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Tryptophan PET-defined gross tumor volume offers better coverage of initial progression than standard MRI-based planning in glioblastoma patients

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Abstract

Objective—Glioblastoma is an infiltrative malignancy that tends to extend beyond the MRI-defined tumor volume. We utilized positron emission tomography (PET) imaging with the radiotracer alpha- ^{11}C methyl-L-tryptophan (AMT) to develop a reliable high-risk gross tumor volume (HR-GTV) method for delineation of glioblastoma. AMT can detect solid tumor mass and tumoral brain infiltration by increased tumoral tryptophan transport and metabolism via the immunosuppressive kynurenine pathway.

Methods—We reviewed all patients in our database with histologically proven glioblastoma who underwent preoperative AMT-PET scan prior to surgery and chemoradiation. Treated radiotherapy volumes were derived from the simulation CT with MRI fusion. High-GTV with contrast enhanced T1-weighted MRI alone (GTV_{MRI}) was defined as the postoperative cavity plus any residual area of enhancement on postcontrast T1-weighted images. AMT-PET images were retrospectively fused to the simulation CT, and a high-risk GTVs generated by both AMT-PET alone (GTV_{AMT}) was defined using a threshold previously established to distinguish tumor tissue from peritumoral edema. A composite volume of MRI and AMT tumor volume was also created (combination of MRI fused with AMT-PET data; $\text{GTV}_{\text{MRI+AMT}}$). In patients with definitive radiographic progression, follow-up MRI demonstrating initial tumor progression was fused with the pretreatment images and a progression volume was contoured. The coverage of the progression volume by GTV_{MRI} , GTV_{AMT} , and $\text{GTV}_{\text{MRI+AMT}}$ was determined and compared using the Wilcoxon's signed-rank test.

Results—Eleven patients completed presurgical AMT-PET scan, seven of whom had progressive disease after initial therapy. GTV_{MRI} (mean, 50.2 cm^3) and GTV_{AMT} (mean, 48.9 cm^3) were not significantly different. Mean concordance index of the volumes was $39 \pm 15 \%$. Coverage of the initial recurrence volume by HR- GTV_{MRI} (mean, 52%) was inferior to both GTV_{AMT} (mean, 68% ; $p = 0.028$) and $\text{GTV}_{\text{MRI+AMT}}$ (mean 73% ; $p = 0.018$). The AMT-PET-exclusive coverage was up to 41% of the recurrent volume. There was a tendency towards better recurrence coverage with $\text{GTV}_{\text{MRI+AMT}}$ than with GTV_{AMT} alone ($p = 0.068$). Addition of 5 mm concentric margin around GTV_{MRI} , GTV_{AMT} , and $\text{GTV}_{\text{MRI+AMT}}$ would have completely covered the initial progression volume in 14, 57, and 71 % of the patients, respectively.

Conclusion—We found that a GTV defined by AMT-PET produced similar volume, but superior recurrence coverage than the treated standard MRI-determined volume. A prospective study is necessary to fully determine the usefulness of AMT-PET for volume definition in glioblastoma radiotherapy planning.

Keywords

MRI; Tryptophan; PET; GTV; Volumetry; Radiation therapy; Recurrence coverage

Introduction

Glioblastoma is the most frequently diagnosed and carries the poorest prognosis among adult primary brain malignancies [1]. Standard therapy for these tumors includes a multimodality approach including surgical resection, radiation therapy (RT), and concurrent chemotherapy [2]. Unfortunately, clinical outcomes remain bleak primarily due to

intracranial recurrence, in part owing to incomplete surgical resection and/or irradiation of this highly infiltrative tumor [3].

At present, morphologic imaging modalities, in particular magnetic resonance imaging (MRI), remain the primary method of diagnosis, follow-up, and treatment planning for patients with glioblastoma. Standard planning for RT relies on both gadolinium-enhanced T1-weighted (T1-Gad) and T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) sequences to image the contrast enhancing portion of the tumor and peritumoral edema, respectively [4]. While gadolinium enhancement is a sensitive indicator of blood–brain barrier breakdown [5, 6], malignant gliomas can infiltrate brain tissue without such disruption [7]. Additionally, differentiating peritumoral edema from other etiologies (e.g., vasogenic edema or ischemic injury) within the hyperintense signal seen on T2-FLAIR is often not possible [8]. This highlights the difficulty in accurate delineation of the full extent of viable tumor for target volume creation in RT planning.

Positron emission tomography (PET) techniques have been used as adjuncts to anatomic imaging in RT treatment planning in many systemic sites of malignancies [9, 10]. The ability to combine morphologic data with visualization of in vivo biologic processes is attractive and has lead several investigators to examine its use in glioblastoma treatment planning [11–14]. Radiolabeled amino acids have been utilized in this setting because of the high contrast in tumoral to normal parenchymal uptake [15], which may be due to the malignant transformation process itself [16].

The amino acid PET tracer alpha- ^{11}C methyl-L-tryptophan (AMT) is transported in tumor tissue by the L-type amino acid transporter (LAT1) but is not incorporated into proteins [17]. Instead, AMT is utilized by the kynurenine immunomodulatory pathway [18, 19]. Under pathologic conditions, induction of this pathway's rate-limiting enzyme, indoleamine 2,3-dioxygenase (IDO), leads to increased metabolism of tryptophan and thus AMT accumulation via the kynurenine pathway [20, 21]. This pathway plays an important role in brain tumor pathogenesis [22]. We have previously demonstrated increased local AMT uptake on PET in all scanned patients with high-grade gliomas [20]. Additionally, we have histologically identified the presence of tumor-infiltrated tissue outside of the contrast-enhanced region, and indirectly differentiated it from vasogenic edema in a recent study comparing MRI and AMT-PET imaging modalities [23].

In the present study, we retrospectively compared the treated RT high-risk gross target volumes (GTVs) generated with contrast enhanced T1-weighted MRI alone (GTV_{MRI}) to hypothetical GTVs generated by both AMT-PET alone (GTV_{AMT}), and the combination of MRI fused with AMT-PET data ($\text{GTV}_{\text{MRI+AMT}}$). These volumes were correlated to the site of first recurrence as visualized on serial follow-up MRI to determine if these hypothetical GTVs would have offered superior coverage of the volume of initial progression.

Methods

Patients

Patients eligible for analysis were those with histopathologically confirmed WHO grade IV glioblastoma who underwent preoperative AMT-PET, adjuvant chemoradiotherapy, and serial post-treatment MRI follow-up at our institution. Institutional review board approval was obtained prior to all data collection and analysis. We identified 11 patients who met the eligibility criteria between October 2008 and September 2011. Seven of these patients with newly diagnosed glioblastoma experienced intracranial progression of disease on follow-up MRI within the time frame of the study. The cohort's median age was 63 years (range, 51–75). Exclusion was primarily due to patients that did not have preoperative AMT-PET imaging or received adjuvant RT at outside institutions closer to their home.

AMT-PET protocol

A high-yield procedure for synthesis of the AMT tracer and PET acquisition procedures have been described in depth previously [21, 24, 25]. In brief, after 6-h of fasting, 37 MBq/kg of AMT was intravenously injected. Twenty-five minutes following tracer injection, a dynamic emission scan of the brain (7×5 min) was obtained using a Siemens EXACT/HR whole body PET (Siemens Medical Systems; Knoxville, TN, USA). Correction for measured attenuation, scatter, and decay were applied to all images. Creation of an AMT standardized uptake value (SUV) image required conversion of averaged activity images obtained between 30 and 55 min post-injection. 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.

Images were analyzed using the 3D Slicer software (www.slicer.org). For each patient, the mean SUV of the uninvolved, contralateral cortex was calculated. To determine the extent of increased gliomatous AMT uptake, a tumoral SUV threshold of 36 % above the calculated mean cortical SUV was utilized. This threshold was selected to exclude vasogenic edema, based on studies of AMT uptake patterns in primary brain tumors [23].

MRI protocol

The postoperative diagnostic MRI scans acquired nearest the time to the initiation of RT, were primarily used for generation of RT planning target volumes. Serial follow-up scans were typically performed in 3-month intervals following the completion of RT. MRI was performed on either a Siemens MAGNETOM Trio TIM 3.0 T scanner (Siemens Medical Solutions; Malvern, PA, USA), GE Signa HDxt 3.0 T scanner (GE Medical Systems; Milwaukee, WI, USA), or Philips Achieva TX 3.0 T scanner (Philips Healthcare, The Netherlands). Both axial T1-Gad and T2-FLAIR sequences (with similar parameters on both scanners) were used for analysis for treatment planning and identification of tumor recurrence. A board-certified neuroradiologist was responsible for diagnostic read of all MR images. The neuroimaging findings were routinely discussed in a multidisciplinary neuro-oncology tumor board where a consensus was achieved regarding likelihood of tumor recurrence versus treatment-related changes.

Treatment

All patients underwent microsurgical resection using intraoperative navigation on a Brainlab Curve™ Image Guided Surgery platform (Brainlab Inc; Westchester, IL, USA). Following neurosurgical intervention, all patients underwent adjuvant RT with concurrent and consolidative temozolomide in concordance with the Stupp protocol [2]. A postoperative MRI within 48 h of surgery to determine extent of residual disease was performed on all patients.

Radiation treatment planning

The RT plan delivered to each patient was generated via fusion of postoperative diagnostic MRI to 3 mm slice CT simulation. Thermoplastic mask immobilization was utilized for all patients. All image fusion, volume contouring, and treatment planning was performed on Eclipse Treatment Planning Software Build Number 8.9 (Varian Medical Systems Inc.; Palo Alto, CA, USA). A high-risk GTV from MRI (HR-GTV_{MRI}) was created to encompass the surgical cavity and any area of gadolinium enhancement suspicious for residual tumor on T1-weighted imaging. If there was significant edema noted on T2-FLAIR, an intermediate-risk GTV (IR-GTV_{MRI}) was created to include all tissue showing hyperintense signal. Per our institutional protocol, these GTVs were uniformly expanded with a 1.5 cm margin and then manually modified to respect anatomic boundaries in order to create both high- and intermediate-risk clinical target volumes (CTVs). Both CTVs were further expanded by 0.5 cm to create high- and intermediate-risk planning target volumes (PTVs). All patients were treated with intensity-modulated radiotherapy technique with daily megavoltage computed tomography or kilovoltage cone beam computed tomography image guidance. Prescription dose to the IR-PTV_{MRI} and HR-PTV_{MRI} was 50 Gy and 60 Gy in 2 Gy fractions, respectively, such that 95 % of the prescription dose covered 95 % of the PTV. Maximum point dose constraints to critical structures (e.g., brainstem, optic nerves, and optic chiasm), was given highest priority in treatment planning.

Investigational target volumes

Retrospectively, AMT-PET images were manually fused to the CT simulation scan and MRI within the treatment planning software, using normal structure anatomy. No attempt to correct for surgical deformity was made. The fused AMT-PET grayscale was windowed to 136 % of the calculated contra-lateral cortical SUV, such that only tumoral uptake was apparent on the PET image. Two experimental volumes were generated: the high-risk volume was contoured to form the GTV_{AMT} and a high-risk tumor volume was created by combining both the GTV_{MRI} and GTV_{AMT} volumes and named GTV_{MRI+AMT}. Additionally, the first follow-up MRI that noted tumor progression was likewise fused in the treatment planning software. Tumor progression was verified by serial MRIs, as described previously [25], and the area of gadolinium enhancement visualized on the first T1-weighted MRI suggesting progression was contoured as the volume of initial progression. As part of an exploratory analysis, we retrospectively created a PTV based on a concentric expansion of each GTV by 0.5 cm (in concordance with the stereotactic boost volume specified in RTOG 0023), in an attempt to determine the feasibility of reduced safety margin relative to progressive volume.

Quantitative and statistical analyses of investigational target volumes

The raw volume (in cubic centimeter) of each of the GTV_{MRI} , GTV_{AMT} , and $GTV_{MRI+AMT}$ was determined and compared. To evaluate the concordance between each volume, the previously described concordance index (CI) was utilized [4, 14]. Briefly, the CI is the ratio of the volumetric overlap of two distinct GTVs to the volumetric composite of the same two GTVs. The CI values were calculated as percentages, whereby 100 % indicates perfect concordance between volumes and 0 % indicates no area of concordance. CI_{MRI} ($GTV_{MRI}/GTV_{MRI+AMT}$), CI_{AMT} ($GTV_{AMT}/GTV_{MRI+AMT}$), and $CI_{overlap}$ (overlap of GTV_{MRI} and $GTV_{AMT}/GTV_{MRI+AMT}$) were calculated. Finally, the percent coverage of the volume of progression by each GTV was calculated and compared. The Wilcoxon signed-rank test was utilized for all comparisons. A p value less than 0.05 was considered significant.

Results

Gross tumor volumes

Eight of 11 patients had no evidence of residual enhancement on immediate postoperative MRI; two patients had a >98 % resection and one patient had a >95 % tumor resection (Table 1). In all 11 patients, there was tumoral AMT uptake seen above the predefined 136 % of the mean cortical SUV threshold. Volumetric analysis of the generated target volumes revealed larger GTV_{AMT} than the GTV_{MRI} in 7 of 11 cases (64 %). The mean volume for these two GTVs were $50.2 \pm 59.1 \text{ cm}^3$ (MRI) and $48.9 \pm 38.5 \text{ cm}^3$ (AMT), with no statistical difference between them ($p = 0.657$; Table 2). Concordance between these two volumes was generally poor, with a mean $CI_{overlap}$ of $39 \pm 15 \%$ ($31.5 \pm 38.3 \text{ cm}^3$; Fig. 1). The composite GTVs ($GTV_{MRI+AMT}$) were larger than the GTV_{MRI} in all patients and had a mean volume of $67.6 \pm 57.7 \text{ cm}^3$ ($GTV_{MRI+AMT}$ vs. GTV_{MRI} , $p = 0.003$).

Recurrence coverage

In seven patients, definitive evidence of intracranial tumor progression was seen on serial MRI follow-up. In five of those seven patients (71 %), the progression occurred within the 2 cm perimeter of the surgical cavity. One patient (#5) developed progression at a satellite lesion within the ipsilateral cortex that was evident on initial AMT-PET but not MRI. Another patient (#1) developed massive progression involving a majority of the ipsilateral hemisphere.

The mean and median volume of initial tumor progression, as measured on follow-up T1-Gad imaging, was 25.8 and 8.5 cm^3 , respectively (Table 3). On average, the GTV_{MRI} covered 52 % (range, 7–88 %) of the volume of progression (Fig. 2). Compared to GTV_{MRI} , both GTV_{AMT} and $GTV_{MRI+AMT}$ offered superior coverage of the recurrent volume with mean values of 68 % (range, 10–98 %; $p = 0.028$) and 73 % (range, 12–99 %; $p = 0.018$), respectively. $GTV_{MRI+AMT}$ showed a tendency towards better coverage of recurrent volume than GTV_{AMT} alone ($p = 0.068$). Further-more, 21 % of the coverage was AMT-exclusive (range, 5–41 %), while only 5 % was confined to MRI-exclusive voxels (range, 0–20 %; $p = 0.028$).

It was determined that a 5 mm concentric margin around the GTV_{MRI} would have completely covered the initial progression volume in one of seven (14 %) patients. Generating the same margin around the GTV_{AMT} and GTV_{MRI+AMT} would have offered complete coverage of progression in four of seven (57 %) and five of seven (71 %) patients, respectively.

Discussion

Glioblastoma remains a diagnostic and therapeutic challenge, in part due to difficulty identifying the full extent of viable disease. Multiple series have demonstrated that the tumor recurrence generally occurs within 2 cm of the primary disease [26, 27], even when the whole brain is treated with adjuvant RT [28]. This has led to the use of large concentric margins in radiation treatment planning and underscores the need for escalation of adjuvant therapy. Such escalation would ideally be accompanied by greater certainty of the extent of viable tumor tissue and a greater conformality to this area to both ensure coverage and limit potential toxicity. Amino acid PET radiotracers, which show low uptake in normal brain but are accumulated in gliomas have been identified as a potential means to achieve this goal.

Indeed, in the present study, we find that retrospectively created GTVs based on preoperative AMT-PET, either alone or in conjunction with postoperative MRI findings, demonstrate significant discordance with the standard clinical high-risk GTV generated via T1-Gad findings alone (Fig. 3). Importantly, there was no significant difference in volumetric size of the GTVs determined by AMT-PET relative to those determined by MRI alone. Despite this, the investigational AMT volume offered superior coverage of the volume of initial progression when compared to the standard MRI-based GTV. This is true even though no correction for surgical deformity has been attempted. Potential errors of coregistration from shifts of surgical margins could be prevented by the use of postsurgical AMT-PET images. However, these images may be confounded by periresection increased AMT uptake caused by postsurgical inflammation (rather than tumor infiltration) as demonstrated on early postsurgical AMT-PET images of patients with failed resective epilepsy surgery [29].

This study includes limited analysis of associated target volumes (e.g., CTV and PTV). We believe the high-risk GTV is a structure of greater importance, as it forms the basis for concentric expansion that creates the high-dose target volumes. An alteration in GTV would create a corresponding change in both CTV and PTV. Ideally, increased accuracy of GTV definition would allow for smaller empiric safety margins for microscopic spread that determines the CTV. In our small cohort, we found this to be the case. Using a combination of MRI and AMT-PET imaging allowed for a 5-mm margin to cover the entire area of progression in five of seven cases. The same margin, when applied to the high-risk volume generated from MRI alone, covered in only one of seven patients.

The above findings are encouraging and hypothesis generating, but must be interpreted carefully. Certainly, the low number of patients and retrospective nature of the analysis are the main limitations and warrant a prospective confirmation of these findings in a larger patient cohort. The limited number of cases precluded inclusion of MGMT methylation

status as a covariate in the statistical analysis. Additionally, our technique for determining the extent of disease on AMT-PET likely requires refining. Similar techniques to the lesion-to-cortex ratio method, utilized in this study to create the GTV, have been used and histologically established for other amino acid PET tracers in high-grade glioma image segmentation and were found adequate [30, 31]. However, these thresholds seem to be tracer specific and thus need to be tested for each tracer separately. Our threshold of 36 % above uninvolved cortical SUV, is based on previously presented meningioma tumoral AMT-PET data, and has been shown to be reasonable on preliminary histopathologic correlation in glioma [23]. When the analysis was repeated with the more inclusive uptake threshold of 18 % above uninvolved cortex, the mean volume generated was predictably larger (80.0 vs. 48.8 cm³) than the volume obtained using 36 % thresholding, but did not significantly improve upon coverage of the recurrent volume when used either alone (mean coverage, 78.9 vs. 72 %; $p=0.083$) or when composite PET-MRI volumes were generated (mean coverage, 80.9 vs. 76.2 %; $p=0.062$). With more patients, such a decrease in threshold may prove to increase the sensitivity of tumor tissue detection; however, it might also increase the chance for false positivity and normal tissue overtreatment. The ideal threshold should balance sensitivity and specificity and has yet to be established, but remains a goal for future studies.

Conclusions

Retrospective target volume creation, using data derived from the amino acid PET tracer alpha-[¹¹C]methyl-L-tryptophan altered both the size and geometric position of the high-risk GTV in patients with glioblastoma. These investigational volumes covered a greater percentage of the volume of initial progression than did the standard MRI-based high-risk GTV used for clinical purposes. These findings and the associated methodology need to be prospectively confirmed and refined in a larger patient population, which will also allow inclusion of known predictors of glioblastoma progression (such as MGMT methylation status), prior to attempts to affect clinical outcome with PET-driven escalation of therapy fields.

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Abbreviations

MRI	Magnetic resonance imaging
PET	Positron emission tomography
AMT	Alpha-[¹¹ C]methyl-L-tryptophan

SUV	Standardized uptake volume
CI	Concordance index
GTV	Gross tumor volume
CTV	Clinical target volume
PTV	Planning target volume
LAT1	L -type amino acid transporter

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Fig. 1.

Diagram demonstrating the mean volumes of intersection and union between the standard MRI-based GTV and the investigational AMT-PET generated GTV for all 11 patients. From this, the concordance index is calculated

Fig. 2.

Illustration of the mean percentage of the volume of initial progression encompassed by each experimental GTV, among the seven patients included with definitive evidence of disease progression on follow-up MRI. The *asterisk* indicates significant difference between the MRI-exclusive and AMT-exclusive coverage ($p = 0.028$)

Fig. 3.

Representative images as viewed in the treatment planning software. *Grayscale* pretreatment AMT-PET image windowed to 136 % the contralateral cortical SUV from which the GTV_{AMT} is created (**a**). T1-weighted postgadolinium MRI at diagnosis (**b**) and postoperatively from which GTV_{MRI} is created (**c**). MRI demonstrating initial progression with GTVs layered over (**d**)

Table 1

Patient demographics and extent of surgery

Patient	Age (years)	Gender	Tumor location	Resection	Residual Tumor on postoperative MRI (%)
1	52	M	R Frontal	GTR	0
2	62	M	R Temporoparietal	GTR	0
3	64	M	R Frontal	GTR	0
4	51	M	R Temporal	GTR	0
5	75	F	R Frontoparietal	near-GTR	4.5
6	68	M	R Frontal	near-GTR	1.5
7	70	F	R Temporoparietal	GTR	0
8	59	F	L Temporal	GTR	0
9	68	M	R Temporal	GTR	0
10	65	M	R Parietal	near-GTR	1.6
11	78	M	L Temporal	GTR	0

L left, *R* right, *GTR* gross total resection

Table 2

Volumetric analyses and concordance indices

Patient	HR-GTV _{MRI} (cm ³)	GTV _{AMT} (cc)	GTV _{MRI+AMT} (cc)	CI _{MRI} (%)	CI _{AMT} (%)	CI _{overlap} (%)
1	6.6	9.9	12.0	55	83	38
2	34.4	73.2	73.9	47	99	46
3	15.9	29.2	35.0	45	83	29
4	52.3	45.2	65.5	80	69	49
5	13.2	32.0	40.0	33	80	13
6	12.0	7.7	16.9	71	46	17
7	23.1	33.5	41.4	56	81	37
8	51.2	52.6	75.1	68	70	38
9	205.7	148.9	217.1	95	69	63
10	108.6	58.7	116.0	94	51	44
11	29.1	46.6	50.4	58	92	50
Mean ± SD	50.2±59.1	48.9±38.5	67.6±57.7	64±20	75±16	39±15

Table 3

Coverage of initial progression by GTV

Patient	Volume of progression (cm ³)	Coverage of progressive volume (%)		
		GTV _{MRI}	GTV _{AMT}	GTV _{MRI+AMT}
1	94.57	6.8	10.0	12.0
2	8.64	70.7	97.7	98.3
3	1.36	54.4	94.9	94.9
4	2.63	87.8	98.1	98.5
5	8.39	65.8	88.6	88.8
6	8.49	39.7	38.0	57.8
7	56.7	36.4	48.8	59.1
Mean	25.8	51.7	68.0	72.8
<i>p</i> value ^a			0.028	0.018

^a*p* value derived from the comparison with GTV_{MRI}