

Diffusion Tensor Invasive Phenotypes Can Predict Time to Progression in Glioblastomas

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Glioblastomas (GBM) account for 70% of primary brain tumors and remain incurable in most cases. Their propensity to invade into normal brain is a key feature that makes current therapies ineffective. The heterogeneity of GBM's is also reflected in their invasive behavior – post mortem studies suggest about a 25% of GBM's invade less than 1 cm from the tumor bulk and 20% invade more than 3 cm. This would suggest that trials of aggressive local therapy (i.e. fluorescence-guided resection with the use of local oncological therapies such as Carmustine wafers) are likely to only work in a subset of patients. At present we cannot predict which patients have a minimally invasive phenotype that are likely to respond well to this strategy. This study aims to use diffusion tensor MR (DTI) to assess the occult tumor invasion of surrounding white matter tracts in a cohort of patients with glioblastomas treated in a similar manner, and see how this relates to the rate of tumor recurrence.

Aim of Study: In this study, we retrospectively, analyzed the DTI images of patients with GBM to further categorize the infiltrative pattern of the tumor using previously reported patterns¹ and see how they related to the time to tumor progression.

Materials and Methods: 21 patients with GBM (mean age 54, range 30-68) that were being treated with chemo-radiotherapy according to the Stupp protocol were retrospectively analyzed. All patients had a WHO performance score of 0-1 and were imaged on a GE Excite3 1.5T MR scanner. The sequences composed of standard anatomical sequences with a DTI scan (TR/TE: 12k/95 ms, Slice thickness: 4 mm, inter-slice gap: 4 mm, resolution: 256x256, 25 directions, b values 0 and 1000).

The DTI images were analyzed using the MedINRIA (Asclepius Research Project, Inria Sophia Antipolis, France). For each voxel, the eigenvalues (λ_1 , λ_2 , λ_3) were calculated and using an in-house built software, these value were used to construct the p and q maps as described previously². For each of the p and q maps, regions of interest (ROIs) were drawn around the visible abnormality on every slice using Image J software (National Institutes of Health, USA). In a sample of patients, the ROIs were drawn by two independent trained readers, both blinded to the survival results of the patients and there was good agreement between them. Where the p abnormality exceeded the q abnormality by 1 cm in only 1 direction, the lesion was called "localized" and where p exceeded the q abnormality in more than 1 direction or by more than 1 cm, it is assigned a "diffuse" pattern of invasion. Where the p and q regions were less than 1cm apart this was assigned a "minimal" pattern of invasion. Patients underwent standard clinical follow up for a minimum of 5 months post-surgery. Progression was defined according to the RANO criteria³ and the time to progression (TTP) determined in days. Statistical analysis was performed using IBM SPSS for Windows (version 19.0.0; 2010). Kaplan Meier plots of survival for the three groups were plotted as were the proportion of patients who had not progressed at 18 months.

Results: 8 (38%) patients had a diffuse phenotype, 9 (42%) had a localized phenotype and 4 (20%) had a minimally invasive phenotype. Each group were matched in terms of age, sex and extent of surgical resection. The mean TTP for the diffuse group was 314 days, for the localized group 466 days and 705 days for the minimally invasive group. None of the diffuse patients and only one of the localized patients were progression free at 18 months. 3/4 of the minimally invasive group were progression free at 18 months (Chi square 6.9; P = 0.02).

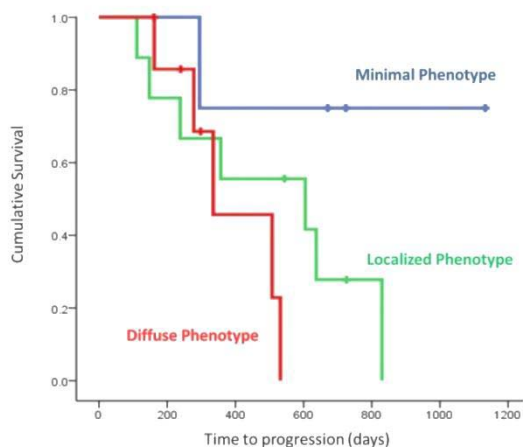


Figure 1: Kaplan Meier survival curves for the time to progression in the three invasive phenotypes

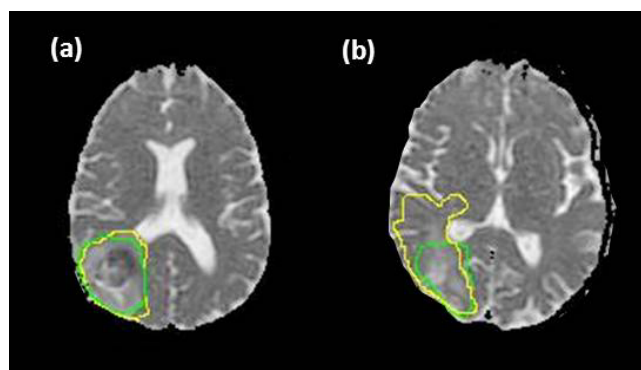


Figure 2: Examples of minimally invasive pattern (a) and localized pattern.

Conclusion: It is possible to identify three invasive phenotypes in glioblastomas using diffusion tensor imaging, and these three phenotypes have different times to progression. In particular, it is possible to identify a minimal phenotype in 20% of patients that predicts prolonged time to progression. The biological nature of this difference needs to be understood. This method may allow tailoring of treatment based on the invasive phenotype.

References:

1. Price SJ et al. (2007) Eur.Radiol., 17:1675-1684.
2. Pena A et al. (2006) The British Journal of Radiology, 79:101-109.
3. Wen PY et al. (2010) J.Clin.Oncol., 28:1963-1972.