Dynamic T1-weighted Magnetic Resonance Imaging and Positron Emission Tomography in Patients with Lung Cancer: Correlating Vascular Physiology with Glucose Metabolism

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ABSTRACT

The management of primary lung cancer relies on sophisticated imaging methods to assist in the diagnosis, staging, and evaluation of tumor regression during treatment. The information provided is generally anatomical in nature, except for that provided by positron emission tomography with $^{18}$F-fluorodeoxyglucose, a modality that yields physiological data that have been shown to be useful in identifying neoplasia, based on an elevated glucose metabolic rate. Because the metabolism of malignant tissue depends intimately on neovascularization to provide oxygen and glucose in sufficient quantities to allow tumor growth, the characterization of tumor vascular physiology could be an important tool for assessing and predicting the likely effectiveness of treatment.

Our goal was to show the feasibility and practical value of parameters of tumor vascular physiology obtained using dynamic T1-weighted magnetic resonance imaging (MRI), to correlate them with glucose metabolism and to demonstrate changes in these parameters during and after treatment in patients with lung cancer. Parameters of vascular physiology [permeability-surface area (PS) product and extracellular contrast agent distribution volume] and glucose metabolism were assessed in 14 patients with lung cancer. Glucose metabolism was measured by using $^{18}$F-fluorodeoxyglucose-positron emission tomography. Vascular physiology was assessed by dynamic T1-weighted, contrast-enhanced MRI. The mean PS product in tumor was 0.0015 ± 0.0002 s$^{-1}$ (n = 13) before, 0.0023 ± 0.0003 s$^{-1}$ (n = 3, P = 0.053) midway through, and 0.00075 ± 0.0002 s$^{-1}$ (n = 5, P < 0.03) 2 weeks after treatment. Values for the extracellular contrast distribution space were 0.321 ± 0.03 before, 0.289 ± 0.02 midway through, and 0.195 ± 0.02 (P < 0.01) 2 weeks after therapy. The glucose metabolic rate was significantly correlated with the PS product (P < 0.01) but not with the extracellular contrast distribution space.

Our results demonstrate that tumor PS product correlates with glucose metabolism, that chemotherapeutic agents induce observable and quantifiable changes in these parameters, and that such changes can be measured by in vivo dynamic MRI. Quantitative dynamic T1-weighted MRI of tumor vascular physiology may have a useful role in the clinical management of lung cancer.

INTRODUCTION

Appropriate management of lung cancer depends on accurate staging of the disease. Although computed tomography remains the dominant technique for this purpose (1-3), in those centers that have access to FDG-PET, measurement of tissue glucose metabolic rate can be of value in identifying unsuspected spread of disease, as well as more accurately defining local distribution of malignant tissue (1, 4-6). These data are predicated on the assumption that actively dividing malignant cells have increased uptake of glucose, resulting in elevated values for glucose metabolic rate, as measured with FDG-PET (5, 7). Although increased metabolic demand is an obvious cause of a raised glucose metabolic rate, it has been suggested that the supply of substrate may also modulate tumor cell glucose uptake (8, 9), and thus, the vascularity of tumor tissue may be an important component in determining the glucose metabolic rate of a neoplasm (10-12). Furthermore, both the degree and distribution of blood flow are important to cancer treatment because relatively hypoxic cells are resistant to radiation and poorly perfused cells often do not receive sufficiently toxic levels of antineoplastic agents (13, 14). Even when perfusion is relatively undisturbed, recent experimental studies have underscored the impact that physiological barriers (namely, a heterogeneous blood supply, interstitial hypertension, and relatively long transport distances in the interstitium) have on the transport of chemical and biological agents from the blood to tumor cells (13, 15).

Receipt by a malignant cell of a sufficient supply of nutrients to permit its growth and division depends, in part, on perfusion rate, vascular density, vessel permeability, and vessel surface area. Thus, it may be possible to use measurements of...
these vascular parameters to determine the propensity for growth in different regions of a tumor (16, 17). Therefore, both the evaluation of tumor vascular physiology and glucose metabolism are likely to be useful in optimizing therapy and monitoring treatment response.

Here, our aim was to assess the relationship between tumor glucose metabolism and vascular physiology in patients with NSCLC of stage IIIa or greater. We also studied whether or not any changes in tumor vascular parameters and relaxation times occurred during treatment (combined chemo- and radiotherapy). Tumor vascular physiology and relaxation times were assessed by using echo-planar MRI, based on a dynamic T1-weighted sequence. A summary of patient demographics is presented in Table 1.

**PATIENTS AND METHODS**

**Patients.** Fourteen patients who had been diagnosed with NSCLC of stage IIIa or worse were included in our study, after its approval by our hospital subcommittee on human studies. Dynamic contrast-enhanced, echo-planar MRI was obtained before treatment in 14 patients, 10 of whom also underwent FDG-PET within 48 h. In 5 of the 14 patients, the dynamic contrast-enhanced MRI study could be repeated 2 weeks after the end of treatment. One of these patients also had a FDG-PET study within 48 h. All the MRI studies, both pre- and posttreatment, included the necessary pulse sequences for measuring T1 and T2 relaxation times and T1 and T2 relaxation parameters. The tumor vascular parameters that we calculated, by using a two-compartment model, were the PS product and V1 (18). MRGlc was obtained by using the simplified kinetic MRGlc determination (19).

**PET patients and methods**

### Table 1 Patient demographics

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*Pre, pretreatment; Mid, midway through treatment; Post, posttreatment; Y, yes; RT, radiotherapy; CT, chemotherapy.*

For the dynamic, pharmacokinetic study, contrast material (Gd-diethylenetriaminepentaacetic acid; Berlex Inc.) was infused through a basilic vein cannula at a rate of 5 ml/s. Doses of 0.05, 0.1, or 0.2 mmol/kg were used, and details for each patient are in Table 1. A single-slice, T1-weighted, SE EPI (TR = 600 ms, TE = 20 ms) sequence was used, beginning 5 s before contrast agent infusion and continuing in a single, uninterrupted acquisition of 500 images for 32 min. The first 200 images were acquired at 600-ms intervals, and the remaining 300 were acquired at a rate of one image every 6 s. Slice thickness was 7 mm, the field of view was 40 cm, the matrix size was 128 × 128, and the effective in-plane resolution was 3.125 mm. In four patients, timed venous blood sampling was performed during the T1 relaxation time constant (T10) was achieved by acquiring a set of images with an EPI, inversion recovery sequence with the TI varied from 100 to 1050 ms in steps of 50 ms (TR = 2000 ms, TE = 25 ms). This resulted in 20 images from which T10 could be calculated in regions of interest by using nonlinear fitting of the function A(1 − 2e−TR/T10 + e−TR/T20). Similarly, the T2 relaxation time constant (T20) was obtained from a set of echo-planar SE images acquired by varying the TE from 20 to 95 ms in steps of 3 ms (TR = 6000 ms). This produced 25 images, from which T20 could be calculated in regions of interest by using monoexponential curve fitting. Following these sequences, dynamic, single-slice T1-weighted EPI was performed at the chosen location. This was designed to record the pharmacokinetics of contrast material (Gd-diethylenetriaminepentaacetic acid) to evaluate tumor vascular physiology, expressed as PS product and V1.
the 32-min acquisition to provide an input function for subsequent compartmental analysis.

Signal time intensity curves were generated and analyzed for each EPI data set (T1, T2, and dynamic data collections) by choosing a region of interest at the periphery of the tumor. The curves were used to calculate regional relaxation time constants, T1 and T2, and to determine parameters of tumor vascular physiology.

\[ \Delta R1(t) = D \cdot PS \sum_{i=1}^{2} \frac{(e^{-PSVT_i/t} - e^{-PSV_{T_i}/t})}{b_i - \frac{PS}{V_i}} \]  

(A)

In this model, \( D \) is a constant, normalizing the dose of contrast given to a standard value of 0.1 mmol/kg; \( PS \) is the PS product; \( V_i \) is the contrast agent distribution space; and \( A_i \) and \( b_i \) are the mean blood curve parameters, obtained by fitting a biexponential function to the Gd concentration input curves determined from the blood samples (18).

The T1 relaxation values of the timed blood samples were measured by using a relaxometer (RADX; Praxis Corp., San Antonio, TX) at 10 MHz. First, the red cells were separated by centrifugation, and a measured volume of plasma (1 ml) was pipetted into measurement tubes supplied with the instrument. \( \Delta R1 \) was obtained from the timed T1 data (\( R1 = 1/T1 \)). A biexponential curve was fitted to each patient’s data.

\[ \Delta R1 = A_1 e^{-b_1 t} + A_2 e^{-b_2 t} \]  

(B)

The resulting parameters (\( A_i \)) and \( (b_i) \) were then pooled to provide a population mean and SE for each parameter. These average amplitude (\( A_i \)) and elimination constants (\( b_i \)) were then used for all the compartmental analyses.

FDG-PET Imaging. Studies of tumor glucose metabolism were performed by using PET and FDG. \(^{18}F\) was produced by 17-MeV proton bombardment of an \( H_2^{18}O \) target and FDG was prepared by robotic implementation of the method of Hamacher et al. (20). The radiochemical purity was evaluated by high-performance liquid chromatography and TLC and was greater than 98%. Pyrogen testing was performed by using a 30-min Limulus test.

Imaging was performed with an eight-ring whole-body imaging system (Scanditronix Positron Emission Tomograph PC4096-16WB). The primary imaging parameters of this instrument are 6.0 mm full width at half-maximum in-plane and axial resolution, an acquisition of 15 contiguous slices with 6.5-mm separation, and a 5000 cps/mCi/ml sensitivity. Images were reconstructed by using a conventional, filtered, back-projection algorithm to a final in-plane resolution of 7 mm full width at half-maximum. Transmission scans, acquired with a rotating pin source containing \(^{68}Ge\), were used to confirm positioning and correct for tissue attenuation. All projection data were corrected for nonuniformity of detector response, dead time, random coincidences, and scattered radiation. All patients were imaged in the supine orientation, with arms extended out of the field of view.

In five patients, a dynamic image collection was initiated immediately before an intravenous injection of 10 mCi of FDG. Subsequent sequential images were then obtained in 15-s frames for the first 1.75 min, 30-s frames for the next 2 min, 60-s 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 single 15-min frame for the final 15 min. The arterial input function was measured from a region of interest either over the ascending aorta or the left ventricle, and a three-exponential model was fitted to these blood data. From these data, the area under the blood curve was calculated directly.

In six patients, a simplified study protocol for the determination of glucose utilization rate in the tumor was performed. An intravenous injection of 10 mCi of FDG was administered to each patient, and a 15-slice study through the tumor region was performed 60 min postinjection. A single blood sample was withdrawn at the time of imaging and used to estimate the area under the blood curve, based on population rate constants (19).

Calculation of the tumor MRGlc was performed by the same technique in both groups of patients. The data were analyzed for regions of interest that were placed over active parts of the tumor periphery, exemplified in Fig. 1B. The MRGlc was then calculated by dividing the activity in the tumor by the cumulative integral under the blood curve (either estimated or directly calculated) and multiplying this by the value of the blood glucose (19):

\[ MRGlc = \frac{C_f(t)}{\beta} \cdot blood \ glucose \]  

(C)

where \( C_f(t) \) is tumor tissue activity at time \( t \) and \( \beta \) is the value of the integral of the blood curve from time of injection to time \( t \).

RESULTS

Table 1 provides demographic details for the 14 patients included in our study. All these patients had been diagnosed with NSCLC of stage IIIa or worse and were studied at the beginning of anticancer therapy. Thirteen patients had complete baseline MRI studies; however, in one (patient 1), equipment failure occurred during the dynamic acquisition, yielding a partial data set only. Three patients underwent MRI at the midpoint of their treatment regimens (patients 11, 13, and 14). Six patients underwent MRI 2 weeks after the end of their radiation treatments (patients 1, 6, 9, 11, 13, and 14); however, for patient 9, only the T2 relaxation time was available for analysis, due to technical difficulties during data acquisition. Usable data from a total of 23 MRI studies were collected, of which 11 were paired with a FDG-PET study obtained within 2 days of the MRI. Of these 11 paired studies, 10 were obtained before treatment, and one was obtained 2 weeks after the end of treatment.

Table 2 provides detailed results of relaxation time measurement in the MRI studies, which are necessary for the compartmental analysis. Using the final postcontrast uptake image as a guide, we identified those regions of tumor that were perfused, usually a rim of tissue at the periphery. Determination of inherent T1 and T2 tissue relaxation times in the perfused...
tumor periphery and normal muscle was made from the stepping T1 and stepping TE studies, respectively. For perfused tumor periphery, the average T1s were $1204 \pm 50$ ms ($n = 13$) before treatment and $1006 \pm 40$ ms ($n = 5$) after treatment. Similarly, for T2, the averages were $77 \pm 2$ ms ($n = 12$) before and $70 \pm 2$ ms ($n = 6$) after treatment. These changes in average T1s and T2s were both determined to be significant ($P = 0.017$ and 0.032, respectively). The average T1s and T2s for normal muscle were $746 \pm 30$ ms and $37 \pm 1$ ms before treatment and $753 \pm 19$ ms and $36 \pm 1$ ms after treatment, respectively. There was no significant change in either value ($P = 0.45$ and 0.35, respectively).

Blood data were available for four patients. After obtaining estimates of the four parameters for each patient, the means ± SE were $0.006592 \pm 0.000035$ s$^{-1}$, $0.00633 \pm 0.00096$ s$^{-1}$, $0.000764 \pm 0.00011$ s$^{-1}$, and $0.00178 \pm 0.000009$ s$^{-1}$ for $A_1$, $A_2$, $B_1$, and $B_2$, respectively.

**Table 2 Relaxation time data**

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"Pre, pretreatment; Post, posttreatment."
and decreased significantly \((P = 0.053)\) and decreased significantly \((P = 0.028)\) 2 weeks after treatment \((Post)\). The distribution volume decreased monotonically and was significantly reduced after treatment \((Post; P = 0.014)\). No significant changes were recorded in muscle, as expected. *, statistical significance.

\(b_1, A_2, \) and \(b_2\) respectively. These means were used in the subsequent two-compartment model analysis.

For perfused tumor periphery, the average PS products before, during, and after treatment were \(0.0015 \pm 0.0002 \text{ s}^{-1}\), \(0.0023 \pm 0.0003 \text{ s}^{-1}\), and \(0.00075 \pm 0.0002 \text{ s}^{-1}\), respectively. With respect to the baseline value \((0.0015 \text{ s}^{-1})\), the midtreatment result \((0.0023 \text{ s}^{-1})\) was just below the level of significance \((P = 0.053)\), a result based only on three cases. However, the final PS product, based upon five cases, was significantly different \((P = 0.028)\). The values for the extracellular contrast agent distribution space \((V_1)\) were also significantly different before and after treatment \((P = 0.014)\). For muscle, no significant change was observed in either parameter, before or after treatment. These results are shown graphically in Fig. 2.

In the 11 MRI studies that were performed within 2 days of MRGlc determination, a positive correlation was observed between tumor MRGlc and PS product, with an \(r^2\) of 0.58 \((P < 0.01)\). No significant correlation was observed for tumor MRGlc and distribution space \((r^2 = 0.04, P = 0.55)\). These data are presented graphically in Fig. 3.

**DISCUSSION**

Here, we used dynamic, T1-weighted MRI to measure tumor vascular physiology in patients with lung cancer before and during the course of therapy. The temporal changes that we observed in PS product and \(V_1\) are consistent with alterations occurring in the underlying microvascular structure.

After treatment, there was a significant decrease in PS product \((P = 0.028)\), presumably reflecting an involution of the vasculature. At the midpoint, the increase we observed in PS product was almost statistically significant \((P = 0.053)\), a circumstance that may be due to the small sample size \((n = 3)\). However, a similar pattern of changes during and after treatment was observed in an experimental R3230AC mammary carcinoma model. There, investigators measured increased PS products 3 days after administration of a single 15- or 30-Gy dose of radiation and 1 day after a 5-Gy dose, both times by using contrast-enhanced MRI \((21, 22)\). When measured serially at 1 and 3 days after a 15-Gy single dose, the PS product was seen to be higher on day 1 than it was on day 3 \((22)\). In this patient study, we observed similar changes in PS product during the course of fractionated tumor irradiation. An observed initial increase in PS product was followed by a decrease 2 weeks after completion of therapy. The overall pattern of behavior of the tumor during treatment could be explained by a number of mechanisms. The initial observation of increased PS product may reflect supervascularization or increased bioenergetic status secondary to decreased cell density and accompanying decrease in interstitial pressure, or a combination of both \((23, 24)\). The posttreatment decrease is most likely due to the development of vascular endothelial damage, radiation-induced vessel occlusion, and stromal reduction, resulting in a decreased PS product and reduced distribution space.

In 11 patients \((10\) before treatment and \(1\) after treatment), we also assessed tumor metabolic status by FDG-PET. This was measured concomitantly with the MRI assessment of PS product and \(V_1\). We observed a significant correlation between glucose metabolism and the PS product \((P < 0.01)\) but not between \(V_1\) and glucose metabolism. These data are consistent with results of experimental studies performed by Gullino *et al.* \((25)\) and Sauer *et al.* \((26)\), who have shown that it is the substrate supply rather than the metabolic demand of tumor cells that limits glucose uptake in tumors. In other words, PS product, which is a parameter of vascularity and permeability, reflects underlying glucose metabolism because generally compromised and anisotropic blood supply in tumors results in oxygen-depleted areas,
Lung Tumor Perfusion and Metabolism

The technique uses contrast-enhanced dynamic MRI, requiring about 45 min of scanner time. The method may provide useful additional data with which to evaluate prognosis and treatment; however, further studies are needed to confirm these preliminary results.

which coincide with both nutrient and energy deprivation and a hostile metabolic microenvironment (9). Furthermore, in a study in which comparison was made between glucose metabolism obtained with FDG-PET and relative tumor blood volume obtained with susceptibility contrast MRI, a positive correlation was determined to exist between the relative blood volume measurement and the uptake of FDG (27).

We did not investigate MRGlc serially. Rather, we set out to study whether or not there was correlation between MRGlc and parameters of vascular physiology in tumor stroma. The demonstration of a positive coefficient of determination ($r^2 = 0.58, P < 0.01$) between the PS product and MRGlc but not between the extracellular contrast agent distribution space and MRGlc, although it is only a preliminary result, nevertheless suggests that MRGlc in NSCLC may, indeed, be limited by substrate supply. If this were confirmed with further studies, it would imply that a viable treatment strategy would be to obliterate vascular supply (28). In this case, MRI could be used to monitor the response to such treatment. Because measures of glucose metabolism have proven to be of significant value in the prognostication and evaluation of malignancy, as well as in determinations of recurrence and dissemination of neoplasia after radiation or chemotherapy, the correlation between MRGlc and PS product seen in our results suggests that tumor vascular status (expressed as PS product) may also represent an important consideration in the evaluation of treatment success or failure and the assessment of tumor aggressiveness.

In summary, we have described a straightforward, clinically applicable method for quantitative measurement of tumor vascular physiology based on PS product and $V_1$. The technique uses contrast-enhanced dynamic MRI, requiring about 45 min of scanner time. The method may provide useful additional data with which to evaluate prognosis and treatment; however, further studies are needed to confirm these preliminary results.

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APPENDIX

$\Delta R1$ in tumor tissue was determined from changes in the longitudinal relaxation rate $R1$. This can be directly calculated when the T1 relaxation time in the presence of contrast agent ($T1_c$) and the T1 relaxation time before the arrival of contrast ($T1_o$) are known. $\Delta R1 = 1/T1_c - 1/T1_o$, $T1_o$ was provided experimentally, and $T1_c$ was obtained through the application of the equation governing the SE experiment:

$$S = M_0 e^{-T1_o (1 - 2e^{-TR/T2} + e^{-TR/T1})}$$  \hspace{1cm} (A1)

where $S$ is the measured signal, $M_0$ is a constant proportional to spin density, $T1$ and $T2$ are the spin-lattice and spin-spin relaxation times, and TR and TE are the repetition and echo times, respectively. In the T1-weighted sequence ($TR = 600 \text{ ms}, TE = 20 \text{ ms}$) that we used, $TR \gg TE$, and Eq. A1 simplifies to a form:

$$S = M_0 e^{-T1_o (1 - e^{-TR/T1})}$$  \hspace{1cm} (A2)

Let $S_o$, $T1_o$, $T2_o$, and $M_0$ be the signal, the T1 relaxation time, the T2 relaxation time, and spin density, respectively, before arrival of the contrast agent ($t = 0$). Let $S$, $T1$, $T2$, and $M$ be these parameters at time $t > 0$, when contrast agent is present. Let us assume that spin density does not change during the experiment; i.e. $M = M_0$. Eq. A2 may now be rewritten to describe the measured signal before (Eq. A3) and after (Eq. A4) the arrival of contrast in a voxel, as follows:

$$S_o = M_o e^{-T1_o (1 - e^{-TR/T1})}$$  \hspace{1cm} (A3)

$$S_o = M_o e^{-T1_o (1 - e^{-TR/T1})}$$  \hspace{1cm} (A4)

Dividing Eq. A3 by Eq. A4 yields:

$$\frac{S_o}{S} = \frac{(1 - e^{-TR/T1})e^{-TR/T1}e^{-T2/T2}}{(1 - e^{-TR/T1})}$$  \hspace{1cm} (A5)

If we express Eq. A5 in terms of $T1$, the following equation results:

$$e^{-TR/T1} = 1 - (S_o/S)(1 - e^{-TR/T1})e^{-T2/T2}$$  \hspace{1cm} (A6)

It has been demonstrated that:

$$\frac{1}{T1} = \frac{1}{T1_o} + r_1[Gd]$$  \hspace{1cm} (A7a)
and

\[
\frac{1}{T2_i} = \frac{1}{T2_0} + r_i^2 [Gd]
\]

(A7b)

where \( r_1 \) and \( r_2 \), respectively, are the longitudinal and transverse relaxivities of Gd in a medium and [Gd] is the concentration of Gd at time \( t \) (29). By combining these expressions, we see that:

\[
\frac{1}{T2_i} - \frac{1}{T2_0} = \frac{r_i}{T1_0} \left[ \frac{1}{T1_i} - \frac{1}{T1_0} \right]
\]

(A8)

Substituting the right side of the expression of Eq. A8 into the T2 term in Eq. A6 eliminates this equation’s reference to T2 and gives:

\[
e^{-\Delta T1/T1} = 1 - \left\{ S_0 \left(1 - e^{-\Delta T1/T1} + e^{-\Delta T1/T1} (T1_i - T1_0) \right) \right\}
\]

(A9)

The ratio of \( r_1 \) and \( r_2 \) is a constant and was independently measured for the scanner used in this study. Eq. A9 was then rearranged to give signal intensity as a function of \( T1_i \):

\[
S_i = \frac{(1 - e^{-\Delta T1/T1}) S_0}{(1 - e^{-\Delta T1/T1}) e^{-\Delta T1/T1} (T1_i - T1_0)}
\]

(A10)

The signal intensity was calculated by assigning discrete values for \( T1_i \) within a range of T1 values extending from 0 (absolute minimum) and \( T1_0 \) (absolute maximum of observed T1 times); a lookup table relating \( S_i \) to \( T1_i \) was generated and used to determine the value of \( T1_i \) for any given \( S_0 \), by interpolation. When \( T1_i \) values are obtained, \( \Delta R1 \) can be calculated.

REFERENCES

Dynamic T1-weighted magnetic resonance imaging and positron emission tomography in patients with lung cancer: correlating vascular physiology with glucose metabolism.
