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Inter-Observer Variability in the Interpretation of ^{68}Ga-PSMA PET-CT Scan according to PROMISE Criteria

Amina Nasir[1], Muhammad Numair Younis[2], Sadia Adnan[2], Tahira Yasmin[2], Ismat Fatima[2], Abubaker Shahid[3]

[1]Pakistan Institute of Engineering and Applied Sciences (PIEAS), Islamabad, Pakistan
[2]Department of Nuclear Medicine and PET Imaging, Institute of Nuclear Medicine and Oncology Lahore (INMOL), Lahore, Pakistan
[3]Department of Clinical Oncology, Institute of Nuclear Medicine and Oncology Lahore (INMOL), Lahore, Pakistan
Email: dr.numair@gmail.com

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Abstract

Aims & Objectives: Aim of the study was to evaluate inter-observer variability in interpretation of Gallium-68 labeled Prostate Specific Membrane Antigen sub-type 11 (^{68}Ga-PSMA-11) Positron Emission Tomography-Computed Tomography PET_CT scan according to Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria. **Method and Materials:** Forty-four consecutive patients of prostate cancer were prospectively studied between the duration of January 2021 to June 2021 at Institute of Nuclear Medicine and Oncology (INMOL), Lahore. All PET-CT scans were assessed by a researcher and 3 nuclear physicians and divided into two groups, interpreted in two phases. In the first phase, each group independently evaluated the scans while in the second phase, a consensus meeting was held and all the cases with discordance were discussed. Cohen's Kappa test was used to measure interobserver variability with the cut-off of K's alpha < 0.61 that was chosen to indicate substantial disagreement. **Results:** The study showed 41 out of 44 scans with positive PSMA findings while 03 scans were negative for any PSMA avid disease. In the first phase of image analysis, the level of agreement was slight in T stage (Kappa = 0.068, p = 0.65), moderate in the miN stage (Kappa = 0.46, p = 0.02) and substantial in miM stage (Kappa = 0.77, p ≤ 0.001) was seen. For PSMA score, overall agreement was substantial agreement (Kappa = 0.64, p < 0.01). In the second phase, miT stage and miN stage showed total agreement (Kappa = 1, p < 0.001), and miM stage showed strong agreement (Kappa = 0.90, p < 0.001) while PSMA score in all three stages showed total agreement (Kappa = 0.9, p < 0.01). **Conclusion:** Remarkable inter-observer agreement was seen in PROMISE criteria.

Keywords

^{68}Ga-PSMA, PET-CT, PROMISE Criteria, PSMA Score, Inter-Observer Variability

1. Introduction

In men, prostate cancer (PC) is the second frequent neoplasm [1] and a primary cause of cancer-associated mortality [2]. It is a commonly diagnosed malignancy and shows a broad spectrum of disease presentation ranging from a subclinical/indolent to very aggressive advanced disease [3].

The imaging modalities which are conventionally used in the management of prostate cancer include: Transrectal Ultrasound (TRUS) which has a sensitivity and specificity of 40% - 50% [4], Magnetic Resonance Imaging (MRI), a gold standard for the detection of localized prostate cancer and which has sensitivity and specificity approaching 75% and 90% respectively [5]. Computed Tomography (CT) is usually used for nodal staging and has documented sensitivity of 40% [6]. ^{99m}Tc-MDP bone scan which is the most used technique in the assessment of bone metastases in advanced PC [6] and Positron Emission Tomography & Computed Tomography (PET-CT) is rapidly evolving imaging technique that detects the functional status of tumors.

^{18}F-FDG (fluorodeoxyglucose) PET-CT is used in the management of various tumors but is ineffective for the diagnosis of PC owing to the low metabolic glucose activity of tumor and the urinary excretion of FDG [7]. ^{18}F-Fluciclovine PET-CT, an FDA approved leucine analog, useful in suspected recurrence and advanced metastatic disease, however, has poor specificity for primary tumors and low sensitivity for nodal disease [8] while various radiolabeled PSMA-ligands identify the location and extent of the recurrent disease better than any other anatomical and functional imaging techniques.

^{68}Ga PSMA-11 PET-CT has high sensitivity and specificity of 80% and 97%, respectively [9]. In newly diagnosed high-risk PC, it is used for the detection of occult regional & metastatic disease [10], prior to surgical procedures or planning external beam radiation [1]. ^{68}Ga PSMA is also performed before and during PSMA-directed therapy, for staging [11] or in biochemical recurrence if serum PSA levels are rising after curative treatment [12] or for localization of tumor tissue in recurrent PC [1].

Due to rapidly evolving role of PSMA PET-CT in management of PC and ever-increasing use of technique globally, consensus criteria have been considered vital to standardize interpretation of PSMA PET-CT scans. Such criterion is expected to reduce variability of terminology in interpretation, minimize differences in interpretation of degree of tracer uptake and also reduced false positive or false negative interpretations. Different interpretation criteria for the standardized reporting and interpretation of PSMA PET-CT have been proposed re-

cently, including Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) criteria by Eiber *et al.* PROMISE criteria comprise of molecular imaging TNM (miTNM) framework for PSMA-ligand PET-CT prostate cancer staging and PSMA score for the expression of PSMA in a tumor lesion. miTNM was proposed for standardized reporting of the presence, location, and extent of local prostate cancer and its regional spread and extra-pelvic metastases. The miPSMA score enables the standardized reporting of PSMA expression in PSMA ligand PET-CT. Expression categories are defined with mean uptake in the blood pool, liver, and parotid glands. Results are reported as 0, 1, 2, or 3 for no, low, intermediate, or high PSMA expression, respectively. Expression level is determined visually, and uptake measurements can be quantitatively analyzed to correctly assign a specific miPSMA score [13].

Before worldwide standardization, validation of PROMISE criteria for appropriate image interpretation and reproducibility between the readers, it is necessary to evaluate intra- and inter-observer variability, as it was based on their joint clinical experience. Many studies have assessed the inter- and intra-observer variability of PROMISE criteria along with other criteria used in the interpretation of PSMA scan, to evaluate their reproducibility among different centers and observers and to device a standard criterion for the interpretation of PSMA PET-CT including Demirci *et al.*, Derwael *et al.*, Tohaira *et al.* and Gultekin *et al.*

INMOL being the pioneer center of the country that started PSMA-11 PET-CT scans in November 2017, receives maximum referral for the scan from across the country. The center regularly performs the scans in PC patients and has recently adopted the PROMISE criteria for routine interpretation of scans.

Objective of the study was to evaluate interobserver variability in reading the ^{68}Ga PSMA-11 scans while applying the PROMISE criteria.

2. Materials and Methods

2.1. Patients

Forty-four patients' scans were prospectively analyzed, performed for various indications at PET-CT Department INMOL during the period between January 2021 and June 2021. All those patients were excluded who had primary pathology of reference organs such as aorta, liver, or parotid glands. Patients who received LHRH agonists before staging of prostate cancer or those who underwent Chemotherapy within six weeks prior to the scan, or patients who received ^{177}Lu Radioligand therapy were also excluded from the study.

2.2. Instrumentation/Protocol

All scans were conducted on Discovery STE PET-CT system (GE, healthcare, USA) with 16 slice CT scanner. CT images were acquired before PET acquisition (3.8 mm slice thickness, 100 kV, 50 mA) and the time of acquisition was 5 seconds per bed position for seven to eight-bed positions while PET emission data were acquired at 3 - 4 minutes/bed position from the base of the skull to

mid-thigh in three-dimensional mode with Bismuth Germanium scanner (BGO). PET images were reconstructed using CT data by iterative reconstruction.

PSMA 11 was obtained from ITM, Germany and the dose of ^{68}Ga-PSMA-11 was calculated as per body weight, on average 02 MBq per kg body weight was given. PET-CT scan was carried out after 45 - 60 minutes post PSMA administration.

2.3. Image Interpretation

All PET-CT scans were interpreted by a researcher and 3 nuclear physicians divided into two groups, in two phases according to templates provided in PROMISE criteria. All observers were blinded to patient's clinical data. During first phase, each group separately evaluated the scans and in the second phase a consensus meeting was held where all the cases with discordance were discussed.

The images were displayed simultaneously as PET, CT, fused PET-CT in axial, sagittal, and coronal sections, and 3D MIP (maximum intensity projection). Image analysis was done by using two reporting systems *i.e.*, ADW 4.4 workstation and MAC Osirix MD software.

Any focal area of increased ^{68}Ga PSMA uptake higher than the physiologic pattern of PSMA uptake or PSMA score ≥ 2, 3 were considered positive for the disease. The location of ^{68}Ga PSMA uptake within the prostate gland and its extracapsular extension, regional and distant nodes, skeletal and visceral involvement were described according to the miTNM template by Eiber *et al.*, except for sextant anatomy template of prostate gland. Due to low dose CT, arbitrary landmarks were used, and localized lesion was classified as unifocal, multifocal or extra-prostatic extension.

For miPSMA score, visually as well as quantitatively SUVmax (maximum standardized uptake value) was measured in parotids, mediastinal blood pool, and liver. A two-dimensional Region of Interest (ROI) was drawn with the width of 1.5 cm on the right parotid, 2 cm on the aortic arch for mediastinal blood pool uptake, and a 3 cm ROI on the 6th segment of the liver. The abnormal uptake was measured with a ROI width of 1 cm for prostatic fossa, nodal and osseous lesions while the lesion sizes were measured on the corresponding CT images in two dimensions as well.

2.4. Interobserver Variability

The two groups independently recorded their findings and concluded miTNM staging as well as PSMA score and interobserver agreement was seen in each stage, *i.e.*, miT, miN and miM stage along with PSMA score in the two phases.

2.5. Statistical Analysis

SPSS 25 was used for statistical analysis and Cohen's Kappa test was used to measure interobserver variability. Values for alpha statistics range from −1 to 1, and a rough guideline for interpreting the degree of agreement adapted from

kappa statistics is as follows: <0.00 = total disagreement, 0.00 - 0.20 = slight agreement, 0.21 - 0.40 = fair agreement, 0.41 - 0.60 = moderate agreement, 0.61 - 0.80 = substantial agreement, 0.81 - 1.00 = almost perfect agreement. A cut-off of K's alpha < 0.61 was chosen to indicate substantial disagreement and a p value of ≤0.05 was considered as statistically significant [14].

3. Results

3.1. Patients Characteristics

In our study, the most common indication for PET-CT scan was the staging of prostate cancer in intermediate and high-risk patients and the mean age of patients was 69.18 ± 7.35 years with a serum PSA levels' median value of 12.3 ± 103 ng/ml. The Gleason score is calculated using histological features and most common observed Gleason score was 7 in our study. Characteristics of patients are given in **Table 1**.

In parotid gland, the physiologic PSMA uptake ranged from SUVmax of 4.3 to 24 with a mean value of 14.1 ± 4.7. In the mediastinal blood pool, the PSMA

Table 1. Patient characteristics (n = 44).

Patient Characteristics		N (%)	Scans		N (%)
Clinical Indications	Staging	17 (39%)	Positive Scans		41 (93%)
	Biochemical Recurrence	15 (34%)	Negative Scans		3 (7%)
	Restaging after therapy	12 (27%)	Lesions*		
Age (years) Range: 48 - 84 years, Mean: 69.18 ± 7.35 years	≤50	1 (2%)	Prostatic Fossa Involvement (T stage) 34 (83%)	T2u	13 (38%)
	51 - 60	3 (7%)		T2m	03 (9%)
	61 - 70	26 (59%)		T3b	09 (26%)
	71 - 80	11 (25%)		T4	07 (21%)
	≥81	3 (7%)			
Serum PSA Level (ng/ml) Range: <0.025 - 544 ng/ml, Median 12.3 ± 103 ng/ml	≤10	23 (52%)	Regional Nodal Involvement (N stage) 17 (41%)	N1	05 (29%)
	11 - 20	7 (16%)			
	21 - 100	9 (20%)		N2	11 (65%)
	≥101	5 (11%)			
Gleason Score	<7	1 (2%)	Distant Metastasis (M stage) 23 (56%)	M1a	11 (48%)
	7	22 (50%)		M1b	17 (74%)
	8	15 (34%)		M1c	05 (22%)
	≥9	6 (14%)			

*Total number of cases in which local, nodal, or distant metastatic lesions are seen.

uptake ranged from SUVmax of 0.25 to 2.1 with a mean value of 1.08 ± 0.4 and in the liver, it ranged from SUVmax of 0.48 to 11.48 with a mean of 5.2 ± 2.2. Following Figure 1 shows the graphical representation of the PSMA expression and its frequency in our study.

The frequency of PSMA Score observed was 7%, 18%, 18%, and 57% for Score 0, 1, 2, and 3 respectively. The most common observed PSMA score was 3, as shown in Figure 1.

Out of 44 scans, 13 (30%) cases had alone prostatic fossa involvement with/without extra prostatic extension. Involvement of regional lymph nodes was seen in 17 (38%) while distant metastatic nodes were seen in 11 (25%) of cases. Unifocal, oligometastatic, disseminated bone involvement osseous metastases and diffuse involvement of bone/marrow was seen was seen in 03 (18%), 03 (18%) cases, 10 (59%) and in 01 (6%) cases, respectively. Liver involvement was seen in 4 out of 5 cases and a single case of non-PSMA avid lung of total 22 % cases of visceral metastases. Summary of total lesion are given in Table 1.

Following Figure 2 shows some of the examples of PSMA scans on miTNM template from our study.

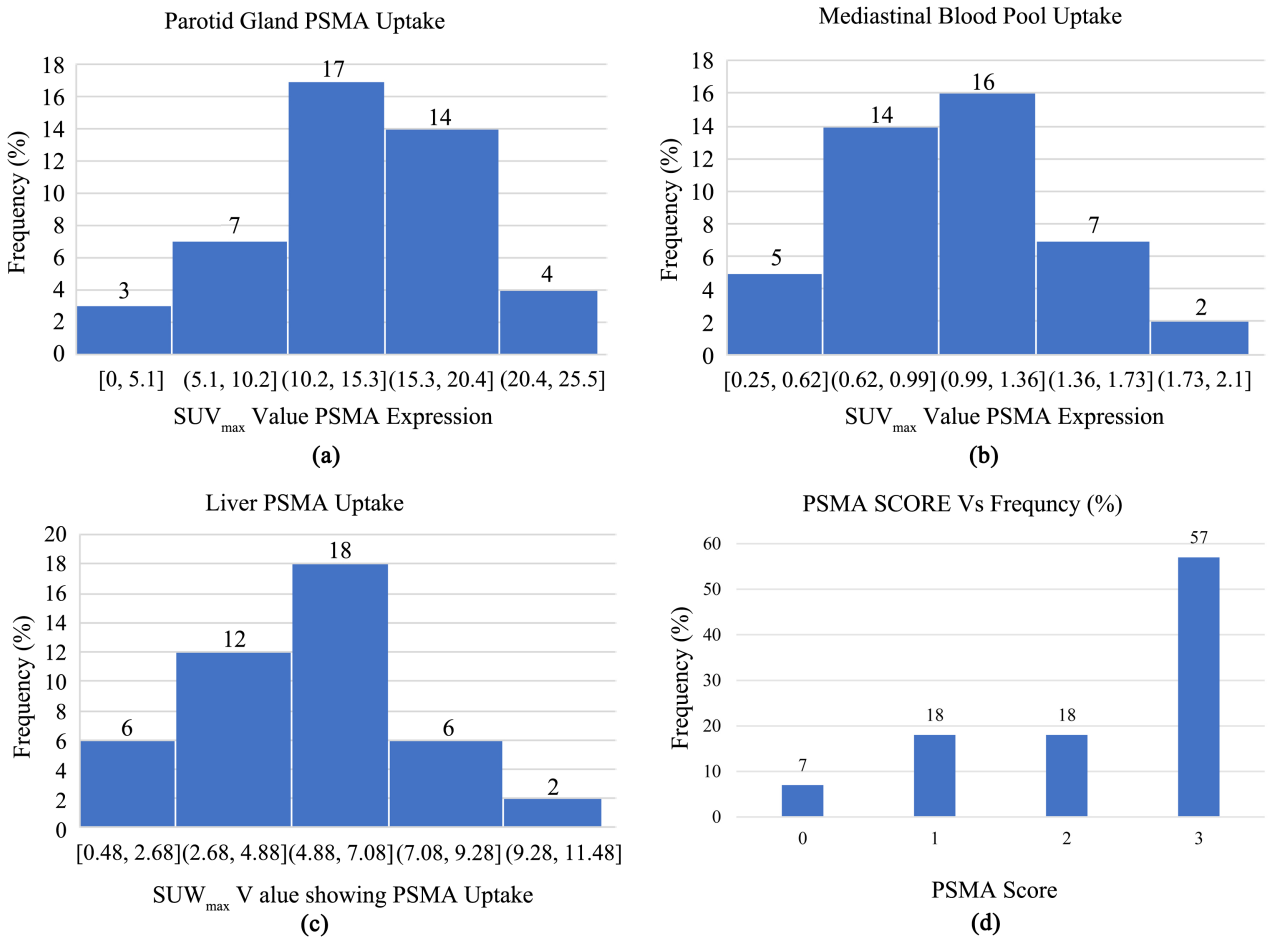

Figure 1. Graphical representation of PSMA expression; (a)-(c): show PSMA expression in parotid glands, mediastinal blood pool and liver respectively, and (d): shows frequency of PSMA score observed in our study.

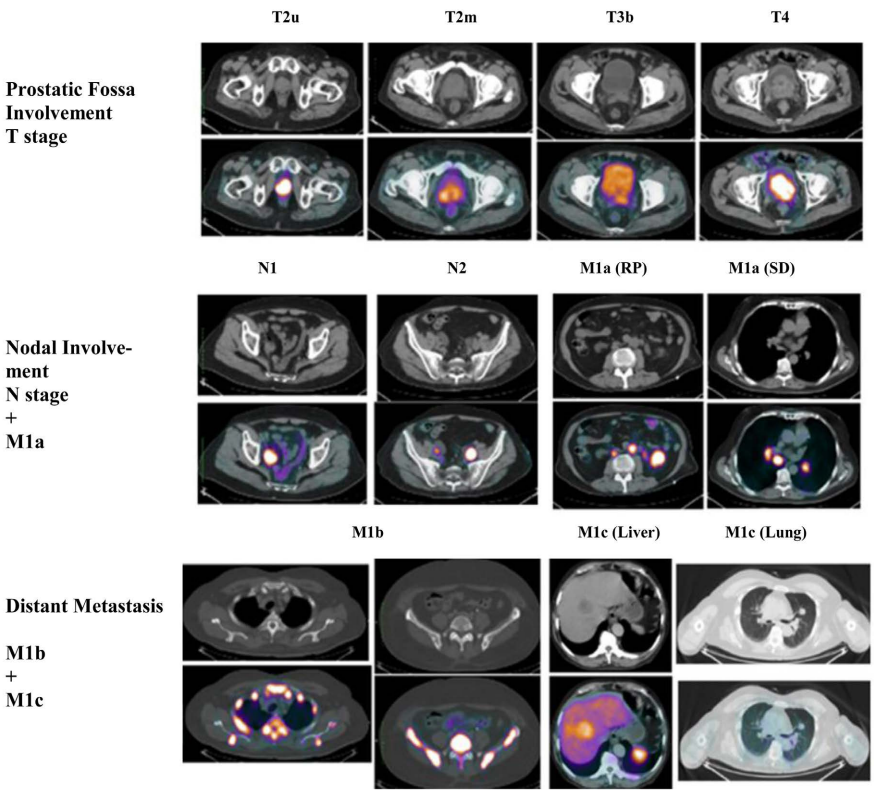

Figure 2. Pictorial representation of miTNM template in our study.

3.2. Interobserver Variability

The summary of interobserver agreement in both phases is shown in Figure 3 in miT, miN, miM and PSMA score.

3.3. First Phase of Image Analysis

The agreement in T stage was on 55% cases (24/44) between the two groups on the involvement of prostatic fossa while disagreement was on 45% (20/44) cases. Out of 24 cases in which agreement was seen, 16 were diseased and 08 cases were not diseased. Slight agreement was found in miT stage with Kappa of 0.068, and a p-value of 0.65.

In N stage, the agreement was on 77% (34/44) cases and disagreement was on 23% (10/44) cases. Out of 34 cases of agreement, 26 cases were not diseased and 8 were diseased. Moderate agreement was found in miN stage with Kappa = 0.46, and significant p-value (p value 0.02).

In M stage, the agreement was on 89% (39/44) cases and disagreement was on 11% (5/44) cases. Out of 39 cases in which agreement was achieved, 20 were diseased and 19 were not diseased. Substantial agreement was observed in miM stage (Kappa = 0.77, $p \leq 0.001$) with a significant p-value.

For PSMA score overall agreement was seen in 77% (34/44) cases, disagreement was seen in 23% (10/44) cases. Substantial agreement was observed in PSMA score with Kappa value of 0.64 and significant p-value (p-value of <0.01).

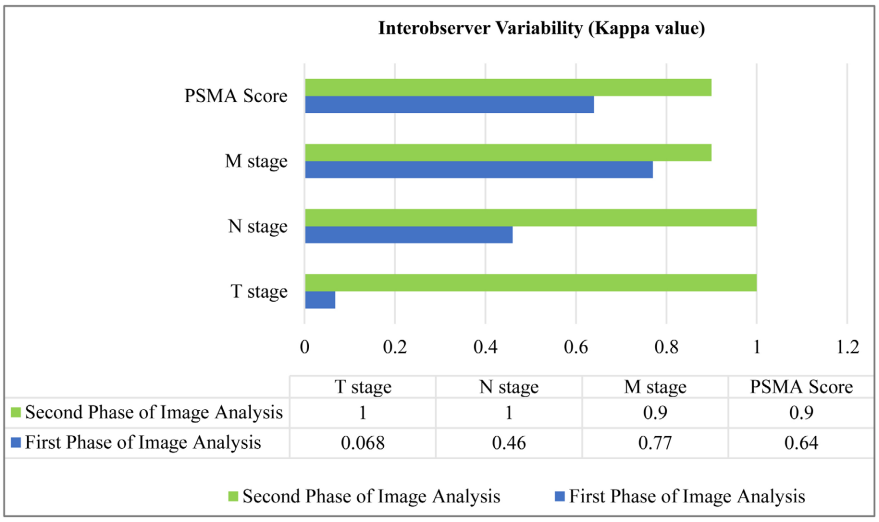

Figure 3. Graphical representation of Interobserver variability (Observer = 4, divided into 2 Groups).

3.4. Second Phase of Image Analysis

A consensus meeting was held and all the cases with disagreement were discussed in this phase. miT stage and miN stage showed total agreement (Kappa = 1) with a highly significant p-value ($p < 0.001$) while in the miM stage, a strong agreement was seen (Kappa = 0.90) with a significant p-value ($p < 0.001$) but in 2 (5%) cases; no agreement could be achieved.

Cases with no agreement consist of one case with *staging of miT0N0M1c*; non-PSMA avid lung nodule (HU of 16, measuring 1.8 cm × 1.7 cm) without any other avid disease, while other case had *miT0N0M1a staging* with a single PSMA avid hilar node of score 3 (SUVmax 33, measuring SD: 4.7 mm).

After the consensus meeting, overall total agreement (Kappa = 0.9, $p < 0.01$) was seen in the PSMA score in all three stages.

4. Discussion

The ^{68}Ga PSMA PET-CT scan has a significant role in the management of the prostate cancer, given to its highest sensitivity, specificity, and accuracy than other imaging modalities and conventional radiotracers. Hence the standardization of an interpretation criterion for the PSMA scan was and is very important need of time. Out of the all-proposed interpretation criteria for PSMA PET-CT scans, PROMISE criteria seem more reproducible due to the incorporation of TNM staging with PSMA expression in the form of PSMA score. But PROMISE criteria still requires validation and standardization for image interpretation with less pitfalls and better reproducibility among readers with different clinical experiences irrespective of different imaging techniques, workstations, and characteristics of studied sample. This study was done to evaluate the reproducibility of PROMISE criteria in our clinical setup among readers of different clinical experiences with different workstations.

This study demonstrated the better level of agreement in nodal and metastatic diseases as compared to localized prostatic uptake in the first phase of image analysis, while in the second phase of image analysis, total agreement was seen in miT & miN stages and strong agreement in miM stage, proving reproducibility of PROMISE criteria.

Demirci *et al.* showed substantial agreement in the miT, miN, and miM reporting of the readers, with the highest agreement level in miM and lowest agreement in miT [15]. In a study by Tohaira *et al.*, 104 patients with prostate cancer were retrospectively reviewed on PROMISE along with other two interpretation criteria *i.e.*, EANM, and PSMA RAD. In the PET/CT group, inter-reader agreements were substantial to almost perfect in any sites according to all the three criteria, except in the evaluation of distant metastases based on PSMA-RADS [16]. In another study, Derwael *et al.* reported the miT and miN classification with a substantial agreement, while the miM classification with an almost perfect agreement. The overall miTNM classification was concordant for 60% patients, and observers' agreement was substantial (K = 0.64; 95% CI 0.48 - 0.76) [17]. In a study by Gultekin *et al.*, the intraobserver agreement was substantial and almost perfect for miT, miN, and miM, respectively [18].

The studies mentioned above are in line with our findings. The lowest interobserver agreement seen in the miT stage of first phase of image analysis was because of physiological PSMA expression in the prostatic tissue as well as activity in the prostatic urethra and poor sensitivity of low dose CT for the pelvic structures. At the consensus meeting, all these possible factors were discussed and hence agreement was achieved.

The 2 cases of discordance in the miM stage were seen in a non-PSMA avid lung nodule with the borderline malignant features and a hilar lymph node of PSMA score 3 without any other PSMA avid lesion specific for prostatic cancer as shown in **Figure 4**.

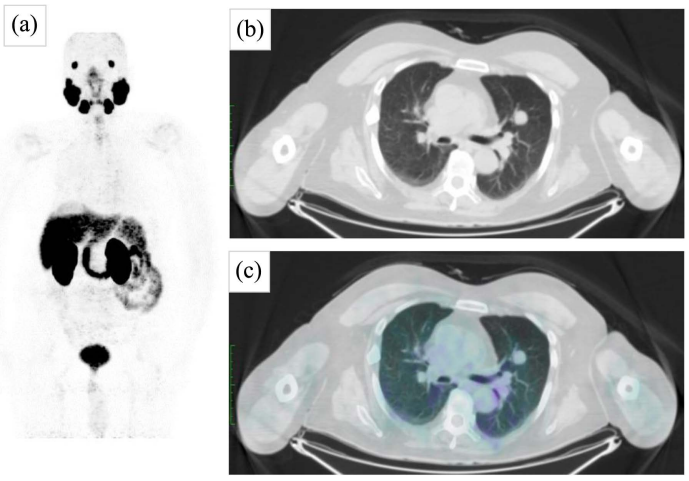

Figure 4. A case of discordance in our study in miM stage during second phase of image analysis; a case of solitary PSMA non-avid lung nodule (measuring 1.8 × 1.7 cm, HU: 16) (a): MIP Image, (b), & (c) on CT lung window and PET hybrid images.

PSMA uptake has been reported in various benign diseases and non-prostatic malignant tumors as well, including lung cancer. According to Keidar *et al.* study, the prevalence and degree of ^{68}Ga-PSMA avidity of non-malignant lymph nodes represents 38% out of all non-malignant findings while up to 10% of findings included focal or diffuse uptake in the thyroid, in lung lesions or ganglions [19]. In a study by Damjanovic *et al.*, the imaging characteristics of pulmonary metastases and opacities on ^{68}Ga-PSMA-PET scan were investigated. Most of the lung metastases showed overexpression of PSMA, PSMA-negative metastases showed decreased uptake and were undetectable directly by ^{68}Ga-PSMA-PET, while pulmonary opacities showed a moderate tracer uptake. The PSMA-negative metastases observed cases in this study were 27.5%. The reason of heterogeneity of ^{68}Ga-PSMA uptake in lung metastases is because of diverse histological variants of prostate cancers metastases, e.g., neuroendocrine differentiation of the metastases [20].

The non-PSMA avid lung nodule observed in our study might be the non-adenocarcinoma variant of the PC that's why no remarkable PSMA uptake was seen.

Dias *et al.* reported 2 cases of ^{68}Ga-PSMA PET-CT in PC patients with symmetrical bilateral involvement of mediastinal and hilar lymph and on endobronchial ultrasound guided biopsy, it was found to be involved by non-necrotic granulomas compatible with sarcoidosis. This demonstrated that false positive PSMA uptake can be seen in lymph nodes with active sarcoidosis [21]. While in a study by Afshar-Oromieh *et al.*, mediastinal and paraaortic lymph nodes were evaluated both histologically and their imaging characteristics were compared to lymph nodes metastases of PC. It was observed that lymph nodes showing strongest PSMA expression had follicular hyperplasia on histopathology and mediastinal lymph nodes which most commonly are activated shows usually lower uptake at 1-hour post injection imaging [22].

The disagreed case of single remarkably PSMA avid hilar node in our study is still debatable as it could be of inflammatory origin leading to false positive PSMA uptake or could be metastatic lymph node given the PSMA score 3 at 1-hour imaging without preserved fatty hilum but the short axis diameter of 4 mm were other factors causing the disagreement. As recommended by Afshar-Oromieh *et al.* in such uncertain grading cases of PSMA-positive lymph nodes additional imaging should be done at 3-hour post injection and in cases of tumor-free PSMA avid mediastinal and paraaortic lymph nodes should be verified histologically [22].

For PSMA score interobserver variability, overall substantial agreement was observed with a significant p-value in our study, and after consensus meeting total agreement was seen. While in Derwael *et al.* study, miPSMA score agreement was substantial in T & M stage while moderate in the N stage [17].

Calculation of PSMA score is highly dependent on the visual assessment of appropriate intensity setting as well as on the system used. In our study we used 2 different systems for the interpretation of scans, and it may require some time

before the observer becomes used to different display settings of the two systems. This may play a role in inter observer variability. Hence the discordance in PSMA score is seen and inter-reader agreement was overall calculated in our study.

Limitation of the study includes small sample size due to relatively new imaging modality with availability in limited centers, the conventional approach of managing prostate cancer; monitoring serum PSA levels in BCR or staging with conventional imaging techniques (Bone scan, CT, and MRI), the import of ^{68}Ge/^{68}Ga generator and the limited radioisotope supply was other limitation.

5. Conclusion

There is minimum interobserver variability in ^{68}Ga PSMA-11 PET-CT interpretation according to PROMISE criteria in our experience. Current prospective study of 44 patients with PC showed remarkable inter-observer agreement in all three stages of miTNM and PSMA score.

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Conflicts of Interest

There were no conflicts of interest.

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