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QUANTITATIVE PET IMAGING OF TRYPTOPHAN ACCUMULATION IN GLIOMAS AND REMOTE CORTEX: CORRELATION WITH TUMOR PROLIFERATIVE ACTIVITY

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Abstract

PURPOSE—Positron emission tomography (PET) studies with α[C-11]methyl-L-tryptophan (AMT) have shown decreased serotonin synthesis based on a decrease of the unidirectional uptake rate (K-complex) in neuropsychiatric conditions such as autism and depression. Increased A M T K-complex in tumors can indicate increased tryptophan metabolism via the immunosuppressive kynurenine pathway. Moreover, apparent AMT volume of distribution (VD') reflects net tryptophan transport from blood to tissue. We evaluated if kinetic parameters (K-complex, VD') of AMT, measured by PET, can predict glioma proliferative activity, and if these AMT parameters are altered in remote cortex.

METHODS—We evaluated dynamic AMT PET images of 30 adult patients with WHO grade III/IV gliomas to determine tumoral AMT VD' and K-complex values, which were correlated with tumor proliferative activity as assessed by the Ki-67 labeling index in resected tumor specimens. We also compared cortical VD' and K-complex values between glioma patients and healthy controls.

RESULTS—Both VD' and K-complex values were significantly higher in gliomas than in contralateral cortex (VD': $p < 0.001$; K-complex: $p < 0.001$). Tumoral VD' values and tumor/cortex VD' ratios, but not the K-complex, showed strong positive correlations with glioma proliferative activity ($p = 0.001$). Contralateral frontal cortex showed decreased AMT VD' and K-complex in glioma patients as compared to controls ($p = 0.01$).

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CONCLUSIONS—Increased net amino acid transport into tumor tissue, quantified by PET, can serve as an imaging marker of glioma proliferative activity. The data also suggest a glioma-induced down-regulation of cortical serotonin synthesis, likely mediated by shunting of tryptophan from serotonin synthesis to kynurenine metabolism.

Keywords

tryptophan; glioma; Ki-67 labeling index; kynurenine; positron emission tomography; serotonin

INTRODUCTION

Proliferative activity in gliomas, as measured by nuclear labeling of the Ki-67 antigen in surgical specimens, has important prognostic significance (1). Because this marker cannot practically be measured serially, various neuroimaging techniques have been studied for their ability to noninvasively assess glioma proliferative activity. Among MRI techniques, proton magnetic resonance spectroscopy shows promise as a surrogate marker of glioma proliferation (2). Positron emission tomography (PET) using 2-deoxy-2[F-18]fluoro-D-glucose (FDG) is a poor predictor of glioma proliferative activity (3). However, tumoral uptake of some other PET tracers (e.g., [C-11]-methionine, 3'-deoxy-3'-[F-18]-fluorothymidine, and 6-[F-18]-fluoro-L-dopa) showed positive correlations with Ki-67 labeling in gliomas (3-7). Some have also suggested that kinetic analysis of PET images may provide a more accurate measure of glioma proliferative activity than radiotracer uptake alone (4,5).

α [C-11]methyl-L-tryptophan (AMT) is an amino acid PET radiotracer that is not incorporated into proteins. AMT PET provides a non-invasive method of imaging tryptophan metabolism into serotonin in the brain (8,9). Focal cortical decrease of the unidirectional AMT uptake rate (K-complex), a measure of AMT trapping related to serotonin synthesis, has been observed in autistic children (10) and a variety of other neuropsychiatric disorders, including depression (11-13), which is also a common comorbidity in patients with glioma (14).

In addition to measuring brain serotonin synthesis, AMT PET can also estimate tryptophan metabolism via the kynurenine pathway under certain conditions (15). The significance of this pathway is negligible in normal brain, but increased tryptophan metabolism via this pathway can occur in cancers, where it contributes to tumoral immunoresistance (16). Increased expression and activity of indoleamine 2,3-dioxygenase (IDO), the initial and rate-limiting enzyme of the kynurenine pathway, was reported in human gliomas (17,18). Increased IDO activity may play a role in accumulation of AMT in both low-grade and high-grade gliomas (18, 19). Increased tumoral AMT accumulation can be also the result of increased AMT volume of distribution (VD), which measures the ratio of radioligand concentration in tissue to that in plasma at equilibrium; this ratio will increase as a result of an increased net transport of the radiotracer from plasma to tissue. Consistent with this, high apparent VD values (i.e., VD') were found in gliomas with gadolinium-enhancement (indicating impaired blood-brain barrier) and also in brain tumors showing high expression of the L-type amino acid transporter (LAT1), which is commonly upregulated in brain tumors (20,21).

In this study, we assessed the ability of dynamic AMT PET imaging to predict the proliferative activity of gliomas *in vivo*. We hypothesized that a positive correlation exists between the Ki-67 labeling index measured in surgically resected gliomas and AMT VD' measured by PET. In addition, since upregulation of the kynurenine pathway in patients with malignant tumors may lead to systemic changes in tryptophan metabolism via the serotonin

pathway (22,23), we also tested whether patients with gliomas have *decreased* unidirectional uptake rates of AMT, indicating reduced serotonin synthesis, in cortical areas remote from the tumor.

SUBJECTS AND METHODS

Subjects

Thirty patients, 20 men and 10 women, with a mean age of 48 years (range: 21-68 years; Table 1) were included in the study based on the following inclusion criteria: (1) age ≥ 18 years; (2) presence of a solid supratentorial brain tumor on MRI; (3) no prior treatment (including surgery, radiation, or chemotherapy) before AMT PET; (4) microsurgical resection of tumor with a diagnosis of WHO grade II-IV glioma on histopathological examination; and (5) body mass index ≥ 20 . Mean time between AMT PET imaging and subsequent tumor resection was 23 days (range: 1 to 105 days). All 10 glioblastomas were resected within 2 weeks after PET. The only tumor where more than 2 months elapsed between PET and surgery was a grade II oligodendroglioma that showed no MRI changes between the time of PET and surgery. In addition, we selected the 7 oldest healthy control subjects (3 women and 4 men) from our AMT PET database (mean age: 33 years; range: 25-48). All control subjects were over 21 years of age, did not have a history of neurological or neuropsychiatric disorder, and were not taking any medication. All subjects underwent dynamic AMT PET scanning using the same protocol (see below). The study was approved by Wayne State University's Institutional Review Board, and written informed consent was obtained from all participants.

AMT PET scanning protocol

All AMT PET studies were performed using the Siemens EXACT/HR whole-body positron tomograph (Knoxville, TN) located at the PET Center of the Children's Hospital of Michigan in Detroit, using a research protocol as described previously (19,24). In brief, after 6 hours of fasting, AMT (0.1 mCi/kg) was injected through a venous line. A second venous line was established for collection of timed blood samples. A 20-minute dynamic PET scan of the heart was performed in 2D mode to obtain the blood input function (concentration of radioactivity in blood) from the left ventricle of the heart. Determination of the blood input function beyond this time was accomplished by direct measurement of radioactivity in serial venous blood samples (0.5 mL/sample, collected at 20, 30, 40, 50 and 60 min after AMT injection). At 25 minutes after tracer injection, a dynamic emission scan of the brain (7 $\times$ 5 minutes) was started. Measured attenuation correction using a rotating Ge-68 rod source was applied to the AMT PET images of the heart, whereas computed attenuation correction was used to correct the brain images.

AMT PET image analysis

Regions of interest (ROIs) were drawn on AMT summed uptake images from 30 to 55 minutes after tracer injection (Figure 1). In tumor patients, ROIs included the tumor mass, excluding apparently necrotic portions (if present) visualized on co-registered MRI scans, using the ROI Editor 1.4.1 software (www.mristudio.org). ROIs of similar size were also drawn in the contralateral homotopic cortex. In addition, ROIs encompassing the middle frontal gyrus region of the frontal cortex were drawn on summed AMT PET images of both study patients (contralateral to the tumor) and normal controls (both sides). All ROIs were then applied to the dynamic AMT PET image sequence. Thereafter, kinetic AMT parameters were calculated using the blood input function entered in the Patlak graphical analysis (25) for both the tumor mass and cortical regions, as described previously (18,19,24). This approach provides two kinetic parameters: (1) the *y intercept* of the Patlak plot yields the tracer's apparent volume of distribution (VD'), which is tightly correlated

with VD values derived from compartmental analysis ($VD = K_1/(k_2 + k_3)$), where K_1 (mL/g/min) represents the forward and k_2 (min^{-1}) represents the reverse combined transport of AMT across the blood vessel, interstitial space, and cell membrane into the cytoplasm, while k_3 (min^{-1}) represents the metabolic rate constant which reflects tracer accumulation in the metabolic (irreversible) compartment [in case of tryptophan metabolism via the serotonin and/or kynurenine pathways] (26); therefore, AMT VD' values are indicative of the net transport of tryptophan into the tissue of interest (tumor or cortex). (2) the *slope* of the Patlak plot, which reflects the unidirectional uptake of tracer into the tissue (K-complex) and correlates with tryptophan metabolism via the serotonin synthesis pathway in cortex (9,15). In brain tumors, with no evidence of serotonin synthesis, the most likely mechanism of an increase in AMT K-complex is tryptophan metabolism via the kynurenine pathway (15). The advantages and limitations of using these kinetic AMT PET parameters have been discussed previously (9, 24).

Histopathology and evaluation of Ki-67 labeling index in resected gliomas

Standard neuropathological examination of all tumor specimens was performed by an experienced board-certified neuropathologist (W.J.K.). Immunohistochemical staining for Ki-67 (CONFIRM™ anti-Ki-67 rabbit monoclonal antibody, clone 30-9, Ventana Medical Systems, Inc., Tucson, AZ) was performed to assess tumor proliferative activity. The Ki-67 labeling index was determined by identifying the areas of greatest tumor cellularity, examining at least 10 fields at 400X (high-power) magnification on an Olympus microscope, and determining the ratio between the number of Ki-67-positive tumor cell nuclei and the total number of tumor cell nuclei in each high-power field (Figure 1). The proliferation index was expressed as a percent range (lowest to highest) in the 10 high-power fields (e.g., 5-10%). Small, isolated fields with higher Ki-67 labeling that were not reflective of the entire tumor mass were excluded from the analysis. The middle value of the defined range was then used in correlations with the PET variables.

Study design and statistical analysis

An abnormal increase of tumoral VD' or K-complex was defined as a value more than 10% higher than the corresponding value in the contralateral homotopic cortex (i.e., tumor/cortex ratio >1.10) (19). For statistical analysis, non-parametric tests were used, because several variables showed non-normal distribution. First, tumoral and contralateral cortical VD' and K-complex values were compared in the patient group using the Wilcoxon signed-rank test. Then, tumoral VD' and K-complex values as well as tumor/contralateral homotopic cortex VD' and K-complex ratios were entered in Spearman's rank correlations with corresponding tumor Ki-67 labeling index (%) values. Next, frontal cortical VD' and K-complex values were compared between glioma patients and normal controls (where the average of the left and right values were used) using the Mann-Whitney U test. This comparison was repeated: (i) in a subgroup of younger patients (age < 50, n = 15), whose age was closer to that of the controls (36 vs. 33 years [$p = 0.49$]); (ii) in a subgroup of patients who were not treated with dexamethasone prior to AMT PET scanning (n = 22), in order to exclude potential confounding effects of steroids on imaging findings caused by decreased blood-brain barrier permeability and altered tumoral perfusion (27); and (iii) in a subgroup that included only younger (age < 50) steroid-free patients (n = 10). Finally, cortical AMT PET kinetic parameters were compared between patients with a high Ki-67 labeling index (mid-range value of Ki-67 > 10%; n = 12) and a low Ki-67 labeling index (< 10%; n = 18) using the Mann-Whitney U test. Statistical analysis was carried out using the SPSS Statistics 19.0 software (SPSS Inc., Somers, NY). A p-value less than 0.05 was considered to be significant.

RESULTS

AMT PET kinetic parameters in gliomas: correlation with Ki-67 labeling index

Of the 30 tumors analyzed, 28 (all except one grade II oligodendroglioma and one grade II oligoastrocytoma) showed increased VD' and 24 tumors demonstrated increased AMT K-complex (Table 1). Both tumor VD' and K-complex values were significantly higher in gliomas than in contralateral homotopic cortex (mean VD': 0.56 ± 0.26 vs. 0.27 ± 0.07 , respectively, $p < 0.001$; mean K-complex: 0.0074 ± 0.0026 vs. 0.0048 ± 0.0013 , $p < 0.001$). Ki-67 labeling indices showed a positive correlation with tumoral VD' values (Spearman's rho $r = 0.58$, $p = 0.001$) and an even stronger positive correlation with tumor/cortex VD' ratios ($r = 0.75$, $p < 0.001$; Figure 2). In contrast, tumoral K-complex values ($p = 0.86$) and tumor/cortex K-complex ratios ($p = 0.25$) did not correlate with the Ki-67 labeling index.

AMT accumulation in cortex: comparison between glioma patients and normal controls

Contralateral frontal *cortical* AMT VD' and K-complex values were both *lower* in the glioma group than the normal control group (VD': 0.28 ± 0.08 vs. 0.41 ± 0.1 , respectively, $p = 0.01$; K-complex: 0.0044 ± 0.001 vs. 0.0056 ± 0.001 , respectively, $p = 0.009$). These group differences remained significant for K-complex values but showed a variable degree of significance for VD' values in the studied subgroups: (i) patients 50 years of age and younger (K-complex: $p = 0.014$; VD': $p = 0.07$); (ii) the subgroup of patients without steroid treatment prior to AMT PET (K-complex: $p = 0.012$; VD': $p = 0.03$); and (iii) the smallest subgroup that included only younger (< 50 years), steroid-free patients (K-complex: $p = 0.04$; VD': $p = 0.11$).

AMT PET kinetic parameters in cortex: effect of glioma proliferative activity

Patients whose tumors had a high (>10%) Ki-67 labeling index showed lower VD' values in the contralateral homotopic cortex (0.24 ± 0.06 vs. 0.29 ± 0.06 ; $p = 0.027$) and also in the contralateral frontal cortex (0.25 ± 0.07 vs. 0.30 ± 0.08 ; $p = 0.06$) than patients whose tumors had a low (<10%) Ki-67 labeling index. In contrast, cortical K-complex values showed no significant differences between patients with high vs. low tumor proliferative activity ($p > 0.25$).

DISCUSSION

While the majority of malignant gliomas demonstrate increased AMT VD' and unidirectional uptake on PET compared to contralateral homotopic cortex, our data indicate that the tumor AMT VD' (a kinetic PET imaging parameter related to net transport of tryptophan from blood into tissue) and tumor/cortex VD' ratio are good imaging predictors of tumor proliferative activity in WHO grade II-IV gliomas. In addition, decreased AMT K-complex values in the frontal cortex contralateral to the tumor indicate impaired serotonin synthesis in non-tumoral cortex in these patients compared to normal controls. This may be the result of a systemic tumor effect on tryptophan metabolism, possibly mediated by an upregulation of the kynurenine pathway leading to decreased availability of tryptophan for serotonin synthesis in extratumoral tissues.

Increased tryptophan transport into the tumor mass may be explained by several mechanisms, including: (i) increased diffusion across an impaired blood-brain barrier; (ii) increased expression and activity of the tryptophan carrier L-type amino acid transporter (20, 28); and/or (iii) increased tumoral microvasculature that can facilitate dissociation of tryptophan from albumin (29). Consistent with this, in our previous studies with AMT PET in various brain tumors, we have found that contrast-enhancing gliomas showed higher VD' values than non-enhancing tumors (24), and we have also found high VD' values in non-

enhancing grade I dysembryoplastic neuroepithelial tumors, which showed high expression of the L-type amino acid transporter at the blood-brain-barrier (21). These data support the notion that high VD' values can be related to a combination of blood-brain barrier impairment, increased tumor vascularity and high expression of the transporter, all of which can result in higher net tracer transport into tumor tissue in gliomas with high proliferative activity.

Increased amino acid influx into malignant gliomas provides more building blocks for cellular protein synthesis. Tryptophan transported from blood into tumor tissue is also a substrate for IDO. Gliomas can express IDO both constitutively (17) and following the release of cytokines (especially interferon- γ) in the tumor microenvironment (30,31). Increased tumoral IDO activity causes much more tryptophan metabolism via the kynurenine pathway than the serotonin pathway, which could lead to tryptophan shortage and accumulation of toxic kynurenine metabolites; both of these promote tumoral immune tolerance (16, 30). Unlike AMT transport, tumoral accumulation of AMT (as measured by tumoral K-complex values) does not seem to be tightly correlated with tumoral proliferative activity. This may be explained by our previous observation demonstrating increased expression of IDO in gliomas with various histologic grades (18).

Decreased tryptophan accumulation in cerebral cortex contralateral to the tumor in glioma patients compared to normal controls have not been previously reported and deserve further investigation. Cortical AMT K-complex is a macroparameter that estimates brain serotonin synthesis (8, 9). Decreased contralateral frontal K-complex values in glioma patients therefore may suggest an overall reduction in cortical serotonergic activity. This decreased activity might be caused by a systemic effect from activation of IDO and the kynurenine pathway in tumor cells. In keeping with this theory, patients with extracranial malignancies (e.g., lung and ovarian cancer) have decreased levels of tryptophan and elevated levels of kynurenine in the blood (22,23). Our results suggest that a similar mechanism may be operative in malignant gliomas, where tumoral IDO activation results in decreased systemic tryptophan availability. Whether this is indeed the case in glioma patients, and whether such systemic tryptophan changes play a role in altered cortical tryptophan metabolism, remains to be determined. PET studies of serotonin synthesis suggested that severe, acute tryptophan depletion can lead to reductions of brain serotonin synthesis (32). However, the AMT K-complex is a relatively stable macro-parameter with a relative independence of actual plasma tryptophan levels (an issue that has been discussed in detail by Chugani & Muzik [15]). It remains to be determined how chronic reductions of blood tryptophan levels, with associated increases in kynurenine metabolites, often seen in cancer patients, can account for a reduction of serotonin biosynthesis in the central nervous system. The observed decreases of AMT K-complex values may be also explained by a chronic, systemic shift between serotonin vs. kynurenine metabolism of tryptophan, with a net result of lower tryptophan metabolism in cortex.

Decreased cortical serotonergic function, suggested by lower AMT K-complex values measured by PET, may have important implications for neuropsychiatric comorbidities in glioma patients. Decreased cortical AMT K-complex values have been reported in previous PET studies of patients with various psychiatric conditions, such as borderline personality disorder (11), alcoholism (13), and major depression (12). Depression is a common and often unrecognized condition in patients with infiltrating gliomas (14, 33). A population-based study found depression in about one-third of patients with primary brain tumors, with similar severity across various tumor types and locations (34). The "serotonin hypothesis" may explain the presence of depression in glioma patients. This hypothesis postulates that depression is caused by a depletion of serotonin, which may be caused by immune-mediated shunting of tryptophan from serotonin to kynurenine synthesis (35-39). There are several

lines of evidence suggesting that this mechanism may play a central role in cancer-associated depression (40). However, further studies are needed to determine the precise role of the accumulation of toxic kynurenine metabolites and concomitant serotonergic abnormalities in the central nervous system, including several other cortical regions, in the development of depression associated with human gliomas.

Although we focused on assessing the Ki-67 labeling of tumor areas with the greatest cellularity, we did not do stereotactic matching of histology and imaging in this study. It is likely that the correlation between tumoral AMT uptake and Ki-67 labeling would be even stronger if the location of tissue sampling were matched accurately with the AMT PET abnormality by image-guided biopsy (7). This approach could also address the contribution of other potential factors, such as glioma microvessel density, to *in vivo* tracer transport. Nevertheless, the present data provide evidence that the net blood-to-tumor transport of AMT (and, potentially, other PET radiotracers with similar transport mechanisms) could be a useful imaging marker of proliferative activity in malignant gliomas.

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Patrick M. Colletti, M.D.

Editor-in-Chief,

Clinical Nuclear Medicine

Dear Dr. Colletti,

Enclosed please find our manuscript entitled “Quantitative PET imaging of tryptophan accumulation in gliomas and remote cortex: Correlation with tumor proliferative activity” for consideration for publication in Clinical Nuclear Medicine as an Original Article. The submitted materials include the main text with one table and two figures (one color figure).

In this study of 30 adult patients with newly diagnosed WHO grade II-IV gliomas, we utilize the unique capability of dynamic α -[^{11}C]methyl-L-tryptophan (AMT) PET imaging to quantify tryptophan net transport and metabolism in gliomas (where high AMT uptake can occur as a result of increased tryptophan transport and metabolism via the kynurenine pathway) and also remote cortex (where AMT PET measures serotonin synthesis). Our previous studies demonstrated AMT accumulation in various gliomas. Here, we report two novel findings:

- i. Tryptophan net transport rates, reflected by the volume of distribution of the radiotracer on PET, can predict *glioma proliferative activity* (as measured by Ki-67 labeling).
- ii. We have also found a simultaneous *decrease* in tryptophan transport and unidirectional uptake rates in *contralateral* frontal cortex of glioma patients (as compared to normal controls), which suggests *decreased cortical serotonergic activity* in these patients. These latter data provide novel imaging evidence for a remote tumor effect on brain serotonin synthesis.

The results may have several important clinical implications, including non-invasive assessment of glioma proliferative activity by quantitative PET imaging; the cortical findings may stimulate further research to explore the role of serotonergic abnormalities in neuropsychiatric complications of adult gliomas (such as glioma-associated depression).

We assure you that there has been no duplicate publication or submission elsewhere of any part of this work. All authors have worked on the manuscript, reviewed the final version, and none of them has a conflict of interest. We hope that the editor and reviewers will find this article suitable for publication in *Clinical Nuclear Medicine*.

Sincerely yours,

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Figure 1.

Co-registered axial post-gadolinium T1-weighted MRI (A) and AMT-PET images (B) (uptake image from 30-55 min post-injection) of a patient (#26 in Table 1) with a right temporal lobe glioblastoma. Ki-67 immunostaining (C) in the resected tumor (original magnification, 400X) showed strong Ki-67-positive nuclei in 10-15% of the cells.

Figure 2.

Strong positive correlation between glioma Ki-67 labeling index and tumor/contralateral cortex AMT volume of distribution (VD') ratios in 30 patients with glioma. Spearman's $\rho = 0.75$, $p < 0.001$. (Spearman's ρ drops only minimally, to 0.73, if the one patient with the highest Ki-67 and VD' ratio values is omitted from the analysis)

Table 1

Clinical data and AMT volume of distribution (VD') and K-complex values (and tumor/contralateral homotopic cortex ratios) measured in tumors, as well as VD' and K-complex values measured in contralateral frontal cortex. Tumors are listed from lower to higher WHO grade and grouped by tumor type within a histologic grade

Patient No.	Sex	Age (years)	Tumor Grade	Tumor Type	Tumor location	Ki-67 (%)	VD' tumor	VD' ratio	K tumor	K ratio	VD' frontal cortex	K frontal cortex
1	F	41	2	Astro	P	5-10	.34	1.13	.0085	1.37	.32	.0040
2	M	57	2	Astro	T	2-3	.42	1.17	.0098	2.08	.24	.0051
3	F	59	2	Astro	F	5-10	.68	2.00	.0060	1.27	.46	.0037
4	M	24	2	OA	T	5-10	.39	2.25	.0094	4.68	.28	.0051
5	F	53	2	OA	F	1-2	.27	1.05	.0073	1.16	.24	.0060
6	M	21	2	Oligo	F	1-2	.34	1.13	.0068	1.11	.30	.0055
7	F	32	2	Oligo	F	2-3	.37	1.23	.0049	1.02	.33	.0041
8	M	34	2	Oligo	F	3-5	.44	2.00	.0072	2.10	.21	.0036
9	M	36	2	Oligo	F	3-5	.20	.81	.0060	1.00	.25	.0054
10	F	37	2	Oligo	F	2-3	.61	1.56	.0069	1.72	.36	.0034
11	M	44	2	Oligo	P	3-5	.67	3.58	.0101	2.23	.22	.0037
12	M	50	2	Oligo	F	1-2	.46	1.44	.0083	1.66	.31	.0049
13	M	54	2	Oligo	F	3-5	.36	1.12	.0066	1.69	.28	.0037
14	M	50	3	Astro	P	3-5	.37	1.28	.0045	1.00	.33	.0037
15	M	55	3	Astro	T	10-15	.35	1.67	.0150	3.00	.19	.0051
16	F	26	3	OA	F	5-10	.83	2.01	.0130	1.71	.53	.0067
17	M	42	3	OA	T	10-15	.80	2.75	.0089	1.85	.27	.0044
18	M	53	3	OA	P	10-15	.50	2.08	.0036	.88	.22	.0038
19	F	62	3	OA	T	10-15	.69	1.77	.0065	1.55	.38	.0037
20	M	28	3	Oligo	T	2-3	.34	1.11	.0050	1.25	.31	.0031
21	M	46	4	GBM	P	20-25	.40	2.20	.0080	1.95	.28	.0035
22	M	51	4	GBM	T	10-15	1.00	4.30	.0080	1.90	.23	.0040
23	M	52	4	GBM	F	5-10	.43	1.72	.0090	2.04	.22	.0046
24	M	53	4	GBM	F	15-20	.76	2.53	.0090	2.57	.30	.0035

Patient No.	Sex	Age (years)	Tumor Grade	Tumor Type	Tumor location	Ki-67 (%)	VD' tumor	VD' ratio	K tumor	K ratio	VD' frontal cortex	K frontal cortex
25	M	59	4	GBM	P	25-50	1.40	6.67	.0055	1.57	.17	.0036
26	F	65	4	GBM	T	10-15	.90	4.50	.0044	.56	.20	.0067
27	M	67	4	GBM	T	20-25	.68	2.61	.0060	1.67	.35	.0027
28	M	67	4	GBM	T	3-10	.55	2.04	.0040	.75	.27	.0049
29	M	67	4	GBM	T	20-25	.60	3.30	.0060	2.00	.16	.0030
30	M	68	4	GBM	F	20-25	.62	2.48	.0100	1.50	.25	.0057

Abbreviations: M=male, F=female, Astro=astrocytoma, OA=oligoastrocytoma, Oligo=oligodendroglioma, GBM=glioblastoma, T=temporal, P=parietal, F=frontal, Ki-67 (%)=Ki-67 labeling index (%) in resected gliomas.