Published in final edited form as:

J Neurooncol. 2011 May ; 102(3): 409–415. doi:10.1007/s11060-010-0327-1.

DIFFERENTIAL KINETICS OF α -[¹¹C]METHYL-L-TRYPTOPHAN ON PET IN LOW-GRADE BRAIN TUMORS

Csaba Juhász, MD, PhD^{1,2,3,6}, Otto Muzik, PhD^{1,2,3,4}, Diane C. Chugani, PhD^{1,2,4}, Harry T. Chugani, MD^{1,2,3}, Sandeep Sood, MD^{2,5}, Pulak K. Chakraborty, PhD^{1,4}, Geoffrey R. Barger, MD^{3,6}, and Sandeep Mittal, MD, FRCSC, FACS^{5,6}

¹ PET Center, Children's Hospital of Michigan, Detroit, Michigan

² Carman and Ann Department of Pediatrics, Wayne State University School of Medicine, Detroit, Michigan

³ Department of Neurology, Wayne State University School of Medicine, Detroit, Michigan

⁴ Department of Radiology, Wayne State University School of Medicine, Detroit, Michigan

⁵ Department of Neurosurgery, Wayne State University School of Medicine, Detroit, Michigan

⁶ The Barbara Ann Karmanos Cancer Institute

Abstract

Increased tryptophan metabolism via the kynurenine pathway is a major mechanism of tumor immuno-resistance. α -[¹¹C]Methyl-L-tryptophan (AMT) is a positron emission tomography (PET) tracer for tryptophan catabolism, and increased AMT uptake has been demonstrated in brain tumors. In this study we evaluated the use of AMT PET for detection of low-grade gliomas and glioneuronal tumors, and determined if kinetic parameters of AMT uptake can differentiate among tumor types. AMT PET images were obtained in 23 patients with newly diagnosed low-grade brain tumors (WHO grade II gliomas and WHO grade I dysembryoplastic neuroepithelial tumors [DNETs]). Kinetic variables, including the unidirectional uptake rate (K-complex) and volume of distribution (VD; which characterizes tracer transport), were measured using a graphical approach from tumor dynamic PET and blood-input data, and metabolic rates (k_3') were also calculated. These values as well as tumor/cortex ratios were compared across tumor types. AMT PET showed increased tumor/cortex K-complex ($n=16$) and/or VD ratios ($n=15$) in 21/23 patients (91%), including 11/13 tumors with no gadolinium enhancement on MRI. No increases in AMT were seen in an oligodendroglioma and a DNET. Astrocytomas and oligoastrocytomas showed higher k_3' tumor/cortex ratios (1.66 ± 0.46) than oligodendrogliomas (0.96 ± 0.21 ; $p=0.001$) and DNETs (0.75 ± 0.39 ; $p<0.001$). These results demonstrate that AMT PET identifies most low-grade gliomas and DNETs by high uptake, even if these tumors are not contrast-enhancing on MRI. Kinetic analysis of AMT uptake shows significantly higher tumor/cortex tryptophan metabolic ratios in astrocytomas and oligoastrocytomas in comparison with oligodendrogliomas and DNETs.

Keywords

gliomas; astrocytoma; low-grade; positron emission tomography; tryptophan; metabolism

Correspondence: Csaba Juhász, M.D., Ph.D. Associate Professor, PET Center, Children's Hospital of Michigan, 3901 Beaubien Blvd., Detroit, MI, 48201, Phone: (313) 966-5136, Fax: (313) 966-9228, juhasz@pet.wayne.edu.

This paper has been published in the Journal of Neuro-oncology (doi 10.1007/s11060-010-0327-1). The final publication is available at www.springerlink.com (www.springerlink.com/content/425506775w60n171)

INTRODUCTION

α -[^{11}C]Methyl-L-tryptophan (AMT) is an amino acid PET tracer that, unlike most other amino acid tracers, is not incorporated into proteins but can be used to image tryptophan metabolism to serotonin and, under certain conditions, metabolism via the immunomodulatory kynurenine pathway [1–3]. Activation of indoleamine 2,3-dioxygenase (IDO), the initial and rate-limiting enzyme of the kynurenine pathway, is considered to be a major mechanism involved in the escape of tumors from the host immune response [4]. In our previous studies of heterogeneous groups of brain tumors, increased AMT uptake was found in both low- and high-grade tumors, and tryptophan metabolic rates measured on PET were lower in tumor samples with no or minimal IDO expression as compared to those with widespread IDO staining [5]. These findings suggested that AMT metabolic rates, measured by PET, may identify brain tumors with widespread IDO expression, which was often seen in low-grade neoplasms.

In the present study, we used dynamic AMT PET scanning with blood input data to quantify kinetic parameters for AMT in low-grade brain tumors, including gliomas and glioneuronal tumors (dysembryoplastic neuroepithelial tumors; DNETs). Low-grade brain tumors often do not show gadolinium enhancement on MRI and most of them have low glucose uptake on 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) PET [6]. Therefore, detection of such tumors is suboptimal, especially after initial treatment, in case of a potential residual/recurrent tumor. In addition, reliable differentiation among various histological types of low-grade gliomas and glioneuronal tumors is not possible using current conventional imaging modalities [7]. We hypothesized that most low-grade brain tumors show increased AMT concentration compared to normal brain tissue, and that AMT metabolic rates measured in brain tumors may differentiate among certain tumor types.

METHODS

Subjects

Twenty-three patients (mean age: 21 years; 3–57 year; 14 males; Table 1) with a recently diagnosed brain tumor underwent dynamic AMT PET scanning before tumor resection. Tumors included 16 WHO grade II gliomas (5 astrocytomas, 3 oligoastrocytomas, 8 oligodendrogliomas) and 7 WHO grade I DNETs, based on post-surgical histological examination performed as described previously [8]. Ten tumors (43%) showed gadolinium enhancement on MRI. FDG PET acquired clinically in 20 patients showed decreased tumor glucose metabolism in 18 and increased metabolism in two, on visual assessment. Imaging (MRI and FDG PET) as well as histologic data of one of these two tumors, a WHO grade II oligodendroglioma showing increased glucose metabolism, have been reported in a previous study, where potential mechanisms of increased glucose uptake in low-grade tumors were discussed [9]. The other patient, a 53 year-old woman, had a non-enhancing oligoastrocytoma, which showed a small increase of glucose metabolism.

AMT PET Scanning Protocol

PET studies were performed using the CTI/Siemens EXACT/HR whole-body positron tomograph (Knoxville, TN, USA) located at the Children's Hospital of Michigan, Detroit. This scanner has a 15 cm field of view and generates 47 image planes with a slice thickness of 3.125mm. The reconstructed image in-plane resolution obtained is $7.5 \pm 0.4\text{mm}$ at full-width half-maximum and $7.0 \pm 0.5\text{mm}$ in the axial direction for the AMT PET. The procedure for AMT PET scanning has been described previously [5,8,10]. In brief, after 6 hours of fasting, a venous line was established for injection of AMT (0.1 mCi/kg). A second venous line was used for collection of timed blood samples (0.5 mL/sample, collected at 0,

20, 30, 40, 50, and 60 minutes after AMT injection). After injection of AMT, a 20-minute dynamic PET scan of the heart was performed (sequence: 12×10 s, 3×60 s, and 3×300 s) in 2D mode to obtain the left ventricular (LV) input function. Continuation of the blood input function beyond this initial 20 minutes was achieved using venous blood samples as described previously [11,12]. At 25 minutes after tracer injection, a dynamic emission scan of the brain (7×5 min) was acquired in high-sensitivity 3D mode. Measured attenuation correction, obtained from 15-min transmission scans, was applied to the AMT PET images. For visualization of brain and tumor AMT concentrations, summed activity images using frames 30–60 min post-injection were created.

Quantitative PET Image Analysis

To quantify unidirectional AMT transport and metabolism in tumors, a Patlak graphical analysis [13,14] was performed using the arterial LV (left ventricle of the heart) input function and the dynamic brain sequence (7×5 min frames starting 25 min after injection), as described previously [5,8]. The Patlak graphical approach provides two kinetic parameters calculated from the Patlak plot: 1. The slope parameter that corresponds to the previously described K-complex [2,10] reflecting the unidirectional uptake of tracer into tissue; 2. The y-intercept of the plot provides the volume of distribution (VD), which characterizes the transport rate of AMT into the tumor tissue. In addition, the quotient between slope and intercept (K/VD) yielded parameter k_3' , an estimate of the k_3 parameter that characterizes the irreversible trapping of AMT, presumably due to enzymatic conversion. The advantages and limitations of using these parameters have been discussed previously [2,10].

The above parameters were measured in tumor regions of interest that were directly defined on the summed activity images and on co-registered axial gadolinium-enhanced MRI images (in patients where increased uptake on the PET scan was not obvious) in all planes where the tumor was visualized (except the very top and bottom planes, to avoid partial volume effects). Only tumor parts showing at least 50% of the average activity were included in the final regions of interest because necrotic tumor regions are not metabolically active [5]. Regions of interest were also obtained from contralateral homotopic cortex, and the same kinetic parameters were calculated for each cortical region.

Design and statistical analysis

First, AMT PET images (summed images from 30–60 min after tracer injection) were inspected for focal increases. Subsequently, tumor/contralateral cortex ratios were calculated for both the measured K-complex and VD values. Tumors with abnormal increases were defined as having either K-complex or VD tumor/cortex ratios above 1.10 (more than 10% increase). This conservative threshold was selected based on our previous studies, showing that asymmetries of cortical AMT uptake in homotopic cortical regions were below 8% (average normal mean asymmetry + 2 SD) in healthy subjects [15]. K-complex and VD values as well as tumor/cortex ratios were compared between gadolinium enhancing vs. non-enhancing tumors using an unpaired t-test. Further, kinetic parameters and tumor/cortex ratios of different tumor types (astrocytomas, oligoastrocytomas, oligodendrogliomas, DNETs) were compared using analysis of variance (ANOVA). In this latter comparison not only K-complex and VD, but also calculated k_3' values and ratios were included. Since age of patients was different among tumor types (patients with DNET were much younger [mean: 11 years] than those with gliomas [mean: 39 years]), significant differences were re-tested by entering age as a co-variate. $P < 0.05$ was considered to be significant.

RESULTS

PET showed increased tumor concentration of AMT by both visual assessment and tumor/cortex K-complex and/or VD ratios in 21/23 cases (91%), including 11 of 13 tumors (85%) with no gadolinium enhancement (Table 1, Figure 1). Two tumors, one patient each with an oligodendroglioma and a DNET, showed no increase in AMT concentration. In the 21 AMT-positive cases, increased AMT tissue concentration was related to increased unidirectional uptake (K-complex; $n=16$) and/or increased transport (VD; $n=15$); both parameters were increased in 10 patients (9 gliomas, 1 DNET). Among AMT kinetic parameters, tumor VD values were higher in contrast-enhancing tumors as compared to non-enhancing lesions (mean: 0.48 ± 0.15 vs. 0.35 ± 0.10 , respectively; $p=0.02$). The four tumor types did not differ in k_3' values, VD values or VD ratios ($p>0.3$), were marginally different in K-complex values ($p=0.05$) and ratios ($p=0.067$), but were highly significantly different in k_3' tumor/cortex ratios ($p=0.001$). Therefore, post-hoc tests were performed for k_3' ratios, and these showed that astrocytomas had higher values than pure oligodendrogliomas ($p=0.014$) and DNETs ($p=0.002$) but they were not different from oligoastrocytomas ($p=0.18$). Therefore, astrocytomas were combined with oligoastrocytomas, and this group showed higher k_3' ratios (1.66 ± 0.46) than oligodendrogliomas (0.96 ± 0.21 ; $p=0.001$) and DNETs (0.75 ± 0.39 ; $p<0.001$) (Figure 2); values of these latter two tumor types were not different from each other ($p=0.29$). A cutoff k_3' tumor/cortex ratio value of 1.3 identified astrocytomas/oligoastrocytomas with 100% specificity and 75% sensitivity. Significant differences between astrocytomas/oligoastrocytomas vs. oligodendrogliomas ($p=0.006$) and DNETs ($p=0.028$) remained after controlling for age-differences among groups.

DISCUSSION

This study demonstrates that increased AMT uptake on PET can detect low-grade gliomas and glioneuronal tumors, including most tumors with no gadolinium enhancement on MRI and decreased FDG uptake. The results of the kinetic analysis also show that AMT tissue concentration in low-grade brain tumors is related to increased tryptophan transport and/or high metabolic rate. However, high tumor/cortex ratios for AMT metabolic rates in tumors with an astrocytic component (astrocytomas and oligoastrocytomas) may differentiate these tumor types from oligodendrogliomas and DNETs prior to surgery. Although the number of cases was limited in this study, these results suggest that AMT k_3' tumor/cortex ratios above 1.3 may be indicative of astrocytomas or oligoastrocytomas in contrast to oligodendrogliomas or DNETs. On the other hand, astrocytomas and oligoastrocytomas may not be differentiated from each other by kinetic AMT parameters.

Low-grade gliomas and glioneuronal tumors are common intracranial tumors in children, comprising about 60% of supratentorial hemispheric lesions [16]. In adults, patients with low-grade gliomas are younger than patients with high-grade gliomas, with a median age below 40 [17]; mean age of patients with gliomas was 39 years in our study. Despite the indolent course of these tumors, the overall long-term prognosis is poor, with a 10-year overall survival of 36% in a recent study [17]. In addition to size and extent of resection, histology of low-grade gliomas is a significant independent factor of survival: astrocytomas have worse prognosis than other tumor types, and high proportions of adult grade II infiltrative astrocytomas undergo malignant transformation [7,17–19]. In contrast, oligodendrogliomas have a longer, although highly variable, latent period to malignant transformation, better response to chemotherapy and better long-term prognosis [7,20–22]. DNETs are most common in children, grow very slowly, and often manifest with seizures. Therefore, differentiation of tumor types, in addition to tumor grades, has clinical significance in designing management. At times, critical decisions regarding the extent of surgical resection require accurately identifying tumoral versus nontumoral tissue and

determining whether anaplastic features are present in the specimen. It is also important to recognize whether an oligodendroglial component is present because of the treatment-related survival advantage afforded to patients with oligodendrogliomas [7]. Many of these patients undergo pre-treatment biopsy, which is prone to sampling error. Use of non-invasive imaging techniques, including AMT PET, could assist predicting tumor grade and type for treatment planning.

Most imaging studies of brain tumors have focused on differentiating among tumor grades and assess prognosis, while imaging markers of specific histology types are scarce and poorly validated. Recent studies using diffusion weighted imaging reported significant differences in apparent diffusion coefficient and fractional anisotropy values as well as histograms in low-grade astrocytomas vs. oligodendrogliomas [23–25]. Increased amino acid tumor tissue uptake, as compared to normal brain tissue, has been reported in low-grade gliomas by ^{11}C -methionine PET [26], with relatively higher concentration values in oligodendrogliomas [27–29]. However, static PET images provide no kinetic information to differentiate tracer transport vs. metabolism, and, therefore, have a limited value in evaluating tumor types when using a single measure. In addition, DNETs typically show low uptake on methionine PET [30,31], while AMT PET showed increased uptake in all but one case in our study; this finding supports the notion that mechanisms of uptake and metabolism of AMT differ from those of methionine (or other amino acids incorporated into proteins). Our previous studies have demonstrated that tumor grades correlate with both AMT VD (positively; higher grade, higher AMT transport) and k_3' values (negatively; lower AMT metabolic rate in high-grade tumors), while the present study shows that tumor/cortex ratios of k_3' may predict if the tumor has an astrocytic component, at least in case of low-grade neoplasms, which often can be suspected by lack of gadolinium enhancement on MRI. Gadolinium-enhancing tumors have higher AMT VD (transport rate) values, suggesting that at least some of the increased transport is related to impaired blood-brain-barrier. Furthermore, our previous studies have shown that high tumor proliferative index (based on ki-67 immunostaining) is associated with higher AMT VD values (5), suggesting that increased tumor tryptophan transport is related to tumor proliferation. In addition, increased transport of AMT may also be related to upregulation of the large neutral amino acid transporter (a transport protein for both methionine and tryptophan) at the tumor vascular endothelium, which has been shown in gliomas in the context of increased methionine uptake [32]. Finally, increased AMT uptake, particularly AMT transport rate, may be related to increased tumor perfusion, although late uptake images (such as the one shown on Figure 1), reflecting uptake 30–60 min after tracer injection, are unlikely to be driven directly by blood flow or perfusion changes. Further comparison of AMT kinetic variables to advanced MRI (such as DWI, perfusion or MR spectroscopic imaging) characteristics may further clarify mechanisms of increased AMT uptake and also provide more accurate differentiation of brain tumor types and grades. Nevertheless, high AMT transport and metabolism in low-grade gliomas and DNETs may render this imaging method a promising future approach to assist with the initial diagnosis, optimal management, and long-term follow-up and treatment of patients with low-grade gliomas. Further clinical validation in larger patient groups and comparisons with other imaging modalities are warranted to explore these possibilities.

The mechanisms of tryptophan metabolism in low-grade gliomas require further investigation. High AMT metabolic rates in astrocytomas and oligoastrocytomas suggest a role of mechanisms responsible for metabolic conversion of AMT (and tryptophan) in these tumors. Our previous studies demonstrated that trapping of AMT in brain tumors may be related to activation of the kynurenine pathway, mediated by increased expression of the initial, rate-limiting enzyme IDO in tumor cells and other tissue components [5]. Expression of IDO was indeed widespread in some low-grade gliomas but was mostly confined to

tumor vessels (or was completely lacking) in high-grade gliomas in our recent study [5]. The findings of the present study suggest that in low-grade tumors, presence of astrocytic tumor cells may be a key to high tryptophan metabolic rates, possibly mediated by increased IDO expression in these cells or other cell types present in these tumors. Since low-grade astrocytomas carry a worse prognosis than other low-grade tumor types, high AMT metabolic rates in such tumors may represent a poor prognostic factor related to upregulation of IDO. This would be in keeping with previous reports of prognostic value of IDO expression in various extracranial tumor types [33–35]. Further studies, comparing AMT kinetics with tissue expression of IDO and kynurenine metabolites as well as long-term outcome of these patients are required to test this hypothesis. Emerging therapeutic approaches with IDO-inhibitors [36], targeting tumor tryptophan metabolism, may be useful to treat brain tumors showing high AMT metabolic rates in future studies.

Acknowledgments

The study was supported by a grant from the National Cancer Institute (#CA123451, to C. Juhász). The authors thank Cathie Germain, MA, Angela Wigeluk, CNMT, Carole Clapko, CNMT, Galina Rabkin, CNMT, Melissa Burkett, CNMT, Andrew Mosqueda, CNMT, Anna DeBoard, RN, Jane Cornett, RN, and Mei-li Lee, MS, for their assistance in patient recruitment and preparation, as well as performing the PET studies.

References

1. Diksic M, Nagahiro S, Sourkes TL, Yamamoto YL. A new method to measure brain serotonin synthesis in vivo. I. Theory and basic data for a biological model. *J Cereb Blood Flow Metab.* 1990; 10:1–12. [PubMed: 2298826]
2. Muzik O, Chugani DC, Chakraborty P, Mangner T, Chugani HT. Analysis of [C-11]alpha-methyl-tryptophan kinetics for the estimation of serotonin synthesis rate in vivo. *J Cereb Blood Flow Metab.* 1997; 17:659–669. [PubMed: 9236722]
3. Chugani DC, Muzik O. Alpha[C-11]methyl-L-tryptophan PET maps brain serotonin synthesis and kynurenine pathway metabolism. *J Cereb Blood Flow Metab.* 2000; 20:2–9. [PubMed: 10616786]
4. Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. *J Clin Invest.* 2007; 117:1147–1154. [PubMed: 17476344]
5. Batista CEA, Juhász C, Muzik O, Kupsky WJ, Barger G, Chugani HT, Chugani HT, Mittal S, Sood S, Chakraborty PK, Chugani DC. Imaging correlates of differential expression of indoleamine 2,3-dioxygenase in human brain tumors. *Mol Imaging Biol.* 2009; 11:460–466. [PubMed: 19434461]
6. Chen W. Clinical applications of PET in brain tumors. *J Nucl Med.* 2007; 48:1468–81. [PubMed: 17704239]
7. Mittal S, Szlachetky MC, Barger GR. Low-grade gliomas in adults. *Curr Treat Options Neurol.* 2008; 10:271–284. [PubMed: 18579014]
8. Juhász C, Chugani DC, Muzik O, et al. In vivo uptake and metabolism of alpha-[¹¹C]methyl-L-tryptophan in human brain tumors. *J Cereb Blood Flow Metab.* 2006; 26:345–357. [PubMed: 16079785]
9. Atkinson M, Juhász C, Shah J, Guo X, Kupsky W, Fuerst D, Johnson R, Watson C. Paradoxical imaging findings in cerebral gliomas. *J Neurol Sci.* 2008; 269:180–183. [PubMed: 18255100]
10. Chugani DC, Muzik O, Chakraborty P, Mangner T, Chugani HT. Human brain serotonin synthesis capacity measured in vivo with alpha-[C-11]methyl-L-tryptophan. *Synapse.* 1998; 28:33–43. [PubMed: 9414016]
11. Muzik O, Behrendt DB, Mangner TJ, Chugani HT. Design of a pediatric protocol for quantitative brain FDG studies with PET not requiring invasive blood sampling. *J Nucl Med.* 1994; 35:104. [abstract]. [PubMed: 8271030]
12. Suhonen-Pulvi H, Ruotsalainen U, Kinnala A, Bergman J, Haaparanta M, Teräs M, Mäkelä P, Solin O, Wegelius U. FDG-PET in early infancy: simplified quantification methods to measure cerebral glucose utilization. *J Nucl Med.* 1995; 36:1249–1254. [PubMed: 7790951]

13. Gjedde A. High- and low-affinity transport of D-glucose from blood to brain. *J Neurochem.* 1981; 36:1463–1471. [PubMed: 7264642]
14. Patlak CS, Blasberg RG, Fenstermacher JD. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. *J Cereb Blood Flow Metab.* 1983; 3:1–7. [PubMed: 6822610]
15. Juhász C, Chugani DC, Muzik O, Shah A, Asano E, Mangner T, Chakraborty PK, Sood S, Chugani HT. Alpha-methyl-L-tryptophan PET detects epileptogenic cortex in children with intractable epilepsy. *Neurology.* 2003; 60:960–968. [PubMed: 12654960]
16. Pollack IF. Brain tumors in children. *N Engl J Med.* 1994; 331:1500–1507. [PubMed: 7969301]
17. Schomas DA, Laack NN, Rao RD, Meyer FB, Shaw EG, O'Neill BP, Giannini C, Brown PD. Intracranial low-grade gliomas in adults: 30-year experience with long-term follow-up at Mayo Clinic. *Neuro Oncol.* 2009; 11:437–445. [PubMed: 19018039]
18. Vertosick FT Jr, Selker RG, Arena VC. Survival of patients with well-differentiated astrocytomas diagnosed in the era of computed tomography. *Neurosurgery.* 1991; 28:496–501. [PubMed: 1851971]
19. McCormack BM, Miller DC, Budzilovich GN, Voorhees GJ, Ransohoff J. Treatment and survival of low-grade astrocytoma in adults—1977–1988. *Neurosurgery.* 1992; 31:636–642. [PubMed: 1407448]
20. Mason WP, Krol GS, DeAngelis LM. Low-grade oligodendroglioma responds to chemotherapy. *Neurology.* 1996; 46:203–207. [PubMed: 8559376]
21. Olson JD, Riedel E, DeAngelis LM. Long-term outcome of low-grade oligodendroglioma and mixed glioma. *Neurology.* 2000; 54:1442–1448. [PubMed: 10751254]
22. Kitange GJ, Smith JS, Jenkins RB. Genetic Alterations and chemotherapeutic response in human diffuse gliomas. *Expert Rev Anticancer Ther.* 2001; 1:595–605. [PubMed: 12113092]
23. Tozer DJ, Jäger HR, Danchaivijitr N, Benton CE, Tofts PS, Rees JH, Waldman AD. Apparent diffusion coefficient histograms may predict low-grade glioma subtype. *NMR Biomed.* 2007; 20:49–57. [PubMed: 16986106]
24. Khayal IS, McKnight TR, McGue C, Vandenberg S, Lamborn KR, Chang SM, Cha S, Nelson SJ. Apparent diffusion coefficient and fractional anisotropy of newly diagnosed grade II gliomas. *NMR Biomed.* 2009; 22:449–455. [PubMed: 19125391]
25. Khayal IS, Nelson SJ. Characterization of low-grade gliomas using RGB color maps derived from ADC histograms. *J Magn Reson Imaging.* 2009; 30:209–213. [PubMed: 19557741]
26. Galldiks N, Kracht LW, Berthold F, Miletic H, Klein JC, Herholz K, Jacobs AH, Heiss WD. [¹¹C]-L-Methionine positron emission tomography in the management of children and young adults with brain tumors. *J Neurooncol.* 2010; 96:231–239. [PubMed: 19575148]
27. Hatakeyama T, Kawai N, Nishiyama Y, Yamamoto Y, Sasakawa Y, Ichikawa T, Tamiya T. ¹¹C-methionine (MET) and ¹⁸F-fluorothymidine (FLT) PET in patients with newly diagnosed glioma. *Eur J Nucl Med Mol Imaging.* 2008; 35:2009–2017. [PubMed: 18542957]
28. Kato T, Shinoda J, Nakayama N, Miwa K, Okumura A, Yano H, Yoshimura S, Maruyama T, Muragaki Y, Iwama T. Metabolic assessment of gliomas using ¹¹C-methionine, [¹⁸F] fluorodeoxyglucose, and ¹¹C-choline positron-emission tomography. *AJNR Am J Neuroradiol.* 2008; 29:1176–1182. [PubMed: 18388218]
29. Kato T, Shinoda J, Oka N, Miwa K, Nakayama N, Yano H, Maruyama T, Muragaki Y, Iwama T. Analysis of ¹¹C-methionine uptake in low-grade gliomas and correlation with proliferative activity. *AJNR Am J Neuroradiol.* 2008; 29:1867–1871. [PubMed: 18687745]
30. Maehara T, Nariai T, Arai N, Kawai K, Shimizu H, Ishii K, Ishiwata K, Ohno K. Usefulness of [¹¹C]methionine PET in the diagnosis of dysembryoplastic neuroepithelial tumor with temporal lobe epilepsy. *Epilepsia.* 2004; 45:41–45. [PubMed: 14692906]
31. Rosenberg DS, Demarquay G, Jouvet A, Le Bars D, Streichenberger N, Sindou M, Kopp N, Mauguière F, Ryvlin P. [¹¹C]-Methionine PET: dysembryoplastic neuroepithelial tumours compared with other epileptogenic brain neoplasms. *J Neurol Neurosurg Psychiatry.* 2005; 76:1686–1692. [PubMed: 16291894]

32. Okubo S, Zhen HN, Kawai N, Nishiyama Y, Haba R, Tamiya T. Correlation of L-methyl-¹¹C-methionine (MET) uptake with L-type amino acid transporter 1 in human gliomas. *J Neurooncol*. 2010;100:1007/s11060-010-0117-9
33. Astigiano S, Morandi B, Costa R, Mastracci L, D'Agostino A, Ratto GB, Melioli G, Frumento G. Eosinophil granulocytes account for indoleamine 2,3-dioxygenase-mediated immune escape in human non-small cell lung cancer. *Neoplasia*. 2005; 7:390–396. [PubMed: 15967116]
34. Okamoto A, Nikaido T, Ochiai K, Takakura S, Saito M, Aoki Y, Ishii N, Yanaihara N, Yamada K, Takikawa O, Kawaguchi R, Isonishi S, Tanaka T, Urashima M. Indoleamine 2,3-dioxygenase serves as a marker of poor prognosis in gene expression profiles of serous ovarian cancer cells. *Clin Cancer Res*. 2005; 11:6030–6039. [PubMed: 16115948]
35. Brandacher G, Perathoner A, Ladurner R, Schneeberger S, Obrist P, Winkler C, Werner ER, Werner-Felmayer G, Weiss HG, Göbel G, Margreiter R, Königsrainer A, Fuchs D, Amberger A. Prognostic value of indoleamine 2,3-dioxygenase expression in colorectal cancer: effect on tumor-infiltrating T cells. *Clin Cancer Res*. 2006; 12:1144–1151. [PubMed: 16489067]
36. Liu X, Newton RC, Friedman SM, Scherle PA. Indoleamine 2,3-dioxygenase, an emerging target for anti-cancer therapy. *Curr Cancer Drug Targets*. 2009; 9:938–952. [PubMed: 20025603]

Figure 1.

Increased AMT concentration in a non-enhancing grade II astrocytoma, in a 57 year-old man. (A) T1-weighted post-gadolinium MRI shows a large, right medial temporal mass with no contrast enhancement. (B) AMT PET shows inhomogeneous high tracer concentration in the tumor mass. (C) MRI/PET fusion image. Kinetic analysis showed a 78% increase of tumor k_3' (as compared to k_3' calculated in the contralateral temporal cortex).

Figure 2.

Astrocytomas and oligoastrocytomas (n=8) show higher AMT metabolic (k_3') tumor/cortex ratios (mean: 1.66 ± 0.46) than oligodendrogliomas (n=8, 0.96 ± 0.21 , $p=0.001$) and dysembryoplastic neuroepithelial tumors (DNETs; n=7, 0.75 ± 0.39 ; $p<0.001$). Circles indicate individual values; crossbars represent mean values in each tumor group.

Table 1

Gender, age, tumor type, MRI contrast enhancement and tumor/cortex ratios of AMT kinetic values of 23 patients with low-grade brain tumors

Gender	Age	Tumor type	MRI: contrast enhancing	K ratio	VD ratio	k ₃ ' ratio
F	33	Astro	no	1.33	0.96	1.39
F	41	Astro	yes	1.37	1.13	1.21
M	49	Astro	no	1.87	1.08	1.74
M	55	Astro	no	1.43	0.97	1.47
M	57	Astro	no	2.08	1.17	1.78
M	24	Mixed	yes	4.68	2.25	2.08
F	53	Mixed	yes	1.53	0.62	2.48
F	53	Mixed	no	1.16	1.05	1.10
M	13	Oligo	yes	1.30	1.68	0.77
M	21	Oligo	no	1.11	1.13	0.98
M	29	Oligo	yes	1.77	1.58	1.12
F	32	Oligo	no	1.02	1.23	0.81
M	36	Oligo	no	1.00	0.81	1.23
F	41	Oligo	yes	1.74	1.70	1.02
M	44	Oligo	yes	2.23	3.58	0.62
M	50	Oligo	yes	1.66	1.44	1.15
M	3	DNET	no	0.99	2.60	0.38
F	6	DNET	no	1.38	1.32	1.04
F	10	DNET	no	1.05	1.70	0.62
M	12	DNET	yes	0.99	1.61	0.61
M	15	DNET	yes	0.43	1.81	0.24
M	15	DNET	no	1.28	1.00	1.28
F	17	DNET	no	1.06	0.95	1.12

DNET: dysembryoplastic neuroepithelial tumor; Astro: astrocytoma, Mixed: mixed glioma (oligoastrocytoma), oligo: oligodendroglioma; K: K-complex; VD: volume of distribution; k₃': AMT metabolic rate