Urinary symptom flare after brachytherapy for prostate cancer is associated with erectile dysfunction and more urinary symptoms before implantation

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OBJECTIVE

To examine the relationship of 'symptom flare' with sexual function and lower urinary tract symptoms (LUTS) before brachytherapy, as we noted that after brachytherapy for prostate cancer, some patients had recurrent LUTS after an asymptomatic period; this secondary exacerbation of symptoms ('symptom flare') occurred at ≈2 years after implantation and was transient in most patients.

PATIENTS AND METHODS

In all, 854 patients with organ-confined prostate carcinoma had transrectal ultrasonography-guided transperineal ^{125}I interstitial brachytherapy of the prostate gland between June 1991 and September 2002, and were considered candidates for this study. Detailed information on urinary function was self-administered and prospectively collected before treatment and at intervals using the International Prostate Symptom Score (IPSS). Sexual function was evaluated with the Sexual Health Inventory for Men (SHIM), a five-question, self-administered diagnostic test that can help to indicate the presence or absence of erectile dysfunction (ED). We used previously established criteria to estimate the risk of prostate-specific antigen (PSA) failure by dividing the men into three risk groups, i.e. low-risk, with a PSA level of ≤10 ng/mL, stage ≤T2a, Gleason ≤6; medium-risk, with a PSA level of ≤15 ng/mL, Gleason 7 or stage T2b; and high-risk, with a PSA level of >15 ng/mL, stage >T2b, or Gleason ≥8.

RESULTS

There was a significant association of flare with ED; men with flare reported significantly more ED than men without ($P = 0.020$). Men with high-risk disease reported more ED because they received more intensive treatment (hormones and increased radiation dose) than men with medium- or low-risk disease. To correct for this confounding factor, multivariate linear regression was used; the regression was significant overall ($P < 0.001$), and the effects of risk group ($P < 0.001$) and flare ($P < 0.026$) on SHIM score were significant and independent of each other. Flare was also significantly associated with a higher pre-implant IPSS; the probability of flare was 62% for a pre-implant IPSS of zero, to 94% for an IPSS of 30.

CONCLUSIONS

Radiation reaction and radiation sensitivity contribute to ED and greater LUTS in men who have had brachytherapy for prostate cancer. This contribution is evident, e.g. in men with ataxia-telangiectasia (ATM) gene mutations. Sequence variants in the ATM gene, particularly those that encode for an amino-acid substitution, are associated with adverse radiotherapy responses among patients treated with ^{125}I prostate brachytherapy. Our finding of the association of urinary symptom flare with ED suggests it would be worthwhile to determine whether sildenafil is as effective in men with flare, and if not, whether higher sildenafil doses would be of value. Alternatively, α_1-selective adrenoceptor-blocking agents, e.g. terazosin, combined with sildenafil, might be of benefit. Also, patients with a high IPSS before brachytherapy can be warned that they have a greater risk of flare and ED.

KEYWORDS

prostate cancer, symptom flare, SHIM, brachytherapy

INTRODUCTION

We noted that after brachytherapy for prostate cancer some patients had recurrent LUTS after an asymptomatic period. This secondary exacerbation of symptoms occurred at ≈2 years after implantation and was transient in most patients. We termed this secondary exacerbation of LUTS 'symptom flare'. The term 'flare' emphasizes the recurrent nature of the LUTS and the that the flare arises after a variable quiescent period [1]. By contrast, acute symptoms after ^{125}I prostate brachytherapy appear to peak at 1 month after a prostate implant and return to their baseline values by 1 year. Patients with greater LUTS before treatment or those having had previous α-blocker treatment are at greater risk of acute LUTS after brachytherapy [2].

Symptom flare is common and can occur in more than half of all patients by 5 years. We now report that symptom flare is associated with erectile dysfunction (ED), as measured with the Sexual Health Inventory in Men (SHIM), and with greater LUTS before brachytherapy.

PATIENTS AND METHODS

In all, 854 patients with organ-confined prostate carcinoma had TRUS-guided transperineal ^{125}I interstitial brachytherapy of the prostate gland between June 1991 and September 2002, and were considered candidates for this study. Detailed information on urinary function was self-administered and prospectively collected before treatment and at intervals using the IPSS [3], the sum of component symptoms associated with urinary tract irritation (incomplete emptying, frequency,

intermittency, urgency, weak stream, straining, and nocturia). Each of the seven components is given a score of 0–5 and then added to achieve a total score of 0–35. An IPSS of 7 is considered mildly symptomatic, of 8–19 moderately symptomatic, and of 20–35 severely symptomatic. Patients eligible for the study had a pre-treatment IPSS form and follow-up at regular intervals of 3–6 months for a total of at least four completed IPSS forms for ≥18 months.

Sexual function was evaluated with the SHIM, a five-question, self-administered diagnostic instrument that can help to indicate the presence or absence of ED. Responses to each of the five items on the SHIM, which are based on a rating scale of 0–5 or 1–5 (depending on the item), are summed to give a total score of 1–25, with higher scores indicating better sexual health. ED is partitioned into five severity grades: no ED (SHIM total score, 22–25), mild (17–21), mild to moderate (12–16), moderate (8–11), and severe ED (1–7). The moderate-to-high correlation and agreement between the SHIM and patient self-assessment of ED validated the SHIM for use in the diagnostic classification of ED severity [4]. The SHIM score used in the present study was obtained ≥2 years after brachytherapy.

We used previously established criteria [5] to estimate the risk of PSA failure by dividing the men into three risk groups, i.e. low-risk, with a PSA level of ≤10 ng/mL, stage ≤T2a, Gleason ≤6; medium-risk, with a PSA level of ≤15 ng/mL, Gleason 7 or stage T2b; and high-risk, with a PSA level of >15 ng/mL, stage >T2b, or Gleason ≥8.

The patients' demographics are listed in Table 1. All patients were staged according to the 1992 American Joint Committee on Cancer system, using a DRE. All patients had their PSA level evaluated before treatment, a bone scan, and CT of the pelvis.

Patients were implanted with ^{125}I seeds (Model 6711, Amersham Health, Princeton, NJ, USA) using an interactive TRUS-guided transperineal technique described previously [6]; 487 (57%) patients received hormone ablation therapy 3 months before the implant and 3 months after the implant for prostate volumes of >50 mL. The radiation prescription dose was 160 Gy, with all values corrected to the TG43 formulation [7]. CT-based dosimetry was performed 1 month after implant and

TABLE 1 *The demographic details of the patients*

Variable	Value
Mean (SD) age, years	65 (7.3)
N (%):	
T stage	
T1a	112 (13.1)
T1b	357 (41.8)
T1c	173 (20.3)
T2a	140 (16.4)
T2b	66 (7.7)
T2c	6 (0.7)
Gleason	
≤6	599 (70.1)
7	172 (20.1)
>7	83 (9.7)
PSA level, ng/mL	
≤4	78 (9.1)
>4 to ≤10	546 (63.9)
>10 to ≤20	168 (19.7)
>20	62 (7.3)
Low risk	438 (51)
Medium risk	239 (28)
High risk	179 (21)

revealed median (range) D90 values of 17 290 (5578–25 692) cGy.

The median (SD) follow-up was 62 (28) months; all patients had an increase in the IPSS from their pretreatment IPSS after implantation. The greatest increase in IPSS was designated as the initial peak value, after which all patients had subsequent IPSS evaluations that showed a return to approximate baseline scores. The lowest IPSS after the peak was designated the IPSS nadir. Patients who then had a second exacerbation in LUTS at ≥1 year, which was defined as an increase of ≥5 points from the nadir, were deemed to have a clinically significant flare in symptoms.

RESULTS

There was a significant association of flare with ED; men with flare reported significantly more ED (*P* = 0.020) than men without (Fig. 1). Men with high-risk disease reported more ED because they received more intensive treatment (hormones and increased radiation dose) than men with medium- or low-risk disease. To correct for this confounding factor, multivariate linear regression was used; the regression was significant overall

FIG. 1. *The mean (SEM) SHIM score in men with and with no flare. The number of cases in each group is shown above the error bar. The difference was significant (P = 0.020). A SHIM score of 22–25 indicates no ED.*
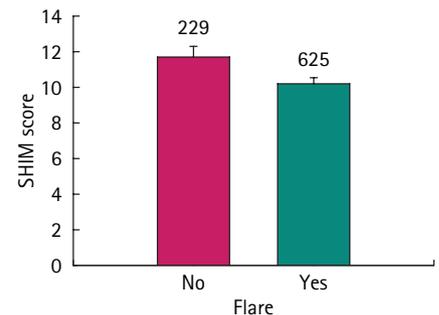
FIG. 2. *The IPSS before implantation in men with and with no flare. The IPSS was significantly higher in men who had flare (P < 0.001).*
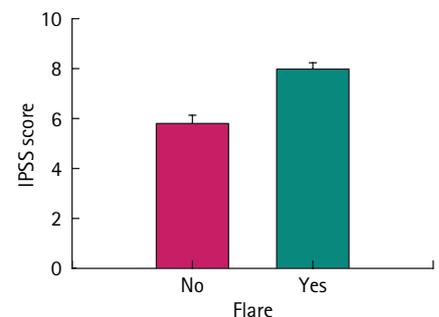
(*P* < 0.001), and the effects of risk group (*P* < 0.001) and flare (*P* < 0.026) were significant and independent of each other.

Flare was also significantly associated with a higher IPSS before implantation (Fig. 2). Probit analysis [8] of the probability of flare vs IPSS is shown in Fig. 3. The probability was 62% for an IPSS of zero, to 94% for an IPSS of 30.

DISCUSSION

Men with LUTS can have sexual dysfunction, including ejaculatory loss, painful ejaculation and ED [9,10]. In one study, the presence and severity of LUTS were independent risk factors for sexual dysfunction in older men [11]. Radiation reaction and radiation sensitivity also contribute to ED and greater LUTS in men who have received ^{125}I brachytherapy for

FIG. 3.

The probability of flare vs pre-implant IPSS; the upper and lower curves indicate the 95% CI.
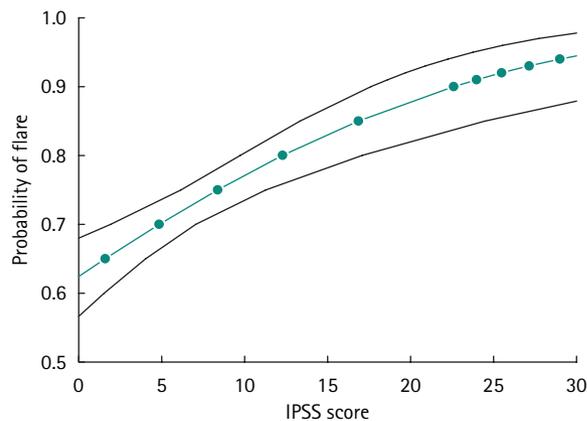
prostate cancer. This contribution is evident, e.g. in men with ataxia-telangiectasia (ATM) gene mutations [12]. Sequence variants in the ATM gene, particularly those that encode for an amino-acid substitution, are associated with radiation reaction and radiation sensitivity, and the development of ED and greater LUTS.

Our finding of an association of urinary symptom flare with a greater IPSS before brachytherapy and with ED is important for two reasons. First, patients with a high IPSS can be warned that they are at greater risk of flare and ED. Second, sildenafil citrate can improve the erectile function in men in whom ED develops after radiation therapy for prostate cancer. There is a clear dependence on time for the response to this therapy, with a stepwise decrease in all endpoints examined serially in a 3-year period [13]. It would be worthwhile to determine whether sildenafil is as effective in men with flare, and if not, whether higher sildenafil doses would be of value. Alternatively, α_1-selective adrenoceptor blocking agents such as terazosin, combined with sildenafil, might be of benefit.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **ED**, erectile dysfunction; **SHIM**, Sexual Health Inventory in Men; **ATM**, ataxia-telangiectasia.