# Interpretation of PET Scans: Do Not Take SUVs at Face Value

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Reliance on imaging to determine therapeutic responses in both clinical practice and clinical trials is ever increasing. When used in advanced, unresectable lung cancer, imaging interpretation helps guide the oncologist on the utility of continuing the patient's current systemic therapy or changing treatment. In general, the two main imaging modalities used to assess treatment response in lung cancer patients are computerized tomography (CT) and [18]F-flourodeoxyglucose (FDG) positron emission tomography (PET). PET imaging can predict tumor response early in the treatment course and possibly shorten treatment in oncology patients responding to therapy; alternatively, imaging provides the opportunity to adjust treatment in cancer patients not responding to therapy. Such is a strategy now employed in Hodgkin's lymphoma where risk-adapted treatment uses PET/CT after two cycles of chemotherapy to determine treatment benefit and mitigate long-term harm.[1]

Although both CT and PET can be used to evaluate tumor response, each modality measures different aspects of the tumor. CT uses ionizing radiation to depict the anatomical features of a tumor. Although it is highly sensitive, it cannot distinguish viable malignant cells from nonmalignant areas of tissue that are often times present after treatment and can be confused with tumor. However, PET provides functional information based on the tumor biology and uptake of PET specific imaging probes such as FDG. FDG is a glucose analog where oxygen at the C-2 position is replaced with 18-fluorine. FDG, like glucose, is actively transported into the cell by glucose transport proteins. Once glucose and FDG are in the cell, they are phosphorylated by hexokinases. Under normal conditions, phosphorylated glucose continues along the glycolytic pathway for energy production. However, FDG cannot be further processed and is trapped intracellularly as FDG-6-phosphate. Thus, FDG accumulates in areas with high levels of metabolism and glycolysis, such as sites of inflammation, tissue repair, hyperactivity (e.g., muscle), and—of particular interest—in cancer cells, which are often highly metabolically active and favor inefficient anaerobic pathways. In cancer, these increases in glucose demands lead to increased uptake of FDG and increased intracellular retention of FDG-6-phosphate in tumor cells relative to normal cells.

Two distinct advantages of PET over CT are PET's ability to more rapidly assess treatment response and quantitatively determine the magnitude of tumor metabolic change. For example, when treatment with imatinib is initiated in gastrointestinal stromal tumors, FDG uptake decreases within hours[2,3] with dramatic reduction in FDG metabolism. Rapid decrease in FDG uptake has been observed within 2 hours in *EGFR* mutant non–small-cell lung cancer cells treated with gefitinib.[4,5]

Quantitation of FDG uptake on PET is generally divided into two types of analysis: dynamic-compartmental analysis to determine the kinetic parameter of uptake and the more routine static semiquantitative approach using standardized uptake values (SUV). SUV is obtained automatically on most modern-day PET/CT scanners and measures normalized radioactivity concentration as follows:

$$SUV = \frac{activity\ concentration\ in\ tissue}{injected\ activity/body\ size}$$

SUVmean and SUVmax of a target lesion or a region of interest are the two most common ways of reporting SUV. SUVmean is less sensitive to image noise as it incorporates voxel information from multiple locations.[6] SUVmean is dependent on the voxels that are selected, and therefore, subject to intra- and interobserver variability.[6] SUVmax reports the highest voxel value within the region of interest and is more susceptible to image noise[6] and can provide less intra- and interobserver variability. Whether SUVmean or SUVmax values are used, SUVs can provide a convenient marker of glucose metabolism, reflecting the presence or absence of metabolically active malignancy. However, the accuracy and reproducibility of SUVs can vary considerably.

Biological factors that can affect SUV measurements include patient weight composition (heavier patients have higher SUV values), body-size calculation (weight loss can decrease SUV values leading to *false-positive* treatment response), blood glucose level (after glucose loading, SUV can decrease by > 50%), postinjection uptake time (increase of ≤30% SUV if measured at 4 hours versus measurement at 1 hour), respiratory motion (can alter SUV by ≤ 30%),[6] lesion

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size (small lesions are more susceptible to count recovery issues, leading to lower SUVs than larger lesions are), motion artifacts from patient discomfort, and inflammation.[7]

Technical factors that can affect SUV measurements include variability of the scanner, image-reconstruction parameters, calibration and/or timing mismatch error between the scanner and the FDG dose calibrator, use of contrast material for PET/CT, residual activity in the administration system or syringe, and intra- and interobserver variability.[6,7]

Individually, each of these factors may affect SUV calculations by 5% to 50%. Cumulatively, these factors could lead to erroneous interpretation of response to therapy, and result in inappropriate continuation of ineffective therapy or premature discontinuation of effective therapy. With so many technical and biological factors that can each individually result in altered SUV measurements, how can a treating oncologist be sure that PET/CT reports are reliable for making treatment decisions? Some potential solutions to these technical and biological factors that can mitigate false interpretation of PET/CT readings are included in Table 1. Although most of these factors are outside the control of a thoracic oncologist, knowledge of these factors can provide reference for the reliability of reported changes in SUV values. However, as more PET imaging is migrating away from radiology centers and academic institutions toward privately held oncology practices, it becomes incumbent on the treating oncologists who own their own equipment to have some basic knowledge of the pitfalls in PET imaging.

Furthermore, although there are guidelines and criteria for evaluating response using CT in solid tumors,[8] similar criteria for PET are less established. Recently, there have been attempts to better standardize criteria for PET interpretation using European Organisation for Research and Treatment of Cancer (EORTC) and/or Positron Emission Tomography Response Criteria In Solid Tumors (PERCIST 1.0) criteria.[9] In particular, both the EORTC and PERCIST 1.0 are published guidelines for comparing FDG PET response results in multicenter trials and for declaring categorical treatment responses based on threshold changes in SUVs after treatment, of which there are four categories: complete metabolic response, partial metabolic response, stable metabolic disease, and progressive metabolic disease. Although PERCIST 1.0 provides more specific instructions about what constitutes a target lesion and treatment response, a large, multicenter, prospective comparison has not yet been conducted to validate either methodology. In this regard, we recently showed that there was no significant difference in categorical response rates between EORTC and PERCIST 1.0 on FDG PET/CT in subjects with metastatic basal cell carcinoma treated with vismodegib.[10]

Nevertheless, when the various biological and technical factors that can drastically affect the reading and interpretation of a PET/CT are not controlled, the interpretation of PET images becomes problematic. Does this negate the added value of PET imaging for determining treatment response to therapy? No. It does, however, require that the treating oncologist be aware of these issues and be cautious to solely make treatment decisions based on SUV measurements alone. In addition, it is important that each oncologist work cooperatively with the interpreting radiology or nuclear medicine team to make sure that each and every one is paying close attention to the details

**TABLE 1.** Recommendations for Factors Affecting PET/CT Interpretation

| | Factor Affecting Interpretation | Recommendation | SUV Variability without Recommendation |
|---|---|---|---|
| A. Before patient scans | Scanner variability | Use the same PET/CT scanner for baseline and follow-up (where possible). | ≤ 22.6%[6] |
| | Calibration and/or timing mismatch error between the scanner and the FDG dose calibrator | Calibrate the FDG dose calibrators and synchronize dose calibrator clocks with the scanner clocks. | ≤ 10%[6] |
| | Patient body-size calculation | Weigh every patient with a calibrated scale before imaging. | Not available, but could observe 11% decrease in weight while on therapy[11] |
| | Blood glucose level | Obtain serum glucose before each PET scan and as an additional quality assurance mechanism, record average SUV in the liver. | ≤ 50%[12] |
| B. During the scan | Residual activity in the administration system or syringe | Measure residual FDG activity in the injection tubing and syringe to accurately determine the dose administered. | ≤ 5%[7] |
| | Postinjection uptake time | Use a minimum uptake time of 60 minutes. Keep the uptake time the same as the baseline scan (+/− 10 min). | ≤ 30%[6] |
| | Reconstruction parameter changes | Use the same acquisition technique and reconstruction parameters for baseline and follow-up scans. Use the same CT protocol for PET image attenuation correction. | ≤ 12%[6] |
| C. After the scan | Intra- and interobserver variability | Use screen saves or other documentation to improve the marked region of interest reproducibility. | ≤ 17%[6] |

PET, positron emission tomography; CT, computerized tomography; FDG, flourodeoxyglucose; SUV, standardized uptake values.

 

before, during, and after a patient undergoes PET imaging. Only in this manner can PET interpretation realize its full potential in lung cancer.

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