Case - Radiation-induced sarcoma

A pitfall during PSMA-targeted radioligand therapy

Khashayar Akbari-Kelachayeh[1], Amirfarhan Jafarinia[2], Mina Swiha[3], Golmehr Sistani[4]

[1]Department of Diagnostic Radiology, Queen's University, Kingston, ON, Canada; [2]Department of Biological Sciences, University of Toronto Scarborough, Scarborough, ON, Canada; [3]Division of Molecular Imaging and Theranostics, Department of Medical Imaging, London Health Sciences Centre, London, ON, Canada; [4]Department of Medical Imaging, Royal Victoria Regional Health Centre, Barrie, ON, Canada

Cite as: Akbari-Kelachayeh K, Jafarinia A, Swiha M, et al. Case - Radiation-induced sarcoma: A pitfall during PSMA-targeted radioligand therapy. *Can Urol Assoc J* 2026;20(7):E287-9. http://dx.doi.org/10.5489/cuaj.9437

Published online March 16, 2026

INTRODUCTION

The management of metastatic castration-resistant prostate cancer (mCRPC) has advanced significantly over the past decade, with newer therapies directed at prolonging survival while maintaining symptom control and quality of life.[1] Despite these therapeutic developments, mCRPC remains incurable and continues to be the leading cause of prostate cancer-related mortality. Current treatment options include androgen receptor pathway inhibitors (ARPI), docetaxel, cabazitaxel, and poly(ADP-ribose) polymerase inhibitors (PARPI).[1,2]

Radioligand therapy targeting prostate-specific membrane antigen (PSMA), particularly using [^{177}Lu]-labelled radiopharmaceuticals, has emerged as a beneficial therapeutic modality, showing improvement in overall and progression-free survival.[2] This therapy selectively targets PSMA-expressing tumor cells and limits radiation exposure to surrounding normal tissue. Among these agents, [^{177}Lu]Lu-PSMA-617 has demonstrated higher PSA50 response rates and improved survival outcomes.[2] In chemotherapy-naive mCRPC, recent evidence indicates that [^{177}Lu]Lu-PSMA-617 may offer superior benefit compared to switching ARPI therapy.[3]

Prostate-specific membrane antigen positron emission tomography (PSMA PET) is instrumental for assessment of patient eligibility and followup during PSMA-radioligand therapy, but it has limitations and recognized pitfalls that may impact assessment of treatment response and influence clinical decision-making. We describe here a case that illustrates one such challenge.

We present the case of a patient with mCRPC and extensive bone metastases, who underwent multiple lines of systemic therapy and was subsequently referred to our center for [^{177}Lu]Lu-PSMA-617 therapy. Although he demonstrated a favorable initial response, he later developed an undifferentiated sarcoma, as detailed below.

CASE REPORT

A 68-year-old male with a long-standing history of prostate cancer presented with castration-resistant disease and bone-only metastatic involvement. He was initially diagnosed with localized prostate adenocarcinoma, International Society of Urological Pathology (ISUP) grade group 5, eight years prior to referral, and underwent radical prostatectomy demonstrating pT2c disease.

Two years postoperatively, he developed biochemical recurrence accompanied by pelvic lymphadenopathy on computed tomography (CT). He subsequently underwent retroperitoneal pelvic lymph node dissection followed by salvage external-beam radiotherapy in September 2013 (6600 cGy to the prostate bed and 5400 cGy to pelvic nodes), and was commenced on androgen deprivation therapy (ADT). His pelvic radiotherapy course was complicated by radiation-induced proctitis and cystitis.

Approximately one year later, his PSA progressively increased to 9.2 ng/mL, and bone scintigraphy revealed metastatic lesions in the left iliac bone and left ischium. He received palliative radiation with a single fraction of 800 cGy to the left hip and ischium in January 2015. Systemic therapy with abiraterone acetate, prednisone, and denosumab was initiated; however, after approximately 16 months, he demonstrated biochemical progression and was switched to enzalutamide.

Due to worsening left pelvic pain, pelvic re-irradiation was delivered using intensity-modulated radiation therapy to minimize bladder and rectal dose exposure (2200 cGy in five fractions) in June 2016. His response to enzalutamide was short-lived, and he commenced alpha-emitting radiopharmaceutical therapy with [^{223}Ra]Radium dichloride in February

2017, completing the standard six-dose treatment by August 2017. In addition, he received 10 cycles of docetaxel by mid-2018.

Subsequently, the patient was enrolled in a clinical trial and received [^{177}Lu]Lu-PSMA-617 at a dose of 7.4 GBq per cycle every six weeks for a total of six cycles, completed in April 2020. He demonstrated both biochemical and radiographic response to therapy. His baseline PSA decreased from 109 ng/mL to 2.1 ng/mL following completion of radioligand treatment. Post-therapy PSMA PET/CT revealed marked reduction in the extent and intensity of radiotracer uptake throughout the skeleton (Figure 1); however, a solitary focus in the left iliac bone demonstrated persistent uptake (Figure 1).

Targeted evaluation with contrast-enhanced CT and magnetic resonance imaging (MRI) identified a destructive osseous lesion with an enhancing soft tissue component, which continued to enlarge despite stability of the remainder of his disease burden (Figure 2). Three months following his final [^{177}Lu]Lu-PSMA-617 treatment — at which time his PSA remained stable — a biopsy of the lesion was performed. Histopathologic and immunohistochemical analysis confirmed an undifferentiated sarcoma.

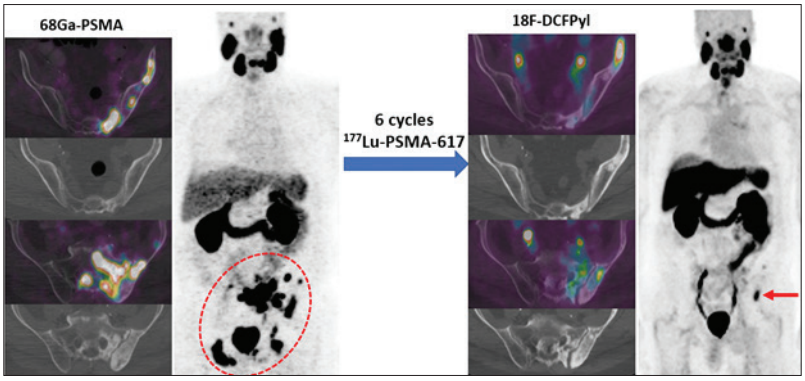

Figure 1. On the left, fused axial positron emission tomography (PET)/computed tomography (CT), axial PET, and maximum intensity projection images of [68Ga]Ga–PSMA-11 PET study demonstrates the extent of disease before treatment. On the right, post-treatment [18F]F–DCFPyL PET/CT imaging after six cycles of [177Lu]Lu-PSMA-617 shows markedly reduced PSMA total tumour volume in all lesions except one, indicating a favorable response to radioligand therapy with a single site of persistent disease. The maximum standardized uptake value (SUVmax) was 5.9 before treatment and 6.9 after treatment.

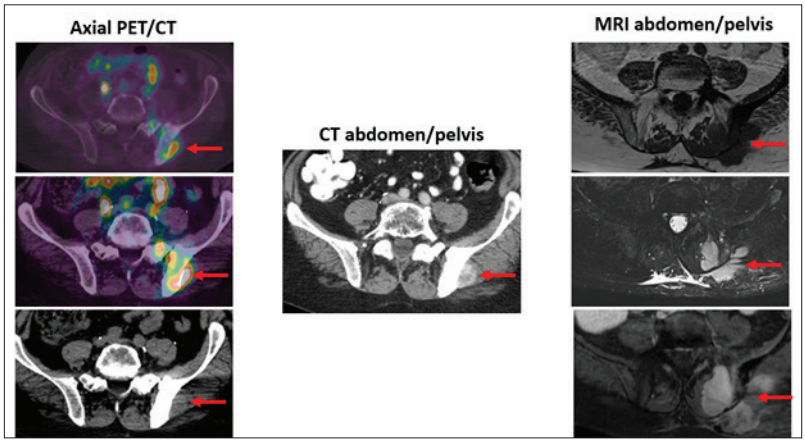

Figure 2. The first column includes axial positron emission tomography (PET), fused axial PET/computed tomography (CT), and CT images; the second column shows contrast-enhanced CT; and the third column presents T1-weighted, T2-weighted, and post-contrast magnetic resonance imaging, demonstrating a PSMA-avid, enhancing, T2-hyperintense lesion in the posterior left iliac bone with a soft tissue component in gluteal muscle.

Review of his treatment history revealed that he had previously received external-beam radiotherapy to the pelvis in 2013, 2015, and 2016. The site of sarcoma development was located within the previously irradiated field, strongly supporting the diagnosis of a radiation-induced sarcoma. Given the relatively short interval between [^{177}Lu]Lu-PSMA-617 administration and sarcoma identification, it is unlikely that radioligand therapy contributed to the sarcoma development.

Surgical resection remains the mainstay of management for localized and resectable sarcomas.[4] The patient was referred to another tertiary center and underwent surgical resection of the lesion in September 2020. He did not receive adjuvant chemotherapy. Unfortunately, by November 2020, he developed a pulmonary embolism, bilateral pleural effusions, and numerous pulmonary "cannonball" metastases most consistent with sarcoma-related metastases. No PSA level was obtained at that time. The patient passed away later that month.

DISCUSSION

External-beam radiation therapy is a recognized risk factor for secondary sarcomas developing within the irradiated field.[5] Although the absolute risk is low, it increases with longer post-treatment survival. It has been estimated that approximately 0.16% of patients who undergo radiotherapy for prostate cancer may later develop a secondary malignancy, such as sarcoma, particularly if survival exceeds 10 years.[6] The risk is also dose-dependent and correlates with cumulative exposure to ionizing radiation.[7]

In this case, the patient received repeated courses of external-beam radiotherapy to the left pelvic sidewall over several years, resulting in substantial cumulative dose burden and placing him at elevated risk for radiation-induced secondary sarcoma. While it is possible that additional radiation exposure from [^{223}Ra]Ra-dichloride may have contributed to cumulative radiation burden, the very short interval between [^{177}Lu]Lu-PSMA-617 administration and sarcoma identification makes a causal role for radioligand therapy unlikely.

In this case, the radiation-induced sarcoma was initially misinterpreted on PSMA PET/CT as persistent prostate cancer metastasis that appeared unresponsive to therapy — an imaging pattern observed in up to one-third of patients undergoing PSMA radioligand treatment;[8] however, it is important to recognize that secondary malignancies may also demonstrate PSMA avidity, although usually with lower intensity than that seen in prostate adenocarcinoma metastases.[9]

This highlights the need to consider treatment-related secondary malignancies, as well as synchronous tumors, in the differential diagnosis when imaging findings do not align with expected treatment response. Correlation with additional imaging modalities, such as CT and MRI, along with confirmatory histopathologic evaluation, is essential when atypical disease progression raises suspicion for an alternative diagnosis.

COMPETING INTERESTS: The authors do not report any competing personal or financial interests related to this work.

This paper has been peer-reviewed.

REFERENCES

1. Raval AD, Chen G, Korn MJ, et al. Real-world treatment patterns and survival in people with metastatic castration-resistant prostate cancer following metastatic hormone-sensitive disease between 2020 and 2023 in the United States. *Clin Genitourin Cancer* 2025;23:102386. https://doi.org/10.1016/j.clgc.2025.102386
2. Sartor O, de Bono J, Chi KN, et al. VISION Investigators. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. *N Engl J Med* 2021;16;385:1091-103. https://doi.org/10.1056/NEJMoa2107322
3. Morris MJ, Castellano D, Herrmann K, et al. PSMAfore investigators. 177Lu-PSMA-617 versus a change of androgen receptor pathway inhibitor therapy for taxane-naive patients with progressive metastatic castration-resistant prostate cancer (PSMAfore): A phase 3, randomised, controlled trial. *Lancet* 2024;404:1227-39. https://doi.org/10.1016/S0140-6736(24)02716-8
4. Inchaustegui ML, Kon-Liao K, Ruiz-Arellanos K, et al. Treatment and outcomes of radiation-induced soft tissue sarcomas of the extremities and trunk: A systematic review of the literature. *Cancers (Basel)* 2023;15:5584. https://doi.org/10.3390/cancers15235584
5. Plouznikoff N, Woff E, Artigas C, et al. Incidental detection of a radiation-induced soft-tissue sarcoma on 68Ga-PSMA PET/CT in a patient previously treated for prostate cancer. *Clin Nucl Med* 2019;44:e501-e502. https://doi.org/10.1097/RLU.0000000000002592
6. Wakabayashi K, Konishi K, Komatsu T, et al. Radiation-induced sarcoma after radiation therapy for prostate adenocarcinoma. *IJU Case Rep* 2019;2:98-101. https://doi.org/10.1002/iju5.12052
7. Turner PG, Jain S, Cole A, et al. Toxicity and efficacy of concurrent androgen deprivation therapy, pelvic radiotherapy, and Radium-223 in patients with de novo metastatic hormone-sensitive prostate cancer. *Clin Cancer Res* 2021;27:4549-56. https://doi.org/10.1158/1078-0432.CCR-21-0685
8. Hofman MS, Emmett L, Sandhu S, et al. TheraP trial investigators and the Australian and New Zealand urogenital and prostate cancer trials group. [177Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): A randomised, open-label, phase 2 trial. *Lancet* 2021;397:797-804. https://doi.org/10.1016/S0140-6736(21)00237-3
9. Shaygan B, Zukotynski K, Bénard F, et al. Canadian Urological Association best practice report: Prostate-specific membrane antigen positron emission tomography/computed tomography (PSMA PET/CT) and PET/magnetic resonance (MR) in prostate cancer. *Can Urol Assoc J* 2021;15:162-172. https://doi.org/10.5489/cuaj.7518

CORRESPONDENCE: Amirfarhan Jafarinia, Department of Biological Sciences, University of Toronto Scarborough, Scarborough, ON, Canada; farhan.jafarinia21@gmail.com