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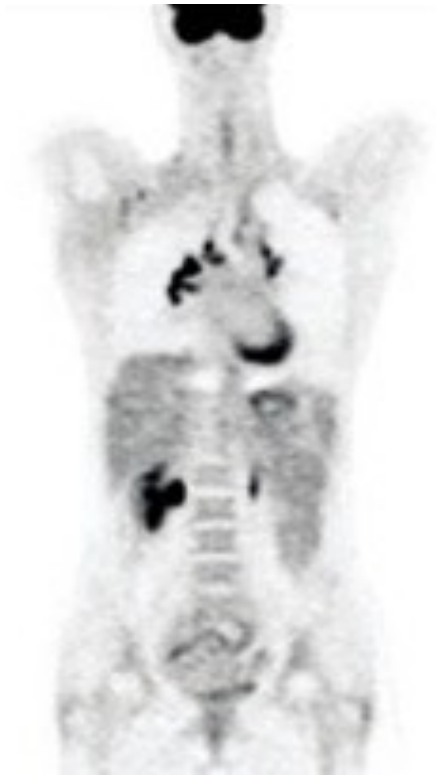

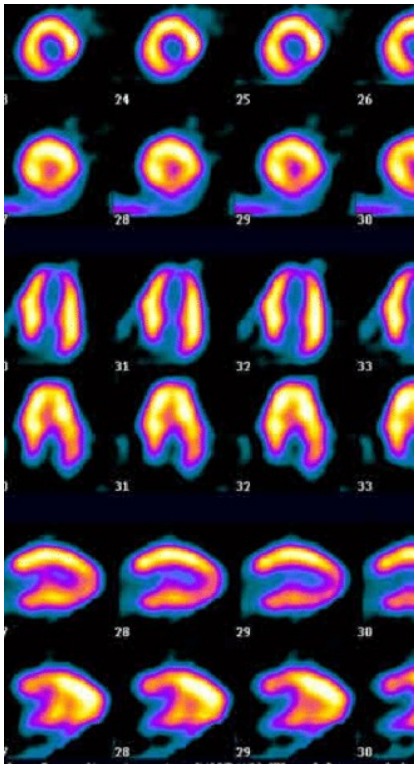

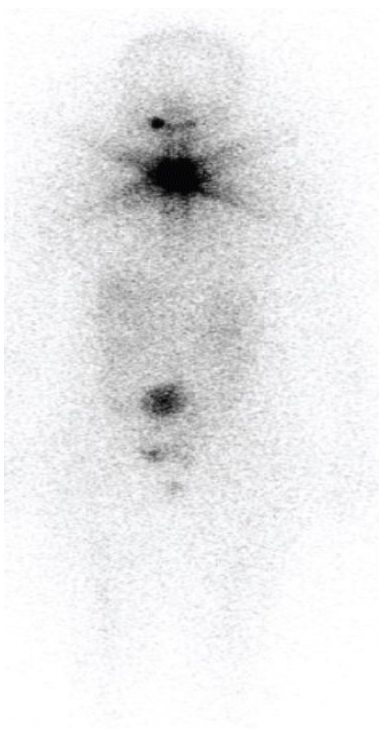

Contents:

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The Philippine Journal of Nuclear Medicine is a peer-reviewed journal published by the Philippine Society of Nuclear Medicine. Subscription is free to all PSNM members in good standing as part of their membership privileges.

The Journal will be primarily of interest to medical and paramedical personnel working in nuclear medicine and related fields. Original works in clinical nuclear medicine and allied disciplines in physics, dosimetry, radiation biology, computer science, radiopharmacy, and radiochemistry are welcome. Review articles are usually solicited and published together with related reviews. Case reports of outstanding interest are likewise welcome. PSNM documents and position papers of interest to the reader will also be published as necessary.

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The text of original scientific and technical articles is usually divided into the following sections: Introduction, Materials and Methods, Results, Discussion, and Summary or Conclusion.

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Generic names must be used throughout the text. Instruments and radiopharmaceuticals must be identified by manufacturer name and address in parentheses.

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Persons or agencies contributing substantially to the work, including any grant support, must be acknowledged.

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> Seabold JE, Conrad GR, Kimball DA, Ponto JA and Cricker JA. Pitfalls in establishing the diagnosis of deep venous thrombophlebitis by indium-111 platelet scintigraphy. J Nucl Med 1988;29:1169–1180.

For book and book chapters:

> Williams LJ. Evaluation of parathyroid function. In: Brock LJ, Stein JB, eds. The parathyroid and its diseases. 4th ed. New York: Wiley; 1985:196–248.
>
> Goodyear B. Bone marrow transplantation in severe combined immunodeficiency syndrome. In: Gree HJ, Blackscmith R, eds. Proceedings of the fourth biennial meeting of the International Society of Transplantation. Houston: International Society of Transplantation; 174: 44–46.

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PASSION FOR PRECISION

Comparison of the treatment outcomes: percent change in the sum of longest diameters (RECIST) and percent change of the lesion with the highest SUL (PERCIST) between standard therapy plus Lu-177 PSMA ligand therapy and standard therapy alone among patients with prostatic cancer status-post castration using Ga-18 PET-CT as an outcome indicator

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ABSTRACT

Introduction:

Prostate cancer is the third most common cancer among Filipino males. Ga-68 PSMA PET-CT and Lu-177 PRLT have been introduced in the Philippines for the diagnostics and therapy of prostate cancer.

Objective:

The aim of this study is to compare treatment outcomes of standard therapy plus Lu-177 PSMA radioligand therapy and standard therapy alone among patients with prostatic cancer status-post castration using Ga-68 PET-CT as an outcome indicator.

Methodology:

This is an ambispective cohort study on Ga-68 PSMA PET-CT scans performed between January 1, 2018 and July 31, 2021. Serum PSA data taken within one month of the PET-CT scans were also collected when available. The PET-CT images were reviewed by a radiologist for RECIST response, and by a nuclear medicine physician for PERCIST response .

Results:

A total of 11 participants were included in the study. Six participants (55.5%) received standard therapy, while five participants (45.5%) received Lu-177 PSMA radioligand therapy plus standard therapy. There was no significant difference in the baseline and follow-up CT as shown by all p values > 0.05. A trend towards higher number of participants with non-complete/non-progressive RECIST response was noted in the control group than the treatment group, as well as higher number of participants with progressive or stable disease using the PERCIST response.

Conclusion:

There were no significant differences noted in the clinical outcomes of participants who received Lu-177 PRLT and those with standard therapy alone. A trend towards decreasing serum PSA, CT and PET measurements were noted among patients given Lu-177 PRLT than those with standard therapy.

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

INTRODUCTION

Prostate cancer is the third most common cancer among Filipino males when non-melanoma skin cancer is excluded [1]. Prostate cancer in Filipinos occurs mainly in the elderly with the average age of 64 years old at the time of diagnosis. It typically presents with more adverse pathological features if compared to prostate cancer seen in American populations [2].

Various prognostic factors must be considered in the management of prostate cancer. Radical prostatectomy and radiotherapy are typically used for definitive treatment with curative intent. However, castration – achieved either through surgery (bilateral orchiectomy) or hormonal therapy – is also considered as part of the standard treatment options offered for Stage II to IV disease [3]. On the other hand, progressive disease with poor castration response is conventionally managed using a variety of treatment modalities such as systemic chemotherapy, immunotherapy and palliative radiotherapy, among others [4].

Prostate cancer follow-up involves biochemical recurrence monitoring through serum prostate-specific antigen (PSA) levels, and radiologic recurrence monitoring using imaging modalities such as multiparametric MRI [5]. In recent years, given the conventional imaging limitations, there has been an emerging role for Gallium-68 (Ga-68) prostate-specific membrane antigen (PSMA) positron emission tomography-computed tomography (PET-CT) for disease monitoring, particularly to check for metastasis, and treatment response evaluation [6]. Imaging entails using a small biomolecule that binds to the transmembrane protein PSMA – which is overexpressed in prostate cancer tissues [7].

Likewise, Ga-68 PSMA PET-CT may be used to determine novel therapy eligibility using beta-emitting radionuclides such as Lutetium-177 (Lu-177). The Lu-177 PSMA radioligand therapy (PRLT) delivers targeted radiation to PSMA-overexpressed prostate cancer lesions [8]. A large, German multicenter study involving advanced prostate cancer patients who received Lu-177 PRLT showed that 45% of patients demonstrated a biochemical decline of at least 50% in their PSA, while a PSA decline of any amount was observed in 60% of patients [9]. The same study showed significant hematologic toxicity in approximately 12% of participants, thus, due caution must be exercised between cycles especially when considering dose escalation [10]. Similar efficacy of PRLT was noted in a smaller Iranian prospective study with no incidence of hematologic toxicity observed [11]. More recently, the international, open-label, phase 3 VISION trial [12] demonstrated that the addition of Lu-177 PRLT to standard therapy not only yielded significant biochemical response identical to the aforementioned studies, but also significantly prolonged imaging-based progression-free survival and overall survival in advanced metastatic castration-resistant prostate cancer patients. The VISION trial relied on Ga-68 PSMA PET-CT scans for the initial participant assessment and Lu-177 PRLT eligibility determination. However, follow-up imaging was mainly done through CT, MRI, and bone scintigraphy. Radiologic response was measured using Response Evaluation Criteria in Solid Tumors (RECIST) relying mainly on morphologic changes between scans [13]. Over the years, other systems for evaluating response have also been established, including the PET Response Criteria in Solid Tumors (PERCIST) [14] which depends molecular activity changes. PERCIST has been found to perform better than morphologic criteria for Ga-68 PSMA PET-CT response evaluation [15].

In recent years, Ga-68 PSMA PET-CT and Lu-177 PRLT have been introduced in the Philippines for the diagnostics and therapy of prostate cancer, respectively [16]. To date, there are no published studies that demonstrate the outcomes of PRLT in local settings.

Significance and Rationale of the Study

Prostate cancer is one of the more common cancers affecting elderly Filipino males. There are limited therapeutic options for those who have undergone castration but still demonstrate progressive disease. Lu-177 PRLT is emerging as a promising treatment for patients who have poor response to standard therapy. The findings of this study will provide local treatment outcomes for Lu-177 PRLT in the Philippines and may aid clinicians in the overall management of prostate cancer.

OBJECTIVES

General Objective

To compare treatment outcomes of standard therapy plus Lu-177 PSMA radioligand therapy and standard therapy alone among patients with prostatic cancer status-post castration using Ga-68 PET-CT as an outcome indicator.

Specific Objectives

- To compare the clinical profile of patients with prostatic cancer status-post castration who had

standard therapy plus Lu-177 PRLT versus those who underwent standard treatment alone

- To compare the levels of PSA (baseline and follow up) among patients with standard therapy plus Lu-177 PRLT versus those who underwent standard treatment alone
- To compare the CT and PET measurements (baseline and follow up) among patients with standard therapy plus Lu-177 PRLT versus those who underwent standard treatment alone
- To determine frequency of RECIST responses based on CT and frequency of PERCIST responses based on PET among patients with standard therapy plus Lu-177 PSMA radioligand therapy versus those who underwent standard treatment alone

METHODOLOGY

Type of Study, Time and Period, Setting and Study Population

This is an ambispective cohort study on the treatment outcomes of standard therapy plus Lu-177 PSMA radioligand therapy and standard therapy alone among patients with prostate cancer status post castration who underwent Ga-68 PET-CT between January 1, 2018 and July 31, 2021 at St. Luke's Medical Center-Quezon City.

Inclusion Criteria

- Patient was previously diagnosed with prostatic cancer.
- Patient must have baseline and follow-up PET-CT scan at SLMC-QC.
- Patient must have follow-up PET-CT scan within 6 months to 1 year post treatment.

Exclusion Criteria

Patient did not undergo chemical or surgical castration

Study Maneuver

All PET CT scans of patients with prostate cancer with castration history between January 1, 2018 and July 31, 2021 were reviewed for study inclusion. All baseline and follow-up PET-CT scans of eligible patients were anonymized for both the nuclear medicine physician and radiologist. They were also blinded to the treatment given to the patient.

Ga-68 PSMA PET-CT Scan Protocol

Initial emission imaging of the pelvis was done 50 minutes after intravenous injection of Ga-68 PSMA, followed by subsequent whole-body emission images using a PET-CT scanner 60 minutes after Ga-68 PSMA administration. Furosemide 20 mg was given intravenously shortly after tracer injection. CT contrast was also given when applicable.

Evaluation of Imaging and Biochemical Response

Imaging Evaluation

All baseline and follow up PET-CT studies were anonymized and were reviewed independently by the radiologist and nuclear medicine physician. Any discrepancy in the findings were resolved by consensus agreement of the readers. The radiologist evaluated the CT images using RECIST (see Appendix A) while the nuclear medicine physician evaluated the PET images using PERCIST (see Appendix B).

Biochemical Evaluation

Serum PSA done within a month from the time of the scan

Data Collection

The following data of eligible participants were collected through Healthcare, Carestream and Medical Records:

1. Age
2. Date of surgery or biopsy
3. Date of starting treatment and type of treatment
4. Baseline and follow-up PSA
5. Baseline and follow-up PET-CT

Outcome Measures

A. Dependent variables:

a) Based on RECIST:
- i) Percent change in sum of longest diameters
- ii) Presence of new lesions
- iii) Frequency and proportion of:
  1. Complete Response
  2. Partial Response
  3. Stable Disease
  4. Progressive Disease

b) Based on PERCIST:
- i) Percent change in highest SUL
- ii) Presence of new PSMA-avid lesions
- iii) Frequency and proportion of:
  1. Complete Response
  2. Partial Response
  3. Stable Disease
  4. Progressive Disease

B. **Independent variables:**
   a) Age
   b) Time to starting treatment
   c) Type of treatment
   d) PSA level

Statistical Analysis

Descriptive statistics were used to summarize the demographic characteristics as well as clinical outcomes of the patients. Frequency and proportion were used for nominal variables, as well as mean and SD for interval/ ratio variables. Non-parametric tests such as Mann Whitney U test, Wilcoxon Signed rank test and Chi-square test were used to analyze data. SPSS version 23 for Windows was used in the data analysis. The missing values will neither be replaced nor estimated. Null hypotheses will be rejected at 0.05α-level of significance .

RESULTS

A total of 11 participants were deemed as eligible participants in the study. Six participants (55.5%) were classified into the control arm, having received standard therapy, while five participants (45.5%) were classified into the interventional arm consisting of Lu-177 PSMA radioligand therapy plus standard therapy.

The mean age of participants in the control arm was 70.67 years, while the mean age in the interventional arm was 63.40 years. There was no significant difference in the age as shown by all p values > 0.05 (see Table 1.). From initial tissue diagnosis of prostate carcinoma, the time to starting therapy in those who received standard therapy was 7.7 years, while the time to starting therapy in those who received Lu-177 PSMA radioligand therapy on top of standard therapy was 5.0 years. There appears to be greater range for participants in the control arm compared to those in the interventional arm.

Not all eligible participants had documented records of serum PSA at the time of the initial and follow-up PET-CT scans. In the control arm, only three out of six (50%) participants have their initial serum PSA on record with a mean cut-off of 3.80 ng/mL, and only 2 (33%) have follow-up serum PSA with a mean cut-off of 32.26 ng/mL. On the other hand, in the interventional arm, five out of the five (100%) participants have their initial serum PSA with a mean cut-off of 451.52 ng/mL, but only 4 (80%) participants have their follow-up serum PSA, yielding 137.20 ng/mL. It must be noted, however, that there is a substantial collected data range in both groups, particularly in the interventional arm. In terms of serum PSA change, there appears to be a greater average serum PSA percentage increase among the proportion of patients in the control arm (459.22%) compared to the interventional arm (10.16%).

Table 2 shows the comparison of baseline and follow-up serum PSA between the two groups. There was no significant difference in the baseline and follow-up serum PSA as shown by all p values > 0.05. Similarly, in each group, there were no significant differences in the serum PSA measurements (p > 0.05). However, a trend towards decreasing PSA was noted in the Lu-177 PRLT than the standard therapy group.

Table 3 shows the comparison of baseline and follow-up CT between the two groups. There was no significant difference in the baseline and follow-up CT as shown by all p values > 0.05. Similarly, in each group, there were no significant differences in the CT measurements (p > 0.05). However, a trend towards decreasing CT measurement was noted in the Lu-177 PRLT than the standard therapy group.

Table 4 shows the comparison of baseline and follow-up PET between the two groups. There was no significant difference in the baseline and follow-up CT as shown by all p values > 0.05. Similarly, in each group, there were no

TABLE 1. Comparison of the demographic profile of patients between the standard therapy group and Lu-177 + standard therapy group

	Standard Therapy (n=6)	**Lu-177 PSMA + Standard Therapy** (n=5)	**p-value**
	Mean ± SD; Frequency (%)		
Age (in years)	70.67 ± 11.57	63.40 ± 4.04	0.20 (NS) †

** p>0.05- Not significant; p ≤0.05-Significant*
† Mann Whitney U -test

TABLE 2. Comparison of the baseline and follow-up serum PSA between standard therapy group and Lu-177 + standard therapy group

	Standard Therapy (n = 3)	**Lu-177 PRLT Group** (n = 5)	**p-value**
	Mean ± SD		
Baseline serum PSA (ng/mL)	3.80 ± 3.37	451.52 ± 716.92	0.24 (NS) †
Follow-up serum PSA (ng/mL)	32.26 ± 36.97	137.20 ± 186.84	0.35 (NS) †
p-value	0.22 (NS) §	0.28 (NS) §	---

** p>0.05- Not significant; p ≤0.05-Significant*
† Mann Whitney U -test; §Wilcoxon Signed test

TABLE 3. Comparison of the baseline and follow-up CT measurement (percent change in sum of longest diameters) using RECIST criteria between standard therapy group and Lu-177 + standard therapy group

	Standard Therapy (n = 6)	**Lu-177 PRLT Group** (n = 5)	**p-value**
	Mean ± SD		
Baseline CT Measurement	2.42 ± 2.26	8.95 ± 12.14	0.36 (NS) †
Follow-up CT Measurement	3.58 ± 4.21	5.52 ± 6.12	0.60 (NS) †
p-value	0.22 (NS) §	0.28 (NS) §	---

** p>0.05- Not significant; p ≤0.05-Significant*
† Mann Whitney U -test; §Wilcoxon Signed test

significant differences in the CT measurements (p > 0.05). However, a trend towards decreasing PET measurement was noted in the Lu-177 PRLT than the standard therapy group.

Table 5 and 6 shows the comparison of RECIST and PERCIST response between the two groups. There were no significant differences noted as shown by all p values > 0.05. However, it can be seen that a trend towards higher number of patients with non-complete/non-progressive RECIST response was noted in the control group than the treatment group, as well as higher number of patients with progressive or stable disease using the PERCIST response.

Using the RECIST response on the Ga-68 PSMA PET-CT scans, participants in the control arm on average showed a 10% increase in the sum of longest diameters of the measurable target lesions. For the frequency of overall RECIST response among participants in the control arm, the following were noted: 1 PD, 1 SD, 1 PR, 2 non-CR / non-PD, and 1 unevaluable. On the other hand, in the interventional arm, there is a mean increase of 59% in the sum of longest diameters of the measurable target lesions. Overall RECIST response in the interventional arm were as follows: 3 PD, 1 PR, and 1 unevaluable.

Meanwhile, using PERCIST on the Ga-68 PSMA PET-CT scans, participants in the control arm showed a mean change of 36% in the highest SUL. For the overall PERCIST response in the control arm, there was 4 PD and 2 SD. On the other hand, in the interventional arm, there is a mean change of -30% in the highest SUL with overall PERCIST response in the interventional showing 3 PD and 2 PR.

DISCUSSION

From the 11 eligible participants, it was observed that the study mainly involves older males above 60 years old. This is consistent with the demographics that are typically diagnosed with prostate cancer [2]. Moreover, the data showed that the time to starting therapy from

TABLE 4. Comparison of the baseline and follow-up PET measurement (percent change of the lesion with the highest SUL) using the PERCIST criteria between the standard therapy group and Lu-177 + standard therapy group.

	Standard Therapy (n = 6)	**Lu-177 PRLT Group** (n = 5)	**p-value**
	Mean ± SD		
Baseline PET Measurement	16.48 ± 10.41	16.04 ± 6.43	0.93 (NS) †
Follow-up PET Measurement	24.50 ± 16.30	14.84 ± 5.51	0.20 (NS) †
p-value	0.22 (NS) §	0.68 (NS) §	---

** p>0.05- Not significant; p ≤0.05-Significant*
† Mann Whitney U -test; §Wilcoxon Signed test

TABLE 5. RECIST response based on Ga-68 PSMA PET-CT

	Standard Therapy	**Lu-177 PSMA + Standard Therapy**	**p-value**
Overall RECIST Response			
Progressive Disease (PD)	1 (16.7%)	3 (60.0%)	0.41 (NS) ‡
Stable Disease (SD)	1 (16.7%)	0	
Partial Response (PR)	1 (16.7%)	1 (20.0%)	
Complete Response (CR)	0		
Non-CR / Non-PD	2 (33.3%)	0	
Unevaluable	1 (16.7%)	1 (20.0%)	

** p>0.05- Not significant (NS); p ≤0.05-Significant (S)*
‡ Chi-square test

TABLE 6. PERCIST response based on Ga-68 PSMA PET-CT

	Standard Therapy	**Lu-177 PSMA + Standard Therapy**	**p-value**
Overall PERCIST Response			
Progressive Disease (PD)	4 (66.7%)	3 (60.0%)	0.13 (NS) ‡
Stable Disease (SD)	2 (33.3%)	0	
Partial Response (PR)	0	2 (40.0%)	
Complete Response (CR)	0	0	

** p>0.05- Not significant (NS); p ≤0.05-Significant (S)*
‡ Chi-square test

the initial tissue diagnosis took more than 5 years. This may be reflective of the more conservative approach of watchful observation during the early stages of prostate cancer, and the more aggressive treatment modalities only being pursued later in the course of the disease [3].

Serum PSA plays a crucial role in the monitoring and response assessment for prostate cancer. The nature of the present study limited the collection of biochemical data from available records. It must also be noted that both baseline and follow-up serum PSA were obtained in close temporal relation to the Ga-68 PSMA PET-CT scans rather than to each arm's therapies. Data from clinical trials [9,11,12] reported that substantial serum PSA reduction was seen in Lu-177 PSMA radioligand therapy-treated prostate cancer patients. In particular, the recently concluded VISION trial showed greater serum PSA reduction when Lu-177 PSMA radioligand therapy was added to standard therapy [12]. Such dramatic reductions in serum PSA were not observed in the present study likely due to the gathered data's limitations. Also, the present study showed that the

proportion of participants in the interventional arm appear to have higher mean serum PSA cut-off compared to those in the control arm. This is consistent with the notion that Lu-177 PSMA radioligand therapy is typically used for more advanced prostate cancer. Although serum PSA increased in both arms of the study, the control arm appeared to have greater mean percentage increase on follow-up compared to the interventional arm. This may suggest that the addition of Lu-177 PSMA radioligand therapy to standard therapy stalls biochemical progression better than standard therapy alone. However, no statistical difference can be inferred from the present data.

Apart from biochemical markers, imaging plays a major role in response assessment for prostate cancer. Radiologic response assessment in the VISION trial [12] used RECIST in objective radiologic response determination, primarily through follow-up CT, MRI and radionuclide bone scans. In contrast, the present study evaluated the role of Ga-68 PSMA PET-CT in determining treatment response. Given the trove of information being provided by hybrid imaging, using both RECIST and PERCIST allowed for post-treatment evaluation of both morphologic and molecular response. It must be noted that using both criteria, progressive disease was the most common response seen in the participants of both arms of the study. Based on the RECIST, more cases of progressive disease were detected in the interventional arm. This may be interpreted as either reflective of poor treatment response after Lu-177 PSMA radioligand therapy, or simply secondary to overall more aggressive disease among participants who received Lu-177 PSMA radioligand therapy. It must be emphasized, however, that the inherent limitations of RECIST – particularly concerning osseous lesions – may affect overall response assessment in some participants. A closer look at individual data revealed that most of the cases in the control arm involved non-measurable RECIST lesions. In contrast, when PERCIST was utilized, there were more participants with progressive disease in the control arm than in the interventional arm. Apparent concordance in PERCIST and biochemical response can be observed in the two study groups with more aggressive progression seen in those who received standard therapy alone. Although RECIST has long been established in response assessment, Gupta and colleagues [15] reported the superiority of PERCIST in treatment response assessment for Ga-68 PSMA PET-CT. Albeit there were no significant difference in both treatment arms using both RECIST and PERCIST, the concomitant use of both criteria in response evaluation may nevertheless help clinicians evaluate treatment response in prostate cancer patients whenever hybrid imaging in the form Ga-68 PSMA PET-CT is available.

The first limitation of this study was small sample size within the study period of 43 months. Second, the PSA levels of three participants on the standard treatment was done in another institution. Third, the study setting was done in a private tertiary hospital with high cost of PRLT and PET/CT study.

We recommend collaborative local study with larger populations to compare for the biochemical and radiologic outcomes between standard therapy and standard therapy plus Lu-177 PRLT among castrate-resistant prostate cancer. Both RECIST and PERCIST should be utilized when evaluating radiologic response in Ga-68 PSMA PET-CT, and serum PSA should likewise be monitored for biochemical response assessment.

CONCLUSION

There were no significant differences noted in the demographic characteristics as well as the clinical outcomes of patients who received Lu-177 PRLT and those with standard therapy alone. However, using PERCIST for the evaluation of Ga-68 PET-CT, there was a greater proportion of participants with progressive disease in those who received standard therapy alone compared to those who received Lu-177 PRLT with standard therapy. The inverse was true when using RECIST with more patients demonstrating progressive disease after the addition of Lu-177 PRLT to standard therapy. In line with the PERCIST findings, greater serum PSA progression was observed in the proportion of patients who were only given standard therapy. Also, a trend towards decreasing serum PSA, CT and PET measurements were noted among patients given Lu-177 PRLT than those with standard therapy.

Disclosure

The authors have no conflicts of interest to declare.

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APPENDIX A. RECIST

Minimum size of measurable lesion	CT: 10 mm
Lymph node	CT: ≥ 15mm short axis (target lesion) ≥ 10 - < 15 mm for (non-target lesion) < 10mm is not pathological
Overall tumor burden	5 lesions (2 per organ)
Response criteria for target lesion	
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis diameter to < 10mm.
Partial response (PR)	At least 30% decrease in the sum of diameters of the target lesions, taking as reference the baseline sum diameters
Progressive disease (PD)	At least 20% increase in the sum of diameters of the target lesions, taking as reference the smallest sum of the study (this includes the baseline sum if that is the smallest). In addition to relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions is also considered progression.
Stable disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking into reference the smallest sum of diameters while on study.
Response criteria for non-target lesion	
Complete response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathologic in size (<10mm)
Non-complete response (Non-CR) / Non-progressive disease (Non-PD)	Persistence of one or more non-target lesion(s) and/ or maintenance of tumor marker level above the normal limits.
Progressive disease (PD)	Unequivocal progression of existing lesions or the appearance of the one or more new lesions

APPENDIX B. PERCIST

Quantitative parameter (SUL)	SUV-peak, normalized to lean body mass (SUL)
Progressive metabolic disease	Any of the following: - SUL increase by at least 30% and increase in by at least 0.8 SUL units of target lesion - Development of at least one new lesion - Increase in target lesion size by 30% - Unequivocal progression of target lesion
Stable metabolic disease	Increase or decrease of SUL by less than 30%
Partial metabolic response	All the following: - Decrease of SUL by >=30% and at least 0.8 SUL units difference - No new PSMA-avid lesions - No increase in size >30% of the target lesion - No increase in SUL or size of non-target lesion
Complete metabolic response	All the following: - PSMA uptake indistinguishable from surrounding background - SUL less than liver

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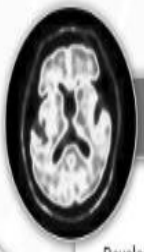

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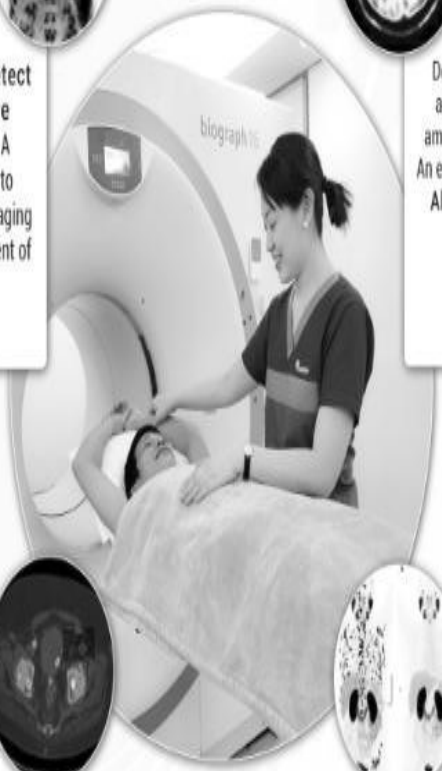

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Association of Hemodynamic Changes with the Scan Parameters of a Dipyridamole-induced Stress Myocardial Perfusion Scintigraphy with Technetium-99m Sestamibi in Patients with Suspected Coronary Artery Disease

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ABSTRACT

Introduction:

A dipyridamole induced stress myocardial perfusion scintigraphy with Tc-99m Sestamibi is utilized for diagnosing coronary artery diseases. The use of dipyridamole as form of pharmacologic stressor has expected hemodynamic changes.

Objective:

The objective of this study was to determine the association of these changes with the scan parameters in patients with suspected coronary artery disease (CAD).

Methodology:

A total of 101 patients, with suspected CAD, who underwent a dipyridamole-induced stress myocardial perfusion scintigraphy using Tc-99m Sestamibi from January 2019 to March 2020 were included in this study. The patient databases, monitoring sheets, and scan results were reviewed .

Results:

The blood pressure responses had no significant association with the scan parameters and results. The normal (> 1.2) and abnormal (<1.2) heart rate ratios (HRR), which is the peak HR/baseline HR, likewise had no significant association with the scan results. However, in terms of the median HRR, the higher ratio of 1.29 (normal scan results) against the ratio of 1.25 (abnormal scan results) was determined to be significant (p-value of 0.032). The HRR also had a direct and indirect weak correlation with stress and rest Left Ventricular Ejection Fraction (LVEF) values (p-values of 0.09 and 0.011) and Summed Rest Score (p-value of 0.007), respectively. For the 12-L ECG, only the baseline normal (P-value of 0.018) and infarct findings (p-value of 0.017) were similarly associated with normal and abnormal scan results, respectively.

Conclusion:

For patients with suspected CAD, the higher HRRs and baseline 12-L ECG of normal and infarct findings relates to the expected scan result. For scan parameters, the higher HRRs were also correlated with higher stress and rest LVEF values, and normal SRS, albeit a weak correlation. Notably, the blood pressure and post-infusion 12-L ECG changes had no significant association. In summary, the higher HRRs indicates normal scan results, normal SRS, and better LVEF values which increases the diagnostic confidence in the interpretation and management, especially in some equivocal cases.

Keywords: *dipyridamole, hemodynamic changes, myocardial perfusion scintigraphy*

INTRODUCTION

Coronary artery disease is chronic condition that affects the morbidity and quality of life and is the third leading cause of cardiovascular disease in the Philippines [1]. Therefore, a myocardial perfusion scintigraphy is used in determining the adequacy of blood flow to the myocardium. To increase its sensitivity, a form of stress is used which may be through exercise, or a pharmacologic stress agent. A vasodilator stress agent such as Dipyridamole produces indirect coronary dilation with a concomitant systemic vasodilatory effect wherein there is a decrease in blood pressure and reflex tachycardia [2]. These hemodynamic changes may provide useful information in imaging abnormalities in coronary artery disease.

It has been well documented that the intravenous use of dipyridamole produces mild hemodynamic changes with a near peak effect at 3 minutes from its infusion with side effects of hypotension, headache, dizziness, and dyspnea [3]. These side effects have demonstrated a correlation with hemodynamic variables but did not affect the imaging or ECG findings [4]. A blunted heart rate response to Dipyridamole infusion was associated with an LVEF of less than 45% and was also an independent predictor of an elevated summed stress scores (SSS), higher resting heart rate, and lower HDL levels [2, 5].

However, several studies have noted that the clinical significance of these hemodynamic responses is currently debatable [6]. An abnormal HRR and systolic blood pressure response may suggest an inadequate patient response to dipyridamole infusion. The aim of this study was to determine the association of hemodynamic changes with the scan parameters of a dipyridamole-induced stress myocardial perfusion scintigraphy with Technetium-99m Sestamibi in patients with suspected CAD.

Methodology

This is a retrospective cross-sectional study that included 101 adult patients referred to the Division of Nuclear Medicine, Philippine Heart Center for a dipyridamole-induced stress myocardial perfusion scintigraphy with Tc-99m Sestamibi for the assessment of suspected coronary artery disease between January 2019 and March 2020. Patients with an incomplete information sheet, database, or images were excluded.

The patients included must have strictly followed the Standard Operating Procedure (SOP-M-AMS-NMD-023) for a dipyridamole-induced stress myocardial perfusion scintigraphy with Tc-99m Sestamibi of this institution. The data compiled was then checked for any inconsistencies/errors to the procedure.

The patients' data were obtained from their information sheet, databases, monitoring sheets, and official scan results. These included the following: demographic data, clinical history, blood pressure and heart rate readings, electrocardiographs, and scan results. The pertinent data were entered into the prepared collection forms/ spreadsheets for statistical analysis.

The patients were then categorized based on their recorded blood pressures and heart rates as normal or abnormal. A normal systolic blood pressure (SBP) response was defined as a reduction of more than or equal to 10 mmHg from the baseline and a normal heart rate response was based on the heart rate ratio (peak HR/baseline HR) of more than 1.2. An abnormal hemodynamic response was less than 10 mmHg from the baseline for SBP and less than or equal to 1.2 for the heart rate ratio (HRR) [7]. Other variables considered were the ECG findings before and after dipyridamole infusion, time when the hemodynamic change was noted, and side effects.

Dependent variables are the scan findings of perfusion defects interpreted as reversible (ischemia) or fixed (infarct/fibrosis) – which were noted in the official reports. The widely adopted American College of Cardiology/American Heart Association (ACC/AHA) 17 segment polar map of the left ventricle with a five-point score scale was used for the summed stress score (SSS), summed rest score (SRS), and the summed difference score (SDS). The left ventricle ejection fraction values (LVEF) at stress and rest were also included. The scan results were likewise determined as either having normal or abnormal as indicated in the official reports. Normal scans were defined by the absence of any defect as seen in the final interpretation of the scan report and any finding that indicates otherwise were noted as abnormal.

Sample Size Calculation

With the G*Power 3.1.9.2, a minimum of 89 patients were needed for this study based on the average heart rate before (82) and after (92) the Dipyridamole test, common standard deviation of 10, 5% level of significance and 90% power.

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical data of the patients. Frequency and proportion were then used for the categorical variables, median and inter quartile range for non-normally distributed continuous variables and mean and SD for normally distributed continuous variables. Independent Sample T-test, Mann-Whitney U, and Fisher's Exact/Chi-square test were used to determine the difference of mean, rank and frequency, respectively, between patients with normal versus abnormal result. Paired sample T-test was used to compare blood pressure and heart rate at baseline and after dipyridamole infusion. Spearman correlation analysis was used to determine the correlation of difference from baseline SBP and HRR to both the myocardial perfusion scores and LVEF values. Chi-square test for association was undertaken to establish the association of Myocardial Perfusion Score category and LVEF to Baseline ECG findings. Shapiro-Wilk was then used to test the normality of the other continuous variables. Missing variables were neither replaced nor approximated. Null hypotheses were rejected at 0.05 α- level of significance. STATA 13.1 was used for the entire data analysis.

RESULTS

In all, a total of 101 patients were included in this study with their demographic profile and test as seen in Table 1. There was a significant difference for the older age (p-value of 0.018) and female sex (p-value of 0.006) with the normal scan results.

A significant difference for patients with abnormal results was noted for those with chronic kidney disease (3.96%). Most of the patients were hypertensive (83.17%). Other demographic and procedural data such as the anthropometrics, administered activities (mCi), dipyridamole infused (0.56 mg/Kg), other comorbidities, and symptoms before infusion showed no significant difference.

TABLE 1. Demographic profile and procedural data of the patients

	Scan result			**P-value**
	Total (n = 101)	**Abnormal (n = 33)**	**Normal (n = 68)**	
	Frequency (%); Mean ± SD; Median (IQR)			
Age (years)	61.02 ± 14.4	56.18 ± 16.03	63.37 ± 13.02	**0.018**
Sex				**0.006**
Male	50 (49.5)	23 (69.7)	27 (39.71)	
Female	51 (50.5)	10 (30.3)	41 (60.29)	
Weight (kg)	67.15 ± 15.89	68.35 ± 16.79	66.57 ± 15.53	0.600
Height (cm)	159.40 ± 9.26	161.24 ± 8.68	158.5 ± 9.46	0.164
Administered Activity				
Rest (mCi)	327 (310 to 355)	326 (303 to 350)	328 (313 to 359)	0.304
Stress (mCi)	834 (815 to 870)	825 (808 to 857)	841 (818 to 873)	0.182
Dipyridamole (mg)	36.4 (31.8 to 44.3)	36.4 (32.4 to 43.7)	36.95 (31 to 44.5)	0.688
Comorbidities				
Hypertension	84 (83.17)	29 (87.88)	55 (80.88)	0.572
Dyslipidemia	44 (43.56)	13 (39.39)	31 (45.59)	0.670
Diabetes Mellitus	33 (32.67)	12 (36.36)	21 (30.88)	0.653
Smoker	7 (6.93)	3 (9.09)	4 (5.88)	0.680
ESRD	4 (3.96)	3 (9.09)	1 (1.47)	0.101
CKD	4 (3.96)	4 (12.12)	0	**0.010**
Symptoms before infusion				
Easy fatigability	24 (23.76)	8 (24.24)	16 (23.53)	1.000
Exertional dyspnea/DOB	23 (22.77)	11 (33.33)	12 (17.65)	0.127
Asymptomatic	17 (16.83)	4 (12.12)	13 (19.12)	0.572

TABLE 2. Blood pressure and heart rate before and after dipyridamole infusion

	Before	After	P-value
	Mean ± SD		
All patients			
SBP	137.62 ± 19.19	119.80 ± 21.4	**<0.001**
DBP	83.26 ± 10.4	70.3 ± 12.37	**<0.001**
Heart rate	69.89 ± 12.64	89.92 ± 13.47	**<0.001**
Patients with Abnormal scan results			
SBP	136.91 ± 19.1	120.15 ± 19.2	**<0.001**
DBP	81.31 ± 9.43	69.56 ± 11.12	**<0.001**
Heart rate	71.06 ± 13.82	87.42 ± 13	**<0.001**
Patients with Normal scan results			
SBP	139.09 ± 19.58	119.09 ± 25.66	**<0.001**
DBP	87.27 ± 11.26	71.81 ± 14.67	**<0.001**
Heart rate	69.32 ± 12.09	91.13 ± 13.62	**<0.001**

TABLE 3. Hemodynamic changes in dipyridamole-induced stress

	Scan result			P-value
	Total (n = 101)	Abnormal (n = 33)	Normal (n = 68)	
	Frequency (%); Median (IQR)			
SBP decrease	20 (30 to 10)	20 (30 to 10)	20 (30 to 10)	0.366
Normal SBP decrease (≥10 mm Hg)	79 (78.22)	27 (81.82)	52 (76.47)	0.615
Abnormal SBP decrease (< 10 mm Hg)	22 (21.78)	6 (18.18)	16 (23.53)	
HR Ratio (HRR)	1.28 (1.2 to 1.42)	1.25 (1.1 to 1.33)	1.29 (1.2 to 1.4)	**0.032**
Normal (> 1.2)	66 (65.35)	18 (54.55)	58 (70.59)	0.124
Abnormal (≤1.2)	35 (34.65)	15 (45.45)	20 (29.41)	

The blood pressure and heart rate before and after dipyridamole infusion (Table 2) were statistically significant. This was also seen for both the normal and abnormal scan results (p value of < 0.001).

For the hemodynamic changes in a dipyridamole-induced stress (Tables 3 & 4), twenty-two patients (21.78%) had an abnormal SBP decrease (< 10 mmHg) while 35 patients (34.65 %) had an abnormal HRR. Overall, 50 patients (49.5%) had abnormal SBP decrease and/or HRR.

The median SBP decrease was at 20 mmHg from the baseline. A normal SBP decrease (> 10 mmHg) was noted in majority of the patients (78.22%) with 52 patients (76.47%) corresponding with a normal scan result. An abnormal SBP decrease was also noted with the normal scan results of 16 patients (23.53%). However, these findings were not statistically significant.

For the HRR, the median ratio was 1.28 with a significantly lower ratio of 1.25 for the abnormal scan results compared to a ratio of 1.29 for a normal scan result (p-value of 0.032). Although, there was no statistically significant difference between the normal (> 1.2) or abnormal (<1.2) HRR and the scan results.

Other hemodynamic changes (Table 4), such as the DBP decrease and patients with abnormal SBP decrease and/or HRR were not statistically significant. In terms of the double product or rate pressure product, which is the product of the HR and SBP, only the post-infusion double product was determined to have a statistically significant difference with the scan results (p-value of 0.044). The post-infusion double product was noted to be higher for normal scans [10.68 (9.2 to 12.84)] than those with abnormal scan results [10.22 (8.46 to 11.18)]. There was also a statistically significant difference from the baseline to post-infusion change of the double product for entire study population and for the those with normal scans (p-value of < 0.001).

TABLE 4. Other hemodynamic changes in dipyridamole-induced stress

	Scan result			p-value
	Total (n = 101)	Abnormal (n = 33)	Normal (n = 68)	
	Frequency (%); Median (IQR)			
DBP decrease	10 (20 to 10)	20 (20 to 10)	10 (20 to 0)	0.113
Abnormal SBP decrease and/or HRR	50 (49.5)	17 (51.52)	33 (48.53)	0.834
Double Product[i]				
Baseline	9.1 (7.93 to 10.64)	8.58 (7.93 to 10.4)	9.33 (7.92 to 11.05)	0.233
Post-Infusion	10.56 (9.02 to 12.18)	10.22 (8.46 to 11.18)	10.68 (9.2 to 12.84)	**0.044**
Difference	0.99 (-0.15 to 2.46)	0.78 (-0.49 to 1.84)	1.10 (0.03 to 2.75)	0.158
p-value (Baseline vs post-infusion)	**<0.001**	0.061	**<0.001**	

[i]Double Product = HR x SBP

TABLE 5. 12-L ECG findings before and after dipyridamole infusion

	Scan result			p-value
	Total (n = 101)	Abnormal (n = 33)	Normal (n = 68)	
	Frequency (%); Mean ± SD			
Baseline ECG				
Normal	42 (42.58)	8 (24.24)	34 (50)	**0.018**
Conduction findings	39 (38.61)	14 (42.42)	25 (36.76)	0.665
Infarct findings	12 (11.88)	8 (24.24)	4 (5.88)	**0.017**
Ischemic findings	14 (13.86)	4 (12.12)	10 (14.71)	1.000
Hypertrophy findings	11 (10.89)	6 (18.18)	5 (7.35)	0.170
After Dipyridamole infusion ECG				
No change	88 (87.13)	26 (78.79)	62 (91.18)	0.113
With change	13 (12.87)	7 (21.21)	6 (8.82)	
ST segment depression	6 (46.15)	2 (33.33)	4 (57.14)	0.592
Other changes	7 (53.85)	4 (66.67)	3 (42.86)	

Most of the baseline ECG findings were normal (42.58%) and with no apparent change after dipyridamole infusion (87.13%). There was a statistically significant difference for the normal baseline (p-value of 0.018) and infarct ECG findings (p-value of 0.017); and normal/abnormal scan results, respectively. The changes in the ECG after dipyridamole infusion were only noted in 13 patients (12.87%), wherein 6 patients were noted with an ST segment depression and that only 2 patients had the presence of ischemia in their scan results. This, however, was not statistically significant.

For the frequency of myocardial perfusion scores (Table 6), majority of the patients had a normal SSS (81.19%), SRS (87.13%), and SDS (84.16%). Ischemia (51.61%) was the most common defect noted followed by fibrosis and infarct findings.

As seen in Table 7, there was no statistically significant correlation between the SBP decrease and myocardial perfusion scores. The HRR showed a statistically significant direct/indirect weak correlation for the rest and stress LVEF values (p-values of 0.09 and 0.011) and SRS (p-value of 0.007). This implies that higher HRRs, the better LVEF values. This is also the case for SRS wherein a score of less than 4 is normal. However, the level of association was weak for these findings.

Table 8 shows the other findings monitored during the dipyridamole infusion period. For the time in which the peak HR (p-value of 0.003) was attained, patients with

TABLE 6. Myocardial Perfusion Scores

	Frequency (%); Median (IQR)
Description of Defect (n=31)	
Ischemia	16 (51.61)
Infarct	4 (12.9)
Fibrosis	5 (16.13)
SSS	8 (4 to 19)
Normal (< 4)	82 (81.19)
Mild (4-8)	8 (7.92)
Moderate (9-12)	1 (0.99)
Severe (>12)	10 (9.90)
SRS	9 (4 to 16)
Normal (< 4)	88 (87.13)
Mild (4-8)	6 (5.94)
Moderate (9-12)	1 (0.99)
Severe (>12)	6 (5.94)
SDS	7 (3 to 15)
Normal (<2)	85 (84.16)
Mild (2-3)	5 (4.95)
Moderate (4-7)	3 (2.97)
Severe (>8)	8 (7.92)

TABLE 7. Correlation of SBP decrease and HRR to Myocardial Perfusion Scores and Left Ventricle Ejection Fractions

	Correlation coefficient	Level of association	p-value
SBP decrease			
SSS	-0.1426	Indirect weak correlation	0.155
SRS	-0.0988	Indirect weak correlation	0.325
SDS	-0.0605	Indirect weak correlation	0.548
Rest LVEF	0.0624	Direct weak correlation	0.536
Stress LVEF	0.0378	Direct weak correlation	0.707
HRR			
SSS	-0.0906	Indirect weak correlation	0.368
SRS	-0.2650	Indirect weak correlation	**0.007**
SDS	0.0013	Direct weak correlation	0.990
Rest LVEF	0.2591	Direct weak correlation	**0.009**
Stress LVEF	0.2516	Direct weak correlation	**0.011**

normal scan results had an average of 8.15 (+ 2.94) minutes compared to 6.56 (+ 2.21) minutes for those with abnormal results. The time attained for the lowest SBP decrease and symptom/s during infusion were not statistically significant. Chest heaviness (35.64%) was the most frequent symptom noted.

For the association of the baseline ECG findings with the myocardial perfusion scores (Tables 9, 10, and 11), the infarct findings showed statistically significant association with the SSS (p-value of < 0.001), SRS (p-value of < 0.001), and SDS (p- value of 0.005); and the normal baseline ECG with SRS (p-value of 0.028).

DISCUSSION

Dipyridamole is a phosphodiesterase enzyme inhibitor that indirectly increases myocardial perfusion by inhibiting the reuptake of endogenous adenosine [8]. Through this mechanism, it provides an alternative form of stress with expected hemodynamic changes which may have a clinical significance.

TABLE 8. Dipyridamole induced stress monitoring

	Scan result			p-value
	Total (n = 101)	Abnormal (n = 33)	Normal (n = 68)	
	Frequency (%); Mean ± SD; Median (IQR)			
Time attained (minutes)				
Lowest SBP decrease	7.07 ± 3.13	7.45 ± 2.84	6.88 ± 3.27	0.392
Peak HR	7.08 ± 2.57	6.56 ± 2.21	8.15 ± 2.94	**0.003**
Symptom during infusion	5.86 ± 2.64	5.66 ± 2.53	6.37 ± 2.91	0.328
Symptom/s during infusion				
Chest heaviness/discomfort	36 (35.64)	10 (30.30)	26 (38.24)	0.510
Light headedness	24 (23.76)	9 (27.27)	15 (22.06)	0.621
Abdominal pain	23 (22.77)	7 (21.21)	16 (23.53)	1.000
Headache	21 (20.79)	6 (18.18)	15 (22.06)	0.796
Dizziness	9 (8.91)	1 (3.03)	8 (11.76)	0.265
SOB	6 (5.94)	1 (3.03)	5 (7.35)	0.661
Others	11 (10.89)	5 (15.15)	6 (8.82)	0.333

TABLE 9. Association of Baseline ECG findings and SSS

Baseline ECG	Normal (n = 82)	Mild (n =8)	Moderate (n = 1)	Severe (n = 10)	p-value
	Frequency (%)				
Normal	39 (47.56)	1 (12.5)	0	2 (20)	0.066
Infarct findings	5 (7.58)	1 (12.5)	1 (100)	5 (50)	**<0.001**
Ischemic findings	12 (14.63)	1 (12.5)	0	1 (10)	1.000
Hypertrophy findings	8 (9.76)	0	1 (100)	2 (20)	0.073
Conduction findings	30 (36.59)	6 (75)	0	3 (30)	0.124

TABLE 10. Association of Baseline ECG findings and SRS

Baseline ECG	Normal (n = 88)	Mild (n = 6)	Moderate (n = 1)	Severe (n = 6)	p-value
	Frequency (%)				
Normal	41 (46.59)	0	0	1 (16.67)	**0.028**
Infarct findings	6 (6.82)	1 (16.67)	1 (100)	4 (66.67)	**<0.001**
Ischemic findings	12 (13.64)	1 (16.67)	0	1 (16.67)	1.000
Hypertrophy findings	9 (10.23)	0	0	2 (33.33)	0.328
Conduction findings	33 (37.5)	5 (83.33)	0	1 (16.67)	0.054

TABLE 11. Association of Baseline ECG findings and SDS

Baseline ECG	Normal (n = 85)	Mild (n = 5)	Moderate (n = 3)	Severe (n = 8)	p-value
	Frequency (%)				
Normal	37 (43.53)	2 (40)	1 (33.33)	2 (25)	0.856
Infarct findings	6 (7.06)	1 (20)	1 (33.33)	4 (50)	**0.005**
Ischemic findings	14 (16.47)	0	0	0	0.782
Hypertrophy findings	8 (9.41)	1 (20)	1 (33.33)	1 (12.5)	0.231
Conduction findings	34 (40)	1 (20)	1 (33.33)	3 (37.5)	0.918

The hemodynamic changes in the SBP showed no significant difference between the myocardial perfusion scores (SSS, SRS & SDS), stress/rest LVEF, and the eventual scan result. The diastolic blood pressure changes likewise showed no significant difference. These findings were congruent with the study by Ghoobli, et al. in 2017 wherein abnormal SBP changes are not associated abnormal scan findings and myocardial perfusion scores [2]. It was also noted that the absence of SBP response correlation may be affected by the

presence of LV dysfunction in the study population.

The normal (> 1.2)/abnormal (< 1.2) heart rate ratios (HRR) also had no significant difference with the scan results while the median HRR was determined to have had a significant difference. The median HRR for this study was noted to be at 1.28 which is a normal response with a higher ratio of 1.29 for normal results compared to 1.25 for the abnormal results. This implies that a higher HRR or greater increase from the baseline HR is associated with normal scan results, but the cut-off value of 1.2, as previously defined, is uncertain for this study [9]. Though, it has likewise been suggested that further investigations are needed to determine the ideal limits for HR response to vasodilators as previous studies have reported a high number of abnormal HRRs [5, 9]. It has also been stated that reduced HRR to vasodilators is associated with increased risk and as well as an independent predictor of cardiac death [2, 5, 10]. For the myocardial perfusion scores, only the SRS had an indirect correlation with HRR albeit the level of association was weak. The stress and rest LVEF values also showed a direct weak correlation. Overall, the higher HRRs may indicate normal SRS (< 4) and higher stress/rest LVEF values which relates to normal scan results. This provides diagnostic confidence in understanding the effects of the Dipyridamole, particularly its effect on heart rate, wherein a substantial increase from baseline implies a normal myocardial perfusion.

For the double product or rate pressure product, the post-infusion value for the normal and abnormal scan results [10.68 (9.2 to 12.84) vs 10.22 (8.46 to 11.18)] was determined to have had a significant difference. The median post-infusion double product was 10.56 (9.02 to 12.18) for this study. The double product is used as a measure of myocardial oxygen demand and that dipyridamole causes a decrease in in BP and increase in HR which supports the values obtained for this study [11]. A preliminary study likewise had similar findings for post-infusion double product and observed a significant difference for Δ double product [11]. It was noted that the double product is related to sympathetic nervous system activity and decreased parasympathetic nervous system activity for which dipyridamole is not affected.

Baseline normal and infarct ECG findings showed a significant difference with normal and abnormal scan results, respectively. Myocardial perfusion scores (SSS, SRS, and SDS) correlated with the baseline infarct findings while only the SRS for the baseline normal ECG findings. Although, it should be noted that SDS is used as an index for ischemic burden and the most frequent defect noted for this study population was also ischemia. After dipyridamole infusion, most ECG findings remained unchanged with no significant difference for those 13 patients (12.87%) with only 6 developing the presence of ST segment depression. This is expected since dipyridamole does not induce absolute ischemia in most patients.

In terms of the demographic profile, patients that were younger (56.18 + 16.03) had abnormal scan results. This suggests that these patients may have developed comorbidities earlier, hence the abnormal scan results. It should also be noted that these patients were preferably requested to undergo a dipyridamole induced stress rather than exercise; and are being considered for suspected CAD, which suggests a higher risk profile. Males were also noted to have an abnormal scan result, likely due to the greater influence of common factors (age, hypertension, etc.) than women thus the greater risk of cardiovascular disease [12, 13].

Another finding noted to be significant was the time (minutes) to reach the maximal HR upon dipyridamole infusion which was longer for those with normal scan results (8.15 + 2.94 vs. 6.56 + 2.21). This implies that a longer and possibly sustained increase in the HR may indicate a better HRR which would be congruent with a normal scan result as previously noted.

This retrospective study is limited as a single-center study referred to our institution for patients with suspected CAD. Cardiac autonomic dysfunction was also not confirmed which may help in understanding abnormal hemodynamic response.

CONCLUSION

In patients with suspected CAD who undergo a dipyridamole-induced stress myocardial perfusion scintigraphy –Tc-99m Sestamibi, the higher HRRs and baseline 12-L ECG (normal and infarct) findings, relates with the expected scan results. This implies that higher HRRs and normal baseline ECG finding are associated with normal scan results, and baseline infarct findings relate with abnormal scan results. The higher HRRs were also associated with the higher stress/rest LVEF and normal SRS, which supports a normal scan result.

However, there was no significant association for the blood pressure responses and post-infusion 12-L ECGs with any of the scan findings/results. Overall, the results may guide the clinician and reader in the study interpretation, thereby increasing diagnostic confidence and having a clearer understanding of the hemodynamic effects of Dipyridamole, especially in equivocal findings

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Clinical Application of Normalized Residual Activity as a Semiquantitative Adjunct in Assessing Renal Emptying in Pediatric Diuretic Scans

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ABSTRACT

Background:

The most recent pediatric diuretic imaging guidelines recommend the use of normalized residual activity (NORA) as a semiquantitative index of renal tracer drainage. It is defined as the ratio of post-void renal counts to 1-2 minute post-injection renal counts, with values less than 1 indicative of good drainage. We present two instances where NORA calculation was adjunctive in the evaluation of obstructive uropathy.

Case Presentation:

The first patient was a 3-month-old male with left-sided congenital hydronephrosis. On dynamic imaging, the diseased kidney showed adequate perfusion and parenchymal extraction; moderate to severe pelvicalyceal tracer retention exhibited good response to diuretic. The pre-diuretic NORA of 1.62 declined to 0.28 after furosemide challenge, concordant with imaging findings that were negative for obstruction. The second patient was a 7-week-old male, also with congenital hydronephrosis of the left kidney. Dynamic images showed the diseased kidney with diminished perfusion and function, as well as pelvicalyceal tracer retention which became more severe after the diuretic was given. The pre-diuretic NORA was 1.81, which became 1.18 post-diuretic. This inadequate decline supplemented imaging findings pointing to significant obstruction. Other semiquantitative parameters have preceded NORA; however, clearance half-time is not validated as a marker of obstructive uropathy in infants and children, and output efficiency requires specialized software to calculate. Standardization of NORA determination is largely provided for by the guidelines recommending a perirenal background region of interest, as well as minimizing the interval between starting camera acquisition and injecting the tracer.

Conclusion:

Semiquantitative analysis through NORA calculation gives relevant supporting information in the reporting of renal tracer drainage among pediatric patients. Further studies are needed to ascertain its applicability among adults and its diagnostic value in a larger sample of affected Filipino children.

Keywords*: normalized residual activity, diuretic renal scan, congenital hydronephrosis, Tc-99m MAG3*

INTRODUCTION

In 2018, the Pediatric Imaging Council of the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Pediatric Committee of the European Association of Nuclear Medicine (EANM) jointly released procedural guidelines for the conduct of diuretic-augmented renography in infants and children [1]. With hydronephrosis being the most commonly detected congenital anomaly of the urinary tract, the goal of imaging is to determine the functional status of the diseased kidney and, if applicable, prevent further loss of function through surgical intervention. Congenital hydronephrosis may be caused by a variety of entities, such as vesicoureteral reflux, ureteropelvic junction stenosis, and ureterovesical junction stenosis, among others. Diuretic renal scans in these group of patients not only give information on renal perfusion and function, but also determine the severity and location of obstructive uropathy when present.

As pediatric patients are not small adults, pediatric diuretic renal scintigraphy is not a carbon copy of the adult protocol. To start, Tc-99m MAG3 is preferred over Tc-99m DTPA. The extraction fraction (percentage of tracer extracted with each pass through the kidney) of

Tc-99m MAG3 is 40-50%, compared to only approximately 20% with Tc-99m DTPA [2]. This results in Tc-99m MAG3 images having better target-to-background ratios with good temporal resolution and faster renal clearance, making it conducive particularly for neonatal renography [3]. Second, tracer dose is calculated based on set guidelines by the SNMMI and EANM [4]. Third, the administered dose of furosemide is weight-based (at 1 mg/kg), rather than the mandated 40 mg dose for adults. Fourth, in drawing the background region of interest (ROI), a C-shaped ROI is preferred along the lateral aspect of the kidney, rather than a quadrilateral ROI in the inferolateral side.

The 2018 guidelines place an emphasis on gravity-assisted post-void imaging. In adults, a 1-minute static post-void image is acquired after each sequence of dynamic images (pre-diuretic and post-diuretic). Because not all pediatric patients are toilet-trained, post-void imaging can pose a challenge to perform. It is advised to acquire post-diuretic post-void images once the bladder has emptied after being kept upright for a standardized period of time (e.g. 10 to 15 minutes). The rationale of this is twofold: (a) the supine position of the patient can affect tracer excretion, and (b) insufficient renal drainage due to a full bladder at the end of dynamic imaging may yield inadequate images for interpretation, particularly in a demographic where vesicoureteral reflux is more prevalent.

Normalized residual activity (NORA) is recommended by the guidelines as the most robust measurement of post-diuretic clearance [1]. It is a semiquantitative parameter which is defined as the ratio of renal counts post-void to the renal counts on the second minute post-tracer injection. The second minute composite image is used as it is deemed to have the maximum tracer accumulation in the renal parenchyma without visualizing tracer activity in the pelvicalyceal system. As post-void images are acquired twice (pre- and post-diuretic), pre-diuretic and post-diuretic NORA values (NORApre and NORApost, respectively) can be obtained using the following formulas:

$$\text{NORA}_{\text{pre}} = \frac{\text{post-void pre-diuretic counts}}{\text{2nd minute pre-diuretic counts}}$$

$$\text{NORA}_{\text{post}} = \frac{\text{gravity-assisted post-void counts}}{\text{2nd minute pre-diuretic counts}}$$

In general, a NORA value less than 1 denotes good tracer drainage. In the context of post-diuretic imaging, a NORA value less than 1 implies good response to diuretic, and consequently, reduced likelihood of significant mechanical obstruction.

Pediatric renal diuretic scans are not as frequently encountered as other general nuclear imaging procedures in the local setting. This report presents two instances where NORA supplemented qualitative findings in the assessment of renal drainage.

CASE 1

A 3-month-old male with congenital hydronephrosis of the left kidney was referred to our department for diuretic-augmented renal imaging to evaluate for ureteropelvic junction obstruction. Dynamic imaging of the kidneys was performed in the posterior view for 20 minutes after injection of 29.6 MBq of Tc-99m MAG3. Sequential imaging was again done after injection of 8 mg furosemide. Gravity-assisted post-void image was obtained afterwards.

Bolus phase (Figure 1) showed good renal perfusion bilaterally. The diseased left kidney exhibited fair cortical tracer extraction, timely excretion, and moderate to severe tracer retention in the dilated pelvis (Figure 2A) which washed out after the diuretic was given (Figure 2B). The time-activity curve (Figure 3) showed an upsloping curve that only declined post-diuretic. The right kidney had good parenchymal and excretory function, with complete radiotracer washout after furosemide was administered; no discrete abnormality was detected in the time-activity curve.

Kidney counts were extracted by producing composite images at three time points: (a) 60-120 seconds after tracer injection, i.e. the second minute of dynamic imaging; (b) the 1-minute static post-void image right before the diuretic was injected; and (c) the 1-minute static gravity-assisted post-void image at the end of diuretic-augmented imaging. Regions of interest were drawn around the kidneys, with C-shaped background ROIs along the lateral aspects (Table 1). The background-corrected counts were then used to calculate for pre-diuretic and post-diuretic NORA values (Table 2).

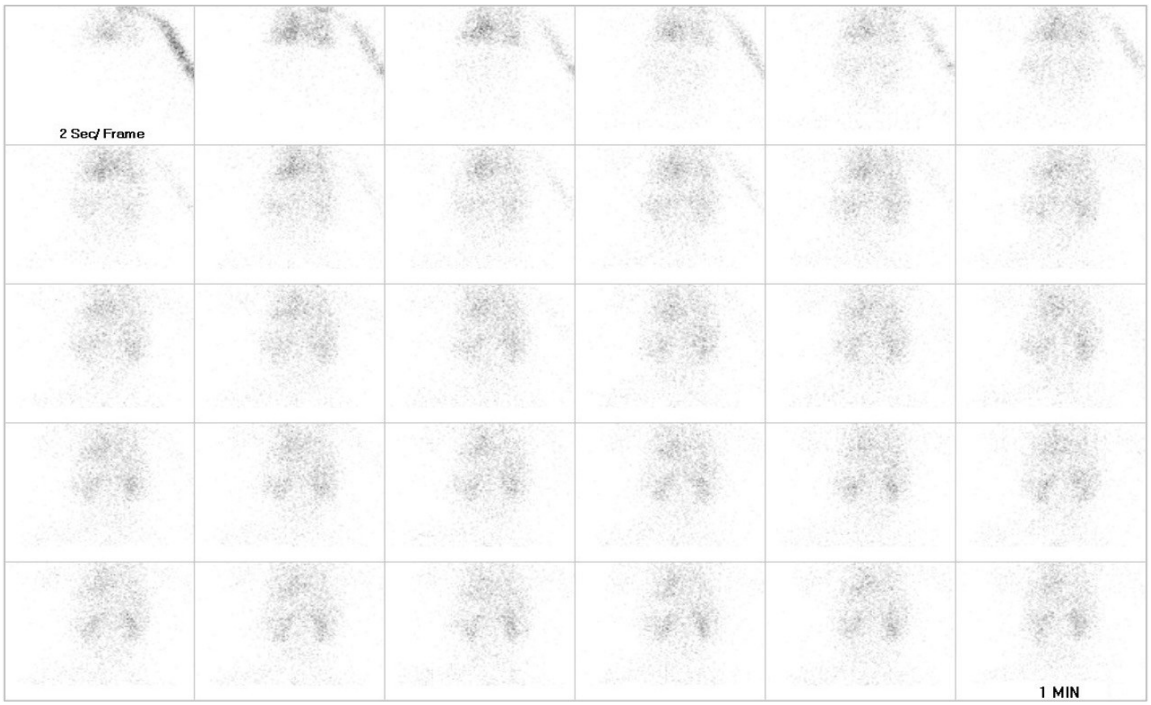


FIGURE 1. Perfusion images of the 3-month-old patient

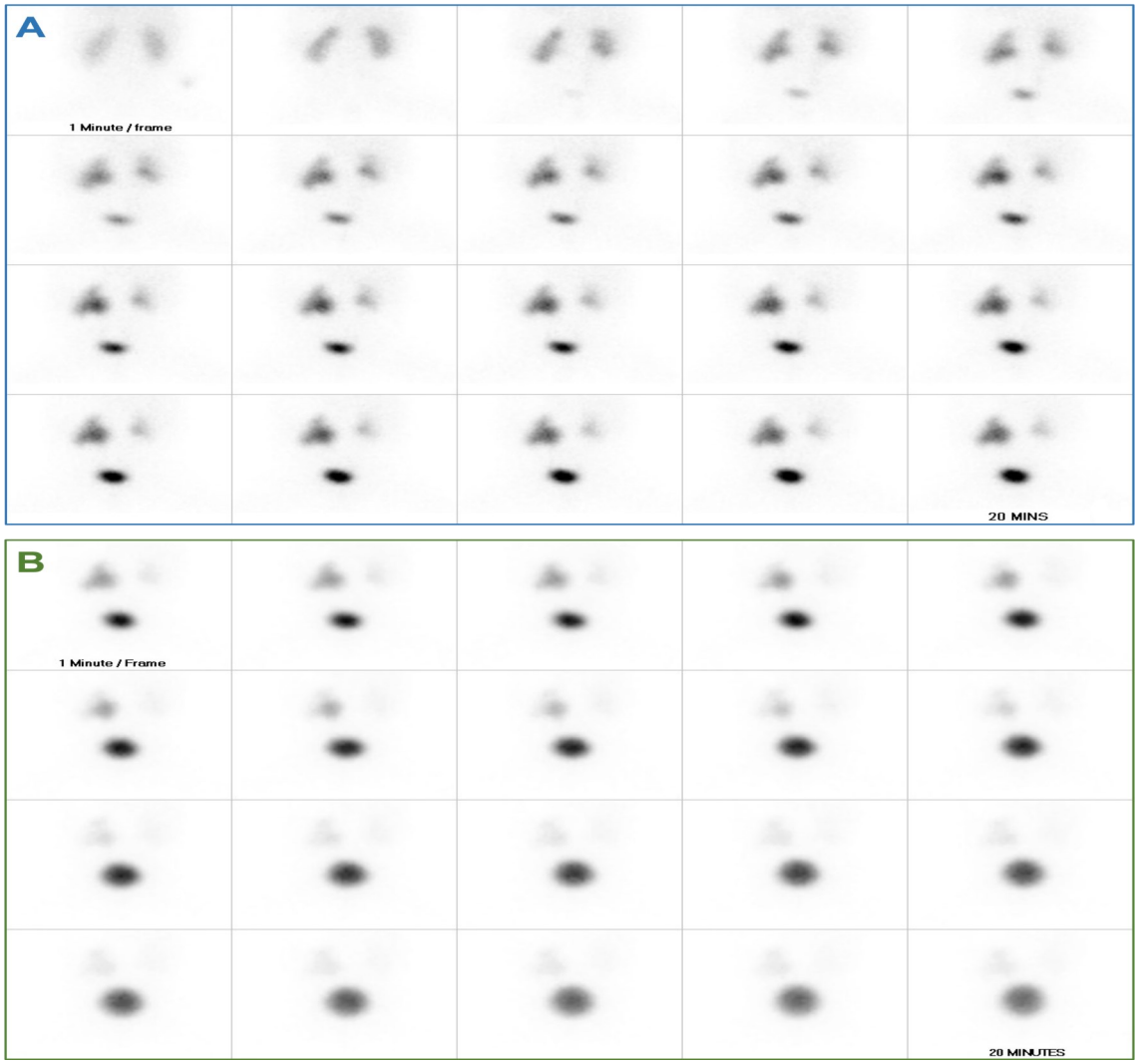


FIGURE 2. 20-minute pre-diuretic (A) and post-diuretic (B) dynamic images of the 3-month-old patient

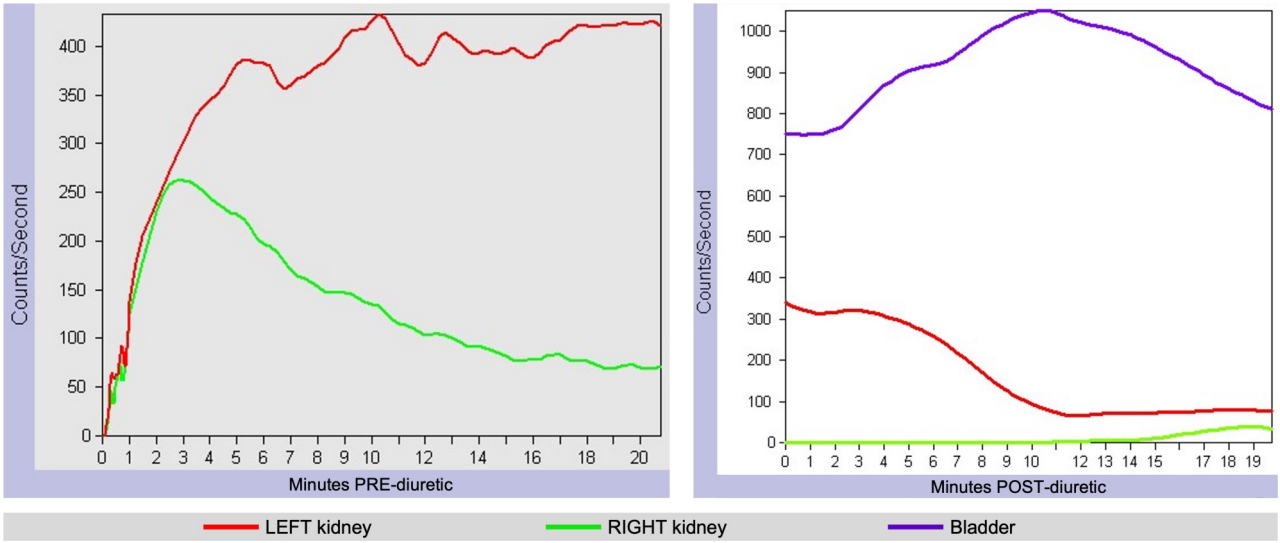


FIGURE 3. Pre- and post-diuretic time-activity curves of the 3-month-old patient

TABLE 1. .Image processing and number of counts were obtained to calculate pre- and post-diuretic NORA values for the 3-month-old patient. Reported kidney counts are after background correction.

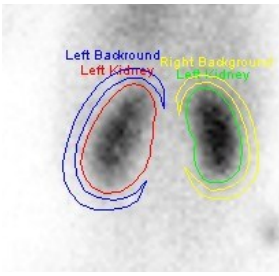
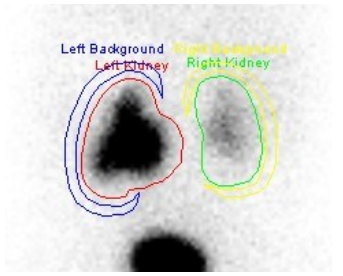
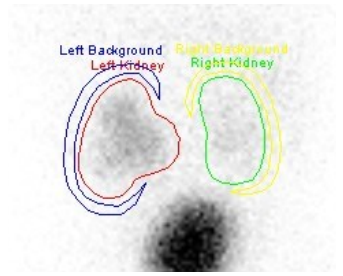
	2ND MINUTE POST-INJECTION	**PRE-DIURETIC POST-VOID**	**POST-DIURETIC *(GRAVITY-ASSISTED)* POST-VOID**
Image			
Left kidney counts	18759	30375	5160
Right kidney counts	16320	5802	1636

TABLE 2. . Differential renal function and calculated NORA values for the diuretic scan of the 3-month-old patient

	LEFT KIDNEY	**RIGHT KIDNEY**
Relative renal function (%)	51.0	49.0
Pre-diuretic NORA	1.62	0.36
Post-diuretic NORA	0.28	0.10

On the hydronephrotic left kidney, a pre-diuretic NORA of 1.62 (i.e. greater than 1) was compatible with the visualized pelvicalyceal tracer stasis. After furosemide was given, the NORA declined to 0.28, denoting significant tracer clearance. The pre- and post-diuretic NORA values on the right were both below 1, which was expected in a normal kidney.

It was thus concluded that while there was moderate to severe left-sided pelvicalyceal tracer retention, both the visualized good response to furosemide challenge and the calculated NORA post-diuretic attest to the absence of significant mechanical obstruction. No surgical intervention was instituted; surveillance sonography was performed multiple times over the following months, with stable findings.

CASE 2

Two weeks after the first case, our department received a 7-week-old male with congenital hydronephrosis of the left kidney for diuretic-augmented renal imaging, also to evaluate for ureteropelvic junction obstruction. Dynamic imaging of both kidneys was performed in the posterior view for 20 minutes after injection of 25.9 MBq of Tc-99m MAG3. Sequential imaging was again done after injection of 6 mg furosemide. Gravity-assisted post-void image was obtained afterwards.

The right kidney showed adequate perfusion, good cortical tracer extraction, prompt excretion, and complete tracer washout post-diuretic (Figures 4 and 5). In contrast, the hydronephrotic left kidney exhibited impaired perfusion and function, with tracer retention in the pelvicalyces that increased in severity after diuretic administration. The time-activity curve (Figure 6) showed an upsloping curve which persistently plateaued, even during the post-diuretic study.

Kidney counts were subsequently extracted and NORA values calculated, as in the first case (Tables 3 and 4). The right kidney NORA values were essentially unremarkable. The left kidney NORA, while showing some decline post-diuretic, remained greater than 1.

It was thus concluded that, apart from the left kidney having reduced perfusion and function, there was significant mechanical obstruction at the level of the ureteropelvic junction. The latter finding is supported visually by severe pelvicalyceal tracer retention without response to furosemide challenge, as well as by the time-activity curve and the post-diuretic NORA.

DISCUSSION

A discussion on normalized residual activity would be insufficient without a prologue on semiquantitative indices in measuring renal drainage, particularly after furosemide challenge. Perhaps the most well-known parameter is clearance half-time (T½), the time it takes for renal activity to fall to 50% of its maximum value. A T½ less than 10 minutes is compatible with absence of mechanical obstruction, while a T½ greater than 20 minutes is indicative of obstructive uropathy [5]. However, data is lacking in the pediatric population that

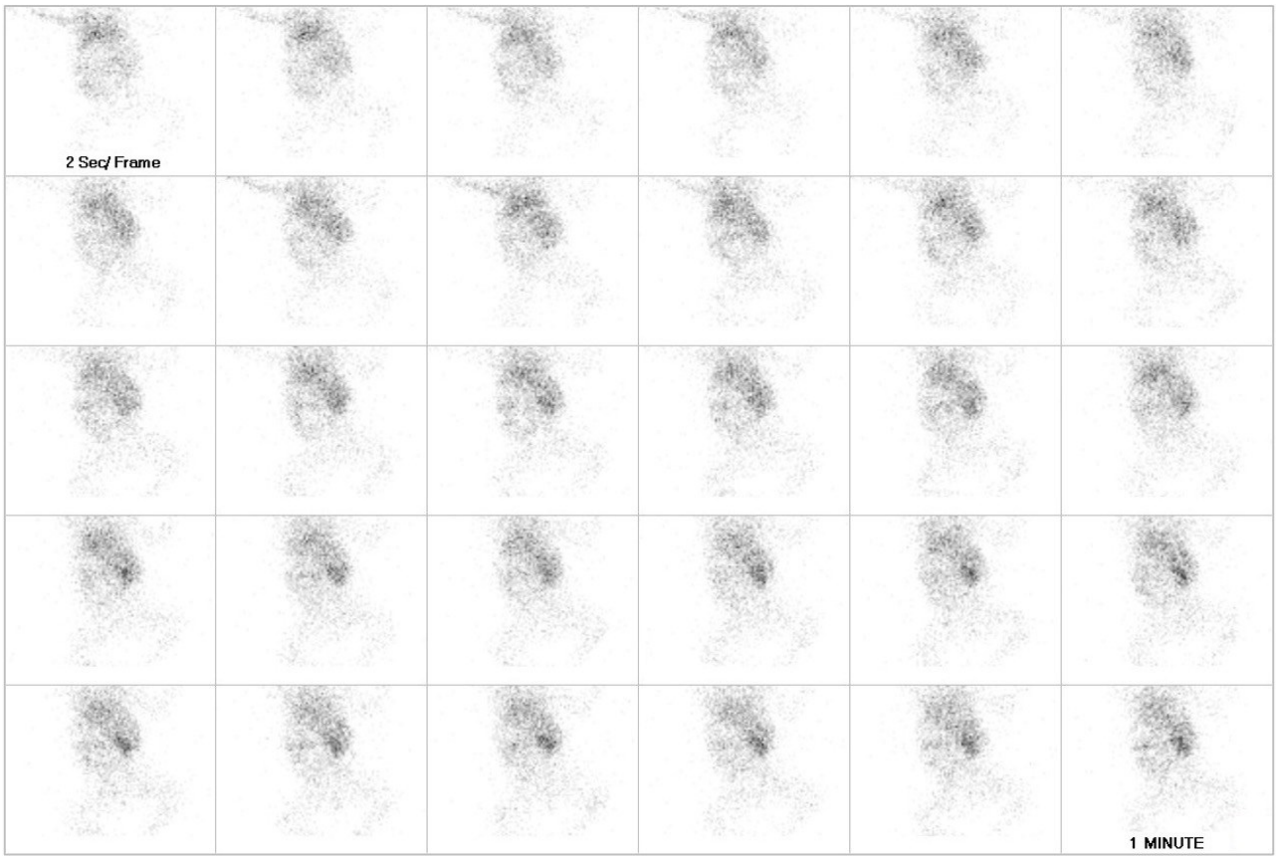


FIGURE 4. Perfusion images of the 7-week-old patient

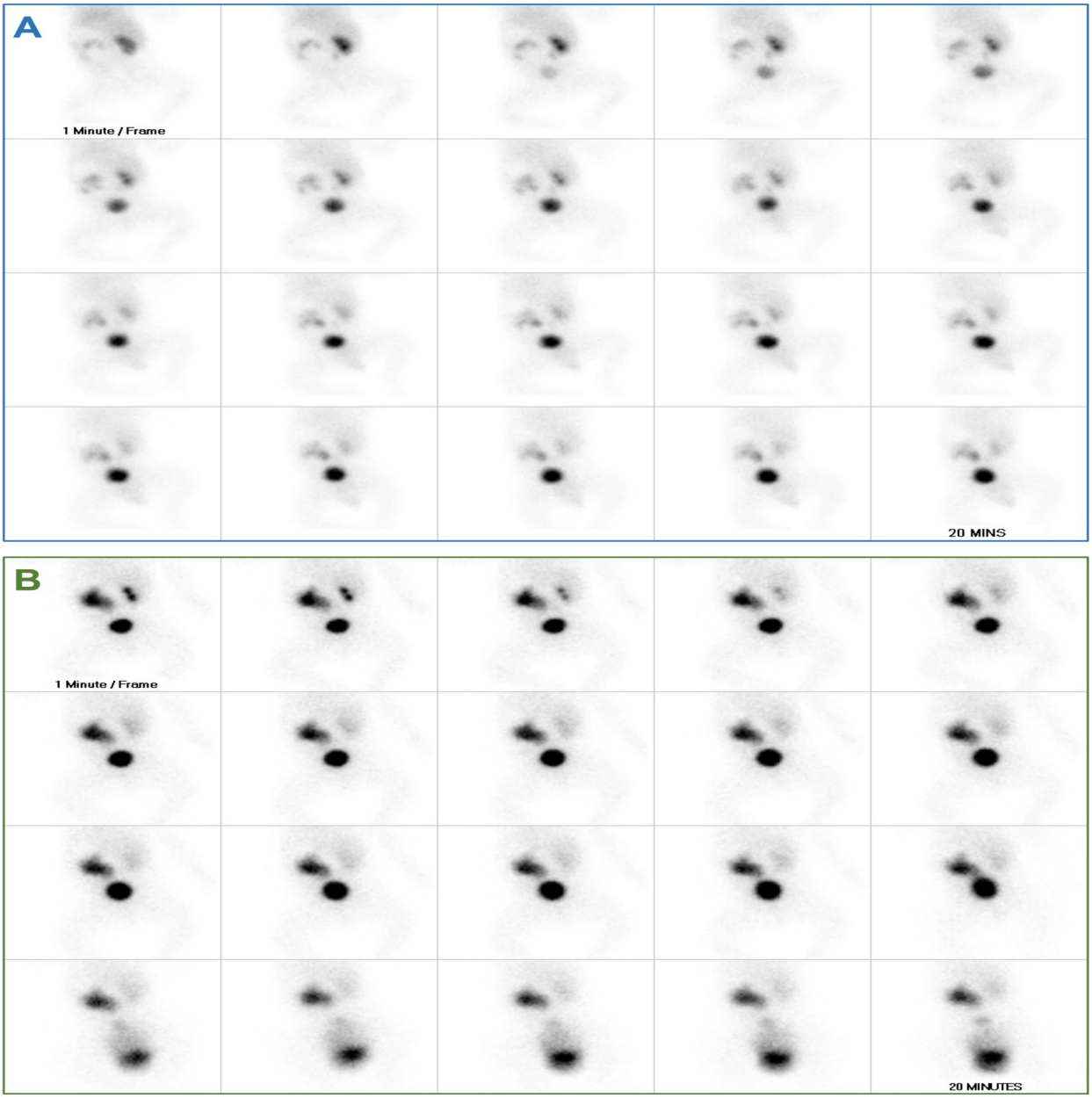


FIGURE 5. 20-minute pre-diuretic (A) and post-diuretic (B) dynamic images of the 7-week-old patient. Acquisition was paused 15 minutes post-diuretic due to involuntary patient voiding, hence the discordant appearance of the 16-20 minute dynamic images.

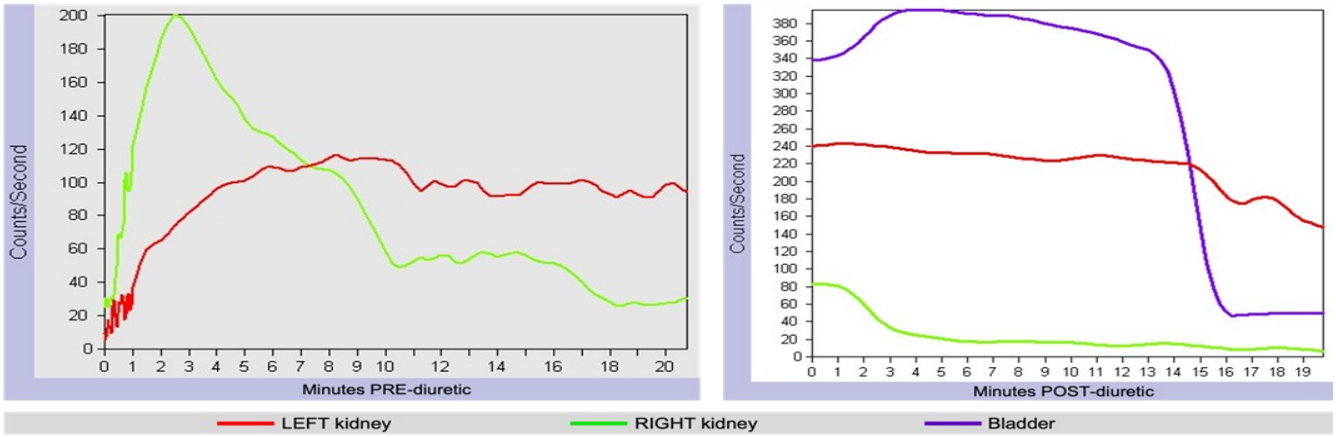


FIGURE 6. Pre- and post-diuretic time-activity curves of the 7-week-old patient. Acquisition was paused 15 minutes post-diuretic due to involuntary patient voiding, hence the abrupt downslope of the bladder curve at around this time.

will allow the interpretation of impaired T½ as obstruction [6]. Another such parameter is output efficiency (OE), defined as the amount of tracer that has left the kidney in proportion to that taken up from the blood. Among children, an OE of less than 89% in normal kidneys and less than 79% in hydronephrotic kidneys is said to be an independent predictor of obstruction, with a diagnostic accuracy of 89% [7]. However, calculation of OE requires specialized software that is not supported by many of the gamma camera vendors.

A formal introduction of NORA as an index of renal emptying was provided by Piepsz et al., showing good correlation between post-diuretic NORA and OE [8]. They defined two parameters that had to be standardized to ensure the robustness of NORA:

- *Background correction.* It was determined that background-corrected NORA was lower than non-background-corrected NORA, regardless of the shape of the background ROI (perirenal or subrenal). This was addressed in the pediatric diuretic scan guidelines by defining the use of a perirenal configuration in the placement of the background ROI.
- *Error of estimating 2-minute renal activity*. A significant delay between starting the acquisition and injecting the tracer would yield a false representative image of maximum tracer accumulation in the renal parenchyma. The seminal paper showed that a delay of 20 seconds led to a systematic 10-15% underestimation of NORA. In our institution, technologists are trained to perform bolus injection within 2-3 seconds of starting image acquisition.

The two cases presented had several common characteristics: both involved infants with left-sided congenital hydronephrosis and were being evaluated for obstructive uropathy. The absence of significant obstruction in the first case was reflected by the NORA value declining to less than 1 after the diuretic was administered. In contrast, the NORA value in the second case remained above 1 post-diuretic in spite of exhibiting some degree of decline, which, concordant with imaging findings, is indicative of significant mechanical obstruction. Apart from the differences in NORA values, the fact that perfusion and function has diminished in the second case is a surrogate indicator of the chronicity of the obstruction, something not seen in the first case.

It can be argued that an adequate interpretation of these cases can be made based solely on the images and renograms. Semiquantitative indices, particularly NORA in this population, provide information that would support what is visually deduced from the acquired images. These parameters may be particularly helpful in cases that are qualitatively equivocal for the presence of obstruction.

While the utility of NORA in infants and children suspected of obstructive uropathy is well-documented, the same cannot be said in the adult population. The latest guidelines on diuretic renal scintigraphy for adults, also released in 2018, acknowledge the potential of semiquantitative indices such as NORA and OE in decreasing the number of false-positive or indeterminate diuretic renal scans. However, it also mentions explicitly that further studies are needed to confirm its utility in the non-pediatric demographic [9].

Pediatric diuretic imaging guidelines endorse the calculation and reporting of normalized residual activity. The case illustrations attest to both the reproducibility of image processing for NORA determination and the utility of NORA as a semiquantitative index of renal emptying. Not all local nuclear medicine institutions are adequately equipped to perform the necessary image processing for every pediatric renal scan patient, and not all pediatric diuretic renal scans would need to be processed as such. Therefore, further studies are suggested to ascertain the overall benefit of NORA calculation in a larger sample of Filipino cases of pediatric hydronephrosis, as well as in those scans where imaging findings are indeterminate for obstructive uropathy.

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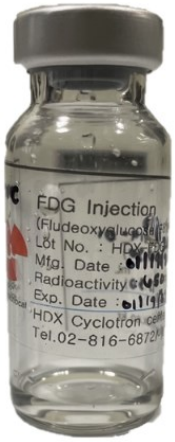

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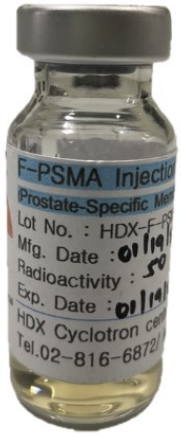

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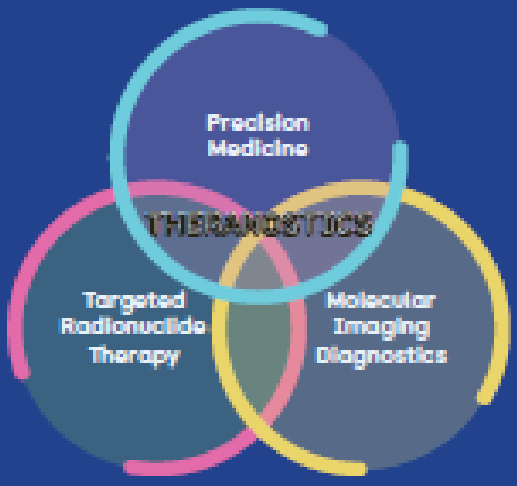

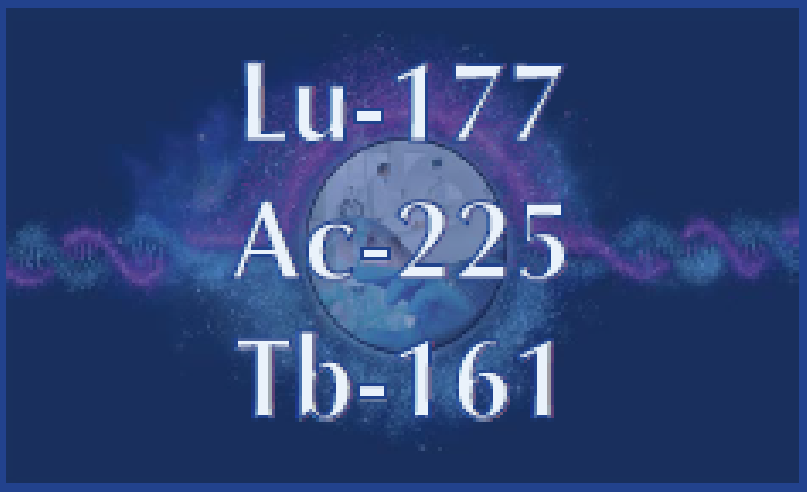

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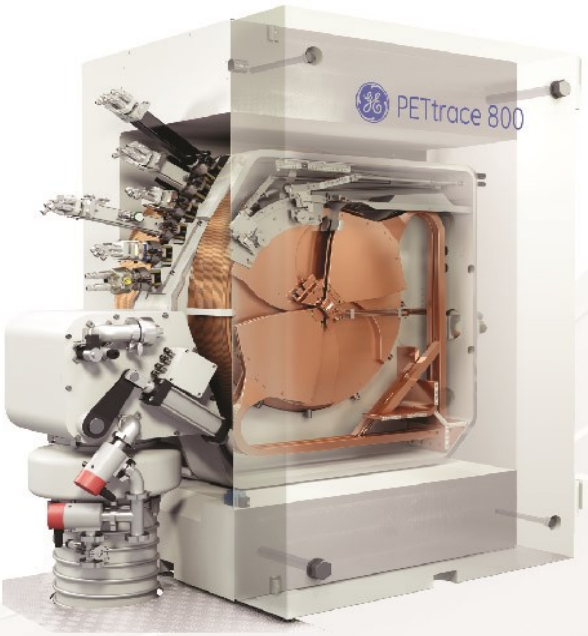

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