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RESEARCH

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Influence of metabolic tumor burden on reference tissues' standardized uptake values in ^{18}F-FDG PET/CT sequential imaging

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Abstract

Background Extremely hypermetabolic neoplastic tissues have been hypothesized to act as a "sink" reducing the amount of radiopharmaceutical available for uptake in other tissues, i.e., superscan phenomenon, the purpose of the study is to correlate the percent of change of metabolic tumor burden (MTB) with the standardized uptake values (SUVs) in reference tissues (liver, blood pool, brain and muscles) in sequential F-18-FDG PET/CT studies after therapy for different response groups (progression, regression and resolution) in all patients and in lymphoma patients.

Results In all patients: there was significant negative correlation between % of change in MTB with % of change of SUV in liver, blood pool, brain and muscles ($p < 0.05$). In progression group: there was significant negative correlation between % of change in MTB with % of change of SUV in liver and in muscles only. In regression group: there was no significant correlation in all organs. In lymphoma patients: there was significant negative correlation between % of change in MTB with % of change of SUV in liver, blood pool and brain but not in muscles.

Conclusions MTB can potentially affect F-18-FDG biodistribution in reference organs, which has a negative impact on semiquantitative analysis during interpretation of sequential studies. In lymphoma patients, normalizing tumor FDG uptake can be done to muscles as a potential stable reference tissue given that all other factors that could alter biodistribution were considered.

Keywords ^{18}F-FDG PET/CT, SUV, Reference organs, Metabolic tumor burden, PERCIST, Deauville

Background

Fluorine-18-fluorodeoxyglucose (F-18-FDG) positron emission tomography (PET)/computed tomography (CT) is a potent widely used imaging tool that has demonstrated significant capacity in oncologic staging and monitoring response to therapy, allowing for timely modification of therapy [1].

F-18-FDG PET/CT uniquely offer quantitative information on FDG uptake for assessing glucose metabolism in tumors [2]. Despite the numerous causes of bias in their measurements, the SUVmax is the most often utilized quantitative parameter [3]. However, it cannot correctly represent the metabolic activity of the tumor as a whole. In contrast, volume-based metrics, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), assess global volume and metabolism [4, 5].

In sequential PET investigations, it is crucial to ensure the comparability from different time points by regulating imaging parameters and quality.

FDG (a glucose analogue) and glucose compete for glucose transporters (GLUT-1 and GLUT-3) that are regulated by tumors, whereas insulin governs FDG and glucose absorption in the majority of normal tissues.

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Extremely hypermetabolic neoplastic tissues have been hypothesized to act as a "sink" reducing the amount of radiopharmaceutical available for uptake in other tissues, i.e., superscan phenomenon [6–8], especially those that have been proposed for semiquantitative analysis (such as the liver or blood pool) for evaluating the tumors' metabolic response to therapy such as PET Response Criteria in Solid Tumors (PERCIST) [9] or the Deauville five-point scale [10].

Methods

Aim of the work

Our objective was to correlate the values of MTB (the sum of TLG values of all lesions in each patient) with the SUVs in reference tissues in sequential PET/CT studies after therapy.

We assumed that this sink effect could be alleviated by normalization of the tumor FDG uptake to a potential stable reference tissue which is least affected by the superscan phenomenon, we attempt to propose the most stable organ that is best suited for use as a reference organ in follow-up scans for lymphoma patients.

Patient selection

This prospective research comprised 200 patients who underwent sequential PET/CT for oncological staging, re-staging, or evaluation of response to treatment, resulting in 400 F-18-FDG PET/CT images.

To determine the effect of superscan phenomenon only, other factors that could alter biodistribution were kept more or less constant between the two studies so only patients whose mean parameters did not change substantially between studies including weight (same body mass index classification), blood glucose level (BGL) (< 50 mg/dl difference), injected dosage (< 50 MBq difference) and interval uptake duration (< 15 min difference), we did include patients where initial scans showed lesions that are clearly visible, large and intensely avid. Patients excluded were those having BGL > 200 mg/dl at the time of FDG injection, who were administered therapeutics that have the potential to affect glucose metabolism within 12 h from the scan, patients with clinical suspicion for neurodegenerative disorders or cerebrovascular accidents or prior history or imaging data that supported it, patients with disease involvement in any of the studied reference tissues and finally patients whose sequential F-18-FDG PET/CT studies were performed in two different medical institutions and/or different scanner models.

Patients' medical records were thoroughly reviewed, and medical history was taken to collect data on age, sex, weight, height, primary type of malignancy, previous therapeutic interventions, thyroid disorders, diabetes status, use of medications (e.g., insulin), and serum creatinine level performed maximum 2 weeks before the study (in patients who received IV contrast).

Data acquisition

The patients were prepared in accordance with the EANM procedural guidelines for F-18-FDG PET/CT imaging of tumors, version 2.0 [11].

BGL was measured and recorded immediately before F-18-FDG injections.

Standardized protocol and conditions for proper patient preparation were met in order to reduce the development of any artefactual uptake patterns that would have resulted in faulty interpretation; patients were asked to refrain from movement on the day of scanning to prevent muscle uptake, they were maintained in a very soothing environment, they were also instructed to avoid excessive talking, chewing, and before, they were positioned on the PET/CT table, 500 ml of water was administered, and regular urination was encouraged.

All patients had imaging from the head to the upper thighs with their arms up. After CT imaging was completed, a PET scan was done in a caudal–cranial orientation. The duration of the scan varied according to the patient's body size and normally included 12 bed positions. During imaging, patients were encouraged to breathe shallowly.

Ingenuity TF 64 (Philips Healthcare, Cleveland, OH, USA) was the integrated PET/CT scanner utilized in this investigation. It combines a modular, LYSO-based PET component with a 64-channel CT component. CT is derived from the Ingenuity CT (Philips Healthcare). The PET component has an 80 cm ring diameter and 28 detector modules comprised of 23 (radial) by 44 (axial) matrices of (4 × 4x22mm3) Lutetium–yttrium oxyorthosilicate (LYSO) crystal components connected to photomultiplier tubes with an 18 cm axial Field of view. The device utilizes a 4.5 ns hardware coincidence window for its standard FOV, gathers data in 3D mode, and logs events from all detector ring combinations in list-style. Data were often rebuilt into static, gated, or dynamic pictures utilizing the scanner's built-in reconstruction procedures. Three alternative reconstruction FOVs are supported by the system: 256 mm for brain investigations, 576 mm for conventional whole-body, and 676 mm for big patient, whole-body research. Time of Flight (TOF), list-mode, blob-based, sorted subsets maximum likelihood expectation maximization technique is used to reconstruct images (TOF-OSEM).

Utilizing the scanner calibration factor, reconstructed pictures of patients are converted from scanner units to radioactive concentration. As recommended by the manufacturer, calibration is conducted quarterly,

and SUV validation is performed biweekly to decrease unpredictability.

Image analysis

OsiriX software was used to co-register and analyze F-18-FDG PET/CT images. Attenuation-corrected pictures based on SUV measurements based on body weight in kilograms (SUVkg) were used for the regions of interest.

Circular regions of interest (ROI) were drawn to best fit the anatomy for measuring SUV in the reference organs, as follows: for the liver; a 3 cm ROI within the right lobe, at the approximate segment VI or VIII level, for the mediastinal blood pool (MBP); a 1.2 cm ROI within the descending aorta excluding vascular wall and/or atherosclerosis, for the brain; a 1.2 cm ROI at the right cerebellum and for the muscle; 1.2 cm ROI within right psoas major muscle at the level of the iliac crest.

The sum of TLG values for all lesions in each scan was used to quantify the MTB. TLG was computed using the following formula: TLG = SUVmean × MTV. The threshold used to characterize tumor tissue was all voxels that are equal to or more than 50% of the maximum voxel value inside the spherical region (50% threshold). MTV was assessed using an automated segmentation program.

The percent of change between sequential studies regarding values of SUVmax in reference organs and MTB was calculated using the following formula: (Follow-up values − Initial values) ÷ (Initial values) × 100. And was performed twice. The first time, it was done in the whole patient population, and in the second time, it was done after dividing the patient population into 3 groups according to their response to treatment: progression, regression and resolution groups. Criteria for progression group (54 patients, 27%) included > 30% increase in 18-F-FDG SUVmax from the baseline scan in patterns typical of tumors and unrelated to infection or treatment effect, or there a noticeable increase in the extent of F-18-FDG tumor uptake, or new lesions with F-18-FDG avidity that is typical of cancer and unrelated to infection or treatment effect. Criteria for regression group (131 patients, 65.5%) included reduction of at least 30% in the target detectable tumor F-18-FDG SUVmax, no rise in SUVmax or size greater than 30% in any other lesions, and no new lesions and criteria and resolution group (15 patients, 7.5%) included patients whose lesions' activity resembling the level of surrounding background blood pool activity together with disappearance of all other lesions to background blood pool levels and no newly developed suspicious F-18-FDG avid lesions. PERCIST standards [9] served as an inspiration for this categorization.

Lymphoma (our most frequently encountered diagnoses; 54 patients, 27%) was studied separately using the same analysis methods and were also divided into progression (11 patients, 20%), regression (37 patients, 68%) and resolution (6 patients, 12%) groups.

It is noteworthy that our studied population all had lesions that are intense enough to be used as a measurable target lesion by the recommendations put forth in PERCIST criteria.

Statistical analysis

Data were statistically reported using the mean, standard deviation (SD), median, and range, or, where applicable, frequencies and percentages.

For the linear relationship of normally distributed variables, the Pearson moment correlation equation was used, while the Spearman rank correlation equation was used for non-normal variables and nonlinear monotonic relationships. It was deemed statistically significant when the two-sided p value was less than 0.05. IBM SPSS (Statistical Package for the Social Science; IBM Corp., Armonk, NY, USA) version 22 for Microsoft Windows was used to do all statistical computations.

Results

Diagnoses of studied population are listed in (Table 1). Demographic data of the studied population are listed in (Table 2). Mean values of MTB, SUVmax of the reference tissues as well as percent of change between initial and follow-up studies in all studied population and in lymphoma patients are listed in (Table 3). The same parameters were studied in different response groups and are listed in (Table 4). Regarding correlation analysis in all the response groups of studied population, there was significant negative correlation between percent of change in MTB with percent of change of SUV in liver (r −3.92, $p < 0.001$), blood pool (r −0.273, $p < 0.001$), brain (r −0.165, $p = 0.017$) and muscles (r −0.165, $p = 0.021$). In progression group: there was significant negative correlation between percent of change in MTB with percent of change of SUV in liver (r −0.318, $p = 0.023$) and in muscles (r −0.324, $p = 0.021$) only. In regression group: there was no significant correlation between percent of change in MTB with percent of change of SUV in liver, blood pool, brain or muscles.

In all patient's cohort, the comparison between different response groups was performed as shown in (Table 5). In progression group, the percent of change of metabolic tumor burden as well as SUVmax of liver, blood pool and brain showed significant difference in comparison with regression and resolution groups. While the percent of change of SUVmax of muscle did not show significant difference between any of the compared response groups.

Table 1 Diagnoses of the studied population

Diagnosis	Frequency	Percentage	Diagnosis	Frequency	Percentage
Lymphoma	54	27	Urinary bladder cancer	2	1
Breast cancer	47	23.5	Tongue cancer	2	1
Lung cancer	24	12	Appendicular cancer	1	0.5
Ovarian cancer	15	7.5	Buttock sarcoma (liposarcoma)	1	0.5
Colon cancer	10	5	Cervix cancer	1	0.5
Endometrial cancer	8	4	Facial cancer (basal cell carcinoma)	1	0.5
Mesothelioma	5	2.5	Laryngeal cancer	1	0.5
Gastro-esophageal cancer	3	1.5	Maxillary cancer	1	0.5
Pancreatic cancer	3	1.5	Neuroendocrine cancer	1	0.5
Rectal cancer	3	1.5	Oro-pharyngeal cancer	1	0.5
Renal cancer	3	1.5	Osteosarcoma	1	0.5
Anal cancer	2	1	Parathyroid cancer	1	0.5
Gastric cancer	2	1	Peritoneal carcinomatosis	1	0.5
Naso-pharyngeal cancer	2	1	Salivary gland cancer	1	0.5
Thyroid cancer	2	1	Seminoma	1	0.5

Table 2 Demographic data of studied population

	Number	Percentage	Range	Mean	± SD
Age	200	100%	21–81	54.8	14.3
Gender					
Males		86	43%		
Females		114	57%		
Received treatment					
CTH	152	76%			
RTH	10	5%			
Surgery	8	4%			
Unspecified	43	21.5%			
Blood glucose (mg/dl)					
Initial			50–200	100.3	22.8
Follow-up			63–198	99.96	22.4
Injected dose (MBq)					
Initial			83–458	281.8	54.4
Follow-up			126–470	284.1	58.1

Table 3 Mean values of MTB, SUVmax of liver, blood pool, brain and muscles as well as percent of change between initial and follow-up studies

	Initial	Follow-up	% of change
Mean values in all different tumors N = 200			
MTB	1062.550	454.32	257.09
Liver SUVmax	2.722	2.754	2.41
Blood pool SUVmax	1.93	1.939	3.08
Brain SUVmax	9.353	9.484	6.09
Muscles SUVmax	0.913	0.871	1.26
Mean values in lymphoma cases N = 54			
MTB	13330.659	3463.75	318.95
Liver SUVmax	2.724	2.820	4.79
Blood pool SUVmax	1.86	1.928	6.56
Brain SUVmax	9.276	9.809	8.62
Muscles SUVmax	0.948	0.850	0.66

The same analysis was applied to lymphoma group patients to identify whether any change would be detected in specific type of tumors. There was a significant negative correlation between percent of change in MTB with percent of change of SUV in liver (r −0.467, $p<0.001$), blood pool (r −0.291, $p=0.033$) and brain (r 0.417, $p=0.002$), but there was no significant correlation between percent of change in MTB with percent of change of SUVmax in the muscles.

In progression group, the percent of change of metabolic tumor burden as well as SUVmax of liver, blood pool and brain showed significant difference in comparison with regression and resolution groups. While the percent of change of SUVmax of muscle did not show significant difference between any of the compared response groups (Table 6).

Discussion

Uniform response criteria may not be the one-stop shop that we think they are and modern oncology is moving toward individualized cancer care, which acknowledges that specific host and tumor characteristics as heterogeneity are likely to affect treatment outcomes in any given patient [12].

The level of FDG uptake is used to gauge a lesion's metabolism and is therefore used to assess how well a tumor has responded to treatment. However, in order for

Table 4 Mean values for percent of change of metabolic tumor burden as well as SUVmax of liver, blood pool, brain and muscle in different response groups

	Progression group *N* = 54	**Regression group *N* = 131**	**Resolution group *N* = 15**
Mean % of change in all different tumors N = 200			
MTB	1249.38	− 88.33	− 100
Liver SUVmax	− 10.62	6.79	11.05
Blood pool SUVmax	− 10.08	7.16	14.87
Brain SUVmax	− 17.89	14.55	18.49
Muscle SUVmax	− 3.85	0.31	− 5.57
	Progression group *N* = 11 (20%)	**Regression group *N* = 37 (68%)**	**Resolution group *N* = 6 (12%)**
Mean % of change in lymphoma cases N = 54			
MTB	1933.66	− 93.16	− 100.00
Liver SUVmax	− 8.15	9.11	1.90
Blood pool SUVmax	− 7.99	11.50	2.78
Brain SUVmax	− 13.55	13.24	20.74
Muscle SUVmax	− 3.05	3.80	− 11.93

Table 5 Comparison between different response groups in all different tumors

In all different tumors (N = 200) % of change in:	**MTB**	**Liver SUVmax**	**Blood pool SUVmax**	**Brain SUV max**	**Muscle SUVmax**
Progression versus regression					
Mean difference	1337.714	− 17.402	− 17.243	− 32.442	− 4.153
p value	< 0.001	< 0.001	< 0.001	< 0.001	NS
Progression versus resolution					
Mean difference	1349.381	− 21.666	− 24.954	− 36.375	1.722
p value	< 0.001	< 0.001	< 0.001	0.034	NS
Regression versus resolution					
Mean difference	11.667	− 4.264	− 7.711	− 3.933	5.875
p value	NS	NS	NS	NS	NS

Table 6 Comparison between different response groups in lymphoma patients

In lymphoma cases (*N* = 54) % of change in:	**MTB**	**Liver SUVmax**	**Blood pool SUVmax**	**Brain SUVmax**	**Muscle SUVmax**
Progression versus regression					
Mean difference	2026.826	− 17.256	− 19.491	− 26.786	− 6.852
p value	< 0.001	0.001	NS	< 0.001	NS
Progression versus resolution					
Mean difference	2033.663	− 10.050	− 10.770	− 34.290	8.882
p value	< 0.001	NS	NS	0.002	NS
Regression versus resolution					
Mean difference	6.837	7.206	8.722	− 7.504	15.734
p value	NS	NS	NS	NS	NS

the comparison of several scans to be valid, an internal reference standard for normal organ uptake, such as that of the liver and mediastinal blood pool, has been proposed [13]. Many technological and biological (patient-related) parameters can influence these suggested reference organs [14, 15] as well as the recently studied phenomenon of metabolic superscan [6–8]. Therefore, inter-patient variability should be considered before sequential PET imaging interpretation [3, 16–21].

According to our correlation analysis results, if a patient has a significant response, the striking change in the MTB of the patients will subsequently lead to a significant change in FDG distribution within normal organs that are frequently chosen by different established PET response criteria as a relatively constant internal reference organ. The clinical implication of this phenomenon is serious and could lead to under- or over-treatment of patients by classifying them to the wrong response group. Supposably this phenomenon is most concerning in patients with partial response where a small change in the reference organs' uptake could change their response class. The cutoff value for the percent of change in each response group needs further evaluation in order to determine the point where correction algorithms are crucial to be applied for appropriate management of each individual patients.

Our comparison analysis results between different groups have led us to the suggestion that the change in distribution will not be constant between patients and supported the recent approach that each patient should be individually evaluated and the formula for correction should be adjustable according to the degree of change in distribution based on each response.

Viglianti et al. [21] examined the effect of metabolic tumor burden on FDG distribution in several organs at similar blood glucose levels in 50 patients (107 scans) and TLG and FDG absorption in reference tissues (blood pool, liver, brain) were found to be negatively inversely correlated. They came to the conclusion that the SUV readings may be significantly impacted by the metabolic tissue load. FDG absorption in the liver, blood pool, and basal ganglia is influenced by the metabolic sink effect, which is reliant on the TLG. They proposed that the influence of TLG and variations in blood glucose on absorption in the liver parenchyma is removed by normalizing to a reference tissue, such as blood.

In lymphoma patients studied separately as described; the results for those patients indicated that the internationally recognized and clinically utilized Deauville criteria reference organs may change between studies in a given patient in a manner that may affect the supposed constancy of these tissues, in addition considering that some sub-types of lymphoma demonstrates remarkable response to therapy so according to our found negative correlation the sink phenomenon will be obviously and more frequently encountered between sequential scans.

However, according to our analysis, the change in muscle uptake was not significant in lymphoma patients, meaning it was the least affected by the changes in metabolic tumor burden. And when comparing different response groups, the percent of change of SUVmax of muscle did not show significant difference. Our recognized relatively constant uptake in muscles between studies led us to suggest their use as a reliable reference organ to be used in the process of normalization in cases with striking change in liver and blood pool values. It is well-known that skeletal muscles make up such a huge part of the body; they are one of the major consumers of glucose, so it could be argued that they cannot be that reliable to have a constant uptake; however, since we excluded patients with conditions that could alter glucose and insulin metabolism so that basal rest insulin level is achieved and FDG absorption in muscles become modest and homogenous [22], so in these conditions, muscle uptake could indeed be used as a stable reference. This finding also led us to propose that different malignancies could potentially have a certain organ that is least affected by the tumor burden of this particular neoplasm and could subsequently be used for normalization. In order to boost confidence in the use of semiquantitative imaging techniques for detecting metabolic activity of a neoplasm, further research is required to find the most stable organ for each malignancy and even for lymphoma sub-types. Mathematical correction methods also need to be created. Nevertheless, our study findings can be used as a broad guideline for physicians in clinical practice, to take into consideration that changes in MTB may result in changes in reference organs uptake.

Similarly, it is proposed that this sink effect may exist in other conditions involving considerable metabolic activity, such as intense brown fat uptake, diffuse bone marrow stimulation, e.g., post chemotherapy and/or diffuse bowel uptake found in metformin-treated patients or patients with inflammatory bowel conditions, this notion needs to be further explored and developing methods for quantification of their uptake will be beneficial so that studying their effect would be feasible.

Our study did have some limitations, other confounding variables were not considered such as effects of interval chemotherapy; studies have shown a significant reduction in brain metabolism after chemotherapy, which in turn decreases normal FDG uptake within the brain [23]; however, the most affected regions were found to be the mesial temporal lobes as well as the frontal lobes, neither region were used in our study to draw ROIs [24]. The number of patients in each response group

was not equal, with predominance of regression group, metabolic flare phenomenon which is a potential pitfall in progression group were not evaluated, there was predominance of certain malignancies such as lymphoma, breast, lung over others such as pancreatic and gastric.

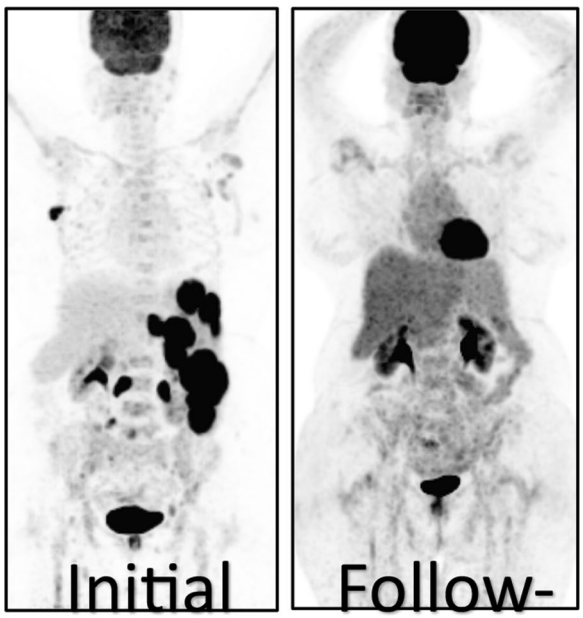

Fig. 1 MIP images of initial (MTB = 6020) and follow-up (MTB = 34) with (% of change = − 99.4%)

Last, adjustments for SUVs were based on body weight normalization rather than lean body mass, which has been shown to provide more reliable assessments, particularly in individuals who are obese [25].

65-year-old female patient with a history of non-Hodgkin's lymphoma (interpretation images are shown in Figs. 1 and 2) is a representative example of our findings. She underwent an initial PET/CT study and a follow-up study after chemotherapy to evaluate her treatment response. The follow-up study showed a remarkable metabolic regression of the supra- and infra-diaphragmatic lymphadenopathy, as well as splenic and bone marrow lesions. Increased FDG uptake was seen in the liver, blood pool and brain as a consequence of the marked reduction in metabolic tumor load, although FDG uptake in the muscles was unaffected.

Conclusions

Metabolic tumor burden can potentially affect F-18-FDG biodistribution in proposed internal reference organs, which has a negative impact on semiquantitative analysis during interpretation of sequential studies. This could potentially affect the patient's management that is based on assessment of clinical response by PET.

In lymphoma patients, normalizing tumor FDG uptake can be done to muscles as a potential stable reference tissue given that all other factors that could alter biodistribution were taken into consideration.

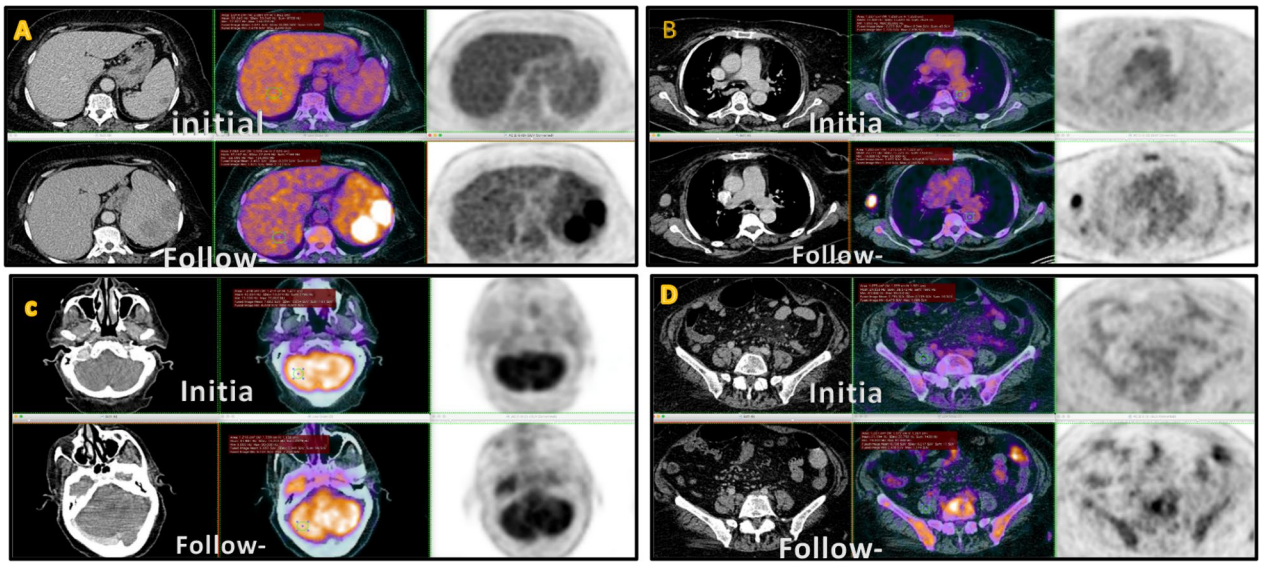

Fig. 2 **A** Liver; 3 cm ROI within the right lobe in initial (SUVmax = 3.1) and at follow-up (SUVmax = 3.7) with (% of change = 19.3%). **B** Mediastinal Blood Pool; 1.2 cm ROI within descending aorta in initial (SUVmax = 2.1) and at follow-up (SUVmax = 2.8) with (% of change = 33.3%). **C** Brain; 1.2 cm ROI at the right cerebellum in initial (SUVmax = 7.2) and at follow-up (SUVmax = 9) with (% of change = 25%). **D** Muscles; 1.2 cm ROI within right psoas major muscle in initial (SUVmax = 1) and at follow-up (SUVmax = 1) with (% of change = 0%)

Abbreviations

BGL	Blood glucose level
CT	Computed tomography
EANM	European Association of Nuclear Medicine
F-18-FDG	Fluorine-18-fluoro-deoxy-glucose
GLUT	Glucose transporters
IV	Intra-venous
LYSO	Lutetium–yttrium oxyorthosilicate
MTB	Metabolic tumor burden
MBP	Mediastinal blood pool
MTV	Metabolic tumor volume
OSEM	Ordered subset expectation maximization
PET	Positron emission tomography
PERCIST	PET response criteria in solid tumors
ROI	Regions of interest
SUVs	Standardized uptake values
SD	Standard deviation
SPSS	Statistical package for the social science
TLG	Total lesion glycolysis
TOF	Time of flight

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Author contributions
All authors read and approved the final manuscript. This study was conducted as MD thesis of MMM who was responsible for collection of data and follow-up patients file, under supervision of the other authors in nuclear medicine departments and each of them had a direct contribution to the thesis and paper preparation. Data were collected by MMM with the direct help of the AB and revising; tabulating data were performed by AAK and HA. Final paper writing, revision and editing was done by MMM (corresponding author).

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All study techniques involving human subjects adhered to the ethical norms of the institution's research committee and the Declaration of Helsinki and its later revisions. Informed consent to participate in the study is obtained from participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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