop a pre-implant clinical nomogram to predict the risk of AUR after I-125 prostate brachytherapy (*chapter 7*). We perform external validation of this nomogram on patient data of the Princess Margaret Hospital, Toronto, Canada (*chapter 8*).
The thesis will be concluded by a general discussion and a summary.

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Chapter 2

Health-related quality of life up to six years after I-125 brachytherapy for localized prostate cancer

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Abstract

Purpose

Health-related quality of life (HRQOL) after prostate brachytherapy has been extensively described in published reports, but hardly any long-term data are available. The aim of the present study was to prospectively assess long-term HRQOL up to 6 years after I-125 prostate brachytherapy.

Methods and Materials

A total of 127 patients treated between December 2000 and June 2003 with I-125 brachytherapy for localized prostate cancer completed a HRQOL questionnaire at 5 time points: before treatment, and 1 month, 6 months, 1 year and 6 years after treatment. The questionnaire included the RAND-36 generic health survey, the cancer-specific European Organization for Research and Treatment of Cancer core questionnaire (EORTC-C30), and the tumor-specific EORTC prostate cancer module (EORTC-PR25). A change in a scores of ≥10 points was considered clinically relevant.

Results

Overall HRQOL at 6 years after I-125 prostate brachytherapy did not significantly differ from baseline. Although a statistically significant deterioration in HRQOL at 6 years was seen for urinary symptoms, bowel symptoms, pain, physical functioning, and sexual activity ($p < 0.01$), most changes were not clinically relevant. A statistically significant improvement after 6 years was seen for mental health, emotional functioning and insomnia ($p < 0.01$). The only clinically relevant changes were seen for emotional functioning and sexual activity.

Conclusion

This is the first study presenting prospective HRQOL data up to 6 years after I-125 prostate brachytherapy. HRQOL scores returned to approximately baseline values at 1 year and remained stable up to 6 years after treatment. I-125 prostate brachytherapy did not adversely affect patient's long-term HRQOL.

Introduction

Iodine-125 (I-125) brachytherapy for localized prostate cancer shows excellent tumor control and survival rates (1-4). The results are equivalent to those achieved by radical prostatectomy or external beam radiotherapy (5). Hence, toxicity and health related quality of life (HRQOL) are considered important endpoints that should be taken into account in the decision of a treatment modality.

Although many studies have reported HRQOL after I-125 prostate brachytherapy (6-15), most were limited by being cross-sectional, by having a short duration of follow-up, or by lacking extended and validated HRQOL questionnaires. Because long-term side effects can occur more than 3 years after treatment (16), long-term follow-up of HRQOL is required. Furthermore, a baseline QOL measure is required to analyze QOL changes over time. To the best of our knowledge, no study has prospectively analyzed HRQOL ≥2 after I-125 prostate brachytherapy.

Some reports have described long-term prostate symptom scores such as the International Prostate Symptom Score (IPSS). Ash *et al.* (15) reported that IPSS scores 9 years after treatment did not differ compared to baseline IPSS. However, besides somatic functioning, HRQOL also includes the patient's perception of social and psychological functioning and well-being (17;18). The appraisal of physical and psychosocial complications following prostate cancer treatment can differ when evaluated by both patients and physicians (19). Therefore, HRQOL assessments should be performed using internationally validated questionnaires (20;21).

Previously, we published our HRQOL data of 127 patients treated with I-125 brachytherapy for localized prostate cancer up to 1 year after treatment (22). In the present study, we present the long-term HRQOL outcomes 6 years after implantation.

Methods and materials

Patients

Between December 2000 and June 2003, 127 patients with localized prostate cancer were treated with I-125 brachytherapy monotherapy at our department according to the EAU guidelines (2;22;23). The patient characteristics are described in *Table 1*. Six months of neoadjuvant hormonal treatment with a LHRH agonist was given to patients presenting with a prostate volume >50 cm^3 (n = 28).

Table 1 Patient characteristics (n = 127).

Characteristic	Value
Age at implantation (y)	
Mean	65
Range	50-78
Tumor stage (n)	
T1b	1 (0.8)
T1c	82 (65)
T2a	43 (34)
T2b	1 (0.8)
Gleason sum score (n)	
2–6	55 (43)
7	72 (57)
Pretreatment PSA (ng/mL)	
Mean	10.1
Range	1.7–38
Pretreatment TURP (n)	
Yes	2 (2)
No	125 (98)
Neo-adjuvant hormonal treatment (n)	
Yes	28 (22)
No	99 (78)
Pretreatment prostate volume (cm^3)	
mean (SD)	37.8 (±11.4)

Abbreviations: PSA = prostate specific antigen level; TURP = transurethral resection of the prostate.
Data in parentheses are percentages

Treatment

The treatment technique used, has been previously described (2;22). Transrectal ultrasonography (TRUS) guided transperineal permanent I-125 seed implantation was performed by a real-time intraoperative-planned approach using the Sonographic Planning of Oncology Treatment (SPOT) system (Nucletron B.V., Veenendaal, The Netherlands). From 2002 the Fully Integrated Real-time Seed Treatment (FIRST) system was used (Nucletron B.V., Veenendaal, The Netherlands). The planned dose to the prostate was 144 Gy according to the guidelines of the Radiation Therapy Committee Task Group no. 43 of the American Association of Physicists in Medicine (24). At 4 weeks after implantation, all patients underwent radiography, computed tomography and mangnetic resonance imaging for postplanning evaluation.

Quality-of-life assessment

All 127 patients received a HRQOL questionnaire at several time points: before treatment (baseline) and 1 month, 6 months and 1 year after treatment. These time points corresponded to the follow-up at visits our department. In July 2008 all previously evaluated patients were contacted again after a median follow-up of 6.4 years (range 5.3 -7.7 years). Of the 127 patients, 102 returned a completed questionnaire. Of the 25 non-responders, 15 had died, 7 were lost to follow-up, and 3 refused to complete the questionnaire.

The questionnaire included the RAND-36 generic health survey (25), the cancer-specific European Organization for Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30) (17), and the tumor-specific EORTC prostate cancer module (EORTC QLQ-PR25) (26).

The RAND-36 health survey (25) contains 4 functional scales (physical role restriction, social role restriction, physical problems, and emotional problems). Also, 3 items concerning well-being (mental health, vitality, and pain), as well as 2 items for general health (general health experience, change in health) are evaluated. All scales of the RAND-36 range in score from 0 to 100, with a higher score indicating a better HRQOL.

The EORTC QLQ-C30 (17) contains 5 functional scales (physical, role emotional, cognitive, and social), a global HRQOL scale, 3 symptom scales (nausea and vomiting, fatigue, pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The EORTC QLQ-PR25 (26) contains 5 scales (urinary symptoms/problems, bowel symptoms/problems, treatment-related symptoms, sexual functioning, and sexual activity). All scales of the EORTC QLQ-C30 and the EORTC QLQ-PR25 range in score from 0 to 100. For functional scales and the global HRQOL scale, a higher score represents a higher level of functioning or global HRQOL. For symptom scales and single items, higher scores indicate more symptoms or more problems.

All questionnaires are well validated and widely used in oncology trials. According to the published data concerning the interpretation of HRQOL data, a change of ≥ 10 points on a 100-point scale was considered clinically relevant (27).

Statistical analysis

The scores of the RAND-36, EORTC QLQ-C30 and the EORTC QLQ-PR25 QOL-items were computed. Descriptive statistics (mean, range, confidence intervals) were used to assess patient characteristics. Differences in HRQOL between baseline and the follow-up points were analyzed with a paired samples *t*-test. Only patients who completed the questionnaire at all time points were included in the analysis.

Cronbach's *α* coefficients were calculated to determine internal consistency reliability of the questions. The reference value of Cronbach's *α* coefficient for sufficient internal consistency was ≥ 0.70. Reliability analysis resulted in Cronbach's *α* coefficients of ≥ 0.70 for all HRQOL items, except for nausea and vomiting in EORTC QLQ-C30, and for bowel and treatment-related symptoms in EORTC QLQ-PR25. This is in accordance with a recent study of Van Andel *et al*. (28) demonstrating acceptable psychometric properties and clinical validity for the EORTC QLQ-PR25, except for bowel function and side-effects of hormonal therapy scales.

To assess if any clinical characteristic predict HRQOL at 6 years after treatment, univariate and multivariate linear regression analyses were applied. Pre-treatment clinical factors included in the analysis were age, neoadjuvant hormonal treatment (HT), iPSA and prostate volume. Predictive factors were selected with backward stepwise selection using a *p*-value of 0.20.

A commercial statistical package (SPSS 16.0; SPSS, Chicago, IL) was used for statistical analysis of the data. To account for multiple comparisons, a *p*-value of ≤ 0.01 was considered statistically significant.

Results

The mean scores and standard deviations of the HRQOL items at five different time points are shown in *Table 2*. For most items an increase in symptoms or a decreased level of functioning or QOL was seen 1 month after treatment. Subsequently, the symptoms gradually diminished and functioning scores improved. Comparing the HRQOL scores 6 years after treatment with those at baseline resulted in statistically significant differences for several HRQOL items. However, by comparing the HRQOL scores 6 years after treatment with these at 1 year after treatment, no statistically significant differences were found for any of the HRQOL items (data not shown).

A statistically significant deterioration after 6 years compared to baseline was seen for physical functioning, pain, urinary symptoms, bowel symptoms and sexual activity ($p \leq 0.01$). A statistically significant improvement after 6 years was seen for mental health, emotional functioning and insomnia ($p \leq 0.01$). For all other HRQOL items no significant difference was seen. The only clinically relevant changes after 6 years were seen for emotional functioning (10-point increase) and sexual activity (15-point decrease).

The most reported adverse events after prostate brachytherapy are urinary and bowel symptoms. *Figure 1* shows the mean change over time in urinary symptom scores (EORTC QLQ-PR25) up to 6 years after I-125 prostate brachytherapy. After an initial increase at 1 month after treatment, the urinary symptoms gradually improved and reached baseline levels at 1 year after treatment.

Table 2 Mean scores (± standard deviations) of HRQOL items at different time points before and after I-125 prostate brachytherapy.

Variable	baseline (n = 127)	1 month (n = 125)	6 months (n = 118)	1 year (n = 91)	6 years (n=102)	baseline vs. 6 y (*p*-value)
RAND-36						
Physical functioning	89 (±14)	84 (±19)	85 (±19)	87 (±16)	84 (±20)	0.01
Social functioning	86 (±18)	73 (±23)	83 (±20)	88 (±17)	88 (±17)	NS
Physical role restriction	84 (±31)	64 (±41)	74 (±37)	77 (±37)	84 (±34)	NS
Emotional role restriction	80 (±32)	78 (±36)	82 (±33)	91 (±23)	88 (±28)	NS
Mental health	77 (±17)	79 (±16)	81 (±14)	81 (±15)	82 (±14)	0.004
Vitality	70 (±19)	67 (±21)	69 (±18)	70 (±19)	72 (±16)	NS
Pain	94 (±13)	82 (±19)	87 (±19)	90 (±17)	91 (±15)	0.003
General health	69 (±15)	67 (±17)	68 (±19)	67 (±18)	70 (±17)	NS
Change in health	47 (±17)	41 (±17)	47 (±19)	56 (±19)	50 (±12)	NS
EORTC QLQ-C30						
Physical functioning	92 (±12)	90 (±13)	89 (±14)	90 (±13)	88 (±14)	0.006
Role functioning	92 (±17)	79 (±25)	85 (±21)	88 (±20)	89 (±20)	NS
Emotional functioning	79 (±18)	84 (±17)	86 (±16)	88 (±15)	89 (±14)	<0.001*
Cognitive functioning	86 (±16)	88 (±16)	88 (±16)	88 (±17)	84 (±21)	NS
Social functioning	92 (±15)	81 (±20)	90 (±15)	91 (±15)	94 (±13)	NS
Global health/QOL	80 (±14)	73 (±16)	76 (±16)	78 (±16)	82 (±12)	NS
Fatigue	19 (±19)	25 (±22)	23 (±20)	20 (±19)	22 (±19)	NS
Nausea and vomiting	1 (±5)	2 (±7)	2 (±5)	1 (±4)	1 (±3)	NS
Pain	6 (±14)	17 (±19)	14 (±20)	10 (±18)	9 (±17)	0.002
Dyspnea	10 (±18)	12 (±22)	15 (±22)	13 (±21)	10 (±17)	NS
Insomnia	20 (±27)	29 (±33)	21 (±29)	16 (±25)	17 (±24)	0.01
Appetite loss	4 (±13)	3 (±13)	3 (±12)	3 (±11)	2 (±7)	NS
Constipation	2 (±10)	13 (±24)	5 (±14)	4 (±13)	3 (±9)	NS
Diarrhoea	6 (±15)	12 (±21)	11 (±19)	6 (±18)	5 (±15)	NS
Financial difficulties	1 (±5)	4 (±12)	3 (±9)	2 (±8)	1 (±6)	NS
EORTC QLQ-PR25						
Urinary symptoms	13 (±12)	40 (±23)	26 (±18)	17 (±15)	18 (±17)	0.002
Bowel symptoms	3 (±5)	8 (±11)	7 (±10)	4 (±7)	6 (±8)	0.002
Treatment-related sympt.	7 (±9)	8 (±8)	9 (±10)	7 (±8)	6 (±8)	NS
Sexual functioning	34 (±26)	25 (±22)	33 (±24)	37 (±23)	39 (±24)	NS
Sexual activity	77 (±24)	61 (±24)	64 (±27)	63 (±25)	62 (±25)	<0.001*

Abbreviations: RAND-36 = RAND-36 generic health survey; EORTC QLQ-C30 = cancer-specific European Organization for Research and Treatment of Cancer core questionnaire; EORTC QLQ-PR25 = tumor-specific EORTC prostate cancer module.
In RAND-36, a higher score represents better health. In EORTC QLQ-C30 and QLQ-PR25, a higher score represents more symptoms or a higher level of functioning or quality of life.
p-value ≤ 0.01 is considered statistically significant; NS = not significant; * = clinically relevant (≥ 10-point difference).

The urinary symptoms then remained stable up to 6 years after treatment. The same trend over time was seen for bowel symptom scores (EORTC QLQ-PR25) (*Figure 2*). At 6 years after treatment 36% of the patients had less urinary symptoms compared to baseline, 47% had more urinary symptoms and 17% had no change in urinary symptoms. For bowel symptoms, 14% of the patients had less symptoms compared to baseline, 32% had more symptoms and 54% had no change in symptoms.

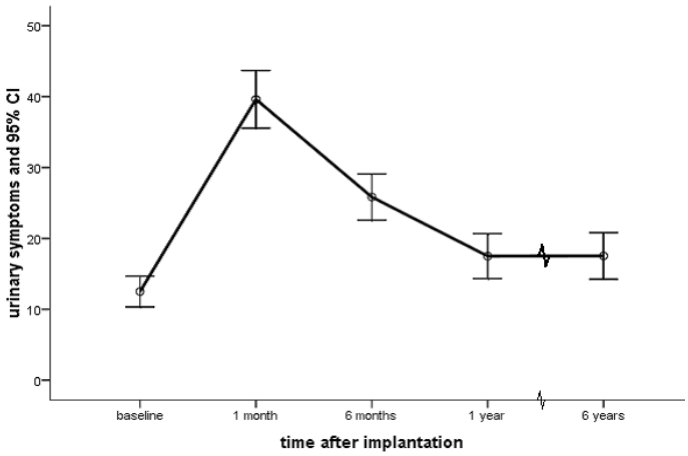

Figure 1. EORTC QLQ-PR25 urinary symptom scores (mean and 95% confidence intervals) up to 6 years after I-125 prostate brachytherapy. A higher score represents more symptoms or more problems

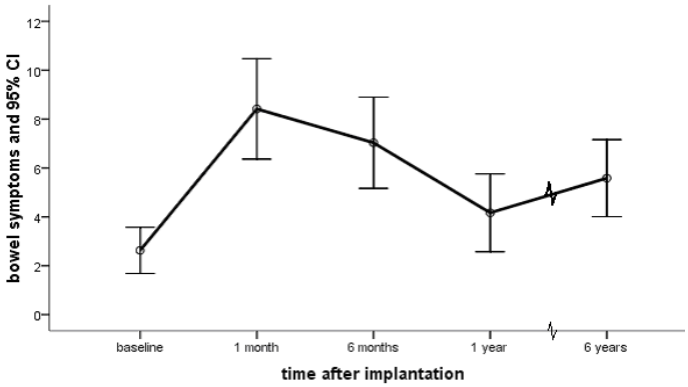

Figure 2. EORTC QLQ-PR25 bowel symptom scores (mean and 95% confidence intervals) up to 6 years after I-125 prostate brachytherapy. A higher score represents more symptoms or more problems

Figure 3 shows the clinically relevant improvement over time in emotional functioning (EORTC QLQ-C30). The development of sexual activity scores (EORTC QLQ-PR25) over time is shown in *Figure 4*. At 6 years after treatment 70% of the patients had diminished sexual activity compared to baseline, 12% had improved sexual activity and 18% had no change in sexual activity.

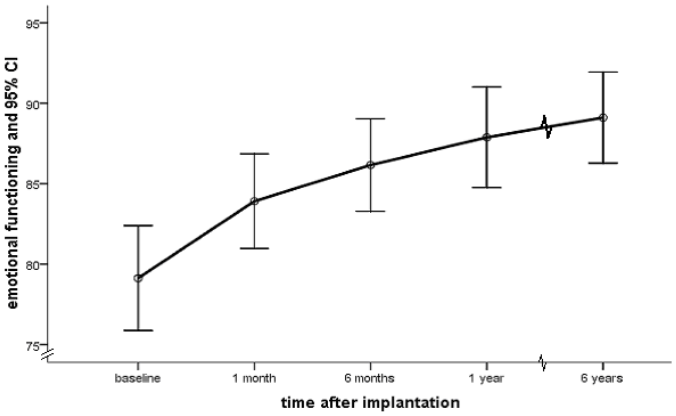

Figure 3. EORTC QLQ-C30 emotional functioning scores (mean and 95% confidence intervals) up to 6 years after I-125 prostate brachytherapy. A higher score represents a higher level of emotional functioning

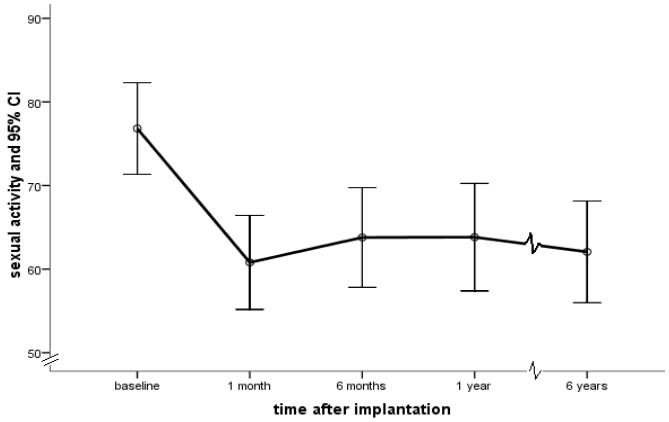

Figure 4. EORTC QLQ-PR25 sexual activity scores (mean and 95% confidence intervals) up to 6 years after I-125 prostate brachytherapy. A higher score represents a higher level of sexual activity

Multivariate linear regression analysis was performed to identify predictors for diminished HRQOL at 6 years after treatment. Predictors for urinary symptoms were HT (β, 8.1;95% confidence interval [CI], -0.07 to 16.2) and iPSA (β, -0.19; 95% CI, -0.48 to 0.09). Prostate volume (β, 0.11; 95% CI, -0.03 to 0.25) was identified as a pre-dictor for bowel symptoms. An older age (β, -1.37; 95% CI, –2.26 to -0.48) predicted diminished sexual activity at 6 years. Age (β, -1.50; 95% CI, -2.13 to -0.86), HT (β, 14.2; 95% CI, 3.8 to 24.6) and iPSA (β, -0.53; 95% CI, -0.89 to -0.16) were predictors for sexual functioning.

Discussion

To the best of our knowledge, this is the first study prospectively assessing long-term HRQOL after I-125 brachytherapy for localized prostate cancer. Long-term QOL is required, because toxicity after prostate brachytherapy may occur more than 3 years after treatment (16). In the present study, we compared HRQOL at 6 years after treatment to baseline measures. Previously, we published our HRQOL data up to 1 year after treatment, showing a significantly worse HRQOL at 1 month after treatment compared to other time points (22). Our long-term data show that overall HRQOL at 6 years after treatment did not differ significantly from baseline. Thus, I-125 brachytherapy does not adversely affect patients' long-term HRQOL.

Although a statistically significant change between 6 years after treatment and baseline was seen for some HRQOL items, most changes were not clinically relevant. A statistically significant deterioration was seen for urinary symptoms, bowel symptoms, pain, physical functioning, and sexual activity. A statistically significant improvement was seen for emotional functioning, mental health and insomnia. Only for emotional functioning and sexual activity a clinically relevant change was seen.

In an additional analysis, we compared HRQOL at 6 years after treatment with that at 1 year after treatment. For none of the investigated HRQOL items a statistically significant difference was found, indicating that the QOL remains stable after 1 year post-treatment. Therefore, our data would suggest that measuring HRQOL in prostate brachytherapy could be limited to 1 year after treatment. However, these data need to be confirmed.

Urinary dysfunction is the most common adverse event associated with prostate brachytherapy. The increase in symptoms at 1 month after treatment has been frequently described (6;15;22). *Figure 1* shows that 1 year after treatment the urinary symptoms had returned to approximately baseline level and remained stable up to 6 years after treatment.

Although numerous studies have reported short-term urinary symptoms after prostate brachytherapy, to date, only a few studies evaluated long-term urinary QOL (8;12;15;29). Ash *et al*. (15) described the IPSS scores up to 9 years after I-125 brachytherapy. However, as mentioned before, HRQOL is a multidimensional concept that includes more than toxicity alone (17;18). The more extended EPIC urinary symptom scores were also evaluated but were limited by a short follow-up of 2 years. At 1 year after treatment the mean EPIC score had returned to pre-treatment level. This finding is similar to the results from Merrick *et al*. (8), who found no significant difference in long-term urinary QOL when brachytherapy patients were compared with a matched control group. Although that study was limited by its cross-sectional design, the results are similar to our data.

The results from studies that evaluated short-term urinary QOL were similar to ours as well. Lee *et al*. (6) described a return to baseline levels for FACT-P and IPSS scores at 1 year after prostate brachytherapy. Downs *et al*. (9) found a return of UCLA-P scores to baseline at 18-24 months after treatment. Feigenberg *et al*. (10) reported no return of IPSS scores to baseline levels 1 year after treatment for 60% of patients. Nevertheless, using the FACT-P, two-thirds of men reported decreased urinary function compared to baseline. Only Caffo *et al*. (11) did not found a return to baseline levels for urinary symptoms until 3 years after treatment. Some other published studies were primarily designed to compare different treatment modalities (7;13;14;16). A difficulty in comparing these studies is the use of different questionnaires, makes interpretation of the results a challenge.

Fewer studies have been published concerning *bowel symptoms* after prostate brachytherapy. In our study, bowel symptoms returned to baseline level at 1 year and then remained stable up to 6 years after treatment (*Figure 2*). Although a statistically significant worsening of symptoms was found at 6 years compared to baseline, no clinically relevant change was seen. However, we must to interpret these results with caution, because Van Andel *et al*. (28) recently described unsatisfactory clinical validity for EORTC QLQ-PR25 bowel function. Also in our analysis, the Cronbach's α coefficient for this item was limited. Despite this possible limitation, our results are in accordance with other published data. Merrick *et al*. (30) demonstrated that prostate brachytherapy adversely affects bowel symptoms in approximately 10% of patients and, in most patients, the changes are minimal and slowly resolve with time. Others confirmed the absence of relevant long-term bowel morbidity after prostate brachytherapy (15;29).

Sexual activity after prostate brachytherapy was also evaluated. Interestingly, a clinically relevant 15-point decrease in *sexual activity* was seen after 6 years, without a significant worsening in *sexual functioning*. Feigenberg *et al*. (10)

confirmed this discrepancy in sexual functioning and sexual activity. At 1 year, 78% of the patients stated that they could achieve an erection with or without assistance; however, almost 50% reported a decrease in sexual activity (10). This is important, because most studies reporting sexual toxicity after cancer therapies focus only on erectile function. Stock *et al*. (31) reported actuarial decreases in erectile function in 29% of patients 1 year after prostate brachytherapy, and Potters *et al*. (32) reported a potency rate of 67% at 5 years. However, the decrease in sexual activity might be explained, not only by the possibility of achieving an erection, but also by ageing, the loss of a partner or by the detrimental effect of cancer treatment to patient's frequency of sexual activity.

As mentioned, in the present study, we did not find long-term sexual dysfunction. This might have been because of our longer follow-up, indicating that improvement in sexual functioning could continue for several years after treatment. Ash *et al*. (15) also found a moderate improvement in sexual function 2 years after prostate brachytherapy. Feigenberg *et al*. (10) demonstrated that the negative impact of prostate brachytherapy on sexuality was significant only in the immediate after treatment period. Finally, one could argue that the Dutch translation of the EORTC QLQ-PR25 requests an answer to the questions concerning sexual activity only when patients had been sexually active in the previous 4 weeks, thus causing a low response rate for this scale and perhaps leading to under- or overestimated QOL in terms of sexual activity. However, in our analysis, the response rate to sexual activity was 71% and even 100% for sexual functioning.

We found a clinically relevant 10-point improvement in *emotional functioning* 6 years after prostate brachytherapy. This improvement after cancer therapy has been described for other cancer types as well and can be explained by patients having had time to adapt to the situation, a response shift mechanism, and a decreasing fear of recurrence and death over time (33). The same mechanisms could apply to the statistically significant improvement in *mental health*.

Although HRQOL at 6 years was not significantly different compared with baseline for the whole cohort, we found some predictors for diminished HRQOL. In particular, the effect of neoadjuvant HT on HRQOL is questioned in literature. Our data showed that HT seemed to predict for more urinary symptoms and worse sexual functioning at 6 years after treatment. Because our data at 6 years hardly showed any clinical relevant changes in QOL compared to baseline, we did not expect any correlation with dose. Therefore, we did not include dosimetric parameters in the analysis. Acute urinary retention, relapse and salvage therapy are factors that might be associated with HRQOL as well. In ongoing research, we will explore the further predictive factors for short- and long-term HRQOL and validate them.

The present study has several limitations. First, we did not have a control group, which precludes a correction for age-related morbidity. Second, patients received the first questionnaire after diagnosis. The knowledge of having cancer might have influenced their HRQOL. Third, our study described the experience of a single centre. Morbidity might vary from center to center, depending on treatment techniques used. Fourth, social and demographic items were not evaluated and these might have influenced patient's HRQOL. The study population was a white Dutch population, and QOL might differ from those of other countries and cultures.

Conclusion

This is the first study presenting prospective HRQOL data up to 6 years after I-125 prostate brachytherapy. The HRQOL scores had returned to approximately baseline values at 1 year and remained stable up to 6 years after treatment. I-125 prostate brachytherapy did not adversely affect the patient's long-term HRQOL.

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Chapter 3

Long-term depression score after I-125 brachytherapy for localized prostate cancer: *a quantitative analysis*

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Abstract

Purpose

To provide long-term descriptive analyses of depression up to 8 years after I-125 brachytherapy for localized prostate cancer, and to assess associations between depression, coping and health related quality of life (HRQOL) factors.

Methods and Materials

A total of 127 patients treated with I-125 brachytherapy for localized prostate cancer between December 2000 and June 2003 received questionnaires at 4 time points: before treatment (baseline) and 1 month, 6 months, and 1 year after treatment. The questionnaires included the Center for Epidemiologic Studies Depression (CES-D) Scale, a well validated and widely used instrument designed to measure current depressive symptomatology in the general population and cancer patients. In addition, well validated instruments were used to assess HRQOL and coping. Spearman's correlation coefficients (Rho) were calculated to assess the correlation between depression, HRQOL and coping variables at 1 month and 1 year after therapy. At 8 years of follow-up, patients received a questionnaire again, consisting of the CES-D scale and the UCL.

Results

At all follow-up moments, from baseline to 8 years after I-125 brachytherapy, approximately 10% (n = 13) of the study population had a CES-D score of ≥ 16, indicating a clinically significant level of depressive symptoms. Compared to baseline the mean CES-D score increased by 1.3 point after a follow-up period of 8 years ($p > 0.05$), indicating a slight increase of depressive symptoms on a scale from 0-60. No significant associations were found between mean CES-D score and patient characteristics (medical and demographic). Relevant negative correlations were found between depression and the HRQOL variables vitality, emotional functioning, and mental health (Rho > 0.5). No relevant correlations were found between coping and depression (Rho < 0.5).

Conclusion

Patients receiving I-125 brachytherapy for localized prostate cancer show favourable scores of depression after treatment. The low scores of depression, even at baseline, suggest that diagnosis of localized prostate cancer and I-125 brachytherapy do not contribute to an increased risk of depression.

Introduction

Treatment results for localized prostate cancer are currently excellent. I-125 brachytherapy as well as prostatectomy and external beam radiotherapy book quite successful results regarding survival rates and tumor control in early stage prostate cancer [1-3]. After primary treatment, the 5-year survival rate is currently nearly 100% for each of these interventions [4-6]. Despite this good prognosis and the growing numbers of prostate cancer survivors, recent urological literature is apprehensive about the increased incidence of depression in prostate cancer patients [7,8]. An increased rate of depression was found in locally advanced and metastatic prostate cancer [9]. In addition, Pirl *et al.* suggests that hormone therapy in particular should be considered as a possible risk factor for depression. In that study, depression was measured in men receiving androgen deprivation therapy for prostate cancer. The observed rate of depression was 8 times higher than the rate in the general male population of the United States, and 32 times higher than the rate in men over 65 years [10]. It is essential to quantify the rate of depression in localized prostate cancer patients since depression is related to poor health related quality of life (HRQOL) [11-13]. In addition, several studies showed that coping styles used by patients with cancer can influence psychological well-being [14-17]. Furthermore, these data can aid in patient counselling.

Rates of depression after prostatectomy and external beam radiotherapy are already described in detail. No increased risk of depression after these treatments was described [18-23]. However, results on depression after brachytherapy are sparse. To our knowledge, no long-term data have been published on depression in patients who receive I-125 brachytherapy.

The main goal of this study is to provide a long-term descriptive analyses of depression up to 8 years after I-125 brachytherapy for localized prostate cancer. In addition, we aim to assess any possible association between depression, coping and HRQOL factors.

Methods and materials

Patients

In the period between December 2000 and June 2003, 127 newly diagnosed patients with localized prostate cancer were treated with permanent I-125 brachytherapy at our department, according to the European Association of Urology guidelines [1,24,25]

Treatment

The Treatment technique used has been previously described [1,26]. Transrectal ultrasonorgraphy-guided transperineal implantation of radioactive I-125 seeds was performed using a real-time intraoperative plan, made with the system for Sonographic Planning for Oncology Treatment (SPOT; Nucletron BV, Veenendaal, The Netherlands). From 2002, the Fully Integrated Realt-time Seed Treatment system was used (Nucletron BV, Veenendaal, The Netherlands). The intraoperative plan was based on 3-dimensional ultrasound images, the positions of the needles, and the delineated prostate volume. The planned dose to the prostate was 144 Gy, according to the Radiation Therapy Committee Task Group No. 43 of the American Association of Physicists in Medicine guidelines [27]. Postplanning evaluation was based on radiographs, magnetic resonance images and computed tomography, performed at 4 weeks after implantation.
Patients diagnosed with a prostate volume >50 cm^3 (n = 30) were treated with a luteinizing hormone-releasing hormone agonist during 6 months prior to treatment. Prostate volume measurements reported in *Table 1* were determined at the time of the implantation procedure.

Depression, coping and QOL assessments

All 127 patients received questionnaires at 4 time points: before treatment (baseline), and at 1 month, 6 months and 1 year after treatment (follow-up). These time points correspond to the follow-up visits at our department. The questionnaires included the Centre for Epidemiologic Studies of Depression (CES-D) Scale, which assesses depression; and other well-validated measurements to assess coping and HRQOL. Demographic information was collected at baseline. In May 2010, all previously evaluated patients received a questionnaire consisting of a coping and depression assessments at their home address, to assess long-term scores. No HRQOL data was assessed at this point of follow-up.
The CES-D Scale [28,29] is a widely used self-report scale designed to measure current depressive symptomatology in the general population [30,31] and in patients with cancer [32,33]. It contains 20 items, addressing depressive symptoms in which respondents indicate on a 4-point Likert scale how frequently they have experienced each symptom in the prior week. Scores range from "rarely or none of the time" (0 point) to "most or all of the time" (3 points). The CES-D scale consists of 4 independent subscales: Depressed Affect (feeling depressed, anxious and miserable), Positive Affect (feeling happy and worthy, being hopeful about the future), Somatic-Retarded Activity (loss of appetite, restless nights and problems making efforts), and Interpersonal Relations

(people react unpleasant, people did not like me) [34]. In addition, items of the positive affect subscale were recoded so that higher scores reflect less positive affect and more feelings of depression. Because they are all dimensions of depression, it is recommended to use the total CES-D score [28,29]. Total CES-D score ranges from 0-60, with higher scores reflecting the presence of more depressive symptoms. A score of 16 or higher suggests a clinically significant level of symptoms of depression, which does not necessarily mean that the respondent has a psychiatric diagnosis of depression.

Coping was assessed by the Utrecht Coping List (UCL) [35], a validated and widely used questionnaire in the Netherlands. In the current study a modified short version of the UCL was used to assess 4 different coping styles in problem situations. This version consists of 21 items comprising 4 coping strategies: active coping (making efforts to solve a problem) consisting of 7 items, palliative coping (seeking distraction to not have to think about the problem) consisting of 5 items, passive coping (being completely preoccupied by the situation, not being able to do anything about the situation) consisting of 7 items, and seeking support (seeking comfort, asking for help) consisting of 2 items. Each of the 21 items were scored using a 5-point Likert scale ranging from "never" (1 point) to "very often" (5 points). The coping strategy with the highest score is considered to be the most predominant style of coping used in problem situations.

HRQOL was assessed by the RAND-36 general health survey, a cancer specific quality of life instrument of the European Organization for Research and Treatment of Cancer (EORTC QLQ C-30), the prostate specific quality of life questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-PR25), and the American Urological Association (AUA) symptom index.

The RAND-36 [36,37] contains 4 functional scales assessing physical functioning, physical role restriction, social functioning, and emotional role restriction. In addition, 3 items concerning vitality, mental health, and pain, and 2 items concerning general health and change in health. All scales range in a score from 0 to 100, with higher scores indicating greater HRQOL.

The EORTC QLQ C-30 [38], contains 5 functional scales assessing physical, role, emotional, cognitive and social functioning, a global HRQOL scale, 3 symptom scales describing nausea and vomiting, fatigue, and pain. In addition 6 single items concerning dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties due to disease or treatment. All scales range in a score from 0 to 100, with higher scores reflecting either more symptoms (symptom scales and single items) or higher level of functioning (functional scales and the global HRQOL scale).

The EORTC QLQ-PR25 [39] contains 5 scales assessing urinary and bowel symptoms, sexual functioning, sexual activity, and treatment related side-

Table 1 Patient and demografic characteristics (n = 127).

Characteristic	Value
Age at implantation (y)	
Mean	66
Range	50-81
Tumor stage (n)	
T1b	1 (0.8)
T1c	84 (63.6)
T2a	46 (34.8)
T2b	1 (0.8)
Pretreatment PSA (ng/mL)	
Mean	11.2
Range	1.7-100
Pretreatment TURP (n)	
Yes	3 (2.3)
No	129 (97.7)
Neo-adjuvant hormonal treatment (n)	
Yes	30 (22.7)
No	102 (77.3)
Pretreatment prostate volume (cm^3)	
Mean	38
Range	8.0-79
Acute Urine Retention (n)	
Yes	19 (9.8)
No	113 (90.2)
Civil status at implantation (n)	
Maried	92 (69.7)
Not-married	5 (3.8)
Divorced	11 (8.3)
Widow	6 (4.5)
Missing	18 (13.6)
Working status at implanatation (n)	
Active	31 (23.5)
ZW/SSD	9 (6.9)
Retirement	72 (54.5)
Missing	20 (15.1)

Abbreviations: PSA= prostate specific antigen; TURP= trans urethral resection of the Prostate; ZW= sickness benefits act; SSD= social security disability.
Data in parentheses are percentages.

effects. Scores range from 0 to 100, with higher scores indicating either more symptoms (urinary, bowel, treatment-related symptoms) or higher levels of functioning or activity (sexual).
The AUA symptom index [40] contains 7 items measuring the frequency of clinically important urinary symptoms. Scores range from 0 to 100, with higher scores reflecting more problems or symptoms.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 16.0. The mean scores and standard deviations of the CES-D, UCL and the HRQOL variables of the RAND-36, the EORTC QLQ-C30, the EORTC-PR25, and the AUA were computed. According to Osoba, we considered a change in score of ≥ 10% on a 100-point scale as clinically relevant. Cronbach's α coefficients, calculated with reliability analysis (model alpha), were used to determine the internal consistency of the questionnaires. The reference value for satisfactory internal consistency was ≥ 0.70 [41]. Patient characteristics were summarized using descriptive statistics. Chi-square tests were used to assess differences between depression and categorical variables by different patient characteristics. CES-D mean scores and standard deviations were computed to assess long term analyses of depression. No complete case analysis was used. Differences in depression between baseline and the follow-up time points were conducted with paired samples *t*-tests. To evaluate the pattern of depression and coping over time, means and 95% confidence intervals were calculated with repeated measurements analyses using the SAS Proc Mixed (mixed models approach).
Spearman's correlation coefficients were calculated to analyse correlations between depression, coping and HRQOL variables. Spearman's correlation coefficients between 0.5-0.75 Rho is considered as moderate to good correlation, and Rho ≥ 0.75 is considered as good to excellent correlation.

Results

The number of questionnaires returned was different at each of the 5 time points. We received 127,122,113, and 88 questionnaires at baseline, 1 month, 6 months, and 1 year of follow-up, respectively. After a median follow-up of 8.2 years (range, 7.0-9.4), all previously evaluated patients were contacted again. Of the 127 included patients, 95 returned a completed questionnaire. Of the 32 non-responders, 3 refused to complete the questionnaire, 16 had died, and 13 were lost to follow-up. Only 49 patients returned the questionnaire at all time points.

Table 2 Mean scores ± standard deviation of depression and coping at different time-points before and after I-125 prostate brachytherapy.

Variabele	baseline (n=127)	1 month (n=122)	6 months (n=113)	1 year (n=88)	8 years (n=95)	Difference between baseline and 1mo (*p*-value)	Difference between baseline and 8y (*p*-value)
CES-D Scale (depression)							
Depressive Affect	1.2 ± 1.8	1.1 ± 1.6	0.9 ± 1.5	0.8 ± 1.6	1.2 ± 2.1	NS	NS
Somatic and Retarded Acitivity	2.0 ± 2.3	2.4 ± 2.6	2.3 ± 2.6	2.0 ± 2.3	2.8 ± 3.2	NS	.026*
Positive Affect	3.1 ± 3.5	2.7 ± 2.9	2.8 ± 3.2	2.7 ± 3.1	3.3 ± 3.6	NS	NS
Interpersonal Reactions	0.3 ± 0.8	0.2 ± 0.6	0.2 ± 0.7	0.6 ± 0.5	0.4 ± 1.0	NS	NS
CES-D total	7.0 ± 6.5	6.7 ± 6.2	6.6 ± 6.8	5.9 ± 6.1	8.3 ± 8.0	NS	NS
Observed CES-D range	0-24	0-25	0-33	0-27	0-42	NS	
Depression score ≥16	12.3%	7.40%	10.6%	6.8%	11.0%	NS	
UCL (coping)							
Active Coping	11.3 ± 7.4	10.7 ± 7.5	9.7 ± 7.0	10.0 ± 7.6	9.0 ± 6.6	NS	.017*
Seeking Support	1.7 ± 1.6	1.6 ± 1.6	1.2 ± 1.4	1.4 ± 1.6	1.0 ± 1.3	NS	< .001*
Passive Coping	4.0 ± 3.4	3.5 ± 3.2	3.9 ± 3.9	3.3 ± 3.8	3.6 ± 3.8	NS	NS
Palliative Coping	3.1 ± 2.8	3.2 ± 2.7	2.8 ± 2.8	2.6 ± 2.4	2.7 ± 3.0	NS	NS

Abbreviations: NS= not statistically significant
Total CES-D scores range from 0-60. Higher scores indicate more depressive symptoms. For the UCL-coping scores, the scale with the highest score is considered to be the predominant style of coping in problem situations.
p-values were conducted with paired samples *t*-tests. * statistically significant ($p \leq 0.05$).

Reliability analyses resulted in Cronbach's α coefficients of ≥ 0.70 for all total CES-D scales. In addition, all UCL subscales resulted in Cronbach's α coefficients of ≥ 0.70, except for palliative coping at 1 year of follow up (α = 0.62) and seeking support at 8 years of follow up (α = 0.62). For all HRQOL items reliability analysis resulted in Cronbach's α coefficients of ≥ 0.70, except for bowel and treatment-related symptoms in the EORTC PR25 and nausea and vomiting in the EORTC QLQ-C30.

Demographic and medical characteristics of all 127 patients are listed in *Table 1*. No significant associations were found between the patient characteristics and depression scores (total CES-D score). In particular, no association between neo-adjuvant hormone therapy and the development of depression was found (data not shown).

Mean scores and standard deviation of depression and coping at different time-points before and after I-125 brachytherapy are shown in *Table 2*. In general, the mean CES-D score increases by 1.3 point after a follow-up period of 8 years compared to baseline. However, this finding is not statistically significant ($p > 0.05$) and is not considered clinically relevant on a scale from 0 to 60. By comparing the 1 month and 1 year scores values to baseline scores, no statistically significant differences were found, except for the depression subscale Somatic-Retarded Activity, for which a slight deterioration (2.3 points) was found at 8 years after therapy ($p = 0.026$).

Approximately 10% (n = 13) of the patients had a total CES-D score of 16 or higher, indicating a clinically significant level of depressive symptoms. The mean CES-D scores and 95% confidence intervals from baseline to 8 years after treatment, calculated with analysis of repeated measurements, are shown in *Figure 1*.

The mean coping scores show that active coping (making efforts to solve a problem) is considered to be the most predominant style of coping used in problem situations. However, the mean scores of active coping show a deterioration of 2.3 points after 8 years of follow-up compared to baseline values. This finding is statistically significant ($p = 0.017$), however, not considered clinical relevant. The same change over time was seen for the coping strategy "seeking support", with a deterioration of 0.7 point ($p = 0.002$). In addition, passive and palliative coping strategies showed a negative trend, though no significant differences were reported.

Mean scores and standard deviations of HRQOL and coping variables, from baseline up to 1 year after treatment, are shown in *Table 3*. For most HRQOL variables a deterioration in the mean score was seen at 1 month after treatment, indicating more symptoms or a deceased level of functioning after therapy. However, these symptoms gradually diminished over time.

Table 3 Mean scores ± standard deviations of HRQOL and coping variables at different time points before and after I-125 brachytherapy. Furthermore, correlations of QOL and coping at 1 month and 1 year with total CES-D scores at 1 month and 1 year, respectively.

Variabele	baseline (n=127)	1 month (n=122)	6 months (n=113)	1 year (n=88)	Spearman's correlation with total CES-D score 1 month (Rho)	1 year (Rho)
HRQOL						
RAND-36						
Physical functioning	89 ± 14	83 ± 20	84 ± 19	87 ± 16	NR	NR
Social role restriction	86 ± 18	72 ± 23	82 ± 20	87 ± 16	NR	NR
Physical role restriction	84 ± 31	63 ± 41	73 ± 38	76 ± 38	NR	NR
Emotional role restriction	80 ± 32	77 ± 36	81 ± 33	91 ± 23	NR	NR
Mental health	77 ± 17	79 ± 16	81 ± 14	81 ± 15	-0,73*	-0,62*
Vitality	70 ± 19	67 ± 20	69 ± 18	70 ± 19	-0,68*	-0,62*
Pain	94 ± 13	82 ± 19	87 ± 19	90 ± 17	NR	NR
General health	69 ± 15	67 ± 17	68 ± 19	67 ± 18	NR	NR
Change in health	47 ± 17	41 ± 17	46 ± 19	56 ± 20	NR	NR
EORTC QLQ-C30						
Physical functioning	92 ± 12	89 ± 13	89 ± 15	90 ± 13	NR	NR
Role functioning	92 ± 17	79 ± 25	85 ± 21	88 ± 20	NR	NR
Emotional functioning	79 ± 18	84 ± 17	86 ± 16	88 ± 15	-0,74*	-0,59*
Cognitive functioning	86 ± 16	88 ± 16	88 ± 16	88 ± 17	NR	NR
Social functioning	92 ± 15	81 ± 21	90 ± 15	91 ± 16	NR	NR
Global QOL	80 ± 14	73 ± 16	76 ± 16	78 ± 16	NR	NR
Fatigue	19 ± 19	25 ± 22	24 ± 20	20 ± 19	NR	NR
Nausea and vomiting	1 ± 5	2 ± 7	2 ± 5	1 ± 4	NR	NR

Continued ►

Pain	6 ± 14	17 ± 19	14 ± 20	10 ± 18	NR	NR
Dyspnea	11 ± 18	13 ± 22	15 ± 22	13 ± 21	NR	NR
Insomnia	20 ± 27	29 ± 33	21 ± 29	16 ± 25	NR	NR
Appetite loss	4 ± 13	3 ± 13	3 ± 12	3 ± 11	NR	NR
Constipation	2 ± 10	14 ± 24	5 ± 15	4 ± 13	NR	NR
Diarrhea	6 ± 15	12 ± 21	10 ± 19	6 ± 18	NR	NR
Financial difficulties	1 ± 5	4 ± 12	3 ± 9	2 ± 8	NR	NR
EORTC QLQ-PR25						
Urinary symptoms	13 ± 12	40 ± 22	26 ± 18	17 ± 15	NR	NR
Bowel symptoms	3 ± 5	8 ± 11	7 ± 10	4 ± 7	NR	NR
Treatment-related symptoms	7 ± 9	8 ± 8	9 ± 10	7 ± 8	NR	NR
sexual functioning	34 ± 26	25 ± 22	32 ± 25	37 ± 23	NR	NR
sexual activity	77 ± 24	62 ± 24	64 ± 27	63 ± 25	NR	NR
AUA symptom index	22 ± 16	55 ± 28	41 ± 21	29 ± 18	NR	NR
UCL (coping)						
Active coping	11.3 ± 7.4	10.7 ± 7.5	9.7 ± 7.0	10.0 ± 7.6	NR	NR
Seeking support	1.7 ± 1.6	1.6 ± 1.6	1.2 ± 1.4	1.4 ± 1.6	NR	NR
Passive coping	4.0 ± 3.4	3.5 ± 3.2	3.9 ± 3.9	3.3 ± 3.8	NR	NR
Palliative coping	3.1 ± 2.8	3.2 ± 2.7	2.8 ± 2.8	2.6 ± 2.4	NR	NR

Abbreviations: HRQOL = health related quality of life; RAND-36 = RAND medical outcomes study short form 36-item health survey; EORTC QLQ C30 = european organization for research and treatment of cancer: core questionnaire; EORTC-PR25 = tumor-specific EORTC prostate cancer module; AUA = american urological association symptom index; NR = no relevant correlation (Rho < 0.5).
All HRQOL variables range in score from 0-100 with higher scores reflecting either more symptoms (symptom scales and single items) or higher level of functioning (functional scales and the global HRQOL scale). For the UCL-coping items, the scale with the highest score is considered to be the predominant style of coping in problem situations.
* statistically significant ($p < 0.001$).

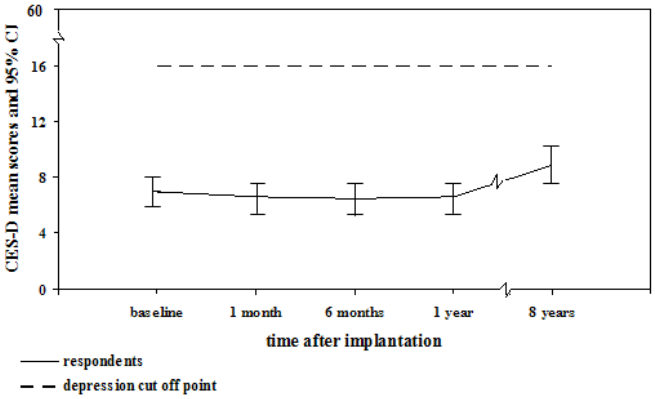

Figure 1 Mean CES-D scores and 95% confidence intervals of the Center for Epidemiologic Studies Depression (CES-D) Scale, up to 8 years after I-125 prostate brachytherapy. Higher scores indicate more depressive symptoms. Scores were calculated with analysis of repeated measurements using the SAS Proc Mixed (mixed models approach).

Spearman's correlation coefficients (Rho) were calculated to assess the correlation between depression, coping and HRQOL scores at 1 month and 1 year after treatment. A significant negative association was found between depression (total CES-D score) and the HRQOL variables vitality (1 month/1 year Rho: -0.68/-0.62), emotional functioning (1 month/1 year Rho: -0.74/-0.59) and mental health (1 month/1 year Rho: -0.73/-0.62). No relevant associations were found between coping and depression (*Table 3*).

Discussion

To our knowledge, this is the first study prospectively assessing long-term depression rates up to 8 years after I-125 brachytherapy for localized prostate cancer, by using validated questionnaires. We found that the rate of depression after I-125 brachytherapy is favourably low. In addition, no significant associations were found between depression and the patient characteristics (medical and demographic). In particular, no significant association between neo-adjuvant hormone therapy and the development of depression was found in the present study. Furthermore, we found that active coping is used as the main coping strategy by patients in problem situations. The use of an active coping style seems to maintain an active and positive view on life, which may lead to adequate psychological adaptation, better psychosocial outcomes and higher levels of HRQOL.

The low depression scores after brachytherapy in our prostate cancer patients are consistent with the findings reported by research on depression after prostatectomy and external beam radiotherapy [18-22].
As mentioned before, Pirl *et al.* [10], showed an increased rate of depression in prostate cancer patients receiving hormone therapy. The rate of depression was 12.8%, which was concluded as 8 times higher than the rate of depression found in the general male population of the United States (1.6%), and 32 times higher than the rate in men over 65 years (0.4%). At the first sight, the observed rate of depression is comparable to the rate found in the present study. However, depression rates observed in the present study (all assessed by the CES-D scale) reflect possible cases of depression, while Pirl *et al.* assessed depression rates by the Structural Clinical Interview for DSM-IV (SCID), which reflect actual diagnosis of a psychiatric depression. Furthermore, in a general Dutch population sample, 20% of the respondents had a CES-D score of 16 or higher [28], suggesting no noteworthy higher prevalence of depression as a result of I-125 brachytherapy in localized prostate cancer. The low level of depression at all time points, even at baseline, might be related to the good prognosis, the little invasive treatment and the generally mild treatment related side effects [42,43].
As mentioned, depression is related to poor health related quality of life (HRQOL). In addition, Roeloffzen *et al.* showed that acute urinary retention after I-125 prostate brachytherapy has a significant negative impact on patient's HRQOL up to 6 years after treatment [44,45]. However, no association between acute urinary retention after treatment and the development of depression was found in the present study. Furthermore, while most HRQOL variables showed an increase in symptoms or decrease in functioning at 1 month of follow-up, no deterioration of depressive symptoms was observed (*Figure 1*). Moreover, the psychosocial items of the HRQOL variables mental health in the RAND-36 and emotional and cognitive functioning in the EORTC-C30 showed slight improvement at 1 month after therapy. This result might be explained by the finding that active coping is used as the main coping strategy by patients in problem situations and that patients adjust well psychologically [46].
An additional goal of the present study was to assess whether HRQOL variables and coping strategies are associated with depressive symptoms (*Table 3*). Higher total CES-D scores were associated with lower emotional functioning (EORTC QLQ-C30) and mental health (RAND-36), as was expected. An inverse association was also observed for vitality (EORTC QLQ-C30). This means that patients who encounter better vitality and/or higher levels of emotional functioning and mental health, experience less feelings of depression. And vica verca, patients who experience less feelings of depression encounter higher levels of emotional functioning and mental health and/or vitality.

This study has some limitations. First, with regard to the definition of depression, caution should be when assessing depression by the CES-D scale. This self-report symptom scale is purposed to assess depressive symptomatology and to identify potential cases of depression [28,29] in discrepancy with diagnostic interviews such as the SCID [47], which measures psychiatric depression. Second, of the 127 patients included in the study, only 49 patients returned the questionnaire at all time points. CES-D mean scores could be biased because of missing data due to selective response (*Table 2*). Therefore, we also performed repeated measurement analyses (mixed models approach) in which all patients were included in order to obtain more reliable analysis of depression over time from baseline to 8 years of follow up (*Figure 1*). However, no significant differences between results of SAS Proc Mixed and SPSS were found. Third, the main goal of this study was to assess a long-term depression rate. Since many adults with depression feel reluctant to answer too many questions, no HRQOL questionnaires were sent (only CES-D and UCL) data was assessed at 8 years of follow-up in order to enhance response rate.

Conclusion

To our knowledge, this is the first study prospectively assessing long-term depression rates up to 8 years after I-125 brachytherapy. The findings of this study indicate that a relatively small proportion (10%) of patients with localized prostate cancer suffer from depressive symptoms after I-125 brachytherapy, which is comparable to patients receiving prostatectomy or external beam radiotherapy for localized prostate cancer. In the present study, depression scores were lower than those observed in the general population, even at baseline. In conclusion, our results suggest that diagnosis of localized prostate cancer and I-125 brachytherapy do not directly contribute to an increased prevalence of depression.

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Chapter 4

The impact of acute urinary retention after I-125 prostate brachytherapy on health-related quality of life

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Abstract

Purpose

The aim of the present study was twofold: 1) to evaluate the impact of acute urinary retention (AUR) in patients treated with I-125 prostate brachytherapy on short- and long-term health-related quality of life (HRQOL); 2) to assess whether pretreatment HRQOL has additional value in the prediction of AUR.

Methods and Materials

Of 127 patients treated with I-125 brachytherapy for localized prostate cancer between December 2000 and June 2003, toxicity and HRQOL data were prospectively collected. Patients received a HRQOL questionnaire at 5 time points: before, and 1 month, 6 months, 1 year and 6 years after treatment. The questionnaire included the RAND-36 generic-health-survey, the cancer-specific European-Organization-for-Research-and-Treatment-of-Cancer core-questionnaire (EORTC-QLQ-C30), the tumor-specific EORTC-prostate-cancer-module (EORTC-PR25) and the American-Urological-Association symptom-index (AUA).

Results

Thirteen of 127 patients developed AUR (10.2%). Patients with AUR had a significantly worse urinary QOL at all time points compared to patients without AUR. The mean difference over time (6 years) between both groups in EORTC-PR25 urinary symptom score was 13.0 points ($p < 0.001$) and 15.7 points ($p = 0.001$) in AUA urinary symptom score. Global QOL scores (EORTC-C30) over time of patients who developed AUR were significantly worse compared to patients without AUR (mean difference 6.7 points; $p = 0.043$). On multivariable logistic regression analysis, pretreatment International Prostate Symptom Score ($p = 0.004$) and neo-adjuvant hormonal treatment ($p = 0.034$) were predictors of AUR. QOL did not have added predictive value.

Conclusion

AUR after prostate brachytherapy has a significant negative impact on the patient's HRQOL up to 6 years after treatment, both regarding global-QOL measures and urinary symptom scores. Furthermore, our results suggest limited value of pretreatment HRQOL measures in the prediction of AUR.

Introduction

Iodine-125 (I-125) prostate brachytherapy (PB) is a common treatment modality in localized prostate cancer and shows excellent tumor control and survival rates (1-3). Results are comparable to those achieved by radical prostatectomy or external beam radiotherapy (4). Hence, toxicity and health-related quality of life (HRQOL) are considered important endpoints that should be taken into account when choosing a treatment modality (5).

The most predominant severe acute toxicity after PB is urinary retention requiring catheterization. Published acute urinary retention (AUR) rates vary from 6% to 34% (6-11). Prolonged catheterization or even a transurethral resection of the prostate (TURP) may be required to relieve obstruction, leading to an increased risk of urethral strictures, urinary incontinence and long-term morbidity (12;13). Therefore, AUR may have an import impact on the patient's HRQOL. Although many studies have reported urinary toxicity after PB (14), to our knowledge, the impact of AUR after PB on HRQOL has never been described before.

Several predictors of AUR after PB have been reported in literature. Factors associated with AUR on multivariable analysis are pretreatment International Prostate Symptom Score (IPSS) (6;8;11), hormonal treatment (HT) (6;9), prostate volume (9), diabetes (8), post-implant edema (8;10;11), and transitional zone volume (15). We are especially interested in pre-implant risk factors, because these can guide decisions when selecting patients for PB. Pretreatment HRQOL measures might contribute to the known risk factors in predicting AUR.

Recently, we reported our 6-year HRQOL data of 127 patients treated with I-125 PB. We showed that there was no significant change in long-term HRQOL compared with baseline for the whole cohort (16). However, we hypothesized that the occurrence of AUR might influence long-term HRQOL negatively. In the present article we aim: 1) to evaluate the impact of AUR on short- and long-term HRQOL in patients treated with I-125 PB; 2) to assess whether pretreatment HRQOL has additional value in the prediction of AUR after PB.

Methods and materials

Patients

Between December 2000 and June 2003, 127 patients with localized prostate cancer were treated with monotherapeutic I-125 implantation at our department, according to the European Association of Urology guidelines (3;16;17). The patient population of the present study is identical to that in our

previous study (16). Six months of neo-adjuvant HT with a LHRH agonist was given to patients presenting with a prostate volume >50 cm^3 (n = 30).

Treatment

The treatment technique used has been previously described (3;16). Transrectal ultrasonography-guided transperineal permanent I-125 seed implantation was performed using a real-time intraoperative-planned approach with the Sonographic Planning of Oncology Treatment (SPOT) system (Nucletron B.V., Veenendaal, The Netherlands). From 2002, the Fully Integrated Real-time Seed Treatment (FIRST) system was used (Nucletron B.V., Veenendaal, The Netherlands). The planned dose to the prostate was 144 Gray, according to the guideline of the Radiation Therapy Committee Task Group No. 43 of the American Association of Physicists in Medicine (18). At 4 weeks after implantation, all patients underwent radiography, computed tomography, and magnetic resonance imaging for postplanning evaluation.

Follow-up

After implantation, patients stayed in the hospital for one night, and were discharged the next day as soon as they were able to void spontaneously. IPSS scores, toxicity data and intervention data were collected prospectively and recorded in the database. AUR was defined as any need for catheterization after implantation. According to our protocol, patients were seen for follow-up at 1 month, 6 months and 1 year after treatment, and yearly thereafter. If AUR occurred, patients were seen immediately. If retention was persistent, a TURP was performed to relieve obstruction.

Quality-of-life assessment

All 127 patients received a HRQOL questionnaire at several time points: before treatment (baseline) and 1 month, 6 months and 1 year after treatment. These time points corresponded to the follow-up visits at our department. In July 2008, all previously evaluated patients were contacted again after a median follow-up of 6.4 years (range 5.3 -7.7). Of the 127 patients, 102 returned a completed questionnaire. Of the 25 nonresponders, 15 had died, 7 were lost to follow-up, and 3 refused to complete the questionnaire. The overall 6-year HRQOL data have been described earlier (16). The current data compare HRQOL between patients with and without AUR on different time points in the same database.

The questionnaire included the RAND-36 generic health survey (19), the cancer-specific European Organization for Research and Treatment of Cancer core questionnaire (EORTC QLQ-C30) (20), the tumor-specific EORTC prostate cancer module (EORTC QLQ-PR25) (21), and the American Urological Association symptom index (AUA) (22). All questionnaires are well validated and widely used in oncology trials.

The RAND-36 health survey (19) contains 4 functional scales (physical role restriction, social role restriction, physical problems, and emotional problems). Also, 3 items concerning well-being (mental health, vitality, and pain), and 2 items for general health (general health experience, change in health) are evaluated. All scales of the RAND-36 range in score from 0 to 100, with a higher score indicating a better HRQOL.

The EORTC QLQ-C30 (20) contains 5 functional scales (physical, role, emotional, cognitive, and social), a global-QOL scale, 3 symptom scales (nausea and vomiting, fatigue, pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The EORTC QLQ-PR25 (21) contains 5 scales (urinary symptoms/problems, bowel symptoms/problems, treatment-related symptoms, sexual functioning, and sexual activity). All scales of the EORTC QLQ-C30 and the EORTC QLQ-PR25 range in score from 0 to 100. For functional scales and the global-QOL scale, a higher score represents a higher level of functioning or global-QOL. For symptom scales and single items, higher scores indicate more symptoms or more problems.

Of the AUA symptom index (22), we analyzed the urinary symptom scale and IPSS. The urinary symptom scale ranges from 0-100 and IPSS ranges from 0 to 35. For both scales, a higher score represents more problems or symptoms.

Cronbach's α coefficients were calculated to determine internal consistency reliability of the questions. The reference value of Cronbach's α coefficient for sufficient internal consistency was ≥ 0.70. Reliability analysis resulted in Cronbach's α coefficients of ≥ 0.70 for all HRQOL items, except for nausea and vomiting in EORTC QLQ-C30, and for bowel and treatment-related symptoms in EORTC QLQ-PR25. This is in accordance with a recent study by Van Andel *et al.* (23) demonstrating acceptable psychometric properties and clinical validity for the EORTC QLQ-PR25, except for bowel function and side-effects of hormonal therapy scales.

Statistical analysis

Scores of the RAND-36, EORTC QLQ-C30 and the EORTC QLQ-PR25 QOL-items were computed. Patient characteristics and HRQOL scores were compared between both groups (AUR versus no-AUR) at different time points using independent samples *t*-tests. Differences in tumor stage, pretreatment TURP

and neo-adjuvant HT were analyzed using χ^2-tests. An independent samples *t*-test was used to compare HRQOL scores at 6 years with baseline values, for AUR and no-AUR patients separately.

To assess the impact of AUR on HRQOL over the whole period (6 years), repeated measurement analyses were performed (generalized estimating equations). We analyzed the EORTC-PR25 urinary symptom score, the AUA urinary symptom score and the EORTC-C30 global-QOL score. to obtain the net effect of the development of AUR on urinary symptoms, we repeated the analyses with a correction for baseline values. Only patients who completed the questionnaire at all time points were included in the analysis.

To assess whether any pretreatment clinical characteristic could predict the development of AUR, multivariable logistic regression analyses were applied. Because of the small patient numbers, the power of the multivariable analysis is limited and should be considered as explorative. Investigated potential predictive factors were IPSS, HT and prostate volume. This limited set of factors is chosen based on the literature. We purposely did not include dosimetric parameters, since we were especially interested in pre-implant factors. Predictors were selected with manual backward stepwise selection using $p = 0.20$ (Wald statistic) (24).

The resulting (basic) model was then extended by adding urinary QOL (EORTC PR-25 urinary symptoms) and global-QOL (EORTC QLQ-C30) to estimate their added predictive value. Differences between the basic model and the extended models were quantified by using the area under the receiver operating characteristic curve (ROC area). The ROC area describes the discriminative ability of the model, i.e. the ability of the model to distinguish a patient with AUR from a patient without AUR. Because of the overlap with IPSS, the AUA urinary symptom score was not added to the model.

A commercial statistical package (SPSS 16.0; SPSS, Chicago, IL) was used for statistical analysis of the data, except for the repeated measurement analysis. To account for multiple comparisons in the analysis of HRQOL items (*Table 2*), $p \geq 0.01$ was considered statistically significant. For all other analyses $p \geq 0.05$ was considered statistically significant.

Results

Thirteen of the 127 patients (10.2%) developed AUR after implantation. The median time to AUR was 1.2 months (range 0.5 to 17.5). 3 of the 13 patients received a suprapubic catheter. Nine of the 13 patients eventually required a TURP to relieve obstruction. The median time to TURP was 20 months (range 9 to 46). Patient characteristics for patients who developed AUR and patients who

did not are listed in *Table 1*. There was a significant difference in pretreatment IPSS between patients with and without AUR (13.8 [± 8.7] versus 7.2 [± 5.5]) and in the use of neo-adjuvant HT (54% versus 19%). Other pretreatment clinical characteristics were comparable between both groups.

Table 1 Pretreatment patient characteristics (n = 127) for patients who developed AUR and for patients who did not (no-AUR).

Characteristic	AUR (n = 13)	No-AUR (n = 114)	Univariate analysis (*p*)
Age at implantation (y)	66 ± 6.7	65.4 ± 6.7	NS
Tumor stage			
T1b	0	1 (1)	
T1c	9 (69)	73 (64)	
T2a	4 (31)	39 (34)	
T2b	0	1 (1)	
Gleason sum score			
< 7	10 (77)	90 (79)	NS
7	3 (23)	24 (21)	
Pretreatment PSA (ng/mL)	13.3 ± 8.9	10.9 ± 11.0	NS
Pre-implant IPSS	13.8± 8.7	7.2± 5.5	< 0.001*
Pretreatment TURP			
Yes	0	2 (2)	NS
No	13 (100)	112 (98)	
Neo-adjuvant hormonal treatment			
Yes	7 (54)	22 (19)	0.005*
No	6 (46)	92 (81)	
Pretreatment prostate volume (cm^3)	39.2 ± 12.2	37.5 ± 11.1	NS

Abbreviations: AUR = acute urinary retention; NS = not statistically significant; PSA = prostate specific antigen level; IPSS = international prostate symptom score; TURP = transurethral resection of the prostate.
Values are mean ± SD or number (percentage). * Statistically significant.

The mean scores and standard deviations of the HRQOL items at baseline and one month after treatment are listed in *Table 2*. Already at baseline, patients who eventually developed AUR had a statistically significant worse EORTC-PR25 and AUA urinary symptom score compared with patients without AUR. Also after one month, a significant worse urinary QOL was seen in patients who developed AUR. For all other HRQOL-items no statistically significant differences were seen between both groups at these time points.

Table 2 HRQOL items at baseline and 1 month after I-125 prostate brachytherapy, for patients who developed AUR and for patients who did not (no-AUR).

Parameter	AUR (n = 13), baseline	No-AUR (n = 114), baseline	Univariate analysis (*p*)	AUR (n = 13), 1 mo	No-AUR (n = 112), 1 mo	Univariate analysis (*p*)
RAND-36						
Physical functioning	88 (±17)	89 (±14)	NS	82 (±22)	84 (±19)	NS
Social functioning	92 (±11)	85 (±18)	NS	61 (±26)	74 (±23)	NS
Physical role restriction	88 (±17)	83 (±32)	NS	54 (±44)	65 (±40)	NS
Emotional role restriction	85 (±26)	79 (±33)	NS	92 (±20)	76 (±38)	NS
Mental health	87 (±11)	76 (±18)	NS	85 (±12)	79 (±16)	NS
Vitality	72 (±14)	70 (±20)	NS	65 (±22)	67 (±21)	NS
Pain	97 (±5)	94 (±13)	NS	81 (±21)	82 (±19)	NS
General health	71 (±14)	69 (±16)	NS	67 (±19)	67 (±17)	NS
Change in health	44 (±15)	48 (±17)	NS	37 (±26)	41 (±15)	NS
EORTC QLQ-C30						
Physical functioning	91 (±12)	92 (±13)	NS	89 (±13)	90 (±13)	NS
Role functioning	90 (±17)	92 (±17	NS	69 (±33)	80 (±24)	NS
Emotional functioning	87 (±13)	78 (±18)	NS	85 (±18)	84 (±17)	NS
Cognitive functioning	87 (±15)	85 (±16)	NS	90 (±13)	88 (±16)	NS
Social functioning	95 (±13)	91 (±15	NS	73 (±23)	81 (±20)	NS
Global health/QOL	81 (±10)	80 (±15)	NS	68 (±19)	74 (±15)	NS
Fatigue	17 (±14)	19 (±20)	NS	27 (±26)	25 (±22)	NS
Nausea and vomiting	4 (±14	0 (±2)	NS	1 (±5)	2 (±7)	NS
Pain	3 (±6)	7 (±14)	NS	23 (±28)	16 (±17)	NS
Dyspnea	10 (±16)	11 (±19)	NS	17 (±30)	12 (±22)	NS

Continued ►

Insomnia	18 (±26)	20 (±27)	NS	46 (±40)	27 (±32)	NS
Appetite loss	5 (±18)	3 (±12)	NS	0 (±0)	4 (±13)	0.002†
Constipation	5 (±18)	2 (±8)	NS	10 (±28)	14 (±24)	NS
Diarrhoea	10 (±21)	5 (±14)	NS	10 (±16)	13 (±22)	NS
Financial difficulties	3 (±9)	1 (±5)	NS	3 (±9)	4 (±12)	NS
EORTC QLQ-PR25						
Urinary symptoms	22 (±14)	11 (±11)	0.002*	56 (±26)	38 (±22)	0.007*
Bowel symptoms	1 (±2)	3 (±5)	NS	10 (±15)	8 (±11)	NS
Treatment-related sympt.	11 (±12)	6 (±9)	NS	8 (±7)	8 (±9)	NS
Sexual functioning	27 (±24)	35 (±26)	NS	22 (±26)	25 (±22)	NS
Sexual activity	74 (±25)	77 (±24)	NS	63 (±24)	61 (±25)	N
AUA, urinary symptoms	15 (±20)	0 (±15)	0.004*	52 (±31)	33 (±27)	0.01*
IPSS	14 (±9)	7 (±5)	<.001*	28 (±7)	19 (±10)	0.001*

Abbreviations: HRQOL = health-related quality of life; AUR = acute urinary retention; RAND-36 = RAND-36 generic health survey; NS = not statistically significant; EORTC QLQ-C30 = cancer-specific European Organization for Research and Treatment of Cancer core questionnaire; EORTC QLQ-PR25 = tumor-specific EORTC prostate cancer module; AUA = american urological association symptom index; IPSS = international prostate symptom score.
Values are mean ± SD. All scales range from 0 to 100, except for IPSS (0–35). In RAND-36, higher score represents better health; in EORTC QLQ-C30 and QLQ-PR25, higher score represents more symptoms or a better level of functioning or quality of life.
† Equal variances not assumed (according to Levene's test for equality of variances). * Statistically significant.

Figure 1 shows the mean change over time in urinary symptom score (EORTC-PR25) for patients with and without AUR up to 6 years after treatment. Patients who developed AUR had a worse urinary QOL at all time points. To assess the impact of AUR on HRQOL over the whole period (6 years), a repeated measurement analysis was performed. Over the whole period, the mean urinary symptom score of patients who developed AUR was 13.0 points worse compared with patients without AUR (95% confidence interval [CI], 5.6 to 20.3) ($p < 0.001$). After correction for differences in baseline values, there was still a significant difference between both groups, (mean difference 6.8 points; 95% CI, -0.25 to 13.9) ($p = 0.05$). To assess whether at 6 years posttreatment the patient's HRQOL had returned to baseline values, we compared urinary symptom scores at 6 years with baseline scores. No statistically significant differences were seen between 6 years posttreatment and baseline for AUR or no-AUR patients.

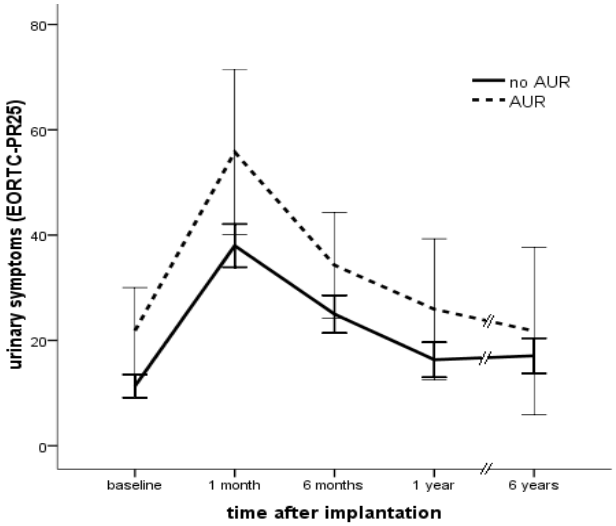

Figure 1 EORTC QLQ-PR25 urinary symptom scores (mean and 95% confidence intervals) up to six years after I-125 prostate brachytherapy for patients who developed acute urinary retention (AUR) ($n = 13$) and who did not (no-AUR) ($n = 114$). A higher score represents more symptoms or more problems.

The same change over time was seen for the AUA-urinary symptom score (*Figure 2*). Repeated measurement analysis over the whole period showed a 15.7-point worse mean AUA-urinary symptom score for patients who developed AUR compared with patients without AUR (95% CI, 5.9 to 25.5) ($p = 0.001$). After correction for baseline values, the mean difference was 8.3 points (95% CI, -1.4 to 15.1) ($p = 0.018$). Also for AUA-urinary symptoms, the symptoms had returned to baseline values at 6 years after treatment for AUR and no-AUR patients.

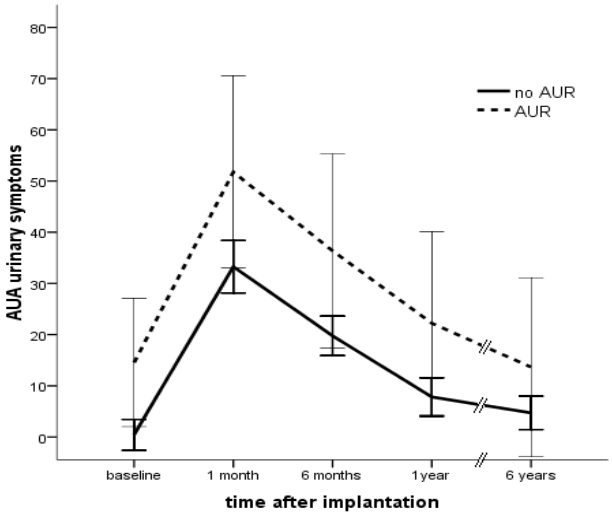

Figure 2 AUA urinary symptom scores (mean and 95% confidence intervals) up to six years after I-125 prostate brachytherapy for patients who developed acute urinary retention (AUR) (*n* = 13) and who did not (no-AUR) (*n* = 114). A higher score represents more symptoms or more problems.

Figure 3 shows the mean change over time in global-QOL scores (EORTC QLQ-C30) for patients with and without AUR up to 6 years after treatment. At baseline, there was no difference in global-QOL between both groups. However, after treatment, patients who developed AUR had worse global-QOL scores compared with patients without AUR. Repeated measurement analysis over the whole period (6 years) showed a 6.7-point worse mean global-QOL score for patients with AUR compared with patients without AUR (95% CI, -13.3 to -0.20) ($p = 0.043$).

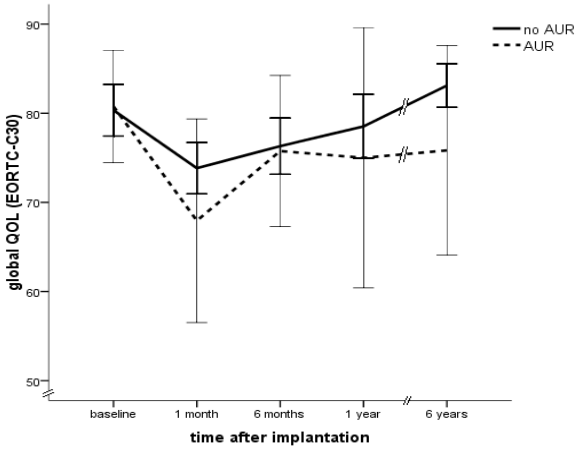

Figure 3 EORTC QLQ-C30 global-QOL scores (mean and 95% confidence intervals) up to six years after I-125 prostate brachytherapy for patients who developed acute urinary retention (AUR) (*n* = 13) and who did not (no-AUR) (*n* = 114). A higher score represents a better QOL.

In an explorative multivariable logistic regression analysis, pretreatment IPSS (OR 1.14; 95% CI, 1.04 to 1.24) ($p = 0.004$) and neo-adjuvant HT (OR 4.0; 95% CI, 1.11 to 14.2) ($p = 0.034$) were predictors of AUR. Per unit increase in baseline IPSS, the risk of AUR was 1.14-fold higher and in patients treated with neo-adjuvant HT the risk was 4.0-fold higher. The discriminative value (ROC area) of pretreatment IPSS and HT to predict the development of AUR was 0.78 (95% CI, 0.64 to 0.92). The addition of pretreatment urinary QOL (EORTC PR-25 urinary symptom score) and global-QOL (EORTC QLQ-C30) did not increase the discriminative power of the model (ROC area 0.79) (*Figure 4*).

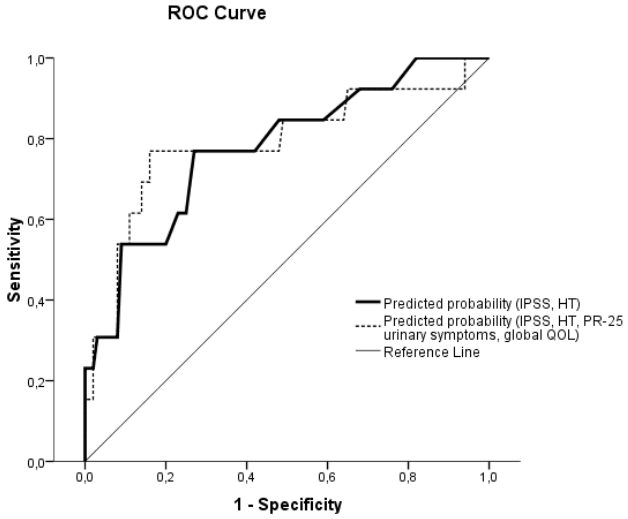

Figure 4 Receiver operating characteristic (ROC) curves for the predictability of AUR for pretreatment IPSS and neo-adjuvant hormonal treatment (black line) and after the addition of PR-25 urinary symptoms and EORTC-C30 global-QOL to the model (dotted line). The areas under the curves are 0.78 (IPSS, HT) and 0.79 (IPSS, HT, PR-25 urinary symptoms, global-QOL).

Discussion

To our knowledge, this is the first study describing the impact of AUR after I-125 PB on long-term HRQOL, by the use of validated HRQOL questionnaires. In our series, the AUR rate was 10.2%, which is comparable to other published rates (6% to 34%) (6-11). In this study, we showed that AUR not only causes acute morbidity, but also negatively influences HRQOL over a posttreatment period of 6 years. These results strengthen the importance to prevent AUR.

Urinary QOL was measured by the EORTC-PR25 and the AUA questionnaires. Already at baseline, there was a significant difference in urinary QOL scores between patients who developed AUR and patients who did not, which means these items might be predictors of AUR. The difference in urinary QOL scores

between both groups persists up to 6 years after treatment, which indicates the negative impact of AUR on long-term urinary symptoms. Even after adjustment for baseline values, the difference remained statistically significant and of clinical importance. The peak in urinary symptoms and the decline in HRQOL at one month after treatment were already described in our previous paper (16). We also showed that at 6 years posttreatment the urinary symptoms had returned to baseline values for both AUR and no-AUR patients. So, although AUR patients have more acute urinary symptoms, they are likely to return to baseline values at 6 years. However, it is important to note that these baseline values are higher than for no-AUR patients.

The worsened urinary QOL in patients who developed AUR can be explained by the known short- and long-term problems associated with AUR. Ikuerowo *et al.* (13) described several side effects associated with prolonged catheterization, including urethral/suprapubic pain, bleeding, loss of dignity, loss of job, lack of sexual intercourse, peri-catheter leakage of urine and recurrent urinary tract infection. Unhappiness was reported by 85% of the patients and furthermore, there were considerable costs associated with prolonged catheterization. With a mean follow-up of 44.8 months, Merrick *et al.* (25) showed that a TURP after prostate brachytherapy results in diminished urinary QOL, measured by IPSS and Expanded Prostate Cancer Index Composite (EPIC) scores. Anderson *et al.* (25) recommended conservative management for AUR occurring until at least 1 year after the implantation procedure, because AUR occurring during the first year usually resolves on its own, and a TURP after PB is associated with long-term urinary incontinence.

Since an overall HRQOL sum-score of the RAND-36 or the EORTC QLQ-C30 questionnaire does not exist, we used the item 'global-QOL' (EORTC-C30) as a measure of HRQOL, which would best reflect overall HRQOL (oral communication N. Aaronson, Ph.D., Amsterdam, The Netherlands). Our data showed that over the whole follow-up period of 6 years, global-QOL was significantly worse in patients who developed AUR. Long-term diminished global-QOL could be explained by long-term urinary problems associated with AUR, an indwelling catheter or a post-implant TURP. In contrast to the urinary symptom scores, no difference in baseline global-QOL scores was seen between both groups. This means that not only worse IPSS scores are responsible for diminished HRQOL, but that also the psychological and emotional burden of AUR and catheterization influences HRQOL.

The second aim of our study was to analyze whether pretreatment HRQOL can add to the known predictors to predict AUR after I-125 PB. In order to prevent AUR, several groups already identified important risk factors. Published pretreatment factors found to be predictive on multivariable analysis are IPSS

(6;8;11), HT (6;9), prostate volume (9) and diabetes (8). In our small series, we also found an association between pretreatment IPSS and AUR, and between neo-adjuvant HT and AUR.

Per unit increase in baseline IPSS, we found the risk of AUR to be 1.3-fold higher, which gave an 11% probability of developing AUR if IPSS is 10 and a 34% probability if IPSS is 20. These percentages are in accordance with other published data. Terk *et al.* (6) also found pretreatment IPSS to be predictive of AUR. In their series of 251 patients, 29% required catheterization if baseline IPSS was >20 compared with 2% if it was <10. Bucci *et al.* (8) showed that the risk of AUR in patients with baseline IPSS of 0-5, 6-15 and >15 was 10%, 17%, and 33%, respectively. Keyes *et al.* (11) found the incidence of AUR to be 3 times higher in patients with IPSS > 16 compared to IPSS <5 (21% vs. 8%). The most reasonable explanation for this increased probability of developing AUR in patients with high baseline IPSS scores, is that IPSS reflects the degree of pre-existent obstruction. If a certain degree of obstruction is present before implantation, additional trauma and edema after the implant may be enough to overcome the compensatory mechanism of the detrusor muscle and result in AUR.

In patients treated with neo-adjuvant HT, we found the risk of developing AUR to be 4.0-fold higher compared with patients without HT. Patients treated with HT had a 23% risk of developing AUR compared with 6% for patients without HT. Crook *et al.* (9) also found an association between prior hormone use and AUR. In their series of 150 patients, 55% of patients with AUR had neo-adjuvant HT compared with 27% of patients without AUR. Terk *et al.* (6) demonstrated a 14% risk of AUR after neo-adjuvant HT in combination with palladium brachytherapy compared with <1% in patients without HT. For patient with HT and IPSS ≥ 10, the risk of AUR was even 37%. Possible explanations for an increased risk of AUR after neo-adjuvant HT can be an incomplete volume reduction effect of the prostate after HT in combination with pre-existing urinary symptoms, or median lobe obstruction which is thought to be poorly responsive to HT (6;9).

The power of the prediction model, including pretreatment IPSS and neo-adjuvant HT, to distinguish between patients who will and who will not develop AUR was fairly good (ROC area 0.78). The addition of global-QOL (EORTC-C30) and PR-25 urinary QOL to this model did not significantly increase the discriminative power of the model (ROC area 0.79). Therefore, we conclude that HRQOL questionnaires, measured by RAND-36, EORTC-C30 and EORTC-PR25, might not add significantly to the known predictors of AUR. This conclusion should be considered with caution since the patient number was low and the power of the model was limited. In ongoing research, we will further explore risk factors of AUR.

This study has several limitations. First, the study describes the experience of a single center. Morbidity may vary from center to center depending on treatment techniques. However, our AUR rate was comparable with other published rates. Second, the number of patients with AUR is only 13. This limits the allowed number of predictors in the prognostic model and the power of the model. Third, the TURP rate under AUR patients was high compared to other published rates. This might depend on a between-center difference in TURP indications. The effect of a TURP on HRQOL can be two-sided. It can negatively influence QOL by the physical and emotional impact of undergoing an operation or by the possible long-term morbidity associated with a TURP, like urethra strictures and urinary incontinence. On the other hand, a TURP is done to relieve severe urinary symptoms, which also might have a positive impact on HRQOL.

Conclusion

We demonstrated that AUR after I-125 prostate brachytherapy has a significant negative impact on the patient's short- and long-term HRQOL. Both urinary symptom scores and global-QOL measures are worse in patients with AUR compared to patients without AUR up to 6 years after treatment. Prior knowledge of an individual's relative risk of AUR would be useful in counseling patients before the procedure. Although pretreatment HRQOL measures, using RAND-36, EORTC-C30 and EORTC-PR25 only add limited prognostic information and therefore have no role in prevention of AUR, validated HRQOL questionnaires are of great value in evaluating the patient's perception of HRQOL after I-125 PB. Since long-term diminished HRQOL after AUR is demonstrated here, further research on predictors of AUR should be advocated.

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Chapter 5

The influence of dose on the risk of acute urinary retention after I-125 prostate brachytherapy

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Abstract

Purpose

To assess the influence of dose on the risk of acute urinary retention (AUR) after Iodine-125 (I-125) prostate brachytherapy.

Methods and Materials

Between January 2005 and December 2008, 714 consecutive patients with localized prostate cancer were treated with I-125 prostate brachytherapy at our department. All patients completed four imaging studies: magnetic resonance imaging (MRI) before treatment and four weeks after treatment, and intraoperative 3-dimensional transrectal ultrasound (TRUS) before and after implantation. The evaluated treatment and dosimetric parameters included: prostate volume, number of needles and seeds used, intra- and postoperative prostate edema, V_{100}, V_{150}, V_{200}, and D_{90} for prostate, and V_{100}, V_{150}, V_{200} for urethra. The development of AUR was prospectively recorded. Logistic regression analysis was used to examine which factors were associated with AUR.

Results

Fifty-seven (8.0%) patients developed AUR. On univariate analysis, the following treatment and dosimetric factors were significantly associated with AUR: IPSS score (odds ratio [OR] 2.07, per 10-point increase) pre-implant prostate volume (OR 1.06), postimplant prostate volume (OR 1.04), number of needles used (OR 1.09), and number of seeds used (OR 1.03). On multivariate analysis, the only independent predictive factors for AUR were: pretreatment prostate volume (OR 1.05) and IPSS score (OR 1.76, per 10-point increase). Patients with a pretreatment prostate volume of >35 cm^3 had a 10.4% risk of developing AUR compared with 5.4% for prostate volumes ≤35 cm^3. There was no association between any of the dosimetric parameters and the development of AUR.

Conclusion

Radiation dose, within the range studied, does not influence the risk of AUR after I-125 prostate brachytherapy. Prostate volume and IPSS score were the most important predictors of AUR.

Introduction

Iodine-125 (I-125) prostate brachytherapy is a common treatment modality in localized prostate cancer. It shows excellent tumor control rates (1-3), with long-term quality of life (QOL) scores not significantly different from baseline QOL scores (4). Adverse events after prostate brachytherapy are generally mild, but the most predominant severe acute toxicity is acute urinary retention (AUR) requiring catheterization. Published AUR rates vary from 6% to 34% (5-10). Patients who develop AUR experience a significantly worse QOL compared to patients without AUR, which does not improve after 6 years of follow-up in most patients (11). Therefore, risk factors that predispose to AUR should be identified.

Several pre-implant risk factors for the development of AUR have been identified, including prostate volume (8,10,12), International Prostate Symptom Score (IPSS) (5,7,10,11), and neo-adjuvant hormonal treatment (5,8,11). Most studies focus on clinical factors. It is also hypothesized that urinary obstruction might be related to dose. However, the number of studies assessing the influence of dose on the risk of AUR is limited (6-8,10,13-17), and delineation was performed on inferior imaging modalities as ultrasound and computed tomography (CT). To accurately delineate the prostate, magnetic resonance imaging (MRI) is required for higher soft tissue contrast (18).

The aim of this study was to assess the influence of dose on the development of AUR in a large prospective cohort of patients treated with I-125 prostate brachytherapy. For dose evaluation, we performed intraoperative 3-dimensional (3D) transrectal ultrasound (TRUS), and at 4 weeks postimplant both computed tomography (CT) and magnetic resonance imaging (MRI) for accurate delineation. To our knowledge, this is the first study that investigates the relationship between AUR and dose using MRI-based prostate delineation. Identification of any relation between dose and AUR might lead to the opportunity of intra-operative dosimetric modifications in order to prevent AUR.

Methods and materials

Patients

Between January 2005 and December 2008, 714 consecutive patients with localized prostate cancer were treated with I-125 implantation at our department according to the GEC ESTRO guidelines (19). Eligibility criteria for prostate brachytherapy were: organ confined prostate cancer, clinical tumor stage <T3, Gleason sum-score <8, and prostate volume ≤50 cm^3. Six months of neo-adjuvant hormonal therapy with a LHRH agonist was given to patients presenting with a prostate volume >50 cm^3 (n = 137). No patients received supplemental external-beam irradiation.

Technique

All patients completed four imaging studies: 1.5 or 3.0 Tesla MRI before and four weeks after treatment, and intraoperative 3D TRUS imaging before and after needle insertion. Delineation of the prostate and the urethra was performed on pretreatment MR images. The pre-implant MR dataset with prostate contours was fused to the intraoperative 3D TRUS dataset to aid in intraoperative prostate delineation, and manually adapted during treatment for the actual prostate contour. Image fusion was performed on the Sonographic Planning of Oncology Treatment (SPOT) system (Nucletron B.V., Veenendaal, The Netherlands) by manual translation and rotation of the MR dataset until it matched the TRUS dataset according to visual inspection.

The UMC Utrecht prostate brachytherapy procedure has been previously described (20;21). All patients were treated under spinal anesthesia in lithotomy position. Two locking needles were inserted before the pretreatment TRUS image was acquired. The entire prostate volume was calculated from the 3D delineations on 1 mm slices. The needles were inserted transperineally under TRUS guidance. The I-125 seeds were delivered automatically using the Fully Integrated Real-time Seed Treatment (FIRST) system (Nucletron B.V., Veenendaal, The Netherlands) or manually using stranded seeds (Oncura UK; IBt, Belgium; Best Medical, USA). Patients were randomly assigned to either loose seeds or stranded seeds (20;21). Average seed strength at time of implantation was 0.51 U (1U = 1μGym^{2}h^{-1}). Online intraoperative treatment planning was performed using the SPOT system. Our criteria for prostate implants were: the percentage prostate volume receiving the prescribed dose of 144 Gy >95% and about 2/3 and 1/3 of the prostate volume receiving 150% and 200% of the prescribed dose; D_{90} above 160 Gy; the urethra dose ≤ 150% and the rectal dose ≤ 100% of the prescribed dose. The entire procedure takes around 90 minutes. The time interval between the two TRUS images was approximately 30 minutes. All three radiation oncologists have at least 5 years of experience and perform at least 60 implantations a year.

The MR images were acquired using a 1.5 or 3.0 Tesla MR scanner (Philips Medical Systems, The Netherlands) and the protocol consisted of T1-weighted axial spin echo (SE) images (1 x 1 x 4 mm^3 resolution), T2-weighted axial turbo spin echo (TSE) images (1 x 1 x 4 mm^3 resolution) and a balanced fast field echo (FFE) 3D acquisition (0.7 x 0.7 x 1 mm^3 resolution) with water selection. The prostate was delineated on the T2-weighted SE images, after which prostate contours were copied to the high resolution FFE dataset. Intraoperative 3D TRUS datasets were acquired using a 8585 biplane US probe connected to a Leopard 2000 US scanner (Bruel & Kjaer, Denmark) by rotating the probe through the rectum over an angle of 220° and image acquisition at each step of 1°.

Dosimetric parameters

The evaluated TRUS-based treatment and dosimetric parameters included: prostate volume before and after implantation, number of needles used, number of seeds used, percentage prostate volume receiving 100%, 150% and 200% of the prescribed dose of 144 Gy (V_{100}, V_{150} and V_{200}, respectively), and minimal dose received by 90% of the prostate volume (D_{90}). The ratio of postimplant and pre-implant prostate volume was used as a surrogate of intraoperative edema. Four weeks after implantation, MRI and computed tomography (CT) scans (Philips, The Netherlands) were performed for postplanning dose evaluation (*Figure 1*).

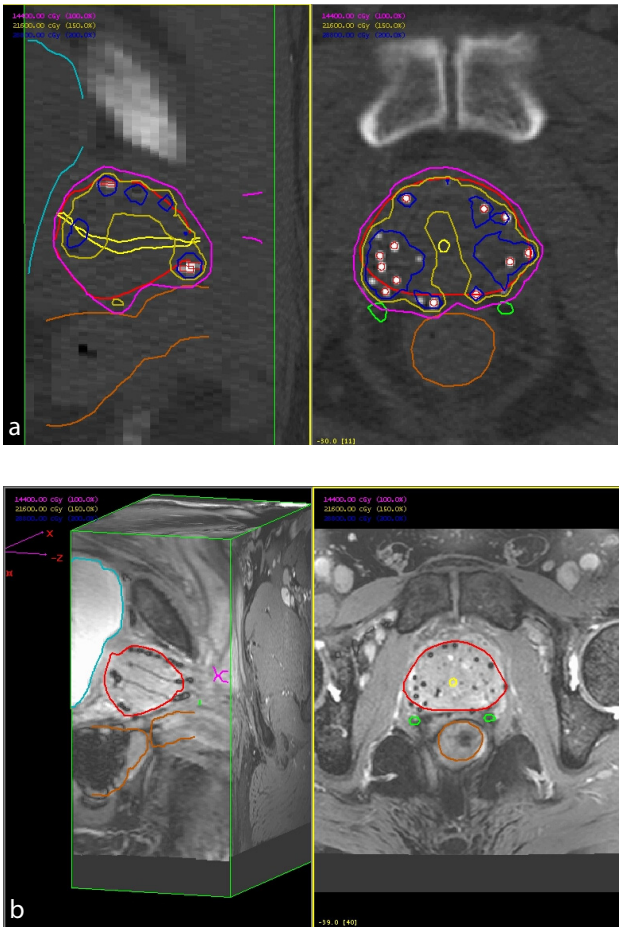

Figure 1 Registration between magnetic resonance imaging (MRI)-based seed localization (a) and computed tomography (CT)-based seed localization (b). Delineation was performed on MRI (a). Dose distribution is shown in Fig. b. Delineation: red = prostate contour; yellow = urethra; brown = rectum; green = neurovascular bundle; and light blue = bladder.
Isodose lines (a): pink = 144 Gy (100%); yellow = 216 Gy (150%); and dark blue = 288 Gy (200%).

Registration between CT-based seed localization and MRI-based seed localization was done with the SPOT image fusion module. Prostate delineation was performed on MRI. The evaluated MRI-based treatment and dosimetric parameters included: prostate volume before and at 4 weeks after implantation, prostate V_{100}, V_{150}, V_{200}, and D_{90}. The ratio of 4week-postimplant and pre-implant prostate volume was used as a surrogate of postimplant prostate edema. The urethra was delineated on MR images and the urethra V_{100}, V_{150} and V_{200} were calculated.

Follow-up

After implantation, patients stayed in the hospital for one night, and were discharged the next day as soon as they were able to void spontaneously. Each patient received an α-blocker for one month and as long as urinary symptoms persisted. No routine steroids were used.
According to our follow-up protocol, patients were seen alternately by the radiation oncologist and the urologist at 1, 3, 6, 9, and 12 months after treatment, and twice annually thereafter. Minimum follow-up (for patients treated in December 2008) was 6 months. IPSS scores, toxicity data and intervention data were collected prospectively and recorded in a database. AUR was defined as any need for urinary catheterization within 3 months after implantation (22). If retention was persistent, sometimes a TURP was performed to relieve obstruction. TURPs were not performed within the first year after implantation, because it is known that AUR usually resolves on its own and that a TURP after prostate brachytherapy is associated with long-term urinary incontinence (23).

Statistical analysis

A commercial statistical package of social sciences (SPSS 16.0; SPSS, Chicago, IL) was used for statistical analysis of the data. The evaluated pretreatment clinical factors included: age, clinical tumor stage, Gleason score, initial prostate specific antigen, pretreatment IPSS, neo-adjuvant hormonal treatment, and pretreatment transurethral resection of the prostate. These factors were compared between the two groups (AUR versus no-AUR) using independent samples *t*-tests. Categorical variables were analyzed using χ^2-tests.
Univariate logistic regression analysis was performed to examine the associations between treatment or dosimetric parameters and AUR. The evaluated parameters included: pretreatment prostate volume, number of needles and seeds used; MRI and TRUS-based V_{100}, V_{150}, V_{200}, and D_{90} for prostate, MRI-based V_{100}, V_{150}, V_{200} for urethra; TRUS-based ratio of postimplant and pre-implant prostate volume (surrogate for intraoperative edema), and MRI-based

ratio of 4week-postimplant and pre-implant prostate volume (surrogate for postoperative edema).
To identify the most important treatment and dosimetric predictors for the risk of AUR, we performed multivariate logistic regression analyses (MVA). Factors included in the MVA were: pre-implant prostate volume, number of needles used, ratio of postimplant and pre-implant prostate volume (surrogate of postimplant prostate edema), prostate V_{100}, prostate D_{90}, IPSS and neo-adjuvant HT. This set of potential associated factors is chosen based on literature, in stead of using the factors significant on univariable analysis automatically as input for the MVA, and because of a high correlation (>0.8) between certain variables (e.g. seeds and volume; seeds and needles). Predictors were selected with manual backward stepwise selection using $p = 0.20$ (Wald statistic) (24). A *p*-value of <0.05 was considered statistically significant.

Results

Of the 714 patients, 57 (8.0%) developed AUR after implantation. The median time to AUR was 30 days (range, 0-90 days). Patients received a urinary catheter alone (n=20), or a catheter followed by insertion of a suprapubic catheter (n=26). Another 11 patients performed intermittent self-catheterization. The median duration of catheter dependency was 37 days (range, 2-140 days). Nineteen (33.3%) of the 57 patients did not recover spontaneous voiding and eventually required a TURP to relieve obstruction. The median time to TURP was 15 months (range, 7-22 months).
Pretreatment clinical characteristics for patients who developed AUR and patients without AUR are shown in *Table 1*. Patients with AUR had a statistically significant higher pretreatment IPSS score (mean 13.8; standard deviation [SD] ± 8.7) compared with patients without AUR (mean 7.2; SD ± 5.5).
There was a clinically relevant difference in the use of neo-adjuvant hormonal therapy between both groups (28% of patients with AUR versus 18% of patients without AUR), although not statistically significant. Other clinical characteristics were comparable between both groups. Mean age was 65 years (SD ± 6.4). Tumor stage was T1 in 70% and T2 in 30% of patients.
To assess whether any treatment or dosimetric parameter was associated with the development of AUR, logistic regression analyses were applied (*Table 2*). Factors significant on univariable analysis included: pre- and posttreatment prostate volume on ultrasound (odds ratio [OR] 1.05; 95% confidence interval [CI] 1.02 to 1.08, and OR 1.04; 95% CI, 1.01 to 1.07, respectively), number of needles used (OR 1.09; 95% CI, 1.02 to 1.17), number of seeds used (OR 1.03; 95% CI, 1.01 to 1.05), pretreatment prostate volume on MRI (OR 1.06; 95% CI,

Table 1 Pretreatment patient characteristics (n = 714) for patients who developed AUR and for patients who did not (no-AUR).

Characteristic	AUR (n = 57)	No AUR (n = 657)	Univariate analysis (*p*)
Mean age at implantation (y)	65.8 ± 6.6	65.0 ± 6.4	NS
Tumor stage			
T1	41 (71.9)	457 (69.6)	NS
T2	16 (28.1)	200 (30.4)	
Gleason sum score			
<7	43 (76.8)	504 (76.7)	NS
7	13 (23.2)	151 (23.0)	
7>	0 (0)	2 (0.3)	
Mean initial PSA (ng/mL)	9.2 ± 4.2	9.9 ± 5.3	NS
Pretreatment IPSS			
0–5	8 (14.1)	249 (37.9)	<.001*
6–10	14 (24.6)	185 (28.2)	
11–20	32 (56.1)	211 (32.1)	
>20	3 (5.3)	12 (1.8)	
Pretreatment TURP			
Yes	1 (1.8)	10 (1.5)	NS
No	56 (98.2)	647 (98.5)	
Neoadjuvant hormonal therapy			
Yes	16 (28.1)	121 (18.4)	NS
No	41 (71.9)	536 (81.6)	

Abbreviations: AUR = acute urinary retention; NS = not statistically significant; PSA = prostate-specific antigen level; IPSS = international prostate symptom score; TURP = transurethral resection of the prostate.
Data presented as mean ± SD or numbers of patients, with percentages in parentheses* statistically significant.

1.02 to 1.09) and 4week-posttreatment prostate volume on MRI (OR 1.04; 95% CI, 1.01 to 1.07). However, when we adjusted the treatment factors (needles/seeds) for the potential confounder volume, the effects diminished and lost significance (OR 1.03 and 1.01, respectively).

None of the dosimetric parameters, including V_{100}, V_{150}, V_{200}, and D_{90} for the prostate as well as for the urethra, were associated with the development of AUR. Measurements of TRUS-determined intraoperative prostate edema and MRI-determined postoperative prostate edema were also not associated with AUR. The mean intraoperative increase in prostate volume was 1.6 cm^3 (SD ± 2.3) for AUR patients and 1.7 cm^3 (SD ± 1.7) for no-AUR patients. The mean postoperative increase in prostate volume was 2.9 cm^3 (SD ± 5.7) for AUR patients and 2.6 cm^3 (SD ± 5.6) for no-AUR patients.

On multivariate analysis, independent predictive factors for AUR were: pretreatment prostate volume (OR 1.05; 95% CI, 1.01 to 1.09) and IPSS score

(OR 1.76 per 10-point IPSS increase; 95% CI, 1.25 to 2.49). Patients with a pretreatment prostate volume of >35 cm^3 had a 10.4% risk of developing AUR compared with 5.4% for prostate volumes ≤35 cm^3.

Discussion

To our knowledge, this is the largest study thus far assessing the influence of 3D MRI-based dosimetric parameters on the risk of AUR after I-125 prostate brachytherapy. In a prospective cohort of 714 patients, we found no association between any of the dosimetric parameters and the occurrence of AUR. In multivariate analysis, pretreatment prostate volume was the only independent predictive factor for the risk of AUR. Our results are in accordance with other published studies (6-8,10,13-17). *Table 3* summarizes these nine studies, including the evaluated dosimetric parameters. Although the type and number of examined dosimetric parameters differed between studies, most of these studies did not found an association between dosimetric parameters and the risk of AUR. However, all these studies, except one, are limited by the small number of patients, which limits the strength of evidence.

In the large study of Keyes *et al.* (10) (N = 805) higher values of prostate V_{100} and V_{150} were associated with a *lower* risk of catheterization. Unfortunately, this inverse relation could not be explained. In accordance to our results, there was no association between the other examined dosimetric parameters, i.e. prostate D_{90} or V_{200}, and AUR. Like most other studies (*Table 3*), the study is limited by the use of CT scans only for prostate delineation and 4week-postoperative dose evaluation. Rasch *et al.* (25) showed that CT-derived prostate volumes are larger than MR-derived volumes, especially towards the seminal vesicles and the apex of the prostate, which might influence delineation accuracy (*Figure 1*) and hence the study results.

The reason that dose does not influence the risk of AUR might be that, given the I-125 half-life of 60 days, it takes a few months before a substantial dose has been delivered to the prostatic tissue. Because most patients developed AUR within the first month after implantation (median time to AUR was 30 days), dose is unlikely an important risk factor. Furthermore, with the use of real-time TRUS-guided needle insertion, we gave special attention to minimize the placement of seeds near the urethra. This avoids the creation of central high dose regions in the area of the urethra. Using the current guidelines (19) with the urethra dose ≤ 150% of prescribed dose, dose seems not to contribute to the risk of AUR. Still, theoretically, dose to specific regions of the prostate, the urethra, the bladder neck or the lower sphincter might contribute to obstruction and the subsequent risk of AUR. In ongoing research, we will further explore this.

Table 2 Univariate and multivariate analyses of TRUS- and MRI-based dosimetric parameters and the development of AUR in 714 patients.

	AUR (n = 57)	No AUR (n = 657)	UVA		MVA†	
Factor	**Mean (±SD)**	**Mean (±SD)**	***(p)***	**OR (95% CI)**	***(p)***	**OR (95% CI)**
Ultrasound dosimetry						
Pre-implant volume (cm^3)	38.9 (9.1)	35.1 (8.9)	.003*	1.05 (1.02-1.08)		
Postimplant volume (cm^3)	40.5 (9.0)	36.8 (9.2)	.004*	1.04 (1.01-1.07)		
Volume change (cm^3)	1.6 (2.3)	1.7 (1.7)	.698			
Postimplant/preimplant prostate volume ratio^	1.044 (0.06)	1.050 (0.06)	.453			
Needles	25.3 (3.5)	24.0 (3.8)	.014*	1.09 (1.02-1.17)	n.s.	
Seeds (n)	78.0 (11.7)	72.9 (13.2)	.005*	1.03 (1.01-1.05)		
V_{100}, prostate (%)	98.4 (1.8)	98.0 (2.4)	.300			
V_{150}, prostate (%)	71.1 (7.4)	71.2 (7.8)	.913			
V_{200}, prostate (%)	31.2 (5.4)	31.2 (7.3)	.951			
D_{90}, prostate (Gy)	184.6 (13.6)	183.1 (14.3)	.424			
Postimplant MRI dosimetry						
Pre-implant volume (cm^3)	38.2 (7.9)	34.4 (8.3)	.002*	1.06 (1.02-1.09)	.009*	1.05 (1.01-1.09)
Post-implant volume (cm^3)#	41.1 (10.3)	36.9 (9.9)	.003*	1.04 (1.01-1.07)		
Delta volume (cm^3)	2.9 (5.7)	2.6 (5.6)	.655			
Ratio of postimplant and pre-implant prostate volume‡	1.081 (0.16)	1.082 (0.16)	.970		n.s.	
V_{100}, prostate (%)	91.5 (12.3)	93.2 (6.0)	.079		n.s.	
V_{150}, prostate (%)	69.5 (13.1)	71.5 (11.5)	.211			
V_{200}, prostate (%)	37.4 (9.7)	39.3 (11.9)	.234			
D_{90}, prostate (Gy)	161.6 (27.4)	164.3 (28.6)	.489		n.s.	

Continued ►

Urethra volume (cm^3)	0.43 (0.09)	0.42 (0.15)	.538			
V_{100}, urethra (%)	88.8 (8.7)	89.1 (8.9)	.815			
V_{150}, urethra (%)	48.2 (28.7)	54.0 (27.4)	.127			
V_{200}, urethra (%)	7.7 (12.1)	9.8 (14.6)	.283			
Clinical factors						
Pretreatment IPSS	13.8 (8.7)	7.2 (5.5)	.000*	2.07 (1.49-2.89)	.001*	1.76 (1.25-2.49)~
Neo-adjuvant HTψ			.079		n.s.	

Abbreviations: TRUS = transrectal ultrasound; MRI = magnetic resonance imaging; AUR = acute urinary retention ; UVA = univariate analysis; MVA = multivariate analysis; OR = odds ratio; CI = confidence interval ; V_{100}, V_{150}, V_{200} = percentage of prostate/urethra volume receiving 100%, 150% and 200% of prescribed dose, respectively; D_{90} = minimal dose received by 90% of prostate/urethra; other abbreviations as in Table 1.

† factors included in the MVA: pre-implant prostate volume, number of needles, ratio of postimplant and pre-implant prostate volume ratio, prostate V_{100}, prostate D_{90}, IPSS and neo-adjuvant HT.

* statistically significant

^ surrogate of intra-operative prostate edema

post-implant MRI was made at 4 weeks after implantation

‡ surrogate of postimplant prostate edema

~ per 10 points IPSS increase

ψ HT is dichotomous variable, see Table 1 for frequencies

Table 3 Summery of published studies evaluating the influence of dosimetric factors on the risk of AUR after I-125 prostate brachytherapy.

Series	Patients (n)	AUR rate (%)	Postimplant imaging	Evaluated parameters	Significant on UVA	Significant on MVA
Lee 2000 (6)#	91	12	CT	Prostate D_{50}, D_{80}, D_{90}, V_{125}, V_{150}, V_{200}, V_{250}, V_{300}; No. of needles	No. of needles	NP
Bucci 2002 (7)	282	15	CT	Prostate D_{90}, V_{100}, V_{150}, V_{200}; Max. and mean urethral dose; No. of seeds, No. of needles	Prostate V_{100}*, V_{150}*, V_{200}*, D_{90}*; Max. and mean urethral dose*, nr of needles	NS
Crook 2002 (8)	150	13	CT or CT+ MRI (n=52)	Prostate D_{90}, V_{100}, V_{150}, V_{200}; Max. and mean urethral dose; No. of seeds	No. of seeds	NS
Elshaikh 2003 (13)	402	10.9	CT	Prostate D_{90}, V_{100}, V_{150}, V_{200}, V_{300}, V_{400}	NS	NS
Williams 2004 (14)	173	19.7	CT	Prostate D_{90}, V_{100}, V_{150}, V_{200}; Urethral V_{100}, V_{150}, max. urethral dose, No. of needles	NS	NS
Henderson 2004 (15)	216	9.3	CT	Prostate D_{90}, V_{100}, V_{150}; Urethral D_{10}, D_{25}, D_{50}	NS	NP
Ohashi 2006 (16)#	227	5.3	CT	Prostate D_{90}, V_{100}, V_{150}, V_{200}; Urethral D_{10}, max. urethral dose, No. of needles, No. of seeds	No. of needles and seeds	No. of needles
Keyes 2006 (10)	805	12.7	CT	Prostate D_{90}, V_{100}, V_{150}, V_{200}, No. of needles, No. of seeds	Prostate V_{100}*, V_{150}*; No. of needles and seeds	No. of needles and seeds
Neill 2007 (17)	219	12.8	CT+MRI	Prostate D_{90}, V_{100}, V_{150}; Urethral D_{30}, V_{150}	Prostate V_{150}*; Urethral D_{30}*, V_{150}*	Urethral V150*
Present series	714	8.0	CT+MRI	Prostate D_{90}, V_{100}, V_{150}, V_{200}; Urethral V_{100}, V_{150}, V_{200}; No. of needles, No. of seeds	No. of needles and seeds	NS

Abbreviations: AUR = acute urinary retention ; UVA = univariate analysis; MVA = multivariate analysis; D_{30}, D_{50}, D_{80}, D_{90} = minimal dose received by 30%, 50%, 80% and 90% of prostate/urethra, respectively; V_{100}, V_{125}, V_{150}, V_{200}, V_{250} V_{300}, V_{400} = percentage of prostate/urethra volume receiving 100%, 125% 150%, 200%, 300% and 400% of prescribed dose, respectively; NP = not performed; NS = not statistically significant; no. = number; max. = maximal.
Some patients received supplemental external beam radiotherapy. * Inversely associated

Trauma might be more important than dose. Pathophysiologically, needles inserted into the prostate gland can cause tissue edema by mechanical trauma, bleeding, haemorrhage, or an inflammatory response. This might cause partial obstruction or even total compression of the urethra. This assumption is consistent with our results. In univariate analysis, we showed an association between the number of needles used and the occurrence of AUR (*Table 2*). However, after adjustment for prostate volume the effects diminished. Needle trauma alone has been found to be related to urinary retention in men undergoing transperineal procedures by Buskirk *et al.* (26). They showed that the number of biopsy cores was predictive for urinary retention. Several other studies found the number of needles used to be related to the risk of AUR after prostate brachytherapy (6,7,10,16). Furthermore, Eapen *et al.* (27) found the number of times each needle was repositioned to be significantly associated with urinary toxicity.

To examine the effect of edema, we determined intra- and postoperative prostate enlargement by TRUS and MRI respectively (*Table 2*). Interestingly, we found no association between the degree of prostate edema and the risk of AUR. Several other studies also failed to show an association (7,9,10,28). This might be due to methodological reasons. Like all other studies, we defined the ratio of prostate volume at 4 weeks posttreatment and pretreatment prostate volume as a surrogate for postoperative edema. However, it has been shown that for the majority of patients, prostate swelling has been resolved within 4 weeks after implantation (28,29). Therefore, by measuring prostate volume at 4 weeks posttreatment the maximal degree of edema will be missed, which might lead to misclassification and dilution of the effect. Furthermore, concerning TRUS-based intraoperative edema measurement, the second volume measurement (30 minutes later) might be too early to determine the maximal swelling.

On multivariate analysis, prostate volume was an independent predictive factor for AUR (*Table 2*). Several other studies also showed an increased risk of AUR in patients with large prostate volumes (8-10,15). This might be explained by a higher degree of pre-existent obstruction in patients with large prostates. If a certain degree of obstruction is present before implantation, additional trauma and edema after implantation may be enough to overcome the compensatory mechanism of the detrusor muscle and may result in AUR. Our results showed statistically significant higher IPSS scores in patients with AUR (mean 13.8) compared with patients without AUR (mean 7.2) (*Table 1*), which is consistent with this assumption. However, although prostate volume and IPSS score seem to be associated with each other, both factors were independent risk factors for AUR in our multivariate analysis.

Strengths of our study are the large patient samples, the wide range of evaluated dosimetric parameters, the use of combined CT and at MRI 4 weeks posttreatment for delineation and dose evaluation, and 3D prostate volume measures before, during and after treatment. However, there are some limitations to this study. First, the study describes the experience of a single center. Morbidity may vary from center to center depending on treatment techniques. Second, there was a spread in time to development of AUR. In literature, inconsistency exists concerning the definition of AUR. According to Trotti *et al.* (22), we defined AUR as any need for catheterization within 3 months after implantation. Some others reported AUR to occur mainly in the first month after implantation (8,10). Therefore, we performed an additional subanalysis on the patients who developed AUR within 1 month after implantation (n = 27). Also in this analysis, there was no association between dose and the development of AUR. Third, a relevant methodological aspect in the analysis of dosimetric parameters is the spread in data. If the ranges of examined parameters are small, a potentially association might be missed. However, in our opinion, the spread in our dosimetric data was large enough to find any possible association (e.g. D_{90} 161.6 Gy; SD ± 27.4).

Conclusion

In the present study, we assessed the influence of dosimetric parameters on the development of AUR after I-125 prostate brachytherapy. We concluded that dose, within the range studied, does not influence the risk of AUR. Therefore, we do not suggest intraoperative dose-limiting modifications (other than those stated in the recommendations (19)), because these do not warrant a reduced AUR risk. A large prostate volume and a high degree of pre-existent obstruction (IPSS), combined with additional trauma from implantation, might be the most important predictive factors for AUR after prostate brachytherapy.

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Chapter 6

Acute urinary retention after I-125 prostate brachytherapy in relation to dose in different regions of the prostate

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Abstract

Purpose

To assess the influence of dose in different prostate regions, and the influence of anatomic variation on the risk of acute urinary retention (AUR) after Iodine-125 (I-125) prostate brachytherapy.

Methods and Materials

In this case-control study, dosimetry and anatomy was compared between 50 patients with AUR (cases) and 50 patients without AUR (controls). Cases and controls were randomly selected from our database. The following structures were delineated on MRI: prostate, urethra, peripheral zone, transitional zone, apex, base, mid-prostate, lower sphincter and bladder neck. The dosimetric parameters analyzed were: D_{10}, D_{50}, D_{90}, V_{100}, V_{150} and V_{200}. The anatomic parameters analyzed were: prostate protrusion into the bladder, bladder overlap, urethra angle and urethra-bladder angle. The delineator was blinded to patient's AUR status. Logistic regression analysis was used to investigate the association of these factors with AUR.

Results

Dose delivered to different regions of the prostate was not significantly associated with the risk of AUR. Only the dose to the bladder neck was significantly associated with AUR (OR 1.13 per 10 Gy; 95% CI 1.02 to1.26; $p = 0.023$). Mean bladder neck D_{90} was 65 Gy in AUR-cases, versus 56 Gy in controls($p = 0.016$), and mean bladder neck D_{10} was 128 Gy versus 107 Gy, respectively ($p = 0.018$). Furthermore, on univariate analysis, a larger extent of bladder overlap and a larger extent of prostate protrusion were associated with a higher risk of AUR (OR 1.16; 95% CI 1.04 to 1.28; $p = 0.005$, and OR 1.83; 95% CI 1.37 to 2.45; $p < 0.001$, respectively). Mean extent of prostate protrusion was 3.5 mm in AUR-cases versus 1.0 mm in controls ($p < 0.001$). Odds ratios did not change substantially after adjustment for potential confounders. On multivariate analysis, the extent of prostate protrusion appeared to be a stronger risk factor for AUR than bladder overlap.

Conclusion

The risk of AUR is not associated with dose delivered to different regions of the prostate. However, a higher dose to the bladder neck and a larger extent of prostate protrusion into the bladder are risk factors for the development of AUR after I-125 prostate brachytherapy.

Introduction

Iodine-125 (I-125) prostate brachytherapy is a common treatment modality for localized prostate cancer. It shows excellent tumor control and survival rates (1-3) and is generally well tolerated (4,5). In a recent study, we showed that long-term (6 years after treatment) quality of life (QOL) after prostate brachytherapy was not significantly different from baseline QOL (6). However, patients who developed acute urinary retention (AUR) experienced a significantly worse QOL compared to patients without AUR, which did not improve on the long term in most patients (7).

AUR requiring catheterization is the most predominant severe acute toxicity after prostate brachytherapy. Published AUR rates vary from 6% to 34% (8-13). In literature, several attempts to identify risk factors for AUR have been made. Most studies have focused on pretreatment clinical factors. Prostate volume (11,13,14), International Prostate Symptom Score (IPSS) (7,8,10,13), and hormonal treatment (7,8,11) have shown to be independent predictors of AUR.

Moreover, it is hypothesized that urinary obstruction might also be associated with radiation dose. However, the published results are inconsistent. Some studies found a relation between dose and AUR (10,13,15), whereas others have not (9,11,16-20). Most of these studies focus on dose to the whole prostate gland, but, theoretically, dose to specific regions within the prostate, the urethra, the bladder neck or the lower sphincter might be more important to the development of AUR. Detailed delineation of these structures can provide information about prostate and bladder anatomy, which might also influence the risk of AUR. The number of studies concerning this detailed segmental prostate dosimetry is limited, and the delineation has been performed on inferior imaging modalities, like ultrasound and computed tomography (CT) (15,21-23). To accurately delineate the segmental structures, magnetic resonance imaging (MRI) is required (24).

It is important to identify potential associations between AUR and dose, because this might lead to the opportunity to make intraoperative dosimetric modifications for preventing AUR. Prevention of AUR will lead to improvement of the patient's QOL after prostate brachytherapy (7). In this study, we aimed to assess the influence of dose in different regions of the prostate and of MRI-delineated anatomic parameters on the risk of AUR after I-125 prostate brachytherapy.

Methods and materials

Patients

Between January 2005 and December 2008, 714 consecutive patients with localized prostate cancer were treated with I-125 seed implantation at our department. Implantations were performed according to the GEC-ESTRO guidelines (25). Eligibility criteria for prostate brachytherapy were: organ confined prostate cancer, clinical tumor stage < T3, Gleason sum-score < 8, and prostate volume < 50 cm^3. Six months of neo-adjuvant hormonal therapy with a LHRH agonist was given to patients presenting with a prostate volume > 50 cm^3 (n = 30). No patients received supplemental external-beam radiation.
After implantation, patients stayed in the hospital for one night, and were discharged the next day. Each patient received an α-blocker for one month and as long as urinary symptoms persisted. No routine steroids were used. According to our follow-up protocol, patients were seen alternately by the radiation oncologist and the urologist at 1, 3, 6, 9, and 12 months after treatment, and half-yearly thereafter. Minimum follow-up (for patients treated in December 2008) was 6 months. IPSS scores, toxicity data and intervention data were collected prospectively and recorded in a database. AUR was defined as any need for urinary catheterization within 3 months after implantation (26). Of the 714 patients, 57 patients (8.0%) patients developed AUR after implantation. Median time to AUR was 30 days (range, 0-90 days). For the present case-control study, 50 patients with AUR and 50 patients without AUR were randomly selected by using a statistical package of social sciences (SPSS 16.0; SPSS, Chicago, IL).

Treatment technique and imaging

All patients completed four imaging studies: 1.5 or 3.0 Tesla MRI before and four weeks after treatment, and intraoperative three-dimensional transrectal ultrasound (3D-TRUS) imaging before and after needle insertion. Delineation of the prostate and the urethra was performed on pretreatment MR images. The preimplant MR dataset with prostate contours was fused to the intraoperative 3D TRUS dataset to aid in intraoperative prostate delineation. Image fusion was performed on the Sonographic Planning of Oncology Treatment (SPOT) system (Nucletron B.V., Veenendaal, The Netherlands).
The University Medical Center Utrecht prostate brachytherapy procedure has been previously described (27;28). All patients were treated under spinal anesthesia in lithotomy position. Two locking needles were inserted before the pretreatment TRUS image was acquired. The entire prostate volume was calculated from the

3D delineations on 1 mm slices. The needles were inserted transperineally under TRUS guidance. The I-125 seeds were delivered automatically using the Fully Integrated Real-time Seed Treatment (FIRST) system (Nucletron B.V., Veenendaal, The Netherlands) or manually using stranded seeds (Oncura UK; IBt, Belgium; Best Medical, USA). Average seed strength at time of implantation was 0.51U (1U = 1μGym^{2}h^{-1}). Online intraoperative treatment planning was performed using the SPOT system. Our criteria for prostate implants were: the percentage prostate volume receiving the prescribed dose of 145 Gy >95% and about 2/3 and 1/3 of the prostate volume receiving 150% and 200% of the prescribed dose; D_{90} above 160 Gy; the urethra dose ≤ 150% of the prescribed dose. The entire procedure took approximately 90 minutes. The time interval between the two TRUS images was approximately 30 minutes.

The MR images were acquired using a 1.5 or 3.0 Tesla MR scanner (Philips Medical Systems, The Netherlands). The protocol consisted of T1-weighted axial spin echo images (1 x 1 x 4 mm^3 resolution), T2-weighted axial turbo spin echo (TSE) images (1 x 1 x 4 mm^3 resolution) and a balanced fast field echo 3D acquisition (0.7 x 0.7 x 1 mm^3 resolution) with water selection. Intraoperative 3D TRUS datasets were acquired using a 8585 biplane US probe connected to a Leopard 2000 US scanner (Bruel & Kjaer, Denmark) by rotating the probe through the rectum over an angle of 220° and image acquisition at each step of 1°. Four weeks after implantation, MRI and CT scans (Philips, The Netherlands) were performed subsequently on the same day, for post-planning dose evaluation. Registration between the CT and the MRI-based delineations was performed with the SPOT image fusion module for manual fusion, using the high intensity seed signals on CT and the seed signal voids on MRI as markers (28).

Since both scans were matched on all seeds within the prostate and a generally good match was found in all prostate image slices, registration and delineation

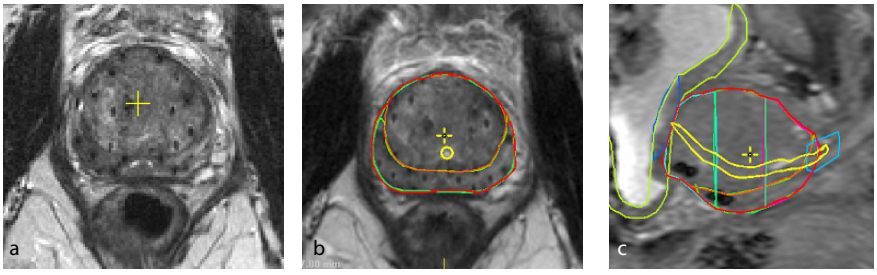

Figure 1 Contouring example, showing the delineated structures on magnetic resonance imaging (MRI). (a) Transversal slice of T2-weighted image. (b) Same transversal slice including contours. (c) Sagital view. Delineation: red = prostate (target volume); yellow = urethra; orange = transition zone; green = peripheral zone; blue = lower sphincter; dark blue = bladder neck; light green = bladder muscle. In figure c, the separation in three equal thirds is seen, representing the apex, midprostate and base.

of prostate structures and bladder neck were not substantially influenced by changes in bladder or rectum filling.

Delineation

A detailed segmental delineation was completed for the 100 randomly selected patients. All delineations were performed by the same physician (E.R.), who was blinded to the patient's AUR-status. MR images at 4 weeks post-treatment were used for delineation, using the T2-weighted spin echo images and the high resolution 3D fast field echo dataset.
Figure 1 shows an example of delineation of the separate structures on MRI. Nine separate structures were delineated: whole prostate, peripheral zone, transition zone, base (upper third of prostate), mid-prostate (mid third of prostate), apex (lower third of prostate), urethra, lower sphincter, and bladder neck (part of the bladder-base where the urethra starts), according to the delineation guidelines described by Villeirs *et al.* and McLaughlin *et al.* (24,29,30). Furthermore, several anatomic parameters were determined (*Figure 2*): urethra angle (angle between the upper and the lower part of the prostatic urethra), urethra-bladder angle (angle between the upper part of the prostatic urethra and the bladder base), extent of prostate protrusion into the bladder (defined as the maximum distance from bladder base to prostate base, in mm), extent of bladder overlap (defined as the distance of bladder lying over the ventral side of the prostate, in mm).

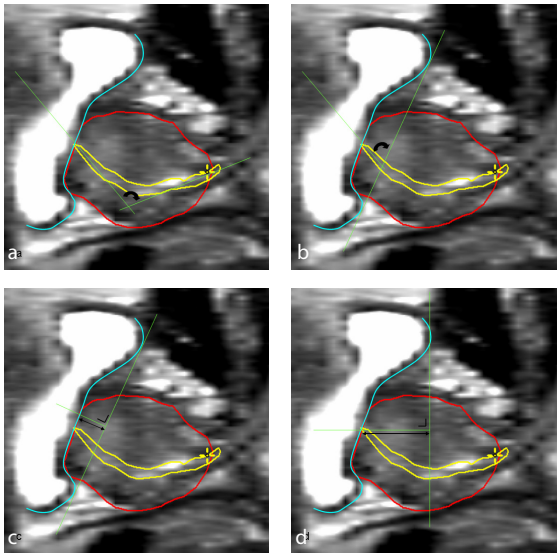

Figure 2 Illustration of the determination of the anatomic parameters. (a) Urethra angle (defined as the angle between the upper and lower part of prostatic urethra). b) Urethra-bladder angle (defined as the angle between upper part of prostatic urethra bladder and the bladder base). (c) Prostate protrusion into the bladder (defined as the maximum distance from bladder base to prostate base). (d) Bladder overlap (defined as the distance of bladder lying over the ventral side of the prostate). Delineation: red = prostate (target volume); yellow = urethra; blue = bladder; green = construction lines.

Dosimetry

At four weeks after implantation, CT-based dose calculation was performed. Registration between the CT and the MRI-based delineations was performed with the SPOT image fusion module (see 'treatment technique and imaging') (28). For all nine delineated structures the following dosimetric parameters were calculated: D_{10}, D_{50} and D_{90} (minimal dose received by 10%, 50%, and 90% of the delineated volume, respectively), and V_{100}, V_{150} and V_{200} (percentage of delineated volume receiving 100%, 150% and 200% of the prescribed dose of 145 Gy, respectively.

Statistical analysis

SPSS (version 16.0; SPSS, Chicago, IL) was used both for the random patient selection from our database of 714 patients, and for statistical analysis of the data. Clinical and treatment characteristics of cases (n = 50) and controls (n = 50) were compared by using an independent samples *t*-test (continuous variables) or a χ^2-test (categorical variables). Differences between cases and controls on dosimetric and anatomic parameters were assessed with an independent samples *t*-test. The evaluated dosimetric parameters for all nine delineated structures were: D_{10}, D_{50}, D_{90}, V_{100}, V_{150} and V_{200}. The evaluated anatomic parameters were: urethra angle, urethra-bladder angle, extent of prostate protrusion, and extent of bladder overlap.
To assess the effect of potential confounders on a possible association between parameters and AUR, we performed univariate and multivariate logistic regression analyses (UVA and MVA). Results were expressed in odds ratios (OR) and 95% confidence intervals (CI). On MVA, we adjusted each parameter of interest for the following potential confounders: prostate volume, number of needles used, IPSS and neo-adjuvant hormonal treatment. We did not include the number of seeds as a potential confounder since it is highly correlated with the number of needles (Pearson coefficient $r > 0.8$). If the difference between the crude OR (UVA) and the adjusted OR (MVA) is < 10%, there is no relevant confounding. Statistical significance was set at $p < 0.05$ for all analysis.

Results

Table 1 summarizes the clinical and treatment characteristics of patients who developed AUR (cases) and patients who did not (controls). Patients who developed AUR had a significantly higher pretreatment IPSS score ($p = 0.042$) and were more frequently treated with neo-adjuvant hormonal treatment compared to controls (30% versus 18%), although not statistically significant.

The mean pretreatment TRUS-based prostate volume was 39.0 cm^3 for AUR-cases and 33.5 cm^3 for controls (p = 0.001). The mean number of needles and seeds used was higher for AUR cases than for controls (mean 25.4 vs. 22.9, and 78.3 vs. 68.9, respectively). Other parameters were comparable between both groups.

Table 1 Clinical and treatment characteristics for patients who developed AUR and patients who did not (no-AUR).

Characteristic	AUR (n = 50)	no-AUR (n=50)	*p*-value
Pretreatment			
Age at implantation (y)	65.5 (±6.7)	64.8 (±5.9)	NS
Clinical tumor stage			
T1	37 (74%)	30 (60%)	NS
T2	13 (26%)	20 (40%)	
Gleason sum-score			
<7	38 (76%)	37 (74%)	NS
7	12 (24%)	13 (26%)	
iPSA (ng/ml)	9.5 (±4.4)	9.8 (±5.0)	NS
Pretreatment IPSS			
0-5	7 (14%)	19 (38%)	0.042*
6-10	13 (26%)	10 (20%)	
11-20	29 (58%)	21 (42%)	
>20	1 (2%)		
Pretreatment TURP			
Yes	1 (2%)	0	NS
No	49 (98%)	50 (100%)	
Neo-adjuvant HT			
Yes	15 (30%)	9 (18%)	NS
No	35 (70%)	41 (82%)	
Treatment			
TRUS volume (cm^3)	39.0 (±8.8)	33.5 (±7.3)	0.001*
Needles (n)	25.4 (±3.6)	22.9 (±3.5)	0.001*
Seeds (n)	78.3 (±11.5)	68.9 (±11.4)	0.000*
Ratio of postimplant and preimplant prostate volume on TRUS†	1.04 (±0.06)	1.04 (±0.05)	NS
Ratio of postimplant and pre-implant prostate volume on MRI‡	1.08 (±0.16)	1.05 (±0.13)	NS

Abbreviations: AUR = acute urinary retention; NS = not statistically significant; iPSA = initial prostate-specific antigen level; IPSS = international prostate symptom score; TURP = transurethral resection of the prostate; HT = hormonal treatment; TRUS = transrectal ultrasound; MRI = magnetic resonance imaging.
*statistically significant; †Surrogate of intraoperative prostate edema; ‡Surrogate of post-operative prostate edema. Valeus are means (±SD) or numbers (%).

Table 2 shows the dosimetric parameters of all separate delineated structures for AUR-cases and controls. The mean MRI-based prostate volume was 41.0 cm^3 for patients with AUR versus 35.2 cm^3 for patients without AUR ($p = 0.004$). Also the volumes of most delineated structures were significant larger in AUR-cases compared to controls. However, most of these volumes were highly correlated to the volume of the whole prostate gland (Pearson coefficient $r > 0.8$). After adjustment for prostate gland volume, all other volumes lost significance (data not shown). There was no association between dose delivered to any of the segmental regions within the prostate, the urethra or the lower sphincter, and the risk of AUR. Conversely, *bladder neck* dose was significantly higher in AUR cases compared to controls. Mean bladder neck D_{90} was 65.1 Gy in AUR cases versus 55.5 Gy in controls ($p = 0.016$), and mean bladder neck D_{10} was 127.7 Gy versus 106.7 Gy, respectively ($p = 0.018$). On univariate logistic regression analysis (*Table 3*), the odds ratio (OR) for bladder neck D_{10} (Gy) and the associated risk of AUR was 1.13 per 10 Gy increase (95% CI 1.02 to 1.26). On multivariate analysis (*Table 3*), OR's did not change substantially after adjustment for the following potential confounders: prostate volume, number of needles used, IPSS, and neo-adjuvant hormonal treatment (indicating that there is no confounding). We chose only one dose parameter of the bladder neck for the logistic regression analyses (and further conclusions) since very high correlations were found between the different dose parameters of the bladder neck (Pearson coefficient $r > 0.8$). The bladder neck D_{10} was chosen because regions with high doses are thought to be most contributive to normal tissue damage (21).

We also determined several anatomic parameters: extent of prostate protrusion into the bladder, extent of bladder overlap, urethra angle and urethra-bladder angle. There was no significant difference in mean urethra angle (121° vs. 123°), or in mean urethra-bladder angle (both groups 69°) between AUR cases and controls. However, both the extent of bladder overlap and prostate protrusion into the bladder were strongly associated with the development of AUR. Mean extent of bladder overlap was 8.0 mm in AUR cases versus 5.4 mm in controls ($p = 0.005$; mean difference 2.7; 95% CI 0.92 to 4.40), and mean extent of prostate protrusion into the bladder was 3.5 mm versus 1.0 mm, respectively ($p < 0.001$; mean difference 2.5; 95% CI 1.60 to 3.37). On univariate logistic regression analysis (*Table 3*), a larger extent of bladder overlap and a larger extent of prostate protrusion were associated with a higher risk of AUR (OR 1.16; 95% CI 1.04 to 1.28, and OR 1.83; 95% CI 1.37 to 2.45, respectively). On multivariate analysis, OR's did not change substantially after adjustment for potential confounders. If both factors were analyzed in the same model, prostate protrusion (OR 2.24; 95% CI 1.49 to 3.38) seemed to be a stronger risk factor for AUR than bladder overlap (OR 0.88; 95% CI 0.75 to 1.04).

Table 2 Dosimetric parameters according to the different delineated structures, for patients who developed AUR and patients who did not (no-AUR).

	AUR (n = 50)	No AUR (n = 50)	*t*-test	
Factor	Mean (±SD)	Mean (±SD)	mean difference (95%CI)	*p*-value
Prostate				
Volume (cm^3)	41.0 (9.8)	35.2 (10.2)	5.8 (1.9; 9.8)	0.004*
D_{90} (Gy)	162.0 (28.1)	161.3 (33.8)	0.7 (-11.7; 13.0)	NS
D_{50} (Gy)	259.2 (23.6)	264.5 (28.7)	-5.3 (-15.7; 5.1)	NS
D_{10} (Gy)	357.2 (27.7)	361.7 (31.0)	-4.5 (-16.2; 7.2)	NS
V_{100} (%)	93.1 (6.1)	92.1 (7.4)	1.0 (-1.7; 3.7)	NS
V_{150} (%)	70.7 (10.2)	71.6 (12.5)	-0.9 (-5.4; 3.7)	NS
V_{200} (%)	37.3 (9.9)	40.0 (11.6)	-2.7 (-7.0; 1.6)	NS
Peripheral zone				
Volume (cm^3)	14.5 (3.5)	13.1 (2.9)	1.5 (0.2 ; 2.7)	0.028*
D_{90} (Gy)	185.2 (29.0)	184.4 (30.1)	0.8 (-10.9; 12.6)	NS
D_{50} (Gy)	283.9 (32.7)	288.4 (34.5)	-4.5 (-17.8; 8.9)	NS
D_{10} (Gy)	382.8 (40.2)	396.5 (39.7)	-13.8 (-29.6; 2.1)	NS
V_{100} (%)	96.9 (3.6)	96.4 (4.6)	0.4 (-1.2; 2.1)	NS
V_{150} (%)	78.3 (10.5)	78.5 (11.2)	-0.2 (-4.5; 4.1)	NS
V_{200} (%)	47.9 (12.7)	49.6 (13.0)	-1.7 (-6.8; 3.4)	NS
Transition zone				
Volume (cm^3)	24.0 (7.5)	20.1 (8.3)	3.9 (0.8; 7.1)	0.014*
D_{90} (Gy)	164.5 (34.9)	161.4 (40.4)	3.2 (-11.8; 18.2)	NS
D_{50} (Gy)	251.6 (29.6)	257.6 (38.1)	-5.9 (-19.5; 7.6)	NS
D_{10} (Gy)	342.6 (28.2)	346.7 (36.7)	-4.1 (-17.1; 8.9)	NS
V_{100} (%)	92.6 (8.7)	91.0 (9.5)	1.6 (-2.0; 5.3)	NS
V_{150} (%)	69.3 (15.0)	69.5 (16.3)	-0.2 (-6.5; 6.0)	NS
V_{200} (%)	32.6 (12.4)	35.0 (14.0)	-2.3 (-7.6; 2.9)	NS
Base				
Volume (cm^3)	10.9 (3.2)	9.3 (3.4)	1.6 (0.3; 2.9)	0.018*
D_{90} (Gy)	144.2 (38.2)	142.7 (39.1)	1.6 (-13.8; 16.9)	NS
D_{50} (Gy)	223.5 (47.7)	224.4 (55.8)	-0.9 (-21.5; 19.7)	NS
D_{10} (Gy)	335.6 (48.5)	327.6 (62.3)	8.0 (-14.2; 30.1)	NS
V_{100} (%)	83.8 (17.4)	81.7 (21.8)	2.1 (-5.7; 9.9)	NS
V_{150} (%)	54.5 (21.6)	54.0 (23.9)	0.5 (-8.6; 9.5)	NS
V_{200} (%)	26.7 (14.8)	27.5 (17.1)	-0.8 (-7.1; 5.6)	NS
Midprostate				
Volume (cm^3)	17.7 (5.3)	15.5 (5.3)	2.2 (0.1; 4.4)	0.039*
D_{90} (Gy)	196.6 (24.3)	193.0 (30.2)	3.6 (-7.3; 14.5)	NS
D_{50} (Gy)	277.8 (27.2)	283.4 (29.1)	-5.6 (-16.8; 5.6)	NS

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D_{10} (Gy)	360.1 (33.8)	273.1 (34.6)	-12.9 (-26.5; 0.7)	NS
V_{100} (%)	98.3 (2.9)	97.2 (3.6)	1.1 (-0.2; 2.4)	NS
V_{150} (%)	80.3 (11.0)	81.2 (11.7)	-0.4 (-4.9; 4.1)	NS
V_{200} (%)	44.6 (12.9)	47.9 (13.3)	-3.2 (-8.4; 1.9)	NS
Apex				
Volume (cm^3)	7.6 (2.6)	6.4 (2.8)	1.3 (0.2; 2.3)	0.022*
D_{90} (Gy)	194.1 (38.0)	193.8 (46.3)	0.2 (-16.6; 17.1)	NS
D_{50} (Gy)	258.6 (43.2)	265.3 (55.6)	-6.7 (-26.4; 13.1)	NS
D_{10} (Gy)	352.7 (45.8)	364.4 (66.9)	-11.7 (-34.4; 11.1)	NS
V_{100} (%)	96.7 (7.7)	96.3 (7.0)	0.4 (-2.5; 3.3)	NS
V_{150} (%)	73.7 (21.0)	75.3 (19.4)	-1.5 (-9.6; 6.5)	NS
V_{200} (%)	36.9 (17.7)	39.3 (20.9)	-2.4 (-10.1; 5.3)	NS
Urethra				
Volume (cm^3)	0.4 (0.1)	0.4 (0.1)	0.01 (-0.01; 0.04)	NS
D_{90} (Gy)	144.2 (41.8)	148.3 (38.5)	-4.1 (-20.0; 11.8)	NS
D_{50} (Gy)	224.3 (30.9)	233.3 (30.6)	-9.0 (-21.2; 3.2)	NS
D_{10} (Gy)	263.3 (43.2)	269.0 (46.4)	-5.7 (-23.5; 12.1)	NS
V_{100} (%)	89.1 (8.5)	89.3 (8.0)	-0.2 (-3.5; 3.1)	NS
V_{150} (%)	50.7 (29.0)	58.4 (26.7)	-7.7 (-18.8; 3.3)	NS
V_{200} (%)	8.0 (8.0)	11.0 (17.2)	-2.9 (-9.0; 3.1)	NS
Lower sphincter				
Volume (cm^3)	0.78 (0.3)	0.63 (0.1)	0.14 (0.05; 0.24)	0.002*
D_{90} (Gy)	135.5 (48.7)	138.5 (46.0)	-3.0 (-21.8; 15.8)	NS
D_{50} (Gy)	178.5 (48.9)	186.9 (50.1)	-8.4 (-28.1; 11.2)	NS
D_{10} (Gy)	236.8 (60.8)	242.1 (53.1)	-5.2 (-27.9; 17.4)	NS
V_{100} (%)	71.4 (32.5)	73.3 (29.9)	-2.0 (-14.4; 10.4)	NS
V_{150} (%)	29.3 (29.9)	34.3 (28.6)	-4.9 (-16.6; 6.7)	NS
V_{200} (%)	6.3 (8.4)	7.3 (10.9)	-1.0 (-4.9; 2.9)	NS
Bladder neck				
Volume (cm^3)	1.9 (0.8)	1.4 (0.7)	0.5 (0.2; 0.8)	0.001*
D_{90} (Gy)	65.1 (22.2)	55.5 (16.1)	9.5 (1.8; 17.3)	0.016*
D_{50} (Gy)	90.3 (31.9)	77.4 (22.4)	12.9 (1.9; 23.9)	0.022*
D_{10} (Gy)	127.7 (50.8)	106.7 (33.8)	21.0 (3.8; 38.3)	0.018*
V_{100} (%)	11.6 (18.2)	4.4 (11.3)	7.2 (1.1; 13.2)	0.021*
V_{150} (%)	1.8 (5.9)	0.4 (1.4)	1.4 (-0.3; 3.1)	NS
V_{200} (%)	0.5 (2.0)	0.1 (0.6)	0.4 (-0.2; 1.0)	NS

Abbreviations: AUR = acute urinary retention; UVA = univariate analysis; MVA = multivariate analysis; OR = odds ratio; CI = confidence interval ; V_{100}, V_{150}, V_{200} = percentage of prostate/urethra volume receiving 100%, 150% and 200% of prescribed dose, respectively; D_{90}, D_{50}, D_{10}, = minimal dose received by 90%, 50% and 10% of prostate/urethra, respectivaly.
* Statistically significant

Table 3 Univariate and multivariate logistic regression analysis.

	AUR (n = 50)	No AUR (n = 50)	UVA		MVA†	
Factor	Mean (±SD)	Mean (±SD)	OR (95% CI)	*p*	OR (95% CI)	*p*
Bladder neck D_{10} (Gy)	127.7 (50.8)	106.7 (33.8)	1.13 (1.02-1.26)‡	.023*	1.11 (1.00-1.24)‡	.080
Bladder overlap (mm)	8.0 (5.0)	5.4 (3.7)	1.16 (1.04-1.28)	.005*	1.11 (0.98-1.26)	.116
Prostate protrusion (mm)	3.5 (3.0)	1.0 (1.1)	1.83 (1.37-2.45)	<.001*	1.77 (1.28-2.44)	<.001*

Abbreviations: AUR = acute urinary retention; UVA = univariate analysis; MVA = multivariate analysis; SD = standard deviation; OR = odds ratio; CI = confidence interval; D_{10} = minimal dose received by 10% of bladder neck.
† Adjusted for prostate volume, number of needles, IPSS and neo-adjuvant hormonal treatment; * Statistically significant; ‡ Per 10 Gy increase

Discussion

To the best of our knowledge, this is the first study to investigate the association between MRI-based segmental prostate dosimetry and the risk of AUR after I-125 prostate brachytherapy. For this study, we compared segmental dosimetry of 50 patients with AUR with that of 50 patients without AUR. We found that only a higher dose to the bladder neck was associated with a higher risk of AUR. We did not find an association between dose delivered to any of the segmental regions within the prostate and the risk of AUR. Furthermore, the extent of prostate protrusion and bladder overlap was highly associated with the risk of AUR.

Literature reports several attempts to find a relation between dosimetry and urinary morbidity after prostate brachytherapy. Most studies have focused on dose to the whole prostate gland. Keyes *et al.* (13) showed an inverse relation between prostate dose and the risk of AUR, whereas most others did not find an association (9,11,16-20). A more segmental delineation was performed in three other studies (31-33), in which the transition zone was specifically looked at. Delineation in these studies was performed by using CT and ultrasound. A larger transition zone volume was associated with more urinary morbidity; however, dosimetric parameters of the transition zone were not reported in any of these studies. Moreover, as far as we know, no studies are available concerning dose to the peripheral zone, prostate base, mid-prostate, apex or lower sphincter. Our findings, combined with findings from the literature, indicate that there is little evidence to link AUR with prostate dose, not even when different regions of the prostate were separately analyzed. A reasonable explanation for the absence

of a relation between dose and AUR might be that given the I-125 half-life of 60 days, it takes a few months before a substantial dose has been delivered to the prostatic tissue. Because most patients developed AUR within the first month after implantation (median time to AUR was 30 days), dose is unlikely an important risk factor.

By contrast, we found that dose to the bladder neck (defined as bladder tissue) was associated with the risk of AUR. This finding is consistent with the study of Steggerda *et al*. (21), which evaluated the effect of bladder hotspot dose on urinary morbidity. In a group of 115 patients, including 15 patients with AUR, they showed that bladder hotspot dose was a predictor of urinary morbidity at 3 and 6 months after implantation. However, because of the small number of patients, the power of their multivariate model was modest. Three studies evaluated segmental urethral dosimetry. Thomas *et al.* (22) found urethra-base dosimetry to be associated with increased urinary toxicity after prostate brachytherapy, whereas Neill *et al*. (15) and Allen *et al.* (23) reported no association between segmental urethral doses and urinary toxicity.

There are several possible hypotheses to explain our findings. First, the radiation sensitivity of the bladder neck may differ from that of prostate tissue. Since the bladder neck is part of the bladder, it consists of smooth muscle cells, whereas the prostate mainly consists of gland cells and striated muscle cells. Second, the correlation between AUR and bladder neck dosimetry could be due to the commonly observed larger variation in dose at the prostate base compared with other segments within the prostate (28). A relatively constant dose in all other prostate segments might have precluded the detection of any relationship between dose and AUR at these segments. However, in our data, dose variation at the bladder neck was not significantly larger than dose variation at other delineated segments (*Table 2*). Third, the presence of a relatively high dose in the bladder neck implies that at least some seeds (and thus needles) have been placed in the bladder muscle. According to Buskirk *et al.* (34) and Eapen *et al.* (35), trauma caused by needle insertions is associated with increased urinary morbidity. Whether dose or needle trauma to the bladder neck is more contributive to the development of AUR remains unclear.

Besides dose, we also studied the influence of several anatomic parameters (i.e., extent of prostate protrusion into the bladder, extent of bladder overlap, urethra angle and urethra-bladder angle) (*Figure 2*) on the risk of AUR. We found a new risk factor for AUR, which has not been described in published reports before. We found that a larger extent of prostate protrusion into the bladder was strongly associated with a higher risk of AUR (*Table 3*). Although the absolute difference in prostate protrusion between both groups was only 2.5 mm, the extent of prostate protrusion was 3.5-fold larger in AUR cases than in controls. Prostate protrusion into the bladder is commonly seen in patients with large transition zones associated with benign prostate hypertrophy. Therefore,

prostate volume could be a confounder; however, even after adjustment for prostate volume, prostate protrusion remained strongly associated with the risk of AUR. The extent of prostate protrusion is easily measurable on MRI before implantation (*Figure 2*) and might, therefore, be a useful parameter in the prediction of the risk of AUR. In our analysis, the extent of bladder overlap was significantly associated with AUR as well; however, this parameter lost significance after addition of prostate protrusion to the model. Furthermore, the extent of bladder overlap is much more prone to bladder filling and, therefore, less useful in clinical practice.

The strengths of our study are the large number of patients with AUR, the use of MRI for delineation and the dosimetric evaluation of a wide range of segmental anatomic structures. However, there are some limitations. First, there is a certain extent of delineation uncertainty. However, it is likely that systematic delineation errors will be equally distributed between both groups, since the delineator was blinded to patient's AUR status. Delineation uncertainty was minimized by using MRI with high soft tissue contrast (24), and by using guidelines for delineation (24,29,30). Second, the study describes the experience of a single center. Morbidity and treatment techniques may vary from center to center. Third, as mentioned before, a relevant methodological aspect in the analysis of dosimetric parameters is the spread in data. If the variation in doses is small, a potentially association might be missed. However, in our opinion, the variation in our dosimetric data was large enough to enable any possible association to be found (*Table 2*).

Conclusions

In this study, we assessed the influence of segmental prostate dosimetry and anatomic parameters on the risk of AUR after I-125 prostate brachytherapy. There was no association between dose delivered to different regions within the prostate and the development of AUR. However, a higher dose to the bladder neck was associated with an increased risk of AUR. Whether the main contributive factor for the development of AUR is dose or trauma, this study reemphasizes the need to avoid insertion of needles and seeds (and thus dose) in the bladder neck, in order to reduce the risk of AUR. Given that about 70% of prostate tumors arise in the peripheral zone (36), it might be recommendable to be more conservative with seed placement at the prostate base, but only in selected patients when tumor location is evident. Furthermore, protrusion of the prostate into the bladder was strongly associated with the risk of AUR. Since prostate protrusion is easily measurable on MRI, it might be useful in the pretreatment determination of the risk of AUR, in addition to the known predictors as prostate volume, IPSS and neo-adjuvant hormonal treatment.

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Chapter 7

Pretreatment nomogram to predict the risk of acute urinary retention after I-125 prostate brachytherapy

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Abstract

Purpose

Acute urinary retention (AUR) after Iodine-125 (I-125) prostate brachytherapy negatively influences long-term quality of life and therefore should be prevented. We aimed to develop a nomogram to preoperatively predict the risk of AUR.

Methods

Using the preoperative data of 714 consecutive patients who underwent I-125 prostate brachytherapy between 2005 and 2008 at our department, we modeled the probability of AUR. Multivariate logistic regression analysis was used to assess the predictive ability of a set of pretreatment predictors and the additional value of a new risk factor (the extent of prostate protrusion into the bladder). The performance of the final model was assessed with calibration and discrimination measures.

Results

Of the 714 patients, 57 patients (8.0%) developed AUR after implantation. Multivariate analysis showed that the combination of prostate volume, IPSS score, neo-adjuvant hormonal treatment and the extent of prostate protrusion contribute to the prediction of AUR. The discriminative value (ROC area) of the basic model (including prostate volume, IPSS and neo-adjuvant hormonal treatment) to predict the development of AUR was 0.70. The addition of prostate protrusion significantly increased the discriminative power of the model (ROC area 0.82). Calibration of this final model was good. The nomogram showed that among patients with a very low sum-score (< 18 points), the risk of AUR was only 0% to 5%. However, in patients with a high sum-score (> 35 points), the risk of AUR was more than 20%.

Conclusion

This nomogram is a useful tool for physicians to predict the risk of AUR after I-125 prostate brachytherapy and can thereby aid in patient counseling and individualized treatment decision making.

Introduction

Iodine-125 (I-125) prostate brachytherapy is a common treatment modality in localized prostate cancer. It shows excellent tumor control rates (1-3), with long-term quality of life (QOL) scores not significantly different from baseline QOL scores (4). Adverse events after prostate brachytherapy are generally mild, but the most predominant severe acute toxicity is acute urinary retention (AUR) requiring catheterization. Published AUR rates vary from 6% to 34% (5-10). Patients who develop AUR experience a significantly worse QOL compared to patients without AUR, which does not improve after 6 years of follow-up in most patients (11). Therefore, preoperative prediction of AUR is required, both for selecting patients for prostate brachytherapy and for patient counseling.
Several preimplant risk factors for the development of AUR have been identified, including prostate volume (8,12,13), International Prostate Symptom Score (IPSS) (5,7,11,13), and neo-adjuvant hormonal treatment (5,8,11). Furthermore, in a recent study, we found the extent of prostate protrusion into the bladder to be an independent risk factor for AUR (14). Although associations between these factors and the risk of AUR have been studied before, a clinical nomogram to preoperatively predict AUR is not available to date. Therefore, the aim of this study was to develop a simple nomogram to predict the risk of AUR after I-125 prostate brachytherapy.

Methods and materials

Patients

Between January 2005 and December 2008, 714 consecutive patients with localized prostate cancer were treated with I-125 seed implantation at our department. Implantations were performed according to the GEC-ESTRO guidelines (15,16). Eligibility criteria for prostate brachytherapy were: organ confined prostate cancer, clinical tumor stage < T3, Gleason sum-score < 8, and prostate volume > 50 cm^3. Six months of neo-adjuvant hormonal treatment with a LHRH agonist was given to patients presenting with a prostate volume > 50 cm^3 (n = 137). Three radiation oncologists performed the implantations. All had at least 5 years of experience at the time of the study and perform at least 60 implants a year.

Treatment technique and imaging

All patients completed four imaging studies: 1.5 or 3.0 Tesla magnetic resonance imaging (MRI) (Philips, The Netherlands) before and four weeks after treatment,

and intraoperative 3D transrectal ultrasound (TRUS) imaging before and after needle insertion. Delineation of the prostate and the urethra was performed on pretreatment MR images. The preimplant MR dataset with prostate contours was fused to the intraoperative 3D TRUS dataset to aid in intraoperative prostate delineation, and manually adapted during treatment for the actual prostate contour. Image fusion was performed on the Sonographic Planning of Oncology Treatment (SPOT) system (Nucletron B.V., Veenendaal, The Netherlands).

The UMC Utrecht prostate brachytherapy procedure has been described previously (14,17). All patients were treated under spinal anesthesia in lithotomy position. Two locking needles were inserted before the pretreatment TRUS image was acquired. The entire prostate volume was calculated from the 3D-delineations on 1mm slices. The needles were inserted transperineally under TRUS-guidance. I-125 seeds were delivered automatically using the Fully Integrated Real-time Seed Treatment (FIRST) system (Nucletron B.V.) or manually using stranded seeds (IBt, Belgium); 50.4% of the patients received loose seeds (FIRST) and 49.6% received stranded seeds. Online intraoperative treatment planning was performed using the SPOT system. Our criteria for prostate implants were as follows: the percentage prostate volume receiving the prescribed dose of 144 Gy >95% and about 2/3 and 1/3 of the prostate volume receiving 150% and 200% of the prescribed dose, respectively; D_{90} above 160 Gy, the urethra dose ≤150% and the rectum dose ≤100% of the prescribed dose. The entire procedure takes around 90 minutes.

At 4 weeks after implantation, both MRI and computed tomography (CT) scans (Philips, The Netherlands) were performed for postplanning dose evaluation. Registration between CT-based seed localization and MRI based prostate delineation was achieved with the SPOT image fusion module.

Follow-up

After implantation, patients stayed in the hospital for one night and were discharged the next day. Each patient received an α-blocker for one month and as long as urinary symptoms persisted. No routine steroids were used. According to our follow-up protocol, patients were seen alternately by the radiation oncologist and the urologist at 1,3,6,9, and 12 months after treatment, and twice annually thereafter. Minimum follow-up was 6 months. IPSS scores, toxicity data and intervention data were collected prospectively and recorded in a database. AUR was defined as any need for urinary catheterization within 3 months after implantation (18).

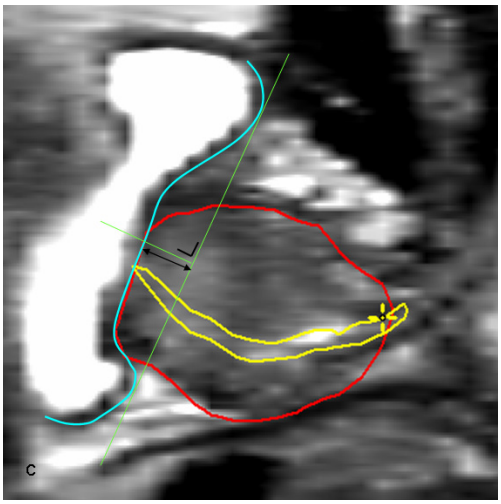

Figure 1 Illustration of determination of the extent of prostate protrusion into the bladder (defined as the maximum distance from bladder base to prostate base).
Red = prostate (target volume); yellow = urethra; blue = bladder; green = construction lines.

Determination of extent of prostate protrusion

Retrospectively, for all 714 patients the extent of prostate protrusion into the bladder (defined as the maximum distance from bladder base to prostate base) was determined on preimplant MR images (*Figure 1*) (14). All delineations were performed by the same physician (E.R.), who was blinded to the patient's AUR-status.
To assess the inter-observer variability of the measurements of prostate protrusion, two other physicians determined the extent of prostate protrusion in 15 randomly selected patients (all with a certain degree of prostate protrusion). The intra-observer variability was determined by repeating the measurements in these 15 patients by the same physician. Mean inter- and intra-observer differences were 0.7 mm (SD ± 0.9) and 0.4 mm (SD ± 0.7), respectively. Pearson correlation coefficients (*r*) were calculated and showed that both inter- and intra-observer repeatability of prostate protrusion measurements were high ($r = 0.97$ and $r = 0.94$, respectively). For patients with no prostate protrusion, inter- and intra-observer repeatability were even higher ($r = 1.0$) (tested in another 15 patients).

Statistical analysis

Clinical and treatment characteristics of patients with and without AUR were compared using independent sample *t*-tests (continuous variables) or χ^2-tests (categorical or dichotomous variables). Multivariate logistic regression analyses were applied to relate pretreatment factors to the risk of AUR. Pretreatment parameters included in the first multivariate analysis (MVA) (basic model) were:

prostate volume, IPSS, and neo-adjuvant hormonal treatment. This predefined set of predictors was chosen based on predictors from literature. We did not use backward selection, because we used the state of the art methodology guidelines (19-21). A second (extended) model was developed including the extent of prostate protrusion as additional factor. To assess whether the performance of the extended model increased compared to the basic model, we applied the -2log likelihood test. Difference in discriminative ability (i.e. the ability of the model to distinguish patients with AUR from patients without AUR) between the models was quantified by the area under the receiver operating characteristic curve (ROC area). Furthermore, net reclassification improvement (NRI) was calculated to evaluate the added predictive ability of prostate protrusion (22).

Calibration of the final model was determined by comparing the predicted risks with the observed proportions of AUR, among 5 risk groups (and performing the Hosmer-Lemeshow test). The regression coefficients (β-coefficients) of the final model were multiplied by a shrinkage factor, which was determined by a heuristic formula (23). Shrinkage was performed to adjust for the optimism that might be expected when the model is applied to new, but similar patients (19,21). Subsequently, the intercept was also adjusted to the new situation, such that the mean predicted risk equaled the observed.

The final model with the shrunken regression coefficients was presented as a nomogram to facilitate clinical application. Risk scores were calculated by multiplying the absolute parameter values by the β-coefficients. Then these risk scores were multiplied by 10 and rounded to obtain full-point scores. Finally, the sum scores were related to predicted risks.

A commercial statistical package of social sciences (SPSS version 16.0; SPSS, Chicago, IL) was used for statistical analysis of the data. Statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Of the 714 patients, 57 (8.0%) developed AUR after implantation. Clinical and treatment characteristics of patients who developed AUR and patients who did not are summarized in *Table 1*. Mean age of the patients was 65 years. Patients who developed AUR had a higher pretreatment prostate volume, a higher IPSS score, a larger extent of prostate protrusion, and were more frequently treated with neo-adjuvant hormonal treatment compared with patients without AUR. The mean number of needles and seeds used was also higher for patients with AUR. Other parameters were comparable between both groups.

Table 1 Clinical and treatment characteristics for patients who developed AUR and patients who did not (no-AUR).

Characteristic	AUR (n = 57)	no-AUR (n = 50)	*p*-value
Pretreatment			
Age at implantation (y)	65.8 (±6.6)	65.0 (±6.3)	NS
Clinical tumor stage			
T1	41 (72%)	457 (70%)	NS
T2	16 (28%)	200 (30%)	
Gleason sum-score			
<7	44 (77%)	504 (77%)	NS
7	13 (23%)	153 (23%)	
iPSA (ng/ml)	9.2 (±4.2)	9.9 (±5.3)	NS
Pretreatment IPSS			
0-5	8 (14%)	249 (38%)	<.001
6-10	14 (25%)	185 (28%)	
11-20	32 (56%)	211 (32%)	
>20	3 (5%)	12 (2%)	
Pretreatment TURP			NS
Yes	1 (2%)	10 (2%)	NS
No	56 (98%)	647 (98%)	
Neo-adjuvant HT			
Yes	16 (28%)	121 (18%)	NS
No	41 (72%)	536 (82%)	0.076
BMI	26.3 (±3.0)	26.2 (±3.6)	NS
Prostate volume, TRUS (cm^3)	38.9 (±9.1)	35.1 (±8.9)	0.002
Prostate volume, MRI (cm^3)	38.1 (±8.3)	34.3 (±8.4)	0.001
Prostate length (cm)	4.2 (±0.6)	4.2 (±0.6)	NS
Prostate protrusion (mm)	3.5 (±2.9)	0.9 (±1.6)	<0.001
Treatment			
Needles (n)	25.3 (±3.5)	24.0 (±3.8)	0.013
Seeds (n)	78.0 (±11.7)	72.9 (±13.2)	0.005
Prostate D_{90} (Gy)	161.6 (±27.4)	164.3 (±28.6)	NS
Prostate V_{100} (%)	91.5 (±12.3)	93.2 (±6.0)	NS
Prostate V_{150} (%)	69.5 (±13.1)	71.5 (±11.5)	NS
Prostate V_{200} (%)	37.4 (±9.7)	39.3 (±11.9)	NS

Abbreviations: AUR = acute urinary retention; NS = not statistically significant; iPSA = initial prostate-specific antigen level; IPSS = international prostate symptom score; TURP = transurethral resection of the prostate; HT = hormonal treatment; BMI = body mass index; TRUS = transrectal ultrasound; MRI = magnetic resonance imaging. Values are means (±SD) or numbers (%).

The median time to AUR was 30 days (range, 0-90 days). Patients received a urinary catheter alone (n = 20), or a catheter followed by insertion of a suprapubic catheter (n = 26). Another 11 patients performed intermittent self-catheterization. The median duration of catheter dependency was 37 days (range, 2-140 days). Nineteen (33.3%) of the 57 patients did not recover spontaneous voiding and eventually required a TURP to relieve obstruction. The median time to TURP was 15 months (range, 7-22 months).

Development of the nomogram

Multivariate logistic regression analysis of the basic model (including pretreatment prostate volume, IPSS and neo-adjuvant hormonal treatment) and the extended model (also including the extent of prostate protrusion) are shown in *Table 2*. Results showed that pretreatment prostate volume, IPSS, and the extent of prostate protrusion add to the prediction of AUR.

Table 2 Multivariate logistic regression analysis.

	MVA (basic model)			**MVA (extended model)†**		
Factor	OR (95% CI)	*p*	ß coefficient	OR (95% CI)	*p*	ß coefficient‡
Prostate volume (cm^3)	1.05 (1.01-1.08)	0.009	0.045	1.02 (0.99-1.06)	0.243	0.021
Pretreatment IPSS		0.003			0.003	
0-5						
6-10	2.18 (0.89;5.32)		0.777	1.78 (0.69;4.64)		0.538
11-20	4.11 (1.84;9.19)		1.414	4.18 (1.78;9.81)		1.332
>20	6.35 (1.43;28.0)		1.848	6.05 (1.18;30.9)		1.677
Neo-adjuvant HT (yes/no)	1.42 (0.76-2.67)	0.273	0.353	1.04 (0.52-2.07)	0.914	0.035
Prostate protrusion (mm)				1.58 (1.40-1.79)	0.000	0.427
Intercept			-5.047			-4.84
-2 log likelihood			-347.6			-284.4
ROC area			**0.70**			**0.82**

Abbreviations: AUR = acute urinary retention; UVA = univariate analysis; MVA = multivariate analysis; SD = standard deviation; OR = odds ratio; CI = confidence interval; IPSS = international prostate symptom score; HT = hormonal treatment; ROC = receiver operating characteristic.
† after addition of the extent of prostate protrusion to the model
‡ ß coefficients were multiplied by a shrinkage factor of 0.93, to adjust for optimism that might be expected when the model is applied to new, but similar patients. The intercept was also adjusted to the new situation.

For each individual patient, the risk of AUR can also be calculated by applying the following formulas:
Linear predictor = -4.84 + (0.021 * prostate volume) + (0.538 * IPSS_1†) + (1.332 * IPSS_2†) + (1.677 * IPSS_3†) + (0.035 * HT) + (0.427 * prostate protrusion)
Risk of AUR = 1 / (1 + EXP(- linear predictor)) * 100%
† IPSS_1 = 1, if IPSS 6-10
† IPSS_2 = 1, if IPSS 11-20
† IPSS_3 = 1, if IPSS >20
For example, the linear predictor value of a patient with a prostate volume of 47 cm3, an IPSS score of 15, no neo-adjuvant hormonal treatment, and 3 mm prostate protrusion is –1.24 [-4.84 + (0.021 * 47) + (1.332 * 1) + (0 * HT) + (0.427 * 3)= -1.24]. The corresponding calculated risk of AUR is then 22% [1/ (1+EXP(1.24)].

Based on the -2log likelihood test, the performance of the extended model increased significantly ($p < 0.001$) compared to the basic model. The discriminative value (ROC area) of the basic model to predict the development of AUR was 0.70 (95% CI, 0.64 to 0.77). The addition of the extent of prostate protrusion to the model did significantly increase the discriminative power of the model (ROC area 0.82; 95% CI, 0.77 to 0.88) (*Figure 2*).

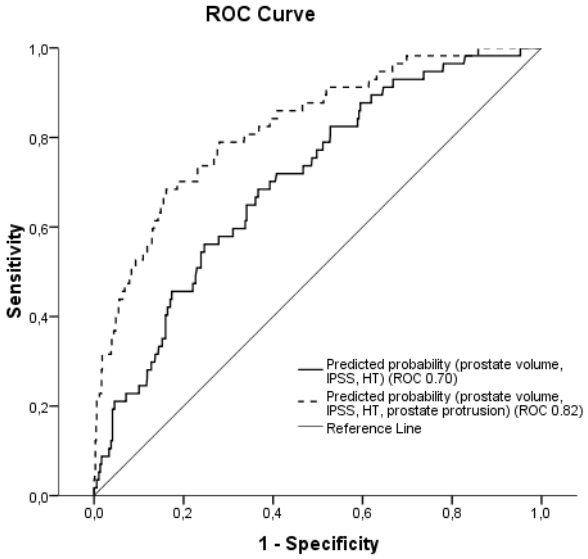

Figure 2 Receiver operating characteristic (ROC) curves for the predictability of acute urinary retention for pretreatment prostate volume, International Prostate Symptom Score (IPSS) and neo-adjuvant hormonal treatment (HT) (black line), and after the addition of prostate protrusion to the model (dotted line). The areas under the curves are 0.70 and 0.82, respectively.

To evaluate the added predictive ability of prostate-bulging, we calculated the NRI of the model according to three risk groups of AUR (i.e. low [< 5%], intermediate [5-15%], and high risk [> 15%] (*Table 3*). In 40% of cases, the second model showed better classification of patients into these risk groups.

Because the performance of the model, the predictive ability and the ROC area increased considerably after the addition of prostate protrusion, the extended model was considered as the final model. *Table 4* shows that calibration (i.e. agreement between predicted risks and the observed frequencies of AUR) of the final model was good. This was also confirmed by a nonsignificant Hosmer-Lemeshow test ($p = 0.98$). To adjust for optimism, the β-coefficients were multiplied by the obtained shrinkage factor of 0.93 (*Table 2*).

Finally, the shrunken regression coefficients were converted into a nomogram to aid simple clinical application (*Figure 3*). The nomogram facilitates calculation of the predicted risk of AUR after I-125 brachytherapy for an individual low-stage prostate cancer patient. For example, a patient with a prostate volume of

Table 3 Reclassification among people who developed AUR and those who did not.

	NRI	Model including prostate protrusion		
		0-5 %	>5-15 %	>15 %
Model without prostate protrusion	Patients with AUR (n = 57)			
	0-5 %	5	1	2
	>5-15 %	5	13	15
	>15 %	0	3	13
	Patients without AUR (n = 657)			
	0-5 %	250	14	4
	>5-15 %	149	119	42
	>15 %	1	59	19

Net reclassification improvement **(NRI) = 40,2 %** (18/57 - 8/57 + 209/657 – 60/657)
Abbreviations: NRI = net reclassifications improvement; AUR = acute urinary retention

47 cm^3, IPSS score 15, no neo-adjuvant hormonal treatment, and 3 mm prostate protrusion, would have a total sum-score of 35 with a corresponding AUR-risk of 20-30%. Furthermore, a patient with a prostate volume of 30 cm^3, IPSS 4, no neo-adjuvant hormonal treatment, and no prostate protrusion would have a total sum-score of 6 with a corresponding AUR-risk of less than 5%. Since external validation has not yet been performed, *Figure 3* should be mainly used to illustrate the relative weights of the different variables.

Table 4 Observed proportions and predicted risks of AUR among 5 risk groups for the development of AUR (= calibration).

	Observed		Predicted
Risk of AUR	*n*/N	(%)	(%)
0-5 %	10/410	2.4	2.4
>5-10 %	12/176	6.8	6.8
>10-20 %	8/52	15.4	13.9
>20-30 %	9/34	26.5	24.1
>30 %	18/42	42.9	47.2

Abbreviations: AUR = acute urinary retention

Figure 3 Nomogram to predict the risk of acute urinary retention after I-125 prostate brachytherapy.

Predictor										
Prostate volume (cm^3)										
Value:	≤16	17-21	22-25	26-30	31-35	36-40	41-45	46-50	51-55	
Score:	3	4	5	6	7	8	9	10	11	...
IPSS										
Value:	0-5	6-10	11-20	>20						
Score:	0	5	13	17						...
Neo-adjuvant HT										
Value:	no	yes								
Score:	0	1								...
Prostate protrusion (mm)										
Value:	0	1	2	3	4	5	6	7	>8	
Score:	0	4	8	12	17	21	25	29	36	...
										+
Total sum score										...

Total sum score	≤18	19-26	27-30	31-34	35-39	40-43	44-48	≥49
Risk of AUR (%)	0-5	>5-10	>10-15	>15-20	>20-30	>30-40	>40-50	>50

Abbreviations: IPSS = international prostate symptom score; HT = hormonal treatment; AUR = acute urinary retention.

Discussion

To our knowledge, this is the first study that developed a clinical nomogram to predict the risk of AUR in patients undergoing I-125 prostate brachytherapy. Because we were interested in predicting the risk of AUR preceding the implantation, we only included pretreatment risk factors in the model. The results of this study show that prostate volume, IPSS score, neo-adjuvant hormonal treatment, and the extent of prostate protrusion predict the risk of AUR. The main predictive factor was the extent of prostate protrusion. The discriminative value to predict the development of AUR was high (ROC area 0.82), and calibration of the model was good. By simply counting the sum score in the nomogram, the predicted risk of AUR can be read off, which could be valuable information for patient counseling and individualized treatment decision making.

In prior research, we demonstrated that patients who developed AUR after prostate brachytherapy had a significantly worse QOL compared with patients without AUR (11). Even at 6 years after treatment, QOL of patients with AUR had not returned to baseline levels (11). In our study, 33% of patients with AUR did not recover spontaneous voiding and eventually required a TURP to relieve obstruction. Other studies confirm that patients who develop AUR are at higher risk of late urinary morbidity (24,25), such as urethra stricture formation (26). These results indicate that AUR can have a long-lasting negative impact on patient's QOL, which underlines the importance of preventing AUR.

A model for pretreatment AUR prediction is sufficient because the intraoperative risk factors to develop AUR are questioned. In two recent studies (14,27), we evaluated the effect of both dose to the entire prostate and dose to different regions of the prostate on AUR. We found no association between dose to the prostate and the development of AUR (27). Nonetheless, the literature suggests that the number of needle insertions (28,29) and dose to the bladder neck might influence AUR (14,30).

In the literature, only one study has been published with the aim of predicting the risk of AUR after prostate brachytherapy. Lee *et al* (31) developed a 'seed implant retention score' based on the following risk factors: supplemental external beam radiation, baseline α-blocker use, neo-adjuvant hormone therapy and prostate size. Their risk score differs from our model with respect to patient population and statistical methods. Of the 835 patients analyzed, only 341 patients received brachy monotherapy of which only 24% was treated with I-125 seeds. Furthermore, no ROC analysis was performed to assess the discriminative value of the model (20).

The pretreatment risk factors we found are in accordance with risk factors published by others. Prostate volume (8,12,13), IPSS score (5,7,11,13), and

neo-adjuvant hormonal treatment (5,8,11) have repeatedly been found to be associated with AUR on multivariate analyses. Although the difference in use of hormonal treatment between AUR and no-AUR patients was not statistically significant, there was a clinically relevant difference (28% versus 18%). Therefore, supported by results from literature, we chose to include this factor in the model as well, based on the current methodological guidelines (19,21). Only the extent of prostate protrusion has never been described before. In a recent case-control study on 100 patients, we found that a large extent of prostate protrusion into the bladder was significantly associated with the risk of AUR (14,27). In the present study, we further explored the additive predictive value of this factor on 714 patients and it appeared to highly increase the discriminative value of the model (ROC area 0.82, compared with 0.70 without prostate protrusion).

A possible explanation for the predictive value of prostate protrusion might be that prostate protrusion into the bladder is often seen in patients with progressive expansion of the transition zone, associated with benign prostate hypertrophy. This process reduces the elasticity of the urethra during voiding and produces gradually increasing bladder outlet obstruction (32). The preexisting urethra obstruction by benign prostate hypertrophy together with additional trauma and edema from implantation might be enough to entirely compress the proximal urethra resulting in AUR. Our determination of prostate protrusion may partly correspond to measurements of the transition zone index examined by others (33-35). These published reports showed that a large preimplant transition zone index was predictive for prolonged urinary morbidity and catheterization after prostate brachytherapy. Because we hypothesized that the main cause of AUR might be due to protruding median lobes, we developed an measurement for this on MRI, i.e., the extent of prostate protrusion. We showed that inter- and intra-observer variation of this measurement was good ($r = 0.97$ and $r = 0.94$, respectively). Furthermore, neo-adjuvant hormonal therapy and prostate protrusion seem to be highly associated (*Table 2*, β-coefficient diminished from 0.35 to 0.035 after addition of prostate protrusion to the model). This might be explained by the fact that neo-adjuvant hormonal therapy diminishes prostate growth mainly at the site of the transitional zone.

The final nomogram is able to distinguish patients at high risk of AUR after prostate brachytherapy from patients with a low risk of AUR. In clinical practice, the benefit of treatment must be compared to the risk of severe acute or long-term adverse events and treatment costs. Since prostate tumors are often slowly dividing with high PSA-doubling-times, the gain of treatment (especially for older patients) is not always clear. This is confirmed by recent studies suggesting that active surveillance has to be considered in selected patients with early-stage, low-grade prostate cancer (36,37). The current nomogram might be a

useful tool to select patients with an 'unacceptable' high risk of AUR. Where to place the cutoff value for 'unacceptable' remains unclear and is dependent on the expert opinion of the physician and the patient's individual preference.
Strengths of our study are the large number of patients treated with I-125 monotherapy, the use of MRI for 3D-delineation, and the extensive and accurate statistical analyses resulting in a clinical nomogram. The nomogram provides information for adequate patient counseling and could, ultimately, lead to improvement of the prevention of AUR. It should be noted that any nomogram performs better on the data from which it was developed (over-optimism). For this reason shrinkage was performed to adjust for over-optimism. In ongoing research, we will perform external validation of the model to assess the accuracy of the model in other patient populations.
Although our prediction nomogram is easy to calculate and implement, it faces a number of limitations. First, the model requires MRI scans to determine the extent of prostate protrusion; however, MRI is not available at all brachytherapy centers. Since soft tissue contrast is better on MRI compared to CT scans, MRI is preferable for delineation (38). Although the use of MRI in prostate brachytherapy is limited thus far, it is rapidly increasing worldwide. Second, our model is based on a limited set of predictors based on literature (20). More potential predictors have been described in single studies or on univariate analysis only. Therefore, further research might lead to an extension and improvement of the predictive value of the model after addition of other relevant risk factors. Third, this is a single center study, and brachytherapy techniques and AUR rates may vary among centers and populations. If patient selection and treatment techniques are different from our institution, the nomogram must be interpret with caution. It should be used mainly as an illustrative tool because external validation has not been performed. As noted before, in ongoing research, we will validate our model in other patient populations to confirm general applicability.

Conclusions

One of the most predominant adverse events after I-125 prostate brachytherapy is the development of AUR, which has a demonstrated negative impact on the patient's QOL. In this study, we developed a nomogram to preoperatively predict the risk of AUR based on the most important risk factors of AUR; i.e. prostate volume, IPSS score, neo-adjuvant hormonal treatment and the extent of prostate protrusion into the bladder. By simply counting the sumscore in the nomogram, the risk of AUR can be read off. The discriminative value and calibration of the model were good. This nomogram might be a useful tool for patient management and counseling to all physicians performing prostate brachytherapy in patients with localized prostate cancer.

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Chapter 8

External validation of the pre-treatment nomogram to predict acute urinary retention after I-125 prostate brachytherapy

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Abstract

Purpose

Acute urinary retention (AUR) after Iodine-125 (I-125) prostate brachytherapy has a negative impact on quality of life. Recently, we developed a nomogram to preoperatively predict the risk of AUR. The aim of this study was to assess the external validity of the nomogram.

Methods

The initial nomogram was developed on 714 patients treated with I-125 prostate brachytherapy at the University Medical Center Utrecht, The Netherlands. Predictive factors included in the nomogram were prostate volume, IPSS, neo-adjuvant hormonal treatment and prostate protrusion into the bladder. For external validation, the data of 715 consecutive patients who underwent I-125 prostate brachytherapy between January 2003 and July 2008 at the Princess Margaret Hospital (PMH), Toronto, were used. The performance of the nomogram was evaluated by discrimination (ability to distinguish between patients who develop AUR yes or no) and calibration (agreement between observed and predicted numbers of AUR).

Results

Of the 715 patients treated at the PMH, 67 patients (9.4%) developed AUR, compared to 8.0% in the UMCU cohort. In the validation dataset, the discriminatory ability of the nomogram was good (ROC area 0.86; 95% CI 0.82 to 0.91), and comparable to the derivation dataset (ROC area 0.82; 95% CI 0.77 to 0.88). Comparison between the predicted risks and the observed frequencies of AUR showed underestimation of the nomogram in the validation dataset for high AUR risk values. Still, the negative predictive value for the risk of AUR, using a cut-off value of 5%, was high (98.1%).

Conclusion

External validation of the nomogram shows adequate discrimination of AUR, but underestimation of the actual AUR risk for high AUR risk values. Since the nomogram is able to correctly identify low risk patients with a negative predictive value of 98%, the nomogram can aid in individualized treatment decision-making.

Introduction

The most predominant severe acute toxicity after prostate brachytherapy is acute urinary retention (AUR). Published AUR rates vary from 6% to 34% (1-6). It is known that AUR negatively influences quality of life (7;8). Preoperative prediction of AUR is useful for clinical decision-making and patient counseling. In a previous study, we developed a clinical nomogram to preoperatively predict the risk of AUR after I-125 prostate brachytherapy, using the data of 714 consecutive patients treated at our center (appendix) (9). The nomogram was based on the most important pretreatment risk factors for AUR, i.e. prostate volume, IPSS score, neo-adjuvant hormonal treatment and the extent of prostate protrusion into the bladder. Both calibration and discrimination were adequate (ROC area 0.82). The nomogram showed that among patients with a very low sum score (<18 points) the risk of AUR was only 0% to 5%, and that in patients with a high sum score (>35 points) the risk of AUR was more than 20%.
However, because the nomogram was based on single-center data and patient selection and treatment techniques may differ between centers, accurate predictions are no guarantee for applicability in other patient populations (10-12). The aim of this study was to perform external validation of the nomogram, by using data of patients treated at the Princess Margaret Hospital in Toronto, Canada.

Methods and materials

Patients

The derivation study population consisted of 714 consecutive patients with localized prostate cancer treated with I-125 seed implantation between January 2005 and December 2008 at the University Medical Center Utrecht (UMCU), The Netherlands (9). The validation population consisted of 715 consecutive patients with localized prostate cancer treated with I-125 seed implantation between January 2003 and July 2008 at the Princess Margaret Hospital (PMH), Toronto, Canada. The PMH was chosen for external validation for two main reasons: 1) MR imaging for post-implant dose evaluation is performed, which is required for adequate determination of prostate protrusion (9;13;14); 2) it is a high volume center with meticulous follow-up and documentation of toxicity.
The implantation techniques and dosimetric analyses were similar and according to the guidelines of GEC-ESTRO and American Brachytherapy Society (15-18). *Table 1* summarizes the similarities and differences in I-125 prostate brachytherapy procedures between the centers. The UMCU and the PMH brachytherapy procedures have both been extensively described previously (4;7;19;20).

Table 1 Summery of the I-125 prostate brachytherapy implantation protocols at the UMCU and the PMH.

	UMCU (derivation dataset)	**PMH (validation dataset)**
Eligibility criteria		
Age at implantation	Any	Any
Clinical tumor stage	T1-T2	T1-T2
Initial PSA	< 20 ng/ml	<10 ng/ml; (10-20 under RTOG protocol)
Gleason sum score	≤ 7	≤ 6; (7 under RTOG protocol)
Prostate volume	≤ 50 cc	≤ 60 cc
Neo-adjuvant HT	Prostate volume >50 cc	Prostate volume >50 cc *
Dosimetry goals		
Prescribed dose	145 Gy	145 Gy
Prostate D_{90}	>160 Gy	170-180 Gy
Prostate V_{100}	>95%	>99%
Prostate V_{150}	±66%	54-60%
Prostate V_{200}	±33%	12-20%
Urethra dose	≤ 150% of prescribed dose	≤ 150% of prescribed dose
Rectal dose	≤ 100% of prescribed dose	No pre-plan goals
Imaging		
3D-TRUS (real-time)	Before and after needle insertion	Before and after needle insertion
Fluoroscopy	After implantation	After each row of needles
MRI	Pre-implant and 4 weeks post-implant (1.5 or 3 Tesla)	4 weeks postimplant (1.5 Tesla)
CT	4 weeks post-implant	4 weeks postimplant
Procedure		
Pre-planning	MRI based	TRUS based
Anaesthesia	Spinal	General
Source type	Iodine 125	Iodine 125
Average seed activity	0.51 U (1U = 1μGym^{2}h^{-1})	0.4 U
Type of seeds	Stranded (50%) or loose (50%)	Stranded (17%) or loose (82%)
Supplemental EBRT	No	No
Post-implant catheter	Taken out immediately after procedure	Taken out immediately after procedure
Routine steroids	No	No
α-blocker use	For 1 month; and as long as symptoms persisted	1 week before to 3 months after implant; and as long as symptoms persisted

Continued ►

Table 1 Continued

	UMCU (derivation dataset)	PMH (validation dataset)
Follow-up		
Frequency	At 1,3,6,9,12 months, and twice annually thereafter	At 1,3,6,9,12 months, and twice annually thereafter
Physician	Alternately by radiation oncologist and urologist	Radiation oncologist
Documentation	AUA, toxicity scores, intervention data	AUA, toxicity scores, intervention data
Minimum follow up	6 months	6 months

* Initially, neo-adjuvant HT for downsizing of the prostate was given to patients with prostate volumes >50 cc, however the use of HT diminished over time after reports on increased urinary retention with this approach and also generalized toxicity of HT

All patients were treated in lithotomy position. The radioactive seeds were inserted transperineally according to the preplan in a modified peripherally loaded Seattle technique (4). All implants were evaluated at 1 month, by using CT and 1.5 or 3.0 Tesla MRI fusion. Implant quality was defined in terms of the standard dosimetric parameters D_{90}, $V_{100,}$ V_{150} and V_{200} (16). Urinary function was assessed using IPSS questionnaires, which were completed at baseline and at each follow-up visit. AUR was defined as any need for urinary catheterization within 3 months after implantation (21).
Research Ethics Board approval was obtained to access the data from the PMH prospective database of patients treated with I-125 prostate brachytherapy monotherapy. A consecutive cohort of patients was selected between January 2003 and July 2008, ensuring adequate patient numbers and a substantial follow-up. Baseline characteristics and posttreatment sequelae were retrieved, including the dates and duration of retention and catheterization.

Determination of prostate protrusion

The extent of prostate protrusion into the bladder was recently shown to be a strong independent predictor of AUR (9;14). It relates to large median lobes and was defined as the maximum distance from bladder base to prostate base (14). The extent of prostate protrusion was determined on sagital MR images for all patients at PMH, retrospectively. All delineations were performed by the same physician (E.R.), who was blinded to the patient's AUR-status.
Our previous study (9) showed that the inter- and intra-observer variability of prostate protrusion measurements were good (i.e., 0.7 mm [SD ± 0.9] and 0.4 mm [SD ± 0.7], respectively). Pearson correlation coefficients (*r*) were calculated and showed that both inter- and intra-observer repeatability of prostate protrusion measurements were high ($r = 0.97$ and $r = 0.94$, respectively).

Statistical analysis

Clinical and treatment characteristics of patients from the derivation and the validation dataset were computed. Multivariate logistic regression analysis was performed to explore the predictive values of the predefined predictors of AUR in the nomogram (i.e. prostate volume, IPSS, neo-adjuvant hormonal treatment, and the extent of prostate protrusion) (9).
Proper validation requires the use of the fully specified existing prognostic model (that is, both the selected variables and their coefficients) to predict outcomes for the patients in the validation dataset and then compare these predictions with the patients' actual outcomes. Therefore, the risk of AUR was calculated for each individual patient in the validation dataset using the following equation (9):

Risk of AUR = 1 / (1 + EXP(- linear predictor)) * 100%
Linear predictor = -4.84 + (0.021 * prostate volume) + (0.538 * IPSS_1†)+
(1.332 * IPSS_2†)+(1.677 * IPSS_3†)+(0.035 * HT)+(0.427 * prostate protrusion)
† IPSS_1 = 1, if IPSS 6-10
† IPSS_2 = 1, if IPSS 11-20
† IPSS_3 = 1, if IPSS >20

The predictive accuracy of the nomogram was quantified using discrimination and calibration measures. Differences in discriminative ability (i.e. the ability of the model to distinguish patients who develop AUR yes or no) between the derivation and validation model were quantified by the area under the receiver operating characteristic curve (ROC area). The ROC area may theoretically range from 0.5 (discrimination equivalent to that of chance) to 1.0 (perfect discrimination) (22). Calibration of the final model (i.e. agreement between observed and predicted numbers of AUR) was determined by comparing the predicted and the observed numbers of AUR among 5 risk groups. In addition, calibration was statistically tested across deciles of predicted risks with the Hosmer-Lemeshow test, where an insignificant test indicates good model fit (12). Furthermore, the negative predictive value using u cut-off value of 5% was computed. The 5% cut-off value was chosen, because the AUR rate in our population was 8.0% and a reduction in AUR rate is aimed for.
A commercial statistical package of social sciences (SPSS version 16.0; SPSS, Chicago, IL) and R was used for statistical analysis of the data.

Results

The AUR rates of patients treated at the UMCU and the PMH were 8.0% and 9.4%, respectively. The mean time to AUR was 30 days (range, 0-90) at the UMCU and 10 days (range, 0-90) at the PMH. The median duration of catheter dependency was 37 days (range, 2-140 days) and 10 days (range, 1-360), respectively.

Table 2 summarizes the clinical and treatment characteristics of patients treated at the UMCU (derivation dataset) and the PMH (validation dataset). The datasets were largely comparable, except for neo-adjuvant hormonal treatment, Gleason-score, and initial PSA values, which were all lower in the validation dataset (due to the institution's eligibility criteria). The mean number of implanted needles and seeds were higher in patients treated at the PMH probably due to the lower average seed strength.

Like in the UMCU dataset (9), patients who developed AUR had significantly higher pretreatment prostate volumes, higher IPSS scores, larger extents of prostate protrusion, and were more frequently treated with neo-adjuvant hormonal therapy compared to patients without AUR. Multivariate logistic regression analyses of the derivation dataset and the validation dataset are shown in *Table 3*. The OR's between the derivation and validation dataset are largely comparable, except for prostate protrusion (higher predictive value).

The discriminative value (i.e. the ability of the model to distinguish patients who develop AUR yes or no) of the nomogram in the validation dataset was high (ROC area 0.86; 95% CI, 0.82 to 0.91), which is comparable with the discrimination in the derivation dataset (ROC area 0.82; 95% CI, 0.77 to 0.88). In *Figure 1* the ROC curve for the validation dataset is shown.

Figure 2 shows the calibration plot (i.e. agreement between predicted risks and the observed frequencies of AUR). The dotted line shows the ideal, and the solid line shows the association between the predicted risk and the observed frequency of AUR. The nomogram underestimated the risk of AUR in the validation dataset for high AUR risks. The Hosmer-Lemeshow test was statistically significant ($p < 0.001$; $\chi^2 = 47.5$), which also indicates poor calibration. However, 70% of the patients had an AUR-risk of < 5%, and for risks < 5% the calibration was sufficient. Moreover, the negative predictive value for AUR (using a clinically useful cut-off value of 5%) was high (98.1%), indicating that for a predicted AUR-risk of less than 5%, indeed 98.1% of patients did not develop AUR.

Table 2 Clinical and treatment characteristics for patients treated at the UMCU and patients treated at the PMH. Values are means (±SD) or numbers (%).

Characteristic	UMCU (n=714)	PMH (n=715)
Pretreatment		
Age at implantation (y)	65.1 (±6.4)	62.2 (±6.9)
Clinical tumor stage		
T1	498 (70%)	481 (67%)
T2	216 (30%)	234 (33%)
Gleason sum-score		
<7	548 (77%)	668 (93%)
7	166 (23%)	47 (7%)
iPSA (ng/ml)	9.8 (±5.3)	5.5 (±2.4)
Pretreatment IPSS		
0-5	257 (36%)	393 (55%)
6-10	199 (28%)	195 (27%)
11-20	243 (34%)	117 (16%)
>20	15 (2%)	10 (1%)
Pretreatment TURP		
Yes	11 (1.5%)	1 (0.1%)
No	703 (98.5%)	714 (99.9%)
Neo-adjuvant HT		
Yes	137 (19%)	24 (3%)
No	577 (81%)	691 (97%)
Pretreatment prostate volume (cm^3)	35.4 (±9.0)	35.1 (±10.6)
Prostate length (cm)	4.2 (±0.6)	3.8 (±0.4)
Prostate protrusion (mm)	1.1 (±1.9)	1.0 (±1.3)
Treatment		
Needles (n)	24.1 (±3.8)	30.5 (±4.3)
Seeds (n)	73.3 (±13.1)	105.3 (±16.6)
Prostate D_{90} (Gy)	164.1 (±28.5)	167.0 (±18.4)
Prostate V_{100} (%)	93.1 (±6.7)	95.3 (±4.2)
Prostate V_{150} (%)	71.3 (±11.6)	60.7 (±10.5)
Prostate V_{200} (%)	39.1 (±11.7)	29.3 (±8.1)

Abbreviations: UMCU = university medical center Utrecht; PMH = Princess Margaret Hospital; iPSA = initial prostate-specific antigen level; IPSS = international prostate symptom score; TURP = transurethral resection of the prostate; HT = hormonal treatment; D_{90} = minimal dose received by 90% of prostate; V_{100}, V_{150}, V_{200} = percentage of prostate/urethra volume receiving 100%, 150% and 200% of prescribed dose, respectively.

Table 3 Multivariate logistic regression analysis for the prediction of AUR after prostate brachytherapy, in the UMCU and PMH dataset

	UMCU (derivation dataset)				PMH (validation dataset)			
Factor	OR	(95% CI)	*p*	ß coefficient†	OR	(95% CI)	*p*	ß coefficient
Prostate volume (cm^3)	1.02	(0.99-1.06)	0.243	0.021	1.00	(0.97-1.03)	0.916	0.002
Pretreatment IPSS			0.003				0.043	
0-5								
6-10	1.78	(0.69;4.64)		0.538	2.03	(1.01;4.08)		0.707
11-20	4.18	(1.78;9.81)		1.332	1.86	(0.81;4.27)		0.619
>20	6.05	(1.18;30.9)		1.677	8.62	(1.45;51.4)		2.154
Neo-adjuvant HT (yes/no)	1.04	(0.52-2.07)	0.914	0.035	0.71	(0.18;2.76)	0.617	-0.348
Prostate protrusion (mm)	1.58	(1.40-1.79)	0.000	0.427	3.13	(2.42;4.06)	0.000	1.141
Intercept				-4.84				-4.69
-2 log likelihood				-284.4				-293.5
ROC area				**0.82**				**0.89**

Abbreviations: AUR = acute urinary retention; UMCU = university medical center Utrecht; PMH = Princess Margaret Hospital; OR = odds ratio; CI = confidence interval; IPSS = international prostate symptom score; HT = hormonal treatment; ROC = receiver operating characteristic.
† ß coefficients were multiplied by a shrinkage factor of 0.93, to adjust for optimism that might be expected when the model is applied to new, but similar patients. The intercept was also adjusted to the new situation.

Discussion

External validation of clinical prediction tools is important. Accurate predictions in patients that were used to develop a nomogram are no guarantee for good predictions in other patient populations (10-12). Only after external validation, a model is considered generally applicable. In this study, we found accurate discrimination for AUR when the nomogram was tested in the validation population (ROC area 0.86). Calibration was sufficient for low AUR risks, but poor for high AUR risks. Since the negative predictive value for AUR at a cut-off value of 5% was high (98.1%), the nomogram is able to correctly identify low risk patients, but for a reliable estimation of risks higher than 5% calibration of the nomogram should be improved.
Theoretically, differences in patient and treatment techniques might influence the risk of AUR. We did not find a major difference in AUR rate between the UMCU and PMH (8.0% versus 9.4%). Patients at the PMH had lower mean iPSA levels, lower Gleason scores, and were less frequently treated with neo-adjuvant HT (*Table 2*), which was due to the eligibility criteria for I-125 prostate

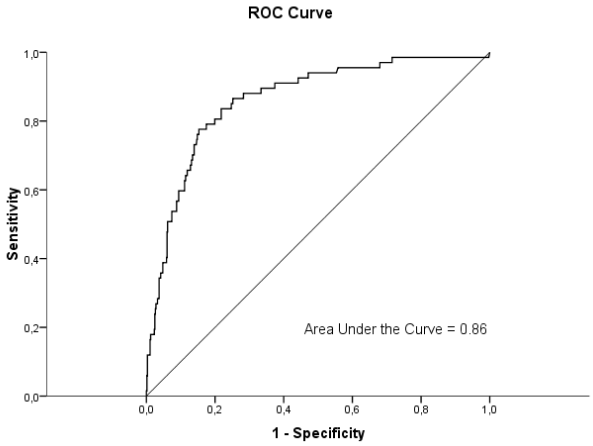

Figure 1 Receiver operating characteristic (ROC) curve for the predictability of acute urinary retention in the derivation dataset, based on pretreatment prostate volume, International Prostate Symptom Score (IPSS), neo-adjuvant hormonal treatment (HT), and prostate protrusion.

brachytherapy (*Table 1*). The higher number of implanted needles and seeds in patients treated at the PMH (*Table 2*) might be explained by the lower average seed strength used. Since the prescribed dose to the prostate was the same at both institutions (145 Gy), a larger number of seeds is required in case of lower average seed strength. Although some minor differences in patient- and treatment characteristics existed, these differences did not influence the discrimination of the nomogram. This implies that the nomogram is also applicable to patients treated at other centers. Furthermore, the high ROC values indicate that the nomogram indeed contained the most important predictors of AUR. An extensive evaluation of these risk factors in the context of recent literature was performed in our previous paper (9).

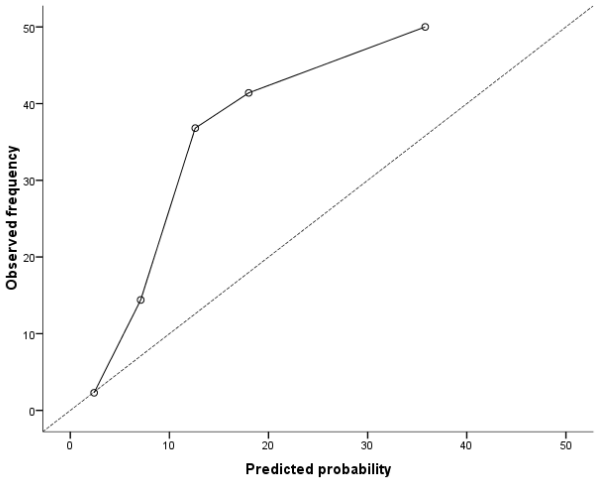

Figure 2 Calibration plot. The continuous line shows the relation between observed frequencies and predicted probabilities. The dotted line indicates perfect calibration, that is, observed frequencies and predicted probabilities are in complete agreement.

The slightly higher ROC value in the validation population compared with that of the derivation population (0.86 versus 0.82) might be explained by the higher predictive value of prostate protrusion combined with the smaller standard deviations in the validation dataset.

When comparing the predicted risks with the observed frequencies of AUR (calibration), the nomogram underestimated the risk of AUR in the validation population for high AUR risk values (*Figure 2*). Several explanations are available for this finding: 1) the higher incidence of patients with AUR in the validation dataset. Although the absolute difference was only 1.4%, the relative difference was 18%; 2) the slight differences in patient- and treatment characteristics might influence calibration measures; or 3) the low number of patients with an AUR risk of > 5% (70% of the patients had an AUR risk of < 5%). In *Figure 2* can be seen that predictions up to 5% are adequate. Therefore, the nomogram can be safely used for risk scores up to 5%. However, caution is warranted for interpretation of risk scores larger than 5%. Since the AUR rate in our population was 8.0% and a reduction in AUR rate is aimed for, a cut-off value of 5% is reasonable. We showed that the negative predictive value for AUR, using a cut-off value of 5%, was high (98.1%). This indicates that for a predicted AUR-risk of < 5%, 98.1% of patients indeed did *not* develop AUR.

Where to place the cut-off value for an 'unacceptable' high risk of AUR remains unclear and is dependent on the expert opinion of the physician and the patient's individual preference. This nomogram provides a more accurate risk assessment to individual patients when discussing brachytherapy as one of their treatment options. Men with a favorable risk score may, therefore, be more confident in their decision to proceed with seed implants, and ultimately the overall rate of retention could decrease in time with appropriate patient selection. Conversely, in patients with a very high risk of retention, alternative treatment options might be considered. However, the risk of AUR still has to be weighed against the toxicity profile of other treatment options.

There are some limitations of this study which should be mentioned. Vergouwe *et al.* (10) recommended at least 100 events for external validation in order to obtain enough power (80%). However, that is the ideal situation, but may not be feasible clinically, especially when the event rate is low. In literature, sample sizes of validation sets differ over a wide range. In a review of Altman *et al.* (23), validation samples with sizes varying between 52 and 479 patients were described, and the number of events ranged from 24 to 115. Therefore, by including 715 patients and 67 events, our validation population can be considered adequate compared to other published validation studies. Furthermore, according to the state of the art methodology guidelines (12), our nomogram is based on a limited set of predictors at multivariate analyses from

reviewed literature. More potential predictors have been described, however, in single studies or on univariate analysis only. Further research might lead to an extension and improvement of the predictive value of the model after addition of other relevant risk factors. Updating of the nomogram might lead to improvement of calibration measures (11). Continued efforts to refine and establish validity of the nomogram across worldwide patient populations are thus needed to realize the goal of assisting men and their care providers in appraising risks and making individualized treatment choices. Nevertheless, we showed that in two individual patient cohorts of more than 700 patients each, the model performs reasonable well.

Conclusions

External validation of the nomogram shows adequate discrimination among patients for the risk of AUR. The nomogram is able to correctly identify low risk patients with a negative predictive value of 98%. Therefore, the nomogram can be widely used to predict the risk of AUR after I-125 prostate brachytherapy. Since the balance between treatment outcome and quality of life is considered very important nowadays, the nomogram might be a useful tool for physicians and patients in individualized treatment decision-making in low risk prostate cancer.

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Chapter 9

General discussion and future perspectives

Nowadays, prostate cancer is the most frequently diagnosed type of cancer and the second most common cause of cancer death in the western world (1). To date, no significant differences in biochemical failure and survival rates have been shown in retrospective studies between radical prostatectomy, EBRT, and brachytherapy (2-5). Therefore, additional outcome measures are required for treatment selection and patient counseling. Health related quality of life (HRQOL) should be one of these, since the balance between treatment outcome and HRQOL is considered very important for patients and is currently gaining lots of interest (6).
HRQOL is influenced by toxicity after treatment. The most common acute grade 3 toxicity after prostate brachytherapy is acute urinary retention (AUR) (7), occurring in approximately 10% of patients (8-13). Since the incidence of prostate cancer is expected to increase further, the social impact of AUR will rise as well. In this perspective, the overall aim of this thesis was to evaluate long-term HRQOL after I-125 prostate brachytherapy, and to identify risk factors for AUR in order to predict AUR prior to implantation. In the following paragraphs, the main findings and the clinical value of the developed prediction model (nomogram) are discussed and future perspectives are considered.

Quality of life

The popularity of prostate brachytherapy is probably attributable to the excellent survival rates combined with a perceived favorable toxicity profile. In *chapter 2* long-term HRQOL after I-125 prostate brachytherapy is described. Extended validated questionnaires including cancer- and prostate specific HRQOL items were used to study HRQOL. We showed that after an initial worsening of almost all HRQOL-items at one month posttreatment, HRQOL generally returns to baseline levels at one year and stayed stable up to six years after treatment.
Some degree of urinary morbidity related to urethritis and prostatitis is common in the postimplant period (14-20). The increase in IPSS score at one month posttreatment is frequently described (14;15;17;21;22). We showed that urinary and bowel symptoms tend to peak at about one month, but improve with time, as do function and bother scores. Since HRQOL at one and six years after treatment was satisfactory, urinary and bowel toxicity after prostate brachytherapy seem mainly to be early events; or, at least, do not influence long-term HRQOL.
Sexual activity was decreased at six years after treatment compared to baseline, without worsening of sexual functioning. Although a certain degree of sexual dysfunction might be expected from literature (erectile dysfunction rates range

from 14% to 66% (7;23)), it is important to recognize the discrepancy between sexual functioning and sexual activity. A decrease in sexual activity might not only be explained by the possibility of achieving an erection, but also by aging, the loss of a partner, or the detrimental psychological effect of cancer on the patient's frequency of sexual activity (24).

No significant differences from baseline were observed in the nonphysical function scales, which is in accordance with the short-term RAND-36 results after prostate brachytherapy of Caffo *et al.* (25). Compellingly, we found a clinically relevant improvement in emotional functioning at six years after treatment. Improvement in emotional functioning after cancer therapy has been described for other cancer types as well and might be explained by patients having had time to adapt to the situation, a response shift mechanism, or a decreasing fear of recurrence and death with time (26;27). This finding corresponds to the results of *chapter 3*, in which we found no evidence for increased depression rates after I-125 prostate brachytherapy treatment.

Comparison of our results with long-term HRQOL after radical prostatectomy or EBRT remains difficult, because of the lack of randomized studies. Several non-randomized studies are available comparing HRQOL after radical prostatectomy, EBRT, and brachytherapy (32-36). In summary, each of the three therapies showed a unique pattern of changes in HRQOL related to urinary symptoms, bowel function, and vitality or hormonal function. In the review of Henderson *et al.* (37), HRQOL outcome following brachytherapy compares favorably with other radical treatment options, except for short-term obstructive and irritative urinary symptoms. Furthermore, the use of different HRQOL questionnaires makes interpretation of the various study outcomes a challenge. For proper HRQOL research, it is therefore recommended to use internationally validated questionnaires, to include baseline measures, and to aim at long-term follow-up (28-31).

Another challenge in HRQOL research is the interpretation of HRQOL scores. A statistically significant difference in HRQOL is not always clinically relevant for the patient (38). According to published data concerning the interpretation of HRQOL scores, a change of ≥ 10 points on a 100-point scale is considered clinically relevant (39). We used this definition for the interpretation of our results. We found that hormonal therapy, iPSA value, prostate volume and older age were associated with a clinically relevant worse HRQOL after I-125 prostate brachytherpy.

The same factors were confirmed by the large study of Sanda *et al.* (32), in addition to obesity and black race, which were not examined in our study. Recognition of these factors by physicians is important for patient counseling and treatment policy. For example, the question whether to prescribe neo-

adjuvant hormonal therapy. Since several studies reported that androgen suppression (also of limited duration), was associated with long-lasting symptoms involving sexuality and vitality (17;32;40), the enthusiasm for adjuvant hormonal therapy in the setting of disease of low or intermediate risk has mitigated worldwide. Of course, notwithstanding the survival benefit of androgen deprivation in randomized clinical trials involving high-risk patients with localized prostate cancer (41).

Because long-term survival might be expected after treatment with prostate brachytherapy, a reasonable HRQOL is considered very important for patients. Moreover, a recent study showed that changes in HRQOL also influence satisfaction with treatment outcomes among patients and their partners (32). Our results indicate a favorable pattern of long-term HRQOL after I-125 prostate brachytherapy and add in individualized decision-making for a primary treatment for low stage prostate cancer.

Acute urinary retention

Although toxicity rates after I-125 prostate brachytherapy are generally low (7;15;18;42-44) and improvements in treatment and imaging techniques continue to reduce adverse events, acute urinary retention (AUR) is still a very distressing event for patients. AUR occurred in 8% of our patients. In *chapter 4*, we showed that the development of AUR has a negative impact on the patient's HRQOL. AUR not only causes acute morbidity, but also negatively influences HRQOL over a posttreatment period of at least 6 years.

The worsened urinary HRQOL in patients who developed AUR can be explained by the known short- and long-term problems associated with AUR. Ikuerowo *et al*. (45) described several side effects associated with prolonged catheterization, including urethral and suprapubic pain, bleeding, loss of dignity, loss of job, lack of sexual activity, peri-catheter leakage of urine and recurrent urinary tract infection. Unhappiness was reported by 85% of the patients and furthermore, there were considerable costs associated with prolonged catheterization. Other studies confirm that patients who develop AUR are at higher risk of late urinary morbidity (14;42), such as urethra stricture formation (21;43). The long-lasting negative impact of AUR on HRQOL strengthens the importance of preventing AUR.

Predictors of acute urinary retention

In a large cohort of patients, we assessed which patient and treatment factors were associated with the development of AUR after I-125 prostate brachytherapy. Since inconsistency existed in literature about the influence of dose on the risk of AUR, we focused on dose in *chapters 5 and 6*. We found that prostate volume, pretreatment IPSS score, neo-adjuvant hormonal therapy, and prostate protrusion into the bladder were independent predictors of AUR.

There is no doubt that patients with a large pretreatment prostate volume are at increased risk of developing AUR (11-13;46). In our cohort, patients with a pretreatment prostate volume of > 35 cm^3 had a 10.4% risk of developing AUR compared with 5.4% for prostate volumes ≥ 35 cm^3. Several studies confirm this finding (11-13;46). The increased risk of AUR in patients with large prostates might be due to the larger number of needles and seeds required, or by the often higher degree of benign prostate hypertrophy (BPH). BPH reduces the elasticity of the urethra during voiding and produces gradually increasing bladder outlet obstruction (47).

Also, the patient symptom score before treatment is a convincing predictor of urinary morbidity after brachytherapy (8;10;13). The probability of developing AUR was 1.3-fold higher per unit increase in baseline IPSS, which implies that the risk of AUR was 11% if IPSS was 10 and 34% if IPSS was 20. Similarly, Bucci *et al*. (10) showed that the risk of AUR in patients with baseline IPSS of 0-5, 6-15 and >15 was 10%, 17%, and 33%, respectively. IPSS score reflects the degree of pre-existent obstruction. If a certain degree of obstruction is present before implantation, additional trauma and edema after the implant may be enough to overcome the compensatory mechanism of the detrusor muscle and result in AUR.

Conversely, the predictive value of neo-adjuvant hormonal therapy (NHT) is less evident. Initially, several groups reported that patients who received NHT were at increased risk of developing AUR (8;11). Terk *et al.* (8) demonstrated a 14% risk of AUR after NHT in combination with seed implantation compared with <1% in patients without NHT. Similar to these data, in our first series of 127 patients we found the risk of developing AUR to be 4.0-fold higher after treatment with NHT independent of prostate volume (*chapter 5*). However, in our larger studies on 714 patients, the predictive value of NHT lost significance in multivariate analyses (*chapter 5*,6,7 *and* 8). The updated large series of Crook *et al.* (48) corroborates this finding. Conversely, in a recent study of Stone *et al.* a lower risk of AUR after NHT was found. They concluded that men with large glands and high IPSS scores may be considered candidates for NHT to decrease the risk of AUR. The inconclusive results on the predictive value of NHT might

be explained by the relatively small amount of low risk prostate cancer patients treated with NHT, diminishing the power of the analyses.
In *chapter 5*, we analyzed the effect of dose to the prostate on the development of AUR. A short review of available studies incorporating dose and AUR was included (9-11;13;22;46;49-51). We concluded that dose to the prostate did not influence the risk of AUR. Moreover, dose to different regions within the prostate was not associated with the risk of AUR (*chapter 6*). A reasonable explanation for the absence of a relation might be that, given the I-125 half-life of 60 days, it takes a few months before a substantial dose has been delivered to the prostatic tissue. Because most patients developed AUR within the first month after implantation (median time to AUR was 30 days), dose is unlikely to be an important risk factor. Therefore, we do not recommend intraoperative dose-limiting modifications (other than those stated in the guidelines (52;53)), because these do not warrant a reduced risk of AUR.
By contrast, we found that a higher dose to the bladder neck was associated with an increased risk of AUR. This finding is consistent with the study of Stegerda *et al.* (54), in which bladder hotspot dose was a predictor of urinary morbidity. Possible explanations might be a higher radiation sensitivity of bladder tissue compared with prostatic tissue, or needle trauma at the bladder neck (55;56). Given that approximately 70% of all prostate tumors arise in the peripheral zone (57;58), it might be recommendable to be more conservative with needle and seed placement at the prostate base, but only in patients where tumor location is evident.
The contributing risk of a quantitatively enlarged median lobe is evident from our data (*chapters 6 and 7*). Prostate protrusion into the bladder is commonly seen in patients with progressive expansion of the transition zone associated with BPH. We hypothesized that a swollen protruding median lobe after implantation might cause bladder outlet obstruction resulting in AUR. Nguyen *et al.* (59) showed that the AUR rate in patients with median lobe hyperplasia was high (20%). They were the first and only thus far, in considering median lobe hyperplasia to be a contraindication to prostate brachytherapy. Several other studies reported that a large pre-implant transition zone index was predictive for prolonged urinary morbidity and catheterization after prostate brachytherapy (60-62).
The exact extent of prostate protrusion remains difficult to measure. Prostate protrusion is best visualized on sagital MR images. CT and TRUS are insufficient because of their low soft tissue contrast (57;58). Cystoscopic evaluation can be another adequate option to depict prostate protrusion; however, the invasiveness of the procedure is a considerable disadvantage (www.uroweb.org/EAU guideline). In clinical practice, it might be more useful to score prostate

protrusion as either present or absent, instead of applying a continuous scale. Further research is needed to confirm the value of dichotomous measurements. Differences between studies in factors found to be predictive for AUR may be caused by different patient selection, different intraoperative techniques, different seed activity, and possibly systematic and random differences in pre- and postimplant prostate contouring, use of steroids, or AUR definition. The exact pathophysiology of AUR is still unknown, however, traumatic edema and hematoma is thought to play a major role.

Clinical implementation of the nomogram

In *chapter 7* we presented a nomogram to preoperatively predict the risk of AUR after I-125 prostate brachytherapy. Since the nomogram is based on single-center data and patient selection and treatment techniques may differ between centers, accurate predictions are no guarantee for applicability in other patient populations (63-65). Therefore, external validation of the nomogram was performed (*chapter 8*). The Princess Margaret Hospital (PMH) in Toronto was chosen for external validation for two main reasons: 1) MR imaging for post-implant dose evaluation is performed (required for adequate measurement of prostate protrusion) (57;58); and 2) it is a high volume center with meticulous follow-up and documentation of toxicity.

We showed accurate discriminative ability of our predictive model when tested in the validation population (ROC 0.86), indicating that the nomogram was able to distinguish patients with and without AUR and that the nomogram was thus correctly based on the most important predictors of AUR (63). The calculated risk scores depict considerable individual variation in the risk of AUR, varying from 0% to more than 50%. Therefore, the nomogram improves selection of ideal candidates for prostate brachytherapy and provides a more accurate risk assessment to patients when discussing brachytherapy as one of their treatment options. Men with a favorable risk score may therefore be more confident in their decision to proceed with seed implants, and ultimately the overall rate of retention could decrease in time with appropriate patient selection. Conversely, in patients with a very high risk of retention, alternative treatment options might be considered.

Where to place the cut-off value for an 'unacceptable' high risk score remains unclear and is dependent on the expert opinion of the physician and the patient's individual preference. In our opinion, estimated risk proportions of 0-5% are low, 5-10% are intermediate and >10% are high. We consider risk scores up to 5% acceptable, but this does not imply to withhold patients with an intermediate risk score from brachytherapy. The risk of AUR has to be discussed

with each individual patient and has to be weighed against the toxicity profile of other treatment options.
The decision on what treatment policy to pursue in case of an 'unacceptable' high risk of AUR also depends on individual preferences. Some patients might prefer a treatment option with a different toxicity profile, while other patients might accept the relatively high risk of AUR. In clinical practice, the benefit of treatment has to be weighed against the risk of severe acute or long-term adverse events and treatment costs. Since prostate tumors are often slowly dividing with high PSA-doubling-times, the gain of treatment (especially for older patients) is not always clear (66;67). Therefore, in selected patients with early-stage, low-grade prostate cancer, active surveillance should be considered as well (68;69). However, identification of indolent tumors and dedifferentiation into high risk tumors during follow-up remain challenges (70). Furthermore, it has to be noted that active surveillance is no guarantee for a better HRQOL, since anxiety and distress of withholding radical treatment and performing repeated biopsies may also negatively influence HRQOL (71). It has been shown that fear for progression to incurable disease is the most common reason for patients to reject active surveillance (72;73).
The fact that the differences in patient characteristics and treatment techniques between the UMCU and PMH did not influence the performance of the model, implies that the nomogram is also applicable to patients treated at centers with implant techniques in between the UMCU and PMH. However, the UMCU and PMH are both high-volume hospitals. The question rises whether the nomogram is applicable to patients treated at smaller centers as well. Based on our results, we recommend to any center performing I-125 prostate brachytherapy to assess prostate volume, IPSS score, hormonal therapy and prostate protrusion prior to implantation for each individual patient, in order to minimize the risk of AUR. Furthermore, since treatment outcomes and toxicity profiles have been shown to be dependent on experience and accreditation (13), one should focus on quality improvement at each center, and adequate toxicity and HRQOL documentation is important.

Future perspectives

Despite external validation and the demonstrated high discriminative power of the model (ROC area 0.82), calculated risk scores remain estimates. The risk of urinary retention is likely multifactorial in nature and is probably only crudely estimated by the available known risk factors. Further research might lead to an extension and improvement of the predictive value of the model after addition of new relevant risk factors.

From the urology point of view, one might notice the lack of functional urinary measurements in our data. According to the EAU guidelines, uroflowmetry is recommended in the work-up of patients with LUTS prior to surgical intervention (www.uroweb.org/guidelines). A low peak flow rate indicates obstructive urinary symptoms and might lead to an increased risk of AUR (22;74;75). Therefore, some centers discourage patients from undergoing brachytherapy if peak flow rate is less than 10 mL/s (75). Although there are suggestions that peak flow rate is a powerful risk factor for AUR (22;74;75), the available studies are limited by the small number of patients. In a preliminary analysis on 715 patients treated at the PMH, we found no association between peak flow rate and the development of AUR. Mean peak flow rate in patients who developed AUR was 17.9 ml/s versus 18.8 ml/s in patients without AUR ($p = 0.50$). This result strengthens our hypothesis that uroflowmetry is not necessarily required prior to prostate brachytherapy. In ongoing research, we will further explore the relation between peak flow rate and the risk of AUR in multivariate analysis.
The worldwide increase in the use of MRI for prostate brachytherapy will enable prostate protrusion measurements at more centers in future. Ongoing developments of imaging techniques might lead to improved depiction of median lobe protrusion, and thereby to more accurate prediction of AUR. Furthermore, diffusion weighted imaging (DWI), dynamic contrast enhanced (DCE) MRI, and MR spectroscopy are promising imaging techniques for tumor localization. In literature, the sensitivity of T2-weighted imaging for cancer detection varies from 60% to 96% (76). Several groups have convincingly shown that DCE-MRI significantly improves the accuracy of prostate cancer localization (76-79). If tumor localization is evident, focal seed implantation might lead to a further reduction of AUR rates in future. However, as 50-90% of prostate tumors are multifocal at diagnosis (80), focal treatment for macroscopic tumor lesions is estimated to be feasible in the minority of cases only. Still, outcomes after focal treatment have to be confirmed in randomized controlled trials.

What can be done in the peri- or postoperative period to reduce retention?
One approach to reduce prostate swelling as a contributing factor to urinary retention is by giving perioperative steroid therapy. Speight *et al.* (81) have documented improved DVH (dose volume histogram) associated with steroid use; however, no data on the rate of urinary retention are available to date. Furthermore, the inflammatory response caused by needle trauma might be reduced by giving peri-operative NSAIDs. Although at some brachytherapy centers peri-operative NSAIDs and/or steroids are standard of care (13), to date no randomized trial is available confirming a decreased risk of AUR after NSAID prescription.

There is a learning curve involved in any technical procedure. Keyes *et al.* (13) showed that increase in volume of work and institutional experience affected not only outcome but also toxicity from prostate brachytherapy. Inexperienced operators may require multiple needle insertions to accurately place seeds causing increased bleeding and inflammation. Therefore, ongoing training and development of technical skills are required to improve implant quality and to reduce AUR rates.
Several attempts have been made to reduce AUR rates by pre-implant limited invasive procedures. Williams *et al.* (22) reported to consider resection or incision of the prostatic median lobe for all patients with prostate protrusion into the bladder after cystoscopic evaluation. Voulgaris *et al.* (82) performed bladder neck resection at their center prior to implantation on patients with small prostates (40 cm^3) but obstructive symptoms and on patients with high bladder neck evident on sagital transrectal ultrasound visualization and endoscopically. Furthermore, laser photoselective vaporization of the prostate is performed in some centers before seed implantation in patients presenting with a peak flow rate of < 5 ml/s (74). Although these new procedures seem promising, to date, no data on reduction of AUR rates after prostate brachytherapy are available and, therefore, further research is warranted.

Continued efforts to refine and establish the validity of the nomogram across worldwide patient populations are needed to realize the goal of assisting men and their care providers in appraising risks and making individualized treatment choices. Ongoing HRQOL research is important, since HRQOL enters into virtually all discussions of treatment for localized prostate cancer. The above-mentioned perspectives might lead to more individualized treatment in future. Due to more experience, improvement in imaging and planning techniques, and due to better understanding of the pathophysiology of AUR, we are likely to see a drop in AUR rate in future. This might lead to a further improvement of HRQOL in patients treated for localized prostate cancer.

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Chapter 10

Summary

Prostate cancer is the most common type of cancer in men in the Western world. In the last decades, the incidence of prostate cancer has risen substantially, which is partly due to the introduction of PSA screening methods. As our population ages, we are likely to see a continuing increase in the prevalence of prostate cancer.

For localized prostate cancer, different curative treatment options are available. The most common are radical prostatectomy, external beam radiotherapy and I-125 prostate brachytherapy. To date, no significant differences in outcome have been shown between these three treatment options. The median 10-years survival for low risk prostate cancer is 95% after all three treatments.

Besides tumor control, toxicity and health related quality of life (HRQOL) are considered important endpoints that should be taken into account in treatment decision making. HRQOL is more than toxicity alone. It comprises not only somatic functioning, but also the patient's perception of his social and psychological functioning and well-being. It might be clear that reporting toxicity and HRQOL after treatment is considered very important. Since outcomes after treatment for low risk prostate cancer are excellent, long-term follow-up of HRQOL is required.

In *chapter 2*, HRQOL up to 6 years after I-125 prostate brachytherapy is described. During 6 years, 127 patients filled in extended validated HRQOL questionnaires. Results showed that after an initial worsening (at 1 month after treatment), HRQOL gradually improved and returned to baseline values at 1 year after treatment. Subsequently, HRQOL scores stayed stable up to 6 years after treatment. This course of symptoms was also seen for urinary and bowel symptoms. The only clinically relevant changes in HRQOL at 6 years after treatment compared to baseline were found for emotional functioning (improvement) and sexual activity (deterioration).

In *chapter 3*, an extended evaluation of depression scores up to 8 years after I-125 prostate brachytherapy was performed. Depression was found in 10% of the patients, which was not different from depression rates after prostatectomy, external beam radiotherapy or from the normal patient population.

In conclusion, chapter 2 and 3 showed that I-125 prostate brachytherapy did not affect long-term HRQOL when considering the whole cohort of patients. However, acute urinary retention (AUR) (the most important severe adverse event after prostate brachytherapy) might have a negative impact on the patient's HRQOL. If AUR is present, prolonged catheterization or even a transurethral resection of the prostate (TURP) may be required to relieve obstruction, leading to an increased risk of urethral strictures, urinary incontinence and long-term morbidity.

Therefore, we examined the influence of AUR on HRQOL (*chapter 4*). Ten percent of the patients developed AUR after treatment. The mean time to AUR was 30 days and the mean duration of catheterization was 37 days. Patients who developed AUR had a significantly worse HRQOL compared to patients without AUR. Up to 6 years after treatment, global QOL and urinary symptom scores were worse for patients with AUR. We found no relation between HRQOL scores prior to treatment and the development of AUR. Because AUR worsens the patient's HRQOL, it would be interesting to predict AUR.

In *chapter 5*, we examined in a group of 714 patients which patient- and treatment factors were associated with the development of AUR. The most important predictors of AUR were: prostate volume and IPSS score prior to treatment. No relation between dose to the prostate and AUR was found. In *chapter 6*, we conducted a case-control study to evaluate more specifically the relation between AUR and dose to different regions of the prostate. Fifty patients with AUR were compared with 50 patients without AUR. Again, no relation between dose and AUR was demonstrated. Only, the dose to the bladder neck was associated with the development of AUR. Furthermore, several anatomic parameters were examined, of which the extent of prostate protrusion into the bladder was associated with the development of AUR. Prostate protrusion into the bladder is commonly seen in patients with large transition zones associated with benign prostate hypertrophy.

The final aim of this thesis was to develop a clinical nomogram to pre-operatively predict the risk of AUR after I-125 prostate brachytherapy. This nomogram is presented in *chapter 7*. Multivariate analysis showed that the main predictors for AUR were: pre-treatment prostate volume, IPSS score, neo-adjuvant hormonal treatment and prostate protrusion into the bladder. By simply counting the sum-score in the nomogram, the risk of AUR can be read off. The discriminative value of the nomogram was high (ROC 0.82) and calibration measures were good.

To confirm general applicability of the nomogram, external validation is required. This was performed using the data of 715 patients treated at the Princess Margaret Hospital, Toronto (*chapter 8*). External validation of the nomogram shows adequate discrimination between patients with and without AUR. The developed nomogram might be a useful tool for patient management and -counseling to all physicians performing I-125 prostate brachytherapy, and might aid in individualized treatment decision making in patients with localized prostate cancer.

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Prostaatkanker is het meest voorkomende type kanker onder mannen in de Westerse wereld. Het aantal mannen bij wie jaarlijks prostaatkanker wordt gediagnostiseerd is de laatste decennia aanzienlijk gestegen, mede door de invoering van PSA screening. Vanwege de vergrijzing van de bevolking is er de komende jaren een verdere toename van het aantal prostaatkanker patiënten te verwachten.
Voor prostaatkanker dat beperkt is tot de prostaat, zonder kapseldoorbraak en zonder uitzaaiingen naar de lymfeklieren, zijn er verschillende curatieve behandelmogelijkheden beschikbaar. De meest gangbare behandelingen zijn chirurgische verwijdering van de prostaat, uitwendige bestraling of inwendige bestraling (brachytherapie) door middel van radioactief jodium (I-125) zaadjes die in de prostaat worden gebracht. Met een gemiddelde 10-jaars overlevingskans van 95%, is de prognose voor laag risico prostaatkanker relatief goed. Vooralsnog is er geen verschil in overleving tussen de bovengenoemde drie behandelingen aangetoond.
Naast overleving vormen toxiciteit (bijwerkingen) en kwaliteit van leven (KVL) belangrijke uitkomstmaten om te bepalen welke behandeling voor de patiënt het meest geschikt is. Voor het beoordelen van de KVL is het bepalen van de toxiciteit alleen onvoldoende, omdat KVL, naast lichamelijk functioneren, ook het sociale en psychologische functioneren en het algehele gevoel van welbevinden van de patiënt omvat. Het rapporteren van toxiciteit en KVL na behandeling is zeer belangrijk. Aangezien de overleving van laag risico prostaatkanker patiënten zeer goed is, is onderzoek naar de lange termijns effecten van toxiciteit en KVL daarbij noodzakelijk.
In *hoofdstuk 2* wordt de KVL tot 6 jaar na I-125 prostaat brachytherapie beschreven. Hiervoor hebben 127 patiënten 6 jaar lang uitgebreide gevalideerde KVL vragenlijsten ingevuld. Na een aanvankelijke verslechtering (1 maand na behandeling), verbeterde de KVL geleidelijk en na 1 jaar was de KVL voor de meeste KVL-items weer teruggekeerd naar het niveau van vòòr de behandeling. De KVL bleef vervolgens stabiel tot 6 jaar na de behandeling. Dit beloop werd o.a. gezien voor mictieklachten (plasklachten) en darmklachten. Na 6 jaar werden alleen voor emotioneel functioneren (verbetering) en seksuele activiteit (afname) klinisch relevante veranderingen gevonden ten opzichte van vòòr de behandeling.
In *hoofdstuk 3* werd een uitgebreide evaluatie van depressie scores tot 8 jaar na I-125 prostaat brachytherapie verricht. Depressie (gevonden bij 10% van de patiënten) werd niet vaker waargenomen dan na chirurgische verwijdering van de prostaat of uitwendige bestraling, en zelfs niet vaker dan in de normale Nederlandse populatie.

Kortom, uit *hoofdstuk 2 en 3* blijkt dat, voor de gehele groep van patiënten, I-125 prostaat brachytherapie de lange termijn KVL niet beïnvloed. Bijwerkingen na deze behandeling zijn over het algemeen mild, echter speciale aandacht verdient acute urine retentie (AUR), de belangrijkste ernstige bijwerking na I-125 prostaat brachytherapie. AUR zou de KVL nadelig kunnen beinvloeden, aangezien patiënten die AUR ontwikkelen niet meer spontaan kunnen plassen en een urine katheter nodig hebben voor vaak langere tijd. In sommige gevallen is men zelfs genoodzaakt een deel van de prostaat te verwijderen (TURP) vanwege het voortduren van de retentie. Deze ingreep leidt op de lange termijn vaak tot urine incontinentie.

In *hoofdstuk 4* werd daarom de invloed van AUR op de KVL onderzocht. Tien procent van de patiënten ontwikkelde AUR na de behandeling. De gemiddelde tijd tot het ontstaan van AUR was 30 dagen en de gemiddelde duur van katheterisatie was 37 dagen. Patiënten die AUR ontwikkelden hadden een significant slechtere KVL vergeleken met patiënten zonder AUR. Tot 6 jaar na de behandeling waren de scores voor onder andere globale KVL en mictieklachten slechter dan voor patiënten zonder AUR. Er werd geen relatie gevonden tussen de KVL scores voorafgaand aan de brachytherapie en het optreden van AUR na de behandeling. Omdat patiënten die AUR ontwikkelen een slechtere QOL hebben, is het belangrijk te onderzoeken welke factoren voorspellen of een patiënt wel of geen AUR ontwikkelt.

In *hoofdstuk 5* werd in een groep van 714 patiënten onderzocht welke patient- en/of behandelingsfactoren van invloed zijn op het ontstaan van AUR. De belangrijkste voorspellers voor het optreden van AUR bleken: prostaatvolume en de IPSS score (een score voor mictieklachten) voorafgaand aan de behandeling. Er werd geen relatie gevonden tussen de bestralingsdosis in de prostaat en het optreden van AUR.

In *hoofdstuk 6* werd door middel van een case-control studie specifieker gekeken naar de bestralingsdosis in verschillende zones van de prostaat. Vijftig patiënten met en 50 patiënten zonder AUR werden met elkaar vergeleken. Wederom kon er geen relatie tussen de bestralingsdosis in verschillende zones van de prostaat en AUR worden aangetoond. Wel was een hoge bestralingsdosis in de blaashals gerelateerd aan een hogere kans op AUR. Tevens werden een aantal anatomische parameters onderzocht, waarvan de mate van prostaatuitpuiling in de blaas voorspellend bleek te zijn voor het ontstaan van AUR. Prostaatuitpuiling in de blaas wordt vaak gezien bij oudere patiënten met goedaardige vergroting van de prostaat (BPH) waarbij er sprake is van een vergrote centrale zone van de prostaat.

Het uiteindelijke doel van dit proefschrift was een voorspellend model te maken voor het risico op AUR na behandeling met I-125 brachytherapie. In *hoofdstuk 7* wordt dit nomogram gepresenteerd. Multivariate analyse toonde dat de belangrijkste voorspellers voor het ontstaan van AUR prostaatvolume, IPSS score, neo-adjuvante hormonale therapie en prostaat uitpuiling in de blaas waren. Aan de hand van puntenscores voor elke voorspellende factor kan het risico op AUR voor elke individuele patiënt worden afgelezen. Het model blijkt goed te kunnen onderscheiden welke patiënten wel en welke patiënten geen acute retentie ontwikkelen.
Om te weten of het model ook in andere radiotherapie centra toepasbaar is, is externe validatie nodig. In *hoofdstuk 8* wordt het model daarom getest op patiëntengegevens uit het Princess Margaret Hospital in Toronto. Externe validatie toonde goede resultaten, waardoor het model breed toepasbaar zal zijn. Het model is nuttig voor alle artsen die I-125 prostaat brachytherapie uitvoeren, zowel voor risicoanalyse als voor patiëntenvoorlichting. Als er namelijk op basis van dit model, zoals beschreven in hoofdstuk 7, een grote kans op AUR blijkt te bestaan, kan de radiotherapeut de patiënt daarop voorbereiden. Zo mogelijk kan er in de toekomst bekeken worden of AUR middels nieuwe technieken voorkomen kan worden.

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Wat is er nog boeiender dan het behandelen van patiënten met kanker? Weinig, dacht ik aan het begin van mijn onderzoek. Toch heb ik gemerkt dat het doen van onderzoek net zo boeiend kan zijn! Elke keer een stapje verder denken, geen enkel feit zomaar aannemen, prikkelende onderzoeksvragen en nieuwe resultaten...: *'Research is to see what everybody has seen and to think what nobody had thought' (Albert Szent-Gyorgyi,1893-1986).*

Dit proefschrift was er niet gekomen zonder de hulp en steun van velen. Daarvoor wil ik iedereen heel hartelijk bedanken. Een aantal personen wil ik in het bijzonder noemen.

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Geachte **prof. J.J. Battermann**, beste promotor. Op het gebied van prostaat brachytherapie bent u een internationale bekendheid. Onlangs verrichtte u de duizendste jodium implantatie op onze afdeling. Ik ben erg blij dat ik mijn onderzoek in deze stimulerende werkomgeving met zeer uitgebreide expertise heb mogen uitvoeren. Bedankt dat ik gebruik mocht maken van uw gegevens als basis voor mijn onderzoek.

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Ik ga nog even een stukje terug in de tijd, want de basis van mijn onderzoekservaringen is gelegen bij de gynaecologie in het UMC Groningen. Onder leiding van **dr. Annemieke Hoek** en **prof. M.J. Heineman** startte ik daar in het 2e jaar van mijn studie geneeskunde met wetenschappelijk onderzoek. Omdat het zo goed liep, werd dit gecontinueerd tot en met mijn 6e studiejaar. Deze ervaring vormt de basis van de interesse en kennis waarmee ik bij de radiotherapie verder ben gegaan met onderzoek. Bedankt voor jullie enthousiaste onderzoeksbegeleiding destijds.

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Dear **dr. Elantholi Saibishkumar**, thank you for your warm welcome in Toronto, the collaboration and your contribution to my research project. Dear **dr. Cynthia Menard**, thank you for your mediation in this opportunity. Without this collaboration, external validation of the nomogram could not have been performed. I'm looking forward to further collaborate in the future.

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Ellen Roeloffzen

Utrecht, oktober 2010

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Ellen Maria Aleida Roeloffzen was born on the 25th of April 1981 in Almelo, The Netherlands, and grew up in Nijverdal. In 1999, she graduated from secondary school (cum laude) at College Reggestein in Nijverdal. From 1999 till 2005, she studied medicine at the University of Groningen. In the second year of her study, she started a scientific research project at the Gynaecology department of the University Medical Centre Groningen, supervised by *prof. dr. M.J. Heineman* and *dr. A. Hoek*. The research continued till the end of her medicine study and resulted in an undergraduate thesis, a poster and some publications as co-author. During her third year, she went to the St. Lukes Hospital in Malta for a foreign students exchange program, where she worked at the Gynaecology department from June till August 2002.

After finishing the first part of her medical study (cum laude) in 2003, she moved to Willemstad, Curaçao to perform the first year of her internships at the St. Elisabeth Hospital. She returned to Groningen for the second year of her internships at the University Medical Centre. Since she got interested in the field of Radiotherapy, she performed her final internship (3 months) at the Radiotherapy department of the Academic Medical Center in Amsterdam.

In September 2005, she obtained her medical degree and started working at the Radiotherapy department of the University Medical Center Utrecht. In September 2006, she started her residency Radiation-Oncology at the same department, under supervision of *dr. C.H.J. Terhaard*. Because of a growing interest in scientific research, she started a PhD-project on I-125 prostate brachytherapy in July 2008. The project was conducted under supervision of *prof. dr. J.J. Battermann* and *dr. M. Van Vulpen*. From January 2009 till June 2010, she was fully dedicated to this program. In June 2010 she went to the Princess Margaret Hospital in Toronto for collaboration, which was supervised by *dr. E.P. Saibishkumar* and was partly granted by the *René Vogels Stichting*. The publications concerning the research project are combined in this thesis. From August 2010 she continued her residency, which she will finish at the end of 2012.

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