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Teaching Case

Longitudinal Changes in U.S. Parameters of Neurovascular Bundles Suggest Mechanism for Radiation-Induced Erectile Dysfunction

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Introduction

Up to 50% of patients with prostate cancer report erectile dysfunction (ED) after treatment.[1] The mechanism of radiation-induced erectile dysfunction remains unknown.[2] Previously damage to the penile bulb was thought to be causal,[3] but may be a surrogate given lack of clear dose-volume constraints.[4] Recent investigations focus on the neurovascular bundles (NVB).[5] NVB-sparing radiation therapy has been demonstrated to be feasible in terms of contour reproducibility[6] and radiation therapy planning,[7] including in the presence of SpaceOAR[8] or with boost to dominant intraprostatic lesion.[9] However, functional assessments of NVB before and after radiation have not been reported. We document a case series of longitudinal quantitative transrectal ultrasound (TRUS) and Doppler assessment of NVB function to evaluate the effect of radiation therapy on patient-reported ED.

Methods and Materials

Through an institutional review board–approved protocol (IRB22692), patients consented to prospective longitudinal data collection. Inclusion requirements included intermediate risk prostate adenocarcinoma, no pretreatment severe ED (composite score of ≥17 on the erectile function component of the International Index of Erectile Function [IIEF]),[10] and a clinical indication for initial TRUS. Patients were treated with definitive radiation alone without androgen deprivation. Radiotherapy was designed without specific NVB avoidance during external beam or brachytherapy procedures as the primary investigation was longitudinal study of physiological changes after standard radiation therapy. Based on prior work,[7] we anticipate that the bilateral NVB received therapeutic dose levels for all 4 patients.

TRUS was performed in lithotomy position with empty bladder. HI VISION Avius ultrasound machine (Hitachi Medical Group, Japan) with a 7.5 MHz prostate biplane probe (EUP-U533C) was used in a mechanical stepper (Bard Medical, Inc, Covington, GA) and 3-dimensional B-mode images with 1-mm step size were acquired to cover the entire prostate. Under the

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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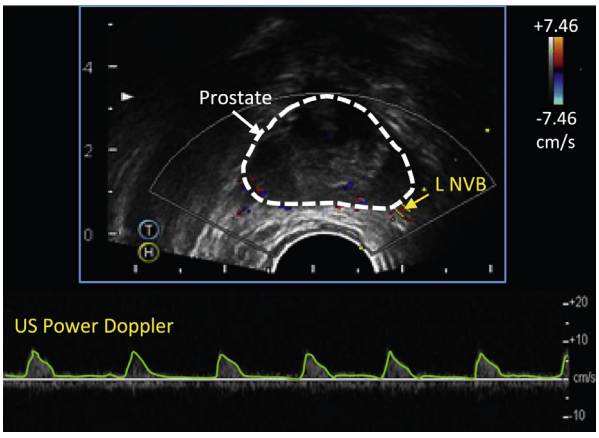

Figure 1 Transrectal ultrasound Doppler parameter measurement of the left neurovascular bundle (LNVB).

color Doppler mode, the locations of bilateral NVB were determined by the radiation oncologist and power Doppler signals were acquired for left and right NVBs. In Fig 1, the upper image shows the color Doppler US image of the prostate midplane and identification of the left NVB; and the lower part is the Power Doppler waveform of the left NVB. Doppler scans from the first visit were used as a reference for subsequent visit(s).

TRUS images were evaluated by a radiation oncologist offline to verify anatomically correct locations for NVB. All patients had pretreatment magnetic resonance imaging (MRI) scans. MRI and TRUS images were fused to further verify the 3-dimensional NVB locations. We extracted pulse waves using ImageJ and quantified morphologic features using an in-house software in Matlab. Six Doppler spectral waveform parameters were used to characterize the NVB blood flow: peak systolic velocity (PSV), end diastolic velocity (EDV), mean velocity (V_m) resistance index, pulsatile index, and upstroke and downstroke velocity ratios (RVSD).

Patients were evaluated pretreatment and at 6-month and in 2 cases 12 months after radiation with TRUS and patient reported assessments of urinary and sexual function consistent with reporting of late toxicity starting 3 to 6 months after radiation. The American Urologic Association Symptom Index (AUA) assesses obstructive and irritative urinary symptoms with a score of 0 to 7 considered mild, 8 to 19 moderate, and 20 to 35 severe. The Expanded Prostate Cancer Index Composite (EPIC-26) was used in its abbreviated, 26-item form to assess urinary, bowel, sexual, and hormonal symptoms before, during, and after prostate cancer treatment. Higher EPIC-26 scores demarcate larger symptom burden. The 15-item IIEF assesses erectile and orgasmic function, sexual desire, and intercourse satisfaction. A subset of 6 items on the IIEF assess ED with a score of 1 to 10 considered severe dysfunction, 11 to 16 moderate dysfunction, 17 to 21 mild to moderate dysfunction, 22 to 25 mild dysfunction, and 26 to 30 no dysfunction.

Cases

Worsening erectile function after radiation therapy

Patient 1 was a 64-year-old man with favorable intermediate risk prostate cancer (cT1c, GS 3 + 4, prostate-specific antigen [PSA] 5.63). He had a history of chronic low back pain after a lumbar surgery, hypertension, hyperlipidemia, and gastroesophageal reflux. He was a never smoker with baseline Karnofsky Performance Status (KPS) 90 and body mass index (BMI) 28. His pretreatment AUA was 18, EPIC-26 was 17, and IIEF was 24 (mild dysfunction) for which he intermittently used Cialis. He was treated with external beam radiation therapy to 70 Gy in 28 fractions. At 6-month follow-up, his AUA was 14, EPIC-26 was 22, and IIEF was 15 (moderate dysfunction). At 12-month follow-up his AUA was 15, EPIC-26 was 22, and IIEF was 8 (severe dysfunction). As shown in Fig 2, the MRI-TRUS fused image shows the right/left NVB locations, and the Power Doppler shows the NVB's blood flow information pre RT and 6-month post RT. The numerical details are in Table 1. Pretreatment PSV (right 13.68 cm/s, left 19.49 cm/s) decreased bilaterally at 6-month follow-up (right 8.89 cm/s, left 8.54 cm/s). Pretreatment V_m (right 7.01 cm/s, left 16.37 cm/s) decreased bilaterally at 6-month follow-up (right 4.54 cm/s, left 2.60 cm/s).

Patient 2 was a 63-year-old man with favorable intermediate risk prostate cancer (cT1c, Gleason Score [GS] 3 + 4, PSA 8.39). He had a history of chronic kidney disease, nephrolithiasis, and monoclonal gammopathy of unknown significance. He was a never smoker with baseline KPS 90 and BMI 28. His pretreatment AUA was 3, EPIC-26 was 5, and IIEF was 23 (mild dysfunction). He was treated with brachytherapy alone to 125 Gy with Pd-103. At 6-month follow-up his AUA was 10, EPIC-26 was 22, and IIEF was 10 (severe dysfunction). At 12-month follow-up his AUA was 1, EPIC-26 was 9, and IIEF was 2 (severe dysfunction). TRUS features and numerical details are in Table 1. Pretreatment PSV (right 8.18 cm/s, left 8.28 cm/s) decreased bilaterally at 6-month follow-up (right 6.14 cm/s, left 7.73 cm/s). Pretreatment V_m (right 3.17 cm/s, left 4.62 cm/s) decreased bilaterally at 6-month follow-up (right 1.81 cm/s, left 4.29 cm/s).

Stable erectile function after radiation therapy

Patient 3 was a 53-year-old man with favorable intermediate risk prostate cancer (cT1c, GS 3 + 4, PSA 4.51). He had hyperlipidemia and gastroesophageal reflux. He was a never smoker with baseline KPS 90 and BMI 29. His pretreatment AUA was 2, EPIC-26 was 4, and IIEF

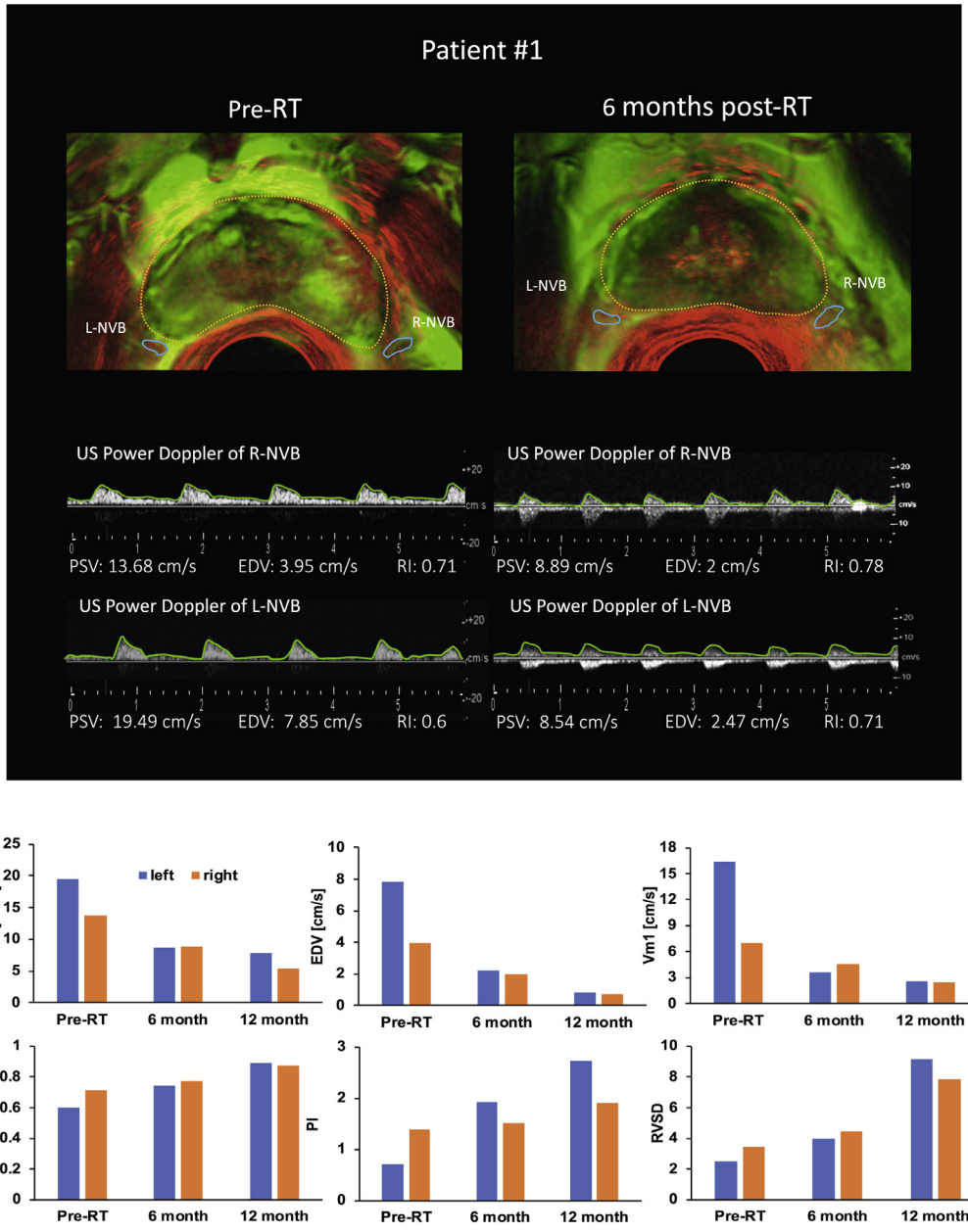

Figure 2 Patient 1 fused magnetic resonance imaging transrectal ultrasound Doppler (MRI-TRUS) images of pretreatment prostate and bilateral neurovascular bundle (NVB). Postexternal beam radiation therapy TRUS images at 6 months fused with pretreatment MRI of prostate and bilateral NVB. US Doppler tracings of bilateral NVB at each time point shown below images with charts of derived metrics from flow tracings at pretreatment, 6 months posttreatment, and 12 months posttreatment. Patient 1 developed erectile dysfunction (ED) after radiation therapy. *Abbreviations*: EDV = end diastolic velocity; PSV = peak systolic velocity; RI = resistance index; RT = radiation therapy.

was 30 (no dysfunction). He was treated with external beam radiation to 45 Gy in 25 fractions followed by brachytherapy boost of 15 Gy in one implant. At 6-month follow-up his AUA was 5, EPIC-26 was 6, and IIEF was 29 (no dysfunction). As shown in Fig 3, the MRI-TRUS fused image shows the right/left NVB locations, and the Power Doppler shows the NVB's blood flow information pre RT and 6-month post RT. The numerical details are in Table 1. Pretreatment PSV (right 10.44 cm/s, left 5.62 cm/s) decreased unilaterally at 6-month follow-up (right 10.33 cm/s, left 11.65 cm/s). Pretreatment V_m (right 4.42 cm/s, left 2.94 cm/s) did not decrease in either NVB at 6-month follow-up (right 6.30 cm/s, left 5.24 cm/s).

Patient 4 was a 64-year-old man with borderline unfavorable intermediate risk prostate cancer (cT1c, GS 3 + 4, PSA 10.29). He had hypertension and hyperlipidemia. He

Table 1 Numerous morphologic features of pulse waveforms

			PSV (cm/s)	EDV (cm/s)	Vm (cm/s)	RI	PI	RVSD
Patient 1	Pre RT	Right	13.68	3.95	7.01	0.71	1.39	3.47
		Left	19.49	7.85	16.37	0.60	0.71	2.48
	6 mo	Right	8.89	2.00	4.54	0.78	1.52	4.44
		Left	8.54	2.47	2.60	0.71	2.34	3.45
	12 mo	Right	5.39	0.68	2.47	0.87	1.90	7.86
		left	7.77	0.85	2.54	0.89	2.73	9.17
Patient 2	Pre RT	Right	8.18	0.91	3.17	0.89	2.29	9.00
		Left	8.28	2.53	4.62	0.69	1.24	3.27
	6 mo	Right	6.14	0.91	1.81	0.85	2.88	6.75
		Left	7.73	2.73	4.29	0.65	1.17	2.83
Patient 3	Pre RT	Right	10.44	2.00	4.42	0.86	2.81	7.22
		Left	5.62	0.90	2.94	0.84	1.61	6.25
	6 mo	Right	10.33	3.74	6.30	0.64	1.05	2.76
		Left	11.65	2.86	5.24	0.75	1.68	4.08
Patient 4	Pre RT	Right	12.34	2.40	5.47	0.69	1.35	5.49
		Left	12.22	2.30	7.02	0.64	0.79	4.39
	6 mo	Right	11.84	1.58	3.88	0.87	2.65	7.50
		Left	13.42	3.55	11.10	0.74	0.89	3.78

Abbreviations: EDV = end diastolic velocity; PI = pulsatile index; PSV = peak systolic velocity; RI = resistive index; RT = radiation therapy; V_m = mean velocity; RVSD = upstroke and downstroke velocity ratio.
RVSD is of both left and right neurovascular bundles between pre and post treatments. RI, PI, and RVSD are dimensionless quantities.

was a never smoker with baseline KPS 90 with BMI 34. His pretreatment AUA was 9, EPIC-26 was 7, and IIEF was 23 (mild dysfunction). He was treated with external beam radiation alone to 70 Gy in 28 fractions. At 6-month follow-up his AUA was 11, EPIC-26 was 6, and IIEF was 24 (mild dysfunction). TRUS features and numerical details are in Table 1. Pretreatment PSV (right 12.34 cm/s, left 12.22 cm/s) decreased unilaterally at 6-month follow-up (right 11.84 cm/s, left 13.42 cm/s). Pretreatment V_m (right 5.47 cm/s, left 7.02 cm/s) decreased unilaterally at 6-month follow-up (right 3.88 cm/s, left 11.10 cm/s).

Discussion

This is the first reported longitudinal TRUS evaluation of bilateral NVB correlated with IIEF pre- and postradiation therapy. Two of 4 patients developed ED after radiation therapy with marked changes in bilateral NVB blood flow. Two patients had preserved erectile function after radiation therapy with minimal changes in at least one NVB on posttreatment evaluation. Although the sample size is too small to evaluate statistically, US changes in NVB correlated with ED, suggesting a potential causal mechanism for radiation therapy-induced ED.

Based on the success of surgical techniques aimed at avoiding transection of the NVB[11,12] and initial reports on NVB-sparing radiation therapy,[13] empirical evidence points to the role of NVB in erectile function. The role of the penile bulb in radiation-induced ED is unclear. Wielen et al note penile bulb sparing radiation "is not sufficiently supported by the current literature"[14] and QUANTEC reported that the penile bulb "seems to be a surrogate for a yet to be determined structure(s)."[4] A phase 2 study assessing potency after NVB-sparing radiation therapy constrained internal pudendal artery to D90 <13 Gy and D10 <37 Gy with 88% sexually active at 5-years. Although promising, the generalizability is limited by selection bias, lack of a comparator arm, and inability to distinguish between NVB and penile bulb sparing radiation (99.3% met corpus cavernosa constraints of D90 <5 Gy and D10 <20 Gy).[13] Furthermore, the fundamental challenge of anatomy remains: some patients have bilateral NVB within typical planning target volume expansions,[15] while other patients can achieve NVB sparing even with focal boost to dominant intraprostatic lesions.[9] This case series suggests that unilateral NVB-sparing radiation therapy may be sufficient to avoid ED, which may be feasible even for patients with NVB closer to the high-dose target volumes. We look forward to the

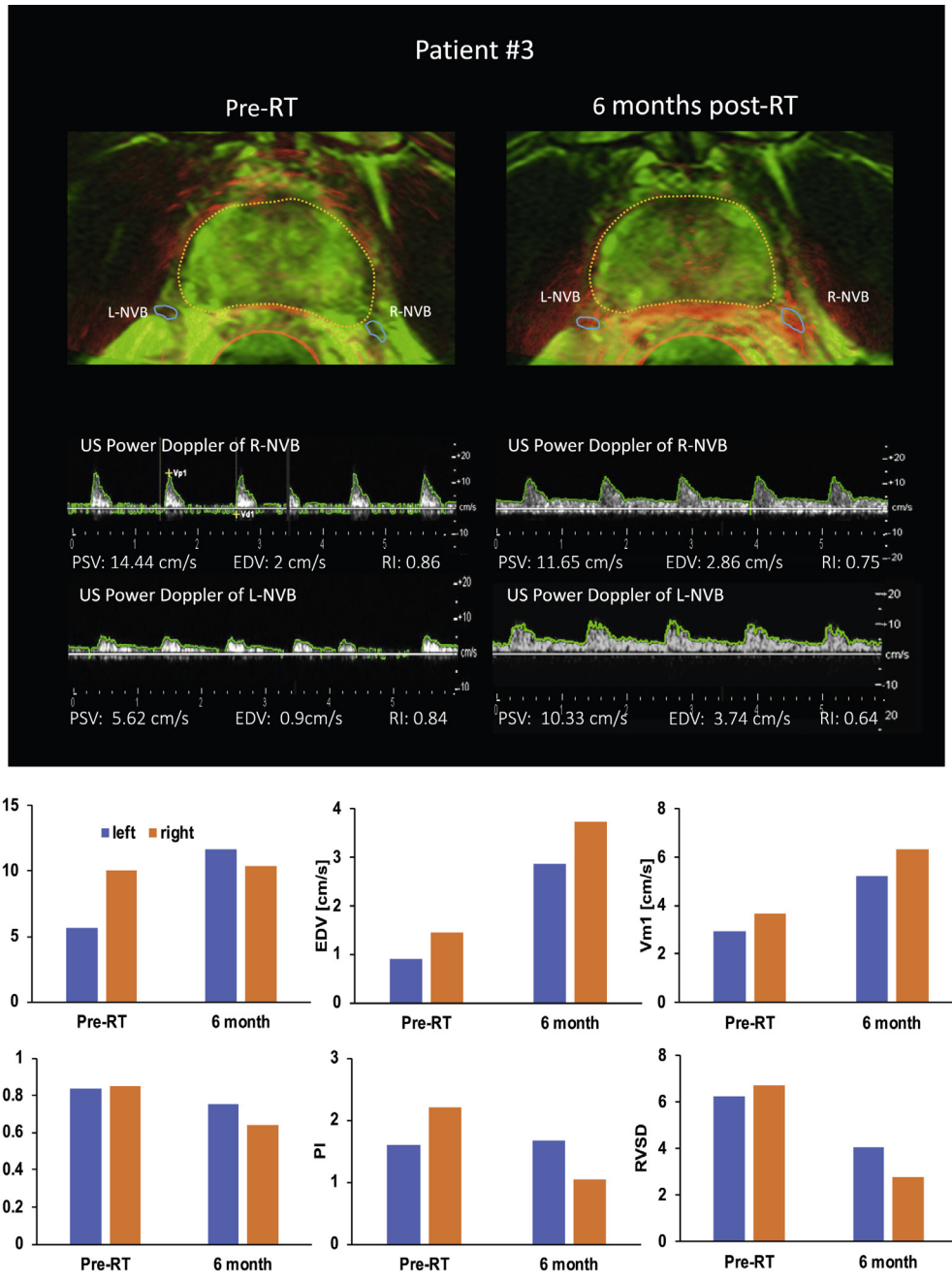

Figure 3 Patient 3 fused magnetic resonance imaging transrectal ultrasound Doppler (MRI-TRUS) images of pretreatment prostate and bilateral neurovascular bundle (NVB). Postexternal beam radiation therapy and brachytherapy TRUS images at 6 months fused with pretreatment MRI of prostate and bilateral NVB. US Doppler tracings of bilateral NVB at each time point shown below images with charts of derived metrics from flow tracings at pretreatment and 6 months post-treatment. Patient 3 had preserved erectile function at all follow-ups. *Abbreviations*: EDV = end diastolic velocity; PSV = peak systolic velocity; RI = resistance index; RT = radiation therapy.

results from the POTEN-C trial, examining potency after prostate stereotactic body radiotherapy with or without unilateral NVB sparing.[16]

This case series has multiple limitations. The numbers are too small for statistical comparisons. US assessment of NVB can be inconsistent with prior work highlighting substantial variability from patient position, recent ejaculation, and medications.[17] In fact, patient 3 showed increase in PSV and EDV at follow-up, likely not a result of radiation improving blood flow. Multiple steps were used to mitigate these limitations, including use of lithotomy position with stirrup support, mechanical stepper for US navigation, coregistration with MRI, and offline review of NVB locations. Additionally, IIEF is subject to

user error and variability; however, IIEF is a validated instrument. The heterogenous patients, comorbidities, and treatment techniques limit generalizability particularly as dose distributions with monotherapy external beam radiation are substantially different from combined therapy or brachytherapy alone. Additionally, initial placement of brachytherapy needles could have damaged NVB even if final positioning of needles did not show any violation of NVB. Furthermore, recruiting patients to longitudinal TRUS assessment is challenging.

Conclusions

The hypothesis that changes in the NVB correlate with ED is both intuitive and preliminary. We present a series of 4 patients where bilateral but not unilateral decrease in NVB blood flow on TRUS is associated with ED. This could increase eligibility for NVB-sparing radiation therapy akin to modern surgical techniques. The results warrant further validation.

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