Role of Early Dynamic PET/CT Scan Imaging with ¹⁸F-PSMA-1007 in Staging and Restaging Prostate Cancer in a Tertiary Private Hospital

Arrene Joy B. Baldonado, MD

Department of Radiological Sciences, Section of Nuclear Medicine and PET-CT center, Cardinal Santos Medical Center, E-mail address: baldonadoarrene@gmail.com

ABSTRACT

Introduction:

¹⁸F-PSMA-1007 is a novel prostate-specific membrane antigen (PSMA)-based radiopharmaceutical for imaging prostate cancer. The recommended imaging time is 60 minutes post-injection of the radiotracer. However, during this time there is a physiologic accumulation of the radiotracer in the urinary bladder which sometimes may obscure lesions adjacent to it.

Objective:

This study aims to determine if early dynamic imaging in addition to the recommended 60-minute postinjection static imaging can improve the detection of PSMA-avid lesions in the staging and restaging of prostate cancer.

Methods:

This is a retrospective cross-sectional study of the detection rate of early dynamic and static imaging using ¹⁸F-PSMA-1007 PET/CT scan in patients with prostate cancer (PCa) who were referred for initial staging or restaging. The McNemar test was used to compare the detection rate between the two imaging. Spearman correlation was used to determine the correlation of Gleason score (GS), PSA, and SUVmax values.

Results:

¹⁸F-PSMA-1007 PET/CT scans of 53 patients with prostate cancer, were referred for either staging (22/53) or restaging (31/53), all of whom had undergone both early dynamic and static imaging. Among the 53 patients, 5 had 2 lesions each, for a total of 58 lesions were included in the analysis. There were 48/58 lesions detected on both early dynamic and static imaging, 2/58 lesions were only detected in the early imaging, 1/58 lesions was only detected in the static imaging, and 7/58 were not detected on both imaging. McNemar the test was not statistically significant (p = 1.000) in the detection rate of the two methods. There is a positive correlation between serum PSA levels and SUVmax measurements for all the patients. Only the correlation between the GS and SUVmax in the static imaging of the staging group was statistically significant.

Conclusion:

Early dynamic imaging may be an adjunctive procedure in detecting PSMA-avid lesions, particularly in the basal segment of the prostate gland near the urinary bladder. However, it is not recommended as a standard component of the comprehensive protocol for imaging using ¹⁸F-PSMA-1007 PET/CT in patients with PCa.

Keywords: ¹⁸F-PSMA-1007 PET/CT scan, dynamic imaging, static imaging, prostate cancer

INTRODUCTION

Prostatic malignancy is the fourth most common cancer worldwide, and the third leading malignancy site in males in the Philippines, with an age-standardized incidence rate (ASR) of 21.9 per 100,000 population [1, 2]. The gold standard for the diagnosis of prostate carcinoma is a histological assessment usually obtained by transrectal ultrasound-guided systematic core needle biopsy [3]. An important histopathologic parameter is the Gleason Score (GS) which reflects the grade of differentiation of prostate cancer (PCa) and thus correlates with tumor aggressiveness [4]. The standard treatment of PCa involves prostatectomy and radiotherapy. Although this treatment is curative for some, 20 to 30% experience a recurrence typically detected when there is a rise in serum prostate-specific antigen (PSA) levels after initial treatment [5, 6, 7, 8].

The role of conventional imaging modalities (CT, MRI, 99mTc-MDP bone scan) is limited in PCa recurrence assessment, as well as in the detection of nodal and distant disease [9, 10, 11, 12]. Due to this, there is a need to develop new diagnostic methods to allow an accurate means of staging and restaging of PCa. In recent years, Positron Emission Tomography (PET) with fluorodeoxyglucose and choline-based radiotracers have been introduced for the diagnosis and staging of PCa with the eventual development of targeted imaging using prostate-specific membrane antigen (PSMA) [13, 14, 15]. PSMA is a transmembrane glycoprotein over-expressed in prostate cancer cells and shows low expression in benign prostatic tissue [16]. It has been used in various clinical management of PCa, such as staging primary tumors, localization of biochemical relapse, planning for radiotherapy, prediction, and assessment of treatment response. Several radiolabeled PSMA probes were developed including the most widely used Gallium-68 Prostate Specific Membrane Antigen-110 (⁶⁸Ga-PSMA-110 [15, 17, 18, 19]. It is superior to conventional imaging and choline-based PET/CT for evaluating PCa patients with biochemical recurrence but also for staging purposes [20]. However, the disadvantage of 68 Ga-PSMA as a radiotracer is its high accumulation in the urinary bladder which may influence the uptake evaluation of the prostate bed [21]. The introduction of a novel PSMA - based radiopharmaceutical, Fluorine-18 Prostate Specific Membrane Antigen-1007 $(18F-PSMA-1007)$, offers several advantages over ⁶⁸Ga-PSMA [14, 15]. It is primarily excreted in the hepatobiliary tract and shows a relatively lower urinary bladder activity, hence it can be used in evaluating cases of local tumor recurrence and unclear lesions adjacent to the urinary bladder [15, 19]. Moreover, 18 F-PSMA has a longer half-life (T1/2 = 109 min), higher physical spatial resolution, and larger dose since it is produced by a cyclotron as compared to Gallium-68 which is derived from elution of 68Ge/68Ga generators [15]. The larger dose produced via cyclotron leads to a greater number of patients that can be accommodated. Studies show that ¹⁸F-PSMA is useful in staging PCa and positively correlates the SUV values of PSMA-avid lesions with PSA level and GS [14, 15, 22].

In the Philippines, several institutions are utilizing 18 F-PSMA-1007 PET/CT scans in the diagnosis of PCa namely: Cardinal Santos Medical Center (CSMC), Chinese General Hospital and Medical Center (CGHMC), Centuria Medical Makati (CMM), iScan Diagnostic Center, National Kidney and Transplant Institute (NKTI), and The Medical City (TMC); all of which are located in Metro Manila. Amongst the said institutions, only the CSMC performed early dynamic imaging in ¹⁸F-PSMA-1007 PET/CT scans from August 2020 to March 2022. With the current clinical data, there is no standard protocol in the imaging time of 18 F-PSMA-1007 published, however, studies recommend static imaging ranging from 40 to 90 minutes post-injection, most commonly used is 60 minutes, to allow for radiotracer uptake [15, 22, 23, 24, 25, 26].

Dynamic PET/CT scan is a modality that allows registration of pharmacokinetic information over time, while classical static whole-body PET/CT protocols enable the acquisition of patient images only at a one-time point after tracer injection [27]. In the dynamic PET/CT scan, studies have shown that in the first few minutes post-injection, radiotracer uptake of local prostate cancer lesions is visible before its accumulation in the urinary bladder [16]. Hence, the use of dynamic imaging can aid in the detection of PSMA-avid lesions within the proximity of the urinary bladder. When viewed in static imaging, these lesions can be obscured by the physiologic activity in the bladder. A study by Barakat et al. demonstrated that early dynamic imaging using ⁶⁸Ga-PSMA PET/CT scan increases the detection of PSMA-avid lesions in the anterior portion of the prostate and is suggestive of prostate cancer or its recurrence [28]. There is limited published data on the diagnostic efficacy of 18 F-PSMA-1007 PET/CT scan and no study on its use with early dynamic imaging. This study aims to show the detection rate of 18 F-PSMA PET/CT scan in early dynamic imaging as an adjunct to the standard 60 minute post-injection static imaging, in the staging and restaging of prostate cancer. Furthermore, to analyze

the correlation between the GS and PSA value with the SUV level of the lesions.

MATERIALS AND METHODS

Ethical approval:

This study was approved by the Ethics Review Board (ERB) of CSMC with RERC CODE 2021-023. The need for written informed consent was waived by the ERB due to the study's use of the retrospective method of data collection. This study was conducted in strict compliance with the provisions of the Philippine Data Privacy Act of 2012 (Republic Act of No. 10173). All imaging procedures performed were following the tenets of the Declaration of Helsinki and its amendments.

Patient:

A pilot sample of 53 patients was retrospectively analyzed in this study. Patients with biopsy-proven prostate carcinoma, who underwent both early dynamic and standard static 18 F-PSMA-1007 PET/CT scans between August 2020 to March 2021 in a single-center hospital (Cardinal Santos Medical Center) were included. All the patients were referred for baseline staging or restaging of prostate cancer. Patients with multiple primary cancer, not-biopsy-proven prostate cancer, and those with technically inadequate studies (e.g. motion artifacts, incomplete study) were excluded. Eligible data such as the patient's age, GS, serum PSA levels (ng/mL), previous and ongoing treatments (radical prostatectomy, radiotherapy, hormonal therapy), and 18 F-PSMA-1007 PET/CT findings were assessed. The scans were assigned to two groups according to clinical purpose: (1) staging of disease and (2) restaging. Patients who underwent 18 F-PSMA PET/CT scans before initiation of treatment were classified under the "staging group" while patients who underwent PET/CT scans after treatment were classified as the "restaging group". Of 53 patients, 22 were included in the staging group and 31 in the re-staging group.

Radiotracer:

¹⁸F-PSMA-1007 radiotracers provided by the Khealth Corporation were utilized in this study.

Image acquisition:

Each patient received $148-444$ MBq of 18 F-PSMA intravenously depending on the computed dose base on the body weight. Data acquisition consists of two parts: early dynamic imaging which is followed by static imaging (whole-body PET/CT). Early dynamic studies

were performed over the lower abdomen to the pelvic area and acquired at the time of injection up to 6  minutes post-injection; while the static (whole-body) imaging was acquired at 60 minutes post-injection. Patients were asked to urinate before both imaging modalities.

¹⁸F-PSMA-1007 PET/CT acquisition was performed on a GE Discovery 71.0 scanner. This system has a time-offlight (TOF) capable technology with a full three-dimensional PET and a 64-slice CT. PET acquisition time was at 2 minutes per bed position for the whole body and 0.5 to 1 minute per bed position for the lower extremities using the TOF-PET technique. The exact CT parameters used for unenhanced acquisition include 0.8 pitch, 0.75-second rotation time, and effective tube current-time product range of 50-300 milliamperes (mA); these were dependent on the body thickness and tube voltage of 120 kilovoltage peak (kVp). Finally, image reconstruction was performed at a slice thickness of 3.75 mm for PET/CT.

Image Evaluation:

Images were interpreted using the dedicated commercially available Autonomous Database Warehouse (ADW) Linux software which provides PET, CT, and fused PET/CT imaging data in the axial, coronal, and sagittal planes. All PET imaging was attenuation corrected (AC) and had undergone Q-clear technology using the GE Discovery 7.10 scanner. The images were reconstructed and the maximum standardized uptake value (SUVmax) of the detected focal lesions was measured. The SUVmax measured in the early dynamic and static images was used for the quantification of tracer data. The visible prostate cancer lesions in the early dynamic and static images were independently reviewed, qualitatively, and quantitatively scored by two nuclear medicine physicians and two radiologists. All disagreements in the interpretation of the results in the provided images were resolved through consensus. Any focal uptake in the prostate or prostate bed with SUVmax greater than 2.5 g/ml or greater than the background was considered pathologic and suggestive of malignancy. In this study, such lesions were categorized as 'positive' while lesions that did not show an increase in tracer uptake in comparison to the surrounding tissue, or those with undetectable lesions were categorized as 'negative'.

Statistical Analysis:

Age was reported as mean ± standard deviation (SD). Serum PSA and SUVmax were reported as median with interquartile range (IQR). Stata 16.1 software was used for data processing and analysis. Continuous variables based on data distribution were presented as mean ± SD or median IQR. Categorical variables were reported as frequencies and percentages. The McNemar test was used to compare the detection rate between early dynamic and static imaging. Shapiro-Wilk test was utilized to test whether the data provided in the GS, serum PSA and SUVmax levels were normally distributed. The null hypothesis of the Shapiro-Wilk test was used as a reference in assessing if the data collected were normally distributed. A significance level of 0.05 was used as the threshold to determine whether to accept or reject the null hypothesis. The result of the Shapiro-Wilk test showed that the data provided on the above-mentioned parameters were not normally distributed hence, Spearman correlation was performed. The following were used to determine the correlation of GS and serum PSA with the SUVmax of the lesions: 0-0.10 (negligible correlation), 0.10-0.39 (weak correlation), 0.40-0.69 (moderate correlation), 0.70-0.89 (strong correlation), and 0.90-1.00 (very strong correlation). P values less than 0.05 were considered statistically significant.

RESULTS

Out of the 53 patients, 22 (41.51%) were referred for initial staging and 31 (58.49%) for restaging. The same 22 patients had not received any treatment at the time of the study. Among those who had undergone treatment, 5 had hormonal therapy only, 14 had radical prostatectomy only, 7 had radiotherapy only, and 5 had received two of the previous treatments. The mean age of all the patients was 68.72 years with an interquartile range (IQR) from 63 to 76 years old. The median serum PSA level of all patients is 11.90 ng/mL (IQR: 2.20 to 68.50 ng/mL), while the median GS is 7.00 (IQR: 6 to 8) (Table 1).

On one hand, the staging group had a median GS of 7 (IQR: 6.00 – 9.00), median serum PSA of 16.68 ng/ml (IQR: 10.10 – 51.83), median early dynamic imaging SUVmax of 5.3 (IQR: 4.75 $-$ 7.55) and median static imaging SUVmax of 25.6 (IQR: 22.43 – 43.20). On the other hand, the restaging group had a median GS of 7 (IQR: 6.00 – 8.00), median serum PSA of 6.21 ng/ml (IQR: 0.80 – 68.50), median early dynamic imaging SUVmax of 4.4 (IQR: 3.45 – 5.15) and median static imaging SUVmax of 11.0 (IQR: 5.80 – 26.05), respectively (Table 2).

It must be noted that although there were 53 patients, 5

patients had two lesions each, making a total of 58 lesions included in the analysis (Table 3).

Out of the 58 lesions in the sample, 48 (84.48%) were detected by both early dynamic and static imaging, 2 (3.45%) were detected by early dynamic imaging and not seen on static imaging, 1 lesion (1.72%) was not appreciated on early dynamic imaging but was observed on static imaging, while 7 lesions (12.07%) were not observed on both early dynamic and static imaging (Table 3). McNemar's test showed that there is no statistical difference in the detection rate of lesions on both early dynamic and static imaging.

From the staging group, 3 out of the 22 patients had two lesions each, with a total of 25 lesions. Out of the 25 lesions, 23 (92%) were detected by both early dynamic and static imaging, and 2 (8%) were detected by early dynamic imaging but were undetected by static imaging. In total, all of the lesions in the patients from the staging group were detected by early dynamic imaging (Table 4). McNemar's test shows no significant difference in the detection rate of both imaging.

Thirty-three lesions were included in the restaging group; of which, 25 (75.76%) were detected by both early dynamic and static imaging, 1 (3.03%) was detected by static imaging but undetected by early dynamic imaging, and 7 (21.21%) were undetected by both methods. In total, 25 out of the 33 (75.76%) lesions were detected by early dynamic imaging, which is slightly lower (78.79%) than the detection rate of static imaging (Table 5). McNemar's test shows that there is no significant difference in the detection rate of the two methods.

In the Shapiro-Wilk test, the GS, PSA, SUVmax of early dynamic imaging, and SUVmax of static imaging are not normally distributed (p = 0.0000).

Based on the results in Table 6, only the correlation between GS and SUVmax levels using static imaging for patients in the staging group is statistically significant. The correlation implies that there is a positive and moderate correlation between GS and levels of SUVmax for static imaging of patients in the staging group. The rest of the parameters for GS correlation are statistically insignificant (weak).

For the serum PSA (Table 6), only the correlation between the values of serum PSA and SUVmax in the restaging group of patients on early dynamic and static imaging, as well as in the staging group for the early

TABLE 1. Clinical profile and indication

 1 No PSA level data were obtained from four (4) patients.

 2 No Gleason Score data were obtained from nine (9) patients.

Profiles	Staging Group	Restaging Group
PSA level (ng/ml)		
Mean (± Standard Deviation)	$35.75 (\pm 36.73)$	52.60 (± 115.03)
Median	16.68	6.21
Interquartile Range	$10.10 - 51.83$	$0.80 - 68.50$
Gleason score		
Mean (± Standard Deviation)	$7.38 (\pm 1.24)$	$7.13 (\pm 1.66)$
Median	7.00	7.00
Interquartile Range	$6.00 - 9.00$	$6.00 - 8.00$
SUV level - Early Dynamic Imaging		
Mean (± Standard Deviation)	6.99 (\pm 4.08)	4.60 (± 1.52)
Median	5.30	4.40
Interquartile Range	$4.75 - 7.55$	$3.45 - 5.15$
SUV level - Static Imaging		
Mean (± Standard Deviation)	$36.51 (\pm 28.91)$	31.05 (\pm 87.33)
Median	25.60	11.00
Interquartile Range	$22.43 - 43.20$	$5.80 - 26.05$

TABLE 2. Gleason Scores, PSA Levels, and SUV Levels of patients per indication

TABLE 3. Number of lesions detected on early dynamic and static imaging using ¹⁸F-PSMA-1007 PET/CT scan in all patients

TABLE 4. Number of lesions in patients from the staging group detected on early dynamic and static imaging using ¹⁸F-PSMA-1007 PET/CT scan

TABLE 5. Number of lesions in patients from the restaging group detected on early dynamic and static imaging using 18F-PSMA-1007 PET/CT scan

dynamic imaging were statistically significant. The three correlation coefficients imply that there are positive and moderate correlations between the said variables.

DISCUSSION

 18 F-PSMA-1007 PET/CT is a new radiotracer used in diagnosing patients with prostate cancer [14, 15]. The recommended imaging time post-injection of the radiotracer is 40-90 minutes [15, 22, 23, 24, 25, 26]. Currently, there is no study on the use of early dynamic imaging using 18F-PSMA-1007 PET/CT in detecting PCa lesions. However, studies using 18F-Choline PET/CT in diagnosing PCa, showed that early dynamic acquisition in the pelvic region within 3-8 minutes post injection helped to distinguish avid lesion from the urinary bladder activity. The basis behind the use of early dynamic imaging is that cancer lesions show radiotracer accumulation before radiotracer buildup in the urinary

TABLE 6. Correlation between the Gleason Scores, PSA, and SUVmax values of all patients

¹ Correlation coefficients between | 0.00 | and | 0.10 | are interpreted as having negligible correlation, | 0.10 | and | 0.39 | as weak, | 0.40 | and | 0.69 | as moderate, | 0.70 | and | 0.89 | as strong, and | 0.90 | and | 1.00 | as very strong.

 2^{2} Criteria: sig-value > 0.05 Not Significant (Accept Null Hypothesis) sig-value < 0.05 Significant (Reject Null Hypothesis)

FIGURE 1. Axial cut of the ¹⁸F-PSMA-1007 PET/CT scan of a 55-year-old, male, for prostate cancer staging. (a) Two foci of increased tracer activity were noted in the prostate gland in the early dynamic imaging (orange arrows). (b) In comparison to static imaging, one of the lesions (lesion 1) was obscured by the radiotracer accumulation in the uribladder, which may obscure these lesions in the standard imaging at 60 minutes. In a similar study by Barakat et al., early imaging of Ga-68 PSMA PET/CT in 115 patients with PCa was examined. They acquired images at 3- and 60-minutes post-injection. In their study, 106 out of 115 lesions were detected on both early and static imaging; while 8 out of 115 lesions were only seen on early dynamic imaging. It showed a statistically significant increase in the detected rate from 64% using standard imaging to 68% when performing early imaging [28]. The author concluded that early images may help increase the detection rate of PSMAavid lesions, in the anterior transition zone of the prostate or anterior aspect of the prostate bed [28]. In contrast to this study, there is no statistically significant difference between the detection rate of PSMA-avid lesions in both the early dynamic and static imaging in all the patients. Although there is no significant difference, the detection of 2/58 lesions in the early dynamic imaging, which was not seen in the static imaging may imply that early dynamic imaging may still aid in assessing lesions in PCa. Upon review of the images, these lesions were located in the basal segment of the prostate gland which is near the urinary bladder neck (Figure 1). This also demonstrates that prostate to bladder ratio is higher in the early dynamic images than in the static-60-minute imaging, due to the lesser radiotracer activity in the bladder during the initial phase.

At present, the recommended methods to reduce radioactivity in the bladder include voiding before the scan or the administration of diuretics like furosemide to wash out accumulated radioactivity within the bladder. However, these approaches are time-consuming, do not sufficiently reduce bladder activity, and the use of diuretics is often avoided in patients with renal impairment [17]. The study of Perveen et al. demonstrated that even after administration of diuretics before imaging at 60 minutes post-injection, the bladder activity remained increased compared to the early imaging [29]. PSMA is a transmembrane glycoprotein overexpressed in prostate cancer cells and shows low expression in benign prostatic tissue, setting forth the rationale for using 18 F-PSMA-1007 PET/CT in detecting prostate cancer lesions [13, 14, 15, 16]. GS reflects the grade of differentiation of PCa and thus correlates with tumor aggressiveness [4]. While PSA is a serine protease enzyme produced by the columnar epithelium of the prostatic tissue which is used in screening and monitoring patients with PCa [5, 6, 7]. The most common parameter used to measure tracer accumulation in PET is the standardized uptake value

(SUV). It is a semi-quantitative measure of normalized radioactivity concentration in PET images. A SUVmax of 2.5 or higher than the background is generally considered to be indicative of malignant tissue [29, 30, 31, 32,33, 34]. Several studies using Ga68-PSMA and 18 F-PSMA-1007 PET/CT scans showed a statistically significant correlation between serum PSA and SUVmax in primary tumors [35, 36, 37, 38]. Therefore, as serum PSA levels increase, the SUVmax value also increases and thus results in a higher probability of detecting lesions in cases of prostate cancer. Reflected in this study, is the positive correlation between serum PSA levels and SUVmax values in all of the patients and restaging group patients. Patients who were referred for restaging following treatment had lower median serum PSA and SUVmax values compared to the group for initial staging. No significant correlation was observed between GS and SUVmax values in both early dynamic or static imaging when all patients were analyzed. A significant correlation was only seen among the initial staging group when stratified. In contrast to the current study, one conducted by Hong et al. showed a strong correlation between the SUVmax and GS values in PCa patients using ¹⁸F-PSMA-1007 PET/CT scan, wherein the value of SUV max was higher in $GS > 7$ [35]. In this study, there were only 17 patients with a GS > 7, which may relate to the lack of correlation due to the small number of patients with GS of 8 and 9.

Of the 58 lesions, only 1 lesion was detected in the static imaging alone which was not seen in the early dynamic imaging. This patient was under the restaging group and had already received hormonal treatment, with a serum PSA of 0.07 ng/ml. This lesion was not well delineated in the early dynamic imaging but was detectable in the static imaging with an SUVmax of 4.6. In this case, the low serum PSA and SUVmax measurements may reflect that the patient's therapy is effective. The detected lesion may not be seen in the early dynamic imaging probably because the lesion is not as metabolically active when compared to an untreated lesion, hence standard static imaging of 60 minutes may improve and enable lesion detection when a sufficient amount of radiotracer has accumulated and the SUV value may be determined.

Out of the 53 patients, 7 had no detectable lesion on both early dynamic and static imaging. These patients were referred for restaging, after receiving treatment. The majority of these patients had undergone prostatectomy and hormonal therapy. These negative findings may relate to favorable or effective treatment responses.

Limitations of this study:

The major limitation of this study is the small sample size and its retrospective nature. A prospective study in multiple institutions with a larger sample size is recommended to strengthen the findings of this research paper. Studies in assessing the sensitivity and specificity of 18 F-PSMA-1007 in the diagnosis of PCa, as well as in evaluating treatment response are likewise recommended. In addition, the correlation of GS, serum PSA, and SUVmax needs further evaluation.

CONCLUSION

Early dynamic imaging may serve as an adjunctive procedure for detecting PSMA-avid lesions; however, it is not recommended as a standard component of the overall imaging protocol with prostate cancer using ¹⁸F-PSMA-1007 PET/CT. It may be particularly useful for identifying lesions near the base of the prostate gland, in proximity to the urinary bladder.

Disclosure. The author declares no conflict of interest relevant to the conduct and authorship of this study.

Acknowledgment. The author expresses her utmost gratitude to Ms. Ma. Kristine Joy S. Calvario and Dr. Candice Genuino-Montaño for their guidance in the construction of the protocol up to the finalization of the manuscript.

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