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Long-term follow-up of International Prostate Symptom Score (IPSS) in men following prostate brachytherapy

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Abstract

Objective To investigate variation in the International Prostate Symptom Score (IPSS) in men following prostate brachytherapy.

Methods From January 2004 to November 2009, 524 consecutive patients underwent prostate brachytherapy either alone or in combination with external beam radiation therapy for T1c–T3b prostate cancer. The IPSS was assessed preimplant and at 1, 6, 12, 24, 36, and 48 months after treatment. Clinical and treatment-related factors were assessed for correlations with the IPSS increase.

Results The mean preimplant IPSS was 7.4, with the greatest mean score of 16.0 at 1 month. At 6 months, the mean total IPSS had decreased to 11.5, but it was still statistically significantly greater than that at baseline ($p < 0.001$). At 12 months, the IPSS was decreased to 8.6, slightly greater than baseline ($p = 0.001$). The IPSS of 45.4 % (69/152) patients gradually returned to preimplant levels and that of 71.1 % (108/152) patients returned to within 3 points of the baseline at 24 months. At 24, 36, and 48 months after seed implantation, the IPSS was 8.6, 7.7, and 8.2, respectively, and none of these values differed statistically significantly from baseline ($p > 0.05$). Sixteen

patients (3.1 %) showed AUR, and 11 patients required catheterization. On univariate and multivariate analyses, the IPSS increase was best predicted by lower preimplant IPSS.

Conclusion In our series, IPSS after prostate brachytherapy peaked at 1 month and gradually returned to approximately baseline at 24 months. The IPSS increase was best predicted by lower preimplant IPSS.

Keywords Prostate cancer · Brachytherapy · IPSS · Follow-up

Introduction

Radioactive seed implantation (brachytherapy) of the prostate for organ-confined prostate cancer has become quite common [1, 2], particularly for low- and intermediate-risk disease following the description of the technique by Holm et al. [3]. A number of series with mature follow-up show biochemical recurrence-free survival rates similar to those achieved by radical prostatectomy [4]. Brachytherapy is well tolerated, but bowel symptoms, decreased erectile function, lower urinary tract symptoms (LUTS), and urinary retention do occur in some patients [5, 6]. Han et al. [7] have reported that most patients develop some degree of acute urinary irritative or obstructive symptoms. The International Prostate Symptom Score (IPSS) has been shown to be a useful tool for evaluating urinary symptoms following prostate brachytherapy [8]. Several previous studies have revealed the urinary symptoms, as measured by the IPSS, showed a significant increase at 1 and 6 months after seed implantation and had returned to baseline 12 months later, but most of the studies were of small series and of follow-up 12 months

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only [9, 10]. So, changes in urinary symptoms following prostate brachytherapy need to be well characterized with longer follow-up.

Here, we report the serial variations in the IPSS and the IPSS increase after prostate brachytherapy with a longer follow-up.

Patients and methods

Following institutional review board approval and written informed consent from patients, we identified patients within our institutional database (UCSF) who underwent transperineal ultrasound-guided prostate brachytherapy either alone or in combination with supplemental external beam radiation therapy (EBRT) for clinical T1c–T3b prostate cancer between January 2004 and November 2009. Patients without complete follow-up data were excluded. The implant procedure has been described in detail previously [6]. In brief, at pre-planning for seed implantation, patients were placed in the lithotomy position and transrectal ultrasound (TRUS) was carried out with a 6.0-MHz probe using a Siemens ultrasound unit (Sonoline SI-250, Erlangen, Germany). Images were obtained at 5-mm increments from the base to the apex using a stepping device. The prostate and urethra were outlined at each level with a track ball. Patients underwent palladium or iodine pre-loaded implantation, as monotherapy or combined with EBRT. All operations were performed by a urologist and radiation oncologist.

Risk groups were created according to the 1997 American Joint Commission on Cancer. For the low-risk group, seed implantation alone (monotherapy) was recommended, while for the high-risk group, a combination of I-125 seed implantation at a reduced radiation dose and supplemental EBRT was recommended (combined therapy). In the intermediate-risk group, individual treatment decisions were made.

The IPSS was prospectively assessed preimplant and at 1, 6, 12, 24, 36, and 48 months after the procedure. Additional clinical and treatment-related factors included age, serum PSA level, Gleason score, T stage, peak flow (Qmax), post-void residual (PVR) urine, hormone therapy, alpha-blocker, EBRT.

For statistical analysis, independent sample *t* test and Chi-square test were used to compare the monotherapy group and combined therapy group. To compare the IPSS and its increase over times, we used a mixed effect ANOVA with a subject-specific random effect and using time as fixed effects. The mean values of the IPSS increase at each time point between patients with preimplant IPSS values of 0–7, 8–19, and 20–35 categories were compared with one-way ANOVA. Clinical and treatment-related

factors including age, serum PSA level, Gleason score, T stage, Qmax, PVR urine, hormone therapy, use of alpha-blocker, use of SEB radiotherapy, and IPSS preimplant were assessed for correlations with the IPSS variation. Univariate and multivariate analyses were performed using the linear regression test. Differences were regarded as statistically significant if the *p* value was <0.05. Analyses were carried out using SPSS 14.0 (SPSS, Chicago, IL, USA).

Results

A total of 518 men met the study inclusion criteria, of whom 387 (75 %) underwent brachytherapy monotherapy, while 131 (25 %) men had combined therapy. Demographic and clinical data stratified by treatment type can be found in Table 1. Small differences in mean PSA ($p < 0.001$), clinical T Stage ($p < 0.001$), hormonal therapy ($p < 0.001$), and alpha-blockers ($p = 0.002$) were observed.

The median follow-up was 37 months (range 5–69 months). The absolute IPSS score versus time after implant is shown in Fig. 1a. The mean preimplant IPSS was 7.4. Urinary symptoms peaked at 1 month after implant, with the greatest mean score of 16.0 (2.2-fold increase over baseline). As seen in Fig. 1b, a statistically significant increase over baseline in urinary symptoms was present until sometime between 12 and 24 months. By 12 months, the IPSS of 43.0 % (89/207) patients eventually returned to preimplant levels and that of 67.6 % (140/207) patients returned to within 3 points of the baseline, while at 24 months, the IPSS of 45.4 % (69/152) patients returned to preimplant levels and that of 71.1 % (108/152) patients returned to within 3 points of the baseline.

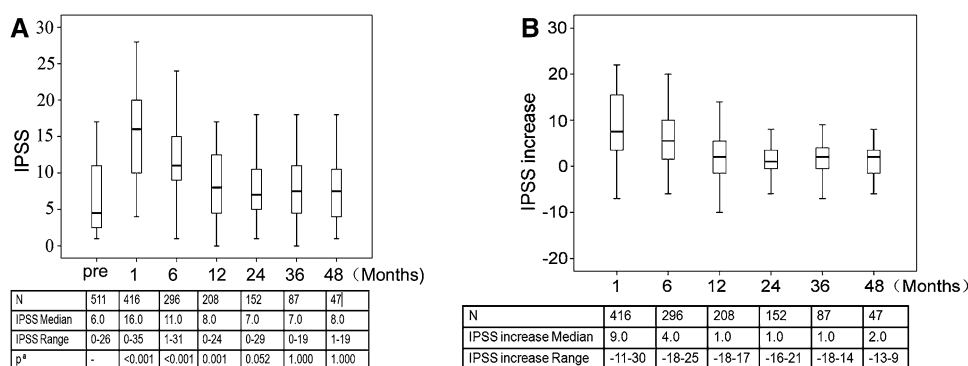
On univariate and multivariate analyses, the IPSS were best predicted by lower preimplant IPSS (data were not shown). So we stratified preimplant IPSS into mild (0–7), moderate (8–19), and severe (20–35) categories and further analyzed preimplant IPSS values of the three categories. The IPSS variations between different groups were shown in Fig. 2 and Table 2. The use of hormonal therapy or alpha-blockers, combined EBRT, and age, serum PSA level, Gleason score, T stage, Qmax, PVR urine were not significantly related to IPSS variation. There was no difference between the monotherapy and combined therapy groups for IPSS or IPSS increase at each time point ($p > 0.05$), except the IPSS of time point of 6 months ($p = 0.027$).

The mean values of the IPSS increase at 1 month in patients with preimplant IPSS values of 0–7, 8–19, and 20–35 were 10.1, 7.5, and 2.5, respectively. In patients with a preimplant IPSS of 0–7, the IPSS increase was

Table 1 Clinical characteristics of patients undergoing permanent seed

	Overall (n = 518)	Monotherapy (n = 387)	Combined (n = 131)	p value ^a
Mean age—years (SD)	63.3 (7.4)	62.9 (7.3)	64.1 (7.6)	0.94
Mean PSA—ng/mL (SD)	6.2 (3.0)	5.9 (2.5)	7.2 (4.0)	<0.001
Gleason score—no. (%)				0.81
4–6	298 (63.7)	282 (80.8)	16 (13.4)	
7	156 (33.3)	67 (19.2)	89 (74.8)	
8–9	14 (3.0)	0 (0.0)	14 (11.8)	
Clinical stage—no. (%)				<0.001
T1c	224 (50.0)	203 (59.2)	21 (20.0)	
T2a	183 (40.8)	128 (37.3)	55 (52.4)	
T2b	13 (2.9)	8 (2.3)	5 (4.8)	
T2c	8 (1.8)	4 (1.2)	4 (3.8)	
T3a	19 (4.2)	19 (5.5)	0	
T3b	1 (0.2)	1 (<0.1)	0	
Mean IPSS—(SD)	7.4 (5.4)	7.5 (5.4)	6.8 (5.1)	0.55
IPSS category—no. (%)				0.54
0–7	306 (59.1)	223 (57.6)	83 (63.4)	
8–19	193 (37.2)	148 (38.3)	45 (34.3)	
20–35	19 (3.7)	16 (4.1)	3 (2.3)	
Mean PVR—mL (SD)	36 (15)	34 (14)	44 (24)	0.52
Mean Qmax—mL/s (SD)	14 (6.7)	15 (6.6)	13 (6.4)	0.55
Hormonal therapy—no. (%)	126 (24.7)	25 (6.5)	27 (21.1)	<0.001
Alpha-blocker—no. (%)	110 (23.9)	74 (20.6)	36 (35.3)	0.002

SD standard deviation

^a p value was comparison of monotherapy and combined therapy groups**Fig. 1** The value of **a** International Prostate Symptom Score (IPSS) and **b** IPSS increase at time points to 48 months. The horizontal line is the median, the *box* is the interquartile range, and the whisker encloses 100 % of the data. p value was comparison of each time point and preimplant

significantly higher when compared to that in patients with a preimplant IPSS of 8–19 or 20–35 ($p < 0.001$ and $p < 0.001$, respectively). In patients with a preimplant IPSS of 20–35, the IPSS increases at 6 and 12 months were –6.1 and –6.8, respectively.

During follow-up, sixteen patients (3.1 %) developed AUR and required catheterization.

Comment

Brachytherapy of the prostate with iodine-125 (I-125) or palladium-103 (Pd-103) seeds has been a common

treatment modality for localized prostate cancer over the last two decades worldwide. De novo or worsened LUTS is one of the most common treatment-associated adverse effects, particularly in the short term. Bottomley et al. [11] found nearly all patients complained of urethritis in the first few weeks after implantation. A respectable amount of data have been published concerning the severity and resolution of the symptoms. Most studies made use of the IPSS, developed by the American Urological Association, to index benign prostatic hyperplasia (BPH) symptoms [12], which facilitates comparisons of results across studies.

Previous studies have revealed the urinary symptoms, as measured by the IPSS, typically start a few days to a few

Fig. 2 The IPSS variations between different categories at **a** 1 month, **b** 6 months, and **c** 12 months. *Error bars* indicate the 95 % confidence interval of the mean

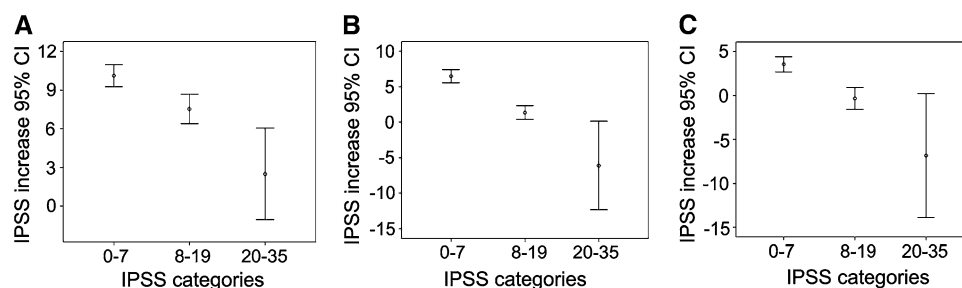


Table 2 The IPSS increase between different categories

IPSS category	IPSS increase 1 month		IPSS increase 6 months		IPSS increase 12 months	
	N (%)	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)
0–7	235 (58.2)	10.1 (6.7)	162 (54.5)	6.5 (6.1)	119 (57.5)	3.6 (4.7)
8–19	155 (38.4)	7.5 (7.5)	126 (42.4)	1.4 (5.6)	82 (39.6)	–3.2 (5.6)
20–35	14 (3.4)	2.5 (6.1)	9 (3.1)	–6.1 (8.1)	6 (2.9)	–6.8 (6.7)
Total	404	8.9 (7.1)	297	3.9 (6.6)	207	1.7 (5.7)

Table 3 Serial variations of IPSS following prostate brachytherapy

Author	N	IPSS to Time					
		Preimplant	1 month	3 months	6 months	12 months	24 months
Merrick et al. [13]	170	5.7 (3.8)	12 (6.3)	8.7 (3.0)	6.2 (0.7)	4.6 (–0.2)	–
Crook et al. [14]	150	6	13 (7.0)	13 (7.0)	10.5 (4.5)	6.5 (0.5)	–
Gelblum et al. [15] ^a	600	7	–	18 (11)	15 (8)	4 (–3)	–
Lee et al. [16]	31	8.3 (5.5)	18.4 (8.0)	15.7 (7.4)	13.7 (7.4)	10.2 (5.7)	–
Williams et al. [17]	173	5.5	17.1 (11.7)	14.4(8.9)	11.6 (6.1)	8.0 (2.5)	–
Ohashi et al. [9]	103	8.2	16.9 (8.7)	–	11.2 (3.0)	10 (1.8)	–
Tanaka et al. [10]	110	9.0 (7.0)	14.2 (8.4)	17.2 (9.0)	14.7 (8.7)	10.3 (8.2)	–
Aaltomaa et al. [18] ^a	409	8	18	–	12	8	9
Keyes et al. [19]	712	4.7	–	–	–	2.6	2.8
Stone et al. [20]	325	7.1 (6.3)	–	–	12.5 (7.4)	9.1 (6.5)	9.5 (7.0)
Current study	524	7.4 (5.4)	16.0 (7.4)	–	11.5 (5.9)	8.8 (5.2)	8.6 (5.5)

^a Studies using IPSS median levels

weeks after implantation, show a peak in the IPSS at 1–3 months, of 7–13 points above baseline, and then gradually decrease, coming back to preimplant levels at 9–18 months. Table 3 shows the comparative IPSS values for eleven studies at various time points, using a combination of median and mean values, but most of the studies are of follow-up of 12 months only [9, 10, 13–20]. Williams et al. [17] reported 57.8 % of patients had returned to baseline at 12-months follow-up, with a median recovery time of 15 months; they also reported that there were some events of returning to baseline within 36 months after brachytherapy. We believe that longer follow-up is necessary to evaluate the long-term changes in urinary function and morbidity.

In our analysis, IPSS after brachytherapy peaked at 1 month and decreased to 8.6 at 12 months, but still slightly greater than baseline, and then gradually returned to approximately baseline at 24 months. The IPSS of 45.4 % (69/152) patients gradually returned to preimplant levels and that of 71.1 % (108/152) patients returned to within 3 points of the baseline at 24 months. Compared with most previous studies [9, 10, 13–20], the urinary symptoms post-brachytherapy need a longer time (24 months) to coming back to preimplant levels in our long-period follow-up analysis.

Several studies have assessed the correlations of clinical and treatment-related factors with the IPSS increase. Merrick et al. [21] reported that use of alpha-blockers

results in significantly less urinary morbidity, and the IPSS normalized significantly faster. Some studies have demonstrated a relationship between urinary symptoms and urethral doses [22, 23]. Salem et al. [22] found the prostate volume to be a predictor for either LUTS severity or resolution. Some studies have demonstrated that a heightened IPSS change was correlated significantly to a lower preimplant IPSS [9, 17]. Agreement exists about the correlation between LUTS after implantation and before implantation [24]. This correlation, however, seems logical and does not associate with the worsening of symptoms with respect to the situation before treatment.

In our study, on univariate and multivariate analyses, the IPSS increase was best predicted only by lower preimplant IPSS. On the other hand, the higher preimplant IPSS was likely to result in less worsening of symptoms than in a lower starting point. Limitation includes retrospective design and data collection. Therefore, our study cohort might be subject to selection and recall bias. Also some incomplete data of our database make contributions to loss of follow-up. Despite the limitations, our study is currently one of the largest reports on the long-term follow-up of IPSS after brachytherapy, and it may assist clinicians in risk stratification and surveillance schedule.

Conclusion

IPSS after prostate brachytherapy peaked at 1 month and gradually returned to approximately baseline at 24 months in 45.4 % of patients. The only significant factor predictive of IPSS increase was a lower preimplant IPSS.

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Conflict of interest None of the contributing authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

References

- Cooperberg MR, Lubeck DP, Meng MV, Mehta SS, Carroll PR (2004) The changing face of low-risk prostate cancer: trends in clinical presentation and primary management. *J Clin Oncol* 22(11):2141–2149
- Zelevsky MJ, Worman M, Cohen GN, Pei X, Kollmeier M, Yamada J, Cox B, Zhang Z, Bieniek E, Dauer L, Zaider M (2010) Real-time intraoperative computed tomography assessment of quality of permanent interstitial seed implantation for prostate cancer. *Urology* 76(5):1138–1142
- Holm HH, Juul N, Pedersen JF, Hansen H, Stroyer I (1983) Transperineal 125iodine seed implantation in prostatic cancer guided by transrectal ultrasonography. *J Urol* 130(2):283–286
- Potters L, Klein EA, Kattan MW, Reddy CA, Ciezki JP, Reuther AM, Kupelian PA (2004) Monotherapy for stage T1–T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation. *Radiother Oncol* 71(1):29–33
- Chen AB, D'Amico AV, Neville BA, Earle CC (2006) Patient and treatment factors associated with complications after prostate brachytherapy. *J Clin Oncol* 24(33):5298–5304
- Ikeda T, Shinohara K (2009) Peak flow rate is the best predictor of acute urinary retention following prostate brachytherapy: our experience and literature review. *Int J Urol* 16(6):558–560
- Han BH, Demel KC, Wallner K, Ellis W, Young L, Russell K (2001) Patient reported complications after prostate brachytherapy. *J Urol* 166(3):953–957
- Terk MD, Stock RG, Stone NN (1998) Identification of patients at increased risk for prolonged urinary retention following radioactive seed implantation of the prostate. *J Urol* 160(4):1379–1382
- Ohashi T, Yoroza A, Toya K, Saito S, Momma T (2006) Serial changes of international prostate symptom score following I-125 prostate brachytherapy. *Int J Clin Oncol* 11(4):320–325
- Tanaka N, Fujimoto K, Hirao Y, Asakawa I, Hasegawa M, Konishi N (2009) Variations in international prostate symptom scores, uroflowmetric parameters, and prostate volume after (125)I permanent brachytherapy for localized prostate cancer. *Urology* 74(2):407–411
- Bottomley D, Ash D, Al-Qaisieh B, Carey B, Joseph J, St Clair S, Gould K (2007) Side effects of permanent I125 prostate seed implants in 667 patients treated in Leeds. *Radiother Oncol* 82(1):46–49
- Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, Cockett AT (1992) The American Urological Association symptom index for benign prostatic hyperplasia. The measurement committee of the American Urological Association. *J Urol* 148(5):1549–1557 (discussion 1564)
- Merrick GS, Butler WM, Lief JH, Dorsey AT (2000) Temporal resolution of urinary morbidity following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 47(1):121–128
- Crook J, McLean M, Catton C, Yeung I, Tsihlias J, Pintilie M (2002) Factors influencing risk of acute urinary retention after TRUS-guided permanent prostate seed implantation. *Int J Radiat Oncol Biol Phys* 52(2):453–460
- Gelblum DY, Potters L, Ashley R, Waldbaum R, Wang XH, Leibel S (1999) Urinary morbidity following ultrasound-guided transperineal prostate seed implantation. *Int J Radiat Oncol Biol Phys* 45(1):59–67
- Lee WR, McQuellon RP, Harris-Henderson K, Case LD, McCullough DL (2000) A preliminary analysis of health-related quality of life in the first year after permanent source interstitial brachytherapy (PIB) for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 46(1):77–81
- Williams SG, Millar JL, Duchesne GM, Dally MJ, Royce PL, Snow RM (2004) Factors predicting for urinary morbidity following 125iodine transperineal prostate brachytherapy. *Radiother Oncol* 73(1):33–38
- Aaltomaa SH, Kataja VV, Lahtinen T, Palmgren JE, Forsell T (2009) Eight years experience of local prostate cancer treatment with permanent I125 seed brachytherapy—morbidity and outcome results. *Radiother Oncol* 91(2):213–216
- Keyes M, Miller S, Moravan V, Pickles T, McKenzie M, Pai H, Liu M, Kwan W, Agranovich A, Spadinger I, Lapointe V, Halperin R, Morris WJ (2009) Predictive factors for acute and late urinary toxicity after permanent prostate brachytherapy: long-term outcome in 712 consecutive patients. *Int J Radiat Oncol Biol Phys* 73(4):1023–1032

20. Stone NN, Stock RG (2007) Long-term urinary, sexual, and rectal morbidity in patients treated with iodine-125 prostate brachytherapy followed up for a minimum of 5 years. *Urology* 69(2):338–342
21. Merrick GS, Butler WM, Wallner KE, Lief JH, Galbreath RW (2002) Prophylactic versus therapeutic alpha-blockers after permanent prostate brachytherapy. *Urology* 60(4):650–655
22. Salem N, Simonian-Sauve M, Rosello R, Alzieu C, Gravis G, Maraninchi D, Bladou F (2003) Predictive factors of acute urinary morbidity after iodine-125 brachytherapy for localised prostate cancer: a phase 2 study. *Radiother Oncol* 66(2):159–165
23. Wallner K, Merrick G, True L, Cavanagh W, Simpson C, Butler W (2002) I-125 versus Pd-103 for low-risk prostate cancer: morbidity outcomes from a prospective randomized multicenter trial. *Cancer J* 8(1):67–73
24. Kelly K, Swindell R, Routledge J, Burns M, Logue JP, Wylie JP (2006) Prediction of urinary symptoms after 125iodine prostate brachytherapy. *Clin Oncol (R Coll Radiol)* 18(4):326–332