Published in final edited form as:

J Neurooncol. 2013 March ; 112(1): 121–132. doi:10.1007/s11060-013-1043-4.

Tryptophan PET in pretreatment delineation of newly-diagnosed gliomas: MRI and histopathologic correlates

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Conflict of interest None of the authors report any conflict of interest or financial disclosure.

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Abstract

Pretreatment delineation of infiltrating glioma volume remains suboptimal with current neuroimaging techniques. Gadolinium-enhanced T1-weighted (T1-Gad) MR images often underestimate the true extent of the tumor, while T2-weighted images preferentially highlight peritumoral edema. Accumulation of α -[^{11}C]methyl-L-tryptophan (AMT) on positron emission tomography (PET) has been shown in gliomas. To determine whether increased uptake on AMT-PET would detect tumor-infiltrated brain tissue outside the contrast-enhancing region and differentiate it from peritumoral vasogenic edema, volumes and spatial concordance of T1-Gad and T2 MRI abnormalities as well as AMT-PET abnormalities were analyzed in 28 patients with newly-diagnosed WHO grade II–IV gliomas. AMT-accumulating grade I meningiomas were used to define an AMT uptake cutoff threshold that detects the tumor but excludes peri-meningioma vasogenic edema. Tumor infiltration in AMT-accumulating areas was studied in stereotactically resected specimens from patients with glioblastoma. In the 28 gliomas, mean AMT-PET-defined tumor volumes were greater than the contrast-enhancing volume, but smaller than T2 abnormalities. Volume of AMT-accumulating tissue outside MRI abnormalities increased with higher tumor proliferative index and was the largest in glioblastomas. Tumor infiltration was confirmed by histopathology from AMT-positive regions outside contrast-enhancing glioblastoma mass, while no or minimal tumor cells were found in AMT-negative specimens. These results demonstrate that increased AMT accumulation on PET detects glioma-infiltrated brain tissue extending beyond the contrast-enhanced tumor mass. While tryptophan uptake is low in peritumoral vasogenic edema, AMT-PET can detect tumor-infiltrated brain outside T2-lesions. Thus, AMT-PET may assist pretreatment delineation of tumor infiltration, particularly in high-grade gliomas.

Keywords

Glioma; MRI; Positron emission tomography; Tryptophan; Volumetry; Vasogenic edema

Introduction

Prognosis of malignant gliomas remains bleak, and low-grade gliomas also pose a major diagnostic and therapeutic challenge [1, 2]. The high recurrence rate in infiltrating gliomas is in part caused by incomplete resection and irradiation of the tumor [3]. The vast majority (>80 %) of tumor recurrence occurs within 2-cm of the resection margin [4, 5]. Extent of resection is a major predictor of outcome [6], however, assessing how much of the tumor is amenable to resection remains suboptimal. Currently, morphological MRI sequences such as post-gadolinium T1-weighted (T1-Gad), T2-weighted, and fluid-attenuated inversion recovery (FLAIR) imaging remain the mainstay of diagnosis, treatment planning, and follow-up for patients with gliomas [7, 8]. Gadolinium enhancement is a sensitive indicator of blood–brain barrier disruption [8, 9], but gliomas can infiltrate adjacent brain tissue without blood–brain barrier breakdown [7]. T2-weighted and FLAIR sequences reveal peritumoral edema. However, it is often difficult to differentiate a hyperintense T2/FLAIR signal related to a non-enhancing tumor from other etiologies (e.g., vasogenic edema or ischemic injury) [10].

Positron emission tomography (PET) provides signals based on the underlying biological activity. Amino acid PET may be a useful tool for microsurgical and radiotherapy planning in patients with high-grade gliomas [11–16]. α -[^{11}C]methyl-L-tryptophan (AMT) is an amino acid PET tracer not incorporated into proteins; rather, it is metabolized via the

immunomodulatory kynurenine pathway, involved in the escape of tumors from the host immune response [17–24]. In our previous studies, we noted increased AMT uptake in the majority of low-grade gliomas and in all high-grade gliomas [21, 25, 26].

In the present study, we assessed if AMT accumulation on PET could identify tumor-infiltrated brain tissue not detected by conventional MRI in newly-diagnosed gliomas. We hypothesized that these tumors would demonstrate increased AMT accumulation beyond the gadolinium-enhancing region and, in some cases, beyond T2 abnormalities in tumor-infiltrated brain tissue, while areas of vasogenic edema would not show elevated AMT uptake. We also hypothesized that the volume of AMT accumulation *outside* the MRI-defined abnormality would increase with higher histologic grade and tumor proliferative activity. Histopathology from stereotactically-resected brain tissue was performed to determine if AMT accumulation indeed detects tumor-infiltrated brain tissue in high-grade gliomas.

Methods

Subjects

We studied 28 adults with a newly-diagnosed glioma (Table 1) based on the following inclusion criteria: (1) a solid supratentorial mass on MRI; (2) no prior treatment; (3) subsequent microsurgical resection with WHO grade II–IV glioma. Twenty patients presented with seizures. The mean interval between AMT–PET and MRI was 19 days for low-grade and 4 days for high-grade gliomas. In addition, newly-diagnosed grade I meningiomas of 4 adult patients (mean age 67 years) were used to establish an AMT uptake threshold to differentiate between solid tumor mass and peri-meningioma vasogenic edema. The study was approved by the Institutional Review Board of Wayne State University, and written informed consent was obtained from all participants.

AMT–PET scanning protocol

PET studies were performed using a Siemens EXACT/HR whole-body positron emission tomograph (Siemens Medical Systems, Knoxville, Tennessee). The AMT tracer was synthesized by using a high-yield procedure as outlined before [27]. The procedure for AMT–PET scanning has been described previously [21, 26, 28]. In brief, after 6 h of fasting, AMT (37 MBq/kg) was injected intravenously. At 25 min after tracer injection, a dynamic emission scan of the brain (7×5 min) was acquired. Measured attenuation correction, scatter, and decay correction was applied to all PET images. For visualization of AMT uptake, averaged activity images 30–55 min post-injection were created and converted to an AMT standardized uptake value (SUV) image. The PET image in-plane resolution was 7.5 ± 0.4 mm at full-width half-maximum (FWHM) and 7.0 ± 0.5 mm FWHM in the axial direction.

MRI protocol

Diagnostic MRI scans acquired nearest in time to the AMT–PET scan were used in this study. MRI was performed on a Siemens MAGNETOM Trio TIM 3.0 Tesla scanner (Siemens Medical Solutions, Malvern, Pennsylvania) in 20 patients and on a GE Signa HDxt 3.0 Tesla scanner (GE Medical Systems, Milwaukee, Wisconsin) in eight. The following axial sequences (with similar parameters on both scanners) were used for analysis: T2-weighted, FLAIR, and post-contrast T1-weighted (T1-Gad) images. FLAIR images were not acquired close to the time of AMT–PET in three patients. In patients with both T2 and FLAIR images acquired close to the PET scan, T2- and FLAIR-defined tumor volumes (see below) showed a very strong positive correlation ($r = 0.95$; $p < 0.001$); therefore, we used T1-Gad and T2 MR (but not FLAIR) for further image analysis.

Image analysis

The 3D Slicer software version 3.6.3 (www.slicer.org) was used for threshold-based volume of interest (VOI) analysis [29]. First, AMT–PET and T2 images were co-registered to the T1 image volumes using the Fast Rigid Registration module [30]. Fused images were automatically resliced and resampled. Subsequently, we defined the threshold for detecting increased AMT uptake, based on AMT SUV increases derived from the four WHO grade I meningiomas, surrounded by peritumoral vasogenic edema with no or minimal tumor cell infiltrate [31]. These meningiomas showed high AMT accumulation with an AMT SUV between 3.5 and 4.1, and tumor/contralateral cortex SUV ratios between 1.51 and 1.63; similar to SUV ratios in the gliomas (1.65 ± 0.26). Using co-registered, fused AMT–PET and MR images of the meningiomas, we determined that with an AMT cutoff of 36 % above mean cortical SUV, AMT–PET and gadolinium-defined tumor volumes overlapped completely (i.e., peri-meningioma edema on T2/FLAIR was not detected) (Fig. 1a). Therefore, we used this cutoff threshold to delineate areas with increased AMT uptake in glioma patients, where regions with increased AMT SUV (>36 % increase) were defined, and their volumes were expressed in cm^3 . In addition, the average AMT SUV and the maximal AMT SUV (SUV_{max}) within these PET volumes was calculated and compared to SUV in contralateral cortex. The site of highest AMT SUV was also determined.

Tumor volumes on MRI were defined as follows: (i) thresholds slightly above the highest signal of normal white matter contralateral to the tumor were used for T2 images; and (ii) area of contrast enhancement was used for T1-Gad images. VOIs (V-T1-Gad, V-T2) were created by segmentation of T1-Gad abnormalities semi-automatically, while T2 images were segmented manually to avoid erroneous inclusion of cerebrospinal fluid in the VOI.

Spatial concordance among imaging abnormalities was determined by calculating the number of overlapping abnormal voxels on both AMT and MRI (T2, T1-Gad) volumes. This was achieved by masking the VOI of AMT increase with the VOIs of the T2 abnormality and T1-Gad enhancement separately using 3D Slicer's Mask module. Spatial discordance was determined by subtracting the volumes of overlaps from the AMT and MRI abnormality volumes using the Subtract module of 3D Slicer.

Neurosurgical planning, resection, and histopathologic examination

In order to assess histopathologic correlates of MRI and AMT–PET abnormalities, AMT–PET and MR images were used for neurosurgical planning and intraoperative navigation on a Brainlab Curve™ Image Guided Surgery platform (Brainlab Inc, Westchester, Illinois) in the five most recent patients with glioblastoma (#20, #23–26; Table 1). Due to the retrospective nature of this study, stereotactically obtained AMT–PET correlated samples were not available from the other patients. Using fused MRI/PET images from the five patients, samples were acquired stereotactically from regions with increased AMT SUV both with and without contrast enhancement (i.e., T1-Gad+/AMT+ and T1-Gad–/AMT+ areas). In addition, T2-positive tissue samples outside the AMT-positive area were also obtained in two patients. Routine histopathologic analysis was performed and tumor infiltration was assessed from all stereotactically obtained specimens by an experienced neuropathologist (W.J.K.). The Ki-67 labeling index (%) was determined in the solid tumor tissue [32]. Presence and density of tumor cells was assessed in each stereotactically acquired specimen as follows: (i) solid tumor tissue (score 4); (ii) tumor-infiltrated brain tissue with high, intermediate, or low tumor cell density (scores 3, 2, and 1, respectively); and (iii) brain tissue with no/minimal tumor involvement (score 0).

Study design and statistical analysis

Most variables showed a non-normal distribution, therefore, non-parametric tests were used. The Wilcoxon signed-rank test was performed to compare tumor volumes derived from the different imaging modalities and also to compare tumor cell density scores in T1-Gad+/AMT+ versus T1-Gad-/AMT+ regions. AMT-accumulating MRI-negative tumor volumes were compared between glioma grades using the Mann–Whitney *U* test. Group correlations were done by Spearman's rank correlation. Statistical analysis was carried out using the SPSS Statistics 19 software (SPSS Inc., Somers, New York). *p* values <0.05 were considered to represent statistical significance.

Results

Comparison of PET and MRI volume abnormalities

All 28 gliomas showed increased T2 signal; 24 gliomas also showed AMT accumulation with the 36 % threshold of increased uptake. The four exceptions included one anaplastic astrocytoma (#7), one anaplastic oligodendroglioma (#11), and two low-grade oligodendrogliomas (#2 and #3) (Table 1). Gadolinium enhancement was noted in 14 patients (including 13 glioblastomas). Mean V-T1-Gad ($8.4 \pm 14.3 \text{ cm}^3$) was much smaller than both V-T2 ($39.7 \pm 33.6 \text{ cm}^3$; $p = 0.001$) and V-AMT ($26.8 \pm 19.9 \text{ cm}^3$; $p = 0.002$); V-AMT was smaller than V-T2 ($p = 0.045$) (Fig. 2). In individual patients, the V-T2 was greater than V-AMT in 20 patients, while the reverse was seen in the remaining eight (Table 1).

Spatial concordance between MRI and AMT–PET abnormalities

In gadolinium-enhancing tumors ($n = 14$), the enhancing tissue volumes on MRI were encompassed in the AMT-accumulating brain volumes, which were larger in all cases. Also, the site of highest AMT SUV was within or in very close vicinity to the gadolinium-enhancing tumor mass. In contrast, there was a variable spatial discordance between AMT-accumulating and T2-positive volumes.

In the 20 patients with WHO grade II–IV gliomas, the combined AMT/T2 abnormalities had an average volume of 54.6 cm^3 ($\pm 32.4 \text{ cm}^3$), with the bulk consisting of T2 abnormalities outside (mean: $23.3 \pm 27.2 \text{ cm}^3$) or within (mean: $19.6 \pm 14.2 \text{ cm}^3$) brain volumes showing high AMT uptake; approximately 23 % of the combined mean volume showed pure AMT abnormalities (mean: $10.7 \pm 9.7 \text{ cm}^3$) outside the T2 abnormalities (Fig. 3a). There were high individual variations regarding concordance and discordance between volumes of T2 and AMT–PET abnormalities (see Fig. 3b).

The AMT-accumulating tissue, which extended beyond the T2-volume, was significantly larger in glioblastomas (mean: $14.3 \pm 9.4 \text{ cm}^3$) as compared to grade II or III gliomas (which were not different from each other: 3.5 and 4.3 cm^3 , in average, respectively) ($p < 0.001$) (Fig. 1b). Also, higher tumor Ki-67 labeling index was associated with more extensive AMT uptake increases *outside* the T2-volume (Spearman's $\rho = 0.64$; $p < 0.001$). Tumor/cortex AMT SUV_{max} ratios correlated with Ki-67 labeling index ($r = 0.50$; $p < 0.01$).

Histopathological correlates of imaging abnormalities

Thirteen stereotactically-resected specimens were obtained from five patients with newly-diagnosed glioblastoma. Tumor cell density scores were highest in T1-Gad+/AMT+ specimens (mean score 3.4, range: 3–4) and lower in T1-Gad-/AMT+ specimens (mean score: 2.0, range: 1–3) ($p = 0.04$) (see example on Fig. 4). T1-Gad-/AMT– specimens (from brain tissue showing increased signal on T2 images), from two patients, showed very low tumor density scores (0 and 1).

Discussion

In this study, we found that AMT accumulation on PET extends beyond the contrast enhancing glioma mass. In addition, while the overall volume of brain tissue showing high AMT uptake was often smaller than corresponding regions with increased T2 signal, high AMT accumulation often extended beyond areas of T2 abnormality, particularly in glioblastomas. This discrepancy suggests that areas with AMT accumulation represent tumor-infiltrated brain tissue, some of which is not detected by contrast-enhancement or T2-weighted images. This is supported by the histopathologic analysis of stereotactically-acquired tissue, where we confirmed highest density of tumor cells in AMT-positive tissue samples taken from the area of gadolinium-enhancement and medium tumor cell density in AMT-positive non-enhancing tissue; no or minimal tumor cell density was seen outside the AMT-positive brain tissue. Altogether, these results suggest that increased AMT uptake may be useful to enhance accurate delineation of glioma-infiltrated brain tissue for neurosurgical planning and postoperative radiation therapy.

Thresholding PET abnormalities for tumor detection

Glioma cells infiltrate the brain via a gradient, hence gliomas lack definitive margins and are associated with infiltrative edema [3]. Therefore, defining a cutoff threshold for glioma definition on imaging requires a decision: for pathology-based thresholds one has to define what density of cell infiltration is important (or feasible) to be detected, and there may be different thresholds for different cell densities. Conversely, low-grade meningiomas are non-infiltrative tumors with a clear interface between tumor and underlying cortex, and are associated with vasogenic edema. Therefore, meningiomas have been used as a model for pure vasogenic edema [33]. Since low-grade meningiomas avidly accumulate AMT (similar to high-grade gliomas), they are useful to generate a cutoff threshold, which can pick up adequate tumor volume while excluding non-infiltrative edema (including peri-glioma edema with low tumor cell infiltration) and non-tumoral brain tissue. It is likely that the selected meningioma-based cutoff threshold (36 %) excludes some glioma-infiltrated brain tissue with relatively low tumor cell density. We have recently reported a preliminary PET study with pathology comparison suggesting that various tumor cell densities may be outlined by various thresholds on AMT-PET [34]; however, this needs further confirmation in larger samples, and only 13 specimens from five patients were used in the present study after the exclusion of patients with recurrent gliomas.

With the threshold established for the current study, we found decreased AMT uptake in peri-meningioma edema, which is consistent with a recent PET study that noted decreased methionine uptake in vasogenic edema [33]. Although we did not have histopathologic evidence of complete absence of infiltrating tumor cells in perimeningioma regions, peritumoral invasion is generally observed only in high-grade meningiomas [31], which were not included in this study.

MRI abnormalities and AMT uptake

Despite inherent limitations of contrast-enhanced MRI [7, 8, 35, 36], the Macdonald Criteria are still widely used for monitoring brain tumor progression [37] and rely on changes in contrast enhancement [7]. In the present study, high AMT accumulation on PET (>36 %, as compared to normal cortex) extended variably beyond the area of contrast uptake in gliomas into non-enhancing regions, frequently in an eccentric fashion. In contrast, grade I meningiomas, which showed high AMT SUVs (and downward sloping time activity curves) similar to high-grade gliomas, showed no AMT uptake beyond the contrast enhancing mass when using the same threshold of increased AMT uptake. High AMT uptake observed outside the contrast-enhancing glioma mass in the present study is likely caused by tumor

infiltration of brain tissue without a major disruption of the blood–brain barrier. This notion is supported by our limited histopathologic analysis, where non-enhancing AMT-accumulating tissue tumor volume showed massive tumor cell presence.

T2 (and also FLAIR) MRI sequences have been recently incorporated in tumor follow-up protocols [7, 38]. We found a partial discordance between T2 and AMT–PET abnormalities. First, the overall extent of T2 abnormalities was larger than the area of AMT accumulation in most cases. It is likely that T2 signal abnormalities in areas with low AMT uptake mostly represent brain tissue with vasogenic edema. This is supported both by our findings in perimeningioma edema and also our histology data from AMT-negative (but T2-positive) brain tissue, where no or very low tumor cell density was observed. A second interesting finding was the variable extension of increased AMT uptake beyond the T2 abnormality, especially in patients with highly proliferative gliomas. Again, the most plausible explanation for this is the presence of tumor cells beyond the regions defined by T2 MRI, in tumor-infiltrated brain tissue without detectable edema. This needs to be confirmed by further histopathologic studies of AMT+/T2– brain tissue.

Potential mechanisms of increased AMT uptake in tumor-infiltrated brain tissue

α -[^{11}C]methyl-L-tryptophan accumulation is not affected by protein incorporation [18]. Using dynamic AMT–PET images, we recently demonstrated that high net tryptophan transport in gliomas is an excellent predictor of glioma proliferative activity [32]. Increased tryptophan transport may occur due to overexpression of the LAT1 amino acid transporter; high LAT1 expression was in fact reported to correlate with high methionine uptake on PET in newly-diagnosed gliomas [39]. Therefore, increased AMT uptake outside the contrast-enhancing tumor mass may detect proliferative tumor cells overexpressing LAT1. However, high AMT transport due to LAT1 may not fully explain high SUVs measured in the late uptake phase (25–60 min after tracer injection, i.e., the time frame of brain scans in our study). High AMT SUV in this late phase may also be related to retention of tryptophan or its metabolite(s), such as L-kynurenine, due to elevated tumoral IDO expression [21], which facilitates increased tryptophan metabolism via the immunosuppressive kynurenine pathway. High IDO is not strongly related to tumor grade, as it has been observed in low-grade gliomas and was not present in some glioblastomas [21]; rather, IDO overexpression may create an immunosuppressive microenvironment. There could be other explanations for peritumoral cortical AMT SUV increases. For example, increased focal cerebral AMT uptake can be associated with epileptogenic regions, mostly seen around epileptogenic tubers and focal cortical malformations, but also reported in some patients with cryptogenic epilepsy [40–43]. However, in non-tumoral epilepsy cases, the degree of AMT accumulation rarely exceeded 20 %, and >30 % increased uptake was exceptional. Reactive gliosis can also cause increased tracer uptake as demonstrated with other amino acid tracers [44]. Similarly, mild increases of AMT uptake were occasionally observed in epileptic foci where histopathology revealed reactive gliosis, but these increases were rarely higher than 10 %, and did not reach the 36 % asymmetry threshold [42, 43]. Therefore, tumor definition by using the 36 % AMT cutoff threshold in our study is unlikely to be confounded by epileptogenic regions or reactive gliosis.

Comparison of AMT-PET to other amino acid PET tracers

Several previous PET studies of various (non-AMT) amino acid PET radiotracers, most commonly labeled methionine (MET) and O-(2-[^{18}F]fluoroethyl)-L-tyrosine (FET), showed accumulation beyond areas of gadolinium enhancement [8, 12, 13, 16, 45, 46]. Such studies suggested that amino acid PET imaging may enhance target delineation for surgery and subsequent radiotherapy of gliomas [15, 45–47]. Identification of high-uptake foci in low-grade gliomas may also be useful to identify anaplastic foci. Four of 6 grade II gliomas had

SUV_{max} in the range of mean SUV of high-grade tumors. Considering the positive correlation between AMT SUV and tumor proliferative index, these high SUV_{max} foci may represent anaplastic regions within a low-grade tumor. Anaplastic tumor foci have been demonstrated in low-grade gliomas based on differing FET-PET uptake kinetics in a previous study [48].

The degree of observed increases of PET tracer uptake and the applied threshold varies moderately across different studies and tracers. Most MET-PET studies used cutoff values between 1.27 and 1.5 above the uptake of the control region [8, 45, 49, 50]. Using histopathologic sampling, Kracht et al. [50] established a cutoff tumor-to-gray matter ratio of 1.3 for tumor delineation with MET, while Pauleit et al. [51] found a ratio of 1.6 to have 92 % sensitivity and 81 % specificity on FET-PET. Grosu et al. [45] showed great concordance of volumes between FET and MET using a 1.5 cutoff. It should be noted, however, that direct comparison of values across studies and tracers is difficult, because different groups use tumor-to-control ratios variably utilizing the mean or maximal SUV for the tumor, and defining white or gray matter or a composite of the two as the control region. We have used cortical SUV to generate the ratios; the ratios would be higher if white matter or a mixed white/gray matter tissue would be used. Although the 36 % threshold for increased AMT uptake defined in the present study is within the range of previous MET and FET cutoff values, the optimal cutoff threshold for increased uptake could be slightly different among various amino acid radiotracers, considering the different mechanism of uptake and metabolism. Nevertheless, our histopathologic studies, albeit not as extensive as the one presented by Pauleit et al. [51] for FET-PET, strongly suggest that delineation of brain regions with increased uptake of AMT can provide added clinical information to conventional MRI regarding tumor extent. In addition, considering the infiltrative nature of malignant gliomas, without a sharp tumor border, it is likely that different cutoff thresholds may delineate brain tissue with various tumor cell infiltration. Less than 36 % increases of AMT uptake could be informative in detecting brain regions with low tumor cell density and further increase the clinical yield of pretreatment AMT-PET. This will require further rigorous comparisons between radio-tracer uptake and histopathology of stereotactic tissue samples. Nevertheless, as AMT-PET imaging detects regions of possible tumor infiltration not revealed by conventional MRI, its integration into treatment planning and/or follow-up imaging holds the promise of better tailored resections, more accurate radiotherapeutic targeting, and/or better assessment of tumor recurrence. Improvements in any of these areas could enhance prognosis. Prior studies with amino acid PET tracers indeed provided preliminary data suggesting that combining PET imaging with MRI in tumor volume delineation may yield better outcomes than using conventional MRI alone [8, 12–16]. Tumoral transport of tryptophan, methionine, tyrosine, and other large neutral amino acids, whose derivatives are being used for PET imaging is likely determined by similar transport mechanisms (mediated by LAT1, see above). Currently, there is no evidence that any of the amino acid tracers are superior to the others for brain tumor detection. From a practical point of view, ¹⁸F-labeled tracers (such as FET) are more suited for distribution and clinical use. Centers with an on-site cyclotron might prefer a particular ¹¹C-labeled tracer, e.g., if the tracer can be used for multiple purposes (such as AMT for detecting epileptic foci). Also, each of these PET radiotracers has different metabolic fates; therefore, there may be tumor types or special situations where one performs better than the others. Further quantification of uptake kinetics may provide additional information to refine the role of amino acid PET radiotracers in presurgical delineation and postsurgical monitoring of gliomas.

Acknowledgments

The study was supported by a grant (R01 CA123451 to C.J.) from the National Cancer Institute, Start-up Funds (Wayne State University School of Medicine to S.M.) and a Strategic Research Initiative Grant from the Karmanos

Cancer Institute (to S.M. and C.J.). We thank Hancheng Cai, PhD and Thomas Mangner, PhD, for assistance in PET radiochemistry. We thank Janet Barger, RN, Kelly Forcucci, RN, and Cathie Germain, MA for assisting patient recruitment and scheduling, as well as Natasha L. Robinette, MD, and Alit Yousif, MD, for reviewing the clinical MRI scans. We are grateful to the entire staff at the PET Center, Children's Hospital of Michigan, who provided invaluable technical help in performing the PET scans

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Fig. 1. T2 MRI and α -[^{11}C]methyl-L-tryptophan (AMT)–PET (fused $\blacktriangleright$ with post-contrast T1 [T1-Gad]) images of three patients. The T2 images were windowed to emphasize the hyperintense signal abnormalities. **a** WHO grade I meningioma with high AMT uptake. The area of AMT accumulation and MRI-defined tumor mass completely overlapped with a 36 % cutoff threshold of increased AMT uptake (compared to normal contralateral cortical uptake), while peri-meningioma vasogenic edema showed low AMT accumulation (*asterisk*). **b** Two gliomas (patient #9 and #24), demonstrating discrepancy between AMT accumulation and T2 abnormalities. The hyperintense areas on T2 are outlined in *blue*, the area with >36 % AMT uptake increase is outlined in *red* on the fusion images. Patient #9 had a grade III astrocytoma with a T2 abnormality that encompassed the AMT uptake increase and also extended beyond it (*arrowheads*). In contrast, in patient #24 with a glioblastoma, a substantial portion of the AMT accumulating tissue extended beyond the T2 signal increase (*arrows*)

Fig. 2. Means (and 95 % confidence intervals) of volumes of imaging abnormalities, in cubic centimeters (cc). Mean V-T1-Gad was significantly smaller than both V-AMT ($p = 0.002$) and V-T2 ($p = 0.001$); mean V-AMT was smaller than V-T2 ($p = 0.045$)

Fig. 3. Mean (a) and individual (b) concordance and discordance between T2-abnormalities on MRI and AMT uptake increases on PET in 24 patients with glioma who showed an area of >36 % increase of tumoral AMT uptake (as compared to contralateral cortical uptake). The y axis shows image abnormality volumes (in cubic centimeters [cc]), and the x axis indicate the entire group (a) or individual patients (b; numbers correspond to patient numbers in Table 1; patients #15–28 had glioblastoma.). On the bars, the *middle black* areas represent tumor volumes abnormal on both T2 MRI and AMT–PET (i.e., the overlapping volume); the *lower dotted* areas indicate the volume of tissue abnormal only on T2 MRI, while *upper dashed* areas indicate volumes abnormal only on AMT–PET

Fig. 4.

a AMT-PET co-registered to the post-contrast T1 (T1-Gad) image of patient #20 with a left parietal glioblastoma. **b** Three-dimensional surface reconstruction of the same subject's brain, visualizing AMT uptake on a rainbow scale where *red* represents the highest and *dark purple* represents the lowest standard uptake values (SUVs). Tissue specimens were obtained with stereotactic guidance from the non-enhancing high AMT SUV region (*red arrows*) as well as the contrast-enhancing high AMT SUV area (*yellow arrows*). **c, d** Hematoxylin and eosin staining of the specimens from the non-enhancing high AMT SUV (**c**) and the enhancing high AMT SUV region (**d**). The *arrows* indicate examples of infiltrating neoplastic cells. Original magnification at $\times 20$

Table 1

Clinical data and imaging abnormalities of the 28 glioma and 4 meningioma patients

Patient no.	Age/sex	Seizures	Tumor grade	Tumor histology	Tumor location	SUV-ratio (tumor/cortex)	SUV _{max-ratio} (tumor/cortex)	Gad. Enh.	Volume of imaging abnormality (cm ³)		
									V _{AMT}	V _{T2}	V _{T1-Gad}
1	57/M	Yes	II	Astro	T	1.54	1.94	No	25.5	43.6	0
2	20/M	Yes	II	Oligo	F	~	1.18	No	0.0	3.0	0
3	32/F	No	II	Oligo	F	~	1.18	No	0.0	2.0	0
4	37/F	Yes	II	Oligo	P	1.65	2.48	No	5.7	9.8	0
5	34/M	Yes	II	Oligo	F	1.63	2.73	No	14.2	26.4	0
6	30/M	No	II	Oligo	F	1.76	2.53	No	63.2	59.2	0
7	50/M	Yes	III	Astro	P	~	1.17	No	0.0	13.4	0
8	36/M	Yes	III	Astro	F	1.71	2.49	No	10.5	14.6	0
9	26/F	No	III	Oligo	F	1.55	1.89	No	14.2	82.3	0
10	42/M	Yes	III	Oligo	T	1.77	2.70	Yes	32.7	55.4	0.9
11	28/M	Yes	III	Oligo	T	~	1.36	No	0.0	98.2	0
12	57/M	Yes	III	Astro	P	1.50	1.78	No	4.2	6.4	0
13	55/M	Yes	III	Astro	T	1.72	3.74	No	37.9	21.7	0
14	61/F	Yes	III	Astro	T	1.61	2.32	No	19.1	44.4	0
15	60/F	Yes	IV	GBM	T	1.67	2.98	No	40.4	41.9	0
16	65/F	Yes	IV	GBM	F	1.75	1.75	Yes	79.3	67.3	59.6
17	51/M	No	IV	GBM	T	2.01	3.77	Yes	41.0	4.3	7.6
18	67/M	Yes	IV	GBM	P	1.61	5.54	Yes	15.4	30.5	7.3
19	46/M	Yes	IV	GBM	P	1.54	1.89	Yes	25.6	35.7	11.1
20	65/M	Yes	IV	GBM	P	1.73	3.40	Yes	44.4	57.5	10.9
21	75/F	No	IV	GBM	F	1.96	1.96	Yes	23.8	30.5	4.9
22	49/M	Yes	IV	GBM	F	1.75	3.11	Yes	37.9	47.5	34.0
23	54/M	Yes	IV	GBM	P	1.67	2.33	Yes	49.8	153.4	22.3
24	62/M	No	IV	GBM	T	1.69	3.62	Yes	38.8	18.7	1.1
25	46/M	No	IV	GBM	T	1.83	3.45	Yes	35.0	28.6	17.4
26	78/M	Yes	IV	GBM	T	2.13	2.13	Yes	42.7	20.4	17.0
27	61/M	Yes	IV	GBM	T	2.22	4.43	Yes	23.7	20.8	6.0

Patient no.	Age/sex	Seizures	Tumor grade	Tumor histology	Tumor location	SUV-ratio (tumor/cortex)	SUV _{max-ratio} (tumor/cortex)	Gad. Enh.	Volume of imaging abnormality (cm ³)		
									V _{AMT}	V _{T2}	V _{T1-Gad}
28	82/F	No	IV	GBM	O	1.48	1.75	Yes	25.6	74.6	36.3
1	39/F	Yes	I	Meningioma	F	1.63	2.23	Yes	55.3	–	55.5
2	74/M	No	I	Meningioma	O	1.51	1.87	Yes	8.7	–	8.6
3	62/M	No	I	Meningioma	F	1.54	1.93	Yes	5.6	–	5.6
4	91/F	No	I	Meningioma	F	1.56	1.87	Yes	28.8	–	28.8

~, did not reach the pre-defined threshold; *Astro* astrocytoma, *Oligo* oligodendroglioma, *GBM* glioblastoma, *F* frontal, *P* parietal, *T* temporal, *O* occipital, *Gad. Enh.* gadolinium contrast enhancement, *VAMT*, *VT2*, *VT1-GAD* volumes of the AMT-PET, T2 and gadolinium enhancing abnormalities, respectively