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Original Article, PET/CT.

Tumor Sink Effect in F-18-PSMA PET/CT.

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ABSTRACT:

Objective: We aimed to examine the impact of the tumor burden on the biodistribution of ^{18}F-prostate-specific membrane antigen-1007 (^{18}F-PSMA 1007) in PET imaging by the use of quantitative measurements. **Methods:** This retrospective analysis included 100 males with prostate cancer who underwent ^{18}F-PSMA PET/CT. For each prostate cancer lesion, the metabolic tumor volume (PSMA-TV) was measured via an automatic segmentation tool based on 50% threshold. Then, the "total lesion PSMA expression" (TL-PSMA) was calculated by multiplying PSMA-TV by SUVmean of each lesion. The whole-body PSMA tumor burden is the sum of TL-PSMA values of all lesions in each patient. Based on this tumor burden, patients were divided by quintiles into 5 groups. A very low (group 1, tumor burden ≤ 400), low (group 2, 401-1250), moderate (group 3, 1251 – 2500), high (group 4, 2501 - 6500), and very high (group 5, ≥ 6501) whole body total lesion PSMA-expression (TL-PSMA) or tumor burden. Different groups were compared and correlation between tumor burden and SUVmax/SUVmean of reference background organs was conducted. Reference organs which were used as representative for the normal background tissue uptake were the parotid glands, lacrimal glands, liver, spleen and kidneys. **Results:** Tumor burden showed a moderate negative correlation with the SUVmean of the right kidney ($r = -0.448$, $P < 0.001$), left kidney ($r = -0.357$, $P < 0.001$), right parotid gland ($r = -0.4$, $P < 0.001$), left parotid gland ($r = -0.413$, $P < 0.001$), and left lacrimal gland ($r = -0.337$, $P = 0.001$) and a

weak negative correlation with the SUVmean of right lacrimal gland (r = −0.327, P= 0.001), liver (r = −0. 247, P = 0.013) and spleen (r = −0.201, P = 0.045). Patients with a very high tumor burden (group 5, ≥ 6500) had a significantly lower PSMA uptake in the lacrimal, salivary glands, kidneys, liver, and spleen compared to other groups (P < 0.001).

Conclusions: Tumor sequestration affects 18F-PSMA 1007 biodistribution in normal organs. As tumor sink effect may occur with PSMA-targeted radioligand therapy (RLT), patients with very high tumor burden might benefit from higher therapeutic doses without exceeding the radiation dose limit for organs at risk.

Keywords: PSMA, radioligand therapy, tumor sink effect

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INTRODUCTION:

The effect of tumor burden on reference tissue uptake in ^{18}F-FDG PET/CT imaging was first examined by **Viglianti et al** in 2018 [1]. In their study, they examined the effect that the metabolic tumor burden has on ^{18}F-FDG distribution in different organs of interest and found that metabolic tumor load can have a significant effect on SUV measurements in PET imaging. In a similar study, Badawy et al evaluated 400 ^{18}F-FDG PET/CT scans of patients with different malignancies and observed that the metabolic tumor burden can affect FDG biodistribution in reference organs [2]. This phenomenon is called the “tumor sink effect” (TSE) and describes the effect that occurs when hypermetabolic tumors sequester a significant amount of the radiopharmaceutical, reducing its availability for uptake in other tissues [3]. In other words, the tumors act as a "sink", reducing the amount of the tracer that is available for the distribution in the normal background organs. By lowering FDG uptake in reference tissues, like the liver, blood pool, or muscles, the TSE can impact

the interpretation of PET scans. These findings regarding FDG biodistribution are important, however, the presence of TSE in radiopharmaceuticals that are used for Theransotics purposes has a more important clinical implication. Tumor sequestration of radiotracer may lead to decreased bioavailability in healthy tissue resulting in lower absorbed radiation dose to critical organs. This may allow the patient to receive higher therapeutic doses with lower side effects and organ toxicity.

MATIAL and METHODS:

This is a retrospective study which included 100 patients who underwent routinely scheduled ^{18}F-PSMA PET/CT scans for oncological staging, re-staging or assessment of response to therapy in the period from 2022 to 2024 at the Department of Clinical Oncology and Nuclear Medicine of Cairo University Hospital. Institutional ethical review board approval was obtained (REC code MS-382-2024). The following patients were excluded: patients with previous ^{177}Lu-PSMA therapy as it may affect reference organs uptake, patients with previous surgical intervention to any of the studied reference organs and patients with reference tissues disease whether metastatic or otherwise (i.e. renal failure, liver failure, chronic sialadenitis).

Imaging protocol:

The scanner used in this study was Ingenuity TF 64 (Philips Healthcare) an integrated PET/CT scanner combining a modular, LYSO-based PET component with a 64-channel CT component. Imaging was performed in accordance with the joint EANM/ SNMMI procure guidelines for prostate cancer imaging 2.0 [4].

Image analysis:

Images co-registration, analysis and semi-quantitative assessment were done using Syngovia software. For the regions of interest, attenuation-corrected images and SUV measurements based on body weight in kilograms (SUV/kg) were employed. The lacrimal glands, salivary glands, liver, spleen and kidneys were included as reference organs. For the lacrimal and salivary glands, the ROI was drawn automatically to fit the whole gland, while for spleen and the kidneys, the ROIs were

drawn semi-automatically as circular or elliptical areas to fit the whole organ in three dimensions. For the liver, a 3 cm ROI placed at the hepatic dome within the right lobe, at the approximate segment VII or VIII level **(Fig.1).**

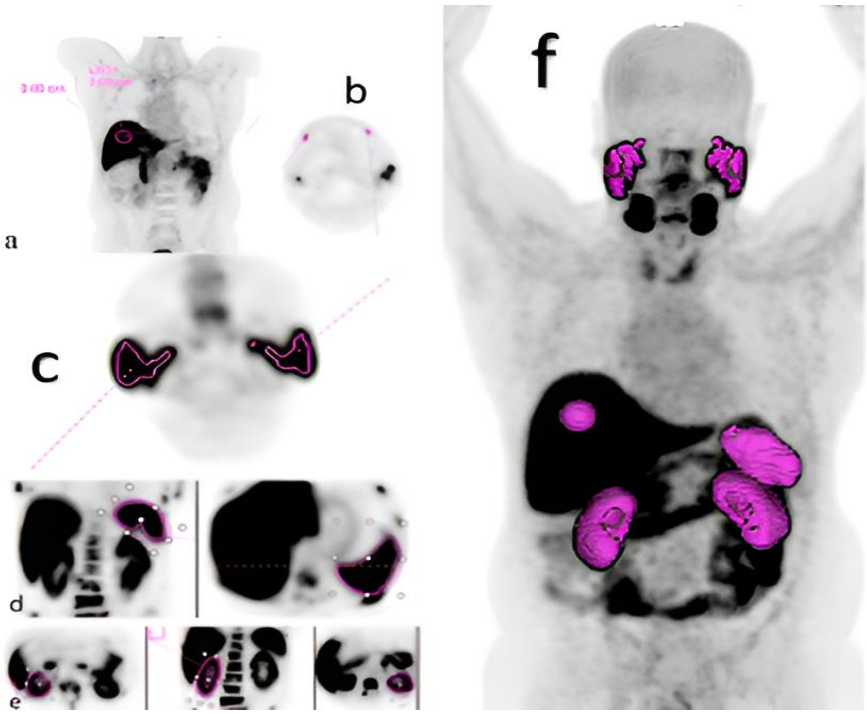

Fig.1 Methods of ROI drawings. (a) VOI drawn on hepatic dome. (b) VOI drawn on lacrimal glands. (c) VOI drawn on parotid glands. (d) VOI drawn on the spleen in 2 projections. (e) VOI drawn on the kidneys 3 projections. (f) Whole body MIP with 3D VOIs of all reference organs.

- **Metabolic Tumor burden calculation**

Metabolic tumor burden: For metabolic tumor burden calculation, lesions that were qualitatively identified as neoplastic were included. The metabolic tumor volume (PSMA-TV) was measured using the semi-automatic method by using the segmentation tool that provides a volume of interest (VOI) based on selected SUV cutoffs. A 50% threshold level was chosen. **Total lesion PSMA expression (TL-PSMA):** Total lesion PSMA expression (TL_PSMA) was calculated by multiplying PSMA-TV by the mean SUV in the ROI (TL-PSMA = PSMA-TV × SUVmean).

Whole-body TL-PSMA or PSMA tumor burden: Whole-body TL-PSMA or PSMA tumor burden was then calculated as the sum of the TL-PSMA values of all lesions in each patient. Diagnostic pattern of neoplastic lesions found in patients in different groups is seen in **Table 1**

Table 1 Diagnostic pattern of neoplastic lesions found in patients in different groups

	Diagnostic pattern
Group 1	- Lesions limited to the prostate gland. - Few loco-regional lymph nodal deposits in addition to the prostate. - Few distant lymph nodal and/or osseous deposits in addition to the loco-regional and prostate. - Many distant osseous and/or lymph nodal deposits with low grade uptake.
Group 2	- Many distant osseous and/or lymph nodal deposits. - Few distant lymph nodal and/or osseous deposits with intense uptake. - Widespread distant osseous and/or lymph nodal deposits with low grade uptake.
Group 3	- Many distant osseous and/or lymph nodal deposits with intense uptake. - Widespread distant osseous and/or lymph nodal deposits.
Group 4	- Widespread distant osseous and/or lymph nodal deposits with variable grades of uptake and density of deposition.

Statistical analysis: Patients were divided into 5 groups by quintiles based on tumor burden into a very low (group 1, tumor burden ≤ 400), low (group 2, 401-1250), moderate (group 3, 125١ – 2500), high (group 4, 2501 - 6500), or very high (group 5, ≥ 6٥01). The SUVmax and SUVmean values of each organ in the different groups were then compared and the calculated tumor burden of each group was correlated

with SUVmax and SUVmean values of each organ as continuous variables and the correlation coefficient was calculated. Data was analyzed using the Social Sciences (SPSS) Comparisons between quantitative variables were done using the non-parametric Kruskal-Wallis and Mann-Whitney tests [5]. Correlations between quantitative variables were done using Spearman correlation coefficient [6]. P-values less than 0.05 were considered as statistically significant.

RESULTS:

Descriptive data

Demographic and clinical data for our cohort are shown in **Table 2**.

Table 2 Demographic and clinical data of our study population

	Number of patients	Mean	Standard Deviation	Median	Minimum	Maximum
Age	100	69.57	8.42	70.50	51.00	92.00
Tumor burden	100	3904.02	4974.04	1634.61	11.00	19536.63
Total PSA	62	239.25	400.76	73.84	0.01	1983.00
Free PSA	44	19.81	22.80	12.36	0.01	125.00
Creatinine	58	1.05	0.24	0.99	0.65	1.70
ALT	15	15.40	8.18	13.00	6.00	36.00
AST	15	22.87	8.92	20.00	14.00	40.00

Pathological grades in our cohort: All pathological grades were represented in our patient cohort with different percentage **(Table 3).** The most frequently diagnosed Gleason score and grade were: score 4 + 4= 8, grade group 4.

Table 3 Pathological grades in our study population

		Number of patients	Percentage %
Gleason score	**3 + 3 = 6 Grade group 1**	2	5%
	3 + 4 = 7 Grade group 2	5	12%
	4 + 3 = 7 Grade group 3	2	5%
	4 + 4 = 8 Grade group 4	15	36%
	4 + 5 = 9 Grade group 5	8	19%
	5 + 4 = 9 Grade group 5	6	14%
	5 + 5 = 10 Grade group 5	4	9%
Total		42	100%

Diagnostic patterns of neoplastic lesions found in patients in different groups

After dividing the patients into 5 groups based on their tumor burden, we observed repeated patterns of PSMA-avid lesions in each group. Two different factors played a role in the final calculated tumor burden: the number of lesions and the intensity of uptake within these lesions. For example, in the first group, where the tumor burden was very low (≤ 400), some patients had few lesions limited only to the prostate, whereas some patients in the same group had many distant metastases, but all of their lesions had low-grade uptake. These observations are summarized in **Figure 2.**

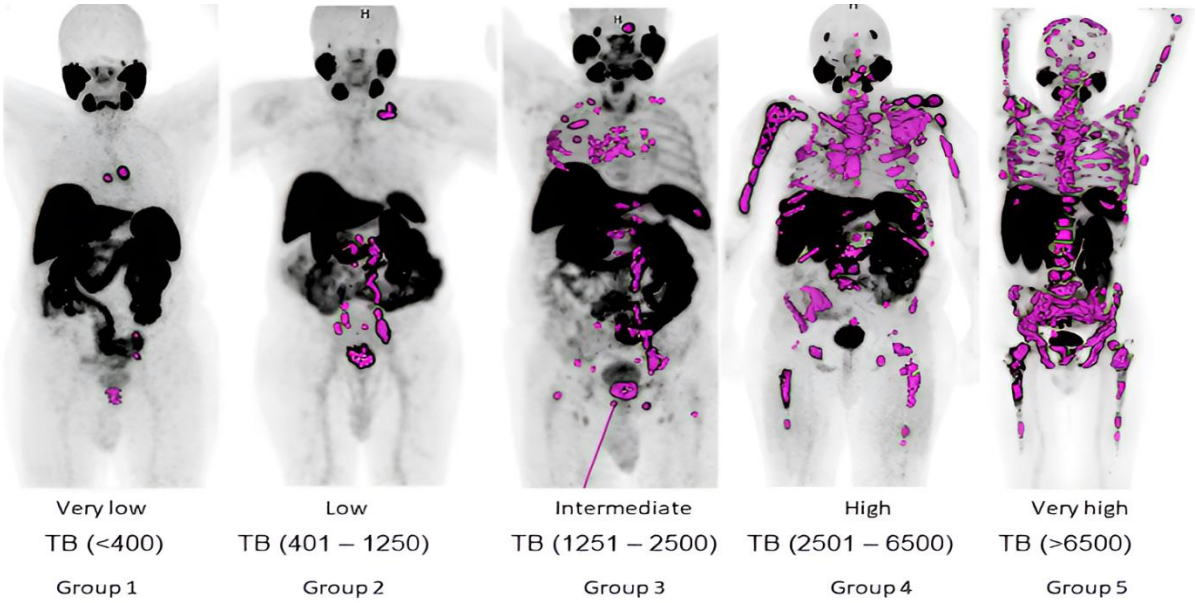

Fig.2 Diagnostic patterns observed in our study cohort

Correlative analytical data:

Correlation between tumor burden and reference organs uptake

There was a significant negative correlation between tumor burden and SUVmax/SUVmean values across all reference organs (**Table 4**). The strongest correlations were observed in the kidneys and the parotid glands (both left and right), with correlation coefficients ranging from -0.357 to -0.448 ($p < 0.001$). While the weakest correlations were noted with the liver and spleen, correlation coefficients ranging from -0.201 to -0.247. The scatter plots in **Figures 3 a and b** illustrate the correlation between SUV values of the right kidney in relation to the tumor burden. Scatter plots of all other included reference organs in our study were found to be similar and are available upon request.

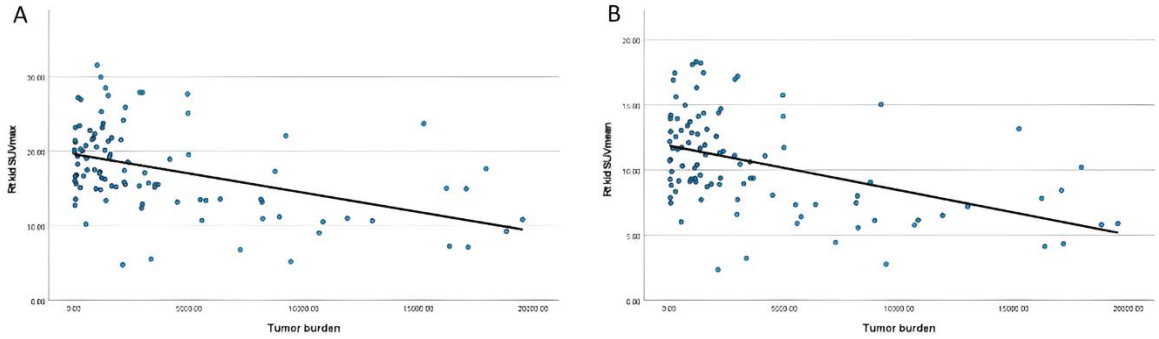

Fig. 3a Scatter plot illustrating the relation between the tumor burden and the right kidney SUVmax **Fig. 3b** Scatter plot illustrating the relation between the tumor burden and the right kidney SUVmean

Table 4 Correlation between tumor burden and reference organs SUVmax & SUVmean

	Tumor burden		
	Correlation Coefficient	**P value**	**N**
Liver SUVmax	-0.206-	**0.040**	100
Liver SUVmean	-0.247-	**0.013**	100
Spleen SUVmax	-0.227-	**0.023**	100
Spleen SUVmean	-0.201-	**0.045**	100
Left kidney SUVmax	-0.378-	**<0.001**	100
Left kidney SUVmean	-0.357-	**<0.001**	100
Right kidney SUVmax	-0.433-	**<0.001**	100
Right kidney SUVmean	-0.448-	**<0.001**	100
Left parotid gland SUVmax	-0.409-	**<0.001**	100
Left parotid gland SUVmean	-0.413-	**<0.001**	100
Right parotid gland SUVmax	-0.422-	**<0.001**	100
Right parotid gland SUVmean	-0.400-	**<0.001**	100
Left lacrimal gland SUVmax	-0.321-	**0.001**	100
Left lacrimal gland SUVmean	-0.337-	**0.001**	100
Right lacrimal gland SUVmax	-0.334-	**0.001**	100
Right lacrimal gland SUVmean	-0.327-	**0.001**	100

DISCUSSION:

The first study that evaluated the potential effect of the TSE in Theransotics agents was published by Beauregard et al in 2011 [7]. It included 10 patients with somatostatin receptor-positive neuroendocrine tumors who underwent ^{68}Ga-DOTA-octreotate PET/CT. The authors found that tumor sequestration of ^{68}Ga-DOTA-octreotate is a major factor leading to a sink effect that decreases activity concentration in healthy organs such as the kidney. They suggested the use of an adjusted-dose regimen tailored to the patient's tumor burden, which would allow greater radiation dose to individual lesions without adding to toxicity in normal tissues. This individualized therapy approach is a hallmark of modern medicine and is superior to the conventional fixed dose approach. In our present day, PSMA-targeted RLT with Lutetium-177 (^{177}Lu) for the treatment of prostate cancer is the most widely used RLT worldwide. Albeit, only a few studies have investigated the sink effect in PSMA-targeted PET. In the current study, we retrospectively analyzed ^{18}F-PSMA PET/CT of 100 males with prostate cancer. Metabolic tumor volume (PSMA-TV) was calculated using a semi-automatic method based on 50% threshold using Syngovia workstation. Total lesion PSMA expression (TL-PSMA) was calculated using the following formula: TL-PSMA = PSMA-TV x SUVmean. PSMA tumor burden is the sum of the TL-PSMA values of all lesions in each patient. Based on the tumor burden, patients were divided by quintiles into 5 groups. A very low (group 1, tumor burden ≤ 400), low (group 2, 400-1250), moderate (group 3, 1250 – 2500), high (group 4, 2500 - 6000), and very high (group 5, ≥ 6000) whole body total lesion PSMA-expression (TL-PSMA) or tumor burden. Reference organs which were used as representative for the normal background tissue uptake were the parotid glands, lacrimal glands, liver, spleen, and kidneys. SUVmax and SUVmean of all reference organs were obtained using the semi-automatic method. Tumor burden showed a moderate negative correlation with the SUVmean of the kidneys, parotid glands and left lacrimal gland, and a weak negative correlation with the SUVmean of

right lacrimal glans, liver and spleen. Patients with a very high tumor burden (group 5, ≥ 6000) had a significantly lower PSMA uptake in the lacrimal glands, salivary glands, kidneys, liver, and spleen compared to other groups ($P < 0.001$). These findings are of utmost clinical significance, since in RLT using ^{177}Lu-labeled PSMA-binding agents, the salivary glands and the kidneys are regarded as dose-limiting organs [8].

Similar to our results, Gaertner et al found that tracer uptake in the kidneys, salivary glands and lacrimal glands was highly dependent on tumor load [9]. Their retrospective study which was published in 2017 included 135 patients who underwent ^{68}Ga-PSMA scans for prostate cancer. Similar to our methodology, they divided the patients into groups according to the tumor load (low, medium, high) and also observed a pronounced influence of tumor load on the biodistribution of radiolabeled PSMA ligands in normal tissues. Nevertheless, it was not until 2022 when the TSE in the context of PSMA imaging and therapy was first systematically explored by **Gafita** et al. In their notable international multi-center study they included 6 institutions where a total of 406 ^{68}Ga-PSMA scans of patients with prostate cancer were retrospectively reviewed [3]. Similar to our study design, the patients were divided into quintiles, and the PSMA volume of total tumor lesions was calculated using auto-segmentation. However, the authors included a control group which included 50 patients. TSE was defined as a 30% or greater decline in ^{68}Ga-PSMA uptake in normal organs, compared with the control group. Their results also showed a moderate negative correlation of the tumor volume with SUVmean of salivary glands, kidney, liver, and a weak negative correlation with the spleen. Similar to our results, patients with very high PSMA volume had a significantly lower PSMA uptake in normal organs than the control group. They suggested that candidates for ^{177}Lu-PSMA RLT with a very high tumor volume on the screening PSMA-PET have a significantly lower normal-organ uptake and might benefit from an increased therapeutic activity without exceeding the radiation dose limit for organs at risk. Different results were found by **Werner** et al [10]. In 2020 they retrospectively investigated whether the uptake in normal organs correlated with an increase in tumor burden in 50 patients who had been imaged with ^{18}F-DCFPyl PET/CT. Similar to our technique, the

authors used an iso-contour threshold of 50%. They found no significant correlation between tumor volume with the vast majority of the investigated organs (lacrimal glands, parotid glands, submandibular glands, spleen and liver), only the kidney showed a significant correlation. They concluded that only a minimal sink effect with high tumor burden is present in patients imaged with ^{18}F-DCFPyl and that other factors such as intra-patient variability of normal organ uptake may be a much more important consideration for personalized dosimetry with PSMA-targeted therapeutic agents structurally related to ^{18}F-DCFPyl PET/CT than the tumor burden. However, their results might be explained by the fact that the TSE is only expected to cause a significant difference in case of high tumor volume levels, whereas their study included only a relatively small number of patients with early stage prostate cancer. Our study has many strength. First of all, it is the first study to our knowledge that investigates the TSE in ^{18}F-labeled PSMA. Although ^{68}Ga-labeled radiotracers targeting PSMA have been more commonly used, novel ^{18}F-labeled radiotracers are increasingly utilized and there have been suggestions of superior imaging characteristics relative to ^{68}Ga-labeled compounds [11]. Given the current trend towards increased use of ^{18}F-labeled PSMA ligands, our study is of special importance in the clinical practice. Second, we are also the first to incorporate the uptake intensity by the tumor burden into the evaluation. Instead of using the PSMA tumor volume only, we calculated the "total lesion PSMA expression" by multiplying the PSMA tumor volume x SUVmean of the lesion. This differentiated between patients with intense uptake lesions and those with low grade lesions from the start or after receiving therapy. For example, if two patients had widespread metastatic lesions with similar tumor volume but showing different grades of SUV, the patient with low uptake will be categorized in group 3 while the patient with intense uptake will be categorized in group 5 as per our work. We believe that this analysis may yield more accurate results, since the TSE is more related to the uptake in the tumor lesions rather than the volume of the tumor lesions per say. Another point of strength in our study is the fact that it included a large variety of tumor volumes ranging from very low to very high, further confirming the results of previous authors that TSE is mainly linked to patients with high tumor burden.

limitation of this study:

The main limitation in our study is the use of a single static scan to evaluate the relationship between tumor and normal organ uptake. A dosimetry study with several fixed time points or a dynamic evaluation of the uptake is needed to confirm our results. Also, the retrospective design does not allow for proper standardization of the injection activity and waiting time. However, **Gafita** et al found very low correlation coefficients between injected activity and uptake in the lacrimal glands and the kidneys, and therefore they concluded that a relevant influence of these parameters on the general result of this study can be excluded [3].

CONCLUSIONS:

Our results come in line with the majority of the studies that investigated the TSE and indicate that patients with high tumor load might tolerate significantly higher activity amounts of ^{177}Lu-labeled PSMA –ligands before adverse effects on the kidney and salivary gland function become relevant. Individual adaptations of therapy protocols might result in increased number of therapy cycles and/or increased activity amount per cycle in patients with low kidney and salivary gland uptake.

Conflict of interest: Not applicable

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