J of Nuclear Medicine Technology, first published online July 9, 2021 as doi:10.2967/jnmt.120.261289

Correlation of lesional uptake parameters and ratios with miPSMA score and estimating normal physiological concentration: an exploratory analysis in mCRPC patients with ^{68}Ga-PSMA-11 PET-CT

[1,2]Ashwini Kalshetty, [1,2]Biju Menon, [1,2]Sutapa Rakshit, [2,3]Atanu Bhattacharjee, [1,2]Sandip Basu

[1]Radiation Medicine Centre, Bhabha Atomic Research Centre, Tata Memorial Centre Annexe, Jerbai Wadia Road, Parel, Mumbai 400012

[2]Homi Bhabha National Institute, Mumbai, India

[3]Department of Biostatistics, ACTREC, Tata Memorial Centre

Author for correspondence:

Sandip Basu, [1]RADIATION MEDICINE CENTRE, BHABHA ATOMIC RESEARCH CENTRE, TATA MEMORIAL HOSPITAL Annexe, Jerbai Wadia Road, Parel, Mumbai, Maharashtra, India, 400 012. [2]Homi Bhabha National Institute, Mumbai, India. Phone: 91 22 24149428. Email: drsanb@yahoo.com

KEYWORDS: ^{68}Ga-PSMA-11 PET-CT; miPSMA score; ^{177}Lu-PSMA-617, Metastatic Castrate Resistant Prostate carcinoma (mCRPC); Peptide receptor radioligand therapy (PRLT), PSA

No potential conflicts of interest relevant to this article exist

Abstract:

Background and Aim:

The employment of prostate-specific membrane antigen (PSMA)-based PET-CT imaging has grown rapidly over the recent years. The aim of the present study was to estimate the lesional uptake across the different levels of molecular imaging PSMA (miPSMA) expression score along with normal physiological concentration of ^{68}Ga-PSMA-11 in a cohort of mCRPC patients including their temporal variation on delayed imaging.

Materials and Methods:

Fifty patients of mCRPC who were being evaluated for ^{177}Lu-PSMA PRLT, and underwent ^{68}Ga-PSMA-11 PET-CT for evaluation of disease status, were retrospectively evaluated. The mean age of the patients undergoing the scan was 67.5 ± 8 years (52-84 years) with an average serum PSA level of 401 ± 1353 ng/ml (0.098-9235.13 ng/ml) at the time of scanning. All patients underwent standard ^{68}Ga-PSMA-11 PET-CT at 65 minutes post-injection on an average (60-90 mins). Tumoral analysis (n= 50) was undertaken to see their correlation with miPSMA expression score and their uptake values. The physiological tracer distribution was estimated by placing a spherical VOI of fixed diameter of 1 cm for smaller organs (in the regions of submandibular glands, parotid glands, lacrimal glands, tubarial glands, renal cortices, blood pool and bowel) and 3 cm for larger organs (liver and spleen). Standardised uptake value maximum (SUVmax) and mean (SUVmean) were estimated for each of the regions. Tumor-to-spleen (T/S), tumor-to-liver (T/L) and tumor-to-parotid (T/P) ratios were calculated for each lesion. A subgroup of 16 patients underwent a delayed scan at 135 mins post injection on average (120 – 150 mins), for whom an additional analysis was performed to evaluate the effect of delayed imaging on uptake values and ratios.

Results:

The maximum uptake was observed in renal cortices followed by salivary glands, bowel, spleen, liver, lacrimal glands and blood pool in the descending order. The average SUVmax with SD of the organs are as: 37.7 ±22.1 for renal cortices, 15.4 ±7.3 for submandibular glands, 14.4 ± 7.1 for parotid glands, 9.4± 4.9 for spleen, 6.2 ± 3.7 for lacrimal glands, 5.9± 2.3 for liver, 5.3 ± 1.41 for tubarial glands, 13.8 ±7.6 for bowel, and 2.4 ±1.9 for blood pool. The average SUVmax of miPSMA expression score 2 was 10.33 ± 3.27 (6.46 - 17) and 38.21 ± 25.9 (7.68 – 119.08) for score 3. The average tumor-to-spleen (T/S) and tumor-to-parotid (T/P) ratios for score 2 lesions were 1.21 ± 0.44 (0.48 – 2.04) and 0.6 ±

0.18 (0.39- 0.87) respectively. The average T/S and T/P ratios for score 3 lesions were 5.05 ± 4.46 (1.25 – 20.89) and 3.15 ± 2.09 (1.06 – 9.45) respectively. The average SUVmax of index score 3 lesions was 18.85 which increased to 26.24 on delayed imaging with statistically significant difference (p=0.0001). However, the T/L, T/S and T/P ratios did not show any significant change. The temporal variation of normal organs showed that the SUVmax was significantly increased in delayed scan in salivary (submandibular and parotid) and lacrimal glands, and renal cortices, while the SUVmean significantly increased in spleen and liver, parotid, tubarial and lacrimal glands and not significant in other organs.

Conclusion:

Thus, the reference ranges of normal organs (physiological uptake) and tumor lesions for uptake and ratios for miPSMA score 2 and score 3 were documented and established in the present study, based upon which a consensus on standard reference range can be proposed for all quantitative assessment values on ^{68}Ga-PSMA-11 PET-CT. The temporal variation trends of the lesions and reference organs should be kept in mind for delayed acquisitions, the T/S, T/Lor T/P ratios could serve as better markers for such scenarios.

Introduction:

PSMA labelled radioligands for PET-CT imaging in patients suffering from prostate carcinoma have brought about a major change in the management of the disease. Furthermore, recent introduction of the PSMA targeted radionuclide therapy for castration resistant prostatic carcinoma patients has opened up new areas of application for the theragnostic pair for diagnosis as well as for treatment, upholding great promise for precision oncology. The role of PET-CT targeting PSMA expression is well documented for staging and for detecting recurrence even in those with low serum PSA levels (*1*). Because of its high sensitivity and specificity, there is currently an expansion in the use of PSMA PET-CT during the course of disease at the various stages.

The recently published PROMISE study has set guidelines for standard miTNM staging on PET-CT (2). The qualitative image assessment systems such as the miPSMA expression score is a proposed robust tool for defining objectivity in interpretation and staging (*2, 3*), though they are yet to be validated for routine clinical use and their reproducibility in larger samples is yet to be tested. The miPSMA expression score takes into account the relative intensity by visual assessment of the lesions with respect to the internal reference of organs such as normal tracer uptake like liver or parotid glands. Confirmation of normal biodistribution with the known range objectively can serve as an in vivo method of quality control as well as validate the observations made in the proposed scoring system, and there is a relative paucity of data on this topic, especially the temporal variation of such uptake (*4-6*). In this study, we attempted to first reproduce the normal ranges of ^{68}Ga-PSMA-11 in a subset of population of prostate carcinoma and subsequently endeavoured to observe the correlation of the miPSMA expression scores with various objective parameters like SUVmax, tumor-to-spleen (T/S), tumor-to-liver (T/L) and tumor-to-parotid (T/P) ratios in an effort to supplement subjective observations and correlating the semiquantitive values with the miPSMA scores.

Materials and Methods:

A total of 50 patients of mCRPC who were being investigated for feasibility of ^{177}Lu-PSMA PRLT and underwent^{68}GA-PSMA-11 PET-CT either for staging or restaging in past 2 years were retrospectively analysed. The institutional medical ethics committee approved this retrospective study and the requirement to obtain informed consent was waived. The various general and clinical data like patient's age, Gleason score (GS), history of surgery, history of prior therapy (Hormonal/Chemotherapy/Radiotherapy/ ^{177}Lu-PSMA PRLT) and recent prostate-specific antigen

(PSA) levels were noted from the patient's medical records. The mean age of the patients was 67.5 ± 8 years (range: 52-84 years) with mean Serum PSA of 401 ± 1353 ng/ml (0.098-9235.13 ng/ml) at the time of PET-CT scanning. The Gleason's score were categorised as per the ISUP Consensus grading, into 5 groups (7). The overall patient characteristics were as described below (Table 1a and 1b).

PET-CT acquisition protocol:

After appropriate preparation and quality control of the radiotracer ^{68}Ga-PSMA-11, all patients were administered an average dose of 103.23 ± 22.2 MBq (range 74 –166.5) and 2 ml furosemide (10 mg/ml) intravenously. Following the injection, an oral contrast (10 ml Urograffin) diluted in 1-litre water was advised to drink within 1 hour for optimal contrast in the abdominal pelvic region. Patients were asked to void before imaging to reduce urinary bladder activity, and whole-body scans were acquired at 65 min on average (range 60–80min) post-injection (p.i.) of the radiotracer. A sub-group of 16 patients underwent delayed scanning 135 mins p.i. on average (120 – 150 mins), after consenting to the procedure.

The PET/CT scans were acquired using a (Philips Gemini TF 16) PET-CT scanner. CT surview (90kV, 20mA) followed by CT scan (100 mA, 120 kV, the field of view about 600 mm, CT slice thickness 2.0mm, standard resolution, 16x1.5 collimation, 0.813 pitch, 512x512 matrix) was performed for PET attenuation correction. After CT, whole-body PET imaging was acquired in 3D mode, 8-10 bed positions, 2-minute emission per bed, from mid-thighs to the base of the skull with the arms-up position. Images were reconstructed using a standard iterative algorithm based upon the Row Action Maximum Likelihood Algorithm 3-D RAMLA. The ^{68}Ga-PSMA PET/CT data were evaluated in a dedicated Philips EBW workstation.

VOI measurements:

The physiological tracer bio-distribution was assessed in each patient by placing spherical VOIs [diameter 1 cm for smaller organs (renal cortex, submandibular glands, parotid glands, lacrimal glands, the newly described tubarial glands (8), blood pool (abdominal and thoracic aorta) and bowel] and 3 cm of larger organs (liver and spleen). The maximum standardized uptake value (SUVmax) and SUVmean for each of the above regions were estimated (average of 2 measurements for smaller organs and 3 for larger). The schematics of measurement is illustrated in figure 1.

For the first part of the study where the miPSMA Score was correlated with SUV, only the most intense lesion per patient was selected. In the second part where temporal analysis was performed on a smaller cohort (n=16), additional lesions per patient were considered to observe the trend in the delayed imaging. These lesions were considered in the following order: primary, nodes, bone (1-2) and then other soft tissue metastases. All these lesions were closer in intensity to the 'index' lesions measured in first part.

In the subgroup of patients with additional delayed scans, we noted the same quantitative parameters in all the regions in similar manner. The lesions with maximum intensity in each scan was marked as the 'index lesion' (n= 50). We used a fixed 1 cm VOI for measuring SUVmax of such lesions. We measured additional lesions for the subgroup temporal analysis amounting to total of 40 lesions. The miPSMA score was used for classifying the lesions as per the PROMISE trial (2):

We noted the SUVmax of all individual lesions against their grades. Apart from the directly measured SUVmax of these lesions, we also estimated tumor-to-parotid (T/P), tumor-to-spleen (T/S) and tumor-to-liver (T/L) ratios. For the sub-group of patients (n=16), who underwent additional delayed imaging), the analysis was undertaken to evaluate the temporal variation of these parameters.

Statistical analysis

Continuous data were represented as mean with SD. All data was verified for normal distribution. Groups with equal variance were tested for any significant difference between them by using paired t-test. The unpaired t test was used for groups with unequal variance. P-value<0.05 was considered significant.

Results:

Physiological uptake:

The SUVmax and SUVmean of the organs with physiological uptake are represented as average values with their standard deviation, shown in (Table 2). The renal cortices showed highest SUVmax and SUVmean, followed by salivary glands, bowel, spleen, lacrimal glands, liver and blood pool. The mean SUVmax of the renal cortices was 37.72 ± 22.1, submandibular glands 15.44 ±7.34, parotid 14.36 ±7.05, bowel 13.81 ± 7.6, spleen 9.33± 4.98 of; lacrimal glands 6.16 ±3.68, liver 5.89 ± 2.32, tubarial

glands 5.3 ± 1.41and 2.36 ± 1.95 was that of blood pool. A chart showing the average values of SUVmean and SUVmax for the above mentioned regions is shown in figure 2.

Tumor Lesions:

When the lesions were scored as per the miPSMA expression score, we got primarily 2 categories, namely scores 2 and 3, primarily, as the patients referred to our centre were for ^{177}Lu-PSMA PRLT feasibility assessment and in the context had overt disease. The averages of SUVmax, T/S, T/L, T/P in each PSMA expression category were recorded. It appeared that score 3 lesions showed a mean of 3 times the PSMA expression of parotid glands and 5 times than that of the spleen (Table 3). The presentation and the relative comparison of SUVmax, T/S, T/L, T/P ratiosfor each categories of lesions (score 2 and 3) are illustrated in figure 3. We performed unpaired t-test for these two scores of PSMA expression (i.e. Score 2 and 3) and found significant differences for all the parameters (Table 3).

Temporal variation of uptake values:

The subgroup of 16 patients with paired early and delayed scans data also passed normality tests. Hence paired t-test was performed.

Temporal variation of normal organ physiological uptake values:

The paired t-test was undertaken to assess the variation of SUVmean and SUVmax between the first and second scan groups. The average SUVmean and SUVmax values for most organs remained similar on delayed images. The SUVmax was significantly increased in delayed scan in salivary (submandibular and parotid) and lacrimal glands, and renal cortices, while the SUVmean was significantly increased in spleen and liver, parotid, tubarial and lacrimal glands. The average of SUVmean and SUVmax in both studies with their respective p values are tabulated as follows (table 4):

Temporal variation of the tumor lesions:

A total of 40 prominent lesions were identified in the subgroup of 16 patients, who had dual time-point imaging, for evaluating the temporal variation of the values with time. After applying paired t tests we observed that there was significant difference of the SUVmax (an increase in the delayed scan) compared to the baseline PET-CT scan (p=0.0001), while there was no significant difference of the T/S, T/L or T/P ratios when compared to the one from second scan. The results are

as tabulated (table 5), while the temporal variation of the lesional parameters are graphically plotted in Figure 4.

Discussion:

The PSMA based PET-CT imaging and theragnostics has brought about a major change in the understanding and management of prostate cancer (*9-17*). The incorporation of semiquantitative and quantitative information continues to evolve and have the potential to enhance the fundamental understanding of tumour heterogeneity, in-vivo kinetics, and response to various therapies, hence can be a valuable supplement to visual interpretation and of paramount importance for undertaking clinical research (*9, 10, 13, 17*). The present study analysed^{68}Ga-PSMA-11, the most common PET tracer used in prostate cancer diagnostics currently. Our results for the physiological uptake align with some of the previously reported studies (*4-6*). Thus, we believe the present study results would allow a consistent pattern of normal range to be generated as a standard reference for future studies and research.

The miPSMA score as proposed by Eiber et al (*2*) gives an elaborate description for miTNM staging on PSMA based PET-CT. It is based on assigning a visual score from 0 to 3 as described above with internal organs as reference points. When physiological uptake is used as an internal reference for a scoring system, the ligand and biodistribution in the presence of high volume disease has to be kept in mind and interpreted accordingly. The demonstration of SUVmax values and their capacity to differentiate the grades of lesions can elicit the incremental benefit of objective evidence to accurately assign the score.

Furthermore, till date, there have been only a few studies that have compared and addressed intra- and inter-patient variability with ^{68}Ga- and ^{18}F- labelled PSMA ligands with the recommendation of using spleen as reference organ for ^{18}F-PSMA-1007 (*2, 4, 5, and 6*). Besides these variations, other factors which also can influence the uptake parameters like the patient-weight, injected dose and waiting duration, have not been conclusively studied. Hence, additionally, in the present study, we evaluated the effect of delayed imaging on the SUVmax and SUVmean in normal organs as well as SUVmax, T/S, T/L and T/P ratios for the tumor lesions.

In our study, the renal cortices showed highest SUVmax and SUVmean, followed by salivary glands, bowel, spleen, lacrimal glands, liver and blood pool. ^{68}Ga-PSMA-11 has been known to

demonstrate high renal uptake, as stated in literature, similar to the results obtained in our study. However, the maximum uptake in kidneys were slightly higher in the previous studies.

With respect to the temporal variation of normal physiological uptakes, the SUVmax showed a significant increase in delayed scan in salivary (submandibular and parotid) and lacrimal glands, and renal cortices, while the SUVmean was significantly increased in spleen and liver, parotid, tubarial and lacrimal glands. In one previous study, where no correlation was found between the uptake time and with ^{68}Ga-PSMA-11 SUVpeak in the liver (*4*). The semi-quantitative measurements in our study have additionally demonstrated the temporal variation of uptake values especially significant for lesions as well. While the SUVmax of lesions as a standalone parameter varied significantly with time, the tumor-to-spleen and tumor-to-parotid ratios did not show significant change. This would indicate that such temporal variations need to be kept in mind while interpreting images with delayed acquisitions and T/S, T/L or T/P ratios may be considered as better parameters. The other area where these values can have potential implications is treatment response assessment: the role of the quantitative parameters with receptor based PET-CT continues to be in developing phase and the various SUVs and ratios and their correlation with visual scoring can be useful for this purpose.

The limitations of this study are those related to retrospective nature, the limited number of cases and being a single centre source. We did not study the effect or variation of SUL (SUV normalised by lean body mass) in our sample, which has been postulated to be a more robust parameter for quantitative analysis (*18*). Our study aimed to establish a reference range for normal organs; however, coexisting pathologies in reference organs, though rare in a given case scenario, are possible (e.g. splenic haemangioma). When present, they would need to be validated and outliers can be identified. In the present study, the ratios were generated from a holistic perspective rather than a particular case in isolation. As standardization of such reference values becomes acceptable, we can get general idea to distinguish between normal and abnormal. We also have to mention here, that partial volume effect (PVE) was not considered in lesion selection in this analysis; the SUV value and visual score of a very small lesion may be underestimated to the partial volume effect.

Conclusion:

In conclusion, the reference ranges of normal organs (physiological uptake) and tumor lesions for uptake and ratios for miPSMA score 2 and score 3 were documented and established in the present study, based upon which a consensus on standard reference range can be proposed for all quantitative assessment values on ^{68}Ga-PSMA-11 PET-CT. The temporal variation trends of the lesion and the reference organs should be kept in mind for delayed acquisitions, the T/S, T/L or T/P ratios serve as better markers for such scenarios.

References:

1. Fendler, W. P., Eiber, M., Beheshti, M., Bomanji, J., Ceci, F., Cho, S., et al. (2017). ^{68}Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging. 44*(6), 1014–1024. https://doi.org/10.1007/s00259-017-3670-z

2. Eiber, M., Herrmann, K., Calais, J., Hadaschik, B., Giesel, F. L., Hartenbach, M., et al. Prostate cancer molecular imaging standardized evaluation (PROMISE): proposed miTNM classification for the interpretation of PSMA-Ligand PET/CT. *J Nucl Med.* 2017; 59(3), 469–478. Doi:10.2967/jnumed.117.198119

3. Rowe SP, Pienta KJ, Pomper MG, Gorin MA. PSMA-RADS Version 1.0: A step towards s standardisingthe interpretation and reporting of PSMA-targeted PET imaging Studies. *Eur Urol*. 2018 Apr;73(4):485-487. doi: 10.1016/j.eururo.2017.10.027. Epub 2017 Nov 11. PMID: 29132714; PMCID: PMC6859641.

4. Ferreira G., Iravani A., Hofman M. S., & Hicks R. J. Intra-individual comparison of 68Ga-PSMA-11 and 18F-DCFPyL normal-organ biodistribution. *Cancer Imaging*. 2019; 19(1). Doi:10.1186/s40644-019-0211-y

5. Prasad, V., Steffen, I. G., Diederichs, G., Makowski, M. R., Wust, P., & Brenner, W. Biodistribution of [68Ga]PSMA-HBED-CC in Patients with Prostate Cancer: Characterisation of Uptake in Normal Organs and Tumour Lesions. *Mol Imaging Biol*. 2016; 18(3), 428–436. Doi:10.1007/s11307-016-0945-x

6. Demirci, E., Sahin, O. E., Ocak, M., Akovali, B., Nematyazar, J., &Kabasakal, L. Normal distribution pattern and physiological variants of 68Ga-PSMA-11 PET/CT imaging. *Nucl Med Commun*. 2016; 37(11), 1169–1179. Doi:10.1097/mnm.0000000000000566.

7. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA; Grading Committee. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. *Am J Surg Pathol*. 2016; 40(2):244-52. Doi: 10.1097/PAS.0000000000000530. PMID: 26492179.

8. Valstar MH, de Bakker BS, Steenbakkers RJHM, de Jong KH, Smit LA, Klein Nulent TJW, van Es RJJ, Hofland I, de Keizer B, Jasperse B, Balm AJM, van der Schaaf A, Langendijk JA, Smeele LE, Vogel WV. The tubarial salivary glands: A potential new organ at risk for radiotherapy. *Radiother Oncol*. 2020; 23:S0167-8140(20)30809-4. Doi: 10.1016/j.radonc.2020.09.034. Epub ahead of print. PMID: 32976871.

9. Demirci, E., Kabasakal, L., Şahin, O. E., Akgün, E., Gültekin, M. H., Doğanca, T., et al. Can SUVmax values of Ga-68-PSMA PET/CT scan predict the clinically significant prostate cancer? *Nucl Med Commun*. 2019; 40(1), 86–91. Doi:10.1097/mnm.0000000000000942

10. Brito AET, Mourato FA, de Oliveira RPM, Leal ALG, Filho PJA, de Filho JLL. Evaluation of whole-body tumor burden with 68Ga-PSMA PET/CT in the biochemical recurrence of

prostate cancer. *Ann Nucl Med*. 2019;33:344–50. https://doi.org/10.1007/s12149-019-01342-z.

11. Miksch J, Bottke D, Krohn T, Thamm R, Bartkowiak D, Solbach C, et al. Interobserver variability, detection rate, and lesion patterns of 68Ga-PSMA-11-PET/CT in early-stage biochemical recurrence of prostate cancer after radical prostatectomy. *Eur J Nucl Med Mol Imaging*. 2020;47:2339–47. https://doi.org/10.1007/s00259-020-04718-w.

12. Stone, L. Predicting 68Ga-PSMA-PET–CT positivity for recurrent disease. *Nat Rev Urol*. 2018; 15, 137. https://doi.org/10.1038/nrurol.2018.15

13. Verburg FA, Pfister D, Drude NI, Mottaghy FM, Behrendt FF. PSA levels, PSA doubling time, Gleason score and prior therapy cannot predict measured uptake of [68Ga]PSMA-HBED-CC lesion uptake in recurrent/metastatic prostate cancer. *Nuklearmedizin* 2017;56:225–32. https://doi.org/10.3413/Nukmed-0917-17-07.

14. OnalCem, Nese Torun, OzanCemGuler, Mehmet Reyhan, Berna AkkusYildrim, and Ali FuatYapar. Is there a correlation between Gleason score and maximum sstandardised uptake value in locally advanced prostate cancer patients? *J Clin Oncol* 2019 37:7_suppl, 68-68

15. Van Leeuwen, P. J., Donswijk, M., Nandurkar, R., Stricker, P., Ho, B., Heijmink, S., et al. (2019). Gallium-68-prostate-specific membrane antigen (68Ga-PSMA) positron emission tomography (PET)/computed tomography (CT) predicts complete biochemical response from radical prostatectomy and lymph node dissection in intermediate- and high-risk prostate cance. *BJU International*, 124(1), 62–68. Doi:10.1111/bju.14506.

16. Jansen, B. H. E., Kramer, G. M., Cysouw, M. C. F., Yaqub, M. M., de Keizer, B., Lavalaye, J., et al.. Healthy Tissue Uptake of 68Ga-Prostate-Specific Membrane Antigen, 18F-DCFPyL, 18F-Fluoromethylcholine, and 18F-Dihydrotestosterone. J Nucl Med. 2019; 60(8), 1111–1117. Doi:10.2967/jnumed.118.222505.

17. Onal C, Guler OC, Torun N, Reyhan M, Yapar AF. The effect of androgen deprivation therapy on 68Ga-PSMA tracer uptake in non-metastatic prostate cancer patients. *Eur J Nucl Med Mol Imaging.* 2020; 47: 632–641. https://doi.org/10.1007/s00259-019-04581-4.

18. Gafita A, Calais J, Franz C, Rauscher I, Wang H, Roberstson A, et al. Evaluation of SUV normalized by lean body mass (SUL) in 68Ga-PSMA11 PET/CT: a bi-centric analysis. *EJNMMI Res*. 2019; 9: 103. https://doi.org/10.1186/s13550-019-0572-z.

Figure 1: Schema for drawing VOIs adopted in this study.

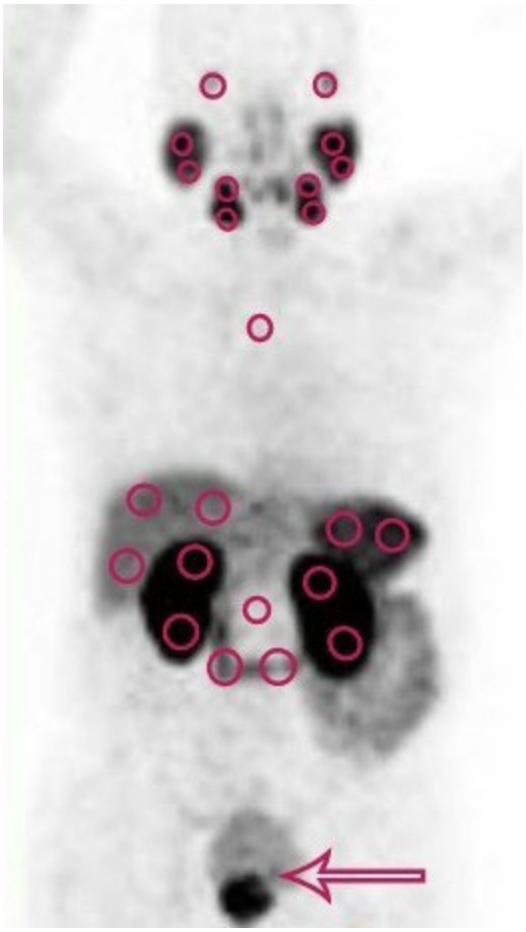

Figure 2: Average SUVmax and SUVmean values of different organs

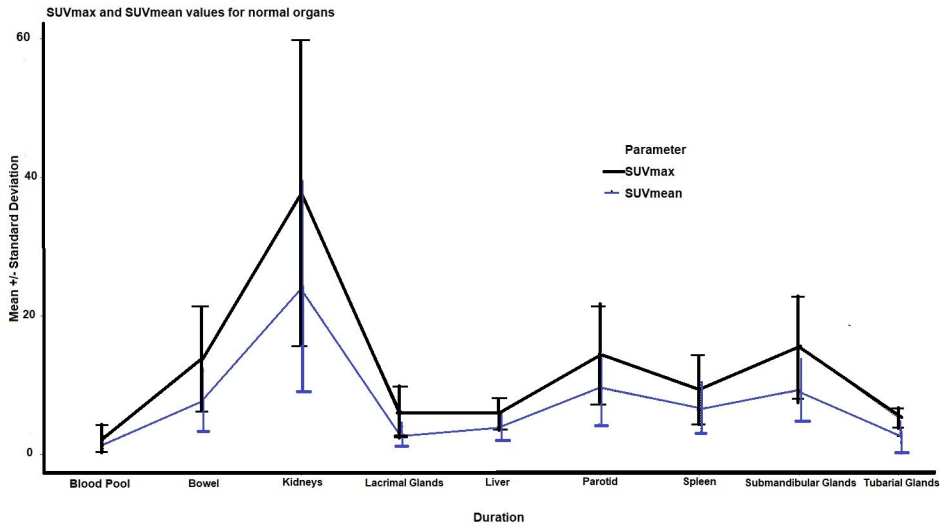

Figure 3: SUVmax, T/L ratio, T/S ratio and T/P ratio presentation by lesion 2 and lesion 3

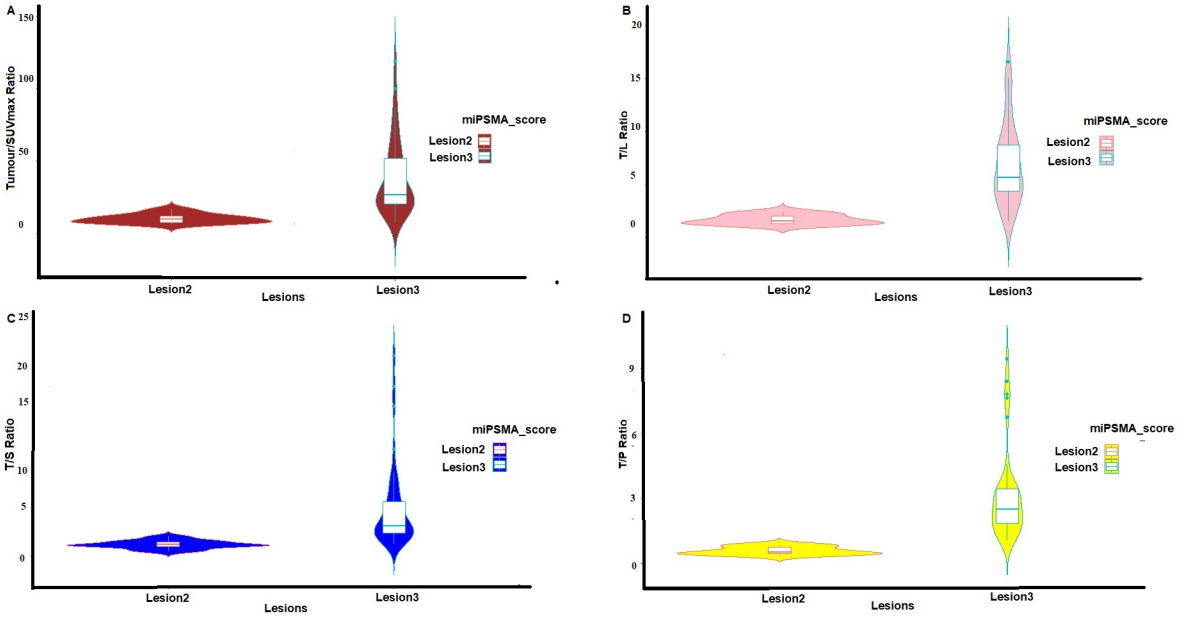

Figure 4: SUVmax, T/L ratio, T/S ratio and T/P ratio comparison between Score 2 and Score 3

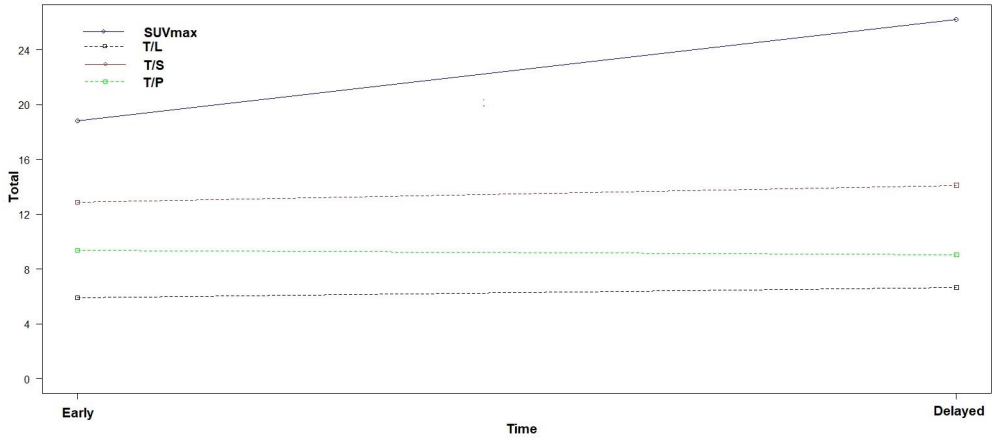

Table 1 (a): Description of patients' characteristics

Parameter	Measurement	Values
Age (in years)	Mean±SD Range	67.5±8 52-84
Sr.PSA	Mean±SD Range	401±1353 0.098-9235.13
Gleason's Score	Group 1	1
	Group 2	6
	Group 3	9
	Group 4	17
	Group 5	17

Table 1 (b). Previous Therapies Received

Therapy		N(%)
Surgery (Prostatectomy±Orchidectomy)	Yes	50(100%)
	No	0(0%)
Hormonal treatment	Yes	46(92%)
	No	4(8%)
Chemotherapy	Yes	39(78%)
	No	11(22%)
EBRT	Yes	24(48%)
	No	26(52%)
^{177}Lu-PSMA therapy	Yes	16(32%)
	No	34(68%)
Initial Staging	Yes	11(22%)
	No	39(78%)
Restaging	Yes	45(90%)
	No	5(10%)

Table 2: SUVmean and SUVmax values for Normal organs

	Mean SUVmean± SD	Mean SUVmax ± SD
Liver	3.98 ± 1.74	5.89 ± 2.32
spleen	6.71 ± 3.8	9.33± 4.98
kidneys	24.13 ± 15	37.72 ±22.1
Submandibular glands	9.16 ±4.56	15.44 ±7.34
parotid	9.51 ± 5.08	14.36 ±7.05
Lacrimal glands	2.64 ± 1.46	6.16 ±3.68
Blood pool	1.52 ±1.22	2.36 ± 1.95
Bowel	7.7 ± 4.34	13.81 ± 7.6
Tubarial glands	2.7 ± 1.97	5.3 ± 1.41

Table 3: Comparative uptake values and ratios of lesions

Score	2	3	p-value
Sample size (n)	11	39	
Average SUVmax±SD	10.33±3.27	38.2±25.92	0.0009
SUVmax range	6.46-17.00	7.6-119.08	
Average T/S ±SD	1.21±0.44	5.05z±4.46	0.0068
T/S range	0.48-2.04	1.25-20.89	
Average T/L ±SD	1.67±0.46	6.98±3.85	0.00004
T/L range	1.2-2.4	1.4-16.56	
Average T/P ±SD	0.61±0.18	3.15±2.09	0.00021
T/P range	0.39-0.87	1.06-9.45	

Table 4: Comparative Temporal Variation of SUV of normal organs with their p values.

Organ	Mean SUVmean	Mean SUVmax	Mean SUVmean delayed	Mean SUVmax delayed	SUVmean p-value	SUVmax p-value
Liver	3.6	5.9	3.1	6.7	0.0222	0.14
Spleen	6.5	9.4	5.8	9.1	0.0001	0.594
Kidneys	20.1	35.7	21.5	41.7	0.095	0.016
Submandibular glands	7.4	13.4	8.1	16.6	0.541	0.002
Parotid	7.1	12.9	8.5	14.1	0.047	0.037
Lacrimal glands	4.2	8.1	4.5	8.3	0.0267	0.01
Aorta	1.33	2.2	2.1	2.1	0.411	0.914
Bowel	5.5	9.7	5.4	10.9	0.41	0.44
Tubarial glands	2.87	5.55	3.3	6.06	0.02	0.08

Table 5: Paired t test values for lesional parameters between early and delayed images (temporal variation)

Parameter	Early Imaging (Mean value)	Delayed Imaging (Mean value)	Paired t test p value
SUVmax	18.85	26.24	0.0001
T/L	5.9	6.65	0.45
T/S	12.89	14.12	0.84
T/P	9.36	9.05	0.62

Graphical Abstract