The Dose Uptake Ratio as an Index of Glucose Metabolism: Useful Parameter or Oversimplification?

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The dose uptake ratio (DUR) has been used as a quantitative index of glucose metabolism for tumor classification and monitoring response to treatment. In order to provide consistent results, DUR measurements should be made when the concentration of tracer has reached a plateau. The time of this plateau cannot be identified from a single static acquisition. **Methods:** In this study, we investigated the changes in DUR as a function of time in eight patients with stage III lung cancer. All patients underwent a quantitative dynamic ^{18}F-FDG PET study before and after treatment and the data were analyzed with a three-compartment model. Using the fitted model parameters, the DUR was predicted at the plateau and intermediate times. **Results:** Tumor concentrations of ^{18}F-FDG did not reach a plateau within the 90 min of imaging in any of the pre-treatment studies and only in one case post-treatment. The average time to reach 95% of the plateau value pre-treatment was 298 ± 42 min (range: 130–500 min); in post-treatment, it was 154 ± 31 min (range: 65–240 min). The difference between the plateau DUR and the 60-min value was 46% ± 6% pre-treatment and 17% ± 5% post-treatment. **Conclusions:** These data indicate that DUR can vary widely with the time of measurement and that DUR should be interpreted with caution in any individual patient.

Key Words: PET-FDG; DUR; glucose metabolism; compartmental analysis; lung cancer; diagnostic imaging

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The dose uptake ratio, DUR, (also referred to as the standardized uptake value, SUV), has been used as a quantitative index of glucose metabolism in ^{18}F-FDG PET studies of normal and malignant tissue (*1–6*). However, to achieve a model independent assessment of glucose metabolism, DUR should be measured after tissue concentrations of ^{18}F-FDG have reached a plateau. At this time, the concentration of ^{18}F-FDG in tissue is independent of the details of FDG transport. As long as DUR is assessed during the plateau, the precise time of measurement is unimportant.

Typically, DUR measurements have been made at 45–60 min after injection. This approach has worked well in normal brain tissue where plateau concentrations are achieved within the first hour after injection of the tracer (*7,8*). In contrast to normal brain, much less is known about the kinetics of glucose and FDG metabolism in tumors. In these tissues, the time to reach plateau is dependent on specific tumor biology, and extrapolations from normal brain data may not be valid. In many clinical studies of tumor metabolism by ^{18}F-FDG-PET, DUR measurements have also been performed at 45–60 min, ignoring that uptake of FDG is still occurring in many tumors at this time (*1–6*). Despite these potential uncertainties, DUR measurements have been used to predict prognosis and to monitor the effects of treatment (*2,4*). On a population basis, DUR measurements performed at a fixed time point (e.g., 60 min postinjection) may correlate with glucose metabolic rate (*6*). However, in individual patients, there is a potential for substantial underestimation if a significant amount of tracer accumulation occurs after this time. Thus if a single measurement of DUR at 60 min is used to classify tumor malignancy or assess treatment outcome, potentially serious errors can result. If DUR measurements are made at the plateau, more robust estimates of treatment response or classification of malignancy might be achieved.

In this study, we examined the temporal changes in DUR and the resulting differences from the plateau value. As an example, we used pre- and post-treatment studies of patients with stage III non-small-cell lung cancer. From dynamic ^{18}F-FDG studies analyzed with a three-compartment model, analytical expressions for the time-dependence of ^{18}F-FDG concentration in the tumors were derived. These relations were used to predict the DUR at plateau and calculate the potential errors associated with making DUR measurements at earlier times.

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MATERIALS AND METHODS

Human Subjects

Eight patients with stage III non-small-cell lung cancer were studied by dynamic ^{18}F-FDG-PET. The study protocol was approved by the human studies committee of Massachusetts General Hospital, and written informed consent was obtained from each patient. Paired studies were obtained in each patient. The first study was performed a few days before treatment and the second was performed 2 wk after completion of therapy. The patients were fasted for at least 6 hr before imaging. Immediately before the study, blood glucose concentration was determined.

Quantitative ^{18}F-FDG PET Studies

All imaging was performed with an eight-ring whole-body imaging system (Scanditronix PC4096-16WB). The primary imaging parameters of this instrument are in-plane and axial resolutions of 6.0 mm FWHM, 15 contiguous slices of 6.5 mm separation and a sensitivity of 5,000 cps/μCi/cc. All images were reconstructed using a conventional filtered backprojection algorithm to an in-plane resolution of 7 mm FWHM. Transmission scans, acquired using a rotating pin source containing ^{68}Ge, were used to confirm positioning and to correct for tissue attenuation. All projection data were corrected for nonuniformity of detector response, dead-time, random coincidences and scattered radiation. Regions of interest (ROIs) were circular with a fixed diameter of 16 mm. The PET camera was cross-calibrated against a well scintillation counter by comparing the PET camera response from a uniform distribution of an ^{18}F solution in a 20-cm cylindrical phantom with the response of the well counter to an aliquot of the same solution.

The subjects were positioned supine on the imaging bed of the PET camera with arms extended out of the field of view. Dynamic image collection was started immediately before intravenous injection of 10 mCi of ^{18}F-FDG. Sequential images were acquired in 15-sec frames for the first 1.75 min, 30-sec frames for the next 2 min, 60-sec frames for the next 2 min, 2-min frames for the next 4 min, 5-min frames for the next 20-min, 10-min frames for the next 40-min and a final 15-min frame.

Arterial input curves were measured from arterial blood samples or regions of interest placed over the left ventricle. The use of left ventricular time-activity curves as arterial input functions is a well established technique (*9*). In addition, in several of the patients that were studied, analysis was performed both with LV-time-activity curves and curves obtained by direct sampling. In all cases, the results were essentially identical. Areas of the tumor were chosen for analysis using a constant circular ROI with a 16-mm diameter. The regions were positioned over areas of the tumor with high metabolic activity, thus avoiding any apparent necrotic areas. Of the several possible methods for defining ROIs, we felt that a fixed ROI centered over the region of greatest FDG activity on the 90-min scan was most appropriate. This type of ROI is very convenient for comparisons between repeat studies. Compartmental analysis by a three-compartment FDG-kinetic model yielded the rate constants of FDG metabolism in metabolically active regions of the tumors.

Simulation of DUR Values

The arterial blood and tissue time-activity curves were fitted to a three-compartment, three-rate constant model of ^{18}F-FDG transport and metabolism (*7*). Assuming that the disappearance of ^{18}F-FDG from plasma can be described by tri-exponential functions, integration of the model equations yields the following expression for the time dependence of the concentration of ^{18}F-FDG in tissue:

$$C_T(t) = \frac{k_1k_2}{k_2 + k_3} e^{-(k_2 + k_3)t} \sum_{i=1}^{3} A_i \left[\frac{1 - e^{-(b_i - (k_2 + k_3))t}}{b_i - (k_2 + k_3)}\right] + \frac{k_1k_3}{k_2 + k_3} \sum_{i=1}^{3} A_i \left[\frac{1 - e^{-b_it}}{b_i}\right], \quad \text{Eq. 1}$$

where k_1 and k_2 are the rates of ^{18}F-FDG transport from plasma into tissue and from tissue back into plasma; k_3 is the rate of ^{18}F-FDG phosphorylation; and k_4, the rate of ^{18}F-FDG dephosphorylation was assumed to be zero. The rationale for this has been discussed by Lucignani et al. (*10*). b_1, b_2 and b_3 are rate constants for disappearance of ^{18}F-FDG from plasma. As t increases, the first term approaches zero and the second term simplifies to:

$$C_T(t) = \frac{k_1k_3}{k_2 + k_3} \sum_{i=1}^{3} \frac{A_i}{b_i}. \quad \text{Eq. 2}$$

By nonlinear least-squares fitting of the plasma and tissue time-activity curves to the model defined by Equation 1, k_1, k_2 and k_3 were derived for each study. The coefficient of determination (R^2) for this fitting was 0.98 for the pre-treatment data and 0.99 for the post-treatment data. Using the fitted values of these rate constants, the time-activity curves were extrapolated to infinity. Based on the data presented by Lucignani, it was assumed that k_1, k_2 and k_3 do not change significantly after 90 min, making extrapolation beyond this time meaningful (*10*). In all cases, the extrapolated time-activity curves reached plateau by 10 hr after injection, this was therefore used as the reference time in all subsequent analysis.

The time-activity curves were transformed to time-DUR curves by dividing by injected dose normalized to the patient's weight. DUR difference curves were obtained by calculating the percentage difference between the DUR value at each time and the plateau reference value. The difference curves from each patient were pooled and a composite time-DUR curve was constructed. The time at which the DUR reached 95% of the plateau value (mean ± s.d.) was also determined. This analysis was performed independently for pre- and post-therapy results.

RESULTS

In all of the pre-treatment studies, tumor concentrations of ^{18}F-FDG did not reach plateau values within the 90 min of imaging. In the post-treatment studies plateau concentrations were reached within 90 min in only one case. The average rate constants derived using compartmental analysis are shown in Table 1. These results indicate that treatment did not affect k_1 but resulted in a significant increase in k_2 ($p < 0.01$) and a significant decrease in k_3 ($p < 0.01$). Linear correlation of the DUR measured at 60 min with MRGlc yielded an R^2 of 0.65.

Figure 1 shows representative time-DUR curves for one of the patients, before and after treatment. In this case, it is clear that plateau DURs are not achieved until several

TABLE 1
Mean ^{18}F-FDG Rate Constants Derived from Compartmental Modeling

Rate constant	Pre-treatment (min^{-1})	Post-treatment (min^{-1})
k1	0.084 ± 0.024	0.079 ± 0.018
k2	0.021 ± 0.025	0.077 ± 0.025
k3	0.072 ± 0.018	0.016 ± 0.004

hours after injection. In the pre-treatment study, the DUR at 60 min is derived from the steeply increasing part of the time-DUR curve, while the post-treatment curve is increasing at a relatively slow rate. Assessment of tumor response based on the 60-min time points would yield a different value from that obtained at plateau. At 60 min, the DUR change is from 11.3 to 6.1 while at plateau it is from 18.5 to 8.7. Similar results were observed in all of the patients that were studied. In the pre-treatment studies, the average time to reach 95% of the plateau DUR was 298 ± 42 min (range: 130–500 min). In the studies acquired after treatment, the average time to reach 95% of the plateau value was 154 ± 31 min (range: 65–240 min).

Figure 2 shows the difference curves, pre- and post-treatment for all patients that were studied. These results indicate that measurements of DUR within 90 min after injection results in significant error in all the pre-treatment studies. Although these errors are less dramatic in the post-treatment studies, an acceptable level of error (within 5% of calculated plateau value) was present in only one case. The large variation between tumors clearly reflects marked heterogeneity in the kinetics of glucose metabolism. For DURs measured at 90 min after injection, the percentage differences from plateau values ranged between 22% and 67% pre-treatment, and up to 28% post-treatment. These data indicate that the use of DUR as an index of glucose metabolism in lung tumors is variable, even when the value is calculated at 90 min. This is particularly true in pre-treatment studies. The magnitude of this error increases as the interval between injection and measurement is reduced.

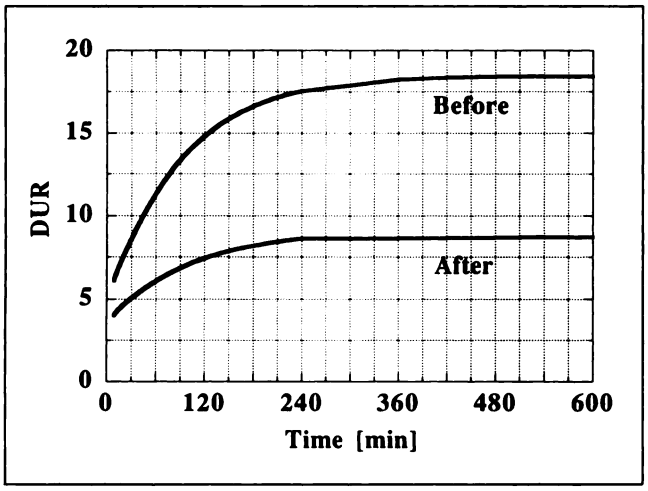

FIGURE 1. Representative time-DUR curves for one of the patients, before and after treatment. Similar results were observed in all patients studied.

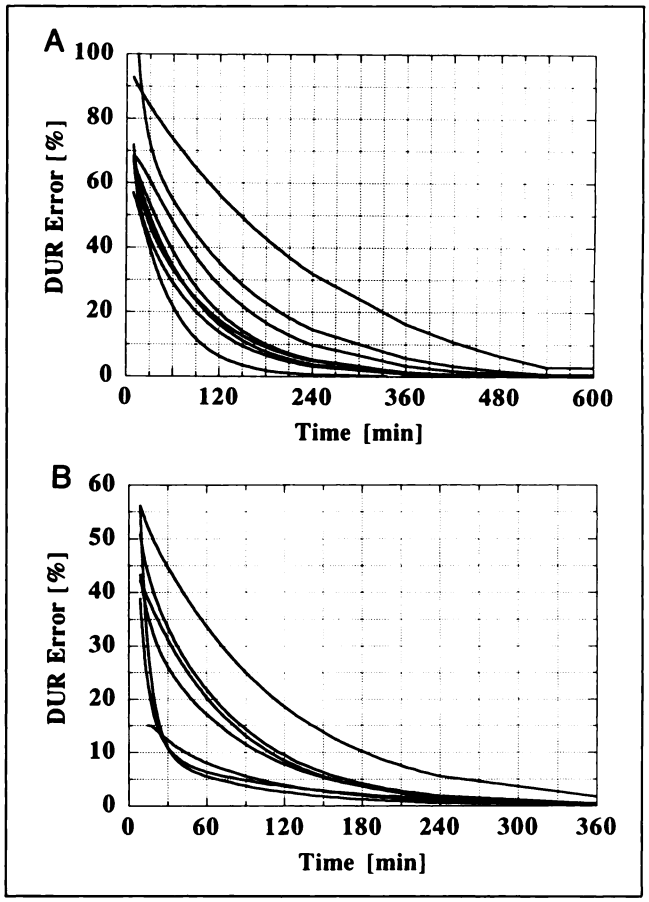

FIGURE 2. Individual DUR error curves, (A) before and (B) after treatment, for all patients studied. Measurements of DUR within 90 min after injection results in significant error in all pretreatment studies. These errors are less dramatic in the post-treatment studies, but an acceptable level of error was present in only one case.

DISCUSSION

Currently, the use of DUR as an index of glucose metabolism is widespread. In the context of the management of patients with cancer, DUR has been used to classify lesions as benign or malignant and to monitor therapy response. Despite its apparent simplicity, some authors do not recommend the use of DUR while others have reported that it is a useful index of glucose utilization (*3,5*). In several studies, attempts have been made to refine DUR measurements in order to make it more reproducible and clinically useful; examples include correction for body surface area (*11*) and serum glucose (*6*). In no case has attention been paid to the effect of the time of measurement on the meaning of the result. In this study, we have explored the impact of measurement time on the validity of DUR.

In the assessment of cancer patients with ^{18}F-FDG, the parameter of choice to classify a particular neoplasm,

and/or to monitor its response to treatment is the glucose metabolic rate, MRGlc. However, because determination of this parameter is complex and time-consuming, it is not routinely performed. In contrast, the use of DUR to monitor metabolic activity in tumors is seductive in its simplicity, since the measurement is convenient to perform for both the patient and the clinician. Justification for the use of DUR is based on the assumption that the concentration of ^{18}F-FDG in tissue, corrected for patient weight and injected dose, is correlated with MRGlc. In the present study, DUR at 60 min was found to be correlated with MRGlc, $R^2 = 0.65$ (n = 8). In a previous study, Lindholm et al. reported an R^2 of 0.76 in five patients (*6*). Although these results confirm that DUR is positively correlated with MRGlc, the quality of the correlation is inadequate to draw meaningful conclusions in individual patients.

In recent reports, it has been suggested that DUR can have significant value in differentiating benign from malignant lesions (*11–13*). However, these studies have reported inconsistent cut-off DUR values for separating benign and malignant activity. Other studies have failed to reach a consensus that DUR can separate malignant from benign lesions (*14–16*). Overall, these studies indicate a potential for considerable variability when DUR is used as an index of MRGlc. These variations can be unpredictable and are, therefore, uncontrollable. The effects of blood glucose levels were examined in a study of bronchial carcinoma by Langen et al. who performed both dynamic and static imaging at two different plasma glucose levels (*5*). The dynamic data were acquired over 60 min and static measurements were performed at between 30 and 60 min after injection. The results of this study indicated that although glucose metabolic rates derived from the dynamic studies were not greatly affected by plasma glucose concentration, widely varying DURs were measured from the static images; the reliability of these data could be improved by correction for plasma glucose concentration. Nevertheless, the authors concluded that the static approach was of questionable value and that: "Where an accurate evaluation of tumor glucose metabolism is needed, such as measuring tumor response to therapy, it is advantageous to adhere to kinetic evaluation."

In order to identify the variability in DUR with time of measurement, we calculated the transport and phosphorylation rate constants for ^{18}F-FDG in a series of lung tumors, by fitting plasma and tissue time-activity curves to a three-compartment, three-rate constant model. Since there was no observed loss of tissue radioactivity during the experiment, the fourth rate constant, k_4, was considered to be negligible. This assumption is supported by the work of Lucignani et al. (*10*). The data were consistently well described by this model.

Using the model parameters, the ^{18}F-FDG uptake curves were extrapolated to plateau and the corresponding time-DUR curves were calculated. In Figure 2, there are substantial variations in the shapes of the curves for different patients. These variations underline the point that large differences exist, even between similar tumors. Clearly, if DUR is measured at a time when tissue radioactivity is still changing rapidly, the potential for incorrect diagnosis, prognosis or classification in any individual patient is magnified.

Thus, as presently measured, the DUR may be a gross oversimplification of a very complicated metabolic situation. At best it is semiquantitative and its use for tumor monitoring may be associated with significant and unavoidable error, *which is unpredictable*. The use of dynamic studies is much more complex but has a firmer theoretical basis (*17*). With dynamic imaging, effects of therapy on metabolic activity can be monitored without assumptions about concentration plateau or the shape of the time-activity curve. By performing dynamic studies in a variety of tumors, it may be possible to categorize the times at which plateau measurements can be made in individual tumor types. This in turn, may result in more robust estimates of DUR. Although this may require extremely delayed imaging with some tumors, recent advances in PET camera technology have made these measurements feasible. For example, new three-dimensional imaging devices have sensitivities that are sixfold to tenfold greater than in our present instrument (*18,19*). With glucose-avid tumors such as lung carcinomas, excellent quality images should be obtainable with these devices as late as 8–10 hr postinjection.

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