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Teaching Case

Successful Stereotactic Body Radiation Therapy for Postbrachytherapy Prostate Recurrence and Penile Bulb Metastasis

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Introduction

Brachytherapy is a highly effective therapy for low-risk localized prostate cancer, with excellent biochemical control rates achieved in patients with localized disease.[1] Local recurrence after low dose rate prostate brachytherapy can be challenging to identify owing to the metal artifact caused by brachytherapy seeds that interferes with prostate magnetic resonance imaging (MRI), although this can be partially overcome with multiparametric MRI (mpMRI).[2] Recent developments in advanced imaging of prostate cancer, such as prostate-specific membrane antigen (PSMA)–based positron emission tomography (PET) imaging, has provided new insights into the patterns of recurrence after definitive treatment with external beam irradiation, prostate brachytherapy, and surgery.

The options for treatment of prostate cancer that recurs locally after prior irradiation are diverse, including reirradiation, prostatectomy, cryotherapy, observation, systemic therapy, and investigational therapies such as high-intensity focused ultrasound (HIFU) and laser ablation.[3] Durable local control can be achieved with a second local treatment, such as reirradiation or salvage prostatectomy, in approximately half of patients with localized prostate cancer.[3] Genitourinary toxicity with a second local treatment is a major concern, with a recent metanalysis of local salvage therapies after radiation demonstrating a rate of severe genitourinary toxicity of 5.6% after stereotactic body radiation therapy (SBRT), 9% with salvage brachytherapy, and 20% with prostatectomy.[3]

Penile bulb metastases of prostate cancer are an uncommon finding; however, the recent adoption of PSMA-based imaging has provided evidence that these recurrences may occur more frequently than previously realized. Penile bulb recurrences are a challenge to confirm pathologically, and treatment is not well defined. We report a case of recurrent prostate cancer in the prostate and penile bulb after prostate brachytherapy, which was treated successfully with focal SBRT guided by mpMRI, tumor mapping with comprehensive biopsies, and PSMA-based PET imaging with ^{18}F-DCFPyL, a United States Food and Drug Administration–approved PSMA-based imaging agent.

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Case Report

A 60-year-old White male presented to an outside institution in 2011 with low-risk prostate cancer, stage T1c, Gleason score 3+2=5 (3/8 cores), and prostate-specific antigen (PSA) level of 8.5 ng/mL. At the time, the patient opted for prostate brachytherapy. He received a Palladium 103 implant with a prescribed dose of 125 Gy, with a D90 of 125.68 Gy (100.54%) and a V100 of 90.26%. The penile bulb dose received from this treatment was not recorded. Following treatment, his PSA level reached a nadir of 0.67 ng/dL. His PSA level began rising soon thereafter until he met criteria for biochemical failure 4 years after treatment. He presented to our institution in 2018 with a PSA level of 6.71 ng/dL. He was without symptoms of recurrence. At presentation, his American Urological Association Symptom Score was 4 and he noted longstanding erectile dysfunction, with a baseline Sexual Health Inventory for Men score of 1. An mpMRI scan of the prostate revealed a right base transition zone lesion (3.0 cm in maximal diameter) extending to the bladder wall. Computed tomography (CT) of the chest, abdomen, and pelvis showed only known pulmonary nodules that were stable compared with those in prior studies obtained more than 6 months before. A ^{99m}Tc-MDP whole-body bone scan showed 2 small indeterminate foci in the proximal femurs that were unchanged from prior studies. An mpMRI scan of the prostate revealed a 3.0-cm lesion in the right base transition zone, and ^{18}F-DCFPyL PET/CT showed an intense area of uptake in the right base transition zone (concordant to MRI, with maximum standardized uptake value [SUVmax] 64.9) and a soft-tissue lesion in the right side of the penile bulb (SUVmax 19.7). In retrospect, this area was visible on mpMRI and CT scans and measured 1.0 cm. Imaging findings are summarized in Figures 1 and 2. Magnetic resonance fusion–guided transrectal prostate biopsy demonstrated treatment effect in 12 systematic cores and poorly differentiated prostatic adenocarcinoma with treatment effect in targeted biopsies from the right base transition zone adjacent to the bladder wall and in the penile bulb.

The patient was treated with androgen deprivation therapy (ADT), Casodex 50 mg daily and Leuprolide for a duration of 6 months, with a resulting undetectable PSA level, reduction in the size of the prostate recurrence from 3 to 2.6 cm, and reduction of the penile bulb lesion from 1.0 cm to 0.8 cm. After placement of SpaceOAR hydrogel, the patient was treated with focal SBRT to the prostate tumor defined on MRI and ^{18}F-DCFPyL (40 Gy in 5 fractions), with a lower dose delivered to the penile bulb metastasis (30 Gy in 5 fractions). Representative images from the treatment plan are included in Figure 3A and 3B. The dose selection to the prostate tumor and prostate was based on a clinical trial (NCT03253744) treating similar patients but for which the patient was excluded owing to the presence of the penile bulb metastasis. Image guidance before and during the treatment included both cone beam CT images and kV images. The patient's brachytherapy seeds were used as fiducials given the proximity to both lesions (Figures 2B and 3B). Groups of brachytherapy seeds were contoured with selection of seeds included in each group based on projection at beam angles that were anticipated to be used for intrafraction kV image monitoring. During image review at the time of each treatment, the physician could rapidly toggle seed group structure sets on and off as needed to verify appropriate positioning and lack of rotational, nonplanar motion (ie, pitch, roll).

The patient tolerated treatment with complaints of urinary frequency, which was treated with Tamsulosin 0.4 mg daily. Treatment concluded in June 2019, and no additional ADT was delivered. By 3 months after completion of SBRT, the patient's testosterone had recovered to above castrate levels. Despite testosterone recovery to within the normal range, the PSA level remained undetectable at 2 years after completion of SBRT. Except for a 2-week episode of dysuria with an unremarkable urinalysis at 9 months after SBRT that was effectively managed with ibuprofen, the patient remained without side effects of SBRT. Flomax was discontinued at the patient's request 18 months after completion of treatment, with no exacerbation of urinary symptoms. His American Urological Association Symptom Score at 2 years after completion of treatment was 7 and his Sexual Health Inventory for Men score remained 1.

Discussion

Penile and penile bulb metastases from prostate cancer are historically considered rare[4,5]; however, they are increasingly reported in the era of PSMA-based PET imaging.[6-11] Many of the reported cases included patients treated surgically who later experienced recurrence in the perineum or in patients treated only with ADT who later developed metastatic disease including a perineal site.[7] The patient described here was previously treated with prostate brachytherapy, raising the concern that the penile bulb disease was a result of tumor seeding along a biopsy tract or the brachytherapy needle track. Perineal seeding along the track of a needle biopsy was reported to occur in 0.17% to 1% of prostate biopsy cases, most often occurring in patients with locally advanced tumors, unlike this patient.[12-14] In 1 series with clinical outcomes, all patients with penile recurrence had metastatic disease discovered simultaneously or within 16 months, and death owing to prostate cancer occurred uniformly.[14] Thus, perineal recurrence is considered to have a poor prognosis. Perineal recurrence after prior prostate brachytherapy is a rare event, with only 4 prior reports available.[15-18]

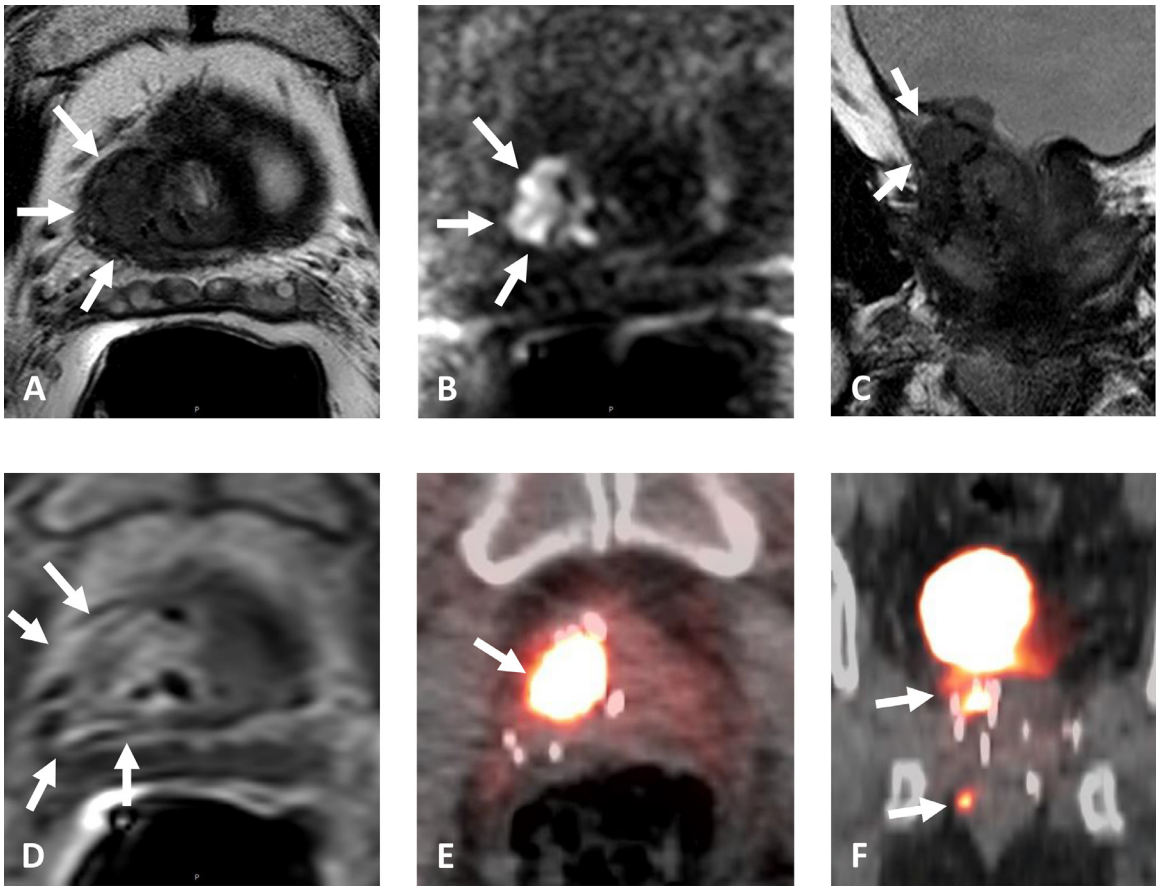

Fig. 1 Suspicious lesion within the prostate. (A) Axial T2-weighted (T2W) magnetic resonance image (MRI). (B) b2000 diffusion-weighted (DW) MRI. (C) Coronal T2W MRI. (D) Dynamic contrast enhanced (DCE) MRI image shows a right midbase transition zone lesion suspicious for recurrent prostate cancer. The lesion shows focal intense ^{18}F-DCFPyL uptake on axial (E) and coronal (F) fused positron emission tomography/computed tomography images (arrows).

Historical approaches to management of penile bulb/perineal metastases have included radiation therapy, surgical resection, or ADT depending on the size and location of the recurrence, prior treatment received, and extent of other sites of disease. A single prior case report previously noted effective treatment of an isolated penile bulb recurrence after brachytherapy with an SBRT regimen of 35 Gy delivered in 5 fractions, with no evidence of recurrence at 1 year after treatment.[18] The patient reported herein was found to have a recurrence in the prostate adjacent to the bladder in addition to noncontiguous disease in the penile bulb. He was treated with a dose of 40 Gy in 5 fractions to the prostate recurrence and a dose of 30 Gy in 5 fractions to the penile bulb metastasis. The rationale for including a lower dose to the penile bulb than in the previously reported case study was the size of the recurrence and the proximity of the lesion to the penile urethra and several brachytherapy seeds, with resultant concern for a higher cumulative dose and long-term toxic effects.

Urethral stricture occurs in approximately 2% of patients with prostate cancer treated with radiation therapy at short follow-up, with rates increasing to 4.9% in patients treated with external beam radiotherapy and brachytherapy.[19] An understanding of the rate of urethral stricture after SBRT is less developed, although rates of severe genitourinary toxicity with SBRT reirradiation are lower than those observed with salvage brachytherapy, with an incidence of 4.2% in a recent metanalysis.[3] Although several studies have described radiation tolerance of the bulbomembranous urethra to primary brachytherapy,[20,21] the optimal dose constraints for SBRT retreatment are not yet established.

In the present case, the tissue at greatest risk when treating the penile bulb lesion was believed to be the adjacent urethra, as the proximity of brachytherapy seeds to the penile bulb and urethra suggested at least some exposure to both. The cumulative dose to the bulbomembranous urethra that leads to an unacceptable risk of stricture in the postbrachytherapy retreatment setting is unknown, and estimation is complicated by the inconsistent inclusion of the penile bulb in post implant dosimetry reporting[22] and the challenges of combining doses in a biologically relevant fashion from 2 distinct treatment

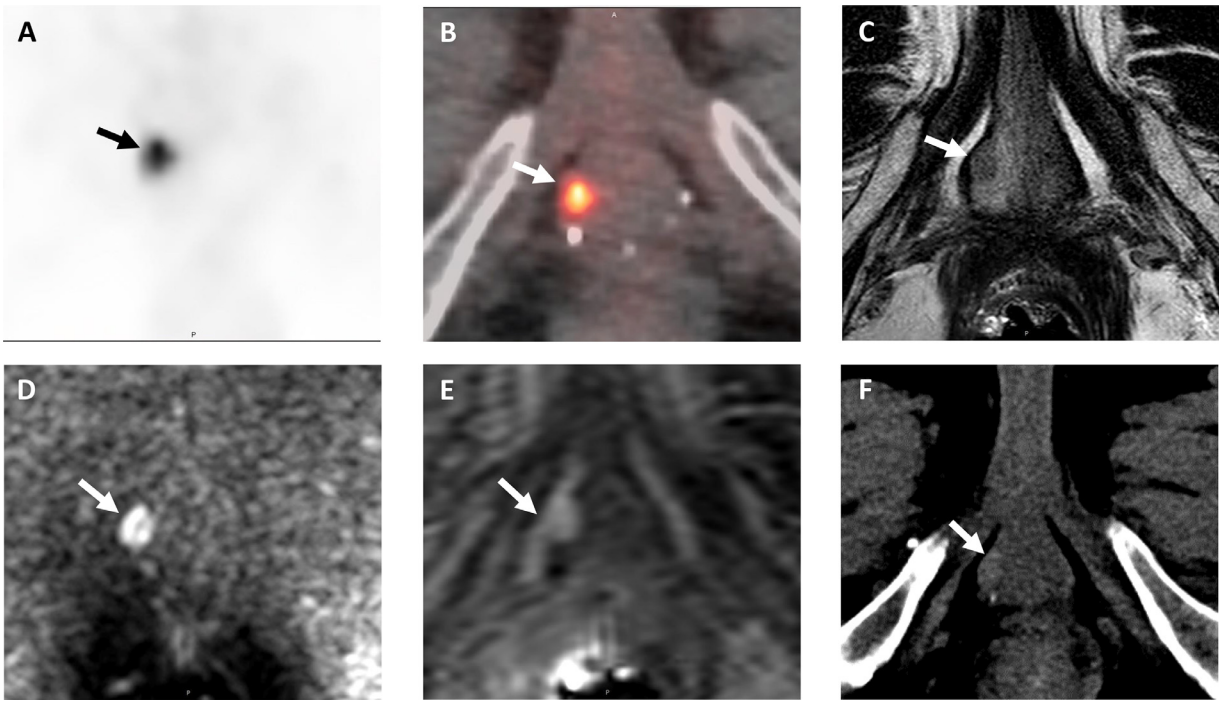

Fig. 2 Suspicious lesion within the right penile bulb. (A) ^{18}F-DCFPyL positron emission tomography (PET) and (B) fused PET/computed tomography images show focal intense uptake within the right penile bulb, which is confirmed by (C) axial T2W magnetic resonance imaging (MRI) (arrows). In (B), note the presence of brachytherapy seeds in proximity to the penile bulb lesion. The right penile bulb lesion (arrows) shows diffusion restriction at b2000 diffusion-weighted MRI (D) and focal early enhancement at dynamic contrast-enhanced MRI (E). (F) Additionally, this lesion shows distinct enhancement on computed tomography (arrow).

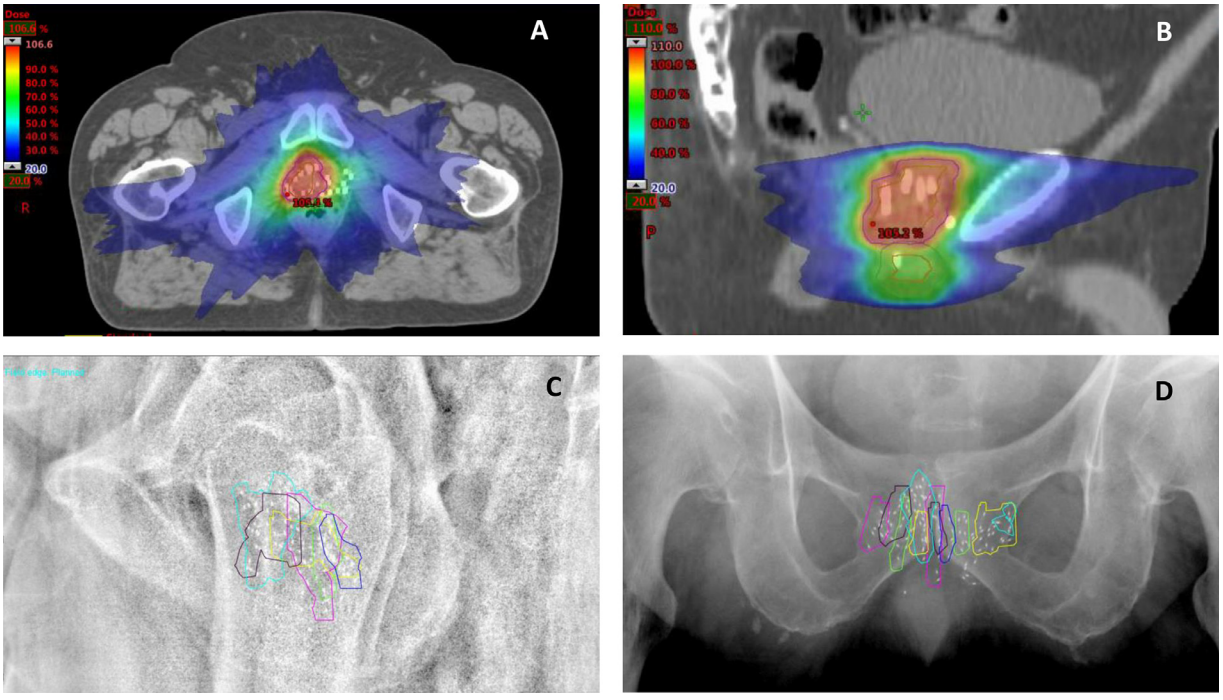

Fig. 3 Radiation treatment plan and imaging. (A) Axial and (B) sagittal images of a radiation treatment plan delivering 40 Gy in 5 fractions to the recurrent tumor within the prostate (gross tumor volume segmented orange and planning target volume segmented purple for the prostate tumor; gross tumor volume segmented orange and planning target volume segmented green for the penile bulb lesion). Dose colorwash is overlayed, showing a lower prescription dose to the penile bulb lesion. (C, D) Brachytherapy seed groups were contoured and used as fiducial markers.

modalities. A majority of published reirradiation studies include dose constraints relating only to the retreatment, irrespective of cumulative dose or the primary treatment modality.[23] Thus, a specific cumulative dose goal for the bulbomembranous urethra or penile bulb SBRT after prior brachytherapy cannot currently be recommended. Penile bulb dose constraints in SBRT retreatment trials with favorable toxicity rates have included $V_{29.5Gy} < 50\%$ and $V_{24Gy} < 50\%$, whereas urethral dose constraints are less conservative (ie, D_{median} <31 Gy), likely owing to the course of the urethra through the target volume (prostate).[23]

A large portion of the prostate received treatment owing to the size and extent of the recurrent tumor, and the dose was preferentially spilled toward the residual uninvolved gland to minimize both the bladder and rectal dose. Thus, even though treatment was focal, much of the uninvolved prostate received what may be a therapeutic dose. Target definition used biopsy findings, mpMRI image fusion, and ^{18}F-DCFPyL PET/CT image fusion. Imaging the prostate after low dose rate brachytherapy with MRI presents several challenges owing to artifact introduced by brachytherapy seeds.[24] Even with multiparametric MRI approaches, apparently uninvolved regions may later be found at biopsy to harbor tumor that was underestimated or occult on imaging.[2] The addition of PSMA-based PET imaging in this case and the use of comprehensive systematic biopsies in addition to MRI-fusion–guided targeted biopsies provided additional confidence that allowed focal dosing of recurrent tumor.

Focal retreatment of recurrent prostate tumors is an area of active study. This approach requires the capacity to accurately localize recurrent tumor to maximize efficacy while allowing exclusion of uninvolved tissue. The low energy of brachytherapy sources combined with internal delivery may provide the greatest capacity to conformally irradiate the target owing to rapid dose fall-off. In contrast, SBRT focal reirradiation may offer an opportunity to reduce heterogeneity in the target but will expose larger volumes of surrounding normal tissues to moderate doses. Additional study is needed to clarify which reirradiation strategy provides superior outcomes in terms of disease control and toxicity and whether the optimal strategy depends on the type of initial treatment received or the location of recurrence.

The brachytherapy seeds from the initial definitive treatment were used as fiducial markers for the SBRT treatment. In this patient, several brachytherapy seeds surrounded both tumor sites or were incorporated within the tumor volume, facilitating image fusion and setup verification. Indeed, numerous brachytherapy seeds were located adjacent to the penile bulb lesion, further supporting the likelihood of seeding during biopsy or the brachytherapy procedure as the mechanism of tumor deposit.

One important component of the management of this patient was the use of ADT to reduce the size of both the prostate lesion and the penile bulb lesion. When the patient first presented for evaluation, the mass appeared to be invading the bladder wall. The capacity to spare critical structures such as the bladder neck, rectum, and urethra was enhanced with the downsizing afforded by the neoadjuvant ADT delivered. Although additional bladder was not targeted, the areas of bladder wall invasion and/or encroachment were maintained with the target volume intentionally. The use of hydrogel spacer material also likely reduced high dose exposure to the rectum, a potential benefit in a retreatment setting. The lack of ongoing toxic effects with no evidence of recurrence or persistence in this patient at 2 years of follow-up is encouraging and may advocate for investigation of aggressive local management in select patients with a similar pattern of recurrence.

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