Brachytherapy for prostate cancer has many good effects, but is also associated, like every treatment, with side-effects, some of which have been previously reported in the BJU International. In this section, authors from New York assessed the pathophysiology underlying LUTS which persisted for at least 6 months after brachytherapy, and found a relatively high incidence of detrusor overactivity and other conditions affecting the lower urinary tract.

The pathophysiology of lower urinary tract symptoms after brachytherapy for prostate cancer

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OBJECTIVES

To determine the spectrum of pathophysiology underlying the lower urinary tract symptoms (LUTS) persisting for ≥6 months after brachytherapy for localized prostate cancer.

PATIENTS AND METHODS

A database of men from two practice settings was searched for men who developed LUTS persisting for ≥6 months after completing brachytherapy for localized prostate cancer. Patients were evaluated with a structured history and physical examination, International Prostate Symptom Score (IPSS), 24-h voiding diary, noninvasive free-flow uroflowmetry, postvoid residual urine volume (PVR), cystoscopy and a video-urodynamic study. Specific data collected included symptoms, elapsed time since brachytherapy, Gleason score, IPSS, total number of voids/24 h, maximum voided volume, cystoscopic findings, and urodynamics findings (PVR, maximum urinary flow rate, Schaefer obstruction grade, Watts factor, incidence of detrusor overactivity (DO) urethral obstruction and low bladder compliance). These data were compared with those from a previous study of men with LUTS who did not have prostate cancer.

RESULTS

The study included 47 men (aged 54–88 years); the median (range) interval between brachytherapy and evaluation was 1.5 (0.5–13) years. Thirty-seven men complained of overactive bladder symptoms (79%), and 31 of incontinence (71%), 21 of obstructive symptoms (44%), and persistent dysuria in 12 (26%). Comparison of urodynamic findings in men with unselected causes of LUTS vs LUTS due to brachytherapy revealed the following comparisons: DO in 252 of 541 (47%) unselected vs 28 of 33 (85%) brachytherapy, ($P < 0.001$); and urethral obstruction in 374 of 541 (69%) unselected vs 24 of 33 (73%) brachytherapy ($P = 0.85$).

CONCLUSION

The pathophysiology and severity of persistent LUTS in men after brachytherapy differs from that of men with LUTS in the general population. Men after brachytherapy have a much higher incidence of DO, prostatic and urethral strictures and prostatic urethral stones.

KEYWORDS

LUTS, brachytherapy, prostate cancer, incidence

INTRODUCTION

The treatment of localized prostate cancer with interstitial radiation (brachytherapy) is often complicated by the development of LUTS [1–10]. In most patients the symptoms are said to subside within a matter of months and patients are usually treated empirically, but there is little reported documentation of this. However, most agree that there is a subset of patients who develop persistent, bothersome symptoms that often defy empirical therapies. The aim of the present study was to determine the underlying pathophysiology of LUTS in such men and to compare them to a historical cohort of men with LUTS who had not had brachytherapy [11].

Variable	Mean (SD)	Median (range)
Clinical		
Age, years	74 (5.4)	74 (54–88)
Years from brachytherapy	3.6 (3.3)	1.5 (0.5–13)
Gleason grade	6 (0.61)	6 (4–7)
IPSS	18.3 (6.7)	19 (5–32)
Total 24-h volume, mL	1720 (724)	1446 (575–4230)
MVV*, mL	226 (123)	180 (0–550)
Voids/24 h*	14.5 (3.7)	14.9 (4–23)
Urodynamic		
Incidence, n/N (%)		
Urethral obstruction	24/33 (73)	
DO	28/33 (85)	
Low bladder compliance	8/32 (25)	
Schaefer grade	3.5 (1.5)	4 (0–6)
Watt's factor	13.4 (3.8)	12.3 (0.5–13)
Q_{max}, mL/s	5 (3.4)	4 (0–18)
PVR, mL	94 (89)	45 (0–450)

TABLE 1
The clinical and urodynamic data

**Excludes 18 patients who were treated with indwelling or intermittent catheterization.*

PATIENTS AND METHODS

A database of men from two practice settings, one community-based and one from a tertiary referral centre, was searched for all men who developed LUTS persisting for ≥6 months after completing brachytherapy for localized prostate cancer. In addition, the community-based practice database was also searched for all patients who had brachytherapy during the same period to determine the incidence of persistent LUTS. Exclusion criteria included neurogenic bladder and patients with severe symptoms requiring treatment before brachytherapy. Patients completed an evaluation consisting of a structured history and physical examination, the IPSS, a 24-h bladder diary, noninvasive uroflowmetry, postvoid residual urine volume (PVR), cystoscopy and a video-urodynamic study (VUDS), the last with the patient seated, with room-temperature radiographic contrast medium infused at a medium fill rate through a 7 F dual-lumen open-ended catheter. Abdominal pressure was recorded via a 7 F balloon catheter. BOO was defined as a grade >2 on the Schaefer nomogram [12]. There are no well-defined values for normal and abnormal bladder compliance. For the purposes of the study we defined a low bladder compliance as <13 mL/cmH_2O based on the studies of Weld *et al.* [13]. Specific data included symptoms, Gleason grade, total number of voids/24 h, maximum voided volume (MVV), PVR, maximum urinary flow rate (Q_{max}) and total IPSS. The urodynamic data were compared with those previously reported for a cohort of men with LUTS who did not have prostate cancer [11]. For statistical analysis we used Fisher's exact test and Student's *t*-test, with significance between the groups denoted by $P < 0.05$.

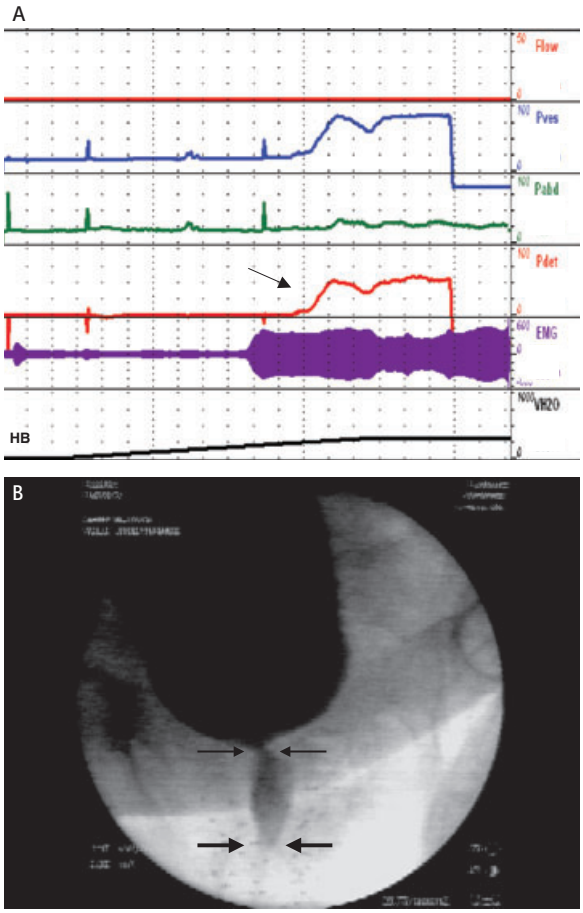
RESULTS

In the community-based practice, 16 of 160 consecutive men who had brachytherapy developed troublesome LUTS that persisted for ≥6 months (10%). An additional 31 men with prolonged bothersome LUTS in a referral practice were retrospectively analysed, to give 47 men in all. The clinical data are shown in Table 1. There was no difference between the primary and tertiary groups in age, pretreatment Gleason score, or the interval between brachytherapy and clinical presentation for evaluation. Thirty-seven men complained of overactive bladder symptoms (79%) and 31 of incontinence (71%). There were obstructive symptoms in 21 men (44%) and persistent dysuria in 12 (26%). In the tertiary practice, five of 31 (16%) men had previously had transurethral prostatic surgery but no patient in the community practice had had such surgery.

Thirty-three men had VUDS and cystoscopy, and eight cystoscopy alone (Table 1). The six patients who had neither included four who had severe dysuria and a small-capacity bladder, and who refused invasive testing, and two who simply refused an invasive evaluation. At urodynamics, 24 of 33 men had urethral obstruction (73%); all eight who only had cystoscopy had urethral strictures, giving 32 of 41 with urethral obstruction (78%). Figure 1 shows the VUD tracing of a typical patient. There was detrusor overactivity (DO) in 28 of 33 patients (85%). Because of the high rate of (often painful) DO, it was not possible to fill the bladder of most patients to capacity, and therefore bladder compliance could not be accurately measured in all. Nevertheless, at least eight of the 32 patients had a low bladder compliance (25%). At cystoscopy 22 of 41 (54%) had prostatic and/or membranous urethral strictures (four of 11 in the community practice, 18 of 30 in the tertiary practice, $P = 0.29$) In four patients the urethra was completely occluded, all in the tertiary practice ($P = 0.56$). Eight of 41 patients (20%) had radiation prostatitis (white, shaggy, necrotic-looking tissue lining the prostatic urethra), five (12%) had severe, persistent, bullous erythema in the bladder that proved to be acute and chronic inflammation by biopsy, and five had stones adherent to the prostatic urethra (12%). The last two were only in the tertiary referral patients ($P = 0.3$). No patient had bladder cancer.

DO and urethral obstruction was previously reported as 47% and 69%, respectively, in men with LUTS who had not undergone brachytherapy. No patient in that series had stones adherent to the prostatic urethra, and urethral strictures accounted for less than 5% of obstructed patients [11]. In that study, DO occurred in 193 of 402 (48%) of community and 59 of 139 (42%) tertiary centre patients ($P = 0.28$). In the same study urethral

FIG. 1. Bladder neck and distal prostato-membranous urethral stricture in a 79-year-old man who had brachytherapy for Gleason 7, T1c prostate cancer 7 years previously. He complained of 'terrible frequency and urge . . . as soon as I open that bathroom door . . . I can't control it" He ordinarily voided every hour during the day and had nocturia about every 1–2 h at night. The force of his stream was usually weak. He wore absorbent pads day and night and changed them four times daily; they were usually soaked. ***A,*** *Urodynamic tracing; the cystometrogram was taken using radiographic contrast medium and a 7 F double-lumen catheter with constant infusion at a 'medium' filling rate, with rectal pressure monitoring and the patient seated. First filling sensation = 237 mL. The first urge (320 mL) coincided with severe, painful urge and a spontaneous involuntary detrusor contraction (arrow). The increased electromyographic activity is probably due his inability to relax because of the pain he was experiencing. Detrusor pressure/uroflow: Q_{max} = 0.5 mL/s (too low to be seen on the tracing), $PdetQ_{max}$ = 58 cmH_2O, $Pdet_{max}$ = 58 cmH_2O, voided volume = 6 mL; PVR = 314 mL; Flow, uroflow (Q); pves, intravesical pressure; pdet, detrusor pressure; pabd, intra-abdominal pressure; EMG, sphincter electromyography obtained with patch electrodes; VH_2O, bladder volume.* ***B,*** *A plain film obtained at Q_{max} shows a narrowed vesical neck (small arrows) and distal prostato-membranous urethral obstruction (large arrows). Note the multiple radiation seeds far outside the anatomical boundary of the prostate.*



obstruction occurred in 278 of 402 (69%) of community and 96 of 139 (70%) tertiary centre patients ($P = 1.0$). Comparing the urodynamic findings in men with unselected causes of LUTS vs LUTS caused by brachytherapy showed the following; DO in 252 of 541 (47%) unselected vs 28 of 33 (85%) brachytherapy ($P < 0.001$); and urethral obstruction in 374 (69%) unselected vs 24 (73%) brachytherapy ($P = 0.85$).

DISCUSSION

The present study combines patients from a practice known for referrals of patients with difficult voiding dysfunction with those from a general community practice. Of the 160 consecutive community practice patients, the incidence of severe, persistent, bothersome LUTS after brachytherapy for prostate cancer was 10%. In the combined group, the most striking results were the higher rates of DO (85%) and lower bladder compliance (25%) than in a general population of men with LUTS (47% and 9%, respectively) [11]. Urethral obstruction and the IPSS were similar amongst the two groups, but it was obvious to the investigators that the severity of symptoms was far greater in the brachytherapy group. Unfortunately, there was no way to capture this using the outcome instruments available in this retrospective study. The IPSS has no domain for dysuria and pain, yet both were common in the brachytherapy group (26%). Furthermore, even though the incidence of urethral obstruction was similar amongst the brachytherapy patients and the general LUTS population, almost all of the obstruction in the former group was due to severe prostatic, vesical neck, and membranous urethral strictures, whereas in the latter group there was such pathology in <10%.

The incidence of LUTS after brachytherapy is not well documented; moreover, the few reports are largely empirical and often do not use validated instruments. The incidence of acute urinary retention was 2–35% [1–3]. Stone and Stock [3], in a review, reported that acute LUT complications included urinary retention (1.5–22%), worsening IPSS and worsening pre-morbid symptoms in nearly all patients by a month after treatment. Significant LUTS persisted in ≈10% at 1 year. Persistent symptoms requiring TURP occurred in 0–8.7% and *de novo* incontinence occurred in 0–18%.

Mallick *et al.* [4] found that patients undergoing prostate brachytherapy had a high rate of acute symptoms, including weak stream, dysuria and both obstructive and irritative LUTS (52%, 50%, 66% and 52%, respectively, at 1 month after implantation), which substantially improved by 6 months (to 34%, 6%, 30% and 30%, respectively). Henderson *et al.* [2] reported a 61% incidence of LUTS in 100 men after prostate brachytherapy, of whom 57% had a urodynamic assessment and 2% required prostatectomy. Of those patients with urinary retention, 15% had unequivocal prostatic obstruction by urodynamic criteria, but the incidence of DO was not reported. Tsui *et al.* [5] stated, 'With respect to urinary symptoms . . . it was evident that patients who underwent brachytherapy had more severe urinary sequelae . . . Tamsulosin was still being used by 78% of patients at

6 months, decreasing to 55% at 1 year and 27% at 2 years. Intermittent self-catheterization was required at 6 months after treatment by 5% of patients who underwent brachytherapy, and a TURP was performed in one of these patients at 12 months.'

Sarosdy [6] reported on 177 consecutive men who had brachytherapy (100 patients) or brachytherapy plus external beam radiotherapy (77). Of the former group, 24% developed urinary retention requiring catheter drainage for a median (range) of 55 (3–330) days; 5% had a TURP at a median of 12 (8–18) months after treatment. Recurrent urethral stricture occurred in 4.9% of the combined therapy group, but not in the monotherapy group ($P = 0.055$). Han *et al.* [7], in a questionnaire study, found that 32% of patients required urethral catheterization by 1 year after treatment. Talcott *et al.* [8] reported a 40% incidence of incontinence after brachytherapy. In a review of 2124 Medicare claims from 1991 to 1993, Benoit *et al.* [9] found that 8.3% of patients had an outlet-reducing operation and 2.3% had a sphincter prosthesis within 2 years after treatment.

The high rate of initial and delayed symptoms, prostatic and urethral strictures and low bladder compliance probably relates to the known effects of radiation on tissue, and probably has a similar pathophysiology to that of radiation cystitis. Several authors suggested that high doses of urethral radiation are the major risk factor [1,4,14–20]. Grills *et al.* [16] reported that 8% of men undergoing high-dose rate brachytherapy developed a urethral stricture, as opposed to 3% of men receiving ^{103}Pd (low-dose) brachytherapy.

Other risk factors proposed include large prostatic volume [17], a high IPSS before treatment [4,21], previous (or subsequent) TURP [3] and previous (or subsequent) external beam radiotherapy [6]. The refractoriness of stricture disease to surgical treatment after brachytherapy is well known, but not reported often [22]. Moreira *et al.* [22] reported on 18 'devastating' complications after brachytherapy in a 3-year period (11 prostatorectal fistulae and seven severe bladder neck contractures). All of the patients with bladder neck contractures had had three or more previous surgical attempts at repair.

The limitations of the present study are inherent in any retrospective, observational design. First, there was no denominator, so the incidence of these troublesome symptoms cannot be estimated. Second, no validated outcome measures were available for objectively measuring symptoms. Third, details of pre-morbid symptoms and radiation techniques were not available to permit an assessment of the risk factors. Finally, long-term follow-up was not available. The shortcomings of all of these studies, including the present series, underlies the importance of conducting prospective studies using validated outcome instruments developed specifically to address the relevant issues.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **PVR**, postvoid residual urine volume; **VUDS**, video-urodynamic study; **MVV**, maximum voided volume; $\mathbf{Q}_{max}$, maximum urinary flow rate; **DO**, detrusor overactivity.

EDITORIAL COMMENT

The data in this article represent an excellent compilation of the urodynamic and cystoscopic findings in men who found their way to a super-specialist's office because of LUTS after brachytherapy for prostate cancer. However, they represent a group of very selected patients. With no denominator and no true history of symptoms or urodynamic studies before brachytherapy, the conclusions are accurate only insofar as they characterize the findings in this particular group of patients at the time of study. Recognizing that I lack a denominator and specific objective data, let me simply say that our subjective impression here at the University of Pennsylvania is that our brachytherapy patients have had no permanent adverse changes in their LUTS or the development of permanent significant new LUT difficulties. Certainly, a transient worsening of symptoms is not uncommon, up to 3 months after treatment. Our seemingly favourable experience could be because substantially many of our patients eventually present to Dr. Blavais' office! However, I suspect that the seeming lack of permanent problems is probably because, at least in part: (i) we do not use brachytherapy in patients with large prostates or with obstructing, partially intravesical 'middle lobes'; (ii) we look for what we consider to be potential predictors of difficulty after treatment (significant LUTS); (iii) we carry out an endoscopic examination in all patients beforehand, and pressure flow urodynamic studies in selected patients with LUTS suggestive of significant prostatic obstruction; and (iv) in patients with such evidence we avoid implantation.

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