Initial Experience with Gallium-68 and Lutetium-177 Prostate-Specific Membrane Antigen Theranostics for Prostate Cancer in the Philippines: A Case Series

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ABSTRACT

In the Philippines, prostate cancer is the third most common malignancy among men. Over time, it tends to recur and/or progress to metastatic castration-resistant prostate cancer, wherein conventional therapies no longer work. Taking advantage of the high expression of prostate-specific membrane antigen (PSMA) on prostate cancer cells, ^{68}Ga- and ^{177}Lu-PSMA theranostics provides a targeted approach to imaging and therapy. With its availability in our country, patients now have an appealing and accessible treatment option. In this paper, we present five cases of metastatic castration-resistant prostate cancer, who have undergone ^{68}Ga-PSMA PET/CT scans and ^{177}Lu-PSMA radioligand therapies in the Philippines, to showcase the usefulness of theranostics in the local setting.

Keywords: *Ga-68 PSMA, Lu-177 PSMA, theranostics, prostate cancer, Philippines*

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INTRODUCTION

Prostate cancer is the second most common cancer in males and the fourth leading cancer in both sexes. In 2012 alone, around 1.1 million men were diagnosed with the malignancy which accounted for 15% of malignancies diagnosed that year [1]. In the Philippines, prostate cancer is the 6th most common cancer in both sexes and the third among men. Local data showed that in 2015, there were an estimated 5,526 new cases and around 2,912 deaths. There is a median survival of 52 months, a 43% 5-year survival rate, and a 31% 10-year survival rate [2]. Most deaths related to prostate cancer are due to advanced stage of disease, likely from lymphatic or contiguous local spread [3].

Thankfully, prostate cancer is one of the diseases being addressed by theranostics, which refers to the use of closely related radiopharmaceuticals to accurately diagnose and treat diseases in a targeted manner [4]. We hereby present five patients with metastatic castration-resistant prostate cancer (mCRPC), who have undergone ^{68}Ga-prostate-specific membrane antigen (PSMA) PET/CT scans and PSMA radioligand therapies (PRLT) using ^{177}Lu, to give an overview of PSMA theranostics in the local setting (Table 1).

CASE SERIES

All patients had salivary gland scintigraphy and renal scintigraphy, as well as necessary blood tests done before the PRLT. Patients who had anemia or

Table 1. Description of five patients with metastatic castration-resistant prostate cancer who each underwent a pre-therapy ^{68}Ga-PSMA PET/CT scan and post-PRLT whole-body scan.

Patient	Age	Gleason Score	Year Diagnosed	Previous Treatments Received	PSA (ng/mL)	^{68}Ga-PSMA dose and scan findings	^{177}Lu-PSMA activity and scan findings
A	72	9	2015	thoracic laminectomy, bicalutamide, leuprolide, abiraterone, denosumab	1.3	119 MBq (3.2 mCi) PSMA overexpression in the prostate and multiple metastases to the lymph nodes, lungs, liver and bones	6.0 GBq PSMA ligand uptake in similar distribution
B	71	9	2012	radical prostatectomy, radiotherapy, androgen deprivation therapy	6.29	157 MBq (4 .2 mCi) PSMA overexpression in the lymph nodes and pleural nodules	7.5 GBq PSMA ligand uptake in similar distribution
C	70	9	2012	multiple radiotherapies, leuprorelin, enzalutamide, abiraterone, denosumab	39.85	134 MBq (3.6 mCi) PSMA overexpression in the prostate and multiple osseous metastases	6.5 GBq PSMA ligand uptake in similar distribution
D	88	biopsy not done	2014	leuprolide, abiraterone, denosumab	174.54	155 MBq (4.2 mCi) PSMA overexpression in the prostate with nodal, osseous, and pulmonary metastases	4.6 GBq PSMA ligand uptake in similar distribution
E	67	official report not available	2018	transurethral resection of the prostate (TURP), bicalutamide, degarelix	20.739	168 MBq (4.5 mCi) PSMA overexpression in the right side of the prostate, multiple lymphadenopathies, and bone metastases	7.5 GBq PSMA ligand uptake in similar distribution

decreased renal function before the PRLT manifested no worsening of the prior condition, as illustrated in Table 2.

All patients did not experience adverse events, although one patient had temporary mild swelling of the cheeks, which resolved after placement of ice packs over the affected areas, and another patient reported mild tolerable xerostomia.

DISCUSSION

The 10-year cumulative incidence of biochemical recurrence is 47.9% for high-risk patients [5]. There is a high probability of recurrent disease for Gleason score of 7 (4 + 3) or higher (as seen in our three patients with Gleason score 9), non-focal extra-prostatic extension, seminal vesicle invasion, lymph node metastasis, or tumor volume of greater than 2 cm [6]. mCRPC is suspected in patients with new symptoms while on androgen deprivation therapy, with a rising PSA, or with new evidence of disease on bone scans or computed tomography scans. However, in less than 1% of patients with metastatic prostate cancer including our first case, a low PSA level is seen, which may be explained by the proliferation of cell lines that either cannot produce PSA or have lost their ability to express PSA [7].

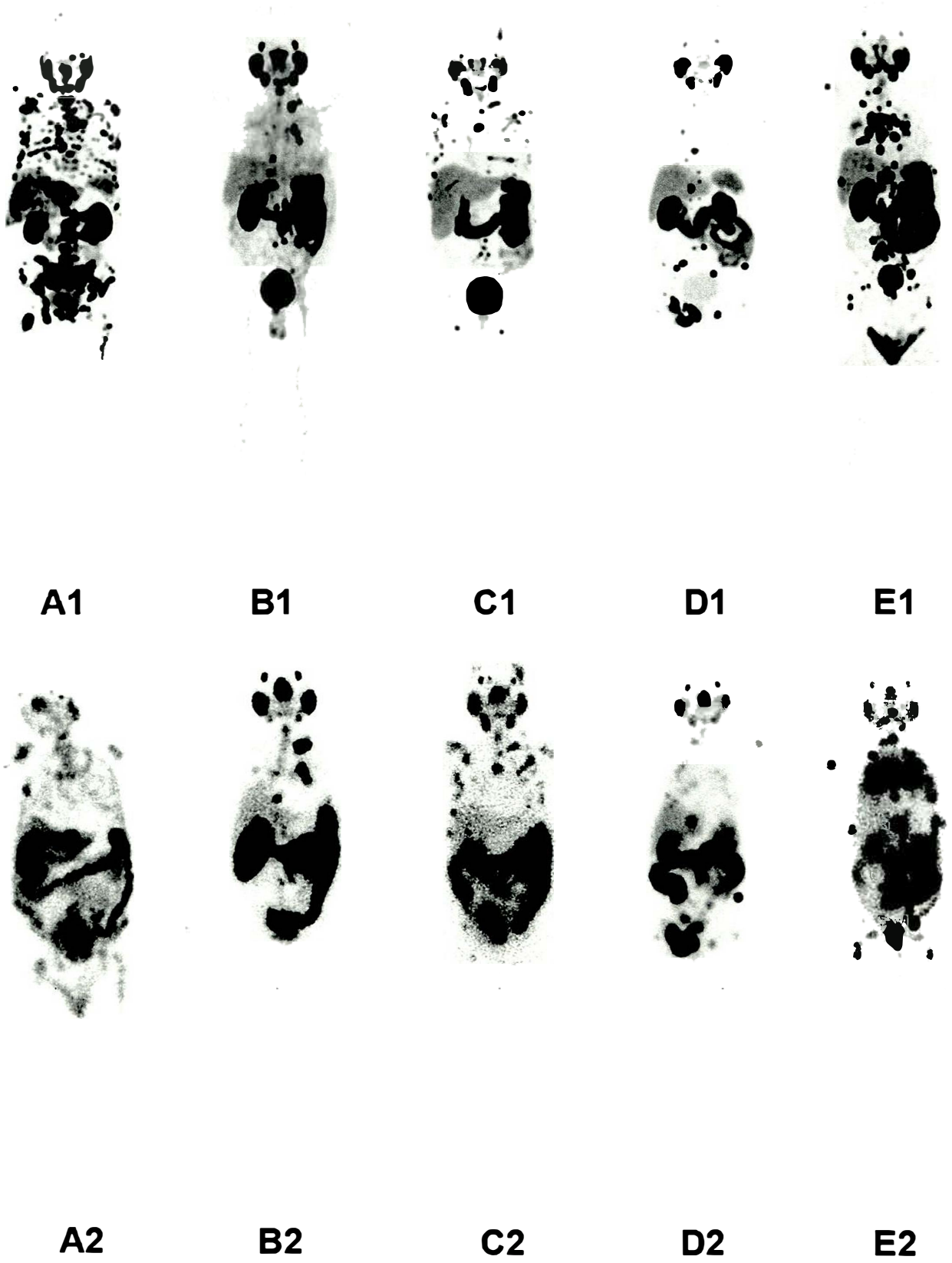
Table 2. Hemoglobin and serum creatinine levels of the patients before and after PRLT

Patient	Hemoglobin		Reference Values	Creatinine		Reference Values
	Pre-PRLT	Post-PRLT		Pre-PRLT	Post-PRLT	
A	122	122	135–180 g/L	56.0	56.1	71.0–114.9 µmol/L
B	12.3	13.2	13.0–17.0 g/dL	0.93	0.71	0.80–1.50 mg/dL
C	12.80	11.60	13.70–17.50 g/dL	1.11	1.34	0.67–1.18 mg/dL
D	73	103	130–180 g/L	2.015	1.399	0.719–1.249 mg/dL
E	13.6	13.8	13.5–18.0 g/dL	81	74	58–110 µmol/L

Recently, small molecules for PET and SPECT imaging targeting PSMA, a transmembrane protein that is overexpressed up to one thousand-fold higher in 95% of prostate cancer cells compared to benign cells [8], are starting to revolutionize the field of prostate cancer diagnostic imaging and treatment in patients with mCRPC. In patients whom biopsy cannot be done, as seen in Patient D, a positive ^{68}Ga-PSMA PET/CT scan is almost tantamount to prostate cancer diagnosis. According to Kallur et al., it has a sensitivity of 95% and a positive predictive value of 98% [9]. The most established use of ^{68}Ga-PSMA PET/CT scan, though, is in the setting of biochemical relapse with potential pre-PRLT screening, as ^{68}Ga-PSMA PET/CT can provide direct information on whether a patient would benefit from PRLT [10]. As seen in Figures A to E, the lesions with ^{68}Ga-PSMA overexpression also took up ^{177}Lu-PSMA, although the intensity was variable. This is likely due to a combination of the following factors: (1) lower sensitivity and spatial resolution of planar imaging and SPECT-CT compared with PET/CT [11], (2) heterogeneity of PSMA receptor activity within the tumour population [12], and (3) different time interval between the ^{68}Ga-PSMA PET/CT scan and the post-PRLT scan ranging from three to ten weeks apart, during which the patients' other treatments could have altered the PSMA overexpression.

^{177}Lu-PSMA therapy for mCRPC has been shown to have anti-tumor effects. This has led to improved quality of life with a median overall survival of 13.5 months compared to standard chemotherapy [13] and additional benefit of pain palliation [1]. Before PRLT, however, other imaging and laboratory tests, aside from the requisite ^{68}Ga-PSMA PET/CT scan, must be ordered for appropriate patient selection. Meticulous pre-therapy assessment and patient education, as well as careful monitoring by responsible nuclear medicine physicians are essential for the success of PRLT. Each of these five patients' initial therapy went smoothly from the satisfactory synthesis of the ^{177}Lu-PSMA and its intravenous administration to the rest of the hospital stay until discharge.

Thus far, since the availability of ^{68}Ga-PSMA PET/CT scan in the Philippines in January 2018, it has been shown to be useful in accurately restaging



Figures A–E. ^{68}Ga-PSMA PET/CT (top row) and post-PRLT (bottom row) scans showing similar distribution but varying intensity of PSMA ligand uptake in five patients with mCRPC.

prostate cancer, as well as determining suitability of patients for PRLT, particularly in these five patients. PRLT has given hope to these patients, who no longer respond to the conventional treatments. They like that PRLT is safe and tolerable, and that they can go back to their usual activities immediately after discharge. After this overview on the application of theranostics, further studies on the utility of ^{68}Ga-PSMA PET/CT and the efficacy of PRLT in the local setting are recommended.

CONCLUSION

The initial ^{68}Ga-PSMA and ^{177}Lu-PSMA theranostics experience in the Philippines is promising. Our study has shown the utility of ^{68}Ga-PSMA PET/CT scan in screening eligible patients for PRLT and has demonstrated the tolerability and safety of PRLT in selected patients.

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