



# Quantitative Assessment of Tumor Metabolism Using FDG-PET Imaging

Wolfgang A. Weber, Markus Schwaiger and Norbert Avril

DEPARTMENT OF NUCLEAR MEDICINE, TECHNISCHE UNIVERSITÄT MÜNCHEN, MÜNCHEN, GERMANY

**ABSTRACT.** Positron emission tomography using the glucose analog fluorine-18 fluorodeoxyglucose (FDG-PET) provides a unique means of non-invasive assessment of tumor metabolism. Several approaches, of varying complexity, can be applied for quantitative image analysis. Previous studies have demonstrated that “standardized uptake values” (SUV) and simplified tracer kinetic modeling, using the “Patlak-Gjedde”-analysis, provide highly reproducible parameters of tumor glucose utilization. Quantification of regional FDG uptake gives complementary information to visual image interpretation and provides objective criteria for differentiation between benign and malignant lesions. Moreover, quantification of tumor glucose metabolism is essential for assessment of therapy induced changes. Clinical studies in breast cancer and lymphoma suggest that serial FDG-PET studies allow the prediction of response early in the course of chemotherapy. Therefore, FDG-PET may be helpful in patient management by avoiding ineffective chemotherapy and supporting the decision to continue dose intense regimens. In addition, FDG-PET allows non-invasive assessment of tumor viability following chemo- and radiotherapy which permits individualized therapy management. NUCL MED BIOL 27;7:683–687, 2000. © 2000 Elsevier Science Inc. All rights reserved.

**KEY WORDS.** FDG-PET, Oncology, Tumor glucose metabolism, Diagnosis, Therapy monitoring

## INTRODUCTION

Improved image resolution of computed tomography (CT) and magnetic resonance imaging (MRI) have yielded excellent sensitivity in detection of tissue abnormalities in patients suspected of having oncological diseases. However, these imaging modalities remain limited in their ability to further characterize such abnormalities. For example, the specificity of CT and MRI to separate malignant from benign tumors is generally low. Furthermore, residual or recurrent tumor after therapy often cannot be reliably differentiated from scar tissue. Tracer techniques targeting special aspects of tumor metabolism, antigenicity, proliferation rate, and surface receptors may overcome some of these limitations when used in combination with morphologic imaging modalities. This promise is supported by the clinical results obtained by positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (FDG). Several decades ago biochemical studies in cell and tissue cultures demonstrated that malignant tumors are generally characterized by altered metabolic profiles and display high rates of glucose uptake and glycolysis. Although these metabolic changes are not the fundamental defects that cause cancer, recent molecular studies have revealed that several of the multiple genetic alterations that cause tumor development directly affect glycolysis (3). FDG-PET allows for the utilization of these well-defined metabolic abnormalities of malignant tumors for clinical diagnosis.

The uptake of FDG into tissue reflects both transport and phosphorylation of glucose by viable cells. FDG is transported across the cell membrane by the same carrier molecules as glucose and subsequently is phosphorylated by hexokinase. In contrast to glucose, FDG-6-phosphate cannot be further metabolized since this

would require the presence of an oxygen atom at the C-2-position. Furthermore, the activity of glucose-6-phosphatase, which mediates the dephosphorylation of glucose-6-phosphate to glucose, is low in most human cells except in the liver. Since FDG-6-phosphate is a highly polar molecule, it cannot diffuse out of the cell and remains trapped intracellularly. Due to this trapping mechanism there is a steadily increasing FDG concentration in metabolically active cells, resulting in high contrast between tumor and normal tissue. Numerous studies have demonstrated in recent years that the high contrast of FDG-PET studies allows the use of this technique for staging of malignant tumors. Based on the available clinical data in the United States and Europe, there is increasing clinical acceptance of FDG-PET as a diagnostic tool in the workup of patients with head and neck cancer, lung cancer, malignant melanoma, colorectal cancer, and malignant lymphoma (13, 18).

## PARAMETERS OF TUMOR GLUCOSE METABOLISM DETERMINED FROM FDG-PET STUDIES

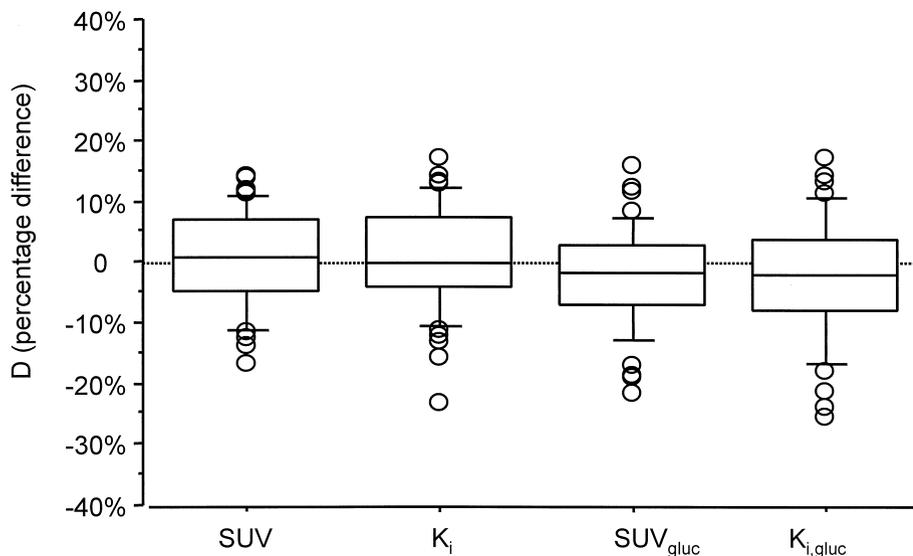
For tumor staging, qualitative interpretation of FDG-PET studies is generally considered to be sufficient. However, PET imaging also allows quantitative measurements of radioactivity concentrations within the body. Due to the simple metabolic pathway of FDG, this data can be used to estimate the glucose utilization of malignant tumors. Several approaches of varying complexity may be applied for this purpose. The most commonly used techniques are “standardized uptake values” and simplified tracer kinetic modeling using “Patlak-Gjedde” analysis. More complex modeling approaches that determine individual rate constants for FDG transport and phosphorylation have also been applied. However, these techniques require complex acquisition protocols and arterial blood sampling during data acquisition. Furthermore, interpretation of the rate constants is difficult due to tumor heterogeneity.

Standardized uptake values (SUV) are confined to the measurement of radioactivity concentrations at a fixed time point. The

Address correspondence to: W. Weber, M.D., Department of Nuclear Medicine, Technische Universität München, Ismaningerstrasse 22, 81675 München, Germany; e-mail: W.Weber@lrz.tu-muenchen.de.

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**FIG. 1. Reproducibility of several commonly used parameters for assessment of tumor glucose utilization by PET imaging.** The mean percentage difference of two repeated measurements within 10 days is shown for 50 lesions in 16 patients. Boxes represent the values between the 25th and 75th percentiles; horizontal bars (inside the boxes) show the median; horizontal cross bars (above and below the boxes) represent the values at the 10th and 90th percentiles. SUV: standardized uptake value normalized to body weight.  $K_i$ : net influx constant of FDG.  $SUV_{gluc}$ : Standardized uptake value normalized to a blood glucose level of 100 mg/100 mL.  $K_{i,gluc}$ : net influx constant of FDG normalized to a blood glucose level of 100 mg/100 mL.

activity concentration is normalized to the injected dose of FDG and body weight or body surface area. Normalization to body surface area or "lean body mass" has been shown to be more advantageous than normalization to body weight (8). However, the differences between the normalization methods appear to be small except for very obese patients (1). SUV calculations are computationally very simple and require considerably less scanner time than dynamic acquisition protocols. A major disadvantage of the SUV approach in therapy monitoring is the dependency on the time of measurement. The SUVs of malignant tumors were shown to steadily increase up to 90 min postinjection (6). Thus, SUVs can only be compared when they are measured at the same time point after tracer injection (19).

Patlak-Gjedde analysis allows determination of a rate constant ( $K_i$ ) for the net influx of FDG in the tumor. This technique requires dynamic data acquisition and measurement of a blood time-activity curve (11). In contrast to compartment modeling, Patlak-Gjedde analysis is less sensitive to errors in individual data points of the blood and tissue time-activity curves, leading to more robust and reproducible results (10). The main advantage of  $K_i$  values compared to SUV is that it takes into account changes in the whole-body distribution of FDG. However, patient movement during acquisition may cause considerable errors, especially with small lesions (19).

#### QUANTITATIVE ASSESSMENT OF TUMOR GLUCOSE UTILIZATION FOR DIFFERENTIATION OF BENIGN AND MALIGNANT TUMORS

In many cases visual image interpretation is sufficient for differentiation of benign and malignant tumors. Most benign tumors show FDG uptake similar to that of surrounding normal tissues, whereas malignant tumors are characterized by focally increased FDG uptake. In two studies of patients with suspected breast or lung cancer, we did not observe a significant difference in the diagnostic accuracy of quantitative analysis of tumor FDG uptake and qualitative image interpretation by experienced observers (1, 12). Nevertheless, we think that quantitative analysis of FDG uptake may complement visual image interpretation because it provides objective criteria for differentiation of benign and malignant lesions, thus minimizing interobserver variability in image interpretation. With-

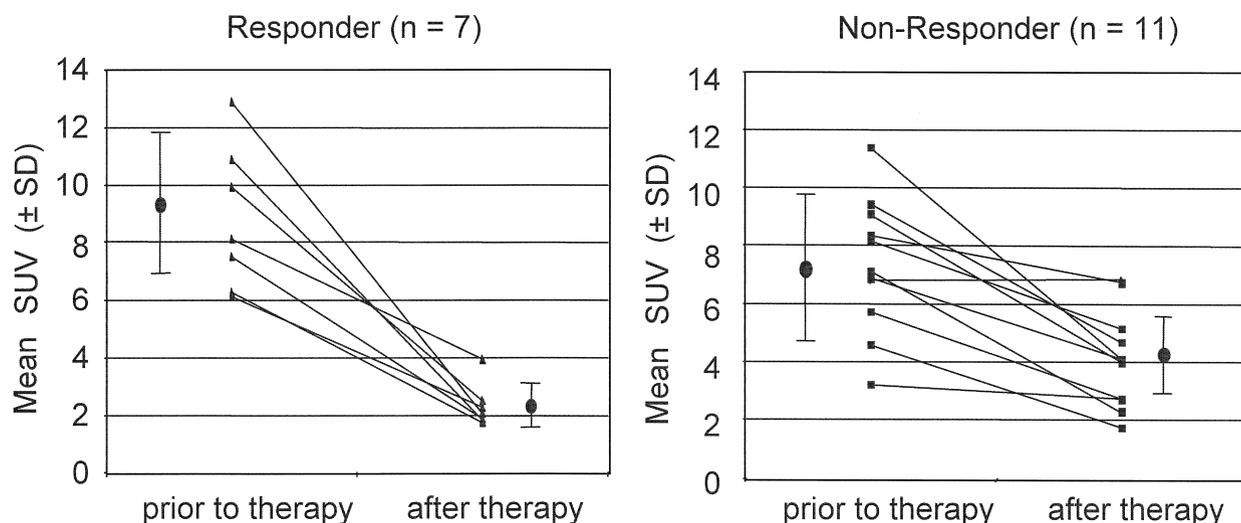
out quantitative criteria subtle abnormalities that are due to inhomogeneous FDG uptake in the region studied or reconstruction artifacts may be confused with a malignant tumor. In our experience, simple quantification of tumor FDG uptake at a fixed time point after tracer injection (e.g., 60 min postinjection) is helpful for differentiation of benign from malignant lesions. Calculation of tumor  $K_i$  values did not improve the diagnostic accuracy in patients suspected of having breast cancer (1).

#### MONITORING OF THERAPY RESPONSE BY FDG-PET IMAGING

Quantitative analysis of FDG-PET studies enables one to monitor the effect of chemo- or radiotherapy on tumor glucose utilization. Studies in cell cultures and animal models indicate that soon after the initiation of therapy an increase in FDG uptake occurs in surviving cells (5, 7). In the clinical situation, however, the FDG signal appears to parallel the loss of tumor cells as a consequence of therapy and seems to be unaffected by a metabolic "flare phenomenon." Several studies support the concept that FDG-PET provides a unique means of assessing the effectiveness of chemo- and radiotherapy (4, 15, 17). In the following sections recent results of our group addressing this issue are summarized.

#### REPRODUCIBILITY OF REPEATED FDG-PET MEASUREMENTS OF TUMOR GLUCOSE METABOLISM

To evaluate the use of FDG as a marker of tumor response, we assessed the biological and methodological reproducibility of FDG-PET in patients scheduled to undergo chemotherapy for metastatic cancer (19). Sixteen patients participating in Phase I studies of new antineoplastic compounds were examined twice by FDG-PET within 10 days while they were not receiving therapy. Standardized uptake values, FDG net influx constants, glucose normalized standardized uptake values ( $SUV_{gluc}$ ), and influx constants ( $K_{i,gluc}$ ) were determined for 50 separate lesions (Fig. 1). The precision of repeated measurements was determined on a lesion-by-lesion and a patient-by-patient basis. None of the parameters showed a significant increase or decrease at the two examinations. The differences of repeated measurements were approximately normally distributed



**FIG. 2. FDG-PET for assessment of response to preoperative chemoradiotherapy in patients with squamous cell carcinoma of the esophagus. Results of FDG-PET are compared with histopathological tumor regression. After chemoradiotherapy there is a reduction of FDG uptake in 17 of the 18 patients. However, this decrease is significantly more pronounced in responding than in nonresponding tumors.**

for all parameters with a standard deviation of the mean percentage difference of about 10%. Thus, for a "typical" lesion, changes of a parameter of more than 20% are outside the 95% range for spontaneous fluctuations, and therefore can be considered to reflect true changes in glucose metabolism of the tumor mass. Obviously, the absolute value of the change must also be considered. According to the findings of our study, a change of  $\pm 0.9$  for SUV or  $\pm 0.7$  mL/100 g/min for  $K_i$  is outside the 95% range for spontaneous fluctuations of the respective parameter. Analysis on a patient-by-patient basis yielded almost identical results, indicating that the main source of variability was the variability in the measurement of individual lesions. There was no clear advantage in using tracer kinetic approaches compared to SUV measurements. Therefore, it appears feasible to use SUV measurements for the evaluation of therapy response. However, the patients were studied under stable conditions (no signs of tumor progression, infection, or new laboratory abnormalities). Furthermore, no patients with overt diabetes mellitus were included. Because diabetes mellitus may affect the blood clearance and whole-body distribution of FDG by multiple mechanisms (16), tracer kinetic approaches may be preferable to SUV measurements in diabetic patients. However, this has to be addressed in future studies comparing the reproducibility of FDG-PET in diabetic and nondiabetic patients.

#### **CORRELATION BETWEEN FDG UPTAKE AND TUMOR VIABILITY AFTER CHEMO- AND RADIOTHERAPY**

To test the validity of FDG-PET for assessing tumor response, we evaluated the reduction of tumor metabolic activity after preoperative (neoadjuvant) chemoradiotherapy (2). Twenty patients with squamous cell carcinoma of the esophagus were studied by FDG-PET prior to the initiation of chemoradiotherapy as well as 3 weeks after completion of therapy. The metabolic activity of the tumors was assessed by using standardized uptake values. In 18 patients the tumors were resected following the second PET study. Two patients were inoperable due to their poor general medical condition. An established scoring system for histopathological tumor regression was

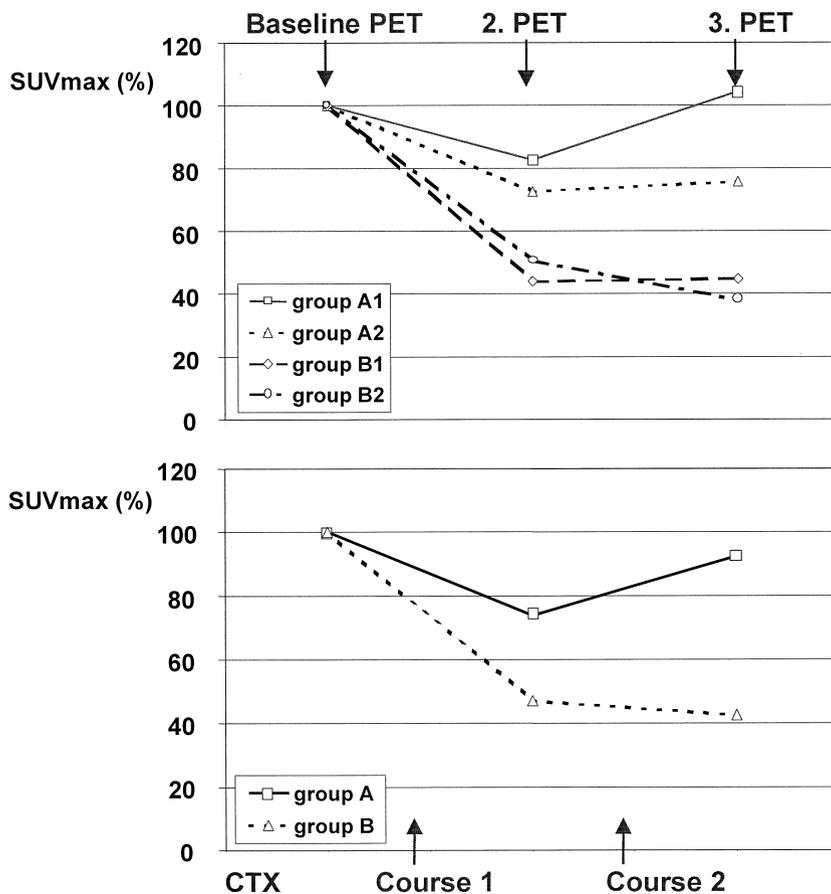
used as the "gold standard" for assessment of response (9). In addition, changes in FDG uptake were correlated with patient survival.

In 17 of the 18 patients who underwent resection, a reduction of tumor FDG uptake was noted at the time of the second PET scan. However, patients classified as histopathological responders showed a significantly higher reduction of metabolic activity than nonresponders (decrease in responders:  $72 \pm 11\%$ ; in nonresponders:  $42 \pm 22\%$ ,  $p = 0.004$ , Fig. 2). In a receiver operating characteristic (ROC) analysis a cut-off value of more than 51% reduction of FDG uptake yielded a sensitivity of 100% and specificity of 55% for detection of responders, while a cut-off of more than 71% reduction of FDG uptake was associated with a sensitivity of 100% and specificity of 100%. For all patients the actuarial 3-year survival rate was 29%. Patients with a decrease in the PET signal of less than 51% had a significantly ( $p = 0.03$ ) shorter survival time (median 9 months) compared to those patients with an SUV decrease of more than 51% (median survival 34 months). These data confirm the concept that FDG uptake following therapeutic interventions reflects the extent of viable tumor cells and correlates with histopathological evaluation.

#### **TIME COURSE OF TUMOR GLUCOSE UTILIZATION DURING CHEMOTHERAPY**

To assess the time curve of metabolic changes during chemotherapy, we performed a study in patients with non-Hodgkin's lymphoma who generally respond well to standard chemotherapy. Eleven patients undergoing chemotherapy were studied by FDG-PET at baseline, 7 days after initiation of therapy, and 42 days later. Tumor glucose metabolism was quantified by standardized uptake values and metabolic rates (MRFDG) derived from Patlak-Gjedde analysis. Before chemotherapy, high FDG uptake was found in all lesions (SUV  $13.3 \pm 4.2$ ). Seven days after initiation of chemotherapy, tumor FDG uptake decreased by 60% (SUV). A further decrease of 42% was seen at day 42 resulting in a total decrease of 79% from baseline to day 42. During a follow-up of  $16.0 \pm 4.2$  months, six of the 11 patients remained in remission. Seven days after initiation of chemotherapy, this group of patients displayed

**FIG. 3.** Changes of relative SUV (median values) in the course of primary chemotherapy. Abbreviations: group A, gross residual disease in histopathology; group B, minimal residual disease in histopathology; group A1, gross residual disease in histopathology and clinical progressive disease or clinical no change; group A2, gross residual disease in histopathology and clinical partial remission or clinical complete remission; group B1, small foci of invasive carcinoma in histopathology; group B2, complete response in histopathology.



significantly lower mean MRFDG than the group of patients with relapse. At day 42, all parameters of FDG uptake showed a significant difference for both patient groups. The relative change of MRFDG from baseline to day 42, as well as from day 7 to day 42, was significantly larger than compared to SUV parameters.

This difference is probably related to a technical factor, since the dynamic range of measurements is greater for MRFDG than for SUV. Due to blood-pool activity SUV values will still be greater than zero even when there is no remaining metabolic activity after therapy. Thus, calculation of an FDG influx rate may be superior in determining low metabolic activity in residual tumor tissue. This hypothesis, however, has to be prospectively tested in a larger patient cohort.

#### CHANGES OF FDG UPTAKE DURING THERAPY AND FINAL OUTCOME OF CHEMOTHERAPY

It has been hypothesized that reduction of tumor glucose metabolism precedes a reduction of tumor volume. Although this has not been evaluated so far in patient studies, reduction of FDG uptake prior to a decrease in tumor size has been observed in animal studies following chemotherapy (20). Furthermore, reduction of FDG uptake may be quantified more easily than reduction of tumor size, which is conventionally assessed by measuring the maximum diameter of the tumor mass. According to our data on the reproducibility of the FDG signal, a 20% reduction of FDG uptake can be reliably determined by PET. However, for a spherical tumor with an initial diameter of 3 cm, a 20% reduction of tumor volume results only in a 2 mm decrease in the diameter. This small difference may be difficult to measure in conventional CT or MRI

studies. These findings indicate that FDG-PET may be a sensitive test for early differentiation of responding and nonresponding tumors.

We evaluated this hypothesis in 22 patients with breast cancer undergoing preoperative chemotherapy (14). PET scans of the breast acquired after the first and second course of chemotherapy were compared with the baseline scan. Quantification of regional FDG uptake was obtained in a total of 24 breast carcinomas. To evaluate the predictive value of PET imaging, histopathological response after completion of chemotherapy classified as gross residual disease (GRD) and minimal residual disease (MRD) served as gold standard. With change of tumor glucose metabolism during chemotherapy, significant differences in tracer uptake between tumors with GRD compared to MRD were observed ( $p < 0.05$ ). PET differentiated between responding and nonresponding tumors as early as after the first course of chemotherapy. After initiation of chemotherapy, tracer uptake showed little change in tumors with GRD found later in pathological analysis but decreased sharply to the background level in most tumors with MRD (Fig. 3). After the first course, all responders were correctly identified (sensitivity 100%, specificity 85%) by a threshold defined as a decrease below 55% of the baseline scan. At this level, histopathological response could be predicted with an accuracy of 88% and 91% after the first and second course of therapy, respectively.

#### CONCLUSION

Quantitative assessment of tumor metabolism by FDG-PET represents a novel approach in monitoring the response of malignant tumors to chemo- and radiotherapy. For this purpose FDG-PET

studies provide several parameters that can be measured with high reproducibility. It is expected that the combination of morphological and metabolic imaging may improve the quantitative nature of these measurements by relating tumor viability to total tumor mass. The results of initial clinical studies suggest that monitoring of tumor glucose metabolism by FDG-PET may allow early treatment regimen adjustments as means to reducing morbidity and costs associated with ineffective therapy. Furthermore, FDG-PET may aid in the selection of the most effective form of therapy in individual patients.

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