Published in final edited form as:

Mol Imaging Biol. 2009 ; 11(5): 343–355. doi:10.1007/s11307-009-0215-2.

NCI-Sponsored Trial for the Evaluation of Safety and Preliminary Efficacy of 3'-Deoxy-3'-[¹⁸F] fluorothymidine (FLT) as a Marker of Proliferation in Patients with Recurrent Gliomas: Preliminary Efficacy Studies

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Abstract

Purpose—3'-Deoxy-3'-[¹⁸F]fluorothymidine ([¹⁸F]FLT) is being developed for imaging cellular proliferation. The goals were to explore the capacity of FLT-positron emission tomography (PET) to distinguish between recurrence and radionecrosis in gliomas and compare the results to those obtained with 2-fluoro-2-deoxy-D-glucose (FDG).

Procedures—Fifteen patients with tumor recurrence and four with radionecrosis, determined by clinical course and magnetic resonance imaging results, were studied by dynamic [¹⁸F]FLT-PET with arterial blood sampling. A two-tissue compartment four-rate constant model was used to determine metabolic flux (K_{FLT}), blood to tissue transport (K_1), and phosphorylation (k_3). FDG-PET scans were obtained 75–90 min postinjection.

Results— K_{FLT} and k_3 , but not K_1 or k_3/k_2+k_3 , reached significance for separating the recurrence from radionecrosis groups. Standardized uptake value and visual analyses of FLT or FDG images did not reach significance.

Conclusions— K_{FLT} (flux) appears to distinguish recurrence from radionecrosis better than other parameters, FLT and FDG semiquantitative approaches, or visual analysis of images of either tracer.

Keywords

3'-[¹⁸F]fluoro-3'-deoxythymidine; FLT; Fluorothymidine; Positron emission tomography (PET); Glioma; Radionecrosis; Proliferation imaging

Introduction

3'-Deoxy-3'-[¹⁸F]fluorothymidine, [¹⁸F]FLT, is a radio-labeled structural analog of the DNA constituent thymidine that is being developed as an imaging agent to assess cellular proliferation with positron emission tomography (PET). Although FLT is not incorporated into DNA, it is trapped in the cell due to phosphorylation by thymidine kinase-1, a cytosolic enzyme of the salvage pathway [1]. As such, it has the potential to image tumor proliferation in proportion to DNA synthesis via the salvage pathway. In the normal brain, FLT is not taken up because there is essentially no proliferative activity and little if any exchange across an intact blood-brain barrier. This gives FLT a distinct advantage for imaging tumors compared to 2-[¹⁸F] fluoro-2-deoxy-D-glucose ([¹⁸F]FDG) as it should only be concentrated in proliferating tumor cells but not in normal brain. It may also allow for improved differentiation of radionecrosis from recurrence after therapy as well as shed light on the newly recognized problem of progression vs pseudoprogression in the immediate months following standard radiotherapy plus concurrent temozolomide chemotherapy [2, 3]. The intent of the present investigation was to explore preliminarily the capacity of [¹⁸F]FLT PET to distinguish radionecrosis in gliomas from recurrent disease and compare it to FDG.

Materials and Methods

Patients

Nineteen adult patients were included in the analysis (13 males, six females, age range 19, 67): four glioblastoma multiforme, two gliosarcoma, six anaplastic astrocytoma, three anaplastic oligodendroglioma, one anaplastic pleomorphic xanthoastrocytoma, and three grade 2 oligodendroglioma (Table 1). Twelve of these patients were included in the safety evaluation of FLT [4], and six were included in a prior report [5]. All tumors were graded by the World Health Organization scheme. All were required to have a glioma and to have had previous radiotherapy with or without chemotherapy. Patients could not enroll in this study if there were clinically significant signs of uncal herniation, such as acute pupillary enlargement, rapidly developing motor changes (over hours), or rapidly decreasing level of consciousness. Female patients were required to be postmenopausal for a minimum of 1 year or be surgically sterile, or on a reliable method of birth control for a minimum of 1 month prior to the PET scans. Negative pregnancy test was required for reproductively capable women.

Patients were tested for hematologic, liver, and renal function prior to and after the FLT scans [4]. All patients were also required to undergo a physical and complete neurological examination before and after the FLT scans.

Each patient had magnetic resonance imaging (MRI) in a 1.5-T device without and with contrast enhancement within 14 days of FLT-PET imaging. All patients except two had a FDG-PET scan within 4 days of their FLT-PET scan; one had none and for another, the interval was 25 days.

Patients 1 through 4 were judged to have radionecrosis because serial MRI studies and clinical examinations preceding and following the PET scans from 16 to 31 months were

stable or improved (Table 1). Ten patients were deemed to be recurrence due to subsequent progression to death within 3 to 16 months accompanied by both clinical deterioration and MRI worsening. In four patients, still living, recurrence was similarly determined by progressively worsening clinical and MRI findings. Surgical resection proved recurrence in patient 15.

The placement of cases into either the radionecrosis or recurrence categories assumed that monitoring changes in clinical findings and MRI examinations, or lack thereof, through the course of the disease allowed this distinction to be made. In this and other publications, radionecrosis was diagnosed when there was no worsening of clinical and MRI examinations over months to years in the absence of any further treatment interventions [6–13]. Recurrence was diagnosed when clinical deterioration progressed along with worsening MRI findings ending in death. It is important to emphasize that the clinical and MRI findings both before and after the FLT studies were used for determining the categories. The separation into categories was not based on the FLT-PET results.

These studies were conducted under an investigational new drug (IND) for [^{18}F]FLT held by the Cancer Imaging Program of the National Cancer Institute. The studies were approved by the University of Washington Human Subjects Committee, Fred Hutchinson Cancer Research Center IRB, and the University of Washington Radiation Safety Committee. Each patient signed informed consent.

FLT Synthesis

3'-Deoxy-3'-[^{18}F]fluorothymidine was synthesized as reported previously [4, 14]. Its radiochemical purity was >98% and the specific activity was such that patients received injection with not more than 1 μg carrier FLT, although the IND allows injections as high as 6.1 μg .

FDG Synthesis

2-[^{18}F]Fluoro-2-deoxy-D-glucose was synthesized by the method of Hamacher et al. [15] using the Nuclear Interface FX box technology. The radiochemical and chemical purity of the product was assayed by analytical high-performance liquid chromatography and thin layer chromatography and was consistently >99% by both assays. The measured specific activity of the FDG was >740 MBq/mmol at end of synthesis.

MRI Imaging Protocol

Standard brain MR imaging was performed with a 1.5-T Signa (GE Medical Systems, Waukesha, WI, USA) whole-body scanner with a standard head coil. The protocol for all subjects included a T1-weighted sequence acquired in the transverse imaging plane before and after administration of intravenous gadolinium (Gd). Axial T2, fluid-attenuated inversion recovery, and coronal T1 plus Gd sequences were included. All images were obtained at 5-mm section thickness with no gap. MRI images were coregistered to sum PET images with a method based on mutual information criteria [16].

FLT Imaging Protocol

This followed exactly the procedure reported previously [4, 5]. Briefly, [^{18}F]FLT doses were calculated based on patient weight (2.7 MBq/kg, 0.07 mCi/kg) with a maximum dose of 185 MBq (5 mCi). [^{18}F]FLT was administered i.v. over 1 min using an infusion pump. Dynamic PET acquisition was carried out for 90–120 min. A radial artery line was inserted to sample arterial blood for determination of radioactivity and plasma metabolite analysis. Arterial samples were obtained at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, and 90 ± 120 min using an automated blood sampler [17]. Three patients had hand-drawn arterial samples at the following time points: 1, 2, 3, 5, 10, 15, 20, 30, 45, 60, 90, 120 min.

For each arterial blood sample, 0.2 mL plasma was assayed for radioactivity using a COBRA gamma counter (Packard Corp, Meriden, CT, USA). Since FLT has negligible serum protein binding [18], all of the activity associated with [^{18}F]FLT in blood was assumed to be available for tissue uptake. An aliquot (0.4 mL) of the plasma from eight arterial samples (5, 10, 15, 20, 30, 45, 60, and 90 min) was assayed for the relative amount of FLT and FLT-glucuronide as previously described [19]. The fraction of total activity present as [^{18}F]FLT in each blood sample was fitted to a mono-exponential curve to provide a continuous function describing the fraction of the total plasma activity associated with [^{18}F] FLT vs metabolites [19].

The PET studies were performed on a GE Advance PET tomograph (GE Medical Systems, Waukesha, WI, USA) providing 35 image planes over a 15-cm axial field of view with a 4.25-mm slice spacing [20]. Images were acquired in 3D mode with the following dynamic sequence: 10×10 , 4×20 , 3×40 s, 3×1 , 5×2 , 4×3 , and 12×5 or 18×5 min time frames for a total duration of 90 or 120 min. After correction for scatter and random coincidences, images were reconstructed by the method of 3D reprojection using 4.5 mm radial and 6 mm axial smoothing filters (Hanning) resulting in approximately isotropic image resolution of about 6 mm [21].

FLT PET Image Analysis

Regions of interest (ROIs) for tumor, brain, gray matter, and white matter were constructed on coregistered MRI T1+Gd or T2 images and transferred to FLT images summed between 30 and 60 min, an interval when transport of the radiotracer from blood to tissue is predominantly unidirectional. Tumor regions were placed on all of the planes containing portions of the lesion as indicated from the coregistered MRI T1+Gd or T2 images. The tumor ROIs were further constricted in size to include regions perimeterized by 50% of the maximum pixel of the entire tumor volume from the FLT summed image set. The ROIs from contiguous slices were combined to create volumes of interest (VOI) for each tissue type by means of AliceTM image processing software (HIPG, Boulder, CO, USA). VOIs were applied to the dynamic image set for data extraction.

Qualitative (visual) assessment of level of uptake in brain tumor and normal brain was performed by two experienced independent nuclear medicine specialists from viewing the 15–60- and 60–90-min uptake images and MR images. The coregistered MRI scans were

available to the readers as they examined the FLT and FDG scans. The [^{18}F]FLT-PET studies were interpreted as to confidence of tumor recurrence: 5=definite recurrence, 4=possibly, 3=equivocal, 2=probably necrosis, and 1=definite radiation necrosis. Visual assessment of FLT images preceded visual reading of FDG scans detailed below.

Semiquantitative assessment of [^{18}F]FLT uptake was performed by calculating the standardized uptake value (SUV) and SUV_{max} on the 15–60- and 60–90-min image sets using standard SUV methodology corrected for decay. The SUV_{max} was obtained for the maximum pixel value within the tumor ROI. [^{18}F]FLT tumor uptake was normalized for body surface area (BSA). The tumor radiotracer concentration $C(\text{T})$ (MBq/L) was determined from the PET image:

$\text{SUV}_{\text{bsa}} = C(\text{T}) / \text{injected dose} / \text{BSA}$ where $\text{BSA} = \text{weight (0.425)} \times \text{height (0.725)} \times 0.00718$. Ratios of the SUV or SUV_{max} of tumor to that of cortex (T/C) or that of white matter (T/WM) were calculated.

Additionally, model-independent estimates of FLT uptake were assessed by a modified graphical analysis (GA) approach which corrects for blood metabolites [22]. The GA determination of flux may be valid for a short interval following injection, when the assumption of unidirectional transfer of FLT from blood to tissue is applicable [23]. Due to restricted transport of FLT, tissue pools of precursor require a greater time to stabilize with respect to blood delivery. Therefore, 30 and 60 min were chosen as the time boundaries for the linear fit in GA after examination of linearity in the contrast enhancing tumor regions. This method assumes that phosphorylated FLT nucleotides are completely retained in the tissue, an assumption that has yet to be validated *in vivo* and is not supported by cell culture experiments [1].

For quantitative analysis of FLT imaging data, we applied the kinetic model reported previously (Fig. 1) [5]. The transfer from blood into tissue across the BBB is represented by K_1 , while the return of nonphosphorylated FLT from a tissue compartment back to blood is represented by k_2 . The metabolic trapping of FLT through phosphorylation to produce FLT nucleotides is represented by k_3 , which is the rate limiting step for the retention of FLT in tissue. The nucleotides of FLT can leave the imaging region either by dephosphorylation back to FLT or through nucleotide transporters [1, 24]. The loss of image signal through these processes is described by k_4 .

FLT flux, K_{FLT} , was estimated by compartmental modeling using parameters derived from fitting the FLT input function and the total blood activity curve to the tissue time–activity curve (TAC) data. The FLT flux constant is determined by the product of the rates of FLT using the following formula [19]:

$$K_{\text{FLT}} = \frac{K_1 k_3}{k_2 + k_3} = \frac{K_1 k_3}{(K_1/V_d) + k_3} \quad (1)$$

where V_d is the early distribution volume for the reversible compartment, given by K_1/k_2 , similar to prior reports [19, 25]. The key parameters for describing FLT uptake in tissue are the flux constant, K_{FLT} , and the FLT blood–tissue transport rate, K_1 .

The regional VOI activity curves, the metabolite-corrected arterial input curve, and the total arterial activity curve were fitted to the FLT compartmental model using the weighted Levenberg–Marquart least squares minimization algorithm as implemented in a software package designed for PET data analysis (PMOD v2.85, PMOD group, Zurich, Switzerland). In the model optimization process, the residuals were weighted by the inverse variance of the total count rate in each frame of data, based on the standard deviation of the total uncorrected counts and the duration of the time frame [26]. Model parameters were estimated by minimizing the weighted residual sum of the square error between the model solution and the PET measurement.

Parametric image maps of each of the parameters were generated by mixture analysis [26–28] with the same dynamic image data, blood input functions, and two-tissue compartmental model used for the tissue TAC analysis. The tissue VOIs used to generate tissue TACs constructed on PET and MRI images were applied to the parametric image maps to determine the extent of FLT flux relative to Gd enhancement on MRI images. They were also used to determine the precision and bias of the parametric image values relative to modeling analysis of tissue TACs by means of the same imaging data and compartmental model.

FDG Imaging Protocol

[¹⁸F]FDG was injected i.v. (3.7 MBq/kg or 0.1 mCi/kg) with patients in a fasting state. Patients returned 45 min postinjection and were positioned in the tomograph in a dimly lit room. A transmission scan was obtained for 25 min followed by a 5-min 2D emission scan to correct the transmission data for patient radioactivity. A 15-min 3D emission scan was then acquired 75 min after the FDG injection. The attenuation-corrected 3D emission scan was reconstructed in transverse sections for interpretation.

FDG Image Analysis

Qualitative (visual) assessment of level of uptake in brain tumor and normal brain was performed by two independent nuclear medicine specialists from the 75–90-min uptake images and MR images. The [¹⁸F]FDG-PET studies were interpreted as to confidence of tumor recurrence: 5=definite recurrence, 4=possibly, 3=equivocal, 2=probably necrosis, and 1=definite radiation necrosis.

Semiquantitative assessment of [¹⁸F]FDG uptake was performed as described above by calculating the SUV and SUV_{max} on the 75–90-min image sets using standard SUV methodology corrected for decay. The SUV_{max} was obtained for the maximum pixel value within the tumor ROI. Ratios of the SUV or SUV_{max} of tumor to that of cortex (T/C) or that of white matter (T/WM) were calculated.

Statistics

Differences between patients with recurrence and those with radionecrosis were assessed with Student's *t* tests, two sample, assuming unequal variances. The more robust Wilcoxon rank-sum test with multiple comparison adjustment was applied with a level of 0.002 considered significant.

Results

Examples of images representing recurrence and radionecrosis are presented in Figs. 2 and 3. Patient 17 with recurrence shown in Fig. 2 progressed continuously to death with worsening clinical and MRI measures from 2 months before to 6 months after the FLT study despite additional treatment attempts. Patient 1 with radionecrosis shown in Fig. 3 was stable clinically and by MRI assessments for 24 months prior to the FLT-PET. His MRI scans up to 36 months after the FLT-PET showed changes of mildly decreasing contrast enhancement while his dexamethasone dose was progressively tapered. His MR perfusion scan showed iso- or diminished perfusion suggesting the changes were related to radiation rather than progressing tumor.

Table 2 shows the FLT-PET results for every patient. Patients 1 through 4 represent the radionecrosis cases and the remainders were recurrences. From these results, the parameters, K_{FLT} , K_1 , and k_3 , separated the recurrence from the radionecrosis groups by the t tests (Table 3; Fig. 4). However, by the Wilcoxon tests, only K_{FLT} and k_3 reached significance ($p=0.0005$). K_1 was next closest with $p=0.0036$. The phosphorylation ratio, k_3/k_2+k_3 , did not reach significance. Of the multiple ways, we analyzed the SUV results, two reached significance by the t tests, SUV T/C 15–60 min, and SUV_{max} T/WM 15–60 min, but none did by the Wilcoxon test. Graphical analysis estimates of FLT flux and visual scores did not reach significance. There were poor correlations between K_{FLT} and SUV 15–60 min ($R^2=0.22$; Fig. 5 a) or SUV_{max} 15–60 min ($R^2=0.23$; Fig. 5b), all 19 patients included.

There are 13 cases in this report not included in the prior report on dynamic FLT-PET in gliomas from our institution [5]. All of these cases showed blood-brain barrier disruption with MRI T1+Gd enhancement. The results in these 13 additional cases conform to those previously reported with respect to the relationship of K_1 and K_{FLT} as well as to the finding that no patient demonstrated FLT uptake outside of the volume of increased permeability defined by MRI T1+Gd enhancement.

The results of the FDG-PET studies are shown in Tables 4 and 5 and in Fig. 6. These show that the FDGSUV tumor to cortex (T/C) and tumor to white matter (T/WM) ratios distinguished the radionecrosis from the recurrence group by the t tests. None of the measurements separated the two groups by the Wilcoxon tests. Visual analysis by one examiner yielded $p<0.004$ by the t test. Neither reached significance by the Wilcoxon test.

Discussion

The intent of this investigation was to explore the capacity of FLT-PET to distinguish recurrence from radionecrosis in previously treated gliomas. The study assumed that monitoring changes in clinical findings and MRI examinations, or lack thereof, through the course of the disease allowed this distinction to be made, since only one case in this report had pathological confirmation. In this and other publications, radionecrosis was assumed when there was no worsening of clinical and MRI examinations over months to years in the absence of any further treatment intervention [6–13]. Recurrence was considered the accurate assessment when clinical deterioration progressed along with worsening MRI

findings ending in death. The quality of our results needs to be judged with these limitations in mind, since it may be inaccurate to assume that radionecrosis cannot cause clinical and MRI deterioration ending in death. Also, in this type of study, selection and measurement biases may influence results. Certainly, surgical pathology and/or autopsy findings would provide important supportive evidence to any claim that one or the other process is active in any given case. Doubtless, in a significant percentage of cases, both tumor progression and radionecrosis may be active at the same time in different proportions such that eventual growth of an inoperable glioma dominates clinical outcome and imaging findings.

That said, the results of the present investigation suggest that FLT-PET may be able to distinguish between recurrence and radionecrosis with dynamic imaging and mathematical modeling to derive parameters of interest. K_{FLT} and k_3 were the only measures that reached significance by the Wilcoxon test. K_{FLT} is more reliably assessed than k_3 as our prior work showed the precision of the estimates (SEE/mean) over the expected range to be acceptable for K_{FLT} (4% error) but not for k_3 (49% error) [5]. The phosphorylation fraction (k_3/k_2+k_3) did not reach significance. Assessed by the Wilcoxon test, all the additional approaches for analyzing the FLT data that did not entail dynamic imaging and parameter estimation failed to distinguish recurrence from radionecrosis in this small data set. These approaches included FLTSUV, $FLTSUV_{max}$, simple visual analysis by nuclear medicine specialists, or deriving uptake ratios of tumor/cortex or tumor/white matter regions.

There are now several FLT-PET reports involving gliomas but only a few have addressed the question of tumor recurrence vs radionecrosis. In most of these reports, uptake was assessed by visual and semiquantitative methods such as SUV and SUV_{max} , or tumor/normal ratios (TNR) [29–33]. Choi et al. reported one case of radionecrosis as a FLT-PET false positive by TNR [30]. Saga et al. showed a case of granuloma after treatment of a GBM that showed FLT uptake by SUV_{max} and the TNR [32]. These approaches fail to separate the uptake due simply to blood-brain barrier breakdown (transport) from uptake due to retention in the salvage pathway (flux). They risk interpreting any uptake as indicative of proliferation when in reality blood-brain barrier breakdown may be all the images are depicting.

Of more relevance, Schiepers et al. reported seven patients with high-grade gliomas and two with metastatic tumors who underwent dynamic FLT-PET studies [34]. Lesions that were predominantly tumor could be separated from lesions dominated by treatment changes by the parameter, k_3 , and the phosphorylation fraction (k_3/k_2+k_3). Neither K_1 nor flux distinguished between the two groups. Small numbers of patients in their and our studies and different analysis methods could explain why these results differ from ours. This same group reported that FLT-PET separated three stable patients from 15 others with recurrence by means of the FLT SUV_{max} [29]. However, these three patients lacked contrast enhancement on MRI T1Gd which could be interpreted to mean there was no blood-brain barrier breakdown to allow access of the FLT to the tumor cells.

Our results suggest that FLT-PET performs better than FDG-PET in distinguishing recurrence from radionecrosis. At the time interval of 75–90 min when we imaged, FDG T/C and T/WM ratios reached significance in the t tests but not the Wilcoxon. This time

interval is later than was used in prior reports on FDG [7, 10, 35–43]. FDG T/C and T/WM ratios increase with time after injection which may partially explain this trend toward favorable results in a small number of cases [44].

From our data, sensitivity and specificity can be compared with results of other FDG studies, but it must be emphasized that the number of cases in our study is small. With a FDG T/C ratio cutoff of 0.4, the sensitivity and specificity for recurrence calculated to be 93% and 75%, respectively. For T/WM with cutoff of 0.61, sensitivity was 93% again and specificity was 50%.

From other reports, the sensitivity of FDG-PET for distinguishing recurrence of glioma from radionecrosis is typically 73% to 86%, although some reports claim 100% [7, 10, 35–43]. Specificity is problematic in that estimates range from 22% to 100%. Among these reports, methods varied; most included visual analysis or comparison of lesion uptake determined visually or by SUV to a reference noninvolved region such as adjacent or contralateral brain. Imaging usually started at about 45 min postinjection and ended by 60 min. The percentage of patients that had pathology confirmation varied as well. In the instructive report by Ricci et al., there were 31 patients suspected of harboring a recurrence in whom the pathology was positive in 22 and negative in nine [41]. With the cutoff of FDG uptake being greater than white matter, the sensitivity was 86% but the specificity only 22%. With the cutoff set at greater than cortex, the sensitivity was 73% and specificity was 56%.

The results of PET with other tracers so far do not single out a best approach for distinguishing recurrence from radionecrosis. From reviewing several studies, Singhal et al. reported that ^{11}C -L-methionine PET yielded a sensitivity of 100% and specificity of 72% for detecting recurrence [45] but more recently, Terakawa et al. reported 75% for both sensitivity and specificity [46]. Chen et al. found that 3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine PET separated four patients with radionecrosis from 37 with recurrence [47]. PET with ^{13}N - NH_3 separated two patients with radionecrosis from six with recurrence [12]. Despite these many reports, the contribution of PET to this important clinical question obviously still requires further studies that include confirmation by analysis of surgical or autopsy pathology. The same can be said for approaches with single-photon emission computed tomography with Tl-201, technetium-99m hexamethyl propyleneamine oxime, technetium-99m sestamibi, and I-123- α -methyl-L-tyrosine [7, 48–52].

It is beyond the scope of this discussion to present an exhaustive review of magnetic resonance imaging methods and results that bear on the question of recurrence vs radionecrosis. Briefly, estimates of sensitivity range from 64% to 89% and specificity from 83% to 89% when choline/creatinine and choline/*n*-acetylaspartate ratios are estimated by spectroscopy [50, 53–55]. MR technology and applications are rapidly evolving such that comparisons among the many reports remain challenging. Nevertheless, by measuring metabolite and/or apparent diffusion coefficient ratios, diagnostic accuracy reaches 86% to 96% in selected series [6, 11, 13, 56, 57]. These results set a high bar of performance for PET imagers to exceed especially in a practice environment where MR is becoming nearly universally available ahead of PET.

Conclusion

Our results suggest that FLT-PET is a promising approach for distinguishing recurrence from radionecrosis when applied rigorously with dynamic imaging and mathematical modeling for parameter estimations of flux and K_1-k_4 , but is not useful by estimates of SUV or SUV_{max} , or visual analysis. Further studies are justifiable but should include surgical pathology and/or autopsy confirmation. FDG-PET may well have more to contribute if rigorous coregistration of the PET images with MRI define better the tumor ROI, and tumor/cortex and tumor/white matter ratios are calculated. Whether delayed interval imaging with FDG (well past 60 min) might better separate radionecrosis from recurrence currently is only a hypothesis, namely that tumor tissue may retain trapped FDG longer than normal brain and the cellular elements associated with necrotic debris.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Pam Pham, Michele F. Wanner, Jeffrey Scharnhorst, and Neha Patel are gratefully acknowledged for their indispensable help. Supported by National Cancer Institute Contract N01-CM-37008 and NIH grants CA42045 and S10 RR17229.

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Fig. 1.

The kinetic model of FLT metabolism is comprised of an exchangeable tissue compartment (Q_e) and a compartment of trapped FLT nucleotides (Q_m). Four rate constants (K_1 – k_4) describe the kinetic transfer rates between the two compartments and blood. *FLTMP* FLT-monophosphate, *FLTDP* FLT-diphosphate, *FLTTP* FLT-triphosphate, *FLT-gluc* FLT-glucuronide synthesized in the liver, C_{pFLT} concentration of FLT in arterial plasma, C_{met} concentration of metabolites in arterial plasma.

Fig. 2.

Recurrence: Patient 17 was a 41-year-old woman who died 6 months after the FLT-PET study from progression of her recurrent glioblastoma multiforme. **a** MRI T1+Gd shows a large right frontal contrast-enhancing lesion at the time of her FLT-PET and FDG-PET scans. **b** MRI T1+Gd taken 2.5 months after the FLT-PET shows definite progression of the contrast enhancing disease. **c** FDG-PET of the same plane and time as in **a** shows that the tumor has uptake focally less than cortex but greater than white matter. **d** FLT-PET shows a high level of uptake corresponding to the MRI T1+Gd abnormality in **a**. **e** Mixture analysis image of the K_1 transport parameter. **f** Mixture analysis image of the K_{FLT} flux parameter. Note that the *color* scale is ten times less for **f** than for **e**.

Fig. 3.

Radionecrosis: Patient 1, a 46-year-old man with a right temporal grade 2 oligodendroglioma diagnosed by biopsy 9 years before FLT-PET and treated with radiotherapy 53 months before FLT-PET. **a** MRI T1+Gd shows extensive contrast enhancement in the right temporal, frontal, and parietal lobes. **b** MRI T1+Gd obtained 13 months after the FLT-PET shows decidedly less volume of enhancement. **c** FDG-PET of the same plane and time as **a** shows that the tracer uptake is focally greater than white matter but less than cortex. **d** FLT-PET shows a high level of uptake corresponding closely to the MRI T1+Gd abnormality in **a**. **e** Mixture analysis image of the K_1 transport parameter. **f** Mixture analysis image of the K_{FLT} flux parameter. Note that the color scale is ten times less for **f** than for **e**.

Fig. 4.

Box plots showing the comparisons between the radionecrosis and recurrence groups for K_{FLT} , k_3 , K_1 , k_3/k_2+k_3 , FLT SUV 15–60 min, FLT SUV_{max} 15–60 min, FLT SUV T/C 15–60 min, and FLT SUV_{max} T/W 15–60 min. See Table 3 for p values.

Fig. 5. Correlations between K_{FLT} and SUV 15–60 (a) or SUV_{max} 15–60 (b) were poor ($n=19$). R^2 values were only 0.22 and 0.23, respectively.

Fig. 6. Box plots showing the comparisons between the radionecrosis and recurrence groups for FDG SUV, FDG SUV_{max}, FDG SUV T/C, and FDG SUV T/WM. See Table 5 for *p* values.

Table 1

Age, pathology, treatments before and after FLT imaging, and survival

Number	Age (sex)	Pathology (location)	Treatment prior to FLT-PET in chronological order	Time between RT and FLT-PET (months)	Time between last chemotherapy and FLT-PET	Course of MRI before FLT-PET	Course of MRI after FLT-PET	Treatment after FLT-PET	Survival after FLT-PET
1	46 (M)	Oligo 2 (right temporal)	59.4 Gy PCV TMZ Carboplatin Etoposide	53	3 months	Stable to improved for 24 months	Slowly improved over 36 months	None	Alive 36 months
2	54 (M)	GS (right frontal)	70 Gy TMZ/ <i>cis</i> -retinoic acid Carboplatin/thalidomide Rapamycin/gefitinib BCNU/irinotecan	45	18 months	Stable for 30 months	Stable for 21 months	Hyperbaric oxygen	Alive 21 months
3	47 (F)	AA (left frontal)	PCV 60 Gy TMZ Intraventricular MTX BCNU/irinotecan Etoposide Irinotecan	44	1 month	Stable for 20 months	Stable for 21 months	None	Alive 21 months
4	36 (M)	AO (right temporal)	6,120 Gy + TMZ 22 Gy gamma knife TMZ 20 Gy gamma knife	28 23 9.5	1 month	Stable to improved for 6 months	Improved over 18 months	TMZ	Alive 18 months
5	62 (M)	GBM (left temporal)	Surgery + BCNU wafers 59.4 Gy TMZ 20 Gy gamma knife Carboplatin Gefitinib/etoposide 6TG/PCB/CCNU/HU	24	4 months	Progression over 6 months	Progression over 6 months documented	HU/imatnib mesylate	9.5 months
6	47 (M)	Oligo 2 (right frontal)	59.4 Gy PCV 1-125 seeds 12-15 Gy Brachytherapy 14 Gy TMZ	107 54 24	2 months	Progression over 3 months	Progression documented for 5 months	TMZ	6 months
7	54 (M)	GBM (left thalamus)	62 Gy + TMZ/celecoxib	4.5	1 month	Progression over 3 months	Progression documented over 3 months	Bevacizumab/irinotecan	4 months

Number	Age (sex)	Pathology (location)	Treatment prior to FLT-PET in chronological order	Time between RT and FLT-PET (months)	Time between last chemotherapy and FLT-PET	Course of MRI before FLT-PET	Course of MRI after FLT-PET	Treatment after FLT-PET	Survival after FLT-PET
8	50 (M)	AA (right frontal)	59.4 Gy PCV	116	96 months	Progression over 6 months	Progression documented over 4 months	TMZ	5 months
9	37 (F)	AA (right frontal)	59.4 Gy PCV	120	108 months	Progression over 6 months	Progression documented over 11 months	TMZ Carboplatin Etoposide Cytoxin HU	14 months
10	40 (M)	AA (left frontal)	59.4 Gy + TMZ	8.5	2 months	Progression over 3 months	Overall progression interrupted by brief stabilization over 16 months	BCNU/irinotecan/erlotinib Bevacizumab/irinotecan/erlotinib Carboplatin Etoposide	16 months
11	62 (M)	AO (right temporal)	55.8 Gy + TMZ	9	1 month	Progression over 1 month	Progression over 2 months	TMZ	3 months
12	50 (M)	Oligo 2 (left parietal)	59.4 Gy	98.5	No prior chemotherapy	Progression over 14 months	Progressive improvement (response) over 14 months in response to TMZ	TMZ	Alive 17 months
13	67 (M)	GS (right frontal and temporal)	63 Gy	2	None	Progression over 4 months	Progression over 6 months despite I-131-TM601	Resection + I-131-TM601	7 months
14	44 (F)	AA (left parietal)	59.4 Gy	29	None	Progression over 7 months	Unknown	Unknown	7 months
15	45 (M)	GM (right temporal)	59.4 Gy + TMZ 18 Gy radiosurgery	15 14	1.5 months	Progression over 1 month	Resection complicated by infarction, no recurrence by MRI for 52 months	Resection with gliadel wafers Pathology showed recurrence	Alive 56 months
16	24 (F)	Anaplastic PXA (left temporal)	54 Gy I-125 seeds 12–15 Gy TMZ Carboplatin	34 30	1 month	Progression over 2 months	Stable after radiosurgery and additional	17 Gy radiosurgery 6TG/PCB/CCNU/HU/FU Etoposide	Alive 49 months

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Number	Age (sex)	Pathology (location)	Treatment prior to FLT-PET in chronological order	Time between RT and FLT-PET (months)	Time between last chemotherapy and FLT-PET	Course of MRI before FLT-PET	Course of MRI after FLT-PET	Treatment after FLT-PET	Survival after FLT-PET
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17	41 (F)	GM (right frontal)	60.4 Gy + TMZ TMZ 18 Gy radiosurgery CDDP/BCNU	12 3	2 months	Progression over 2 months	chemotherapy but complicated by intratumoral hematoma chemotherapy but complicated by intratumoral hematoma chemotherapy but complicated by intratumoral hematoma chemotherapy but complicated by intratumoral hematoma Progression over 3 months	<i>cis</i> -retinoic acid/etoposide	6 months
18	19 (F)	AO (pineal)	59.4 Gy 20 Gy radiosurgery TMZ	16 12	2 months	Progression over 1 month	Progression over 1.5 months	None	3 months
19	34 (M)	AA (right frontal)	61.2 Gy TMZ	11	6 months	Progression over 6 months	Stable on chemotherapy for 21 months	TMZ	Alive 23 months

Numbers 1–4 are radionecrosis cases; numbers 5–19 are recurrences

HU hydroxyurea, *TMZ* temozolomide, *BCNU* carmustine, *CCNU* lomustine, *PCB* procarbazine, *PCV* procarbazine/lomustine/vincristine, *6TG* 6-thioguanine, *MTX* methotrexate

Table 2

The results for FLT-PET on all 19 patients

Case #	K_{FLT}	K_1	k_2	k_3	k_4	$k_3/k_2 + k_3$	$SUV_{mean} 15-60$	$SUV_{max} 15-60$	Visual score A	Visual score B
1	0.005	0.013	0.029	0.018	0.013	0.386	0.94	1.44	5	5
2	0.006	0.032	0.031	0.008	0.006	0.196	0.90	1.33	2	5
3	0.002	0.017	0.025	0.004	0.001	0.136	0.71	1.14	1	4
4	0.003	0.014	0.032	0.010	0.015	0.236	0.77	1.25	4	5
5	0.011	0.035	0.098	0.042	0.020	0.299	1.00	1.57	2	5
6	0.018	0.042	0.098	0.074	0.028	0.431	0.94	1.43	3	5
7	0.016	0.042	0.128	0.078	0.020	0.379	0.97	1.69	2	5
8	0.016	0.050	0.069	0.031	0.027	0.315	1.26	2.11	5	5
9	0.017	0.047	0.105	0.060	0.029	0.365	1.09	1.67	4	4
10	0.013	0.032	0.505	0.330	0.015	0.395	0.74	1.11	3	5
11	0.017	0.050	0.045	0.024	0.005	0.345	1.78	2.95	5	4
12	0.012	0.014	0.017	0.092	0.004	0.842	0.31	0.53	1	3
13	0.018	0.058	0.170	0.076	0.027	0.310	1.337	2.15	5	5
14	0.018	0.062	0.109	0.045	0.026	0.290	0.958	1.41	4	5
15	0.022	0.057	0.211	0.129	0.032	0.380	0.640	0.97	3	5
16	0.013	0.040	0.227	0.105	0.028	0.316	0.759	1.18	5	5
17	0.015	0.036	0.138	0.101	0.032	0.422	0.704	1.05	2	5
18	0.033	0.126	0.309	0.107	0.020	0.257	1.619	2.92	5	5
19	0.018	0.085	0.085	0.023	0.012	0.213	0.65	0.92	1	4

Table 3

Results of the statistical analysis of the FLT-PET data

Variable	<i>t</i> test (<i>p</i> values)	Wilcoxon (<i>p</i> values)
FLT data		
K_{FLT}	<0.0001	0.0005
K_1	0.0009	0.0036
k_3	0.0012	0.0005
$k_3/k_2 + k_3$	0.086	0.08
SUV 15–60 min	0.14	0.41
SUV _{max} 15–60 min	0.16	0.66
SUV 60–90 min	0.67	0.88
SUV _{max} 60–90 min	0.74	0.80
SUV T/C 15–60 min	0.03	0.04
SUV _{max} T/C 15–60 min	0.084	0.10
SUV T/WM 15–60 min	0.15	0.47
SUV _{max} T/WM 15–60 min	0.014	0.10
Graphical analysis	0.51	0.47
Visual score A	0.75	0.72
Visual score B	0.79	0.95

Note a level of 0.002 is considered significant by the Wilcoxon rank-sum test with multiple comparison adjustment

Table 4

The results for FDG-PET on 18 patients

Case #	FDG SUV _{mean}	FDG SUV _{max}	FDG T/C	FDG T/WM	Visual score A	Visual score B
1	4.20	8.74	0.455	0.620	1	5
2	3.81	8.41	0.386	0.594	1	4
3	3.78	9.07	0.331	0.694	1	3
4	3.32	7.31	0.233	0.350	1	4
5	6.06	12.03	0.700	1.132	4	5
6	3.59	6.01	0.637	1.243	1	5
7	4.86	7.25	0.525	0.827	5	5
8	4.44	7.83	0.894	0.869	5	5
9	6.82	9.83	0.917	1.122	1	5
10	5.47	6.74	0.620	0.964	1	3
11	3.23	5.40	0.468	0.612	1	2
12	5.24	9.78	0.617	0.874	1	3
14	6.018	9.928	0.595	0.897	5	4
15	2.678	5.662	0.425	0.615	1	4
16	3.261	8.016	0.421	0.630	5	4
17	3.248	5.236	0.589	0.765	4	4
18	5.954	8.247	0.878	0.607	5	4
19	2.712	4.52	0.332	0.438	1	4

Table 5

Results of the statistical analysis of the FDG-PET data

Variable	<i>t</i> test (<i>p</i> values)	Wilcoxon (<i>p</i> values)
FDG data		
SUV	0.08	0.65
SUV _{max}	0.39	0.38
SUV T/C	0.003	0.008
FDG _{max} T/C	0.12	0.28
SUV T/WM	0.03	0.06
FDG _{max} T/WM	0.06	0.28
Visual score A	0.004	0.10
Visual score B	0.89	0.82

Note a level of 0.002 is considered significant by the Wilcoxon rank-sum test with multiple comparison adjustment