Measuring Response with FDG-PET: Methodological Aspects

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ABSTRACT

The use of fluorodeoxyglucose positron emission tomography (FDG-PET) for the evaluation of tumor response to chemotherapy and radiation therapy has been studied in a number of malignancies. By imaging tumor metabolism and therapy-related changes, FDG-PET has demonstrated advantages over anatomical imaging in the assessment of treatment response. More recent investigations have indicated that FDG-PET can predict tumor response early during the course of therapy, potentially allowing for early treatment adjustments. The aim of this review is to provide oncologists with a basic knowledge of the practical aspects of PET quantification for treatment.

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INTRODUCTION

The traditional approach to treatment monitoring through imaging has relied on anatomical changes assessing tumor size before and after treatment using criteria published >20 years ago [1]. The original World Health Organization (WHO) criteria included bidimensional measurements of the tumor. Response was defined as a decrease in the product of two perpendicular diameters of the tumor by ≥50%. The more recent Response Evaluation Criteria in Solid Tumors (RECIST) introduced by the National Cancer Institute (NCI) and the European Association for Research and Treatment of Cancer (EORTC) define response as a 30% decrease in the sum of the diameters of target lesions [2]. Given these somewhat arbitrary response criteria, it is not surprising that a consistent correlation between tumor response (by WHO criteria or the RECIST) and patient survival has not been demonstrated [3–6].

As illustrated by a recent review by Juweid and Cheson [7] in the New England Journal of Medicine, there is growing interest in fluorodeoxyglucose positron emission tomography (FDG-PET) as a tool for monitoring tumor response to therapy. Several studies have demonstrated that treatment-induced changes in tumor FDG uptake correlate well with patient survival. A number of these studies concluded that even changes observed early during chemotherapy (i.e., after the first course of chemotherapy) correlate well with patient survival, whereas a lack of a significant decrease in FDG uptake accurately predicts a poor prognosis. This information could be used for adapting treatment early during the course of therapy.

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This review focuses on the methodological aspects of \(^{18}\text{F}-\text{FDG}\) PET for treatment monitoring and on how quantitative assessment of tumor \(^{18}\text{F}-\text{FDG}\) uptake can be performed in clinical studies, as well as the efforts for developing generally applicable response criteria for \(^{18}\text{F}-\text{FDG}\)-PET.

**Visual Interpretation Versus Quantitative Measurement of Tumor FDG Uptake**

For staging of malignant disease and evaluation after the completion of chemotherapy or radiotherapy, quantitative analysis of FDG-PET scans is generally not required. At these time points, focally increased FDG uptake not explained by the normal biodistribution of FDG suggests metastatic disease or residual viable tumor tissue. In patients with Hodgkin’s disease and non-Hodgkin’s lymphoma, a large series of studies has indicated that focal tumor FDG uptake after completion of therapy indicates a poor prognosis. The criteria for response assessment in lymphoma were recently standardized as part of the International Harmonization Project. According to these criteria, patients are considered to be in complete remission as long as the FDG uptake of the lymphoma is less than or equal to the mediastinal blood pool. Exceptions are made for small lesions (<2 cm in diameter). In this case, any FDG uptake above background is considered as positive, because FDG uptake by small lesions is underestimated as a result of the limited spatial resolution of PET scanners [8].

In various solid tumors, including non-small cell lung, esophageal, and cervical cancer, focal FDG uptake after completion of chemoradiotherapy has also been shown to be an indicator of a poor prognosis [9–23]. Thus, for assessment of tumor response after completion of therapy, visual assessment of tumor FDG uptake is considered to be sufficient and the technical requirements for PET imaging do not differ significantly from those of a routine whole-body PET scan used for tumor staging.

If PET scans are performed during treatment to predict subsequent tumor response in solid tumors, quantitative assessment of tumor metabolism becomes necessary, because at this time point there still is considerable residual \(^{18}\text{F}-\text{FDG}\) uptake, even in patients responding to treatment.

A number of studies have looked at the time course of tumor uptake during treatment [24, 25]. For example, Wieder et al. [26] evaluated changes in FDG uptake in patients with locally advanced esophageal cancer treated with chemoradiotherapy and followed by surgical resection. FDG-PET scans were performed before treatment, 2 weeks after the start of therapy, and 3–4 weeks after the completion of chemoradiotherapy. Subsequently, tumors were resected and histopathologically evaluated. Responders were defined as having <10% viable tumor cells in the resected specimens. Baseline scans demonstrated no significant differences between FDG uptake of responding and nonresponding tumors. Even though FDG uptake of responding tumors had decreased significantly compared with nonresponding tumors (\(p < .001\)), most of the responding tumors still showed significant FDG uptake at this early time point. Only after the completion of neoadjuvant therapy at the time of the third scan had the FDG uptake of responding tumors decreased almost to background levels.

These studies therefore indicate that, besides a baseline scan performed before the start of treatment, quantitative analysis of changes in FDG uptake is needed to assess response early during the course of treatment.

**Basic Aspects of Quantification for Monitoring Treatment Response**

In essence, three components contribute to the FDG concentration that can be measured in tissue by PET scanning: phosphorylated intracellular FDG, nonphosphorylated intracellular FDG, and nonphosphorylated intravascular FDG. Only the amount of phosphorylated FDG is directly related to the metabolic activity of tumor cells. Static measurements of FDG uptake cannot differentiate among these three components, and therefore do not necessarily correlate with glucose metabolic rates.

As discussed in a recent review by Krak et al. [27], the two main approaches for dealing with these limitations are nonlinear regression analysis with a two-tissue compartment model and simplified tracer kinetic approaches, such as the Patlak–Gjedde analysis. However, both these approaches are only of limited value in the clinical setting, because both methods require images to be acquired in a dynamic mode, limiting the imaging field to only one bed position covering a length of about 15–20 cm (depending on the scanner) of the patient’s body. In the case of nonlinear regression analysis, additional arterial blood sampling is required. It is therefore not surprising that neither method has been widely used outside the research setting.

The most commonly used method for assessing tumor glucose metabolism in clinical studies is a semiquantitative analysis [28] known as the standardized uptake value (SUV). The basic concept underlying the SUV is that the activity concentration in the plasma is low compared with the activity concentration in the tissue, and \(K_t\), the net rate of FDG phosphorylation as a measure of tumor glucose use, becomes approximately proportional to the activity concentration \((c)\) in the tissue \((t)\) di-
vided by the ratio of the injected dose \((D)\) to the body weight, which is the SUV:

\[
K_i = \frac{c(t)}{D/\text{body weight}} = \text{SUV}.
\]

However, this implies that the volume of distribution of FDG is solely dependent on the patient’s body weight and that the rates of clearance of FDG from the plasma are identical in all patients. Yet the volume of distribution of FDG depends not only on a patient’s body weight but also on the patient’s body composition. SUVs of malignant tumors tend to be markedly higher in obese patients because the FDG concentration in adipose tissue is significantly lower than that in the remaining body. Accordingly, the volume of distribution of FDG per kilogram of body weight is smaller in obese patients than in lean patients. Dividing the injected dose by the body weight thus leads to falsely high SUVs [30]. SUVs normalized to body surface or lean body mass have been shown to provide more reliable estimates of FDG metabolic rates in obese patients [30, 31]. These normalizations are only approximations; none of them, for example, takes into account differences in plasma FDG clearance.

Even though the use of SUVs for quantitative assessment of tumor glucose use has been severely criticized [32], it should be noted that there is a fundamental difference between measuring absolute metabolic rates and measuring changes in metabolic rates for treatment monitoring. In the first situation, tumor glucose metabolism generally is quantified to compare different groups of patients. In this situation, the dependence of SUVs on body composition and plasma FDG clearance is a clear limitation for this technique compared with nonlinear regression or the Patlak–Gjedde analysis. In the second situation, however, only an intraindividual comparison of metabolic rates before and after treatment is made. As long as the treatment does not result in significant changes in renal function and body weight, the relative changes in SUVs should be identical.

This notion has been confirmed in studies looking at the correlation between changes in \(K_i\), as determined by Patlak–Gjedde analysis, and changes in SUV. In a study of 32 patients with advanced non-small cell lung cancer treated with platinum-based chemotherapy and undergoing FDG-PET scans before and after the first cycle of therapy, a close correlation between changes in SUV and changes in \(K_i\) was observed [33]. Changes in SUV and changes in \(K_i\) also yielded near identical diagnostic accuracies for the prediction of a subsequent reduction in tumor size and a significant correlation with overall survival after chemotherapy. More recently, Hoekstra et al. [34] came to a similar conclusion in a study of 47 patients with non-small cell lung cancer, in which measurements of SUV changes were as powerful as Patlak graphical analysis in predicting response and patient outcome early after the start of treatment.

Since SUV measurements do not require complicated scanning procedures and can be measured with relative ease, SUVs are clinically the most attractive parameter for monitoring tumor response. As discussed below, the only caveat is the need to follow a standardized protocol from scan to scan, because multiple factors (Table 1) can affect the results of SUVs.

**FACTORS AFFECTING SUV CALCULATION**

In most malignant tumors, FDG uptake increases continuously for at least 90 minutes after FDG injection [35, 36], and FDG uptake is usually significantly higher at later time points. For example Stahl et al. [36] demonstrated a 50% higher tumor FDG uptake 90 minutes after FDG injection compared with 40 minutes postinjection (12.0 ± 4.0 versus 8.2 ± 2.0) in 43 patients with locally advanced gastric carcinomas. Thus, when comparing SUVs from a baseline scan of a patient with SUVs from a follow-up scan after treatment, it becomes unreliable to compare SUVs obtained at different time points after injection. Therefore, every effort should be made to keep the range of variations in the uptake period <5–10 minutes.

Since FDG and glucose compete with each other for intracellular transport and phosphorylation, plasma glucose levels have a significant influence on tumor FDG uptake [37]. Thus, FDG uptake tends to be lower in diabetic patients because of elevated plasma glucose levels [38].

A paravenous injection of FDG decreases the amount of tracer available for uptake by the tumor and can result in incorrectly low SUVs. Similarly, if the injected activity is not decay corrected (with the half-life of \(^{18}\text{F}\) being 110 minutes, approximately 30% of the injected activity has decayed after 60 minutes) for the time between FDG injection and imaging, SUVs will be markedly underestimated.

In order for the counting rates of the scanner to be correctly converted to activity concentrations, precise calibration of the PET scanner needs to be performed. This is usually done using the PET scanner to measure the counts from a cylinder with a known dose of \(^{18}\text{F}\). Errors in the calibration process can lead to incorrectly high or low SUVs. A side-by-side visual evaluation comparing the baseline and follow-up studies can help detect errors in SUV measurements. For visual comparison of changes in tumor FDG uptake, it is advisable to set the maximum intensity of the display no lower than the maximum tumor SUV. Otherwise, quite significant changes in tumor \(^{18}\text{F}\)-FDG uptake...
may be missed (Fig. 1). If both studies are normalized to the same maximum FDG uptake, normal tissues should show approximately the same intensities in both studies. Because SUVs of the normal liver remain relatively stable over time, the intensity of FDG uptake in the liver provides a helpful orientation [39]. The presence of marked differences in liver FDG uptake strongly suggests an error in the calculation of the SUVs in one of the studies.

These days PET scans are more commonly performed as PET/computed tomography (CT) scans. Depending on the institution, imaging protocols will include the administration of oral and/or i.v. contrast for optimal delineation of anatomical structures on the CT images. Initially there was concern that the high density of the contrast material would cause significant problems for SUV measurements [40, 41]. However, initial studies were based on phantom studies or compared contrast-enhanced CT attenuation-corrected PET images with nonattenuation-corrected images. More recent clinical studies have refuted the initial concern and have found the potential clinical impact of i.v. and oral contrast on SUV measurements to be not significant [42–44].

To avoid attenuation correction artifacts and subsequent incorrect SUV measurements in lesions situated in anatomical regions undergoing significant motion during breathing (i.e., near the diaphragm) [45], CT and PET images should be acquired during the same respiratory state (shallow breathing) [46, 47]. Respiratory gating,

### Table 1. Factors affecting SUV measurements in clinical PET studies

<table>
<thead>
<tr>
<th>Error</th>
<th>Effect on tumor SUV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose level</td>
<td>Lower values with increasing blood glucose levels</td>
</tr>
<tr>
<td>Region-of-interest definition</td>
<td>Lower mean uptake for larger regions of interest; larger random errors for small regions of interest</td>
</tr>
<tr>
<td>Paravenous FDG injection</td>
<td>Incorrectly low SUV</td>
</tr>
<tr>
<td>No decay correction of injected activity</td>
<td>Incorrectly low SUV</td>
</tr>
<tr>
<td>Incorrect crosscalibration of scanner and dose calibrator</td>
<td>Incorrectly low or high SUV, depending on error of calibration factor</td>
</tr>
<tr>
<td>Time between injection and imaging</td>
<td>Higher SUV with longer uptake period</td>
</tr>
</tbody>
</table>

Abbreviations: FDG, fluorodeoxyglucose; PET, positron emission tomography; SUV, standardized uptake value.
available in most state-of-the-art PET/CT scanners, is a viable alternative.

**Optimal Imaging Time Point for Treatment Assessment with FDG-PET Scanning**

Assessment of tumor response can be performed after the completion of treatment or during chemotherapy or radiation therapy (Figs. 2 and 3). When FDG-PET is performed after completion of potentially curative chemotherapy or radiotherapy, one has to consider that only small amounts of residual viable tumor may be present. In this situation, differentiation between “responders” and “nonresponders” by FDG-PET can be challenging. In order to achieve the highest sensitivity for detection of residual tumor tissue, FDG-PET should therefore be performed as late as possible after completion of therapy in order to enhance the detection of residual tumor tissue. Obviously, waiting too long could result in delayed treatment of patients requiring additional treatment. In our experience, a waiting period of 4–6 weeks after completion of therapy represents a reasonable compromise.

Several studies have demonstrated that effective treatment leads to a decrease in FDG uptake in malignant tissue as early as after the first cycle of chemotherapy [25, 34, 48–62] (Fig. 4).

Unfortunately, however, a clear consensus of what constitutes a significant change has yet to be reached. Based on reproducibility studies of $^{18}$F-FDG uptake in untreated tumors, relative changes $\geq 20\%$ are unlikely to be caused by measurement errors or variations in tumor metabolic activity [63–65]. However, this only applies if significant baseline metabolic activity is present. The significance of a decrease in tumor FDG uptake of 20% for prognosis was studied in patients with advanced non-small cell lung cancer undergoing palliative platinum-based chemotherapy. A decrease in the SUV of the primary tumor $\geq 20\%$ was prospectively defined as a metabolic response by PET criteria. Of 57 patients included in the study, 28 had a metabolic response after the first cycle of chemotherapy. There was a significant correlation with overall survival and progression-free survival. The median progression-free survival time of metabolic nonresponders was only 1.8 months, whereas it was 5.9 months in metabolic responders. The median overall survival time of metabolic responders was
8.4 months, versus 5 months in metabolic nonresponders [33]. These data indicate that a minimum decrease of 20% in tumor FDG uptake after the first cycle of chemotherapy is associated with a palliative effect of therapy. These data were confirmed in an independent study in patients with ovarian cancer treated with neoadjuvant chemotherapy. In that study, including 33 patients, overall survival was significantly longer in patients with a reduction in tumor FDG uptake \( \geq 20\% \) after the first chemotherapy cycle. The median overall survival time was 38 months in patients with a reduction in tumor FDG uptake \( \geq 20\% \), compared with 23 months for patients with a less pronounced decrease in FDG uptake [62].

The optimum threshold value for differentiation of patients with favorable or unfavorable outcomes of therapy may, however, differ from the minimum measurable change in tumor FDG uptake. Several studies have indicated that a change in \(^{18}\)F-FDG uptake by 25%–50% within the initial weeks of chemotherapy provides the highest accuracy for predicting a complete or near-complete histopathological response in patients with solid tumors treated with preoperative chemotherapy [53, 54, 66–71].

These differences in changes in tumor \(^{18}\)F-FDG uptake are not unexpected given the different clinical situations. For example, chemotherapy given as palliative treatment of non-small cell lung carcinoma induces only a minor reduction in tumor size, whereas a complete or near-complete reduction in viable tumor cell mass can be seen if a malignancy is successfully treated with curative intent. Thus, the clinical context significantly influences the interpretation of a given metabolic response by \(^{18}\)F-FDG-PET.

**IMPACT OF PET/CT ON TREATMENT MONITORING**

Most studies of PET and treatment monitoring have been performed with stand-alone PET scanners. Since the advent of PET/CT in the clinical reality several years ago, this combined modality has pretty much replaced stand-alone PET. It can be assumed that in the future all PET done for oncology purposes will be PET/CT [72]. PET/CT allows for precise anatomic localization of abnormalities noted on PET, thereby reducing the number of false-positive studies and improving staging accuracy significantly when compared with either PET or CT [73]. The shorter scan times result in greater patient throughput and have increased overall patient access to this modality. More importantly, from a clinical point of view, the anatomic information gained from a PET/CT scan allows for more confident interpretations and easier communication between the treating clinicians and the physicians reading the scans [74].

Despite some technical challenges, PET/CT offers several potential advantages for the quantitative analysis of tumor FDG uptake [45, 66, 75].

The feasibility of quantitative analysis of contrast-enhanced FDG-PET/CT studies was demonstrated in a recent study in patients with non-small cell lung cancer. Patients were treated with preoperative chemoradiotherapy and the CT information was used to improve the quantitative analysis of the FDG-PET studies by integrating the FDG signal with the anatomic information from the CT images. Size measurements derived from CT were used to correct tumor FDG uptake for partial volume effects. The authors reported that quantitative changes in tumor FDG uptake after induction chemotherapy were predictive of histopathologic tumor response as well as recurrence-free survival. A reduction in tumor volume was not significantly correlated with a histopathologic response [76].

On the other hand, Beer et al. [77] recently observed that a reduction in tumor volume during chemotherapy for esophageal cancer was a good predictor of histopathologic response. Thus, combining the metabolic and volumetric changes observed with PET/CT could improve accuracy for gauging tumor response. One such approach was proposed by Larson et al. [78], who suggested combining anatomic and functional information and monitoring changes in this “total lesion glycolysis” derived from multiplying the tumor volume on CT with the FDG uptake on PET.

**FUTURE DIRECTIONS**

Despite the lack of generally accepted “metabolic response” criteria, initial attempts at including metabolic changes into response evaluation have been made by the EORTC and others [79, 80]. Larger trials are necessary for establishing generally accepted “metabolic response” criteria for different malignancies. Further, in order to be able to compare results from different studies and to perform multicenter trials, guidelines for PET and PET/CT image acquisition are necessary. Recently, such guidelines were issued by the NCI. These guidelines not only contain precise recommendations of how scanning should be performed but also list a number of steps to assure adequate and reproducible quantification of FDG uptake in malignant lesions [81]. For lymphoma, this was recently accomplished by Juweid et al. [8] with the publication of guidelines on behalf of The International Harmonization Project in Lymphoma specifically incorporating PET for the assessment of treatment response in patients with lymphoma.
SUMMARY
PET has established itself as a vital and important technique for the staging of malignant disease. To date, glucose metabolism as a readout of treatment response should be used cautiously depending on the type of malignancy and medical intervention. However, with efforts at establishing uniform imaging and interpretation guidelines along with data from research into what constitutes a significant treatment response by FDG-PET for individual malignancies, PET is now poised to become an essential tool for cancer treatment monitoring.

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Manuscript writing: Martin Allen-Auerbach, Wolfgang Weber
Final approval of manuscript: Martin Allen-Auerbach, Wolfgang Weber

REFERENCES


64 Berthelsen AK, Holm S, Loft A et al. PET/CT with intravenous contrast can be used for PET attenuation correction in cancer patients. Eur J Nucl Med Mol Imaging 2005;32:1167–1175.


66 Brun E, Kjellén E, Tennvall J et al. FDG PET studies during treatment: Pre-

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