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For avid glucose tumors, the SUV peak is the most reliable parameter for [^{18}F]FDG-PET/CT quantification, regardless of acquisition time

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Abstract

Background: This study is an assessment of the impact of acquisition times on SUV with [^{18}F]FDG-PET/CT on healthy livers (reference organ with stable uptake over time) and on tumors.

Methods: One hundred six [^{18}F]FDG-PET/CT were acquired in list mode over a single-bed position (livers ($n = 48$) or on tumors ($n = 58$)). Six independent datasets of different durations were reconstructed (from 1.5 to 10 min). SUV_{max} (hottest voxel), SUV_{peak} (maximum average SUV within a 1-cm^3 spherical volume), and $SUV_{average}$ were measured within a 3-cm-diameter volume of interest (VOI) in the right lobe of the liver. For [^{18}F]FDG avid tumors ($SUV_{max} \geq 5$), the SUV_{max}, SUV_{peak}, and $SUV_{41\%}$ (isocontour threshold method) were computed.

Results: For tumors, SUV_{peak} values did not vary with acquisition time. SUV_{max} displayed significant differences between 1.5- and 5–10-min reconstruction times. $SUV_{41\%}$ was the most time-dependent parameter. For the liver, the $SUV_{average}$ was the sole parameter that did not vary over time.

Conclusions: For [^{18}F]FDG avid tumors, with short acquisition times, i.e., with new generations of PET systems, the SUV_{peak} may be more robust than the SUV_{max}. The $SUV_{average}$ over a 3-cm-diameter VOI in the right lobe of the liver appears to be a good method for a robust and reproducible assessment of the hepatic metabolism.

Keywords: [^{18}F]FDG uptake, SUV_{peak}, Acquisition time

Background

Assumed to be more accurate and less operator-dependent than visual analysis, quantification is increasingly used in positron emission tomography (PET) studies in routine practice or clinical trials. This is particularly relevant for treatment monitoring since it has been shown that objective quantification of [^{18}F]FDG uptake changes may improve the prognostic value of [^{18}F]FDG-PET compared with visual analysis [1]. Even prone to many sources of errors and variability, the semi-quantitative method (standardized uptake value SUV) is currently preferred to the absolute quantification of glucose metabolic rate, which requires dynamic imaging and measurement of the arterial input function, and thus considered to be too complex for a use in routine practice. SUV_{max} (SUV of the hottest voxel within a defined volume of interest (VOI)) is the most widely used parameter, easy-to-use, and operator-independent. However, SUV_{max} may be affected by noise and may merely reflect statistical fluctuations when the acquisition time is too short [2]. Among the other SUV, SUV_{peak} has been suggested as an alternative to SUV_{max} [3]. SUV_{peak} is an average SUV computed within a fixed-size VOI, most often containing (and not necessarily centered on) the hottest pixel value. Because this VOI encompasses several pixels, SUV_{peak} is assumed to be less affected by image noise than SUV_{max} [4, 5] and then more reliable and

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appropriate for monitoring tumor response, while remaining easy-to-use with very little or no operator dependency. The major drawback of SUV_{peak} is that its associated volume of interest (VOI_{peak}) is not uniquely defined, leading to a few dozen of SUV_{peak} definitions, differing in the shape, size, and location of the VOI_{peak} [6]. In one hand, VOI_{peak} should be large enough to prevent SUV_{peak} to be affected by noise and partial-volume effects, and in other hand, VOI_{peak} should not be too large to avoid inclusion of voxels outside the tumor. These considerations lead to a fixed 1-cm^3 sphere recommended by PERCIST [3] as a standard definition of SUV_{peak}.

The use of time of flight (TOF) in reconstruction algorithms of new generations of hybrid PET/CT machines (positron emission tomography scanner/X-ray computed tomography scanner) improves signal-to-noise ratio, spatial resolution, and lesion detectability, theoretically allowing reduced injected activity (and thus radiation exposure) and/or acquisition time [7]. Furthermore, point spread function (PSF) reconstruction, also available in new generations of PET systems, is known not only to improve sensitivity but also to overestimate SUV [8, 9]. The quantitative accuracy of these techniques is not fully known [8], especially their impact on the SUV_{max} determination when acquisition time is reduced to its lower limit for optimizing acquisition protocol in clinical practice. The implementation of these new techniques therefore presents a challenge for centers to define an acquisition protocol that can be used for visual and quantitative analysis, while respecting the European Association of Nuclear Medicine (EANM) guidelines [10], i.e., either by determining the minimum FDG-administrated dose in relation to PET acquisition duration and patient weight or by choosing to apply a higher activity to reduce duration of the study. The aim of this study was to evaluate the impact of acquisition time on SUV on healthy livers (reference organs with stable uptake over time) and on tumors.

Methods

Materials

One hundred six whole-body PET/CT scans with 2-[^{18}F]-2-deoxy-D-glucose ([^{18}F]FDG) were performed in 102 patients (39 women, 63 men), for staging or for the evaluation of treatment response of neoplastic or inflammatory diseases. Patients' characteristics and tumor histology are summarized in Table 1. The Ethics Committee of the University of Angers approved the study protocol.

Table 1 Patients characteristics: mean ± standard deviation

Characteristics	All	Women	Men
Age	60 ± 17		
Height (cm)	169 ± 10		
Weight (kg)	69 ± 13.2		
Body mass index (kg/m^2)	24.2 ± 3.9	23.9 ± 4.2	24.4 ± 3.7
Injected activity (MBq)	220 ± 57		
Whole-body PET/CT uptake time (min post-injection)	62 ± 4.6		
PET/CT uptake time for 10 min LM acquisition (min post-injection)	83 ± 5.8		
Tumor histology (n = 58)			
Non-small cell lung cancer	29		
Mesothelioma	1		
Non-Hodgkin lymphoma including:	14		
Diffuse B cell lymphoma	6		
Follicular lymphoma	4		
T cell lymphoma	2		
Mantle cell lymphoma	2		
Hodgkin disease	6		
Multiple Myeloma	1		
Esophageal cancers	3		
Pheochromocytoma	1		
Breast cancer	1		
Cervical-uterine cancer	1		
Ovarian cancer	1		

PET/CT scanning

Patients fasted for at least 6 h before the intravenous injection of 220 ± 57 MBq (3 MBq/kg) of [^{18}F]FDG. Data were acquired on a PET/CT Discovery-690 system (LYSO scintillation PET detector; 64-slice CT; GE®, Buc, France) with an acquisition time of 3 min/bed position. PET images were reconstructed with an ordered-subset expectation maximization (OSEM) 3D algorithm (3 iterations, 8 subsets, 192 × 192 matrix, 3.65 mm pixels, slice thickness 3.27 mm, post-reconstruction Gaussian 4 mm filter) with VPFX time-of-flight (TOF) algorithm and point spread function (PSF) correction (Sharp IR). CT-based attenuation correction (120 kV, Auto mA, collimation 20 mm, pitch 1.375, 0.8 s/rot) was applied.

Whole-body PET/CT were performed 62 ± 4.6 min after [^{18}F]FDG injection, and an additional PET/CT acquisition of 10 min in list mode (LM) was acquired using a single-bed position 83 ± 5.8 min after [^{18}F]FDG injection.

After the whole-body scan acquisitions (n = 106), additional list mode acquisitions were performed on the most avid tumor (tumor $SUV_{max} > 5$; n = 58) or on normal healthy liver (no history of liver metastasis and no evidence of liver lesion on whole-body [^{18}F]FDG-PET/CT scans; n = 48).

Six datasets (called R for replay) were reconstructed from this LM additional acquisition, mimicking acquisition

times of 1.5, 2, 2.5, 3, 5, and 10 min (respectively $R_{1.5,}$ R_2, $R_{2.5}$, R_3, R_5, and R_{10}).

Image analysis

Two experienced nuclear medicine physicians analyzed all images datasets on an Imagys® workstation (Keosys®, Saint-Herblain, France), allowing the computation of different SUV. SUV was corrected for body weight (SUVbw).

For tumor [^{18}F]FDG uptake quantification, a manual VOI encompassing the entire tumor was drawn on R_{10}. VOIs were registered and repositioned identically for the five other replays ($R_{1.5}$ to R_5) using 3D coordinates that allow the reposition of the VOI on all replays. SUV_{max} (SUV of the hottest voxel), SUV_{peak} (maximum average SUV within a 1-cm^3 sphere), $SUV_{41\%}$ (threshold-based tumor delineation applying a threshold of 41 % of the SUV_{max}), and metabolic tumor volume (applying a threshold of 41 % of the SUV_{max} on R_{10}) were then automatically generated. A threshold of 41 % was chosen following the EANM guidelines [10] and because the most common thresholding value chosen in the clinical setting is 40–43 % of the SUV_{max}.

For the liver, a 14-cm^3 VOI was positioned on the right lobe of the liver on R_{10}, as proposed in PERCIST [3]. As for tumors, VOIs were repositioned identically for the five other replays using 3D coordinates that allow the reposition of the VOI on all replays. SUV_{max}, SUV_{peak}, and $SUV_{average}$ (average SUV within the fixed 14-cm^3 VOI) were automatically generated.

Statistical analysis

For tumors, SUV_{max}, SUV_{peak}, and $SUV_{41\%}$ were analyzed. For livers, SUV_{max}, SUV_{peak}, and $SUV_{average}$ were analyzed.

Paired *t* tests were performed to study the inter-observer reproducibility of tumor and liver measurements.

Repeated-measures ANOVA (Tukey post-tests) was performed to test the variations of measurements over time, i.e., between the six replays ($R_{1.5}$ to R_{10}).

Individual SUV fluctuations Δt over time (i.e., at 1.5, 2, 2.5, 3, and 5 min) were evaluated using the SUV at 10 min as reference SUV and were calculated as follows:

$$\Delta_t = \frac{(SUV_t - SUV_{10\,min})}{SUV_{10\,min}}$$

For each replay, and for liver and tumors, the maximum individual fluctuations were registered.

Statistical tests were performed using Prism 4 software (GraphPad software, CA, USA). The level of significance was set at 5 %.

Results

No significant differences were observed between the two readers for the evaluated image datasets (tumor and liver).

Tumors

SUV_{peak} was the only parameter stable over time with no significant statistical difference between the six replays.

SUV_{max} and $SUV_{41\%}$ decreased significantly with time ($p \le 0.0005$) (Table 2). For SUV_{max}, statistical differences were observed between the shortest acquisition time $R_{1.5}$ versus the longest R_5 and R_{10} ($p = 0.0005$).

$SUV_{41\%}$ was the most time-dependent parameter, with significant statistical differences between $R_{1.5}$ and R_2 versus R_5 and R_{10} and between $R_{2.5}$ and R_{10} ($p < 0.0001$) (Table 2).

SUV_{peak} was the least variable parameter with individual fluctuations up to 38 % (from 7.22 to 9.96) versus 58 % for SUV_{max} (from 10.82 to 17.1) and 56 % for $SUV_{41\%}$ (from 6.22 to 9.7) (Table 3). For all tumor SUVs, maximal fluctuations were observed between the shortest replay ($R_{1.5}$ or R_2) and R_{10}. Considering a maximum fluctuation of 10 % as an acceptable level of variation for tumor SUV [11], the number of patients with tumor SUV fluctuations >10 % (compared to R_{10}) was noted. $R_{1.5}$ and R_2 were the replays in which the higher number of patients with SUV fluctuations >10 % was observed, whatever the type of SUV. SUV_{peak} was the least variable

Table 2 SUV_{max}, $SUV_{41\%}$/$SUV_{average}$, and SUV_{peak} (mean ± SD of all datasets) of tumors and livers for each replay

	SUV $R_{1.5}$ (mean ± DS)	SUV R_2 (mean ± DS)	SUV $R_{2.5}$ (mean ± DS)	SUV R_3 (mean ± DS)	SUV R_5 (mean ± DS)	SUV R_{10} (mean ± DS)	*p* ANOVA
Tumor							
SUV_{max}	17.4 ± 9.5 (R_5, R_{10})	17.3 ± 9.6	17.2 ± 9.7	17.1 ± 9.6	16.9 ± 9.5	16.9 ± 9.7	0.0005
$SUV_{41\%}$	10.4 ± 5.6 (R_5, R_{10})	10.3 ± 5.5 (R_5, R_{10})	10.2 ± 5.6 (R_{10})	10.2 ± 5.6	10.1 ± 5.5	10.1 ± 5.6	<0.0001
SUV_{peak}	13.6 ± 8.3	13.6 ± 8	13.6 ± 8.1	13.5 ± 8	13.6 ± 8.1	13.5 ± 8.2	NS
Liver							
SUV_{max}	2.9 ± 0.5 ($R_{2.5} \rightarrow R_{10}$)	2.8 ± 0.5 ($R_3 \rightarrow R_{10}$)	2.8 ± 0.5 (R_5, R_{10})	2.7 ± 0.5 (R_5, R_{10})	2.6 ± 0.5 (R_{10})	2.5 ± 0.5	<0.0001
$SUV_{average}$	2.2 ± 0.4	2.2 ± 0.4	2.2 ± 0.4	2.2 ± 0.4	2.2 ± 0.4	2.2 ± 0.4	NS
SUV_{peak}	2.5 ± 0.4 ($R_2 \rightarrow R_{10}$)	2.5 ± 0.4 (R_5, R_{10})	2.4 ± 0.4 (R_5, R_{10})	2.4 ± 0.4 (R_5, R_{10})	2.4 ± 0.4	2.4 ± 0.4	<0.0001

(R_2) means a significant difference with the replay R_2, ($R_{2.5}$) with $R_{2.5}$, (R_3) with R_3, (R_5) with R_5, and (R_{10}) with R_{10}

Table 3 Maximal individual SUV fluctuations (Δmax) compared to the reference SUV at 10 min

	Δmax $R_{1.5}$ vs R_{10} (%)	Δmax R_2 vs R_{10} (%)	Δmax $R_{2.5}$ vs R_{10} (%)	Δmax R_3 vs R_{10} (%)	Δmax R_5 vs R_{10} (%)	Δmax mean value (%)
Tumor						
SUV_{max}	58	43	31	24	31	37
$SUV_{41\%}$	56	41	26	25	26	35
SUV_{peak}	34	38	29	26	13	28
Liver						
SUV_{max}	41	35	26	29	19	30
$SUV_{average}$	16	15	14	14	9	14
SUV_{peak}	17	19	19	18	11	17

Δmax R_t-R_{10} (%) is the maximal individual fluctuation between SUV value at R_t and SUV value at R_{10}. Δmax mean value is the mean Δmax from "$R_{1.5}$ vs R_{10}" to "R_5 vs R_{10}"

parameter with fluctuations >10 % observed in only five patients ($R_{1.5}$) compared to SUV_{max} (11 patients, $R_{1.5}$) and $SUV_{41\%}$ (seven patients, R_2).

Metabolic tumor volumes ($VOI_{41\%}$) measured on R_{10} varied widely from 1.1 to 369.32 cm^3 (median 6.47 cm^3).

Livers

$SUV_{average}$ was stable over time with no significant statistical difference, whereas a significant tendency to decrease with time was observed for SUV_{max} and SUV_{peak} ($p \leq 0.0005$; Table 2).

For SUVpeak, statistical differences were observed between $R_{1.5}$ and the other replays and between R_2, $R_{2.5}$, and R_3 versus R_5 and R_{10} ($p < 0.0001$).

SUV_{max} was the most time-dependent parameter ($p < 0.0001$) (Table 2).

$SUV_{average}$ was the least variable parameter with individual variations up to 16 % (between $R_{1.5}$ and R_{10}) versus 19 % for SUV_{peak} and 41 % for SUV_{max} (between $R_{1.5}$ and R_{10}).

Discussion

The SUV definitions used in the present study are usually described to be particularly suitable for response-monitoring purposes. Indeed, these semi-automatic and operator-independent methods allow a simple and reproducible evaluation of SUV that is a basic requirement to provide an added value to the quantitative measurement compared to visual assessment. There is no actual consensus about the best SUV parameter to be used to assess response to therapy, but most response assessment studies use SUV_{max}, the first reason being related to its easy implementation and operator-independent character. Moreover, for small lesions or during an effective treatment with a decrease in tumor size, when partial-volume effect may result in an underestimation of [^{18}F]FDG uptake, SUV_{max} may be best suited as metabolic index than the other SUVs [12]. In a clinical point of view, identification of a suitable SUV for response quantification requires clinical trials with patients' clinical outcomes, and SUV_{max} demonstrated positive predictive values and accuracies for outcome prediction in lymphoma [1] as well as in solid tumors [13, 14]. Although the increase in counting statistics with new PET/CT systems contributes to reduce image noise, SUV_{max} remains adversely affected by noise, leading to uncertainty in the uptake quantification and thus in the treatment response categorization. Theses inaccuracies may be more pronounced in case of tumor heterogeneity that moreover may change during the course of treatment [15]. Consequently, SUV_{peak} has been recently proposed as a more robust alternative of SUV_{max} [3]. SUV_{peak} has a larger volume compared to the single pixel value of SUV_{max} and thus should be less affected by image noise [4, 5, 16].

Acquisition times recommended by the manufacturer are most often used in clinical routine, even though the actual influence of acquisition time upon SUV is not fully known. Regarding different quantifications of the same metabolic process (for a given tumor), a correlation does exist between SUV_{max} and SUV_{peak} and the uncertainties of these two parameters are probably comparable, although from different causes [4]. Nevertheless, these considerations do not allow an assessment of the influence of acquisition time on SUV, and substantial differences may exist between SUV_{max} and SUV_{peak} in individual tumors that affect the treatment response quantification and the response categorization.

Because the current worldwide trend is to reduce patient exposure to ionizing radiation, it is not conceivable to increase the injected activity to overcome a low statistical quality of PET images due to a too short acquisition time. Conversely, increasing the acquisition time may lead to discomfort of the patient and to motion artifacts. In our study, the highest fluctuations of SUV were observed when acquisition times were the shortest, whereas no significant difference was observed for replays superior or equal to 3 min. Brown et al. [17] investigated the effect of varying acquisition times on phantom and patient

PET images on a 3D GE Discovery-STE PET/CT system. Patient data were investigated using list mode acquisition to obtain comparable 2-, 3-, and 4-min frames. As we reported for tumors, no significant difference was observed over 3 min at standard clinical [^{18}F]FDG activities. In two other studies, the image quality was slightly adversely affected by an acquisition time of 1.5 min compared to 3 min [18] and the volume and SUV variability were significantly larger for images with scan times below 3 min [19].

For tumors, we did not observe any significant difference for SUV_{peak} over time, and regarding individual variations, SUV_{peak} was also the least variable parameter. Using a reference time of 15 min, Lodge et al. [20] reported similar results with a significant lower bias for the SUV_{peak} compared to the SUV_{max} for the 1-, 2-, 3-, and 4-min images. In our study, large SUV_{max} variations up to 58 % ($R_{1.5}$ versus R_{10}) were observed for the same tumor in the same patient, which is obviously unacceptable for response-monitoring purposes, particularly when accumulated to other sources of bias [11, 21] and if a threshold value is applied to determine treatment response as with PERCIST criteria [3]. As previously reported [2, 4, 22], we noted that fluctuations of SUV_{max} also affected threshold method SUV since the VOI was determined by selecting pixel values equal to 41 % of the maximum pixel value.

For all these reasons discussed, SUV_{peak} may be a robust alternative for the assessment of [^{18}F]FDG avid tumor uptake at standard clinical activities. We implemented a SUV_{peak} algorithm using a fixed-size 1-cm^3 VOI, automatically positioned so as to maximize the enclosed average (maximum average), typically including but not necessarily centered on the maximum pixel value. However, for small tumor sizes, the automatic placement of the VOI may be impossible, but in these cases, the placement of the VOI can be performed manually.

Finally, an important additional result is the absence of significant difference for the liver SUVaverage over time. These results confirm that the liver metabolism can be used as the reference organ for quality comparison of repeated [^{18}F]FDG-PET studies in the same patient, or as a reference threshold for evaluating tumor response. In PERCIST criteria, the size of the VOI and its placement in the right lobe are mentioned, but not the position to which the measure should be made. However, a recent study found an excellent inter-observer agreement and no significant difference whether the VOI is placed in the upper part, the portal level, or at the bottom of the right liver lobe [23]. Our results are also in agreement with those of Grohien et al. [24], who showed a larger dispersion of values and a higher variance for hepatic SUV_{max} compared to hepatic $SUV_{average}$.

Conclusions

Tumor SUV_{peak} (volume 1 cm^3) was the most stable quantitative parameter for acquisition times over 1.5 min at standard clinical [^{18}F]FDG activities.

Although not yet widely available, commercial development of SUV_{peak} may increase the reproducibility and accuracy of quantitative PET studies, this quality of measure being essential for response-monitoring purposes. Average SUV over a 3-cm VOI in the right liver lobe was a good method for a robust assessment of hepatic metabolism, confirming the choice of the liver as the reference organ in [^{18}F]FDG studies.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AS, FB, DD and OC designed the study. Data acquisition was conducted by AS, FB, DD, PF and LV. Statistical analysis were performed by AC, AS, OC, FL, FB and DD. Results were analysed by AS, FB, DD, AC, FL and OC. The manuscript was written by AS, FL, FB and OC. All authors read and approved the final manuscript.

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