Increased tryptophan uptake on PET has strong independent prognostic value in patients with a previously treated high-grade glioma

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Background. Previously, we demonstrated the high accuracy of alpha-[11C]methyl-L-tryptophan (AMT) PET for differentiating recurrent gliomas from radiation injury. The present study evaluated the prognostic value of increased AMT uptake in patients with previously treated high-grade glioma.

Methods. AMT-PET was performed in 39 patients with suspected recurrence of World Health Organization grades III–IV glioma following surgical resection, radiation, and chemotherapy. Mean and maximum standardized uptake values (SUVs) and unidirectional AMT uptake (K) were measured in brain regions suspicious for tumor and compared with the contralateral cortex (ie, background). Optimal cutoff thresholds for 1-year survival prediction were determined for each AMT parameter and used for calculating the prognostic value of high (above threshold) versus low (below threshold) values for post-PET overall survival (OS).

Results. In univariate analyses, 1-year survival was strongly associated with 3 AMT parameters (SUVmax, SUVmean, and tumor-to-background K-ratio; odds ratios: 21.3–25.6; \( P \leq .001 \)) and with recent change in MRI contrast enhancement (odds ratio: 14.7; \( P = .02 \)). Median OS was 876 days in the low- versus 177 days in the high-AMT groups (log-rank \( P < .001 \)). In multivariate analyses, all 3 AMT parameters remained strong predictors of survival: high AMT values were associated with unfavorable 1-year survival (binary regression \( P \leq .003 \)) and shorter overall survival in the whole group (Cox regression hazard ratios: 5.3–10.0) and in patients with recent enhancement change on MRI as well (hazard ratios: 7.0–9.3; \( P \leq .001 \)).

Conclusion. Increased AMT uptake on PET is highly prognostic for 1-year and overall survival, independent of MRI contrast enhancement and other prognostic factors in patients with a previously treated high-grade glioma.

Keywords: amino acid PET, high-grade glioma, MRI, survival, tryptophan.

High-grade gliomas have a dismal prognosis despite the survival benefit provided by microsurgical resection and subsequent radiation and chemotherapy. Long-term clinical management of this patient population can be very challenging. It is often difficult for the clinician to determine when to initiate additional treatment or redirect efforts toward palliative care. Clinical decision making is routinely guided by findings on serial conventional MRI, which includes T1-weighted gadolinium enhanced (T1-Gad) and T2-weighted or fluid attenuation inversion recovery (FLAIR) MR sequences. Generally, persistent enlargement or changing pattern of enhancement or increase in nonenhancing T2 or FLAIR signals is considered a sign of tumor recurrence or progression. The routine follow-up protocols for conventional MRI carry serious limitations. One of the greatest hindrances is the overlapping location and similar appearances of treatment-related necrosis and tumor recurrence. Discrepancies between the clinical and radiological status are also not uncommon. There are a handful of advanced MRI techniques, such as perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI), and MR spectroscopy, as well as PET imaging using amino acid and nucleotide radiotracers, that hold the promise of overcoming these limitations of conventional MRI. These newer techniques may help identify...
residual tumor or differentiate radiation necrosis from recurrent neoplasm.8–14 However, the prognostic values of these imaging methods have yet to be investigated in depth.

In the present study, we utilized alpha-[11C]methyl-L-tryptophan (AMT) PET for prediction of survival. AMT is an amino acid radiotracer that is capable of tracking tumoral tryptophan transport and metabolism via the immunosuppressive kynurenine pathway.15–18 Earlier, we showed that both contrast-enhancing and nonenhancing gliomas have increased AMT uptake19 and that increased trapping in the glioma tissue is associated with the upregulation of indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme of the kynurenine pathway.20 Detailed volumetric analysis has also demonstrated that the increased AMT uptake on PET is not confined to the area of contrast enhancement in high-grade gliomas but often extends to nonenhancing tissue, which was proven to have tumor cell infiltration in image-guided stereotactically acquired tissue samples.21 Furthermore, we have demonstrated that AMT-PET can differentiate radiation injury from tumor recurrence with a high degree of accuracy.14

In the present study, we assessed the ability of AMT-PET to predict survival in patients with high-grade astrocytic tumors who had previously undergone microsurgical resection with subsequent radiation and chemotherapy. AMT-PET was performed due to the ambiguity of the information provided by conventional MRI. We hypothesized that higher degree of focal increase of AMT uptake in the previously treated cerebral hemisphere is associated with shorter survival. We also evaluated whether AMT-PET can provide added prognostic information to clinical and MRI data.

Materials and Methods

Patient Population

AMT-PET scans were acquired and analyzed from 39 patients (mean age, 57 y; range, 28–89; Table 1) (15 of these patients were included in our previous study on AMT-PET for differentiating recurrent gliomas from radiation injury14). The following inclusion criteria were used: (i) history of histologically proven high-grade (World Health Organization grade III or IV) astrocytic glioma; (ii) previous treatment with surgery (tumor resection or debulking) followed by radiation and chemotherapy; (iii) one of the following diagnostic abnormalities: increasing size of contrast-enhancing tissue, which was proven to have tumor cell infiltration in image-guided stereotactically acquired tissue samples.21 Furthermore, we have demonstrated that AMT-PET can differentiate radiation injury from tumor recurrence with a high degree of accuracy.14

AMT-PET Scanning Protocol

The PET studies were performed using a Siemens EXACT/HR whole-body positron emission tomograph. The PET image in-plane resolution was 7.5 ± 0.4 mm at full-width half-maximum and 7.0 ± 0.5 mm at full-width half-maximum in the axial direction. The AMT tracer was synthesized by using a yield-procedure as outlined previously.22 The procedure for AMT-PET scanning has also been described previously.14,15 In short, following 6 h of fasting, a slow bolus of AMT (3.7 MBq/kg) was injected over 2 min via a venous line. For collection of timed blood samples, a second venous line was established. In the initial 20 min of the scan following tracer injection, a dynamic PET scan of the heart was performed to obtain the blood input function from the left cardiac ventricle noninvasively. The blood input function was continued beyond these initial 20 min by using venous blood samples (0.5 mL/sample, collected at 20, 30, 40, 50, and 60 min after AMT injection) as described previously.19,24 At 25 min after tracer injection, a dynamic emission scan of the brain (7 × 5 min) was obtained. Measured attenuation correction, scatter, and decay correction were applied to all PET images. For visualization of AMT uptake, averaged activity images 30–55 min postinjection were created and converted to an AMT standardized uptake value (SUV) image. For quantification of AMT accumulation, a Patlak graphical analysis was performed,25 which yielded AMT K-values, as described previously.14,15,19,23 The AMT K-value reflects the unidirectional uptake of tracer into tissue,26 which is proportional to the metabolism of tryptophan via the serotonin (in normal brain) and/or the kynurenine pathway.16

MRI Protocol

Diagnostic MRIs with routine T2, FLAIR, and T1-Gad sequences acquired closest in time to the AMT-PET were used in this study. MRI was performed on either a Siemens MAGNETOM Trio TIM 3.0 Tesla scanner, a GE Signa HDxt 3.0 Tesla scanner, or a Philips Achieva TX 3.0 Tesla scanner, using similar parameters on all scanners.

PET Image Analysis

For image analysis, the 3D Slicer 3.6.3 software suite was used (http://www.slicer.org).21,23 On the AMT SUV images, regions of interest (ROIs) were drawn on suspicious (tumor and/or treatment affected) areas of increased AMT SUV in corresponding brain regions with contrast enhancement and/or T2/FLAIR signal changes on MRI (Fig. 1). In cases with no obvious AMT increases on visual assessment, ROIs were placed on brain tissue adjacent to the surgical cavity showing suspicious MRI abnormalities. As a reference (background) region, at least 3 ROIs were drawn on the homotopic cortex contralateral to the suspicious lesional area, and the values from these ROIs were averaged. Visual cortex, which has high physiologic AMT uptake, was not used as a background region. Using the AMT SUV image and K-values derived
from the Patlak plot, the following AMT-PET parameters were assessed: SUV\textsubscript{mean} (the mean SUV in the ROI with the highest SUV), SUV\textsubscript{max} (the maximal SUV measured in a single voxel within the area of suspicious imaging abnormality), SUV\textsubscript{mean} tumor-to-background ratio, SUV\textsubscript{max} tumor-to-background ratio, K\textsubscript{mean} (the mean K-value in the suspicious lesion or area in the ROI with the highest K), and K\textsubscript{mean} tumor-to-background ratio (the mean K-value in the ROI with the highest K divided by the mean K of the reference cortical ROIs). For the sake of simplicity, we will refer to the K\textsubscript{mean} as K and to the K\textsubscript{mean} tumor-to-background ratio as K-ratio.

### Statistical Analysis

First, a receiver operating characteristic (ROC) analysis was performed, and areas under the curve (AUCs) were used to determine the most accurate AMT-PET–related variable(s) and an optimal cutoff threshold value (with highest sensitivity plus specificity) to predict 1-year survival. These threshold values were then applied to categorize the values of each AMT measure as either “high” or “low” to be used for the analysis of overall survival (OS) after the PET scan.

Survival time distribution among the high and low value groups of each AMT measure, as defined by the ROC analyses,
was examined using the Mantel–Cox log-rank test. First, univariate analyses were performed to explore the association of survival and potential clinical and MRI prognostic factors (age, gender, World Health Organization grade of tumor, a second surgery or bevacizumab treatment after AMT-PET, as well as enhancement change on T1-Gad [as defined in the Patient Population section] within 6 mo preceding AMT-PET) and AMT parameters. Prognostic factors found significant in the univariate analysis along with factors reported to be strongly prognostic by the literature (such as age and histologic grade) were included in multivariate analyses with each significant AMT parameter. In both the univariate and multivariate analyses, binary logistic regression was used to obtain odds ratios (ORs) for 1-year survival, and the proportional hazard Cox regression was utilized to obtain hazard ratios (HRs) for OS.

Cox regression survival analyses were also performed to test the ability of the various AMT-PET parameters to predict survival. Based on the results of these comparisons and in continuity with our previous studies, we have restricted the Results section to the presentation of the 3 best performing PET parameters: the SUVmean, SUVmax, and K-ratio. From here on, we will refer to these as the studied AMT parameters. Results for the other parameters (SUV tumor-to-background ratios and tumor K-values), which showed poorer performance, are not shown.

Finally, because of the strong prognostic association, survival analyses were repeated in a subgroup of patients with enhancement change on T1-Gad (ie, increasing size of contrast enhancement or the appearance of a new enhancing lesion) suspicious for tumor progression on MRI within 6 months before AMT-PET (n = 29). Statistical analysis was carried out using SPSS Statistics 20.0 software. P < .05 was considered statistically significant.

**Results**

**Prediction of Survival by AMT-PET in the Whole Group**

The estimated median survival time was 417 days (95% confidence interval [CI]: 245–589 d), that is, 13.9 months after the AMT-PET scan and 27.4 months from the initial surgery. Of the 39 patients, 28 (72%) were alive 6 months, 20 (51%) 1 year, and 8 (25%) 2 years after the AMT-PET scan. The longest survivor was still alive more than 6 years after the PET scan.

For prediction of 1-year survival, the ROC analyses showed high AUCs (0.83–0.86) with all studied AMT parameters. SUV mean had the highest sensitivity with 89%, while SUV max had the highest specificity (80%) among the SUV-based parameters. The K-ratio also showed high specificity (88%; Table 2). Estimated median survival times were significantly different between the high and low groups in all AMT measures on the log-rank tests (P < .001).

Values deemed as low (ie, below threshold, as defined by ROC analysis) were associated with ≏5-fold longer OS time (876 d for low-uptake groups of each AMT parameter vs 177 d for high-uptake groups; Table 3, Fig. 2).

In univariate analyses, 1-year survival was significantly associated with SUVmean (OR: 25.6), SUVmax (OR: 21.3), and K-ratio (OR: 24.4) (P ≤ .001 for all), as well as with recent change in
enhancement on MRI (OR: 14.7, P = .02), but not with other potential prognostic factors (Table 4). Univariate analyses of the same variables with OS also showed similar results, with high values in AMT parameters associated with up to 10-fold hazard (P < .001 for all 3 AMT parameters; Table 4), while recent enhancement change on MRI was associated with ~9-fold hazard (P = .003; Table 4). Repeat surgery (16 patients) and/or bevacizumab treatment (16 patients, including 5 who also had repeated surgery) after AMT-PET were not prognostic (Table 4).

In multivariate analyses with each studied AMT parameter, including age, histologic grade, and (based on the results of the univariate analyses) recent enhancement change as covariates, AMT SUVmean, SUVmax, and K-ratio were all significant independent predictors of 1-year survival (ORs: 18.5–35.7, P ≤ .003; Table 5), while recent enhancement change reached significance only in the analysis with SUVmean (OR: 14.3, P = .04; Table 5; see examples in Fig. 3). Using the same covariates, SUVmean, SUVmax, and K-ratio were also independent predictors of OS (HRs: 5.3–10.0, P ≤ .001 for all), and recent enhancement change was significant in all analyses as well (HRs: 5.6–11.4, P ≤ .001; Table 5).

**Prediction of Survival in the Subgroup With Recent MRI Enhancement Change**

The ROC analyses for 1-year survival prediction indicated high AUCs (0.77–0.87) for all studied AMT parameters in the subgroup with recent MRI enhancement change. Threshold values were identical to those of the whole patient population except for SUVmax, which was slightly lower in this patient subgroup (Table 2). The estimated median survival was ~3.5 times longer in the low-uptake groups defined by the AMT parameters (log-rank P ≤ .001 in all; Fig. 2). For 1-year survival, the age- and grade-adjusted multivariate analyses of separate AMT parameters again found all 3 AMT parameters to be significant independent predictors (K-ratio OR: 30.3, 95% CI: 2.6–333, P = .006; SUVmean OR: 23.8, 95% CI: 3.0–200, P = .003; SUVmax OR: 14.5, 95% CI: 2.2–100, P = .005). The age- and grade-adjusted OS prediction also showed similar results to the whole population, with K-ratio (HR: 9.3, 95% CI: 2.7–32.3, P ≤ .0005), SUVmean (HR: 7.0, 95% CI: 2.2–22.2, P = .001), and SUVmax (HR: 7.0, 95% CI: 2.2–22.2, P = .001) being highly significant predictors.

**Discussion**

The main finding of this study is that increased AMT uptake measured by PET is a very strong predictor of 1-year and overall survival in patients with previously treated high-grade gliomas. Importantly, the studied PET parameters showed a strong prognostic value independently of enhancement changes on MRI and independently of several other potential clinical and MRI prognostic factors. Since SUVs showed excellent prognostic performance (similar to AMT K-ratios, which require dynamic image acquisition
and blood input function), the results strongly indicate that a single time-point static posttreatment AMT-PET scan could provide valuable prognostic information to supplement conventional MRI. 

**Advanced MRI and PET in Posttreatment Glioma Prognosis**

Current clinical follow-up protocols mainly look for changes in the enhancing and/or the T2/FLAIR hyperintense volume to...

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Table 4. Univariate analyses of potential prognostic factors for 1-y survival (binary regression analysis) and OS (Cox proportional hazard regression analysis) after AMT-PET

<table>
<thead>
<tr>
<th>Univariate Analysis of Prognostic Factors</th>
<th>1-y Survival</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>0.98 (0.9–1.0)</td>
<td>.38</td>
</tr>
<tr>
<td>Gender</td>
<td>0.87 (0.2–3.2)</td>
<td>.84</td>
</tr>
<tr>
<td>Changing enhancement on MRI, yes/no</td>
<td>14.7 (1.6–125)</td>
<td>.016*</td>
</tr>
<tr>
<td>Bevacizumab after AMT-PET, yes/no</td>
<td>1.7 (0.45–6.6)</td>
<td>.42</td>
</tr>
<tr>
<td>Surgery after AMT-PET, yes/no</td>
<td>0.89 (0.25–3.2)</td>
<td>.86</td>
</tr>
<tr>
<td>Histologic grade, III vs IV</td>
<td>6.0 (0.6–55.5)</td>
<td>.12</td>
</tr>
<tr>
<td>$SUV_{mean}$, high vs low</td>
<td>25.6 (4.2–142)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>$SUV_{max}$, high vs low</td>
<td>21.3 (4.0–111)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>K-ratio, high vs low</td>
<td>24.4 (3.8–166)</td>
<td>.001*</td>
</tr>
</tbody>
</table>

*Significant.

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Fig. 2. Kaplan–Meier survival curves of patients grouped as high versus low by $SUV_{max}$ and K-ratio in the whole study population and in the subgroup of patients with recent contrast enhancement change on MRI. (Note: to simplify interpretation, the curves were truncated at 4.1 y.)

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Whole population

![Graphs showing Kaplan–Meier survival curves for whole population](image)

Patients with recent enhancement change

![Graphs showing Kaplan–Meier survival curves for subgroup with recent enhancement change](image)
Table 5. Multivariate analyses of prognostic factors for 1-y survival (binary regression analysis) and for OS (Cox proportional hazard regression analysis) after AMT-PET, with separate analyses performed involving \( \text{SUV}_{\text{mean}} \), \( \text{SUV}_{\text{max}} \), and K-ratio AMT parameters.

### Multivariate Analysis of 1-y Survival

<table>
<thead>
<tr>
<th></th>
<th>( \text{SUV}_{\text{mean}} )</th>
<th>( \text{SUV}_{\text{max}} )</th>
<th>K-ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \text{OR} ) (95% CI)</td>
<td>( \text{P} )</td>
<td>( \text{OR} ) (95% CI)</td>
</tr>
<tr>
<td>AMT-PET, high vs low</td>
<td>25.0 (3.40–200)</td>
<td>.002*</td>
<td>18.5 (2.9–125)</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 (0.95–1.09)</td>
<td>.66</td>
<td>1.0 (0.95–1.10)</td>
</tr>
<tr>
<td>Histologic grade, III vs IV</td>
<td>2.0 (0.04–111)</td>
<td>.73</td>
<td>3.2 (0.08–143)</td>
</tr>
<tr>
<td>Changing enhancement, yes vs no</td>
<td>14.3 (1.07–200)</td>
<td>.04*</td>
<td>9.1 (0.71–111)</td>
</tr>
</tbody>
</table>

### Multivariate Analysis of OS

<table>
<thead>
<tr>
<th></th>
<th>( \text{SUV}_{\text{mean}} )</th>
<th>( \text{SUV}_{\text{max}} )</th>
<th>K-ratio</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>( \text{P} )</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>AMT-PET, high vs low</td>
<td>5.9 (2.2–16.7)</td>
<td>.001*</td>
<td>5.3 (1.96–16.7)</td>
</tr>
<tr>
<td>Age</td>
<td>0.99 (0.97–1.03)</td>
<td>.62</td>
<td>1.00 (0.97–1.03)</td>
</tr>
<tr>
<td>Histologic grade, III vs IV</td>
<td>0.77 (0.15–4.0)</td>
<td>.76</td>
<td>0.93 (0.18–5.0)</td>
</tr>
<tr>
<td>Changing enhancement, yes vs no</td>
<td>11.4 (2.4–100)</td>
<td>.002*</td>
<td>7.5 (1.61–50.0)</td>
</tr>
</tbody>
</table>

*Significant.

Fig. 3. Coregistered T1-Gad, AMT-PET, and MRI/PET fusion images of 2 patients with a contrast-enhancing lesion in the right hemisphere, suspicious for glioblastoma recurrence. (A) Patient #25 had low AMT uptake in this lesion (\( \text{SUV}_{\text{max}} \): 4.18; K-ratio: 1.30) and survived for almost 3 years after the PET scan. (B) Patient #9 showed very high AMT uptake (\( \text{SUV}_{\text{max}} \): 5.04; K-ratio: 2.17) and died within 6 months after AMT-PET.

determine disease progression or response to therapy in patients with treated malignant gliomas. As shown by others and corroborated by our study as well, contrast enhancement changes on MRI are prognostically significant. However, such changes can be caused by therapy-induced tissue damage (eg, radiation necrosis), tumor recurrence, or, commonly, a combination of
both.6–8 Additionally, patients often present with a conflicting radiological and clinical status, showing worsening disease in one and stable status in the other. The situation is further complicated by the use of antiangiogenic agents, such as bevacizumab, which may mask progressive disease by temporarily decreasing enhancement on MRI.9,42 Thus, there is a definite need for imaging modalities of superior prognostic value. Advanced MRI involving PWI, DWI, and MR spectroscopy, as well as PET imaging utilizing glucose, amino acid, and nucleotide radiotracers, were shown to distinguish radiation necrosis from recurrent tumor and may be used to overcome the prognostic limitations of conventional MRI.8–14

Prognostic MRI studies mainly utilized PWI to investigate blood volume or DWI to assess the apparent diffusion coefficient in the areas suspicious for tumor recurrence.30,32,35,36 PET studies of the same kind utilized [18F]FDG, a measure of glucose metabolism; [18F]fluoro-L-thymidine (FLT), a marker of tumoral proliferative activity; or amino acid tracers such as [11C]methyl-L-methionine (MET), [18F]fluoro-ethyl-tyrosine (FET), [18F]fluoro-deoxy-phenylalanine (FDOPA), and AMT, which measure amino acid transport and/or metabolism in tumor tissue. While all these amino acid PET tracers are predominantly transported into the brain tissue via the neutral L-amino acid transfer system37,38, their intratumoral metabolic fates are different. In contrast to FET and FDOPA, which are not metabolized (although FDOPA is a substrate of aromatic acid decarboxylase, an enzyme that can be present in some tumors), MET and AMT can be metabolized within the tumor cells following transport. AMT uptake and trapping are partly driven by metabolism via IDO, the rate-limiting enzyme of the immunosuppressive kynurenine pathway, which is commonly upregulated in brain tumors.39,41 IDO-mediated tryptophan depletion and accumulation of toxic kynurenine metabolites may lead to proliferation arrest of tumor-invading cytotoxic T-lymphocytes, inhibiting a major mechanism of antitumoral immune response.39,41 IDO expression has also been linked to worse survival in glioblastomas.39,41 These data, at least in part, could explain the strong prognostic value of in vivo uptake of AMT, which is a substrate of IDO due to the low specificity of this enzyme. Inhibition of the kynurenine pathway is a potential target for potent IDO inhibitors,40,42 and AMT-PET may be utilized to identify patients who could potentially benefit from such new medicaments in future trials.

The few PET studies that utilized a single time-point posttreatment scan, similar to our current one, reported mixed results in terms of prognostic value. Van Laere et al.,43 using FDG and MET in a posttreatment mixed low- and high-grade glioma population, found the uptake of both tracers to be predictive of OS both individually and in combination. However, tumor histologic grade was not included in the multivariate analysis, and no separate survival analysis was performed with high-grade gliomas.43 A subsequent study using the same combination of PET tracers could not reproduce these findings in a pure glioblastoma population,44 while Ceyssens et al.45 also did not find MET SUVmax to be predictive of OS in posttreatment gliomas. Narai et al.,46 measuring MET uptake in a large glioma population, reported the lack of residual MET-PET uptake after initial treatment (resection and radiation) to be associated with better OS; however, their subgroup without residual MET uptake comprised only 8 patients versus the 27 patients with MET positive remnants. Also, they did not perform multivariate analysis involving conventional MRI parameters; neither did they report the time frame in which MET-PET was performed after the initial therapy. Therefore, their findings are difficult to compare to the results of our current study.

The majority of previous PET and advanced MRI studies that investigated OS utilized a dual (or multi) time-point approach acquiring one scan before and another during or after treatment. These studies often generated parametric response maps (PRMs) based on voxel-wise perfusion, diffusion, or radiotracer uptake changes between time points within the regions suspicious for the presence of tumor.8,30,36 PRMs can be used for early stratification of responders versus nonresponders to a specific therapy. This prognostic information is quite different from that of our current study, which provides indirect information on response to therapy, yet represents a clinically more feasible single time-point approach. Perfusion and/or diffusion PRMs on MRI between the pre- and intratreatment scans were found to be predictive of OS.30,32,35,36 In the assessment of response to radiation, FET-PET showed reduction of the high-uptake volume to be associated with longer OS.47 Since the reference images in all of these studies were acquired from treatment-naïve patients, their findings are not comparable to ours. Another set of PET studies that utilized the same dual time-point approach investigated response to bevacizumab therapy in recurrent high-grade gliomas. Decrease in the high FET uptake volume was also associated with an OS benefit in this setting; FET responders lived 20 months longer than nonresponders.48 PRMs of regional FLT uptake decreases were associated with better 1-year survival as well as with a 7- to 8.7-month OS benefit after bevacizumab treatment.13,69,50 These findings are more modest than our 23.3-month OS benefit in the entire population with low AMT uptake, or the 13.5 months in patients with recent enhancement change. According to one study, changes in FLT uptake kinetics could predict 1-year survival with 100% accuracy, but the study had only 6 patients surviving longer than 1 year after bevacizumab treatment.65 Another study reported the lack of FLT reduction 6 weeks after bevacizumab treatment to be an independent negative predictor of OS, with HRs of 10.1 in multivariate and 7.9 in univariate analyses.13 In our current cohort, the K-ratio predicted OS with a similar HR value (10.0). Lastly, a recent study using FLT and FDOPA PRMs in bevacizumab treatment response assessment showed that although both radiotracers could predict 6-month survival, only FDOPA predicted OS; however, the arms of the Kaplan–Meier curve met at the 400th day.66 None of these above-mentioned studies reported any single time-point parameter that could predict OS.

Potential Implications of the Findings

As mentioned above, our study aimed to investigate the prognostic value of AMT-PET in a clinically broader sense, not restricted to response assessment for a certain kind of therapy. The present paper is one of the few imaging studies that found a single time-point study to be highly predictive of OS in posttreatment high-grade gliomas. In fact, we found a multitude of AMT parameters to have similarly strong prognostic value. The most clinically feasible and practical parameter was SUVmax, which can be assessed semiautomatically without the need for any additional measurements or procedures such as blood radioactivity sampling, which is required for the estimation of K. The prognostic
information provided by AMT-PET could greatly clarify disease status and associated prognosis, even in the presence of treatment-induced changes that make conventional MRI findings difficult to interpret (as illustrated in Fig. 3). Based on our study, the potential clinical value of AMT-PET is particularly high in patients with MRI contrast enhancement suspicious for tumor progression. In our cohort, changing contrast enhancement was associated with survival ranging from 14 to 2498 days, while AMT uptake was a strong predictor in this subgroup. Compared with dual time-point prognostic studies, a single posttreatment AMT-PET could be easily incorporated into the clinical follow-up at any time point after suspected progression on conventional MRI, without prior enrollment in a study; thus, it might be a cost-efficient tool to determine when to start or stop antiangiogenic or other rescue therapy. Comparative studies have yet to be performed to investigate whether our present findings are specific to AMT, or can be achieved using other amino acid tracers and to test how AMT-PET can complement advanced MRI techniques in the posttreatment imaging of malignant gliomas.

Limitations

Our studied population is likely biased toward cases with better outcomes, since patients with very severe early posttreatment progression did not survive long enough to reach the eligibility period of this study, and patients in severe condition requiring urgent intervention were excluded from the PET studies (see Materials and Methods). Although our cohort may not be completely representative of the general high-grade glioma population, it does represent patients for whom prognostic imaging was highly relevant. There was some variability in the treatment that patients received in their later disease course—for instance, some received bevacizumab around the AMT-PET scan or had a second surgery. However, neither of these factors turned out to be a significant predictor of survival. Also, a recently concluded large bevacizumab trial suggests that this drug does not have a robust effect on OS.51 Tumor recurrence suggested by MRI was not corroborated by histologic data in a sufficient number of cases to provide meaningful information on progression-free survival, at least not beyond the findings of our recent study on radiation necrosis versus glioma recurrence.52 Besides, although OS is a relatively crude measure of outcome that ignores quality of life, it is still the most reliable, least ambiguous, and easiest to interpret outcome measure for both patients and clinicians. Throughout the imaging literature, clinical, radiographic and histologic disease progression are defined in different ways while our results emphasize that progression assessment on conventional MRI can be greatly enhanced by AMT-PET in terms of both 1-year and overall survival prediction.

AMT is a carbon-11-labeled radiotracer with a short (20 min) half-life requiring an on-site cyclotron for its synthesis, restricting the availability of AMT to only a few centers currently. It has yet to be determined how specific our observations are to AMT and whether similar strong results can be achieved with other PET radiotracers. Still, these findings do support the clinical usefulness of amino acid radiotracers in posttreatment glioma imaging and might encourage other centers to test and compare other amino acid PET probes for these applications.

Conclusion

Several AMT-PET parameters, including a simple SUV measure, were found to be strongly predictive of OS in posttreatment high-grade astrocytic gliomas. The prognostic value of AMT-PET was independent of age, histologic grade, or recent changes in contrast enhancement on MRI. Therefore, AMT-PET can be a useful imaging tool to supplement clinical follow-up imaging in conjunction with conventional MRI in patients with previously treated malignant gliomas.

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References


