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Reduced Radiation Tolerance of Penile Structures Associated With Dose-escalated Hypofractionated Prostate Radiotherapy

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Abstract

Objective—To investigate the effect of hypofractionated external beam radiation therapy (RT) on sexual function in patients treated for localized prostate cancer, and also to determine the effect of radiation dose to the penile bulb or crura of the corpus cavernosum on sexual function outcome.

Materials and Methods—Forty-one patients treated with hypofractionated RT without androgen deprivation were prescribed 67.6–70.2 Gy to the prostate, delivered in 26–28 fractions. The primary endpoint was erectile dysfunction (ED) category based on the Sexual Health Inventory for Men (SHIM) score closest to 2 years from RT. The penile bulb and crura were contoured and mean radiation dose calculated for each structure.

Results—The mean pretreatment SHIM score was 19.8, and the mean posttreatment SHIM score was 15.1. The ED category was decreased by 2 in 50% of patients with a mean penile bulb of >20 Gy compared with that in 9% of patients with a mean penile bulb dose of ≤20 Gy ($P = .003$). Mean dose to the crura was highly correlated with mean dose to the penile bulb (Pearson correlation = 0.842; $P < .001$) but did not reach statistical significance as a predictor of ED after radiation.

Conclusion—Radiation dose to the penile bulb is predictive of posttreatment ED in patients treated with dose-escalated hypofractionated prostate RT. The cutpoint at which this effect was observed with this treatment is substantially lower than the previous reports.

Multiple treatment modalities are effective in controlling low-risk prostate cancer; therefore, side-effect profile and patient preferences drive decisions of whether to pursue a surgical or radiation therapy (RT) approach.¹ Despite different toxicity profiles in general, both modalities are associated with a risk of decreased sexual function after treatment. Radiation-induced erectile dysfunction (ED) in particular remains poorly understood, although alterations of the hemodynamics within erectile tissues have been demonstrated after RT.²

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Several authors have identified dose to the penile bulb as a possible predictor of posttreatment ED,³ despite recognition that the penile bulb may not be the critical component of erectile function in this setting.⁴ Radiation doses to other structures involved in achieving and maintaining an erection have also been investigated, including the crura of the corpora cavernosum, neuro-vascular bundle, and internal pudendal arteries.⁵ However, these early studies have been inconclusive, and sparing any of these structures is currently not recommended.

Recently, hypofractionated radiotherapy to the prostate has been suggested as a means of improving cancer control based on low estimates of the alpha-beta ratio (α/β) of prostate cancer.^{6,7} Early results have shown acceptable rates of genitourinary and lower gastrointestinal toxicities,⁸ but outcomes related to sexual function are lacking. Although no α/β estimates of the erectile tissues have been published, we suspect their response to changes in fractionation is likely similar to that of other normal tissues within the pelvis. With this in mind, we hypothesized that moderately hypofractionated radiotherapy would not worsen post-RT sexual function scores compared with conventional fractionation. We also sought to determine if radiation dose to the penile bulb or crura was predictive of outcome.

Materials and Methods

Inclusion Criteria

The records of all patients receiving external beam RT for clinically localized prostate cancer at the University of Alabama at Birmingham since 2004 were reviewed. All patients with at least 1 year of clinical follow-up who received hypofractionated external beam RT alone and had no worse than moderate ED (defined as SHIM ≥ 12 by Rosen et al⁹) before treatment were included in the analysis; patients who received androgen deprivation therapy (ADT) at any time were excluded. This study was approved by the University of Alabama at Birmingham Institutional Review Board.

Radiotherapy Dose and Fractionation

All patients underwent CT simulation in the supine position with a custom immobilization device and retrograde urethrogram. The prostate was contoured with the prostate apex defined beginning 9-12 mm superiorly to the peak of the urethrogram contrast. The prostate planning treatment volume was generated by a 7-mm expansion of the prostate contour, except for posteriorly, where a 4- to 5-mm margin was used.

Patients receiving hypofractionated therapy were prescribed 67.6-70.2 Gy to the prostate over 26-28 fractions with or without simultaneous 56 Gy to the seminal vesicles. Dose prescriptions were delivered simultaneously by IMRT, Tomotherapy, or volumetric modulated arc therapy (VMAT). Daily image guidance was by cone beam or megavoltage CT with alignment to the prostatic interface; fiducial markers were not used for alignment. No penile structures were included in the objective function for inverse planning. A description of radiation dose fractionation schedules and delivery technique is presented as part of Table 1.

Dose-volume Histogram Generation for the Penile Bulb and Crura

For each patient, the penile bulb and crura of the corpus cavernosum were contoured on the simulation CT using the Varian Eclipse software (Varian Medical Systems Inc., Palo Alto, CA). The penile bulb was contoured as described by Wallner et al¹⁰ and the crura as described by Mulhall et al²; contours from an example patient is presented as Figure 1. The mean dose delivered to each structure was then calculated from the original plan for each patient using the Varian Eclipse software.

Follow-up and Endpoint Definitions

Patients were scheduled for follow-up visits every 4 months for the first year, every 6 months for an additional 4 years, and annually thereafter. At the initial consultation and each subsequent clinic visit, patients were asked to complete the Sexual Health Inventory for Men (SHIM) questionnaire,⁹ and if the patient indicated that he had attempted sexual intercourse then the sum of each ordinal response was recorded. If the patient indicated that he had not attempted sexual intercourse then this encounter was excluded from the analysis because the SHIM questionnaire is not validated to assess erectile function in patients who are not sexually active.¹¹ All recorded SHIM score values were taken directly from the questionnaire completed by the patient, not physician documentation.

Statistical Methods

The primary endpoint of the analysis was the ED severity grouping as defined by Rosen et al⁹, based on the SHIM score closest to 2 years from the completion of RT (SHIM_{Post}). The median time to the defining SHIM score was 24.0 months (interquartile range, 5.55 months). Dosimetric cutpoints were generated by maximizing the discriminatory ability of the receiver operating characteristic (ROC) curves for each structure of interest. Frequency of outcomes between groups were compared by the Pearson chi-square test, and the univariate binomial logistic regression was used to measure the effect of variables on the likelihood of a decrease in erectile function by 2 categories from the pretreatment value. All statistical analyses were performed using IBM SPSS Statistics, version 22 software (IBM Corporation, Armonk, NY).

Results

Patient Population Characteristics

We identified 433 patients who had been treated with hypofractionated prostate radiotherapy with charts available for review. Of these patients, 326 received ADT at some time point, 46 had <1 year of SHIM score follow-up or indicated that they were not sexually active, 8 had radiotherapy plans, which were not available for review, and 12 had moderate-to-severe or severe ED before treatment. With these patients excluded, a total of 41 patients met the criteria to be included in this analysis. The pretreatment and treatment characteristics are listed in Table 1.

Sexual Health Outcomes

The median SHIM_{Pre} was 20, with 25 patients (61%) initially having some component of ED (ie, SHIM_{Pre} $\geq$ 21). The median SHIM_{Post} was 17, with 33 (81%) patients having some component of ED after RT. The prevalence of PDE-5 inhibitor use was 20% before RT and 44% afterward. Four patients (10%) also received additional interventions, such as intracorporeal injections, urethral suppositories, or vacuum pumps, after RT.

Effect of Radiation Dose to the Penile Bulb and Crura

The group average of mean doses to the penile bulb and crura separated by the magnitude of decrease in erectile function is presented as Table 2. The mean dose to both structures was increased in a statistically significant manner for patients whose ED decreased by ≥ 2 categories (Fig. 2). Based on this result, we hypothesized that there may be a threshold dose above which the likelihood of this endpoint is increased, and performed ROC analysis assessing this outcome against radiation dose to the penile bulb and crura. ROC analysis of penile bulb dose yielded a C statistic of 0.812 with maximal discriminatory ability for penile bulb doses between 19.9 and 21.9 Gy. Within this range, 20 Gy was arbitrarily selected as a cutpoint. The ROC curve generated for the crura dose yielded a C statistic of 0.773, and the discriminatory ability was essentially stable for doses between 9.2 and 36.7 Gy; 20 and 30 Gy were therefore arbitrarily chosen as cutpoints for this structure.

The ED category was decreased by ≥ 2 in 50% (9 of 18) of patients with a mean penile bulb of ≥ 20 Gy compared with that in 9% (2 of 23) of patients with a mean penile bulb dose of < 20 Gy ($P = .003$). Mean dose to the crura was highly correlated with mean dose to the penile bulb (Pearson correlation = 0.842; $P < .001$) but did not reach statistical significance as a predictor of ED after radiation using cutpoints of 20 Gy (46% vs 18%; $P = .057$) or 30 Gy (50% vs 27%; $P = .099$).

Age at RT ($P = .591$) was not a statistically significant predictor of a ≥ 2 category drop in ED category by the univariate binomial logistic regression. Having a mean penile bulb dose of ≥ 20 Gy yielded a hazard ratio of 10.5 ($P = .007$).

Comment

Conventionally fractionated external beam RT requires daily treatments for ~ 8 weeks. Given that this length of treatment can be logistically challenging, hypofractionation has been suggested as a way to shorten the overall treatment time to < 6 weeks. One large phase III trial has compared a moderately hypofractionated regimen with a conventionally fractionated regimen and found similar rates of biochemical control between the 2 arms.⁸ Data regarding the effect of hypofractionation on posttreatment sexual function are lacking because the prospective and large retrospective studies to date have focused primarily on gastrointestinal and urinary toxicities.^{8,12-14}

We observed a decrease of 3 points in the median SHIM score after hypofractionated RT, and the rate of PDE-5 inhibitor use more than doubled to 44%. Although comparison between studies is somewhat difficult due to significant variations in defining posttreatment potency, our outcomes with hypofractionated RT appear similar to other reports of

conventionally fractionated treatment. Two studies of patients included in dose-escalation trials that considered only patients who were fully potent before RT reported potency preservation rates of 60%-64%.^{15,16} In comparison, 50% of patients with an initial SHIM score >22 and 66% of patients with initial SHIM score >17 retained the same level of erectile function after RT in our study. Finally, the Prostate Cancer Outcomes Study reported erectile difficulties in 61% of patients treated with external beam RT.¹⁷

Roach et al¹⁵ found mean penile bulb dose of ≥ 52.5 Gy to be predictive of postradiation erectile function in the analysis of patients treated on the Radiation Therapy Oncology Group 94-06 protocol, and 50 Gy is the mean penile bulb dose limit suggested by the QUANTEC review.⁴ Assuming $\alpha/\beta = 3$, the recommended limit of 50 Gy in 40 fractions converts 44.9-45.8 Gy in 26-28 fractions. In our analysis, because of the use of modern treatment planning and delivery allowing relatively small PTV expansions, only 2 patients exceeded these converted limits. Despite this apparently favorable dosimetry, the rate of ED in this analysis is similar to historic controls. When radiation dose to the penile bulb and crura was analyzed for the effect on outcome in our study, mean dose to the penile bulb >20 Gy increased the frequency of a significant decrease in erectile function after radiation. For comparison purposes, our dose threshold of 20 Gy in 27 fractions would convert to 21.2 Gy in 40 fractions assuming $\alpha/\beta = 3$.

Our finding of a penile bulb dose threshold for post-radiation ED at 20 Gy is substantially lower than the previously reported values, and simply correcting this value for the number of fractions using the linear-quadratic model cannot explain this lower threshold. The use of hypofractionation preferentially increases the BED in high-dose areas, including the neurovascular bundle of the prostate, which is contained within the PTV. Because both structures are involved in achieving a functional erection, the increased biologic effect to the neurovascular bundle may serve to decrease the dose at which radiation effects to the penile bulb are observed. Additionally, patients in our study were treated to relatively lower penile bulb doses compared with the previous studies, making a dose response in this range more apparent. This finding also illustrates that dosimetric guidelines generated by analyzing patient populations treated with conventional fractionation and comparatively higher doses to the penile bulb may not accurately predict outcomes for patients receiving hypofractionated RT, even when attempting to correct these values using the linear-quadratic model.

Dose to the crura approached but did not reach statistical significance for predicting the rates of ED after RT. This trend is likely simply reflective of the high degree of correlation with the mean penile bulb dose; however, we cannot rule out the independent effects of the radiation to the crura because of this close association.

The primary limitations of this study are the retrospective nature of the analysis and limited sample size. However, all outcomes data used for the analysis were prospectively gathered from the original patient-completed form, helping to minimize any bias from physician interpretation. Furthermore, the SHIM questionnaire is well validated as are the ED groupings.⁹ As suggested by Roach et al,⁴ we investigated multiple potentially critical structures but our dosimetric investigation was limited to the penile bulb and crura of the

corpus cavernosum because other structures, such as the neurovascular bundle or internal pudendal arteries, are only visualized with MRI.⁵ Finally, patient reported outcomes of this type can introduce bias because patients with better sexual function are more likely to be compliant with the questionnaire.

Despite these limitations, our experience suggests that hypofractionated RT results in comparable rates of posttreatment ED with published estimates associated with conventional fractionation, despite the relatively favorable penile bulb dosimetry in our study due to the use of modern treatment planning and delivery techniques. The hypothesis that hypofractionated prostate RT reduces the penile bulb tolerance more than can be accounted for by the linear-quadratic model should be investigated further, optimally by analyzing clinical trials of hypofractionation, which contain a conventionally fractionated treatment arm treated by a similar technique. Our experience also adds to a growing body of literature suggesting that mean dose to the penile bulb is predictive of posttreatment ED.

Though PTV coverage should not be compromised, including the penile bulb in the objective function for inverse planning should be considered, with the goal of limiting penile bulb mean dose to <20 Gy for moderately hypofractionated regimens. This goal is likely reasonable given that half of the patients included in this study met this objective despite this structure not being taken into account for planning purposes. The penile bulb should continue to be studied in terms of further elucidating its role in erectile function, or describing how it may be a surrogate for another vital structure. Future prospective studies should continue to focus on improving quality of life outcomes for all patients receiving treatment for prostate cancer.

Conclusion

Moderately hypofractionated RT appears to result in equivalent sexual outcomes compared with historic studies of conventional fractionation despite relatively favorable penile bulb dosimetry. Dosimetry of the penile bulb is correlated with posttreatment ED with mean penile bulb dose >20 Gy predicting worse posttreatment ED in this fractionation scheme. Limiting the penile bulb mean dose to 20 Gy over 26-28 fractions appears to be a reasonable treatment planning goal so long as PTV coverage is not reduced.

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Figure 1.
Delineation of the penile bulb and crura of the corpora cavernosa. (Color version available online.)

Figure 2.

(A) Scatter plot of decrease in erectile function grouping vs mean radiation dose for the penile bulb. (B) Scatter plot of decrease in erectile function grouping vs mean radiation dose for the crura. ED, erectile dysfunction.

Table 1
Pretreatment and treatment characteristics

	Mean ($\pm$ SD)	Frequency (%)
Pretreatment		
Age at RT (y)	68.1 ($\pm$ 6.7)	
SHIM	19.8 ($\pm$ 4.1)	
PDE-5 inhibitor use		
Yes		8 (20)
No		33 (80)
Severity of erectile dysfunction *		
None		16 (39)
Mild		16 (39)
Mild-to-moderate		9 (22)
Posttreatment		
SHIM	15.1 ($\pm$ 6.8)	
PDE-5 inhibitor use		
Yes		18 (44)
No		23 (56)
Severity of erectile dysfunction *		
None		8 (20)
Mild		13 (32)
Mild-to-moderate		7 (17)
Moderate		4 (10)
Severe		9 (22)
Technical		
Volume of crura (cc)	12.8 ($\pm$ 3.8)	
Volume of penile bulb (cc)	6.8 ($\pm$ 2.1)	
Mean dose to penile bulb (Gy)	20.0 ($\pm$ 14.8)	
Mean dose to crura (Gy)	16.2 ($\pm$ 13.8)	
Prostate dose/fractions		
67.6 Gy/26 fractions		3 (7)
70 Gy/28 fractions		31 (76)
70.2 Gy/27 fractions		7 (17)
Type of plan		
IMRT		12 (29)
VMAT		17 (29)
Tomotherapy		12 (42)

IMRT, intensity-modulated radiation therapy; PDE-5, phosphodi-esterase-5; RT, radiation therapy; SD, standard deviation; SHIM, Sexual Health Inventory for Men; VMAT, volumetric modulated arc therapy.

* SHIM score ranges for erectile dysfunction categories are: none (22-25), mild (17-21), mild-to-moderate (12-16), moderate (8-11), and severe (5-7).

Table 2
The group average of mean doses to the penile bulb and crura separated by the magnitude of decrease in erectile function

	Penile Bulb Mean Dose	Crura Mean Dose
No change in erectile function (n = 18), Gy	17.7 [*]	13.8 [†]
1 Category decrease (n = 12), Gy	12.9 [*]	10.7 [†]
2 Category decrease (n = 11), Gy	31.7	26.1
<i>P</i> value [‡]	.006	.027

^{*} Pairwise comparison, *P* = .249.

[†] Pairwise comparison, *P* = .692.

[‡] Independent samples Kruskal-Wallis test.