Advances in Brief

2-[18F]Fluoro-2-deoxyglucose and Glucose Uptake in Malignant Gliomas before and after Radiotherapy: Correlation with Outcome1


Abstract

**Purpose:** To examine whether quantitative 1-[11C]glucose- or 2-[18F]fluoro-2-deoxyglucose (FDG)-positron emission tomography performed before and/or after radiotherapy (RT) of malignant gliomas correlates with treatment outcome. Changes in metabolism between the start and finish of RT, and immediate post-RT studies have received little attention.

**Experimental Design:** Adults with malignant gliomas were imaged within 2 weeks before and/or 2 weeks after RT. Four patients were imaged only before RT, 12 only after RT, and 14 both before and after RT. Each 1-[11C]glucose and FDG study included arterial plasma sampling. Kinetic parameters, glucose metabolic rate (MRGlc), and FDG metabolic rate (MRFDG) were estimated by an optimization program based on a three compartment, four rate constant model. Changes in MRGlc or MRFDG from pre-RT to post-RT were calculated for the 14 patients studied at both times. Overall survival was examined, and survival was computed relative to historical controls in matched prognostic classes.

**Results:** Low pre-RT MRGlc (P < 0.02) or MRFDG (P < 0.03), or an increase from pre- to post-RT in MRGlc (P < 0.004) or MRFDG (P < 0.006) are correlating with longer survival (4 patients still alive). Strikingly, the post-RT studies (n = 26) showed no correlation between MRGlc or MRFDG and survival (P = 0.73 and P = 0.46 respectively).

**Conclusions:** Low MRGlc or MRFDG before RT probably indicates less aggressive disease. An increase in MRGlc or MRFDG from pre- to post-RT in the tumors of patients with longer survival could be because of one or more of the following or other reasons: (a) apoptosis of tumor cells in response to RT requires energy; (b) decreased tumor cell density by the RT leaving normal cells with higher metabolism; or (c) inflammatory cells infiltrate and take up glucose or FDG where tumor cells are dying. Quantitative 1-[11C]glucose or FDG uptake in the early weeks post-RT correlates poorly with survival.

Introduction

PET3 imaging with FDG is being used clinically in the management of malignant gliomas for grading, planning biopsies, and distinguishing recurrent disease from radionecrosis (1–12). In fact, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology has stated that, “cerebral glucose metabolic studies are extremely useful in the management of brain neoplasms (13).” However, from investigations undertaken to date it is not clear whether quantitative FDG-PET has a role in determining the response of malignant gliomas to therapy or how accurately FDG-PET studies after, rather than preceding, RT predict long-term treatment outcome (6, 14–19).

In previous reports we presented measurements of metabolic rates in gliomas and normal brain determined with PET imaging of FDG as well as 1-[11C]glucose (20, 21). Our approach involved dynamic PET imaging of the kinetic behavior of the two tracers. We used compartmental mathematical models designed for the two tracers individually to calculate the MRGlc and the MRFDG for glioma and normal brain ROIs. From these, we determined the regional lumped constant for FDG as the ratio MRFDG/MRGlc. The two tracers, FDG and 1-[11C]glucose, behave differently in transport, phosphorylation, and glycolysis. Although FDG uptake is proportional to the glucose metabolic rate, an accurate MRGlc cannot be calculated from FDG data without an accurate lumped constant. Nevertheless, it is important to emphasize that MRFDG and MRGlc individually and separately are valid quantitative assessments of metabolism although they are not identical. Quantitation of

1 The abbreviations used are: PET, positron emission tomography; DG, deoxyglucose; FDG, 2-[18F]fluoro-2-deoxyglucose; MR, metabolic rate; Glc, glucose; RT, radiotherapy; ROI, region of interest; BCNU, 1,3-bis(2-chloroethyl)-1-nitrosourea; HPLC, high-performance liquid chromatography; CT, computed tomography; MRI, magnetic resonance imaging; TAC, time-activity curve; RTOG, Radiation Therapy Oncology Group.
FDG- and Glucose-PET in Gliomas before and after RT

showed no correlation whatsoever with survival.

Materials and Methods

Patients. Thirty patients were studied, all with supratentorial malignant gliomas and all within 2 weeks before and/or 1–3 weeks after RT, except for 1 post-RT patient studied 6 weeks after RT. Fourteen patients were imaged both before and after RT, 4 only before RT and 12 only after RT. Two cases were multicentric, and 5 had bilateral tumors with involvement of the corpus callosum. Table 1 shows additional details. Twenty-four patients received 59.4 Gy conformal external beam RT in 33 fractions at 1.8 Gy/fraction. Five patients received different fractionation and total dose prescriptions between 50 and 67.8 Gy, and 1 patient in the pre-RT group received only 3.6 Gy in 2 fractions before he died. The majority of patients received one or more chemotherapy regimes after RT. The majority of these treatments were nitrosourea-based with procarbazine/1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea/vincristine, BCNU/cisplatin, or BCNU alone. All of the patients signed informed consent.

Radiopharmaceutical Synthesis. 2-[18F]Fluoro-2-deoxy-
\( \alpha \)-glucose was synthesized by the method of Hamacher et al. (26). The radioactive and chemical purity of the product was measured by analytical HPLC using an aminopropyl normal phase column (Alltech and Associates, Inc.) with a CH\(_3\)CN:H\(_2\)O (93:7 v/v) mobile phase, and refractive index and radioactivity detection of the effluent. Silica gel TLC with a CH\(_3\)CN:H\(_2\)O (95:5 v/v) mobile phase was also used to assess radiochemical purity, which was consistently >99% for both methods.

The synthesis of 1-[\(^{11}\text{C}\)]glucose (D isomer) followed the method of Shiue and Wolf (27, 28) as modified recently by Dence et al. (29). Typically, 1.7 Ci of [\(^{11}\text{C}\)]cyanide at end of bombardment yielded 35–40 mCi of 1-[\(^{11}\text{C}\)]glucose at the end of synthesis. The glucose was separated from mannose and any other impurities using an Aminex HPX-87P, 30 cm \( \times \) 7.8 mm, HPLC column (Bio-Rad Laboratories) at 70°C and eluted with sterile USP water. The radiochemical and chemical purity of the product was measured by analytical HPLC using another Aminex HPX-87P column at 70°C eluted with deionized water, and with refractive index and radioactivity detection of the effluent.

PET Devices and Procedures. Two different PET systems were used over the course of this study. In all of the cases the pre- and post-RT scans for a given patient used the same tomograph. The first PET scans were obtained on a time-of-flight PETT Electronics SP-3000 device containing four rings of BaF\(_2\) detectors with 320 crystals in each ring (30–32). Axial collimation of photons in the tomograph allowed direct and cross-plane data to be collected, yielding seven image planes. This PET device acquired emission data in list mode format with timing markers that allowed selection of time binning of data after acquisition. The limiting resolution at the center of the field of view was 5 mm in the transaxial plane and 7.5 or 11 mm in the axial plane. The interplane distance was 15 mm.

The second scanner was a General Electric Advance whole body positron emission tomograph providing 35 image planes of data over a 15 cm axial field of view (33–35). The tomograph includes 18 rings of bismuth germanate oxide detectors with 672 crystals/ring. The system sensitivity in two-dimensional mode (axial septa in place) is 135 kcps/mCi/ml. The limiting transaxial resolution is 4.1 mm with a slice thickness of 4 mm.

Imaging Procedure. Patients fasted for at least 9 h before the scans. Before the PET scans all of the patients had either X-ray CT or MRI scans without and with contrast injections. From the scout images of these studies axial image planes were selected for the PET scans to correspond with the planes containing the greatest tumor areas. After head immobilization was secured, patients were positioned in the tomograph. Alignment of the axial PET scan planes with those selected from the CT or MRI images was accomplished in the SP3000 by using a lateral skull radiograph overlain with grid lines that corresponded to the planes of the tomograph. Patient and tomograph position and angulation were adjusted so that the PET tomograph planes corresponded to the desired CT or MRI axial planes. A system of laser beams then allowed for advancing the head of the patient into the tomograph to maintain the exact positioning in relation to the rings. Head positioning in the General Electric Advance tomograph was similar except no scout films were required.

An attenuation scan was obtained with a rotating sector source of \(^{68}\text{Ge}\) around the brain and tumor-containing region. While this was underway, an i.v. line was introduced for isotope injection, and a wrist radial artery line was inserted for plasma sampling for the isotope TAC. The arterial line was connected...
to an automated blood sampler, which could be preprogrammed for the desired sampling sequence (36). Before scanning and isotope injection a blood glucose level was drawn and analyzed by a Glucose Analyzer II (Beckman Instruments, Fullerton, CA). This was repeated several times after isotope injection.

After completion of the transmission/attenuation scans and placement of the vascular accesses, tomograph emission scan acquisition was started 1 min before injection of radioactive tracers. Calibration of the tomograph for μCi/ml was accomplished by imaging a 10-cm diameter cylinder of known activity, as determined by a dose calibrator (Capintec, Ramsey, NJ), under similar conditions as the patient imaging protocol (30 cm field of view; 6 mm Hanning filter). For some studies, calibration was performed with the patient in the tomograph during the patient imaging procedure.

After a 1-min emission scan, 1-[11C]glucose (typically 20 mCi) in 10 or 20 ml of sterile normal saline was injected i.v. over 1 or 2 min. 1-[11C]Glucose imaging data were collected and reconstructed in time bins as follows: 4 of 20 s; 4 of 40 s; 4 of 60 s; 4 of 180 s; and 14 of 5-min duration.

Arterial blood was sampled at a frequency similar to the dynamic image acquisition. The 1-ml blood samples were centrifuged, and then 0.5 ml of plasma was pipetted and counted for total plasma radioactivity using a Cobra multichannel gamma counter (Packard Corp., Chicago, IL). Three 1-ml samples of the calibration cylinder were also obtained for well counting, which allowed us to convert sample cpm/ml to μCi/ml.

A FDG study followed each 1-[11C]glucose study. Typically we injected 7–10 mCi of FDG in 10 ml of normal saline over 1 or 2 min. Emission data and blood samples were collected as described above for 1-[11C]glucose.

Image Analysis. ROIs in the gliomas were selected to include the contrast-enhancing volume and adjacent nonenhancing tumor as defined by MRI or CT images. They were drawn from the integrated FDG images while referencing MRI or CT images. Generally ROIs were placed on the FDG uptake scans (30–60 min), and cysts and resection cavities were avoided. For nonenhancing tumors the region of biopsy and T2 signal-enhancing areas were selected conservatively. The model described below used the TACs from these regions and the plasma input functions both expressed as μCi/ml.

Glioma ROI TACs were analyzed by the three compartment models shown in Fig. 1. The glucose model is similar to that described by Blomqvist et al. (37); the FDG model is that described by Phelps et al. (38) as a modification of Sokoloff’s model (39) for 2-DG. The program incorporating these models used the plasma TACs as input functions. The tissue data were not decay corrected because the models were formulated to account for this. Plasma data were corrected to time of sampling, not time of injection. The 1-[11C]glucose plasma data were corrected for metabolites (CO2 and lactate), assuming linear accumulation of metabolites such that 18% of plasma activity at 60 min could be ascribed to metabolites in the same fashion as reported by Spence et al. and Blomqvist et al. (21, 37). It was assumed that the metabolites remained in the vascular space and were not taken up into tissue.

The predicted tissue TACs were calculated using numeric integration of the differential equations for each model. The tail of the 1-[11C]glucose activity was appropriately added to the FDG activity, because the FDG was injected second. There were a total of 11 variable parameters: K1, k2, k3, and k4 for 1-[11C]glucose; K1, k2, k3, and k4 for FDG; a delay term to shift the tissue activity relative to the plasma curve for both tracers; and a blood volume term to account for activity in large blood vessels. The best fit of the models to a given data set was achieved using an established nonlinear weighted least squares algorithm (40). The algorithm minimized the sums of the squares of the differences between the model output and the tissue data, weighted proportionally to the inverse square root of the count of each data point. With this optimization program, the kinetic rate constants were estimated for 1-[11C]glucose and FDG for ROI TACs. The metabolic rate for each hexose was calculated with their kinetic rate constants and the plasma glucose concentration (Cp) as: MR = Cp · (K1 · k3)/k2 + k3.

Statistics. Survival was determined from the date of diagnosis and calculated by two approaches. The first was simply months from diagnosis. The second was based on the historical data reported by the RTOG (25). Patients were individually placed in the appropriate RTOG classes by age, neurological status, and histology. The increase (or decrease) in survival (ΔS) relative to the appropriate RTOG class was calculated as: ΔS = patient actual survival/median survival for their RTOG class.

Data were compared by regression and univariate analysis with the Wilcoxon test. For both hexoses, Glc and FDG, the patients were ranked by MR pre-RT, the MR post-RT/MR pre-RT ratio, or MR post-RT; then survival or ΔS in the higher 50% was compared with the lower 50%.

The relation between the response (time to death) and the measured prognostic factors was evaluated using a standard statistical analysis based on the Cox proportional hazards model (41) as implemented in S-plus (Math Soft Inc., Cambridge, MA). This analysis permits the examination of the influence on survival of the MRGlc and MRFDG while controlling for the impact of tumor histology, RTOG prognostic group, treatment procedures, and other potentially relevant patient information such as age and sex. Both MRGlc and MRFDG were considered as prognostic indicators of survival. The Cox model allows us to assess the percentage change in the risk of a death associated with increasing the MR value by one unit, while keeping all of the other variables (e.g., histology and RTOG prognostic group).
fixed. We should emphasize that this is a retrospective analysis, and the findings presented would need to be confirmed with a proper prospective study.

Results

The complete results are shown in Table 2. The results from the regression and univariate analyses are shown in Tables 3 and 4, and Figs. 2–5. With survival assessed in months after diagnosis or ΔS, higher pre-RT MRGlc or MRFDG correlated with shorter survival; that is, lower MRGlc or MRFDG before RT indicated longer survival (Figs. 2 and 4). Significance is indicated on the graphs.

Our chief hypothesis was that tumors of patients who responded to treatment would show reduced metabolism after RT, whereas the tumors of patients who did not respond would show unchanged or increased metabolic rates. The results of the studies performed both before and after RT clearly did not support this hypothesis. Unexpectedly, an increase in metabolism, measured with either 1-[11C]glucose or FDG, from the beginning of RT to the end, correlated with longer survival (Tables 3 and 4; Figs. 3 and 4). A decrease in metabolism was associated with shorter survival.

Also, somewhat unexpected were the results that neither MRGlc nor MRFDG measured shortly after RT correlated with survival examined as months after diagnosis or ΔS (Tables 3 and 4; Fig. 5).

These results from regression and univariate analyses suggest various relationships between survival and prognostic indicators. A more complete understanding is provided by the

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**Table 2** Additional clinical data, survival measurements, and outcome of metabolic studies

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<td>16.40</td>
<td>0.37</td>
<td>M</td>
<td>GM 70</td>
<td>Y</td>
<td>N</td>
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<th>Table 3</th>
<th>Regression statistics</th>
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<td></td>
<td>Survival</td>
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<td>Regr. Significance (P)</td>
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<td>MRGlc</td>
<td>Pre</td>
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a (μmol/100 g/min).
b Karnovsky performance score.
c Chemotherapy.
d Dexamethasone.
In all of the multivariate analyses (pre-RT, post-RT/pre-RT, and post-RT) histology emerged as significant as expected ($P/\text{H9005} 0.038, 0.033, \text{and} 0.027$, respectively), because glioblastoma multiforme yields a shorter survival than anaplastic astrocytoma. In none of the three analyses did the RTOG prognostic grouping reach significance, a reflection of the small sample size. The analysis of the post-RT data showed that chemotherapy was associated with a 65% lower risk of death ($P/\text{H9005} 0.025$).

The multivariate analysis of the pre-RT assessments of MRGlnc and MRFDG showed that MRFDG did not perform as well as MRGlnc. Increasing the pre-RT MRGlnc by 1 unit was associated with a 47% increase in the risk of death ($P/\text{H9005} 0.002$), a remarkable finding given the small sample size. This corroborated the significance of the pre-RT MRGlnc shown by the regression and univariate approaches above.

The post-RT/pre-RT multivariate analysis showed a significant relationship between the change in MRGlnc and survival. A 10% decrease in the MRGlnc was associated with a 75% increase, not decrease, in the risk of death ($P = 0.038$), i.e., an increase in metabolism, measured with $1\text{-}[^{11}\text{C}]\text{glucose}$, from the beginning of RT to the end correlated with longer survival.

In the post-RT multivariate analysis a relationship was suggested between MRFDG and survival. That is, a 1-unit increase in MRFDG reduced the risk of death by 10%. However, this effect failed to reach significance ($P = 0.07$).

### Discussion

This response monitoring study used the most quantitative analytical imaging methods available, namely, dynamic imaging and full compartmental modeling of the data as recommended in
Metabolic Studies at the Time of Recurrence. Two FDG-PET studies looked at malignant glioma metabolism specifically at the time of clinical and/or radiographic recurrence (8, 43). The PET scans in the 50 patients reported by Janus et al. (8) followed RT and chemotherapy by several months. Among these patients there was significant variability in histology, RT parameters, chemotherapy, correlation of imaging findings with tissue sampling, and timing of the PET studies, which were only analyzed visually. Thirty patients did not have tissue sampling at the time of suspicion of recurrence. Decreased uptake of FDG tended to correlate with prolonged survival whereas increased uptake of FDG did not. The overall conclusion from this study was that “FDG-PET for evaluation of patients with possible recurrent tumors requires more study.”

Barker et al. (43) evaluated the prognostic value of FDG-PET in 55 patients with malignant glioma suspected of having tumor progression or radionecrosis by MRI findings. All of the patients had received previous initial surgery and radiation therapy. Forty patients had grade 4 and 15 had grade 3 tumors. The median time of the PET study was 13 months after initial diagnosis, and survival was measured from the time of the first PET scan. The FDG-PET scans were assessed visually on a four-level scale: 0 = no visible uptake; 1 = uptake visible but less than adjacent cortex; 2 = uptake greater than adjacent but less than contralateral cortex; and 3 = uptake greater than contralateral cortex. In univariate and in multivariate analysis, the FDG-PET score was a significant predictor of survival, demonstrating that FDG-PET scanning at the time of suspected recurrence had prognostic value.

Metabolic Studies Both before and after Treatment. The most striking result from our investigation is the longer survival associated with increased FDG or glucose metabolism from the beginning to the end of RT. Several groups have examined the change in FDG metabolism in response to therapy, but none looked exclusively at RT in gliomas (17, 18, 44–46). Results similar to ours but involving chemotherapy were reported for 10 patients with recurrent glioblastoma studied with quantitative FDG-PET before and after a single cycle of BCNU (47). The first PET scan was 4 h before the first of two successive daily doses of BCNU of 120 mg/M². The second scan was 24 h after the second dose. The change in metabolic rate was correlated with survival. The changes in the metabolic rates ranged from a 49% increase to a 25% decrease. There was a significant positive correlation between survival and glucose metabolism that increased after BCNU (P < 0.002). An increase in metabolism in the tumors predicted longer survival. These findings showing an early increase in metabolism in response to chemotherapy agree with our results after RT. De Witte et al. (47) speculated that this chemotherapy response resulted from predominant killing of low energy-consuming cells or stimulation of quiescent cells, either tumor or normal, to become more active metabolically. An additional potential explanation is that therapy destroys tumor cells leading to an uncrowding effect that allows more active metabolism as imaged by PET in surviving normal elements, i.e., within a volume of tissue, the ratio and density of normal cells to tumor cells improves leading to increased regional metabolism.

Aside from gliomas, Maruyama et al. (48) presented 19 brain tumors (17 metastatic, 2 primary, 1 meningioma, and 1...
central neurocytoma) in 8 patients who had stereotactic radiosurgery from 24 to 32 Gy and were studied with FDG-PET within a week before and 4–5 h after the radiosurgery. A net influx constant was calculated using graphical analysis, and the ratio of tumor:ipsilateral cerebellum was used as an index of FDG uptake by the tumor. All of the tumors except the neurocytoma showed an increase in the influx ratio. The average increase was 29.7% ± 14.0%, significantly higher than seen in nonirradiated tumors. This correlated with a decrease in the size of the metastatic tumors seen at later follow-up with CT or MRI.

Biological Reasons for Our Results. Potential reasons to explain how therapy could lead to increased metabolism and relatively better outcome are suggested from tissue culture and animal tumor experiments. Haberkorn et al. (49–52) and others have reported several studies of tumors exposed to chemotherapy in vitro or in vivo in which FDG or 18F-DG uptake increased after treatment: rat prostate carcinoma cells treated with gemcitabine; MCF7 human breast carcinoma treated with hexadecylphosphocholine; rat osteosarcoma treated with cisplatin and cis-cyclohexane-1,2-diamine-[nitrilo tris(methyl phosphonato)](2-)O1,N1]platinum(II); and SW620 colonic tumor cells treated with Tomudex, a thymidylate synthase inhibitor (49–53). Increased transport was considered the leading explanation for this increased uptake.

Other studies have considered the effect of RT in vitro on the uptake of FDG. Higashi et al. (54) measured the uptake of FDG in a human ovarian carcinoma cell line, HTB77IP3, exposed to 30 Gy by irradiation. FDG uptake per tissue culture was increased after irradiation despite a decline of 6.25-fold in viable cells. FDG uptake per cell increased 9.8-fold from Day 0 to Day 12 after irradiation. It was suggested that the increased uptake may have been a result of formation of giant cells and possibly radiation repair processes that required energy. Although the single radiation dose was very high, these data suggested that early assessment of response to RT by FDG-PET could be complicated, because early radiation-induced cell death was not associated with an early decline in tumor cell uptake of FDG.

A study of DG uptake in LS180 human colon adenocarcinoma cells treated with X-irradiation was reported recently by Fujibayashi et al. (55). DG uptake increased as much as 140% at 3 h after 30 Gy of RT. There was a similar but lesser effect at 3 Gy. Actinomycin D, cycloheximide, and brefeldin all individually suppressed the increased accumulation to the baseline level, indicating that mRNA synthesis, protein synthesis, and P-glycoprotein transport processes, respectively, were involved to some extent. GLUT 1 mRNA and hexokinase activity were increased in association with the increased DG uptake. These data were consistent with a transient elevation of glucose metabolism that resulted from altered levels of gene expression. In their words, “enhancement of accumulation of DG immediately after irradiation is considered to be a marker of cellular response, but not a marker of cellular damage.”

In conclusion, there are several results of this report. First, consistent with previous studies, low MRFDG or MRGlc pre-RT indicates less aggressive disease; conversely, high MRFDG or MRGlc signifies more aggressive disease and shorter survival. Second, increase in MRFDG or MRGlc from pre- to post-RT clearly correlates with longer, not shorter, survival. This unexpected result could be because of decreasing tumor cell density leaving normal cells with higher metabolism, infiltration by inflammatory cells that take up 11C-glucose or FDG where tumor cells are dying, or energy consumption for apoptosis of tumor cells in response to RT. Finally, immediate post-RT quantitative PET with either FDG or 11C-glucose does not correlate with length of survival.

Our quantitative approach would be difficult and time consuming to implement as a routine clinical study with two tracers, arterial sampling, dynamic imaging, and modeling. Single tracer studies, obviously FDG and not 11C-glucose, and semiquantitative assessments with standard uptake value would be more feasible. Our data are being additionally analyzed to clarify how well standard uptake value measurements correlate with prognosis and predict survival in the malignant glioma patient population.

References


2-[\textsuperscript{18}F]Fluoro-2-deoxyglucose and Glucose Uptake in Malignant Gliomas before and after Radiotherapy: Correlation with Outcome

Alexander M. Spence, Mark Muzi, Michael M. Graham, et al.