Case Report

Radiation-Induced Soft Tissue Sarcoma after Prostate Brachytherapy

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Abstract
Secondary malignancy arising following brachytherapy for prostate cancer is rare in medical literature. We present a case of post-brachytherapy soft tissue sarcoma in the pelvis approximately 7 years after 103-P permanent seed implant. The patient developed a large left pelvic mass associated with significant left leg pain. He was not a good candidate for radical surgery, chemotherapy, or re-irradiation. Due to the paucity of high-quality studies, the exact role of prostate brachytherapy in radiation-induced soft tissue sarcoma is still unclear. We seek to review the existing literature on radiation-induced soft tissue sarcoma.

ABBREVIATIONS
PSA: Prostate-Specific Antigen; DVT: Deep Vein Thrombosis; mCi: Millicurie; Pd-103: Palladium-103; Gy: Gray; SPC: Second Primary Cancer; CT: Computerized Tomography; IHC: Immunohistochemical

INTRODUCTION
The development of radiation-induced second primary cancers (SPC) has long been recognized as a possible late side effect following radiation therapy. It is often difficult to determine the exact rate of SPC because of the long latency time between irradiation and SPC development. This is particularly concerning in diseases such as localized prostate cancer which often have more indolent courses and high rates of long-term survival. With continued advancement in prostate cancer therapy the incidence of SPC will likely continue to rise and become a prominent issue in radiation oncology. There is relatively little data in the medical literature regarding SPC following prostate brachytherapy. We report a case of high-grade soft tissue sarcoma arising 7 years after prostate brachytherapy implant.

CASE PRESENTATION
A 64-year old male presented with a T1c NX MX gleason 7 prostate adenocarcinoma. He initially presented to his urologist with an elevated PSA value found on routine screening blood test. His medical history is significant for diabetes, dyslipidemia, and a leg DVT. The patient has no family history of malignancies and did not meet the 2016 NCCN guidelines for genetic cancer syndrome testing. A transrectal ultrasound-guided prostate biopsy was performed in June 2009 which revealed 2 cores involved with prostate cancer out of 12 sample cores removed. A Gleason 3+3=6 and Gleason 4+3=7 prostate carcinoma was found. The patient opted for prostate seed brachytherapy treatment. The pre-implant volume study performed demonstrated a 36cc prostate minimal pubic arch interference.

The brachytherapy implant was performed in November 2009. A total of 99 sources each containing about 1.6 mCi of Pd-103 were placed at pre-planned coordinates within the prostate (Figure 1). This gave a total of 158.42 mCi to the prostate treatment volume. The prescription dose was 125 Gy. Post-implant dosimetry was performed to analyze dose parameters

Figure 1 Initial treatment planning computed tomography showing prescription isodose line (100% - outer orange line).
and to assess quality of implant (Figure 2). The dose parameters of V200, V150, and D90 showed the acceptable values of 46.7%, 68.6%, and 88.6%, respectively. No urethra or rectal dose was recorded but visual exam of the dosimetry did not reveal any unacceptably high dose. The patient tolerated the implant well and his post-implant PSA fell to a nadir below 1 ng/mL by 2010.

The patient had done well with no evidence of disease until 2015 when he began developing shooting pains in his left leg, hip, and buttck. The pain worsened significantly by July 2016. He was worked up for back pain but a CT of the pelvis incidentally revealed a large 10cm pelvic mass located in the left lower pelvis (Figure 3). He developed a colonic obstruction and underwent a diverting colostomy. Several biopsies were taken of the pelvic mass and the pathology slides were reviewed at two outside hospitals. The IHC staining was performed and found to be negative for all of the classic sarcoma markers (Table 1). A review by two independent pathologists confirmed the histopathology and immunophenotype to be consistent with undifferentiated pleomorphic sarcoma (Figure 4). The mass was found to be extraperitoneal and was not removed during the operation.

Radical surgery to resect the sarcoma was offered initially but the patient declined. There were concerns regarding the significant morbidity associated with a large pelvic exenteration. The patient was also deemed not to be a candidate for Ifosfamide and Adriamycin chemotherapy due to his age and general frail health. He was then evaluated for possibly palliative radiation therapy. The tumor was located in the left lower pelvis immediately adjacent to the previously seed-implanted prostate (Figure 5). Due to the close proximity of the tumor to the previously irradiated prostate it was felt that further radiation therapy could not be delivered to this tumor safely without significant risk of normal tissue complications. Re-irradiation of this region would result in high risk of bowel perforation or tissue necrosis. The patient elected to continue with pain management and comfort care at this time.

Figure 2 Post-implant computed tomography showing implanted seeds within the contoured prostate (prostate contour – red solid line).

Figure 3 Axial computed tomography image demonstrating the sarcoma adjacent to the prostate (black arrow).

Figure 4 Spindle cell neoplasm shown with hematoxylin-eosin staining at 200x magnification. The histomorphology was found to be consistent with undifferentiated pleomorphic sarcoma.

Figure 5 Coronal computed tomography image demonstrating the sarcoma located to the left of midline just superior to the left pubic arch (black arrow).
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In the setting of prostate cancer there are as a SPC has been well documented in the literature for a number of years. Nonetheless, radiation-induced sarcoma studies suggest a fairly high threshold dose (>48Gy) is required for tissue sarcoma to develop. However, the incidence of prostate sarcoma among surviving prostate cancer patients is still very low (estimated at 0.03-0.2%). Some studies have shown that the latency period between radiation exposure and the occurrence of an SPC may be as long as 5 to 30 years. This is particularly problematic in tumors with a higher incidence of prostate sarcoma. The diagnosis of a radiation-induced SPC can be especially tricky since histology, irradiated fields, and timing of the new lesion must be considered. 

### DISCUSSION

Prostate cancer is the most common non-skin cancer found among men. Surgery and radiation therapy are the two most common treatment options for patients diagnosed with localized prostate cancer. Among the radiation therapy treatment modalities the two most common are external beam radiation therapy (EBRT) and prostate seed brachytherapy. During EBRT beams are generated outside the body and targeted toward the prostate. In contrast, prostate seed brachytherapy entails the permanent implantation of radioactive seeds into the prostate. Both surgery and radiation therapy are associated with certain expected side effects. But, a complication unique to radiation therapy is an increased risk of developing a second primary cancer (SPC). The diagnosis of a radiation-induced SPC can be especially tricky since histology, irradiated fields, and timing of the new lesion must be considered. SPC induced by radiation therapy are relatively rare. However, with the advent of more effective cancer treatments we are seeing increasing survival within various patient populations. Prostate cancer generally has a low disease-specific mortality rate compared to other cancers. Patients tend to live for longer periods of time following treatment. The utilization of PSA screening also leads to a younger population of men being diagnosed. The latency period between radiation exposure and the occurrence of an SPC may be as long as 5 to 30 years. As such, SPC is becoming a more pressing concern within the population of surviving prostate cancer patients.

The poorly differentiated soft tissue sarcoma seen in this case meets criteria for a radiation-induced sarcoma given its location within the previously irradiated region and its latency period of greater than 6 years. These sarcomas tend to exhibit clinically aggressive behavior, but the incidence of radiation-induced soft tissue sarcoma is still very low (estimated at 0.03-0.2%) [6]. Some studies suggest a fairly high threshold dose (>48Gy) is required to induce a sarcoma. Nonetheless, radiation-induced sarcoma as a SPC has been well documented in the literature for a number of body sites [8-10]. In the setting of prostate cancer there are numerous documented cases of EBRT leading to sarcoma SPC. However, there is relatively scant literature discussing the incidence of prostate brachytherapy radiation-induced sarcoma.

The risk of SPC is often expressed as a no-threshold linear model which assumes a proportional relationship between absorbed radiation dose and risk of SPC. This assumes that there is no safe threshold dose below which there is no risk [13]. There is still some controversy regarding the perceived risk of SPC following radiation therapy. Several studies have demonstrated no increased risk of SPC following radiation therapy for prostate cancer when compared to surgically treated patients [14,15]. Other studies, however, indicate that certain types of cancers were seen in higher incidence following radiation treatment [16,17]. One of these studies even mentioned sarcoma as the most likely subtype of radiation-induced SPC [18]. The majority of these aforementioned studies discuss the rate of genitourinary and gastrointestinal SPC so its applicability to the case of sarcoma is uncertain. Nonetheless, all of these studies still seem to agree that radiation therapy plays a significant role in carcinogenesis.

When it comes to choosing a radiation therapy modality patients often have the choice between EBRT and prostate seed brachytherapy. The majority of literature discussing SPC following radiation therapy for prostate cancer focuses on EBRT treatment modalities. This leads to the question of whether one modality confers a lower rate of SPC than the other. Based on the no-threshold linear model, delivering lower integral dose should theoretically lead to lesser risk of SPC [13]. Brachytherapy generally delivers a more local dose to the prostate than EBRT since less integral dose may be given to surrounding tissue with implantable seeds. One may assume that brachytherapy should confer lesser risk of SPC. One study indeed found decreased incidence of SPC with brachytherapy in comparison to EBRT patient populations [19]. Another study, however found no difference in SPC incidence between EBRT and brachytherapy patient populations [20,21]. The majority of SEER (Surveillance, Epidemiology, and End Results) registry studies looking at prostate radiotherapy do not uniformly agree on an increased risk of SPC [22,23]. But, based on the no-threshold model it is likely that brachytherapy still confers some theoretical increase in absolute risk of developing SPC.

The existing brachytherapy SPC data is also obscured by the heterogeneous populations reported in many of these studies. This may be a result of selection bias or simply a lack of reportable cases. Confounding factors such as vigilant screening, incidental discovery during the workup of radiation toxicity, or even genetic or environmental risk factors may all lead to overestimation of SPC incidence. The extended latency time between irradiation and development of tumor may also lead to underestimation of the proportion of SPC caused by radiation treatment. Death from intercurrent diseases would also interfere with patient follow-up longer than 5-10 years. This is particularly problematic in tumors with longer latency. Given the relative paucity and retrospective nature of these studies it is still difficult to draw strong conclusions about the relationship between brachytherapy and induced SPC. Nonetheless, brachytherapy-induced SPC remains a significant concern in the surviving prostate cancer patient population.

### Table 1: A listing of IHC stains performed routinely for diagnosis of sarcoma. All results were negative pointing to a likely diagnosis of undifferentiated pleomorphic sarcoma by IHC criteria.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Controls</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>CD117</td>
<td>Adequate</td>
<td>Negative</td>
</tr>
<tr>
<td>S100</td>
<td>Adequate</td>
<td>Negative</td>
</tr>
<tr>
<td>CK, cocktail</td>
<td>Adequate</td>
<td>Negative</td>
</tr>
<tr>
<td>CD31</td>
<td>Adequate</td>
<td>Negative</td>
</tr>
<tr>
<td>Desmin</td>
<td>Adequate</td>
<td>Negative</td>
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<tr>
<td>Vimentin</td>
<td>Adequate</td>
<td>Negative</td>
</tr>
<tr>
<td>Actin</td>
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<td>Negative</td>
</tr>
<tr>
<td>CD34</td>
<td>Adequate</td>
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</tr>
<tr>
<td>NKX3.1</td>
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<td>Negative</td>
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<td>Negative</td>
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<tr>
<td>DOG1</td>
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CONCLUSION

Our report describes a case of a high-grade soft tissue sarcoma diagnosed 7 years following brachytherapy implant. The evidence for radiation-induced SPC in the setting of prostate seed brachytherapy is lacking, especially in comparison to the SPC data for EBRT. The risk for SPC is still very low and does not undermine or defer the need for radiotherapy in prostate cancer. Nonetheless, secondary malignancy is still a concern for patients with lower-risk disease who have a minimal risk of dying from prostate cancer. It is essential for the clinician to have informed discussions with the patient regarding the risks of each treatment modality for prostate cancer.

REFERENCES