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Reduced Penile Size and Treatment Regret in Men With Recurrent Prostate Cancer After Surgery, Radiotherapy Plus Androgen Deprivation, or Radiotherapy Alone

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Abstract

OBJECTIVE—To report the relative incidence of the perceived reduction in penile size across prostate cancer treatment modalities and to describe its effect on quality of life and treatment regret.

MATERIALS AND METHODS—The incidence of patient complaints about reduced penile size was calculated for 948 men in the Comprehensive, Observational, Multicenter, Prostate Adenocarcinoma (COMPARE) registry who experienced biochemical failure (per registry definition) and were assessed a median of 5.53 years after prostatectomy or radiotherapy (RT) consisting of either external beam RT or brachytherapy, with or without androgen deprivation therapy (ADT). Multivariate logistic regression analysis was used to determine the factors associated with treatment regret and interference with emotional relationships.

RESULTS—Of 948 men, 25 (2.63%) complained of a reduced penile size. The incidence of reduced penile size stratified by treatment was 3.73% for surgery (19 of 510), 2.67% for RT plus ADT (6 of 225), and 0% for RT without ADT (0 of 213). The surgery ($P = .004$) and RT plus ADT ($P = .016$) groups had significantly more shortened penis complaints than the RT alone group. The rate of a shortened penis after surgery and after RT plus ADT was similar ($P = .47$). On multivariate analysis adjusting for age, treatment type, and baseline comorbidity, a perceived reduction in penile size was associated with interference with close emotional relationships (odds

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ratio 2.36, 95% confidence interval 1.02–8.26; $P = .04$) and increased treatment regret (odds ratio 3.37, 95% confidence interval 1.37–8.26; $P = .0079$).

CONCLUSION—Complaints about a reduced penile size were more common with RT plus ADT or surgery than RT alone and were associated with greater interference with close emotional relationships and increased treatment regret. Physicians should discuss the possibility of this rarely mentioned side effect with their patients to help them make more informed treatment choices.

The National Cancer Institute has estimated that 241,740 new cases of prostate cancer will have been diagnosed in 2012.¹ For each of these men, several treatment choices await. Although some men will choose active surveillance, for those who proceed with treatment, the possibilities include radical prostatectomy, brachytherapy, external beam radiotherapy (RT), and the possible addition of androgen deprivation therapy (ADT). In addition to which treatment choice might offer the best chance of cure, many men will also decide on a treatment according to the associated side effect profile. With the long life expectancy assumed for most men treated for prostate cancer, these side effects are not a trivial consideration, and for many men can have a significant effect on quality of life.

One relatively unstudied sequela from prostate cancer treatment is that of changes in penile size after treatment. Although a few studies have been published on penile size after surgery,^{2–4} it is generally a side effect not widely reported or researched, especially in a comparison of treatment modalities. However, it can be an important consideration to men and is a topic that deserves attention. Thus, we sought to study the possible association between the type of treatment received and the development of a perceived reduction in penile size, and, moreover, what effect a reduced penile size might have on the quality of life of prostate cancer survivors.

MATERIAL AND METHODS

COMPARE Registry

In February 2004, the Comprehensive, Observational, Multicenter, Prostate Adenocarcinoma (COMPARE) registry was opened across 150 different sites in the United States.⁵ This observational, prospective database was opened with the goal of collecting data on men with biochemical recurrence after primary therapy for prostate cancer. Men of any age presenting with an increasing prostate-specific antigen (PSA) level after treatment of primary nonmetastatic prostate adenocarcinoma were eligible, with the increased PSA level defined per protocol as follows: (1) an increase of ≥ 0.2 ng/mL on repeated testing after radical prostatectomy (RP), or (2) 2 increases greater than nadir, with a PSA value $\geq 50\%$ greater than the nadir and a minimal PSA value ≥ 0.2 ng/mL greater than the post-RT nadir. The exclusion criteria included any ongoing treatment of prostate cancer and certain comorbidities. The full exclusion criteria have been detailed more thoroughly in previous reports.⁵ Ultimately, 1129 men were enrolled in the study, which closed in August 2006.

Inclusion Criteria and Outcomes Assessment

For inclusion in our study, the men must have had complete demographic information and data on current urinary function, sexual performance and satisfaction, and whether they

perceived themselves to have a reduced penile size, all of which were assessed using either a physician- or patient-completed questionnaire. All patients also had to have undergone definitive therapy with radical prostatectomy, RT (external beam RT or brachytherapy), or RT plus androgen deprivation therapy (ADT). A total of 948 men met the inclusion criteria and constituted the study cohort. Patients' perception of reduced penile size was assessed by a physician-completed questionnaire on entry to the registry. Physicians were asked "Does the patient have any other complaints" and given a list in which reduced penile size was included. For each item on the list, the physicians were required to mark whether the patient complained of it and the severity, which could be mild, moderate, or severe.

On entry into the study, the patients also completed a questionnaire on prostate health-related quality of life. Regarding sexual function, they were asked "During the past 4 weeks, how often has your sexual functioning made it difficult to enjoy your life? Responses were given on the following scale: never (1), rarely (2), some of the time (3), frequently (4), or most of the time (5). To assess for interference with personal relationships, we asked, "During the past 4 weeks, how did your sexual function, or concerns or feelings about your sexual function, affect your close, emotional relationships (eg, a relationship with a spouse or partner)?" The response scale was as follows: did not interfere (1), interfered a little (2), interfered moderately (3), interfered very much (4), and interfered almost all the time (5).

Treatment regret was also assessed using a 2-question questionnaire. Patients were asked "If I had known everything I could have known, I would still have chosen the same treatment approach for prostate cancer" and were considered to have treatment regret if they either answered "definitely false" or "mostly false." Similarly, if they answered "mostly true" or "definitely true" to the question "During the past 4 weeks, I felt I would be better off if I had chosen a different treatment approach for prostate cancer," they were considered to have treatment regret.

The responses to reduced penile size were dichotomized into "yes" or "no" categories for the purposes of our analysis, without regard to severity, because too few events were available for meaningful analysis of severity. For whether sexual functioning interfered with enjoyment of life, the results were dichotomized into 1 (never) and 2–5 (rarely to most of the time). For sexual functioning interference with emotional relationships, the responses were dichotomized into 1 (did not interfere) and 2–5 (did interfere). The responses to treatment regret were dichotomized into "yes" or "no" categories for our analysis.

Patient comorbidities were also assessed by the physician and documented in the physician questionnaire on entry into the registry. For the purposes of the present analysis, they were divided into "cardiovascular" and "noncardiovascular" comorbidities. The cardiovascular comorbidities included myocardial infarction or heart attack, congestive heart failure, and angina or chest pain. The noncardiovascular comorbidities included diabetes, hypertension, stroke, amputation, circulation problems, chronic lung disease (chronic obstructive pulmonary disease, asthma, emphysema), ulcers (stomach), inflammatory bowel disease, kidney problems, major depression, and seizures.

Statistical Analysis

Fisher's exact test was used to perform a univariate analysis to compare reduced penile size by treatment type, which was radical prostatectomy, RT, or RT plus ADT.⁶ Firth's penalized maximum likelihood estimation was then used as a multivariate analysis to determine whether treatment type was associated with reduced penile size, after adjusting for age and comorbidity.⁷ The method of analysis was used, because it allowed us to compare the effect of treatment types using the RT-alone group as a baseline because it had no events.

Multivariate logistic regression analysis was used to determine whether a reduced penile size was associated with treatment type, interference of sexual function with overall enjoyment of life, or treatment regret, after adjusting for age at treatment and comorbidities. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were reported for the covariates, and $P < .05$ was used as a cutoff to indicate significance. SAS, version 9.3, software (SAS Institute, Cary, NC) was used for all calculations.

RESULTS

Patient Baseline Characteristics

A total of 948 men from the COMPARE registry had complete information available on sexual function and health, urinary function, and penile length and constituted the study cohort. The baseline and demographic information is listed in Table 1. No significant differences were found in the baseline or demographic information between the included and excluded patients, except that the included patients had a greater proportion of stage T2 tumors and the excluded patients had a greater proportion with an unknown T stage ($P < .001$). A history of definitive treatment of prostate cancer included 510 (53.8%) who underwent radical prostatectomy, 225 (23.7%) who underwent ADT plus RT, and 213 (22.5%) who received RT alone. Of the 948 patients, 212 (22.3%) were <60 years old, 717 (75.6%) were 60–80 years old, and only 19 (2%) were >80 years old. Finally, 171 patients (18%) had a cardiac comorbidity and 530 (55.9%) other noncardiac comorbidities.

Incidence of Reduced Penile Size by Treatment

Overall, 25 of 948 patients (2.64%) complained of a reduced penile size. The incidence of reduced penile size by treatment was 3.73% for surgery (19/510), 2.67% for RT with ADT (6/225), and 0% for RT alone (0/213; Fig. 1). The surgery ($P = .004$) and RT plus ADT ($P = .016$) groups were associated with significantly more complaints of a shortened penis than the RT alone group. The rates of a shortened penis for the surgery and RT plus ADT groups were not significantly different ($P = .47$).

Using Firth's penalized likelihood method, on multivariate logistic regression analysis, radical prostatectomy was associated with a significantly greater rate of reduced penile size than RT alone (OR 19.6, 95% CI 1.2–316.4, $P = .035$). Patients who received RT plus ADT had a near-significant increased risk of reduced penile size compared with patients who received RT alone (OR 11.9, 95% CI 0.70–202.9, $P = .08$). Neither age nor comorbidity status was associated with reduced penile size (Table 2). The association between RP and the complaints of reduced penile size did not vary much by whether nerve-sparing or non-

nerve-sparing RP was performed. When both forms of RP were evaluated separately in the same multivariate model, non-nerve-sparing RP had an OR of 22.3 (95% CI 1.36–367.0; $P = .0297$) for complaints of a shortened penis, and nerve-sparing RP had an OR of 17.03 (95% CI 0.995–291.4; $P = .0507$).

Effect of Reduced Penile Size

On multivariate analysis, adjusting for age, treatment type, and baseline comorbidity, reduced penile size was associated with more treatment regret (OR 3.37, 95% CI 1.37–8.26, $P = .0079$) and increased risk of interference with close emotional relationships (OR 2.36, 95% CI 1.02–5.47, $P = .044$; Tables 2 and 3). In addition, it was associated with a near-significant increase in the interference with overall enjoyment of life (OR 2.35, 95% CI 0.997–5.546, $P = .0507$).

COMMENT

In the present study, we sought to identify a possible link between prostate cancer treatment type and risk of reduced penile size. In our analysis, we found that both RP and RT plus ADT were associated with significantly more reduced penile size complaints than RT alone. On multivariate logistic analysis, we also found reduced penile size to be associated with increased treatment regret and an increased risk of having sexual function interfere with close, emotional relationships and the patient's overall enjoyment of life.

Although few studies have compared the incidence of reduced penile size across all 3 major treatments, such as was done in our analysis, some groups have reported the effect of RP on penis length.^{2–4} In a study by Engel et al,³ the stretched penile length was measured before and after bilateral nerve-sparing RP and showed a significant decrease in length from 11.77 to 11.13 cm at 1 month. In a similar study by Savoie et al,⁴ in which penile length was measured before and after retropubic RP, significant decreases were seen for the flaccid and stretched measurements and circumference. These results are consistent with our findings of significantly more patient-reported complaints after surgery than after RT alone. A hypothesized mechanism for the reduction in penile length after RP results from postoperative denervation atrophy associated with erectile dysfunction and possibly fibrosis of the cavernous smooth muscle, although the exact process has not been fully characterized.²

Our results showed a significant association of RT plus ADT and complaints of reduced penile size compared with RT alone. The combined effects of RT plus ADT on penile size have been less widely studied than those of RP. However, a few studies have commented on its effect. In a series by Park et al,⁸ a prospective study was done, measuring the penile length of patients receiving ADT alone as the initial therapy for prostate cancer. At 15 months, a significant decrease in the mean penile length from 10.76 to 8.05 cm was observed. Some have suggested that the loss of erectile function from ADT might contribute to shortening. However, that study found no significant relationship between potency and penile shortening. They suggested that serum testosterone maintains a role in sustaining penile length beyond puberty and that this effect explains the results observed.

Although our study did not find that any patients with RT alone complained of reduced penile size, a study by Haliloglu et al⁹ speculated that RT itself can play a role in penile shortening. The mechanism they propose included long-term inflammatory changes to the microvasculature, neural tissues, and structural changes to the corporeal smooth muscle, all resulting from external beam RT that can contribute to penile length changes.

Our findings are a unique addition to the currently published data on the sequelae from prostate cancer treatment in that we have compared the perception of a reduction in penile size across the 3 common treatments of RP, RT alone, and RT plus ADT. Moreover, we explored the effect such a reduction has on the quality of life of men, most of whom have a long life expectancy after treatment of prostate cancer. We found a significant effect of reduced penile size on the close, emotional relationships of men who underwent treatment and a near-significant effect on their overall enjoyment of life. These findings highlight the importance of this relatively unstudied phenomenon, and the overall role that treatment choice can play in the quality of life of men with prostate cancer.

We also found that a perceived reduction in penile size was significantly associated with increased treatment regret, suggesting that men with newly diagnosed prostate cancer should factor the possibility of diminished penile length into their treatment decisions to minimize later regret about their choice.^{10,11}

A few points deserve additional consideration. Unlike the cited series studying RP, our findings of reduced penile size were not determined by actual measurements taken before and after treatment, but rather the patients' perception of change. Similarly, in the reporting of reduced penile size, it is unclear whether patients reported outcomes according to their perception of the erect or flaccid size. Furthermore, our data were determined by physician-reported information according to concerns expressed by the patients and likely underreported the incidence, because patients who experienced penile shortening might not mention this concern in an interaction when the topic of prognosis or oncologic control might seem more pressing.¹² Also, our patient population consisted of those with prostate cancer recurrence; thus, they were likely to be focused more on the outcomes of treatment than the effect on quality of life in a physician encounter. In addition, the relatively small number of shortened penis events (n = 25) could have reduced our ability to perform robust multivariate analyses with many covariables predicting for this outcome. Finally, we did not have information on the baseline perception of penile length before the initial treatment and thus could not adjust for that data.

CONCLUSION

Our study found that compared with RT alone, both RP and RT plus ADT were associated with more complaints of reduced penile size among men treated for prostate cancer. Perhaps more striking, however, was that the reduced penile size resulting from treatment had a significant effect on patients' regret about the treatment decision and the quality of close, emotional relationships maintained by the patients, and a near-significant effect on their overall enjoyment of life. Physicians should discuss the possibility of this rarely mentioned side effect with their patients to help them make more informed treatment choices.

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Figure 1.
Graph showing percentage of patients with reduced penile size stratified by treatment.
(Color version available online.)

Table 1

Baseline characteristics

Characteristic	Value
Age group	
60 y	212 (22.3)
>60 but 70 y	442 (46.4)
>70 but 80 y	275 (29.0)
80 y	19 (2.0)
Median interval since treatment (y)	5.53
Treatment	
RP	510 (53.8)
Nerve-sparing RP	228
Non-nerve-sparing RP	282
ADT+RT	225 (23.7)
RT alone	213 (22.5)
Clinical T stage	
T1	403 (42.5)
T2	393 (41.4)
T3	75 (7.9)
T4	4 (0.42)
Unknown	73 (7.7)
Comorbidity	
Cardiovascular	171 (18.0)
Noncardiovascular	530 (55.9)
None	247 (26.0)

ADT, androgen-deprivation therapy; RP, radical prostatectomy; RT, radiotherapy.

Data presented as numbers, with percentages in parentheses, unless otherwise noted.

Table 2

Risk of reduced penile size

Parameter	OR	95% CI	P Value
RP	19.6	1.2–316.5	.04
RT + ADT	12.0	0.71–202.9	.09
RT alone	1.0 (reference)	—	—
Age	1.03	0.97–1.09	.33
Comorbidity *	1.64	0.60–4.48	.33

CI, confidence interval; OR, odds ratio.

* Included both cardiovascular and noncardiovascular.

Table 3

Effect of reduced penile size on quality of life

Covariables	Treatment Regret			Interference of Sexual Function With Close Relationships			Interference of Sexual Function With Overall Enjoyment of Life		
	OR	95% CI	P Value	OR	95% CI	P Value	OR	95% CI	P Value
Shorter penis	3.37	1.37–8.27	.008	2.37	1.02–5.48	.04	2.35	0.99–5.54	.0507
RP	0.77	0.46–1.30	.33	1.24	0.88–1.77	.22	1.30	0.92–1.83	.13
RT + ADT	0.98	0.55–1.74	.93	1.34	0.90–1.99	.15	1.36	0.93–2.00	.12
RT alone	1.00 (reference)	—	—	1.00 (reference)	—	—	1.00 (reference)	—	—
Age	0.97	0.95–1.00	.048	0.95	0.93–0.97	<.0001	0.97	0.95–0.99	.0009
Comorbidity	1.03	0.66–1.62	.89	0.89	0.66–1.20	.45	1.05	0.78–1.41	.74