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Location of brain tumor intersecting white matter tracts predicts patient prognosis

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Abstract

Background—Brain tumor cells invade adjacent normal brain along white matter (WM) bundles of axons. We therefore hypothesized that the location of tumor intersecting WM tracts would be associated with differing survival. This study introduces a method, voxel-wise survival analysis (VSA), to determine the relationship between the location of brain tumor intersecting WM tracts and patient prognosis.

Methods—113 primary glioblastoma (GBM) patients were retrospectively analyzed for this study. Patient specific tumor location, defined by contrast-enhancement, was combined with diffusion tensor imaging (DTI) derived tractography to determine the location of axons intersecting tumor enhancement (AXITEs). VSA was then used to determine the relationship between the AXITE location and patient survival.

Results—Tumors intersecting the right anterior thalamic radiation (ATR), right inferior fronto-occipital fasciculus (IFOF), right and left cortico-spinal tract (CST), and corpus callosum (CC) were associated with decreased overall survival (OS). Tumors intersecting the CST, body of the CC, right ATR, posterior IFOF, and inferior longitudinal fasciculus are associated with decreased progression-free survival (PFS), while tumors intersecting the right genu of the CC and anterior IFOF are associated with increased PFS. Patients with tumors intersecting the ATR, IFOF, CST, or CC had significantly improved survival prognosis if they were additionally treated with bevacizumab.

Conclusions—This study demonstrates the usefulness of VSA by locating AXITEs associated with poor prognosis in GBM patients. This information should be included in patient-physician conversations, therapeutic strategy, and clinical trial design.

Keywords

Brain Tumor; glioblastoma; diffusion; white matter tracts

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Conflicts of Interest

None.

INTRODUCTION

Glioblastoma (GBM) is the most common and deadly primary brain tumor in adults. Despite advancements in therapy, prognosis remains poor with a mean survival of 14.6 months¹. Interestingly, a number of prognostic factors including age, performance status, extent of resection, and adjuvant therapy have been found to moderately predict differences in survival^{2–7}. Other prognostic factors, such as tumor location, have been more difficult to assess.

Some studies suggest that tumor location affects survival and may play a role in prognosis^{6–8}. One recent study found a relationship between long-term responders and tumors located in the left and right hemispheres, where greater than 36 month survivors tended to have tumors located in the left hemisphere, while patients with survival greater than 12 months tended to have right hemisphere tumors⁹. Other studies, however, with smaller patient numbers have not found a relationship¹⁰. Interestingly, Ellingson et al. found that responders of radiochemotherapy (i.e. patients with greater than 12 month time to progression) presented with tumors at two cerebral locations, one in each hemisphere⁹. Along similar lines, promoter methylation of O6-methylguanine DNA methyltransferase (MGMT), a regulatory gene associated with a favorable survival outcome, has been shown to be more prominent in left-hemispheric GBMs, particularly located in the posterior subventricular zone¹¹.

Glioma cell migration into healthy brain tissue has been shown to occur along the path of white matter (WM) tracts^{12,13}. This occurs through a complex process of adhesion, motility, and invasion¹⁴. Recent studies suggest that imaging can predict the benefit of gross total versus subtotal resection based on calculated invasiveness metrics¹⁵. Cell invasion maps also can predict response to bevacizumab at recurrence¹⁶. This suggests that imaging prior to therapy can predict patient prognosis.

Diffusion tensor imaging (DTI) is sensitive to the orientation and density of WM tracts due to water preferentially diffusing along WM tracts¹⁷. DTI is commonly used for surgical planning in neuro-oncology^{18–22} allowing surgeons to distinguish and avoid major WM tracts. Diffusion imaging has also more recently been used in mathematical calculations modeling brain tumor migration and infiltration^{23,24}. Serial diffusion scans^{25–29} as well as DTI directional information have also been used to model glioma invasion^{30,31}. It remains unclear however whether tumors intersecting specific WM tracts are associated with prognosis.

In this study, DTI atlas-based tractography is used as a pre-surgical prognostic indicator for a clinical population presenting with GBM. Since glioma cells are known to infiltrate along WM tracts, we explored patient survival as a function of tumor-intersecting WM tract location. We hypothesized that GBMs intersecting the corpus callosum or WM tracts leading to critical brain stem regions such as the cortico-spinal tracts would be associated with a poor patient outcome *prior to any therapy*. To accomplish this, we introduce a method for determining the spatial relationship between a binarized patient specific metric (location of tumor intersecting WM tracts in this case) and patient outcome.

METHODS

Patient Population

Patients with pathologically confirmed primary GBM were screened retrospectively from our clinical database for this IRB approved study. Inclusion criteria required patients to have a T1-weighted pre- and post-contrast (T1+C) MRI prior to any therapy, outcome information including overall survival (OS). If available, progression-free survival (PFS) was defined as the time between diagnosis and progression noted radiographically, progression of neurological symptoms (i.e. RANO criteria)³², or by consensus of our institution's Brain Tumor Board. 113 patients fit these criteria and were subsequently included in this study. PFS data was available on 76 (67.3%) of the patients. Following initial presentation, 85 (75.2%) underwent a sub-total surgical resection (i.e. some contrast enhancement left behind), 20 (17.7%) underwent gross-total resection, and 8 (7.1%) had a biopsy only and no resection.

Image Acquisition

Imaging was gathered prior to surgery using one of our institutional MRI scanners. This included either 1.5T or 3T GE magnets (General Electric Health, Waukesha, WI). Commonly employed 2D T1 weighted spin echo sequences were collected before and after a dose of gadolinium contrast agent. Though some variance in parameters is common on our site, example parameters at 1.5T scan were a TR of 500ms and an echo time (TE) of 9.5ms. For 3T a TR of 600ms and a TE of 10ms were used.

Image Processing

The pre-surgical T1+C image was used to generate a tumor region of interest (ROI) for each patient using a semi-automated thresholded segmentation technique followed by manual correction of mis-classified voxels. To bring each patient into the same anatomical space, the T1+C images were co-registered to the Montreal Neurological Institute (MNI) brain template using a 12 degree of freedom affine transformation^{33,34}. The tumor ROIs were then brought into the same space using the T1+C co-registration matrix parameters. Whole brain deterministic atlas-space tractography was generated using the 3dProbTrackID^{35,36} program from the Analysis of Functional Neuroimages (AFNI)³⁷ toolbox applied to the freely available DTI brain atlas from the Illinois Institute of Technology³⁸. Tractography datasets for each patient were then reduced to those template space tracts that intersected enhancing tumor. These tracts were then transformed into binarized maps of AXon bundles Intersecting Tumor Enhancement (AXITEs) (Figure 1). To allow for greater overlap between patients and to fill in gaps between WM fibers, the binary maps were three-dimensionally convolved with a 5mm fwhm Gaussian kernel then binarized (Figure 1. Left).

Statistical Comparisons

Voxel based analytic methods³⁹ were adapted for use in this experiment using custom in-house MATLAB (Mathworks; Natick, MA) software. A nonparametric log-rank (Kaplan Meier) survival test was computed for each voxel, where groups were defined by the presence or lack of an AXITE (method shown in Figure 1). To control for population

sampling errors, voxels with 10 or more patients in each survival group (those *with* versus those *without* AXITEs present in each specific voxel) were included in the statistical analysis. The whole brain map of z-scores corresponding to the log-rank comparison was thresholded at a significance level of $p < 0.05$. To control for multiple comparisons, we ran a simulation to determine what cluster size minimized sensitivity to false positives using AFNI's 3dClustSim command. Clusters of at least 15 contiguous voxels were found to indicate significance free from multiple comparison errors. OS and PFS map level comparisons were generated. To ease labeling and interpretation of WM tract clusters, major WM ROIs from the FSL toolbox were used to mask the statistically thresholded clusters. Each cluster is reported according to the specific ROI it fell into. The number of patients in each survival groups in the voxel with the most significant p-value in each cluster is also reported along with the median survival of each group (Table 1).

Bevacizumab became standard of care during the retrospective period analyzed for this study. To determine if there was a spatial relationship between patient survival and the addition of this treatment, we performed a voxel-wise two-sample t-test comparing patient survival between those who received the drug and those who did not. Voxel inclusion required AXITE presence from at least 10 patients in each treatment group (w/bev versus w/o bev).

Age has been shown to predict patient outcome. Therefore to assess whether age was a factor in tumor location, a voxel-wise analysis was done comparing age of patients with an AXITE in each voxel to those with AXITEs elsewhere. Clusters were again limited to those comprised of at least 15 voxels.

RESULTS

VSA revealed that patients with tumors intersecting the right anterior thalamic radiation (ATR), right inferior fronto-occipital fasciculus (IFOF), bilateral cortico-spinal tracts (CSTs), and corpus callosum (CC) had decreased OS compared to patients with tumors intersecting WM tracts elsewhere. Figure 2 (top) displays axial slices of the statistically thresholded OS map ($p < 0.05$, corrected for multiple comparisons). The PFS analysis showed clusters associated with decreased PFS, including the left inferior longitudinal fasciculus (ILF), right ATR, and the left and right CST white matter ($p < 0.05$, corrected for multiple comparisons). The PFS analysis also showed WM clusters associated with increased PFS including the right genu of the CC and anterior IFOF. Figure 2 (bottom) shows axial views of the statistically thresholded PFS map ($p < 0.05$, corrected for multiple comparisons). Table 1 contains details for each cluster including the median survival and number of patients in each group along with the Talairach coordinates⁴⁰ corresponding to the peak p-value in each cluster.

The voxel-wise t-test comparing survival with patients dichotomized by bevacizumab treatment, revealed that patients with tumors intersecting clusters in the CST, CC, ATR, and IFOF were associated with increased overall survival (Figure 3) ($p < 0.05$, corrected for multiple comparisons). Our requirement of at least 10 patients in each group per voxel led to

a much smaller mask in this analysis compared to the OS and PFS (Supplemental Figure 1). Voxels outside the masks were excluded.

Interestingly, age turned out to be a factor with tumor location. A large cluster in the posterior left parietal lobe was associated with younger patients, while a smaller subset of clusters in the right frontal lobe was associated with older patients (Supplemental Figure 2). The peak blue cluster voxel was located at coordinates [24.5, 63.5, 26.5] with an average age of 55, while the peak red cluster was located at [-11.5, -18.5, -3.5] with an average age of 67.

DISCUSSION

This study introduces a new technique for assessing the survival implication of brain tumor-intersecting WM tracts. We found that GBMs intersecting major WM tracts such as the cortico-spinal tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and anterior thalamic radiations are associated with decreased OS and PFS, *even prior to any therapy*. This is likely due to brain tumors having direct infiltration routes to the brain stem and other structures imperative for physiological function such as breathing, swallowing, and maintaining blood pressure.

The results from this study are clinically relevant in several ways. First, patient expectations and prognosis should be assessed when brain tumors present intersecting WM tracts we found to be associated with decreased survival. Unfortunately in many of these regions, the balance of resectability versus maintaining function limits surgeons. Radiation oncologists may however have the option of treating these tumors more aggressively. Finally, when patients are selected and grouped for clinical trials, the location of tumors may need to be assessed and those associated with poor prognosis placed equally in test groups.

An area of decreased PFS but not the OS was found in the left inferior longitudinal fasciculus. Several previous studies have found this region associated with language and semantics specifically on the left (for a recent meta-analysis see Binder et al. 2009)⁴¹. Our definition of PFS included increased neurological symptoms, which may have been more apparent as language deficits. This may also be the case for the cortico-spinal tracts where decreased motor and sensory function may be noticed earlier by patients and physicians.

Clusters of significantly increased overall survival were not observed anywhere in the brain using VSA. This suggests that only AXITEs associated with poorer overall survival prognosis exist. We have found, however, that the right genu of the CC and anterior IFOF are regions associated with increased PFS. This prolonged progression free survival in these areas could come from a decrease in tumor enhancement caused by the inclusion of bevacizumab in some subjects' treatment plans. Tumor phenotype may also play a role.

The areas of increased overall survival associated with subjects who had additional bevacizumab therapy were promising. Anti-angiogenic drugs are thought to reduce vascular growth in tumors by disrupting the VEGF pathway. While these drugs have not consistently been shown to increase overall survival, we have found that there may be a survival benefit based on the spatial location of the tumor. Antiangiogenic drugs have been shown to

increase local invasion⁴², yet it remains to be seen whether there is a tumor location dependence of this phenomenon. It should be noted that the mask of included data (Supplemental Figure 1) was substantially smaller than the OS and PFS analyses. This is an interesting topic for future research in a much larger study.

There are several potential shortcomings to this analysis. Full treatment regimen, was not controlled for. To properly control for treatment, greater than 10 patients in each treatment arm would need to be present in each voxel. Because our study was limited to 113 patients, this approach was unfeasible. Controlling for treatment variables such as number of resections, radiation dose, chemotherapy regimens, etc would require a much larger patient population. These variables provide potential routes for future research. Age dependence of tumor location we believed to be unlikely, yet we found subtle age dependence of two clusters. Our findings appear to go against a recent analysis where older patients were found to have more posterior tumors⁹. Differences in methods may account for the discrepancy. We did however find R/L differences in addition which was not reported in Ellingson *et al*⁹. Given our much smaller sample size, we believe more research is necessary in a larger population with more similar methods.

Patient specific DTI was also not assessed. We relied on a DTI atlas for tractography calculations. We believe however that our atlas approach provided superior AXITE assessment, as it was not affected by patient specific degrading of fractional anisotropy near tumors due to edema. A formal comparison of atlas based results and those found with patient specific DTI is another avenue for further research. Alternative approaches using FA maps rather than tractography should also be performed to determine the significance of the directionality of tracts.

This study demonstrates the usefulness of VSA by locating AXITEs associated with poor overall survival prognosis in GBM patients, while showing the spatially dependent survival advantage to GBM patients who were given bevacizumab. Tumors intersecting the right ATR, right IFOF, right and left CST, and CC were associated with decreased OS. Tumors intersecting the CST, body of the CC, right ATR, posterior IFOF, and IFL are associated with decreased PFS, while tumors intersecting the right genu of the CC and anterior IFOF are associated with increased PFS. Subjects who had bevacizumab have a significantly improved survival prognosis if their tumors intersect the ATR, IFOF, CST, or CC. This information should be used to guide therapy options and patient expectations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABREVIATIONS

VSA	voxel-wise survival analysis
AXITE	axons intersecting tumor enhancement
WM	white matter
OS	overall survival
PFS	progression free survival
ATR	anterior thalamic radiation
IFOF	inferior fronto-occipital fasciculus
CST	cortico-spinal tract
CC	corpus callosum

References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005; 352(10):987–996. [PubMed: 15758009]
2. Ewelt C, Goeppert M, Rapp M, Steiger HJ, Stummer W, Sabel M. Glioblastoma multiforme of the elderly: the prognostic effect of resection on survival. *J Neurooncol*. 103(3):611–618.
3. Filippini G, Falcone C, Boiardi A, et al. Prognostic factors for survival in 676 consecutive patients with newly diagnosed primary glioblastoma. *Neuro Oncol*. 2008; 10(1):79–87. [PubMed: 17993634]
4. Jeremic B, Milicic B, Grujicic D, Dagovic A, Aleksandrovic J. Multivariate analysis of clinical prognostic factors in patients with glioblastoma multiforme treated with a combined modality approach. *J Cancer Res Clin Oncol*. 2003; 129(8):477–484. [PubMed: 12884028]
5. Li SW, Qiu XG, Chen BS, et al. Prognostic factors influencing clinical outcomes of glioblastoma multiforme. *Chin Med J (Engl)*. 2009; 122(11):1245–1249. [PubMed: 19567131]
6. Fontaine D, Paquis P. Glioblastoma: clinical, radiological and biological prognostic factors. *Neurochirurgie*. 56(6):467–476. [PubMed: 20869088]
7. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001; 95(2): 190–198.
8. Simpson JR, Horton J, Scott C, et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. *Int J Radiat Oncol Biol Phys*. 1993; 26(2):239–244. [PubMed: 8387988]
9. Ellingson BM, Lai A, Harris RJ, et al. Probabilistic radiographic atlas of glioblastoma phenotypes. *AJNR Am J Neuroradiol*. 2013; 34(3):533–540. [PubMed: 22997168]
10. Hammoud MA, Sawaya R, Shi W, Thall PF, Leeds NE. Prognostic significance of preoperative MRI scans in glioblastoma multiforme. *J Neurooncol*. 1996; 27(1):65–73. [PubMed: 8699228]
11. Ellingson BM, Cloughesy TF, Pope WB, et al. Anatomic localization of O6-methylguanine DNA methyltransferase (MGMT) promoter methylated and unmethylated tumors: a radiographic study in 358 de novo human glioblastomas. *Neuroimage*. 2012; 59(2):908–916. [PubMed: 22001163]
12. Pedersen PH, Edvardsen K, Garcia-Cabrera I, et al. Migratory patterns of lac-z transfected human glioma cells in the rat brain. *Int J Cancer*. 1995; 62(6):767–771. [PubMed: 7558428]

13. Belien AT, Paganetti PA, Schwab ME. Membrane-type 1 matrix metalloprotease (MT1-MMP) enables invasive migration of glioma cells in central nervous system white matter. *J Cell Biol.* 1999; 144(2):373–384. [PubMed: 9922462]
14. Lefranc F, Brotchi J, Kiss R. Possible future issues in the treatment of glioblastomas: special emphasis on cell migration and the resistance of migrating glioblastoma cells to apoptosis. *J Clin Oncol.* 2005; 23(10):2411–2422. [PubMed: 15800333]
15. Baldock AL, Ahn S, Rockne R, et al. Patient-specific metrics of invasiveness reveal significant prognostic benefit of resection in a predictable subset of gliomas. *PLoS One.* 2014; 9(10):e99057. [PubMed: 25350742]
16. Ellingson BM, Cloughesy TF, Lai A, Nghiemphu PL, Pope WB. Cell invasion, motility, and proliferation level estimate (CIMPLE) maps derived from serial diffusion MR images in recurrent glioblastoma treated with bevacizumab. *J Neurooncol.* 2011; 105(1):91–101. [PubMed: 21442275]
17. Bassar PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophys J.* 1994; 66(1):259–267. [PubMed: 8130344]
18. Ulmer JL, Salvan CV, Mueller WM, et al. The role of diffusion tensor imaging in establishing the proximity of tumor borders to functional brain systems: implications for preoperative risk assessments and postoperative outcomes. *Technol Cancer Res Treat.* 2004; 3(6):567–576. [PubMed: 15560714]
19. Witwer BP, Mofthakar R, Hasan KM, et al. Diffusion-tensor imaging of white matter tracts in patients with cerebral neoplasm. *J Neurosurg.* 2002; 97(3):568–575. [PubMed: 12296640]
20. Le Bihan D. Looking into the functional architecture of the brain with diffusion MRI. *Nat Rev Neurosci.* 2003; 4(6):469–480. [PubMed: 12778119]
21. Yamada K, Kizu O, Mori S, et al. Brain fiber tracking with clinically feasible diffusion-tensor MR imaging: initial experience. *Radiology.* 2003; 227(1):295–301. [PubMed: 12668749]
22. Clark CA, Barrick TR, Murphy MM, Bell BA. White matter fiber tracking in patients with space-occupying lesions of the brain: a new technique for neurosurgical planning? *Neuroimage.* 2003; 20(3):1601–1608. [PubMed: 14642471]
23. Yuan J, Liu L, Hu Q. Mathematical modeling of brain glioma growth using modified reaction-diffusion equation on brain MR images. *Comput Biol Med.* 2013; 43(12):2007–2013. [PubMed: 24290915]
24. Swanson KR, Bridge C, Murray JD, Alvord EC Jr. Virtual and real brain tumors: using mathematical modeling to quantify glioma growth and invasion. *J Neurol Sci.* 2003; 216(1):1–10. [PubMed: 14607296]
25. Pope WB, Lai A, Mehta R, et al. Apparent diffusion coefficient histogram analysis stratifies progression-free survival in newly diagnosed bevacizumab-treated glioblastoma. *AJNR Am J Neuroradiol.* 32(5):882–889.
26. Ellingson BM, Malkin MG, Rand SD, et al. Validation of functional diffusion maps (fDMs) as a biomarker for human glioma cellularity. *J Magn Reson Imaging.* 2010; 31(3):538–548. [PubMed: 20187195]
27. Hamstra DA, Chenevert TL, Moffat BA, et al. Evaluation of the functional diffusion map as an early biomarker of time-to-progression and overall survival in high-grade glioma. *Proc Natl Acad Sci U S A.* 2005; 102(46):16759–16764. [PubMed: 16267128]
28. Ellingson BM, LaViolette PS, Rand SD, et al. Spatially quantifying microscopic tumor invasion and proliferation using a voxel-wise solution to a glioma growth model and serial diffusion MRI. *Magn Reson Med.* 2011; 65(4):1131–1143. [PubMed: 21413079]
29. Ellingson BM, Cloughesy TF, Lai A, Nghiemphu PL, Pope WB. Cell invasion, motility, and proliferation level estimate (CIMPLE) maps derived from serial diffusion MR images in recurrent glioblastoma treated with bevacizumab. *J Neurooncol.* 105(1):91–101.
30. Jbabdi S, Mandonnet E, Duffau H, et al. Simulation of anisotropic growth of low-grade gliomas using diffusion tensor imaging. *Magn Reson Med.* 2005; 54(3):616–624. [PubMed: 16088879]
31. Painter KJ, Hillen T. Mathematical modelling of glioma growth: the use of Diffusion Tensor Imaging (DTI) data to predict the anisotropic pathways of cancer invasion. *J Theor Biol.* 2013; 323:25–39. [PubMed: 23376578]

32. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010; 28(11): 1963–1972. [PubMed: 20231676]
33. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Med Image Anal*. 2001; 5(2):143–156. [PubMed: 11516708]
34. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*. 2002; 17(2):825–841. [PubMed: 12377157]
35. Taylor PA, Cho KH, Lin CP, Biswal BB. Improving DTI tractography by including diagonal tract propagation. *PLoS One*. 7(9):e43415. [PubMed: 22970125]
36. Taylor PA, Saad ZS. FATCAT: (an efficient) Functional and Tractographic Connectivity Analysis Toolbox. *Brain Connect*. 3(5):523–535.
37. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996; 29(3):162–173. [PubMed: 8812068]
38. Varentsova A, Zhang S, Arfanakis K. Development of a high angular resolution diffusion imaging human brain template. *Neuroimage*. 2014; 91C:177–186.
39. Bates E, Wilson SM, Saygin AP, et al. Voxel-based lesion-symptom mapping. *Nat Neurosci*. 2003; 6(5):448–450. [PubMed: 12704393]
40. Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. 3-Dimensional proportional system: an approach to cerebral imaging. 1988
41. Binder JR, Desai RH, Graves WW, Conant LL. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex*. 2009; 19(12):2767–2796. [PubMed: 19329570]
42. Paez-Ribes M, Allen E, Hudock J, et al. Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer Cell*. 2009; 15(3):220–231. [PubMed: 19249680]

Figure 1.

Illustration of voxel-wise survival analysis (VSA) applied to axons intersecting tumor enhancement (AXITE). Regions of interest are generated from template-derived tractography intersecting each patient's tumor (Left). A Kaplan Meier survival analysis is then performed on a voxel-wise basis comparing the overall and progression-free survival between patients with and without AXITE maps at each individual voxel. A representative voxel (Right) is shown along with the resulting survival plot (Middle). Voxels are then p-value thresholded $p < 0.05$ (Right blue clusters as an overlay).

Figure 2. Statistically thresholded VSA clusters of AXITEs associated with decreased overall (top) and both increased and decreased progression-free (bottom) survival.

Figure 3. Statistically thresholded map showing regions of increased survival in subjects who were treated with bevacizumab. No regions of decreased survival were present.

Table 1

Summary of significant voxel-wise survival analysis (VSA) clusters in major WM regions. Results from the OS, PFS, and survival differences due to bevacizumab are shown. The major WM regions are the cortico-spinal tract (CST), the anterior thalamic radiation (ATR), the inferior fronto-occipital fasciculus (IFOF), and the inferior longitudinal fasciculus (ILF). Decreased survival was found in all clusters in the OS analysis. Decreased PFS was found in all clusters except those marked with an asterisk (*) which were found to be associated with increased PFS. The bevacizumab group survived longer than the non-bevacizumab group in all clusters indicated (all clusters $p < 0.05$ corrected for multiple comparisons).

Survival Analysis	WM Region	Cluster Size	Talairach Coords (x,y,z)	Peak p-value	N Tract Group	N Non-Tract Group	Median Survival Tract Group (days)	Median Survival Non-Tract Group (days)	
Overall Survival	CST	1: 153 voxels	(-21.5, 17.5, 42.5)	2.31E-04	47	66	194	433	
		2: 46 voxels	(22.5, 25.5, 44.5)	2.68E-03	46	67	254	431	
	CC	1: 1290 voxels	(4.5, 13.5, 24.5)	3.06E-07	29	84	160	427	
		2: 185 voxels	(2.5, -20.5, 16.5)	4.00E-04	46	67	164	390	
	ATR	1: 472 voxels	(-3.5, 15.5, 6.5)	7.19E-05	35	78	164	387	
		2: 194 voxels	(4.5, 5.5, 4.5)	6.10E-04	50	63	234	435	
		3: 59 voxels	(22.5, -22.5, 16.5)	1.83E-03	49	64	222	387	
		4: 41 voxels	(-21.5, -38.5, 0.5)	3.38E-04	25	88	164	373	
	IFOF	1: 124 voxels	(-25.5, -18.5, -1.5)	1.76E-04	28	85	163	383	
	Progression-Free Survival	CST	1: 423 voxels	(-23.5, 15.5, 36.5)	1.05E-04	35	41	145	259
			2: 151 voxels	(22.5, 19.5, 46.5)	7.19E-05	38	38	147	244
		CC	* 1: 61 voxels	(-19.5, -22.5, 22.5)	6.73E-03	15	61	388	148
2: 1625 voxels			(16.5, 47.5, 22.5)	8.22E-07	17	59	112	209	
ATR		1: 215 voxels	(8.5, 23.5, 2.5)	1.28E-04	32	44	124	219	
		2: 92 voxels	(-9.5, 9.5, -7.5)	1.04E-03	19	57	111	209	
IFOF		* 1: 43 voxels	(-39.5, -38.5, 0.5)	1.21E-02	10	66	509	151	
		2: 50 voxels	(-33.5, 25.5, 2.5)	1.98E-04	41	35	126	259	
		3: 41 voxels	(34.5, 53.5, -3.5)	1.91E-04	13	63	117	195	
		ILF	1: 75 voxels	(34.5, 69.5, 4.5)	3.86E-05	12	64	115	196
					w/Bev w/o Bev		w/Bev w/o Bev		

Survival Analysis	WM Region	Cluster Size	Talarach Coords (x,y,z)	Peak p-value	N Tract Group	N Non-Tract Group	Median Survival Tract Group (days)	Median Survival Non-Tract Group (days)
Overall Survival Difference Due to Bevacizumab	CST	1: 160 voxels	(22.5, 15.5, 36.5)	1.14E-04	15	32	516	167
		2: 96 voxels	(12.5, 23.5, -13.5)	1.95E-03	12	17	455	222
		3: 48 Voxels	(-23.5, 27.5, 42.5)	9.15E-06	20	36	456	162
	CC	1: 536 voxels	(-1.5, -20.5, 14.5)	1.62E-05	16	35	692	157
		2: 319 voxels	(18.5, 15.5, 34.5)	4.24E-04	14	32	448	162
		3: 169 voxels	(-7.5, 43.5, 18.5)	6.61E-05	13	25	781	164
	ATR	4: 115 voxels	(-9.5, 35.5, 8.5)	5.31E-06	21	38	445	168
		1: 167 voxels	(10.5, 13.5, 2.5)	6.78E-03	11	16	379	144
		2: 110 voxels	(20.5, -16.5, 18.5)	2.13E-05	17	38	557	162
	IFOF	3: 55 voxels	(-23.5, -24.5, 18.5)	4.19E-06	16	42	684	162
		1: 53 voxels	(36.5, 15.5, -5.5)	9.50E+04	12	17	721	222
								337