What Do We Measure in Oncology PET?

Kyoungjune Pak¹ · Seong-Jang Kim^{1,2}

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Abstract Positron emission tomography (PET) has come to the practice of oncology. It is known that ¹⁸F-fluorodeoxyglucose (FDG) PET is more sensitive for the assessment of treatment response than conventional imaging. In addition, PET has an advantage in the use of quantitative analysis of the study. Nowadays, various PET parameters are adopted in clinical settings. In addition, a wide range of factors has been known to be associated with FDG uptake. Therefore, there has been a need for standardization and harmonization of protocols and PET parameters. We will introduce PET parameters and discuss major issues in this review.

Keywords Computer-assisted image processing · Medical oncology · Positron-emission tomography · Radiopharmaceuticals

Introduction

To plan targeted therapy or to assess the response of treatment, measurement of tumor size or estimation of radioactivity con-

centrations in regions of interest (ROI) are essential [1]. However, anatomic size changes often come later and less specific than functional and molecular changes [2]. Therefore, positron emission tomography (PET) has an advantage over conventional imaging modalities in the use of quantitative analysis of the study [3].

There have been efforts to establish a common measurement standard and criteria for reporting alterations in ¹⁸F-fluorodeoxyglucose (FDG) PET to assess clinical and subclinical response. In 1999, European Organization for Research and Treatment of Cancer (EORTC) PET response criteria was proposed [4]. As it was the first response criteria with PET, there were several things to be supplemented. The number of lesions and PET parameters were not defined in EORTC PET response criteria [4]. Ten years after EORTC PET response criteria, Richard Wahl et al proposed the new PET criteria (PET Response Criteria in Solid Tumors, PERCIST) [5]. In EORTC PET response criteria, standardized uptake value (SUV) was adopted as a parameter, however, neither size of ROI nor number of lesions was stated [4]. In PERCIST, SUVpeak of ROI with 1 cm³ sphere was proposed as a parameter with normalization to lean body mass (LBM) (Table 1). In addition, to acquire repeatability and reproducibility of PET scans, common imaging procedures have been suggested by the Uniform Protocols for Imaging in Clinical Trials (UPICT), now as a part of the Quantitative Imaging biomarkers Alliance (QIBA) [6, 7], and Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) [8], which will lead to consistency in values between platforms and institutes and enhancement in the role of quantitative image interpretation [8].

In this review, to address these issues, we evaluated 1) definitions of PET parameters, 2) ROI and threshold, 3)

✉ Seong-Jang Kim
growthkim@hanmail.net

Kyoungjune Pak
ilikechopin@me.com; ilikechopin@daum.net

¹ Department of Nuclear Medicine and Biomedical Research Institute, Pusan National University Hospital, Busan, Korea

² Department of Nuclear Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Pusan National University, Yangsan, Korea

Table 1 Previous PET response criteria

	Year	Parameter	SUV correction	ROI size	Thresholds (delineation)	Number of lesions	Parameter	Percentage change
EORTC	1999	SUV	Not defined	Not defined	Not defined	Not defined	SUV	−25 ~ +25
PERCIST1.1	2009	SUVpeak	lbm	1 cm ³ sphere	1.5 x Liver SUVmean (lbm) + 2*SD	Maximum 5 (2 per organ)	SUV	−30 ~ +30

PET, positron emission tomography; SUV, standardized uptake value; ROI, region of interest; EORTC, European Organization for Research and Treatment of Cancer; PERCIST, PET Response Criteria in Solid Tumors; lbm, lean body mass; SD, standard deviation

factors associated with PET parameters, and 4) considerations for PET parameters.

Pet Parameters

Definitions

SUV is the most widely used PET parameter, however, there are several things to consider calculating SUV. SUV is calculated as follows; activity concentration in tissue/(injected activity/body size) [3]. To measure SUV, defining a ROI to be drawn within a tumor is essential, as well as not including surrounding tissues such as the urinary bladder [9]. The highest voxel value within ROI is usually measured, and defined as SUVmaximum (**SUVmax**) [10]. SUVmax may be the most widely used PET parameter due to its easy access with commercial workstations. SUVmax might be most advantageous in small tumors with less dependency on partial-volume effects [5], however, it can be substantially affected by image noise and therefore depend on reconstruction parameters [1]. Although **SUVmean** might provide a more representative value for the whole tumor, it will vary depending on which voxels are included in ROI [1, 9]. **SUVpeak** is a subcategory of SUVmean where ROI is defined specifically [7]. SUVpeak usually includes voxels with highest activity to maintain the reproducibility of SUVmax with reduced effects by noise [9]. A 3-dimensional spherical volume of interest (VOI) with a diameter of 1.2 cm (1 cm³) was adopted for SUVpeak in PERCIST criteria. Although SUVpeak is suggested as a more robust alternative than SUVmax, changes to the size, shape, and location of ROI result in substantial variation in SUVpeak [11]. Volumetric parameters have been widely used nowadays because of adoptions in commercial workstations. Volumetric parameters of metabolic tumor volume (**MTV**) and total lesion glycolysis (**TLG**) are measured after delineation of tumor and known to have prognostic values over SUV [12]. However, MTV and TLG have a difference in the sense of definition. Although MTV is a PET parameter, it does not reflect the activity of radiotracer directly, but the volume above the threshold [12]. Therefore, MTV is measured mostly as a unit of cubic centimeter (cc) or

milliliter (ml). TLG is calculated by multiplying MTV by SUVmean, which weights the volumetric burden and metabolic activity of tumors [13]. The example of ROI is drawn in Fig. 1a. After a threshold is applied, activities of a radiotracer are presented in a histogram assuming that they follow the equation of $h(x)$ between SUV and number of voxels (Fig. 1b). Then, MTV and TLG can be calculated as follows;1212121

$$\begin{aligned} \bullet \quad \text{MTV} &= \int_{\text{Threshold}}^{\text{SUVmax}} h(x) dx \\ \bullet \quad \text{TLG} &= \int_{\text{Threshold}}^{\text{SUVmax}} x h(x) dx \end{aligned}$$

The differences between MTV (Fig. 2a) and TLG (Fig. 2b) are depicted in Fig. 2. The number of voxels above the threshold is counted and becomes MTV regardless of the activity of each voxel. However, TLG takes account of total activities of voxels above thresholds, thus reflecting a more comprehensive value beyond MTV or SUVmax. Both MTV and TLG are strongly influenced by the definition of thresholds, tumor delineation.

ROI and Threshold

All PET parameters except SUVmax are affected by the definition of thresholds. Presently, there is no consensus on which methods should be preferred for tumor segmentations [14]. A fixed SUV such as 2.5, 3.0, or percentages of SUVmax are usually adopted as thresholds to delineate tumors [12]. The gradient-based [15], contrast-oriented [16], iterative [16], and fuzzy clustering [17] methods are also available for tumor segmentation. In addition, a tumor can be delineated manually with less dependency on tumor heterogeneity than other methods [18]. In PERCIST, Wahl et al. proposed the threshold calculated by multiplying liver SUV by 1.5 adding twofold standard deviation [5], which was based on the study by Ott et al [19]. As activities of liver and blood pool show stable over time [20], they might be applied as a threshold in the future response criteria. According to the study by van den Hoff et al., tumor SUV divided by aortic SUV is highly

Fig. 1 (a) In a tumor, a region of interest is drawn after applying a threshold. (b) Activities of a radiotracer are presented in a histogram assuming that they follow the equation of $h(x)$ with x axis of standardized uptake value and y axis of number of voxels

correlated with metabolic rate of FDG from the Patlak equation, more than SUV corrected by lbm or body surface area (bsa) [21].

Factors Associated with PET Parameters

To prepare for PET scans, at least 4–6 hrs of fasting are necessary before injection of FDG to ensure both low blood glucose and low insulinemia [8]. Patients with plasma glucose level of 200 mg/dL or higher are recommended to reschedule FDG PET scans [8]. Scheduling for patients with diabetes varies according to their medication. Activities and fluid intake are also important in preparation before FDG PET scans. In addition to preparation before PET scans, various factors are known to be associated with FDG uptake in PET (Table 2). They can be categorized into five groups; 1) patient preparation, 2) imaging-related preparation, 3) data acquisition, 4) data reconstruction, and 5) image analysis [3, 22]. Although there are continuing efforts to propose the standardized protocols in PET imaging [6–8], considerable uncertainties still exist.

Consideration for PET Parameters

What are the requirements for an ideal PET parameter? Accuracy, reproducibility, and repeatability are necessary [8]. However, there is much more concerned. PET parameters, SUV, MTV, and TLG can be normalized by body size; body weight (bw), lbm, and bsa. SUVbw has lower variability than the 1 and 2-dimensional size measurement of CT [23]. However, SUVbw overestimates FDG uptake of normal organs in patients with high body mass index (BMI), because FDG does not accumulate in white fat in the fasting state [5]. In contrast, SUVlbm and SUVbsa show weight-independency for FDG uptake [24]. Nowadays, SUVlbm and SUVbsa as well as SUVbw are easily calculated from commercial workstations following formulas to calculate lbm [25–27] and bsa [28–30]. However, patient's bw is measured directly, while lbm and bsa are estimated from one's weight and height. Therefore, different formulas of lbm and bsa might lead to variability of SUV. Previous studies evaluated the correlation between pathologic tumor size and PET parameters [31]. Both PET and CT overestimated the pathologic tumor volume of lung cancer, but PET was closer to it [18]. There was a contradictory result by Hatt et al. that PET underestimated the

Fig. 2 Difference between metabolic tumor volume (MTV) and total lesion glycolysis (TLG): (a) Regardless of activities above the threshold (dotted line), the number of voxels or volume is counted and defined as MTV. (b) Total activities above the threshold (dotted line) are summed

Table 2 Factors influencing PET parameters

Classification	Factors
A. Patient preparation	1) Diet, fluid intake 2) Activities 3) Glucose control
B. Imaging-related preparation	1) Timing (time interval between FDG administration and the start of scan) 2) Dose 3) Administration route
C. Data acquisition	1) PET component - time per table 2) CT component - contrast material - CT dose (mAs, pitch, collimation, kVp)
D. Data reconstruction	1) Matrix size 2) Zoom factors 3) Voxel size 4) Filter 5) Reconstruction method
E. Image analysis	1) ROI 2) SUV correction - bw - lbm - bsa 3) Plasma glucose correction 4) Threshold (delineation) 5) Number of lesions 6) Definition of target lesions 7) Tool (software)

PET, positron emission tomography; FDG, fluorodeoxyglucose; CT, computed tomography; ROI, region of interest; SUV, standardized uptake value; bw, body weight; lbm, lean body mass; bsa, body surface area

pathologic tumor size [32]. However, pathologic tumor size is measured after excision of the tissue, and a reduction up to 82 % of the original tumor volumes and deformation after fixation with formalin and slicing has been reported [33]. In addition, time difference between PET scans and the specimen excision may also lead to an error between PET parameters and pathologic tumor size [31]. Therefore, a PET parameter strongly associated with a pathologic tumor size might not be a requirement to be an ideal PET parameter. In view of the interobserver and intraobserver variability, SUV_{max} is more reproducible than size measurement in CT [23] and SUV_{mean} is subjective due to sensitivity to ROI definition [34]. In addition, tumor SUV divided by background SUV is more dependent on observers than other SUV parameters [34].

Summary

The use of quantitative approaches with PET can be used as a biomarker of treatment response in oncology. Several PET parameters have been suggested; SUV, MTV, and TLG. A

range of factors has been known to affect the measurement of PET parameters. Further studies regarding harmonization and standardization of PET scans are encouraged.

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Compliance with Ethical Standards

Conflict of Interest Kyoungjune Pak and Seong-Jang Kim declare that they have no conflict of interest.

Ethical statement No research interventions were done in this review (no ethics approval needed).

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