Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 4, pp. 1023–1032, 2009

0360-3016/09/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2008.05.022

CLINICAL INVESTIGATION **Prostate**

PREDICTIVE FACTORS FOR ACUTE AND LATE URINARY TOXICITY AFTER PERMANENT PROSTATE BRACHYTHERAPY: LONG-TERM OUTCOME IN 712 CONSECUTIVE PATIENTS

Mira Keyes, M.D.,* Stacy Miller, M.D.,* Veronika Moravan, M.Sc.,† Tom Pickles, M.D.,* Michael McKenzie, M.D.,* Howard Pai, M.D.,† Mitchell Liu, M.D.C.M.,‡ Winkle Kwan, M.D.,‡ Alexander Agranovich, M.D.,‡ Ingrid Spadinger, Ph.D.,* Vincent Lapointe, M.Sc.,* Ross Halperin, M.D.,§ and W. James Morris, M.D.*

* Vancouver Cancer Center, Vancouver, BC, Canada; † Population and Preventive Oncology, Vancouver Island Cancer Centre, Vancouver, BC, Canada; ‡ Fraser Valley Cancer Centre for Southern Interior Provincial Prostate Brachytherapy Program, Vancouver, BC, Canada; and § British Columbia Cancer Agency, Vancouver, BC, Canada

Purpose: To describe the frequency of acute and late Radiation Therapy Oncology Group (RTOG) urinary toxicity, associated predictive factors, and resolution of International Prostate Symptom Score (IPSS) in 712 consecutive prostate brachytherapy patients.

Methods and Materials: Patients underwent implantation between 1998 and 2003 (median follow-up, 57 months). The IPSS and RTOG toxicity data were prospectively collected. The patient, treatment, and implant factors were examined for an association with urinary toxicity. The time to IPSS resolution was examined using Kaplan-Meier curves, and multivariate modeling of IPSS resolution was done using Cox proportional hazards regression analysis. Logistic regression analysis was used to examine the factors associated with urinary toxicity.

Results: The IPSS returned to baseline at a median of 12.6 months. On multivariate analysis, patients with a high baseline IPSS had a quicker resolution of their IPSS. Higher prostate D90 (dose covering 90% of the prostate), maximal postimplant IPSS, and urinary retention slowed the IPSS resolution time. The rate of the actuarial 5-year late urinary (>12 months) RTOG Grade 0, 1, 2, 3, and 4 was 32%, 36%, 24%, 6.2%, and 0.1%, respectively. At 7 years, the prevalence of RTOG Grade 0-1 was 92.5%. Patients with a larger prostate volume, greater number of needles, greater baseline IPSS, and use of hormonal therapy had more acute toxicity. On multivariate analysis, the significant predictors for late greater than or equal to RTOG toxicity 2 were a greater baseline IPSS, maximal postimplant IPSS, presence of acute toxicity, and higher prostate V150 (volume of the prostate covered by 150% of the dose). More recently implanted patients had less acute urinary toxicity and patients given hormonal therapy had less late urinary toxicity (all $p < 0.02$).

Conclusion: Most urinary symptoms resolved within 12 months after prostate brachytherapy, and significant long-term urinary toxicity was very low. Refined patient selection and greater technical experience in prostate brachytherapy were associated with less urinary toxicity.

Prostate brachytherapy, Urinary toxicity, Predictive factors.

INTRODUCTION

Permanent low-dose-rate prostate brachytherapy (PB) is a standard option for the treatment of early-stage prostate cancer. PB is often chosen because of its excellent long-term disease control, convenience, and relative absence of severe long-term side effects (1–3). Additional research into brachytherapy-related toxicity and measures to reduce side effects and preserve patients' quality of life are essential.

Irritative and obstructive urinary symptoms are the main sequelae of PB (4, 5). Acute urinary retention (AUR) is

Reprint requests to: Mira Keyes, M.D., F.R.C.P.C., Department of Radiation Oncology, Department of Surgery, University of British Columbia, Provincial Prostate Brachytherapy Program, BC Cancer Agency, 600 W. 10th Ave., Vancouver, BC V5Z 4E6 Canada. Tel: (604) 877-6000, ext. 2660; Fax: (604) 877-0505; E-mail: mkeyes@bccancer.bc.ca

Presented at the ESTRO Leipzig, September 2006 and ABS Chicago, May 2007.

Conflict of interest: none.

Acknowledgments—BC Cancer Agency Prostate Brachytherapy Program: Drs. Mira Keyes (program head), W. James Morris (quality assurance chair), Michael McKenzie, Alexander Agranovich, Tom Pickles, Eric Berthelet, Howard Pai, Winkle Kwan, Mitchell Liu, Jonn Wu, Ross Halperin; medical physics: Ingrid Spadinger (physics head), Robert Harrison, William Kwa, Vincent Lapointe; data analyst: Barb Baerg; statistician: Veronika Morvan.

Received March 14, 2008, and in revised form May 14, 2008. Accepted for publication May 15, 2008.

a frequent acute urinary toxicity with published rates of 6–36% (5). Although many publications have described urinary toxicity after PB, few reports have included a large number of patients (>300) (3, 4, 6–8), described a systematic analysis of treatment and dosimetry predictive factors (4, 7–12), or have had long-term follow-up (4, 6–8).

We describe the frequency of acute and late urinary toxicity and associated predictive factors for Radiation Therapy Oncology Group (RTOG) toxicity, International Prostate Symptom Score (IPSS) resolution, and changes in urinary bother score in 712 consecutive PB patients with a median follow-up of 57 months. The incidence and predictive factors for AUR in this cohort have been previously published by our group (5).

METHODS AND MATERIALS

The Prostate Brachytherapy Program at the British Columbia Cancer Agency was established in 1997. As of March 2008, >2,200 patients had undergone PB. The outcome analysis of the first 1,006 consecutive patients revealed a 5-year Kaplan-Meier freedom from biochemical failure rate of 95.7% (13, 14). The program maintains a large prospective database containing baseline clinical and dosimetric data, follow-up prostate-specific antigen (PSA) level, and testosterone level. Toxicity data were collected from all patients who had attended one of four British Columbia Cancer Agency provincial clinics. This report examined the first 932 patients treated between July 20, 1998 and June 30, 2003. Patients included in the analysis had a minimal follow-up of 34 months and sufficient IPSS data (minimum of baseline IPSS and three subsequent measurements) and RTOG data recorded. A total of 220 were excluded from additional analysis: 35 had died with <34 months of follow-up, 142 men lived in areas remote from British Columbia Cancer Agency clinics and were followed elsewhere, and 41 patients had insufficient IPSS data. By September 2007, the cohort had reached a minimal follow-up of 34 months. Because urinary toxicity after PB decreases with longer follow-up (1, 16, 22), a minimal follow-up of 34 months should result in a reasonable estimation of late urinary toxicity. The research ethics board approved the access and analysis of the data.

Eligibility criteria for PB

Eligible patients included those with low-risk disease (clinical stage T2a or less, initial PSA [iPSA] level of ≤10.0 ng/mL and Gleason score ≤6), and ''low-tier'' intermediate-risk disease (Stage T2c or less and iPSA of 10-15 ng/mL and Gleason score of ≤6 or Gleason score 7 with an iPSA of <10 ng/mL).

Patients with low-risk disease and a prostate volume of ≤50 cm^3 (≤40 cm^3 in the first few years) were treated with PB alone. Patients with Gleason score 7, iPSA level of 10–15 ng/mL, or a prostate volume larger than the cutoffs described received 3 months of neoadjuvant and 3 months of adjuvant hormonal therapy (HT) (luteinizing hormone-releasing hormone agonist, with 4 weeks of a nonsteroidal antiandrogen), together with PB.

Implant procedure

Our implant procedure has been previously described in detail (5, 23, 24). In brief, radioactive seeds were implanted using a preplanned, ''real-time'' ultrasound-guided transperineal technique, as described by the Seattle group (15). We used 0.33-mCi (National Institute of Standards and Technology report 99) ^{125}I seeds and a modified peripheral loading system for seed placement (VariSeed, Varian Medical Systems, Palo Alto, CA). The first 334 patients were implanted with loose seeds (Model 6711, Nycomed Amersham, Arlington Heights, IL) and the remainder with RAPID Strand (Oncura). A prescribed dose of 144 Gy (Task Group report 43) was planned to cover ≥98% of the planning target volume (prostate with 1–5-mm margins). The prostate and rectal dosimetry was obtained using Day 30 postimplant computed tomography, using VariSeed software. Postimplant contouring was done by an implanting oncologist. The minimal dose received by 90% of the prostate (D_{90}) and the percentage of prostate volume receiving 100% and 150% of the prescribed minimal peripheral dose (V_{100} and V_{150}, respectively) were recorded.

All patients were discharged a few hours after the procedure, received an α-blocker (terazosin) for a minimum of 8 weeks, and a tapering course of dexamethasone. Patients were seen in the clinic for follow-up at 6 weeks, every 6 months after implantation for ≤2–3 years, and annually thereafter.

Outcome measurements

IPSS endpoints. Baseline (before HT and before implantation) and follow-up IPSS questionnaires were collected at each visit (16). Gastrointestinal and genitourinary toxicity were graded using RTOG scale (17). The 712 patients had a total of 5,985 follow-up visits, and 86.2% of the visits had an IPSS recorded and 82% had a bother score (last question on the IPSS questionnaire) recorded. IPSS resolution was defined as a return of the total IPSS to within 2 points of the baseline score (18).

RTOG endpoint. RTOG toxicity was recorded at 92.3% of visits, reported as the actuarial 5-year late toxicity and as the prevalence: the total number of patients with each toxicity scale (RTOG Grade 0–4) in the population at risk. Predictive factors were calculated using the actuarial 5-year late toxicity.

The RTOG urinary toxicity scale is as follows:

RTOG Grade 0, no symptoms
RTOG Grade 1, frequency, nocturia twice as often when comparing to pretreatment habits, dysuria, urgency not requiring medication
RTOG Grade 2, frequency and nocturia less frequent than every hour, dysuria, and urgency, bladder spasm requiring medication
RTOG Grade 3, frequency with urgency or nocturia hourly or more frequently, dysuria, pelvic pain or bladder spasm requiring frequent narcotics, gross hematuria, obstruction requiring indwelling catheter or minor procedure
RTOG Grade 4, ulceration, necrosis, major surgical procedure

Analysis of predictive factors

The factors analyzed as independent and dependent predictive variables included (5, 10) independent and dependent variables. The independent variables included patient factors (age, diabetes, vascular disease, baseline IPSS, and HT), treatment factors (planning ultrasound-determined target volume, number of needles used [during the study period, we reduced the number of needles used per prostate volume; this was used as a surrogate for trauma], [ratio between postimplant CT-determined volume and preimplant ultrasound volume; used as a surrogate for postimplant edema], and the sequential implant order number, used as a surrogate for the ''learning curve'') (5, 34), and dosimetry factors (prostate V_{100}, V_{150}, and D_{90}). The dependent variables included the presence of AUR and the maximal postimplant IPSS recorded between 6 weeks and 6 months after implantation (10).

Statistical analysis

An association between the categorical variables was tested using the chi-square test. Differences between the mean values were tested using the *t* test. The interval to IPSS resolution was examined using Kaplan-Meier curves and the log–rank test for individual factors. Cox proportional hazard regression analysis was used in the multivariate models. Logistic regression analysis was used to examine the factors associated with acute and late urinary toxicity. All factors were input into multivariate models. The method of backward elimination was used to select the best model. The significance level for removal from the model was $p = 0.05$. The Statistical Analysis Systems, version 8.02 (SAS Institute, Cary, NC), statistical package was used for data analysis.

RESULTS

A total of 712 patients (76.4% of all implanted patients) with ≥34 months of follow-up were included in this analysis. The median follow-up was 57.1 months (range, 34–103.9). The demographics are listed in Table 1.

IPSS resolution

Of the 712 patients, IPSS resolution (Table 2 and Figs. 1–3) was achieved in 607 (85.3%). The median interval to resolution in this group was 12.6 months (Fig. 1). Figure 2 shows the Kaplan-Meier curve for the interval to IPSS normalization in all 712 patients. The median baseline IPSS for all patients was 5 (range, 0–35). On multivariate analysis (MVA), the patients who received HT ($p < 0.001$) and those with a greater baseline IPSS ($p < 0.001$) had a quicker IPSS resolution. A greater prostate D_{90} ($p = 0.033$), greater maximal postimplant IPSS ($p < 0.001$), and AUR ($p = 0.037$) were associated with a longer interval to IPSS resolution. The patients whose IPSS failed to normalize had had a lower baseline IPSS (4.5 vs. 7.3; *t* test, $p < 0.0001$), better baseline bother score (median, 1 vs. 2, Wilcoxon $p = 0.0212$), and were less likely to have undergone HT (41.9% vs. 69.2%; chi-square test, $p < 0.0001$). All prostate dosimetry measurements showed statistically significant greater mean values for patients with failure of the IPSS to normalize. Figure 3 graphically presents the relationship among the D_{90}, IPSS resolution, and late RTOG 2 or greater toxicity.

IPSS bother score

The mean baseline bother score for all 712 patients was 1.7; 90% of patients had a baseline bother score of 0–3 (mean, 1.4; mean baseline IPSS, 6) and had a normalized score at 12 months (Fig. 4). Additionally, 9.4% of patients with a worse baseline bother score before implantation experienced overall significant improvement in their bother score. Their mean score at baseline and 1, 2, and 5 years after implantation was 4.7, 2.6, 2.8, and 2.8, respectively (*t* test, $p < 0.001$; Fig. 4).

At 5 years after PB, 40% had an improved bother score, 29 had an unchanged score, and 30% had a worsened score (18% of the patients had increased in score by 1 point, 8.5% by 2 points, 1.7% by 3 points, and 0.6% by each 4 and 5 scale points).

Table 1. Demographics

Factors	Patients (*n*)
Patient related	
Total	712 (100)
Clinical stage*	
T1c	314 (44.1)
T2a	310 (43.5)
T2b	88 (12.4)
Gleason score	
2–4	21 (2.9)
5–6	541 (76.0)
7	150 (21.1)
iPSA (ng/mL)	
<10	611 (85.8)
10–15	99 (13.9)
15	2 (0.3)
HT	464 (65.2)
Diabetes	47 (6.6)
Vascular disease	132 (18.5)
Age (y)	
Median	65.5
Range	46–82
Quicker IPSS resolution	
Median	5
Range	0–35
Planning related	
PUTV (cm^3)	
Median	38.0
Range	17.0–67.2
Missing information (*n*)	5 (0.7)
Needles used (*n*)	
Median	29
Range	18–56
Missing information (*n*)	31 (4.35)
Seeds (*n*)	
Median	100
Range	57–144
Missing information (*n*)	1 (0.1)
Seeds per needle (*n*)	
Median	3.5
Range	1.7–5.8
Missing information (*n*)	32 (4.49)
Postimplant CT dosimetry	
Postimplant volume (cm^3)	
Median	34.8
Range	15.5–75.9
Missing information (*n*)	36 (5.05)
CT/PUTV ratio	
Median	1.0
Range	0.5–1.7
Missing information (*n*)	41 (5.7)
V_{100} (%)	
Median	92.2
Range	51.2–100
Missing information (*n*)	30 (4.2)
V_{150} (%)	
Median	57.9
Range	16.0–89.3
Missing information (*n*)	31 (4.3)
D_{90} (Gy)	
Median	151
Range	70–212
Missing information (*n*)	31 (4.3)

Abbreviations: iPSA = initial prostate-specific antigen; HT = hormonal therapy; IPSS = International Prostate Symptom Score; CT = computed tomography; PUTV = planning ultrasound-determined target volume; V_{100}, V_{150} = percentage of prostate volume receiving 100% and 150% of prescribed minimal peripheral dose, respectively; D_{90} = minimal dose received by 90% of prostate.

Data in parentheses are percentages.

* 2002 TNM staging system.

Table 2. Interval to quicker IPSS resolution (Cox proportional hazards regression analysis)

	UVA		MVA	
Factor	*p*	Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)
Patient related				
Age (y)	0.412	—	—	—
Vascular disease	0.164	—	—	—
Diabetes	0.893	—	—	—
HT	<0.001	1.611 (CI)	<0.001	1.408 (1.169–1.695)
AUR	0.032	0.753 (CI)	0.037	0.732 (0.545–0.982)
Baseline IPSS	<0.001	1.059 (1.044–1.074)	<0.001	1.045 (1.029–1.061)
Maximal IPSS increase	<0.001	0.910 (0.898–0.923)	<0.001	0.912 (0.899–0.925)
Implant related				
PUTV (cm^3)	0.015	0.989 (0.979–0.998)	—	—
Edema CT/PUTV ratio	0.239	—	—	—
Needles (*n*)	0.523	—	—	—
Implant order	0.167	—	—	—
Dosimetry related				
V_{100} (%)	0.001	0.978 (0.966–0.990)	—	—
V_{150} (%)	0.001	0.989 (0.983–0.996)	—	—
D_{90} (Gy)	0.001	0.993 (0.989–0.997)	0.033	0.995 (0.991–0.999)

Abbreviations: UVA = univariate analysis; MVA = multivariate analysis; CI = confidence interval; AUR = acute urinary retention; other abbreviations as in Table 1.

Results of MVA indicated that HT resulted in quicker IPSS resolution. Higher baseline IPSS, greater maximal postimplant IPSS, greater prostate D_{90} and AUR resulted in slower IPSS resolution.

RTOG urinary toxicity

The degree of acute/subacute (≤6 months of follow-up) RTOG toxicity, the maximal actuarial RTOG late toxicity grade at 1–5 years after implantation, and the prevalence of RTOG toxicity at 7 years are shown in Fig. 5. The rate of actuarial 5-year late (≥12 months) urinary RTOG Grade 0, 1, 2, 3, 4 toxicity was 32%, 36%, 24%, 6.2%, and 0.1%, respectively. The prevalence of RTOG Grade 0, 1, 2, and 3 toxicity at 7 years was 74%, 18.5%, 7.4%, and 0%, respectively. One patient (0.14%) developed Grade 4 RTOG toxicity (vesicourethral fistula).

Acute urinary RTOG score 2 or greater

On MVA, HT before implantation ($p = 0.046$), greater baseline IPSS ($p < 0.001$), and greater number of needles per implantation ($p = 0.006$) contributed to greater acute toxicity (Table 3). Less acute toxicity was seen in patients implanted later in the study period ($p = 0.003$).

Late urinary RTOG score 2 or greater

On MVA, patients with a greater baseline IPSS ($p < 0.001$), greater maximal postimplant IPSS ($p < 0.001$), greater prostate V_{150} ($p = 0.004$), and more acute toxicity ($p = 0.035$) had worse late urinary toxicity (Table 4 and Fig. 6). The use of HT decreased the probability of late urinary toxicity by almost 50% ($p = 0.047$). Figure 6 shows the Kaplan-Meier curves for late RTOG toxicity Grade 2 or greater and Grade 3 or greater.

Acute urinary RTOG Grade 3 toxicity

Acute urinary RTOG Grade 3 toxicity was recorded in 89 patients (16.2%). Of these 89 patients, 65 (73%) had AUR and 24 had severe symptoms (27%). On MVA, a greater

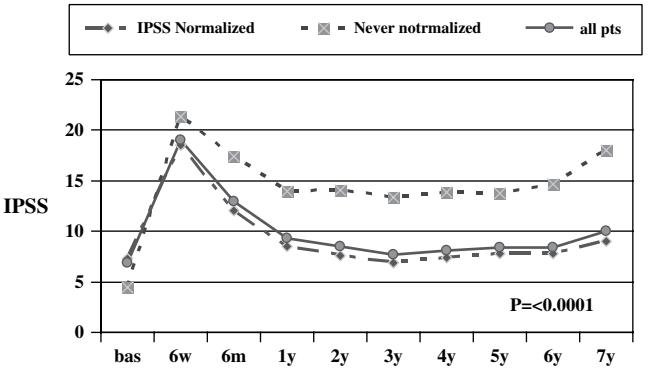

Fig. 1. Mean International Prostate Symptom Score (IPSS) for all 712 patients (pts), those whose IPSS normalized (85.3%) and those whose IPSS never normalized (14.7%). bas = baseline.

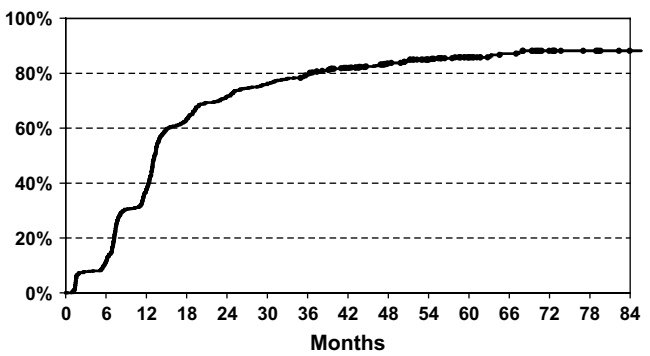

Fig. 2. Kaplan-Meier curve of interval to International Prostate Symptom Score (IPSS) normalization in all 712 patients.

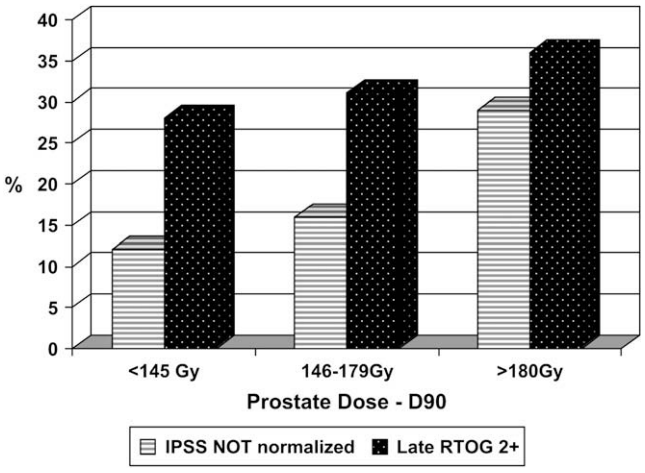

Fig. 3. Minimal dose to 90% of prostate volume (D_{90}) in patients with failure to normalize International Prostate Symptom Score (IPSS) and patients who had late Radiation Therapy Oncology Group (RTOG) toxicity of 2 or greater.

baseline IPSS ($p \leq 0.0001$), larger degree in postimplant edema ($p = 0.001$), and larger preimplant prostate volume ($p = 0.02$) increased the likelihood of acute RTOG 3 toxicity (Table 5). More recently implanted patients had less RTOG Grade 3 toxicity ($p = 0.007$).

Late urinary RTOG Grade 3 toxicity

Late RTOG Grade 3 toxicity was found in 46 patients (6.46%). Of these 46 patients, 33 had had acute RTOG Grade 3 toxicity and 13 had not (Table 6 and Fig. 6). On MVA, only the baseline IPSS ($p = 0.008$) and the presence of acute RTOG Grade 3 toxicity were predictive of late RTOG Grade 3 toxicity. Overall, 2.2% had severe urinary symptoms, 2.1% had prolonged urinary obstruction, 1.3% had stricture, 0.4% had incontinence, 0.1% had hematuria, and 1.3% underwent transurethral resection or transurethral incision of the prostate. (A detailed analysis will be published separately.)

HT and urinary toxicity

From the analysis detailed in the preceding subsections, patients given preimplant HT had significantly faster IPSS

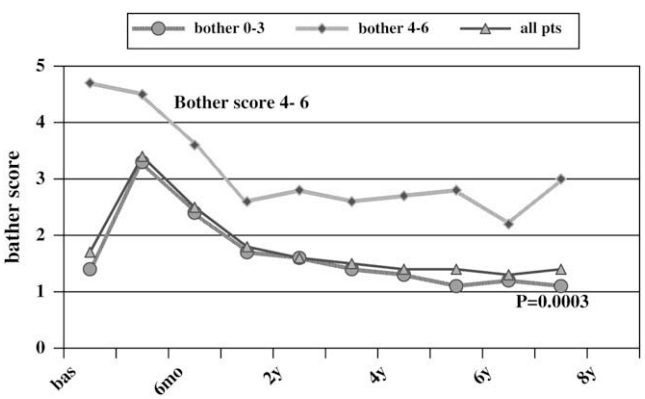

Fig. 4. Bother score by year of follow-up for all patients and patients with low and high baseline bother score (bother score 0–3 vs. 4–6). bas = baseline.

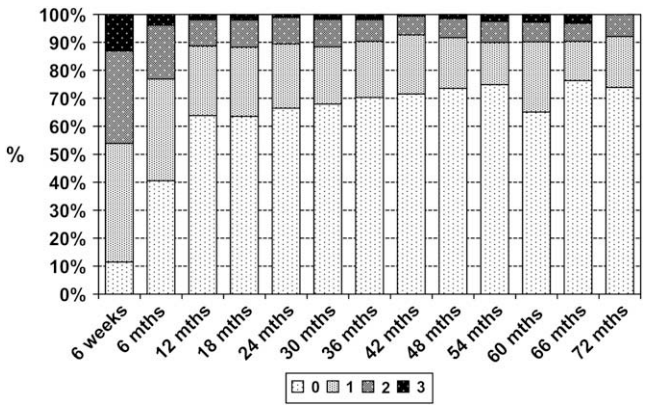

Fig. 5. Prevalence of urinary toxicity stratified by Radiation Therapy Oncology Group (RTOG) toxicity grade and follow-up visit.

resolution and a significantly greater likelihood of acute urinary toxicity (RTOG Grade 2 or greater): 50.1% vs. 38.6% ($p = 0.004$). They also had a significantly reduced probability of having late urinary toxicity (27% vs. 35%; chi-square test, $p = 0.025$). This contradiction was examined by dividing the patients into four groups to further examine the effects of the pretreatment prostate size and HT. The four groups were determined by the treatment protocol as follows:

1. Low-risk disease, no HT, small prostate volume (<40–50 cm^3)
2. Low-risk disease, HT given to downsize prostate, large prostate volume (>40–50 cm^3)
3. HT given for intermediate-risk features, small prostate volume (<40 cm^3)
4. HT given for intermediate-risk features and large prostate volume (>40 cm^3)

The corresponding median preimplant prostate volume for these four groups (after 3 months of HT) was 40, 39.5, 29, and 47 cm^3. Logistic regression analysis showed that, overall, the treatment groups were a significant predictor of acute ($p = 0.0004$) and late ($p = 0.01$) toxicity. The odds ratios and their confidence intervals for each group are shown in Table 7. Patients with a small prostate and no HT (Group 1) were considered the baseline risk group (odds ratio, 1). Patients given HT who also had a larger prostate volume (Groups 2 and 4) had a two times greater risk of more severe acute toxicity. Patients with a smaller prostate volume who received HT (Group 3) had significantly less late toxicity (odds ratio, 0.5). Because 3 months of HT decreases the prostate size by ≥30% (19, 20), we believe that the larger pretreatment/pre-HT prostate size, not the use of HT, was a predictor for acute and also late urinary toxicity.

In addition, the use of HT was the predictor of worse acute toxicity and less late toxicity, although, acute toxicity was also the predictor of worse late toxicity. This contradiction was examined by grouping the patients into four groups according to preimplant HT use and the presence of acute urinary toxicity. Figure 7 shows the Kaplan-Meier curves of the interval to IPSS resolution for each group. The log–rank test results

Table 3. Acute RTOG Grade ≥2 toxicity at ≤6 months after prostate brachytherapy (logistic regression analysis)

	UVA		MVA	
Factor	*p*	OR (95% CI)	*p*	OR (95% CI)
Patient related				
Age (y)	0.137	—	—	—
Vascular disease	0.490	—	—	—
Diabetes	0.809	—	—	—
HT	0.004	1.50 (1.161–2.207)	0.046	1.42 (1.01–2.02)
Baseline IPSS	<0.001	1.08 (1.05–1.12)	<0.001	1.08 (1.05–1.12)
Implant related				
PUTV (cm^3)	0.145	—	—	—
Edema CT/PUTV ratio	0.038	2.52 (1.05–6.01)	—	—
Needles (*n*)	0.003	1.06 (1.02–1.09)	0.006	1.052 (1.02–1.09)
Implant order	0.002	0.99 (0.99–1.00)	0.003	0.99 (0.99–1.00)
Dosimetry related				
V_{100} (%)	0.124	—	—	—
V_{150} (%)	0.001	0.98 (0.96–0.99)	—	—
D_{90} (Gy)	0.357	—	—	—

Abbreviations: RTOG = Radiation Therapy Oncology Group; OR = odds ratio; other abbreviations as in Tables 1 and 2.

Results of MVA indicated that more recent implants resulted in decreased risk of acute RTOG toxicity. HT, greater baseline IPSS, and more needles per implantation all increased the risk of acute RTOG toxicity.

showed that overall a statistically significant difference existed between groups ($p < 0.001$). The patients with the worst IPSS resolution were those not given HT who also experienced acute urinary toxicity.

DISCUSSION

To our knowledge, this is the second largest single-institution report of long-term urinary toxicity after PB (7) and the largest study reporting the predictive factors for urinary toxicity. Our group had previously published a detailed analysis of AUR and its predictive factors in the same group of patients; therefore, the AUR analysis was not repeated for the purposes of the present study. In our previous work, we found that AUR rates had dramatically decreased in our program. The AUR rate in the first 200 vs. the last 200 patients in this cohort was 17% vs. 6.3%, respectively ($p = 0.002$). MVA showed that a greater baseline IPSS, larger prostate size, significant postimplant edema, implant order (''learning curve''), and number of needles used (''prostate

Table 4. Late RTOG Grade ≥2 toxicity at ≥12 months after prostate brachytherapy (logistic regression analysis)

	UVA		MVA	
Factor	*p*	OR (95% CI)	*p*	OR (95% CI)
Patient related				
Age (y)	0.614	—	—	—
Vascular disease	0.173	—	—	—
Diabetes	0.036	1.92 (1.06–3.49)	—	—
HT	0.027	0.69 (0.50–0.96)	0.047	0.67 (0.46–0.99)
AUR (any)	0.057	—	—	—
Baseline IPSS	<0.001	1.08 (1.05–1.11)	<0.001	1.11 (1.07–1.15)
Maximal IPSS increase	0.006	1.03 (1.019–1.06)	<0.001	1.06 (1.03–1.08)
Presence of acute toxicity (Grade ≥2)	<0.001	2.14 (1.54–2.99)	0.035	1.53 (1.03–1.28)
Implant related				
PUTV (cm^3)	0.213	—	—	
Edema CT/PUTV ratio	0.713	—	—	—
Needles (*n*)	0.447	—	—	—
Implant order	0.722	—	—	—
Dosimetry related				
V_{100} (%)	0.244	—	—	—
V_{150} (%)	0.140	—	0.004	1.02 (1.01–1.04)
D_{90} (Gy)	0.096	—	—	—

Abbreviations as in Tables 1–3.

Results of MVA indicated HT resulted in decreased risk of late RTOG Grade ≥2 toxicity. Greater baseline IPSS, greater maximal postimplant IPSS, greater V_{150}, and acute toxicity all increased the risk of late RTOG toxicity.

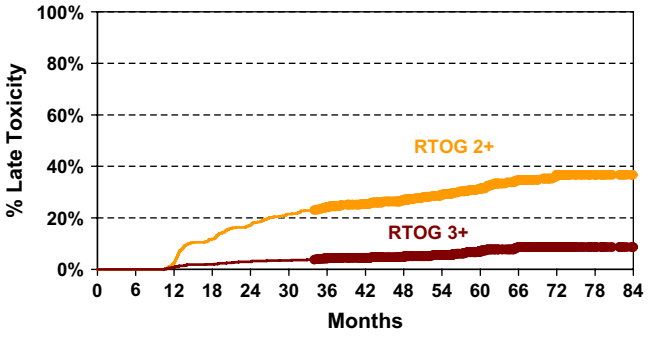

Fig. 6. Kaplan-Meier curve of late Radiation Therapy Oncology Group (RTOG) Grade 2 or greater and RTOG Grade 3 or greater urinary toxicity.

trauma'') were all significant predictors of development of AUR (5).

The present report found that the incidence of long-term urinary toxicity after brachytherapy is very low. A summary of the factors identified on MVA as predictive of worse urinary symptoms and the factors predictive for less toxicity is given in Table 8. A slower IPSS resolution was seen more frequently in patients with AUR and in patients with a high maximal postimplant IPSS and/or high prostate dose. Worse acute toxicity (RTOG Grade 2 or greater) was seen more frequently in patients with a greater baseline IPSS, a greater number of needles used, a larger prostate volume, worse postimplant edema, and HT. Worse late toxicity (RTOG Grade 2 or greater) was seen more frequently in patients with a greater baseline IPSS, greater maximal postimplant IPSS, high prostate V_{150}, and worse acute toxicity. Urinary toxicity was related to prostate size before HT, rather than the use of HT *per se*. Implant order (''learning curve'') was a consistently significant predictor for less acute and, consequently, less late urinary toxicity.

Our median interval to IPSS normalization was 12.6 months, consistent with the findings of others (7, 18, 21). In our study, 14.8% of the patients never had IPSS normalization after implantation. Those patients had a lower baseline IPSS and higher prostate dosimetry. This has also been reported by some investigators (18), but not by all (7, 10). Patients with a greater baseline IPSS returned to their baseline IPSS more quickly than did patients with minimal urinary symptoms before brachytherapy (18, 22, 23). This might be related to patient expectations and/or to the preexisting urinary symptoms, which might mask any new dysfunction caused by PB. Of all 712 patients, 53% experienced ''urinary symptom flare'' at a median of 26.5 months after implantation. This has been described in detail elsewhere (24).

Only a few institutions have reported on brachytherapy toxicity using the RTOG scales (4, 9, 25, 26). Our 5-year actuarial RTOG Grade 2 toxicity rate was 23%, comparable to the rate reported by Zelefsky *et al.* (26), who described a 5-year actuarial late RTOG Grade 2 urinary toxicity rate of 41%.

In the present series, a greater prostate dose was associated with slower IPSS resolution, failure to normalize IPSS, and more late urinary toxicity. Several institutions have reported worse urinary symptoms with a greater prostate dose (6, 25, 27, 28), but many others have not (4, 7–10, 12).

Consistent with other reports (4, 7, 10, 12, 21, 29), we found that a greater baseline IPSS predicted for worse urinary toxicity after PB. Although the use of HT was independently predictive for more acute and less late toxicity on MVA, this phenomenon might have been related more to the pretreatment prostate size than to the use of HT, which

Table 5. Acute RTOG Grade 3 toxicity at 6 weeks after prostate brachytherapy (logistic regression analysis)

	UVA		MVA	
Factor	*p*	OR (95% CI)	*p*	OR (95% CI)
Patient related				
Age (y)	0.1750	1.024 (0.99–1.059)	—	—
Vascular disease	0.7407	—	—	—
Diabetes	0.6547	—	—	—
HT	0.1644	1.418 (0.867–2.318)	—	—
Baseline IPSS	<0.0001	1.091 (1.053–1.130)	<0.0001	1.097 (1.056–1.140)
Implant related				
PUTV (cm^3)	0.3569	—	0.0207	1.035 (1.005–1.065)
Edema CT/PUTV ratio	0.0010	8.173 (2.347–28.458)	0.0014	9.230 (2.366–36.005)
Needles (*n*)	0.0552	1.048 (0.999–1.100)	—	—
Implant order	0.0013	0.999 (0.998–0.999)	0.0074	0.999 (0.997–1.000)
Dosimetry related				
V_{100} (%)	0.0023	0.952 (0.922–0.982)	—	—
V_{150} (%)	<0.0001	0.965 (0.948–0.982)	—	—
D_{90} (Gy)	0.0265	0.987 (0.975–0.998)	—	—

Abbreviations as in Tables 1–3.

Results of MVA indicated that more recent implants resulted in decreased risk of acute RTOG 3 toxicity. Greater baseline IPSS, presence of edema (CT/PUTV ratio), and greater PUTV (prostate pretreatment size in cc) resulted in increased risk of acute RTOG Grade 3 toxicity.

Table 6. Late RTOG Grade 3 toxicity ≥2 months after prostate brachytherapy (logistic regression analysis)

	UVA		MVA	
Factor	*p*	OR (95% CI)	*p*	OR (95% CI)
Patient related				
Age (y)	0.296	—	—	—
Vascular disease	0.564	—	—	—
Diabetes	0.076	2.29 (0.92–5.71)	—	—
HT	0.518	—	—	—
AUR	0.001	3.26 (1.61–6.61)	—	—
Baseline IPSS	0.084	1.04 (0.99–1.09)		
Maximal IPSS increase	0.003	1.07 (1.02–1.11)	0.009	1.06 (1.02–1.11)
Acute urinary symptoms (RTOG Grade ≥3)	<0.001	5.14 (2.66–9.93)	<0.001	3.97 (1.92–8.22)
Implant related				
PUTV (cm^3)	0.906	—	—	—
Edema CT/PUTV ratio	0.251	—	—	—
Needles (*n*)	0.286	—	—	—
Implant order	0.319	—	—	—
Dosimetry related				
V_{100} (%)	0.786	—	—	—
V_{150} (%)	0.426	—	—	—
D_{90} (Gy)	0.784	—	—	—

Abbreviations as in Tables 1–3.

Results of MVA indicated that greater maximal IPSS resulted in increased risk of late RTOG Grade 3 toxicity; and acute urinary symptoms (RTOG Grade 3) resulted in increased risk of late RTOG Grade 3 toxicity.

might not be an independent predictor of toxicity. Overall, published data on the association between the use of HT and urinary morbidity have been conflicting (7, 12, 22, 31). Likewise, data regarding urinary toxicity and prostate size have been inconsistent (4, 6–8, 10, 12, 25). In contrast, the transition zone volume was found to be consistently predictive for worse urinary toxicity after PB (22, 30).

Our study had several limitations. First, we did not report the urethral dose in our cohort. This cohort of patients had undergone Day 30 computed tomography, and the use of a urethral catheter purely for gathering dosimetric data was not done. In contemporary brachytherapy series, in which the urethral doses have been 100–140% minimal peripheral dose, there is no evidence to link urinary morbidity with urethral dosimetry (18, 21, 28). Nonetheless, the lack of urethral dose data for our patients is a shortcoming of this report. In our recent report on the association of urethral dose and urinary toxicity in selected patients, without urinary symptoms before PB, a greater urethral dose at the prostatic base predicted for worse urinary toxicity after PB. This might have been the direct effect of a significant variation in the urethral dose at the prostatic base (23). Another limitation was related to the toxicity scale used for the assessment of patients' toxicity. The RTOG scale is a well-recognized physician assessment (17); however, patient-reported side effects can be worse than physician-reported symptoms (32). Likewise, the IPSS might not be an ideal tool for the assessment of postbrachytherapy toxicity (16).

Table 7. Hormonal therapy and acute and late RTOG urinary toxicity

Risk group	Patients(n)	RTOG 0-1 (%)	RTOG ≥ 2 (%)	OR(95% CI)
Acute GU RTOG toxicity				
Low risk disease				
No HT (small PUTV)	236	61.4	38.6	1
HT, >40 cc (large PUTV)	213	45.1	54.9	1.94 (1.33-2.83)
Intermediate risk, HT				
HT<40cc (small PUTV)	169	59.2	40.8	1.10 (0.73, 1.65)
HT<40cc (large PUTV)	63	41.3	58.7	2.27 (1.29, 3.99)
Late GU RTOG toxicity				
Low risk disease				
No HT (small PUTV)	248	64.1	35.9	1
HT, >40cc (large PUTV)	220	70.0	30.0	0.77 (0.52, 1.13)
Intermediate risk, HT				
HT<40cc (small PUTV)	178	78.1	21.9	0.50 (0.32, 0.78)
HT<40cc (large PUTV)	66	63.6	36.4	1.02 (0.58, 1.80)

Abbreviation: PUTV= planning ultrasound target volume (prostate volume)

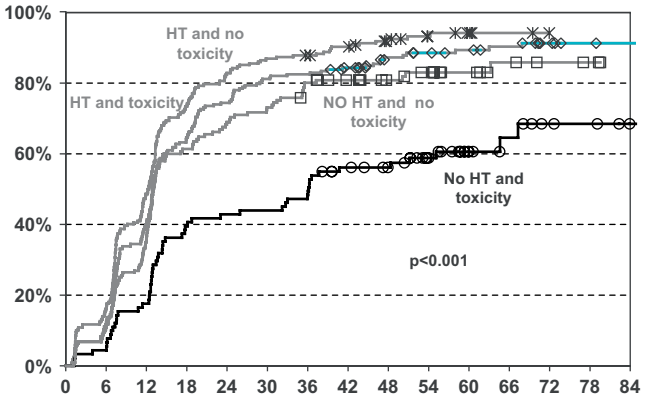

Fig. 7. Kaplan-Meier curves of interval to International Prostate Symptom Score resolution for each group according to presence of acute toxicity and use of hormonal therapy (HT). Log–rank test p value shows that statistically significant difference present between groups overall ($p < 0.001$). Patients with worst International Prostate Symptom Score (IPSS) resolution were those without hormonal therapy, who had experienced acute urinary toxicity.

Also, we did not have transition zone data to incorporate into this analysis, and we did not systematically record the pre- and post-HT prostate volumes. Finally, varying degrees of institutional experience with PB, variable treatment techniques and planning (33), and differences in institutional patient eligibility criteria might make our results less generalizable to other institutions.

The two new significant findings in this report included the effect of the learning curve and prostate trauma on the degree of urinary toxicity after PB. We have previously reported that trauma and the learning curve are significant predictors for urinary obstruction (5) and sexual potency after PB (34). The findings of the present report have confirmed that implant order and the number of needles used per prostate volume (both considered to be surrogates for the degree of prostate trauma) remain significant predictors of worse acute urinary toxicity. We also found that patients treated in more recent cohorts had less severe acute toxicity. This phenomenon was observed even though the implanted prostate volumes increased during the study period (data not shown), possibly concealing the true (and much larger) magnitude of the learning curve and trauma effects on acute and late urinary toxicity. In addition to the direct effects of the radiation dose, unlike with external beam radiotherapy, trauma to the prostate during the procedure itself could be a direct contributor to acute urinary toxicity. Because worse acute toxicity predicts for late urinary toxicity, it is plausible that surgical trauma to the prostate is also a contributor to a greater degree of late damage (consequential late reaction). On the basis of our findings, overall urinary toxicity is likely to be less severe in the hands of an experienced brachytherapy team.

CONCLUSION

The results of our study have shown that long-term urinary toxicity after PB is very low. In most patients, the IPSS normalized within 12–18 months after implantation. A greater prostate dose, greater maximal postimplant IPSS, and AUR slowed the IPSS resolution time. Patients with a larger prostate volume, a larger number of needles used, a greater baseline IPSS, and given HT had more acute toxicity. Patients with late RTOG Grade 2 or greater toxicity had a greater baseline IPSS, greater maximal postimplant IPSS, and greater prostate V_{150} and were more likely to have had worse acute toxicity and less likely to have received HT. Our more recently implanted patients (learning curve effect and fewer needles per prostate volume effect) had less acute urinary toxicity. We are the first institution to report that less trauma to the prostate and greater procedure experience are strongly predictive of less urinary toxicity after permanent ^{125}I PB.

Table 8. Summary of multivariate analysis results

	Quicker IPSS resolution		Slower IPSS resolution	
	Use of HT Greater baseline IPSS		AUR Greater maximal IPSS Greater D_{90}	
	Predictors for less toxicity		Predictors for worse toxicity	
RTOG	Acute	Late	Acute	Late
Grade ≥2	Recent implant (learning curve)	Use of HT	Use of HT Greater baseline IPSS More needles	Greater baseline IPSS Greater maximal IPSS Acute RTOG Grade 2 Greater V_{150}
Grade ≥3	Recent implant (learning curve)	—	Greater baseline IPSS Prostate edema Larger PUTV	Maximal IPSS Acute RTOG Grade 3

Abbreviations as in Tables 1 and 3.

REFERENCES

1. Grimm PD, Blasko JC, Sylvester JE, *et al*. 10-Year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;51:31–40.
2. Potters L, Morgenstern C, Calugaru E, *et al*. 12-Year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2005;173: 1562–1566.
3. Zelefsky MJ, Yamada Y, Cohen GN, *et al*. Five-year outcome of intraoperative conformal permanent I-125 interstitial implantation for patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;67:65–70.
4. Gelblum DY, Potters L, Ashley R, *et al*. Urinary morbidity following ultrasound-guided transperineal prostate seed implantation. *Int J Radiat Oncol Biol Phys* 1999;45:59–67.
5. Keyes M, Schellenberg D, Moravan V, *et al*. Decline in urinary retention incidence in 805 patients after prostate brachytherapy: The effect of learning curve? *Int J Radiat Oncol Biol Phys* 2006; 64:825–834.
6. Stone NN, Stock RG. Long-term urinary, sexual, and rectal morbidity in patients treated with iodine-125 prostate brachytherapy followed up for a minimum of 5 years. *Urology* 2007; 69:338–342.
7. Niehaus A, Merrick GS, Butler WM, *et al*. The influence of isotope and prostate volume on urinary morbidity after prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2006;64:136–143.
8. Crook J, Fleshner N, Roberts C, *et al*. Long-term urinary sequelae following ^{125}Iodine prostate brachytherapy. *J Urol* 2008;179:141–146.
9. Brown D, Colonias A, Miller R, *et al*. Urinary morbidity with a modified peripheral loading technique of transperineal ^{125}I prostate implantation. *Int J Radiat Oncol Biol Phys* 2000;47: 353–360.
10. Merrick GS, Butler WM, Lief JH, *et al*. Temporal resolution of urinary morbidity following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2000;47:121–128.
11. Henderson A, Ismail AK, Cunningham M, *et al*. Toxicity and early biochemical outcomes from ^{125}Iodine prostate brachytherapy in the UK: A prospective study. *Clin Oncol (R Coll Radiol)* 2004;16:95–104.
12. Kelly K, Swindell R, Routledge J, *et al*. Prediction of urinary symptoms after 125iodine prostate brachytherapy. *Clin Oncol (R Coll Radiol)* 2006;18:326–332.
13. Morris WJ, Keyes M, McKenzie MR, *et al*. LDR brachytherapy for prostate cancer: Analysis of outcomes for the first 1006 patients treated at the British Columbia Cancer Agency (BCCA [Abstract].) *Brachytherapy* 2008;7:Abstract 20.
14. Morris J, Keyes M, McKenzie M, *et al*. The five-year relapse-free and overall survival following permanent 125 iodine prostate brachytherapy. *Radiother Oncol* 2006;80:S42.
15. Blasko JC, Mate T, Sylvester JE, *et al*. Brachytherapy for carcinoma of the prostate: Techniques, patient selection, and clinical outcomes. *Semin Radiat Oncol* 2002;12:81–94.
16. Barry MJ, Fowler FJ Jr., O'Leary MP, *et al*., for the Measurement Committee of the American Urological Association. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol* 1992;148:1549–1557; discussion 1564.
17. Lawton CA, Won M, Pilepich MV, *et al*. Long-term treatment sequelae following external beam irradiation for adenocarcinoma of the prostate: Analysis of RTOG studies 7506 and 7706. *Int J Radiat Oncol Biol Phys* 1991;21:935–939.
18. Neil M, Studer G, Lee LN, *et al*. The nature and extent of urinary morbidity in relation to prostate brachytherapy urethral dosimetry. *Brachytherapy* 2007;6:173–179.
19. Merrick GS, Butler WM, Wallner KE, *et al*. Efficacy of neoadjuvant bicalutamide and dutasteride as a cytoreductive regimen before prostate brachytherapy. *Urology* 2006;68:116–120.
20. Kucway R, Vicini F, Huang R, *et al*. Prostate volume reduction with androgen deprivation therapy before interstitial brachytherapy. *J Urol* 2002;167:2443–2447.
21. Allen ZA, Merrick GS, Butler WM, *et al*. Detailed urethral dosimetry in the evaluation of prostate brachytherapy-related urinary morbidity. *Int J Radiat Oncol Biol Phys* 2005;62:981–987.
22. Hinerman-Mulroy A, Merrick GS, Butler WM, *et al*. Androgen deprivation-induced changes in prostate anatomy predict urinary morbidity after permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2004;59:1367–1382.
23. Thomas C, Keyes M, Liu M, *et al*. Segmental urethral dosimetry and urinary toxicity in patients with no urinary symptoms prior to permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2008;72:447–455.
24. Miller S, Keyes M, Moravan V, *et al*. Late urinary symptom flare following prostate brachytherapy [Abstract]. *Radiother Oncol* 2006;80:S39. Abstract 133.
25. Salem N, Simonian-Sauve M, Rosello R, *et al*. Predictive factors of acute urinary morbidity after iodine-125 brachytherapy for localised prostate cancer: A phase 2 study. *Radiother Oncol* 2003;66:159–165.
26. Zelefsky MJ, Hollister T, Raben A, *et al*. Five-year biochemical outcome and toxicity with transperineal CT-planned permanent I-125 prostate implantation for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;47:1261–1266.
27. Stock RG, Stone NN, Dahlal M, *et al*. What is the optimal dose for ^{125}I prostate implants? A dose-response analysis of biochemical control, posttreatment prostate biopsies, and long-term urinary symptoms. *Brachytherapy* 2002;1:83–89.
28. Van Gellekom MP, Moerland MA, Van Vulpen M, *et al*. Quality of life of patients after permanent prostate brachytherapy in relation to dosimetry. *Int J Radiat Oncol Biol Phys* 2005;63: 772–780.
29. Henderson A, Bott SR, Sooriakumaran P, *et al*. Urinary morbidity after ^{125}I brachytherapy of the prostate. *BJU Int* 2004;93:890.
30. Merrick GS, Butler WM, Galbreath RW, *et al*. Relationship between the transition zone index of the prostate gland and urinary morbidity after brachytherapy. *Urology* 2001;57:524–529.
31. Zelefsky MJ, Yamada Y, Marion C, *et al*. Improved conformality and decreased toxicity with intraoperative computer-optimized transperineal ultrasound-guided prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2003;55:956–963.
32. Talcott JA, Clark JA, Stark PC, *et al*. Long-term treatment related complications of brachytherapy for early prostate cancer: A survey of patients previously treated. *J Urol* 2001;166:494–499.
33. Merrick GS, Butler WM, Wallner KE, *et al*. Variability of prostate brachytherapy pre-implant dosimetry: A multi-institutional analysis. *Brachytherapy* 2005;4:241–251.
34. Macdonald AG, Keyes M, Kruk A, *et al*. Predictive factors for erectile dysfunction in men with prostate cancer after brachytherapy: Is dose to the penile bulb important? *Int J Radiat Oncol Biol Phys* 2005;63:155–163.