Assessing PET Parameters in Oncologic \(^{18}\)F-FDG Studies

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PET imaging, particularly oncologic applications of \(^{18}\)F-FDG, has become a routine diagnostic study. To better describe malignancies, various PET parameters are used. In \(^{18}\)F-FDG PET studies, SUV\(_{\text{max}}\) is the most commonly used parameter to measure the metabolic activity of the tumor. In obese patients, SUV corrected by lean body mass (SUL), and in pediatric patients, SUV corrected by body surface area, are recommended. Metabolic tumor volume is an important parameter to determine the local and total tumor burden. Total lesion glycolysis (SUV\(_{\text{mean}}\times\)metabolic tumor volume) provides information about averages. Some treatment response assessment protocols recommend using the SUV\(_{\text{peak}}\) or SUL\(_{\text{peak}}\) of the tumor. Tumor-to-liver ratio and tumor-to-blood-pool ratio are helpful when comparing studies for treatment response assessment. Dual-time-point PET imaging with retention index can help differentiate malignant from benign lesions and may help detect small lesions. Dynamic \(^{18}\)F-FDG PET imaging and quantitative analysis can measure the metabolic, phosphorylation, and dephosphorylation rates of lesions but are mainly used for research purposes. In this article, we will review the currently available PET parameters in \(^{18}\)F-FDG studies with their importance, uses, limitations, and reasons for erroneous results.

**Key Words:** PET; parameter; \(^{18}\)F-FDG; oncology; SUV


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PET imaging is based on detecting 2 simultaneously released 511-keV photons after a positron (emitted from the injected radiotracer in the body) moves in the tissue for a distance (positron range) until it reaches rest mass and then collides with a tissue electron, causing an annihilation reaction. PET imaging is a high-technology product but still has certain limitations related to various factors such as the noncollinearity of 511-keV photons, positron range, and parallax error, which affect its sensitivity and spatial resolution in detecting small lesions (1–3). Noncollinearity causes less of a problem in small-animal PET scanners, and therefore, small-animal PET scanners have a higher spatial resolution than standard human PET scanners (~1 vs. 4–6 mm) (4).

PET imaging, particularly with \(^{18}\)F-FDG, has been used commonly since the introduction of PET/CT fusion cameras in the early 2000s. PET images are visually assessed and also supported by quantitative parameters. Currently, the most commonly used PET parameter is SUV in oncologic \(^{18}\)F-FDG studies. The other parameters include SUV normalized by lean body mass (SUL), metabolic tumor volume (MTV), total lesion glycolysis (TLG), tumor-to-liver and tumor-to-blood-pool ratios, retention index in dual-time-point PET studies, and dynamic PET imaging parameters. Various other parameters are available with various radiotracers in oncologic, neurologic, and cardiac PET studies, which will not be discussed in this review article. However, most of the PET parameters described in this article can also be used in other oncologic PET studies, with different SUVs in normal tissues and thresholds in differentiating malignant from benign lesions.

**SUV**

SUV is a commonly used PET parameter to measure the uptake of various radiopharmaceuticals, mainly \(^{18}\)F-FDG, in normal tissues and lesions (5–7). SUV is simply the ratio of the activity concentration in the target tissue or lesion to the activity concentration in the whole body:

\[
\text{SUV} = \frac{k\text{Bq/cm}^3}{\text{lesion or target tissue}} \times \frac{\text{decay corrected injected activity (MBq/patient weight (kg))}}{\text{decay corrected injected activity (MBq/patient weight (kg))}}
\]

This equation assumes that the injected activity is uniformly distributed in the whole body and that 1 cm\(^3\) of tissue weighs 1 g (8). Activity in the lesion or target tissue is decay-corrected.

Because of metabolic heterogeneity or irregular tumor borders, SUV\(_{\text{max}}\) is used instead SUV\(_{\text{mean}}\). SUV\(_{\text{max}}\) is the maximum voxel value of SUV in the tumor. SUV\(_{\text{max}}\) does not represent the whole tumor metabolic burden and is sensitive to image noise (9).

SUV generally accurately estimates the degree of uptake of radiopharmaceuticals in lesions and normal tissues but is affected by various patient, biologic, and technical factors that can cause over- or underestimation of the activity in lesions and tissues. Examples include suboptimal patient preparation; high blood glucose and insulin levels; diabetic status; body mass index; age; sex; significant extravasation of activity;
image acquisition and reconstruction parameters; conditions during the postinjection uptake period; inaccurate entry of weight, height, and injected activity; clock synchronization errors; inaccurate entry of injection time and imaging start time; effect of CT contrast material on attenuation-corrected PET images; patient and organ motion; and other diseases and medications affecting $^{18}$F-FDG uptake (Figs. 1–3) (8,10–15).

In the normalization of SUV, usually the patient’s total weight is used. However, in obese people, SUV is overestimated in lesions and normal tissues (Fig. 1) (16,17) because $^{18}$F-FDG is distributed mainly in nonfat tissues and the percentage of adipose tissue is high in obese people, with minimal $^{18}$F-FDG accumulation in the fat. Use of SUV, instead of normalization by total weight, is recommended in obese patients (16,17). SUV also allows for a better comparison of the PET images of a patient whose weight has changed significantly between PET studies. Weight changes, particularly loss, are common in oncolgic patients because of treatments or disease progression. SUV will be overestimated when the patient is overweight or obese and underestimated when the patient is underweight or has cachexia. There are various ways of measuring lean body mass. It can be calculated through predictive equations using height and body weight (18). However, semidirect measurements of lean body mass such as bioelectrical impedance analysis, dual-energy x-ray absorptiometry, CT, and MRI can provide more accurate results (19). Using a more accurate method to measure lean body mass will provide a more accurate SUL. However, all these methods have certain limitations, advantages, and disadvantages. CT and MRI are the most precise and accurate methods but are costly and complex to operate (19). Bioelectrical impedance analysis and dual-energy x-ray absorptiometry are more accessible, easier to use, and less costly (19). CT is not recommended in pregnant women and in children because of radiation exposure. MRI is not suitable for patients with metallic parts. A standard method for calculating lean body mass will allow more accurate comparison of PET studies obtained at different institutes. SUL can be measured either directly by simply entering the patient’s lean body mass instead of total weight or indirectly by calculating it from SUV with the following formula:

$$\text{SUL} = \frac{\text{SUV} \times \text{lean body mass}}{\text{total weight}}$$

In heavy patients, the SUVs of blood, liver, and spleen were up to twice those of lighter patients (16). In our recent study, the SUVs of the liver and blood pool were significantly higher in obese patients than in patients with a normal body mass index, and SULmean was approximately 75% of SUVmean in patients with a normal body mass index and 55% of SUVmean in obese patients (20). For comparison, the percentage of fat is 20%–25% of total body weight in young women with a normal body mass index and 38%–40% in young obese women (21). If SUV is going to be used routinely, standard values (thresholds for differentiating benign from malignant lesions, and normal liver and blood-pool values) should be determined. In our recent study, SULmean in the liver and blood pool were 2.2 and 1.8, respectively, in patients with a normal body mass index and were similar in obese patients (20). SUL is not affected by body weight or lean body mass (20).

Studies assessing SUV in children found that SUVs in the liver and tumor are lower than those in adults (22,23). SULs in children are also lower than normal adult values (23). These studies recommended using a body-surface-area–based SUV in children (22,23). The lower SUV and SUL in children than in adults could be due to the higher amount of brown fat in children, which could competitively reduce the uptake of activity in other normal tissues and lesions.
Hyperglycemia reduces 18F-FDG SUV in the tumor to an extent that may be similar to the above reductions in the brain. Measured tumor SUVmax can be multiplied by reduction factors of 1.25, 1.5, 2, 2.5, and 2.8 for the blood glucose ranges of 111–120, 121–140, 141–160, 161–200, and at least 201 mg/dL, respectively, to correct SUV in hyperglycemic adults (12). Including the brain in whole-body images can provide a better idea of the effect of hyperglycemia with 18F-FDG uptake and SUV (Fig. 3) (12).

MTV AND TLG

MTV is an important parameter that measures the metabolically active tumor volume (local and total tumor burden). Tumor tissue may contain necrotic or dead tissues or atelectasis, and the volume of the tumor may therefore look larger on CT than on PET. PET shows uptake in the metabolically active parts of the tumor and in inflammation and lack of uptake in dead tissues, necrosis, and atelectasis. There are various methods (threshold-based and algorithm-based) to measure MTV via computer programs (9,26). Fixed-absolute-threshold methods may be more suitable to assess the prognostic value of MTV, and algorithm-based methods seem to be better than fixed-threshold methods to predict tumor response or accurately delineate the tumor for radiotherapy applications (9). If a computer program is not available to measure MTV, gross manual measurement in each slice can be performed, which is time-consuming. TLG is obtained by multiplying SUVmean by MTV (27). SUVmean is obtained by placing a region of interest around the hottest part of the tumor.

MTV and TLG have prognostic value in a variety of malignancies, and high MTV and TLG predict a worsening prognosis (28–30). MTV and TLG are reported to correlate better with histopathologic response than does SUVmax (31). SUVmax is a single value reflecting only the highest pixel activity; however, TLG reflects 2 parameters: average whole-tumor metabolic activity and volume of the tumor. MTV and TLG are also important when adjusting the dose of treatments. If there is metabolic heterogeneity in the tumor, TLG may be overestimated because SUVmean is obtained by placing a region of interest over the hottest part of the tumor. Moreover, TLG can be calculated accurately by measuring total lesion activity and multiplying it by MTV. MTV and TLG appear to be useful parameters but have not been commonly used in routine clinical practice.

UPTAKE RATIO

Tumor–to–reference-region activity ratio is another PET parameter. The most commonly used reference regions are liver and blood pool (32–35). Tumor SUVmax–to–liver SUVmean ratio and tumor SUVmax–to–blood-pool SUVmean ratio are generally used. In liver and blood pool, SUVmean provides more accurate results than SUVmax. The SUVpeak of the tumor can also be used (36). SUVpeak is the average value within a small, fixed-size region of interest in the hottest part of the tumor. PERCIST, a grading system for PET lesions in oncology, recommends using SUVpeak from the tumor when comparing 2 studies (37,38). Tumor-to-liver and tumor–to–blood-pool ratios are usually used to compare 2 PET studies for treatment response assessment (35,37–39). In treatment response assessment of lymphomas, the Deauville 5-point scale is recommended (1, no uptake in the tumor;
2, tumor uptake equal to or less than mediastinum; 3, tumor uptake greater than mediastinum but equal to or less than liver; 4, tumor uptake moderately greater than liver; and 5, tumor uptake markedly greater than liver) (35,39).

Uptake ratios may provide a better understanding of the metabolic activity of the tumor than can a numeric value (SUV). For example, describing the metabolic activity of the tumor as 3 times the metabolic activity of the normal liver may give a better idea than providing a numeric value (tumor SUV, 9). These parameters are also not affected by patient weight or injected activity. Tumor-to-blood-pool ratio may be preferred over tumor-to-liver ratio because treatments and diseases may affect the metabolic activity of the liver. On the other hand, reduced renal function can cause increased blood-pool activity, which may reduce the accuracy of tumor-to-blood-pool ratio.

High blood glucose generally reduces tumor 18F-FDG uptake, but there are various reports on its effect on liver and blood-pool activity. Per our recent assessment, hyperglycemia does not affect liver and blood-pool activity (12,40,41). However, various other studies and a recent meta-analysis study reported that hyperglycemia increases liver and blood-pool activity (42–46). Thus, in hyperglycemic patients, tumor-to-liver or tumor-to-blood-pool activity ratio should be used carefully.

**DUAL-TIME-POINT PET IMAGING AND RETENTION INDEX**

Dual–time-point PET imaging (obtaining both early standard and delayed PET images) has been used extensively in various cancers to differentiate benign from malignant lesions. In addition to visual assessment, retention index (percentage difference in SUV between early and delayed images) is calculated in these studies as follows:

\[
\text{Retention index (\%)} = 100 \times \left( \frac{\text{SUV}_{\text{max delayed}} - \text{SUV}_{\text{max early}}}{\text{SUV}_{\text{max early}}} \right).
\]

Dual–time-point PET imaging improved the diagnostic accuracy for malignant lung nodules (47). However, in lung lesions whose size and SUVmax are greater than 10 mm and 2.5, respectively, authors did not recommend dual–time-point 18F-FDG PET imaging to differentiate between malignant and benign lesions (48). Tian et al. found a significant difference in retention index between malignant and benign bone lesions: approximately 18 versus 7, respectively (49). In the breast, dual–time-point imaging improved PET/CT accuracy in patients with a suspected breast malignancy over single–time-point imaging, demonstrating increasing 18F-FDG uptake over time in breast tumors and decreasing uptake in benign lesions (50). In grading brain tumors, SUVmax and SUVpeak from delayed images were more efficient than those from early images (51). Delayed imaging may also allow better detection of small lesions due to improved contrast between the lesion and the background (52).

**DYNAMIC PET IMAGING**

Dynamic PET imaging with 18F-FDG and quantification approaches helps to estimate the rates of glucose transport, phosphorylation, and dephosphorylation in the tumor (53,54). Compartment modeling is used to analyze the dynamic imaging data. A 2-tissue-compartment model was first described by Sokoloff et al. (55). Tracer flows between the blood compartment and tissue compartments. Four transport rates (k1, k2, k3, and k4) describe the exchange of the tracer between blood and tissue compartments (54). In 18F-FDG studies, k1 reflects the influx, k2 the efflux, k3 the phosphorylation rate, and k4 the dephosphorylation rate of the glucose analog (54). Patlak graphical analysis is an approach for calculation of the metabolic rate of glucose (56). The metabolic rate of 18F-FDG can then be calculated as influx rate \( K_i \times [\text{plasma glucose/lumped constant}] \) (54). The lumped constant is the ratio of 18F-FDG uptake to glucose uptake and is not exactly known for tumors (54). \( K_i \) can be calculated using the rate constants of the 2-tissue-compartment model and the formula \( [k_1 \times k_3/k_2 + k_4] \) (54). Dynamic PET with quantification is time-consuming and requires dedicated evaluation software and expertise and is usually applied in research. When software is not available to measure dynamic PET parameters, 18F-FDG uptake rate can be grossly assessed by obtaining dynamic images over the tumor (e.g., 1 min, 60 frames) after the injection of 18F-FDG and generating a time–activity curve by placing a same-sized region of interest in the same slice of the tumor in all frames and applying decay correction.

18F-FDG dynamic PET imaging has been studied in various malignancies for differentiating malignant from benign lesions and grading malignant tumors (57–59). In a study of soft-tissue sarcomas, SUV, \( k_i \), \( K_i \), and fractal dimension were higher in sarcomas than in benign tumors, and SUV, vascular fraction, \( k_3 \), \( K_i \), and fractal dimension were higher in recurrent lesions than in scar tissues (59). In another study, \( k_3 \), \( K_i \), and metabolic rate of 18F-FDG were significantly higher in higher-grade tumors, progesterone-receptor negative tumors, and highly proliferating tumors, as well as in triple-negative and hormone-receptor negative/HER2-positive subtypes (53). It also appears that \( K_i \) was significantly higher in node-positive than in node-negative disease (53).

**CONCLUSION**

Various PET parameters are available for 18F-FDG studies. We have summarized them in this article, with their importance, uses, limitations, and reasons for erroneous results.

**DISCLOSURE**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**