Comparison of Gallium - 68 Prostate-Specific Membrane Antigen (Ga-68 PSMA) Normal Tissue Uptake across Tumor Burden Groups among Filipino Patients with Prostate Cancer

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ABSTRACT

Background:

PSMA-targeted radiopharmaceuticals have been widely studied for their theragnostic role in prostate cancer and were introduced in the Philippines in 2018. The optimal administered activity of ^{177}Lu-PSMA for targeted endoradiotherapy has not yet been established and is thought to be influenced by several factors, including tumor burden. This study investigates the effect of tumor burden on the normal tissue PSMA uptake among Filipino patients with prostate cancer using its diagnostic counterpart, ^{68}Ga-PSMA I&T

Methods:

One hundred four patients imaged with ^{68}Ga-PSMA I&T PET/CT in our institution from January 2018 to May 2020 were included. Patients were visually classified into low, medium, and high tumor burden groups. Maximum and mean standardized uptake values (SUVmax and SUVmean) of the lacrimal glands, parotid glands, submandibular glands, kidneys, liver, spleen, and bone were measured and compared among tumor burden groups.

Results and Conclusions:

^{68}Ga-PSMA I&T uptake in the kidneys, the salivary glands, and the liver, were significantly reduced by approximately 25-50% in patients with high tumor burden. This finding supports the hypothesis that patients with higher tumor load can tolerate higher activity doses of ^{177}Lu-PSMA for endoradiotherapy before developing significant damage to the critical organs. This may serve as a guide towards optimizing and personalizing ^{177}Lu-PSMA I&T administered activity dose for radionuclide therapy.

***Keywords**: Prostate-specific membrane antigen, Ga-68 PSMA I&T, Positron Emission Tomography, PET/CT, bio-distribution, prostate cancer, tumor burden*

INTRODUCTION

Prostate cancer is the second most common cancer among males globally and the third most prevalent in men in the Philippines [1]. Prostate-specific membrane antigen (PSMA) is a cell surface protein overexpressed in most clinically significant prostate cancer cells, up to 1000 times higher than normal prostate [2]. Its expression increases with Gleason score, androgen insensitivity, metastasis, and disease progression [3]. The unique expression of PSMA makes it an excellent marker for detecting prostate cancer recurrence and metastases. In recent years, extensive research has demonstrated excellent diagnostic accuracy of several PSMA-targeted radiotracers for prostate cancer imaging [4], which led to the development of PSMA-labeled radiopharmaceuticals for endoradiotherapy [5]. PSMA labeled with a positron-emitter (Ga-68) is used to image prostate cancer while its counterpart, labeled with a beta-emitting nuclide (Lu-177), is used for targeted radionuclide therapy [6,7]. Ga-68 PSMA I&T (imaging and therapy) is among the most commonly utilized since it is more suited for its theragnostic (the term for therapy plus diagnosis) role with its biodistribution reflective of its ^{177}Lu-labeled counterpart [8]. Lu-177 PSMA radioligand therapy (PRLT) has been shown to be a safe and effective systemic treatment of metastatic castrate - resistant prostate cancer [9,10], but its optimal dose has not yet been established [11]. Despite the term "prostate-specific," lower PSMA accumulation is noted

in several normal organs such as the lacrimal glands, salivary glands, liver, spleen, and kidneys [12]. Clinically, this means that although the expression of PSMA on these cells is significantly lower than prostatic cancer cells, the radiation dose is still delivered to these non-target healthy tissues when ^{177}Lu- PSMA is used for PRLT. The organs identified to be most at risk are the kidneys and salivary glands due to their high physiologic activity [11-13].

In the Philippines, modern theragnostics was first introduced at our institution in January 2018 as it offered ^{68}Ga-PSMA I&T PET/CT and ^{177}Lu-PSMA I&T radioligand therapy (PRLT) services to prostate cancer patients [14]. Targeted endoradiotherapy (i.e., PRLT) aims to provide the maximum radiation dose delivery to the tumor without causing significant radiation-related, non-target healthy tissue damage [15]. This translates to the careful planning of appropriate radionuclide dose for endoradiotherapy. Understanding the factors that may affect tracer biodistribution is necessary to achieve this goal.

One factor that may influence normal tracer biodistribution is the degree of tumor burden. A phenomenon called the tumor sink effect is observed in Nuclear Medicine when high tumor load results in a marked reduction of normal tissue tracer uptake. This occurrence has been reported in several radiotracers used in Nuclear Medicine, such as ^{99m}Tc-methyl diphosphonate (MDP) [16], ^{18}F-fluorodeoxyglucose (FDG) [17] and ^{68}Ga-DOTA-octreotate [18]. On the other hand, there are limited and conflicting data investigating this sink effect using PSMA-targeted radiopharmaceuticals [19-22]. For example, Gaertner et al. concluded that ^{68}Ga-PSMA-11 biodistribution in normal tissues was dependent on tumor load [19], whereas Werner et al. recently reported no sink effect from F-18 DCFPyL [20]. This theory has yet to be extensively investigated with PSMA-targeted radiopharmaceuticals and no data have been recorded in the local setting. This retrospective analysis aims to explore the effect of tumor burden on the ^{68}Ga-PSMA I&T biodistribution in normal tissues among Filipino patients with prostate cancer.

MATERIALS AND METHODS

Patient population

We retrospectively evaluated all patients aged 18 years and older, and histologically or clinically diagnosed with prostate carcinoma who underwent their first ^{68}Ga-PSMA PET/CT at our institution from January 2018 to May 2020. Patients with known renal disease or patients with eGFR <60 during the scan, as well as studies that did not follow proper protocol (i.e., uptake time of >100 minutes and low administered activity of <100 MBq or <2.7 mCi) were excluded from the study. Relevant patient characteristics (age, height, weight, nationality, Gleason score, date of diagnosis, recent PSA value at the time of the scan, and prior interventions), as well as scan-related information (reason for referral, administered activity, and uptake time), were all collected from the institution's database. Body mass index (BMI) and years since initial diagnosis were extrapolated from the given information. This study was approved by the institution's technical and ethical review committees.

Imaging procedure

As part of our institution's standard protocol and in accordance with the joint EANM and SNMMI procedure guideline for prostate cancer imaging version 1.0, ^{68}Ga-PSMA I&T PET/CT scans were acquired approximately 60 minutes after intravenous injection of Ga-68 PSMA I&T and 20 mg furosemide. All PET/CT scans were obtained on a Philips Gemini TF 64 PET/CT scanner. Non-contrast enhanced low-dose CT scan (120 Kv, 50 mAs) was taken, followed by PET imaging in 3D mode at a rate of 2-3 minutes per bed position from skull vertex to toes with patients in supine position. Emission (PET) images were corrected for attenuation based on the low-dose CT data and reconstructed using BLOB-OS-TF (spherically symmetric basis function ordered subset algorithm time of flight). Depending on the clinical situation and referring physician's request, diagnostic CT scans with or without IV contrast were also performed.

Image analysis

PET/CT images were reviewed and analyzed using Philips IntelliSpace Portal (version 10.1, Koninklijke Philips N.V. 2017). Visual classification of tumor burden and uptake quantification were adopted from the Gaertner study [19]. Patients were classified into low, medium, and high tumor burden (TB) groups. Visual classification of the patients' scans was done independently by two experienced Nuclear Medicine physicians. Representative images are shown in Figure 1. Classification of tumor burden was defined as:

1. Low: disease confined to the pelvis or those not classified as high or medium
2. Medium: widespread but faint bone uptake or bone lesions with intense uptake involving less than half of the skeleton (≤ 30 solitary lesions), extensive PSMA - positive lymph node on both sides of the mediastinum, or extensive PSMA-positive lung metastases
3. High: intense disseminated bone uptake (> 30 solitary lesions or diffusely confluent bone lesions involving more than half of the skeleton)

Before the conduct of the study, independent inter-rater reliability (IRR) was done to ensure consistency between the two experts. During the study, the two experts made a careful discussion to resolve discordance.

Tracer uptake was quantified by maximum and mean standard uptake values (SUVmax and SUVmean) based on body weight. For calculation of the SUVs, volumes of interest (VOIs) were drawn as follows: automatic 50% isocontour for lacrimal glands, parotid glands, submandibular glands, and kidneys; spherical 50 mm diameter for liver, 30 mm diameter for spleen, and 25 mm diameter for bone. L3 was preferred for SUV measurement of the bone, but if L3 was seen to have metastasis, then either L4 or L5 was used. Drawing of the VOIs was done independently by three Nuclear Medicine technologists. Mean of measured SUVs was used for final analysis.

Data analysis

Patients were classified into the three independent groups according to tumor burden. Data were statistically analyzed using STATA 14.1. Homogeneity of baseline characteristics was assessed using analysis of variance (ANOVA) and Fisher's exact test with $p \leq 0.05$ for quantitative and qualitative variables, respectively. Tracer uptake SUVmax and SUVmean between patient groups were compared using one-way ANOVA and Kruskal-Wallis H tests, as appropriate. A p-value of ≤ 0.05 was rated as significant. For significant tests, Tukey-Kramer Test and Mann-Whitney U Test were performed as fitting for post-hoc analyses. Normality was tested using the Shapiro-Wilk test. Correlation of SUVs among visual TB, PSA (surrogate TB marker), weight, BMI, administered activity (AA), and uptake time (UT) was evaluated using Spearman and Pearson Correlation Coefficient.

RESULTS

A total of 104 male Filipino patients diagnosed with prostate cancer were included in our analysis. Seventy - six (76) patients were classified in low, 18 in medium, and 10 in high tumor burden groups. IRR for visual classification between the two experts before conducting the study yielded an almost perfect agreement of 90% (27/30).

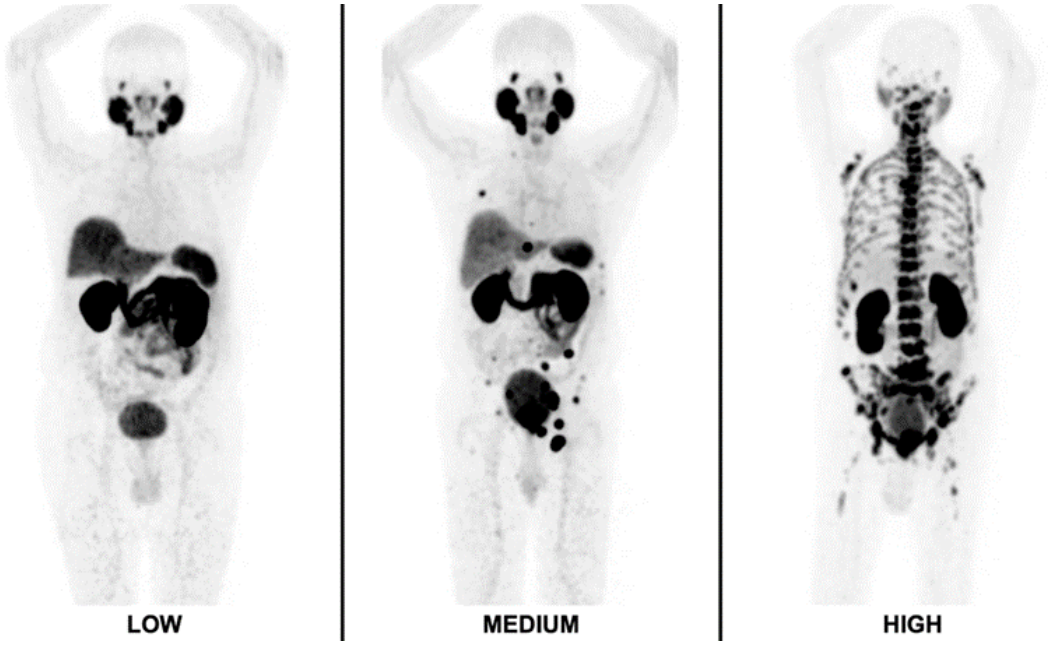

FIGURE 1. Representative maximum intensity projection (MIP) images of Ga-68 PSMA I&T PET/CT visually rated as low, medium, and high tumor burden.

Patient characteristics

The baseline characteristics showed no statistically significant differences among TB groups regarding age, height, weight, BMI, number of years since the initial diagnosis, and Gleason score. Characteristics are summarized in Table 1.

Mean patient age was 69 ± 9 years (range 44-88 years), mean BMI was 26.4 ± 3.5 kg/m2 (range 16.8-33.5 kg/m2) and mean number of years since initial diagnosis was 3 ± 4 (range 0-19 years). A great bulk of the patients were newly diagnosed or referred within the first year of diagnosis (n = 45, 43.3%). Gleason score (GS) was available for only 57 of 104 patients; 47 from the low, 9

TABLE 1. Representative Summary of patients' characteristics

			TUMOR BURDEN			
			Low (n=76)	Medium (n=18)	High (n=10)	p-value
Age (years)		68.7 (9.1)	68 (8.8)	69 (10.2)	72 (9.5)	0.49
Height (cm)		168.2 (6.3)	167.9 (6.4)	169.3 (6.0)	169.2 (6.7)	0.59
Weight (kg)		74.7 (11.3)	74.7 (11.0)	77.7 (10.1)	69.4 (15.1)	0.18
BMI (kg/m^2)		26.4 (3.5)	26.5 (3.4)	27.1 (3.2)	24.2 (4.7)	0.10
Gleason Score		7.6 (1.2)	7.4 (1.1)	8.3 (1.2)	9*	0.06
PSA (ng/mL)		38.11 (90.67)	16.18 (31.14)	41.35 (49.21)	214.34 (224.09)	<0.001
Years since diagnosis		3.0 (4.2)	2.7 (3.9)	3.72 (4.5)	3.8 (5.8)	0.50
Prior surgery	Yes	46 (44.2%)	36 (78.3%)	6 (13%)	4 (8.7%)	0.06
	No	58 (55.8%)	40 (69%)	12 (20.7%)	6 (10.3%)	
Prior chemotherapy	Yes	12 (11.5%)	4 (33.3%)	5 (41.7%)	3 (25%)	0.004
	No	92 (88.5%)	72 (78.3%)	13 (14.1%)	7 (7.6%)	
Prior radiotherapy	Yes	23 (22.1%)	14 (60.9%)	7 (30.4%)	2 (8.7%)	0.19
	No	81 (77.9%)	62 (76.5%)	11 (16.6%)	8 (9.9%)	
Prior hormone therapy	Yes	43 (41.3%)	24 (55.8%)	12 (27.9%)	7 (16.3%)	0.004
	No	61 (58.7%)	52 (85.3%)	6 (9.8%)	3 (4.9%)	
Administered activity		161.1 (27.7)	161.2 (27.0)	167.7 (28.5)	148.7 (29.7)	0.22
Uptake time (mins)		69.6 (10.7)	69.3 (10.7)	67.8 (9)	74.5 (13)	0.27
Indication	Assess recurrence	53 (51%)	41 (77.4%)	7 (13.2%)	5 (9.43%)	
	Primary staging	35 (33.6%)	28 (80%)	6 (17.1%)	1 (2.9%)	
	Others	16	7 (43.8%)	5 (31.2%)	4 (25%)	

Quantitative data presented as Mean (Standard Deviation) while qualitative data presented as Number (%).

*Only one datum available

from the medium, and 1 from the high TB groups. The majority had a Gleason score between 7 and 9 (44/57, 77.2%).

Serum PSA was noted in 102 of 104 patients. PSA was not available in two patients (one from the low and one from the high TB group). There were significantly higher PSA values in the high TB group compared to the low and medium groups. Mean PSA in the high TB group was 214.34 ± 224.09 ng/mL (range 0.76-746.99 ng/mL), whereas the mean PSA for the low and medium TB groups were 16.18 ± 31.13 ng/mL (range 0.003-160.54 ng/mL) and 41.35 ± 49.21 ng/mL (range 0.03-171.21 ng/mL), respectively.

The clinical indications for imaging included assessment for recurrent/metastatic disease (53/104, 51.0%) and primary staging/preoperative evaluation (35/104, 33.7%), among a few others (e.g., PRLT planning and treatment monitoring). All of those referred for assessment of recurrent disease had prior intervention (e.g., surgery, chemotherapy, radiation therapy, and hormone therapy). A statistically significant difference was detected in the proportion of patients who received chemotherapy and prior hormone therapy than those who did not, as seen in Table 1. Other prior interventions showed no significant difference.

PET Imaging

Patients' scans with low administered activities (<100 MBq) or long uptake time (>100 minutes) were excluded for analysis. As a result, no significant differences were observed for AA and UT. Mean AA was 161.1 ± 27.7 MBq (range 100-228 MBq), and mean UT was 69.6 ± 10.7 minutes (range 50-100 minutes).

Tissue uptake

Tracer uptake (SUVmax and SUVmean) in the salivary glands, kidneys, and liver showed a significant reduction in the high tumor burden group compared to the low TB group. Uptake reduction by 25.9% to 27.4% for the parotid glands, 24.8% to 27.3% submandibular glands, 39.4% to 45.8% for the kidneys, and 33.7% to 36.1% for the liver was observed. In general, SUVmean of these organs had more noticeable declines compared to their SUVmax. Kidneys SUVmean exhibited the most prominent drop of 45.8% ($p = 0.002$) between low and high TB groups. Normal tissue uptake results are listed in Table 2; SUVmax and SUVmean are illustrated in Figure 2.

SUVmax in the bone showed a significant increase in patients with high tumor burden compared with low tumor burden. No significant difference was observed for the other normal tissue uptake sites (lacrimal glands, spleen, and bone SUVmean). The lacrimal and salivary glands SUVs could not be delineated in two patients (one from the high TB group and one from the medium TB group) due to low uptake or bone metastases involving the adjacent skull. In five patients belonging to the high TB group, normal bone SUVs could not be measured due to extensive bone metastases.

Correlative Analysis of Tissue Uptake

Weak but significant negative correlations ($rho \approx 0.2$-0.3; $p \leq 0.05$) were noted between TB groups and the SUVmax and SUVmean of the salivary glands, and kidneys. Uptake in the salivary glands, kidneys and liver correlated negatively with serum PSA, a surrogate tumor burden marker ($rho \approx 0.2$-0.3; $p \leq 0.05$). Correlation of SUVmean and PSA is illustrated in Figure 3. PSMA uptake of the kidneys was also noted to have weak but significant positive correlation with weight ($rho \approx 0.2$), not BMI. No significant correlation was noted for the other studied tissues with the other parameters (e.g., AA, UT, weight, and BMI).

DISCUSSION

The rapidly expanding use of PSMA - ligand radiopharmaceuticals in imaging and therapy of patients with prostate cancer is accompanied by the need to understand factors that may affect normal tissue uptake. This retrospective analysis explored the effect of tumor burden on the PSMA uptake in non-target healthy tissues among Filipino patients with prostate cancer. Here, we show the significant impact of high tumor burden on the Ga-68 PSMA I&T uptake of the kidneys, salivary glands, and liver, where mean tracer uptake in these organs was notably reduced approximately 25% to 50% in patients with high tumor burden.

TABLE 2. Normal tissue Ga-68 PSMA uptake across tumor burden groups.

			TUMOR BURDEN			
			Low	Medium	High	P value
	SUV	N	Mean (SD)	Mean (SD)	Mean (SD)	
Lacrimal glands*	max	102	6.77 (3.22)	6.66 (3.34)	5.64 (2.25)	0.605
	mean	102	3.92 (1.86)	3.64 (1.70)	3.28 (1.33)	0.539
Parotid glands*	max	103	16.44 (4.85)	15.50 (4.65)	**12.18 (5.89)**	**0.041**
	mean	103	10.09 (2.94)	9.57 (3.0)	**7.32 (3.71)**	**0.036**
Submandibular glands*	max	103	19.13 (5.24)	16.01 (5.49)	**14.39 (6.54)**	**0.010**
	mean	103	11.66 (3.31)	**9.51 (3.50)**	**8.48 (3.65)**	**0.005**‡
Kidneys†	max	104	47.73 (17.2)	43.20 (14.03)	**28.70 (12.28)**	**0.007**
	mean	104	28.82 (10.71)	26.66 (8.82)	**15.63 (7.58)**	**0.002**§
Liver†	max	104	5.21 (1.65)	5.30 (1.69)	**3.45 (1.80)**	**0.013**
	mean	104	4.06 (1.37)	4.07 (1.34)	**2.59 (1.52)**	**0.011**
Spleen†	max	104	7.60 (2.71)	7.30 (2.92)	8.17 (4.48)	0.835
	mean	104	5.79 (2.08)	5.67 (2.44)	5.97 (3.08)	0.845
Bone†	max	99	1.35 (0.35)	1.43 (0.35)	1.97 (0.66)	0.038
	mean	99	0.81 (0.22)	0.83 (0.22)	1.06 (0.26)	0.059

Legend:

*Normally distributed data: used one-way ANOVA and Tukey-Kramer tests

†Not normally distributed data: used Kruskal-Wallis and Mann-Whitney U tests

Values in bold signify statistically significant reduction of P values (≤ 0.05) between tumor groups and in patients with high and low TB groups

‡Significant difference between medium and low TB groups P values (≤ 0.05)

§Significant difference between medium and high TB groups P values (≤ 0.05)

Similar to the established biodistribution studies of Ga-68 PSMA I&T [5,13] and other PSMA-targeted radiotracers [23-26], the kidneys and the salivary glands exhibited the highest uptake among the studied organs. This is followed by the lacrimal glands, liver, and spleen, and minimal uptake in the bone. Due to the high physiologic uptake of the kidneys and salivary glands, these two have previously been identified as the relevant critical organs or the dose-limiting organs for PRLT [27,28].

Remarkably, these at-risk organs are found to have a significant reduction in uptake with high TB. Despite the patient population being Filipino and predominantly with low TB, our results with ^{68}Ga-PSMA I&T are compatible with previous studies supporting the tumor sink effect using Ga-68 PSMA-11 [19] and Lu-177 PSMA-617 [21,22]. In addition, liver uptake has also shown to be significantly reduced with high TB in the current study. A significant inverse correlation between visual TB and PSA (surrogate tumor burden marker), and uptake in these organs is also noted, although with weak correlation coefficients (rho ≈ 0.2-0.3). A small, positive correlation (rho ≈ 0.2) was also observed between kidney uptake and weight. No significant difference or correlation with tumor burden, PSA, AA, UT, or weight was noted among the other organs studied. These observations remind us that although normal tissue biodistribution may depend on tumor load, several other factors can cause uptake variability. In a study investigating inter-patient and intra-patient variability using a related PSMA-targeted radiotracer 18F-DCFPyl, the intra-patient variability factors mostly influenced liver and kidney uptake,

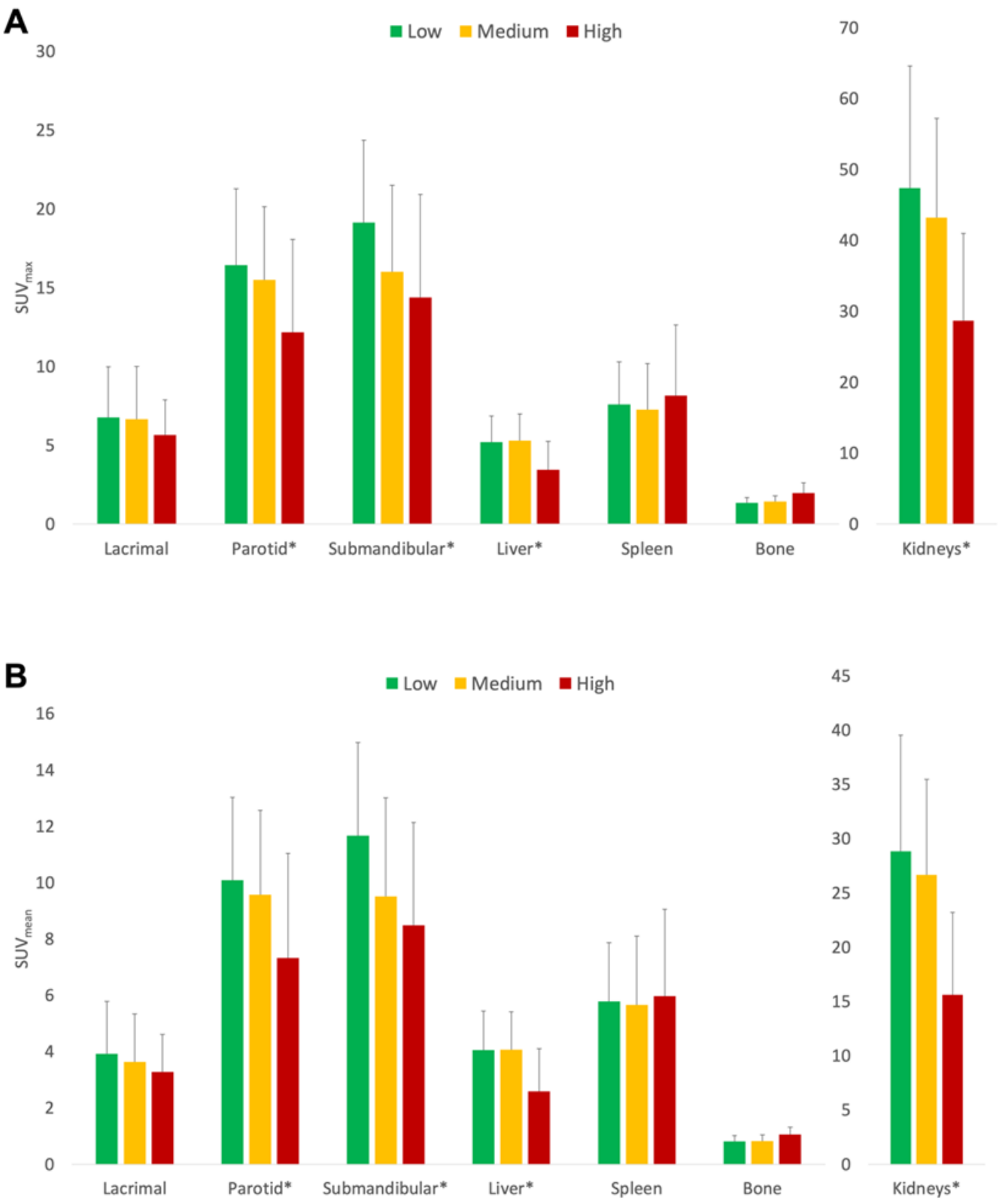

FIGURE 2. Bar graphs showing influence of tumor burden on the 68Ga-PSMA I&T normal tissue uptake (A. SUVmax and B. SUVmean) with error bars (SD), relating to tumor burden groups (low, medium, and high). *Significant reduction ($P \leq 0.05$) of PSMA uptake across TB groups

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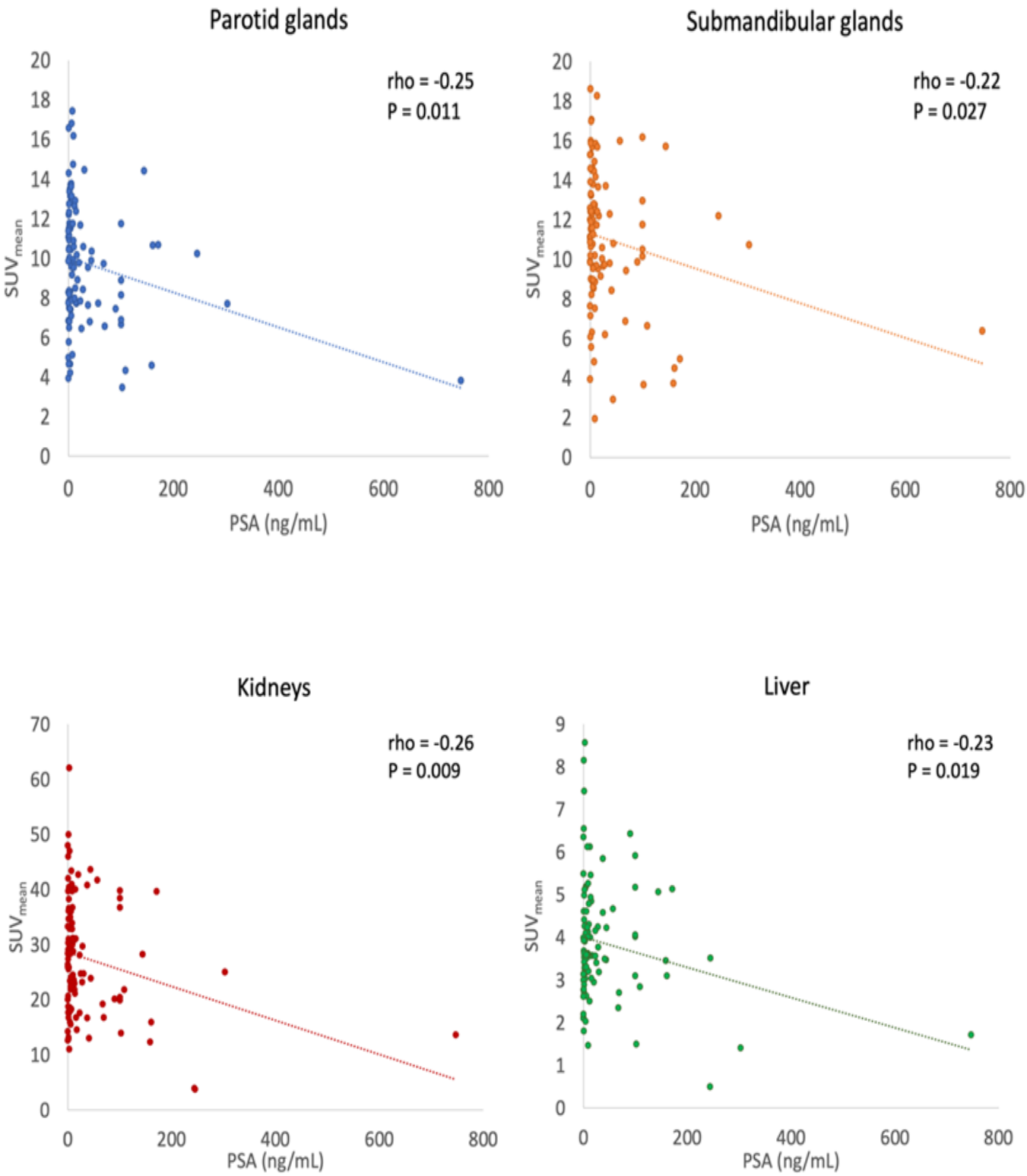

FIGURE 3. Scatter plots showing weak but significant negative correlations of the salivary glands, kidneys, and liver ^{68}Ga-PSMA I&T uptake (SUVmean) with serum PSA. .

and weight. No significant difference or correlation with tumor burden, PSA, AA, UT, or weight was noted among the other organs studied. These observations remind us that although normal tissue biodistribution may depend on tumor load, several other factors can cause uptake variability. In a study investigating inter-patient and intra -patient variability using a related PSMA-targeted radiotracer ^{18}F-DCFPyl, the intra-patient variability factors mostly influenced liver and kidney uptake, whereas inter-patient variability factors largely affected the lacrimal glands, salivary glands, and spleen [29].

While this study focuses mainly on the effect of tumor burden on the biodistribution, there were several attempts to lessen interpatient variability from other factors in the analysis. For example, patients with known or suspected renal impairment and those scanned beyond the institution's standard protocol (low administered activities and prolonged uptake time) were excluded. Moreover, homogeneity of patient characteristics (age, height, weight, BMI, nationality, Gleason score, years since diagnosis, recent PSA value at the time of the scan, and prior interventions) and imaging parameters (AA and UT) were investigated. Baseline characteristics were relatively uniform; only the PSA, prior chemotherapy, and hormone therapy were found to be significantly different, and no significant correlations between tissue uptake and AA nor UT were observed. Conversely, factors that contribute to intra-patient variability (e.g., time of day, recent meals, and hydration status) [29] were not evaluated.

Following the tumor sink effect, all normal tissue uptake should be reduced with high tumor burden. However, this study records a statistically significant increase in patients' normal bone uptake with high tumor burden. This is possibly due to the small number of successfully measured bone uptake in the high TB group, only five out of ten. It may also be potentially caused by the inherent difference of biodistribution in the bone and blood pool of ^{68}Ga-PSMA I&T, which has been shown to have higher retention than ^{68}Ga-PSMA-11 [7]. Additionally, occult skeletal metastases cannot be discounted. Despite being statistically significant, uptake in the bone was found to be minimal in all patients. SUVmean of the bone ranges from 0.19 to 1.74; both the lowest and highest values were found in the low TB group. Further research is suggested to verify this observation and to explore its clinical significance.

This study has several strengths. First, this is the first study evaluating the effect of tumor burden on normal Ga-68 PSMA I&T biodistribution in the Philippines and Filipino patients with prostate cancer. Second, patient homogeneity with baseline characteristics, administered activity, and uptake time for the PET imaging was observed. As a result, the probability of inter-patient variability affecting the outcomes is low. Third, Ga-68 PSMA I&T is the radiopharmaceutical used, reflective of our local real-world scenario, and is likely more representative of its therapeutic arm counterpart's biodistribution. Moreover, all patients were scanned in the same PET/CT scanner assuring uniform SUV measurements.

This study's potential restrictions include visual classification of tumor load instead of quantitative tumor volume measurement as part of our institution's limited workstation capabilities. Also, a large bulk of the patients studied have low tumor load. Nevertheless, this patient population represents our typical patient population, and statistically significant results were observed. Owing to the study's retrospective nature, collected data on the patient's history (e.g., prior intervention and date of initial diagnosis) were vulnerable to recall bias of informants and recorded information by the interviewer. Only single static scans were analyzed, precluding evaluation of intra-patient factors.

Our present analysis shows tumor burden's significant influence on the normal biodistribution of PSMA tracer uptake wherein high tumor burden results in substantially reduced physiologic tissue uptake of the kidneys, salivary glands, and liver. Although extensive research has shown high accuracy, efficacy and safety of ^{68}Ga/^{177}Lu-PSMA theragnostics, limited data are available on factors that may affect the tracers' biodistribution. This is the first study to document such findings in our local setting. As these have implications on possible dose adjustment for PRLT in our local setting, it is highly recommended that subsequent studies investigate tumor load quantitatively and explore other factors that may cause variability of ^{68}Ga/^{177}Lu-PSMA biodistribution.

CONCLUSION

Significantly reduced 68Ga-PSMA I&T uptake is observed in the kidneys, the salivary glands and the liver in patients with high tumor burden. As ^{68}Ga and ^{177}Lu-PSMA I&T have comparable biodistribution, this study has significant implications on PSMA-targeted radionuclide therapy. It corroborates the hypothesis that

patients with higher tumor load can tolerate higher activity doses of 177Lu-PSMA for radionuclide therapy before developing significant damage to the critical organs. Further studies are needed to extrapolate these data in optimizing and personalizing ^{177}Lu-PSMA I&T dose for PRLT.

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