

¹²⁵Iodine prostate brachytherapy: outcome from the first 100 consecutive patients and selection strategies incorporating urodynamics

A. HENDERSON, D. CAHILL, R.W. LAING and S.E.M. LANGLEY

St Luke's Cancer Centre, Guildford, Surrey, UK

Objective To report the results from the first 100 consecutive patients treated with ¹²⁵I transperineal interstitial prostate brachytherapy between March 1999 and June 2001, and to determine if the International Prostate Symptom Score (IPSS), prostate volume or urodynamic variables correlate with acute morbidity.

Patients and methods Patients were assessed prospectively by uroflowmetry, the IPSS, a physical examination and transrectal ultrasonography. Of the 100 patients, 57 had a full urodynamic assessment, 61 presented with lower urinary tract symptoms (LUTS), 25 were screen-detected and 14 presented with other problems. The IPSS was recorded at 1, 6 and 12 weeks, and then at 3-monthly intervals after treatment; significant events, e.g. acute urinary retention (AUR) and rectal symptoms, were recorded prospectively; the mean follow-up was 16 months.

Results No patients were incontinent after treatment. There was a temporary deterioration in IPSS in 89% of patients. Peak symptoms occurred at 6 weeks and a statistically significant deterioration in IPSS persisted until 9 months, but continued to improve throughout the follow-up. AUR affected seven patients, with a

further 20 using clean intermittent self-catheterization (CISC) for symptoms. In most patients the symptoms resolved spontaneously to the levels before treatment, with only two patients requiring surgery for bladder outlet obstruction. The IPSS before treatment did not predict urodynamic obstruction. Urodynamically unobstructed patients did not require catheterization. By 2 years after implantation the mean IPSS was better than before treatment. Five patients had mild, transient proctitis.

Conclusion Selecting patients with a low prostate volume and IPSS is likely to optimize the outcome of brachytherapy. Urodynamic studies may be helpful in predicting the risk of AUR and symptoms requiring CISC. Despite many patients presenting with LUTS, acute morbidity was no worse than that reported in large American series of predominantly screening-detected cancers. Prostate brachytherapy is well tolerated and may be safely delivered to patients with prostate cancer in the UK.

Keywords prostate cancer, brachytherapy, clean intermittent self catheterization, urodynamics, IPSS

Introduction

Transperineal interstitial prostate brachytherapy (TIPB) is an accepted treatment option for patients with early prostate cancer. ¹²⁵Iodine and ¹⁰³Palladium are the available isotopes used for this procedure, and results from the current technique spanning up to 12 years have been reported [1–4]. The technique is increasingly available to patients in the UK where most centres implant ¹²⁵I as Rapidstrand™ (Amersham Health, UK). ¹²⁵I-TIPB may be used as monotherapy or as a boost, following a course of EBRT (45 Gy in 25 fractions) [1]. The urodynamic evaluation of patients before brachytherapy to predict outcome has not been reported, nor have prospective data using validated measures been reported from a UK centre.

Previous studies suggested that the risk of acute urinary retention (AUR), and hence of bladder outlet surgery when retention does not spontaneously resolve, is related to the IPSS before treatment [5]. Patients undergoing rigorous pretreatment selection (with an IPSS of <9 in 74% of patients treated with TIPB) were reported to have rates of AUR as low as 5%, with only half of these patients eventually requiring surgery to relieve retention or intractable LUTS [5]. However, other American centres have not achieved such low rates of AUR, with a typical incidence of 7–15% [6–8], which may be a result of less stringent patient selection. Even in this wider group of patients, brachytherapy appears well tolerated and retention resolves with conservative management in most cases.

The IPSS is useful as a screening tool to assess the symptom burden, but it is a qualitative measure of LUTS and correlates poorly with the degree of urodynamic obstruction.

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Table 1 The patients' demographics at presentation

Variable	Value
Mean age, years	65
Mean (range) presenting PSA, ng/mL	9.1 (2.9–26)
No. with:	
Gleason sum	
2–4	30
5–6	56
7–10	14
TNM stage	
T1NOMO	26
T2NOMO	68
T3NOMO	6
Mean (range):	
prostate volume, mL	35 (16–71)
presenting IPSS	7.7 (0–26)
Presenting complaint, n	
screen-detected	25
LUTS	61
Other (e.g. haematuria, UTI)	14
Brachytherapy boost after EBRT	26
Neoadjuvant hormone therapy	64
Urodynamic evidence of obstruction on ICS nomogram	
Obstructed	34
Equivocal	10
Unobstructed	13
Urodynamic assessment of bladder stability	
Stable bladder	48
Unstable bladder	9

tion, as it is not designed to quantify BOO or diagnose detrusor instability [9]. A urodynamic assessment allows an accurate and reproducible measure of maximum flow rate and detrusor pressures, and hence the calculation of derived indices to measure the degree of BOO and instability. This might provide a more accurate measure of lower urinary tract dysfunction before brachytherapy, with a greater ability to identify patients unsuitable for this treatment.

Patients and methods

The first 100 consecutive patients were treated with ^{125}I -TIPB between March 1999 and June 2001; the demographics of the patients are summarized in Table 1. EAU/ESTRO Guidelines for selecting and treating patients, as detailed in Table 2, were used after their publication in 2000 [10].

All patients were assessed using a history, physical examination, TRUS, IPSS, uroflowmetry and a measure of the postvoid residual urine volume (PVR); those with a PVR of >200 mL were offered surgical treatment. No patients had undergone TURP although one had been previously treated with bladder neck incision. Patients who

Table 2 The EAU/ESTRO Guidelines for selecting and treating patients [10]

Condition	Brachytherapy outcome		
	Recommended (fare well)	Optional (fair)	Investigational (fare poorly)
Presenting PSA, ng/mL	<10	10–20	>20
Gleason sum	5–6	7	8–10
TNM stage	T1c–T2a	T2b–T2c	T3
IPSS	0–8	9–19	>20
Prostate volume, mL	<40	40–60	>60
Max. flow rate, mL/s	>15	15–10	<10
PVR, mL	–	–	>200
Previous TURP	–	–	+

had prostate volumes of >50 mL were treated with an LHRH analogue as a cytoreductive agent. Patients were offered alternative treatment if the planning TRUS identified significant pubic arch interference with anterior needle placement.

All patients were treated with ^{125}I sources and doses were prescribed to an isodose envelope that encapsulated the prostate. A minimum dose of 145 Gy was prescribed to patients who were treated with brachytherapy as monotherapy. Patients with TNM stage >T2a, a PSA level of >10 ng/mL or a Gleason sum of >6 were treated with a 3-month course of neoadjuvant androgen deprivation using LHRH analogues or bicalutamide, followed by ^{125}I monotherapy. EBRT at a dose of 45 Gy in 25 daily fractions combined with a brachytherapy boost to the prostate of 110 Gy was reserved for those patients with T3 disease or more than one unfavourable factor (PSA >10 ng/mL, Gleason sum >6, clinical stage >T2a) and was required in 26 men; all of these patients received neoadjuvant androgen ablation.

LUTS were the initial presenting complaint in most patients, with 61 of the first 100 presenting to their GP with LUTS; 52 had moderate to severe LUTS (IPSS of 8–35) with only 48 presenting with mild symptoms (IPSS of 0–7). The mean IPSS in the first 100 men was 7.7, reflecting the prevalence of these symptoms in the UK, where guidelines have not recommended routine PSA screening and men often present through a LUTS assessment clinic. This is higher than in most American series reported to date [5,11,12]. Preoperative α -blockers (alfuzosin 10 mg once daily) were used in patients with an IPSS of >15.

Formal urodynamic studies were conducted in an unselected group of 57 patients, comprising filling cystometry and a pressure-flow study. The obstruction was classi-

fied according to the ICS nomogram [13] and detrusor instability determined as an unprovoked rise of > 15 cmH₂O in detrusor pressure.

After brachytherapy α -blockers (alfuzosin 10 mg once daily) were prescribed to all patients for 3 months or until bothersome symptoms resolved. In the event of urinary retention, patients were taught CISC in preference to using an indwelling catheter, to reduce bacterial colonization of the bladder [14]. CISC was also used to improve symptoms in patients who although able to void had troublesome LUTS. Analgesia and anticholinergics were prescribed as needed. The mean follow-up was 16 months and comprised prospective IPSS questionnaires at 1 and 6 weeks, then at 3, 6, 9 and 12 months. Thereafter follow up was at 6-monthly intervals. Significant complications, e.g. rectal discomfort or bleeding, were also recorded prospectively.

Results

No patients have had permanent urinary incontinence to date and only two have needed surgery for BOO. One of these patients, who had been catheterized for 10 months, had transient stress incontinence after TURP but continence returned with pelvic floor exercises. This patient was the fifth treated in the series and would have been excluded by the guidelines [10] in current use (presenting IPSS 21, maximum flow rate 9 mL/s, initial prostate volume 68 mL).

AUR occurred in seven patients and a further 20 who were able to void used CISC to empty their bladder fully and thus decrease nocturia. The median duration of catheter use was 4 weeks. Patients using CISC often continued the technique to improve nocturnal frequency, despite being able to void urethrally. Multiple logistic regression analysis of risk factors for catheter use, e.g. presenting complaint, antiandrogen therapy, use of EBRT, flow rate, PVR, IPSS and dosimetric values of radiation delivered, were not statistically significant. The factors most closely related to AUR and catheter use are presented in Table 3; 24 of 62 patients with a prostate volume of > 35 mL used catheters, as opposed to only three of 38 patients with a volume of < 35 mL (by TRUS). The prostate volume also affected the rate of AUR, with no cases in patients with a prostate of < 35 mL. Urodynamic variables were promising predictors of the need for catheter use, with no urodynamically unobstructed patients requiring catheterization. Patients with equivocally obstructed voiding traces had a 30% risk of catheter use for symptoms, although no cases of AUR occurred. In the obstructed group AUR occurred in 15% of patients and a further 20% used catheters to relieve LUTS.

Figure 1a shows that 89% of patients had a deterioration in their urinary symptoms, with the worst symptoms

Table 3 The risk assessment for AUR, with factors identified as most closely related by logistic regression analysis

Variable	Events/cases (%)	
	AUR only	All catheter users
Prostate volume, mL		
> 35	7/62 (11)	24/62 (39)
< 35	0/38	3/38 (8)
Urodynamic obstruction (ICS nomogram)		
Unobstructed	0/13	0/13
Equivocal	0/10	3/10 (30)
Obstructed	5/34 (15)	12/34 (35)
IPSS		
0–7 (mild)	2/48 (4)	8/48 (16)
8–16 (moderate)	4/47 (9)	17/47 (36)
17–35 (severe)	1/5 (20)	2/5 (40)
EBRT + brachytherapy boost used		
No	7/74 (10)	25/74 (34)
Yes	0/26	2/26 (8)

at 6 weeks after implantation. These findings were mirrored by a deterioration in urinary symptom bother (Fig. 1b) as assessed by the single question on quality of life included in the IPSS. The deterioration in IPSS and urinary symptom bother persisted at statistically significant levels for 9 months after treatment but the IPSS and symptom bother continued to improve throughout the follow-up.

Notably, 64% of patients had the same or better IPSS 2 years after implantation; this gradual improvement in IPSS over a long period is shown in Fig. 1c and the mean change in IPSS (current IPSS – initial IPSS) fell below zero at 2 years.

The IPSS over the entire period remained significantly lower (Kolmogorov-Smirnov test, $P < 0.05$) in those presenting with mild LUTS (IPSS < 7) although the significance of the difference became less over time (Fig. 2a). There were no statistically significant differences in the change in IPSS in patients who were treated with brachytherapy alone vs EBRT and a brachytherapy boost (Fig. 2b), or in terms of dosimetric values assessed.

No serious rectal symptoms were reported but five patients were treated for mild proctitis with hydrocortisone suppositories, with good effect.

Discussion

The IPSS is helpful in predicting the outcome of treatment [5] and is widely used to screen for symptoms in men considering brachytherapy. However, it is only one of many factors and the initial prostate volume and urodynamic values seem likely to be good predictors of outcome.

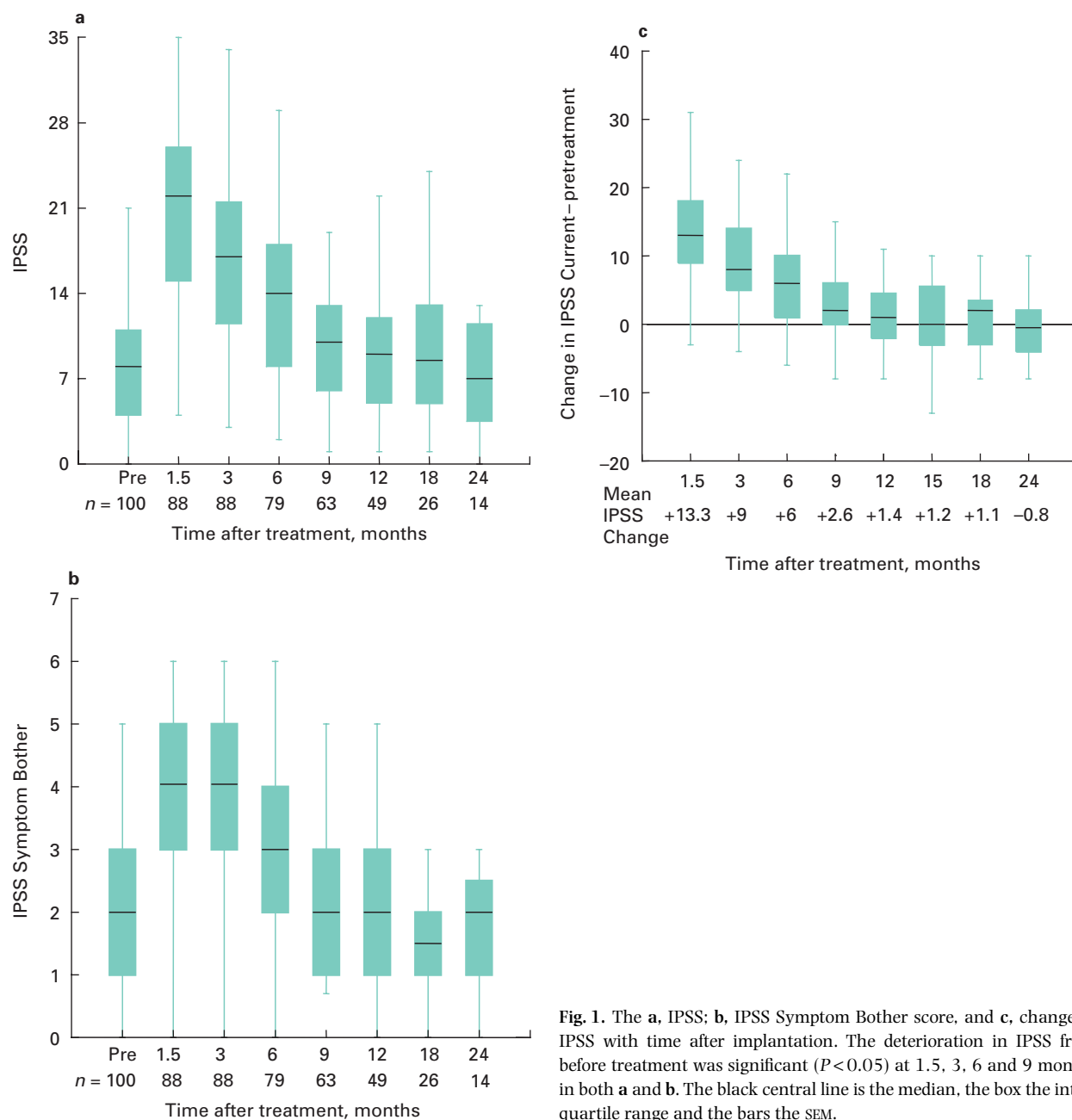


Fig. 1. The **a**, IPSS; **b**, IPSS Symptom Bother score, and **c**, change in IPSS with time after implantation. The deterioration in IPSS from before treatment was significant ($P < 0.05$) at 1.5, 3, 6 and 9 months in both **a** and **b**. The black central line is the median, the box the interquartile range and the bars the SEM.

It is unclear whether the deterioration in LUTS after implantation is caused by radiation cysto-urethritis or increased BOO from prostatic swelling. Our early urodynamic data suggest that unobstructed patients are unlikely to have AUR and troublesome symptoms requiring CISC. That a low prostate volume and unobstructed pressure-flow studies both make AUR less likely suggest that the well documented prostate swelling [15] rather than radiation cysto-urethritis is most likely to cause this complication.

When compared with large American series [5–8] the present patients had worse initial LUTS, but their outcome of treatment in terms of acute morbidity seems to be similar to that from large American centres, which pioneered TIPB. This is encouraging and the advent of PSA screening, which is increasingly used on an ad-hoc basis in the UK, makes the group of patients with few urinary symptoms at presentation likely to increase. Although there was a statistically significant deterioration in IPSS up to 9 months after treatment, it was small, with a mean dete-

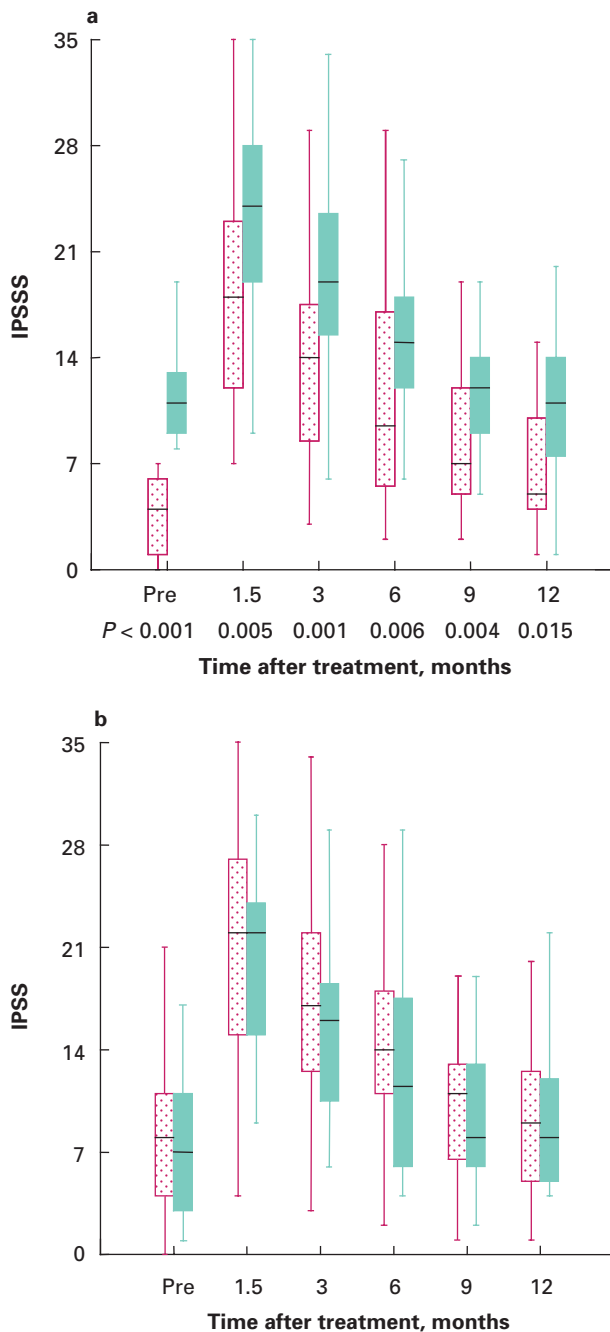


Fig. 2. The IPSS after brachytherapy in **a**, 53 patients with initial scores of > 7 (moderate, green boxes) or 47 with < 8 (mild, red stippled boxes); *P* values show significant differences between the mild/moderate symptom groups maintained over time; **b**, patients treated with (red stippled boxes) and with no (green boxes) additional EBRT; there were no significant difference in IPSS at any time. The black central line is the median, the box the interquartile range and the bars the SEM.

rioration of 2 on the IPSS at 9 months (Fig. 1). A recent prospective American quality-of-life study using the FACT-P instrument showed a return to pretreatment indices by 3 months after implantation [16], despite similar changes in IPSS.

Men with high-grade obstruction diagnosed on urodynamic assessment or severe urinary symptoms on the IPSS may be better treated by radical prostatectomy, which usually results in decreased LUTS and bothersome symptoms, as assessed by the IPSS, and improved urodynamic values, although this is offset by the risk of incontinence [17,18]. Urodynamics may therefore have a wider role in treatment selection for men with early prostate cancer, to improve outcomes in brachytherapy.

We are encouraged by our initial experience, with none of the first 100 patients treated becoming incontinent or having serious side-effects. Urinary symptoms were self-limiting and resolved with conservative treatment in all but two men. We will present the PSA outcome data from this cohort, which we hope will underline the excellent cancer control rates achieved in the large American centres.

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Authors

A. Henderson, MRCS, Urology Research Registrar.
 D. Cahill, FRCS(Urol), Urology Specialist Registrar.
 R.W. Laing, MRCP, FRCR, Consultant Clinical Oncologist.
 S.E.M. Langley, MS, FRCS(Urol), Consultant Urological Surgeon
 Correspondence: A. Henderson, Department of Urology, Royal Surrey County Hospital, Egerton Road, Guildford, GU2 5XX, UK.
 e-mail: AliHenderson@Freenet.co.uk

Abbreviations: **TIPB**, transperineal interstitial prostate brachytherapy; **AUR**, acute urinary retention; **PVR**, postvoid residual urine volume.