RESEARCH ARTICLE

Re-treatment of Prostate Cancer with Radiation Therapy: A Case Report

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Abstract

As treatment for prostate cancer matures with many options for local, regional and systemic care, patients are living longer. Coupled with aggressive therapy for oligometastatic disease and improvements in multiple treatment pathways including radiopharmacy, both disease-free and overall survival are improving for many patients. Success can also bring new challenges that require new thought processes for care. In this paper we present two patients who had undergone previous radiation therapy for adenocarcinoma of the prostate with curative intent who required consideration for re-irradiation each more than 15 years away from primary management.

Keywords: Prostate cancer, intensity modulated radiation therapy, re-treatment management

1. Introduction

Radiation therapy delivered through multiple pathways remains an important component to the primary care of patients with primary and metastatic cancers including adenocarcinoma of the prostate. Advanced technology including intensity modulation image guidance and image-guided brachytherapy has permitted increased dose of radiation therapy to be delivered safely to patients and improving control rates without additional normal tissue toxicity. This has led to highly favorable 10- and 15-year survival for patients affected with this disease. When patients recur, often systemic therapy is applied including re-application of hormone therapy as most recurrences are distant metastasis and not within the initial radiation therapy treatment field.

In the less common circumstance when disease recurs in previously treated tissue, considerations for care becomes more limited. Although surgery is a consideration and can be performed after radiation therapy, patients are older at the time of failure than the time of their primary disease and often medically frail. Often medical co-morbidities preclude consideration for surgery. Protracted hormone therapy can have sequelae including unwelcome changes in neuromuscular, neurocognitive, and cardiovascular health and with protracted application limit quality of life.

In this paper we present two cases of re-treatment with radiation therapy. Both patients had primary therapy more than 15 years prior to re-irradiation. Investigators have studied re-treatment with radiation therapy including but not limited to high dose rate radiation therapy. In these two cases information gained from advanced technology imaging is used to developed strategy for care using conformal avoidance to normal tissue with intensity modulation for care.[1-10]

2. Description

Patient One

In 1997, at the age of 67, the patient was noted to have a prostate-specific antigen assay (PSA) of 9.2 ng/mL. The patient was evaluated prior to the advent of formal image-guided biopsy and magnetic resonance (MR) fusion technology. Single biopsy was obtained from the right and left lobe of the prostate. The biopsy from the left revealed Gleason pattern 4 adenocarcinoma and the single biopsy from the right was negative for disease. The patient received 9 months of Lupron therapy and was subsequently evaluated by radiation oncology. Volume study was performed and the prostate volume was measured at 20.4 cc. He underwent definitive brachytherapy with Iodine 125. Fifty-eight (58) seeds were placed using 32 needles in a geometry outlined in Figure 1 (right image). As defined by ultrasound and volumetric treatment planning available at that time 95.08% percent volume received 144 Gy.

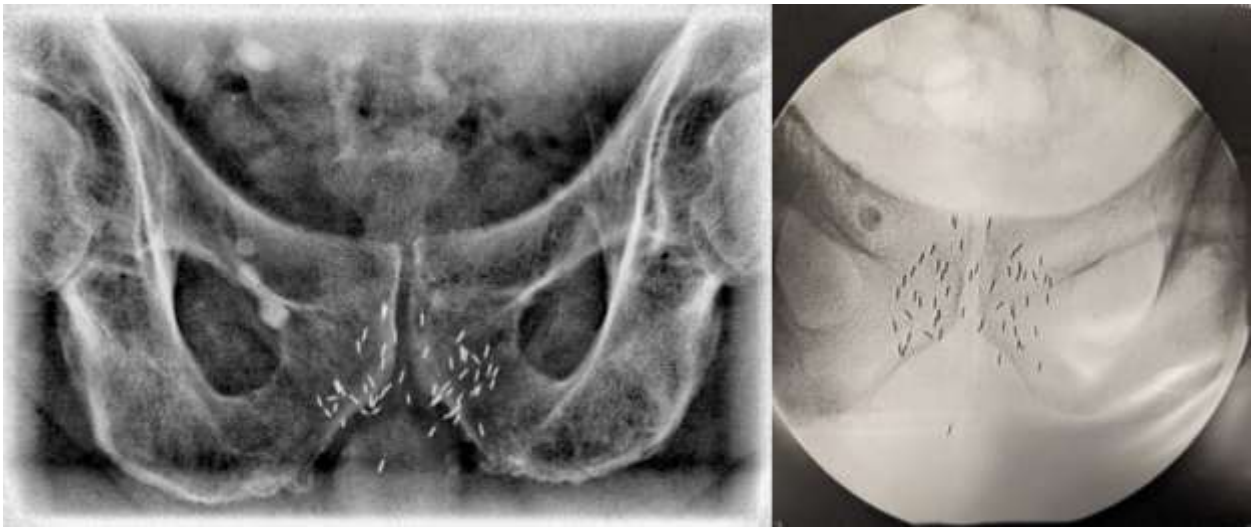

Figure 1. AP image of brachytherapy implant 1997 on the right and displaced seeds at the time of re-treatment in 2021 on the left.

The patient did well until 2018 when elevation in PSA assay was detected and rose to a level of 45.0 ng/mL. Lupron was re-initiated and intermittently withdrawn when PSA decreased below 4 ng/mL. He returned to the New England area and was evaluated by urology (RE). PSA had again increased to 34.0 ng/mL and consideration for Lupron was discussed. Figure 1 on the left depicts the displacement of the iodine seeds to the left by the recurrence of disease at the right base. The patient underwent an Axumin scan seen in Figure 2. The only disease seen on study was in the lateral right base "pushing" the residual seeds to the left. The patient was referred to radiation oncology, now at the age of 91, to consider re-treatment. The patient accepted radiation therapy in lieu of additional hormone therapy as he did not want to re-visit sequelae of hormone treatment.

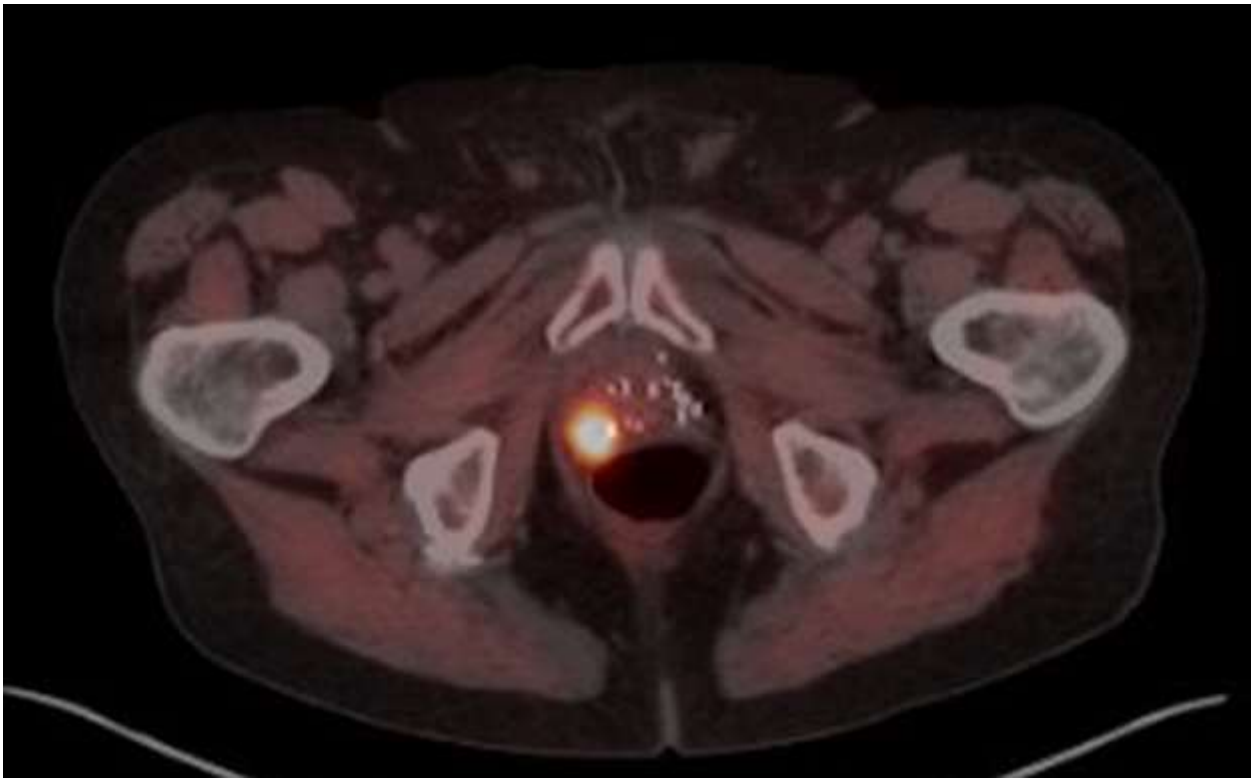

Figure 2. Axumin scan depicting the area of recurrence more than 20 years after brachytherapy.

Patient Two

This patient presented for initial management at age of 62 of adenocarcinoma of the prostate in 2004 when PSA was elevated to 17.3 ng/mL. Ultrasound revealed a 30-cc gland. Biopsy from the left lobe revealed Gleason 8 adenocarcinoma (5+3) involving 90% of the single core and Gleason grade 9 (5+4) adenocarcinoma involving 50% of the core. The computerized tomography (CT) study revealed no adenopathy or metastatic disease. The patient received 2 years of hormone therapy with comprehensive external radiation therapy with intensity modulation. His total dose was 7560 cGy in 180 cGy fractions and he was treated with MeV imaging of target. His post treatment course was complicated by rectal bleeding which responded to laser ablation. Patient remained with negligible PSA until 2016 when PSA became elevated. He initiated hormone therapy when PSA was 6.44 ng/mL. His treatment course was six months off, six months on, secondary to side effects. He became symptomatic with gynecomastia and hot flashes which could not be readily controlled, and issues of management were re-visited. He underwent an Axumin scan off hormone which showed involvement of the prostate as the sole site of disease which was further validated on MR imaging (Figure 3) which was consistent with diffuse involvement of the prostate including the left seminal vesicle. Given the sequence of events and medical co-morbidities, decision was made to move forward with external radiation management without biopsy using dose painting technique to treat the prostate and seminal vesicles as the patient, now 78, was not a good medical candidate for brachytherapy.

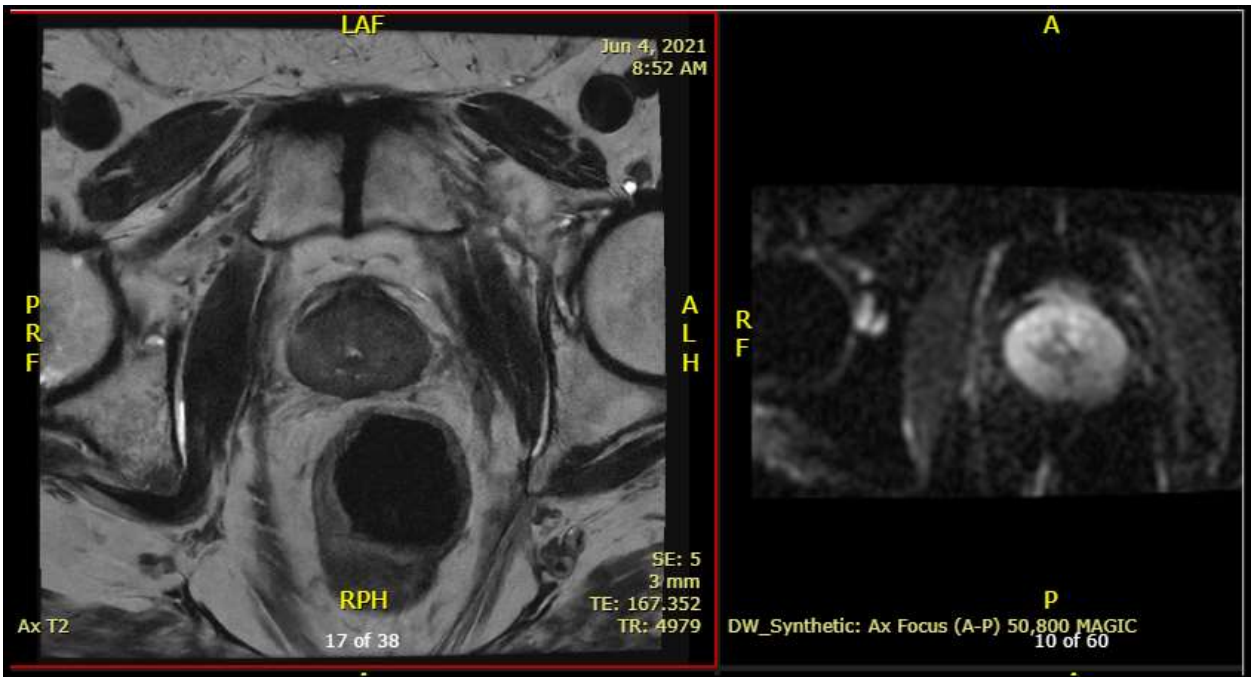

Figure 3. MR of prostate recurrence on 2021 status post definitive radiation therapy in 2004.

Patient One

The patient had an Axumin study which demonstrated an isolated area of uptake in the superior lateral right base displacing the iodine seeds to the left (Figure 3). This provided an interesting opportunity to consider sub-total prostate volume therapy. This approach was used in part because of 1) the anatomical location of the recurrence and 2) previous brachytherapy had generated dose to the urethra which could create a stricture if significant additional dose was applied. Therefore, a volume directed to the site of recurrence was created using dose painting to create a lower dose margin around the site of recurrence defined on metabolic imaging. The patient received 6000 cGy to the primary target in 300 cGy fractions with dose painting used as part of an integrated plan at 4000 cGy in 200 cGy fractions around the primary area of concern without intentionally treating the entire gland in part due to previous brachytherapy. The patient tolerated treatment well without incident with favorable reduction in PSA to date. Figure 4 is the radiation therapy dose distribution to the area of recurrent disease.

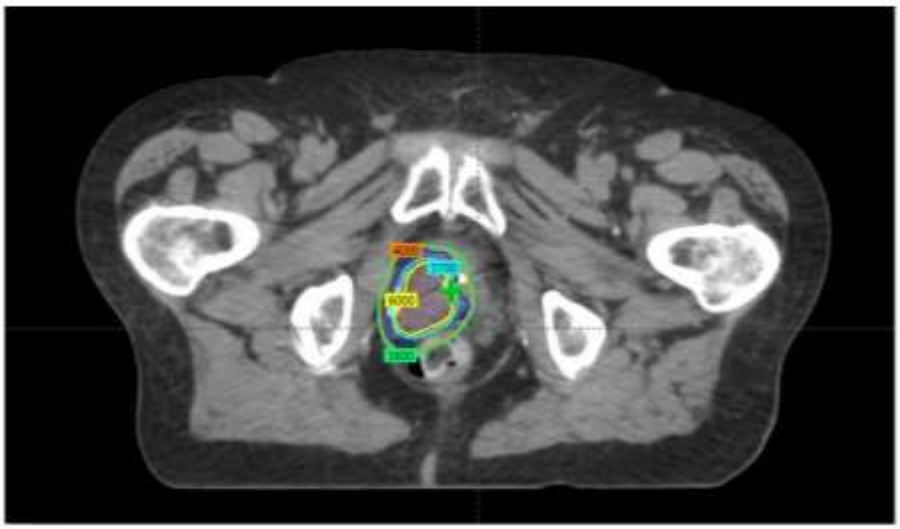

Figure 4. The radiation therapy dose distribution to the area of recurrent disease for Patient One.

Patient Two

In this patient the prostate gland was small (21 cc), therefore brachytherapy was not considered for this patient due in part to the possibility of generating a urethral stricture with either a high or low dose rate application. MR demonstrated diffuse T2 intermediate signal dispersed throughout the entire gland including the region of the seminal vesicles (mostly on the left) where they enter the prostate gland. Dose painting was used with the entire gland and inferior seminal vesicles receiving 6000 cGy in 300 cGy fraction and the more peripheral seminal vesicles received 4000 cGy in 200 cGy fractions. The patient tolerated therapy without incident with favorable reduction in PSA to date. Figure 5 is the radiation dose distribution to the re-treatment volume.

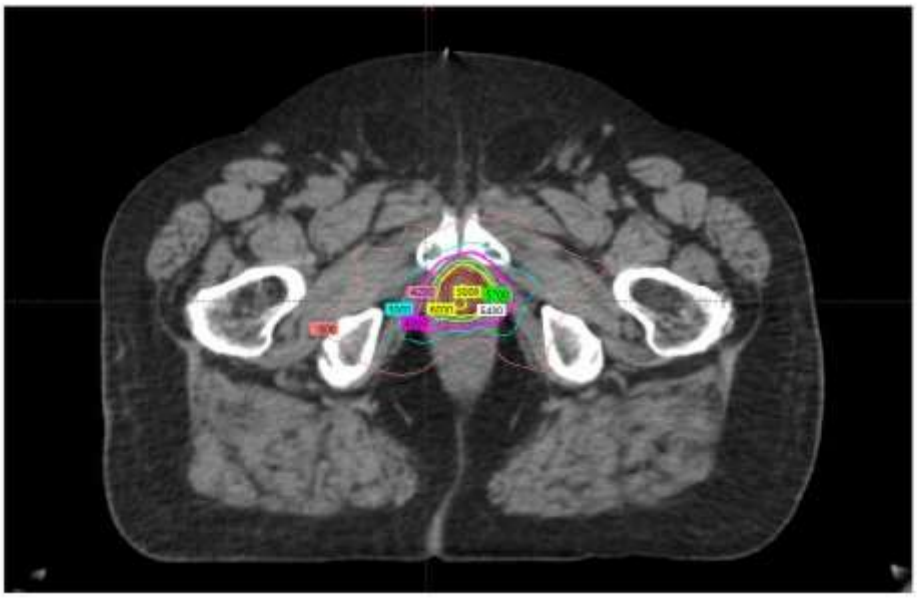

Figure 5. The radiation therapy dose distribution to the re-treatment volume for Patient Two.

3. Discussion

Radiation therapy is an important component to the care of patients with prostate carcinoma. Treatment is applied with curative intent and outcomes continue to improve and remain durable. Radiation therapy tools for management have greatly improved with every decade of progress. Our targets are now volume driven with daily image guidance to insure appropriate targeting and reproducibility of each treatment. Image fusion technology is serving to further refine our targets and dose painting can be easily applied for both conformal avoidance of structures including nerve bundles and dose augmentation to critical targets as needed. We are now able to deliver higher daily doses of treatment than we have in the past with avoidance technologies and compressed fractionation is moving towards the standard of care in primary management. These changes are promoting the use of radiation therapy at an enterprise level for primary management of disease and treatment of oligometastasis.

In part due to success of primary management including improvements in local regional and systemic management, patients are living longer. Accordingly, clinicians need to remain prepared to manage unanticipated recurrences with the understanding that, despite outstanding tumor control more than a decade post primary therapy, late recurrences can occur within primary targets. Often patients are told at presentation that surgery cannot be performed if patients are initially treated with radiation therapy. This was studied in the National Clinical Trial Network and contrary to common opinion, surgery was shown to be feasible in selected patients.[11] However, when late recurrence occurs, patients are older and often affected with additional comorbidities for which surgery may be contraindicated. Therefore, radiation oncologists are re-visiting the potential role of supplemental radiation therapy in these challenging clinical situations. Approaches have included high dose rate brachytherapy (HDR) in patients treated with external therapy for primary management. In this circumstance, often brachytherapy delivers unintentional dose to the urethra and tissues in close approximation to normal tissue including the rectum and bladder. Recently stereotactic radiation therapy has been used as a surrogate to HDR due to improvements in teletherapy technology. This has the advantage of providing service without operative/anesthesia risk. Further study is needed to optimize targeting and how to apply dose to target with conformal avoidance of critical structures including the rectum, bladder, and possibly the urethra in selected patients. Metabolic imaging both with prostate-specific membrane antigen (PSMA) analogues and amino acids coupled with advanced MR technologies will help us assess sub-volume segments requiring dose augmentation and areas of dose titration. This is a potential significant improvement in care as, similar to patient one, advanced technology imaging provided an advantage to augment dose to the PET avid region without additional dose to areas thought controlled with initial brachytherapy.

When Patient One underwent brachytherapy, there was no vehicle for volumetric dosimetry nor image tool to define disease in the gland nor disease potentially at/beyond the prostate capsule. Biopsies at that time were only single biopsies from the right and left lobes, not the multiple image directed biopsies that are performed with routine today. In retrospect, it is plausible disease in the lateral right base may have only been partially treated with brachytherapy as we do not have a volumetric image of dosimetry to define this point relative to the volume of the prostate. We know the entire gland was planned for treatment based on ultrasound, however how dose was applied to volume is

not known as both CT and dose computational analytics were less available at the time of the implant. For Patient Two, therapy was designed with volumetric imaging, however image guidance was nascent at that time without daily kilo voltage (kV) image set up or cone beam CT for target validation. One can also argue that total dose and daily fractionation (7560 cGy/180 cGy) may be low by modern standards, especially without modern image guidance. Although these tools are now standard of care and used with routine in the daily practice of radiation oncology, radiation oncologists have re-worked our craft to optimize the use of these tools in our daily workflow during the past decade. Both patients would likely have benefited from application of modern technology at the time of their primary therapy if technology was available. Nevertheless, patients treated at that time are vulnerable to relapse as the patients presented in this paper and radiation oncologists will need to develop strategies to provide care to these patient populations treated prior to the current improvements in radiation technology.

In this paper we present two patients who required re-treatment more than a decade after primary management. Neither were candidates for surgery at the time of failure. Both had sequelae associated with additional hormone therapy and sought alternative approach to care. We were able to treat these two patients to the entire extent of disease as defined using modern imaging tools with more traditional fractionation patterns as both required dose gradients across the rectum and bladder due in part to target location and previous therapy. Both patient remain well with decrease in PSA.

4. Conclusion

As radiation therapy matures as a discipline, technology is inviting radiation oncologists to expand the scope of practice and apply technology to areas previously considered unapproachable. These two patients are examples of situations that options for care were limited and supplemental therapy was considered reasonable and could be applied in a safe and comprehensive manner. Although there remains considerable work to be done at the clinical, translational, and basic science level to better understand risk to normal tissue including tissue of limited self-renewal potential, re-treatment with radiation therapy is now a more common discussion point at tumor boards and multidisciplinary meetings. Our discipline needs to find a mechanism to further validate this effort, nevertheless, it remains a privilege and an opportunity to offer extended additional care to patients.

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