Diffusion Tensor Imaging in Glioblastoma Multiforme and Brain Metastases: the Role of p, q, L and FA

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Title: Diffusion Tensor Imaging in Glioblastoma Multiforme and Brain Metastases: the Role of ***p***, ***q***, ***L*** and **FA**

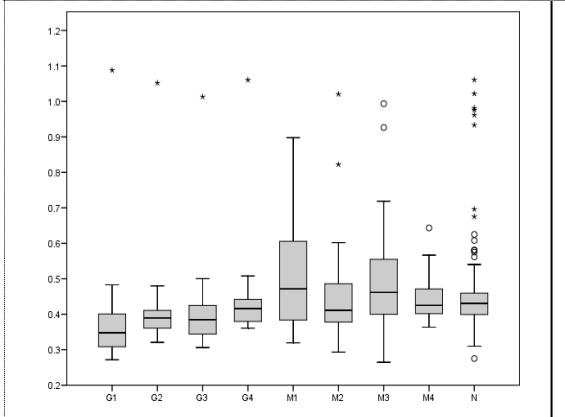
Aim: Micro-invasive tumour cells, which are not detected on conventional imaging, contribute to poor prognoses for patients diagnosed with glioblastoma multiforme (GBM; WHO grade IV). Diffusion tensor imaging (DTI) shows promise in being able to detect this infiltration. This study aims to detect a difference in diffusion properties between GBM (infiltrative) and brain metastases (non-infiltrative). In particular, to compare the diffusion tensor metrics **p**, **q**, **L**, and **FA** from tumoural and peritumoural regions of glioblastoma multiforme and metastatic brain tumours 2/ To determine whether these parameters can be correlated with the type of tumour and the extent of infiltration into surrounding white matter 3/ To determine whether these parameters, and more broadly DTI, has a significant clinical meaning, and thus whether it should be included in imaging protocols for suspected brain tumour and for treatment planning.

Methods: 49 Patients scanned between January 2004 and June 2006 for clinical purposes. The inclusion criteria: Histological report within 2 weeks of imaging, Histological report indicating GBM or brain metastasis and DTI with 6 non-collinear gradient directions. Exclusion criteria were: Imaging performed within 2 weeks of any brain surgery (e.g. biopsy). Total tumours: 49 (30 GBM, 19 metastases). All scans were performed on a 1.5 T clinical MRI scanner (General Electric Echospeed Plus LX 9) using a standardised brain tumour imaging protocol. Namely, DTI (pre-contrast): 6 non-collinear gradient directions, Axial T2-weighted (pre-contrast): spin-echo EPI, Axial T1-weighted (contrast enhanced): volumetric and/or spin-echo T1-weighted scans were used for delineating gross tumour. The T2-weighted scans were used for delineating oedema. 4 ROIs were placed - Gross tumour (excluding necrotic or haemorrhagic core), Peritumoural oedema, Peritumoural margin (5 voxels from the edge of gross tumour), Adjacent normal appearing white matter (NAWM; 3 voxels from the edge of peritumoural oedema). All ROIs were mirrored in 3D to the contralateral normal brain using the MINCtools software.

Results: When comparing ipsilateral to contralateral sides: For GBM: mean ***p, q, L*** and **FA** values were all significantly different in **gross tumour**, **peritumoural oedema** and **peritumoural margin** ($p<0.001$). For GBM: mean ***p, L*** and **FA** values were all significantly different in **adjacent normal appearing white matter** ($p<0.001$). For metastases: mean ***p, L*** and **FA** values were significantly different in **all** regions ($p<0.001$). Mean ***q*** values were **not** significantly different between the sides in any region for metastases ($0.147 \leq p \leq 0.904$). Mean ***q*** values were **not** significantly different between **adjacent NAWM** in GBM ($p=0.360$). When comparing between patient groups: Mean ***q* value** differed significantly between GBM and metastases patients in **gross tumour** and **peritumoural margin** ($p<0.001$ and $p=0.007$). Mean **FA value** differed significantly between GBM and metastases patients in **gross tumour** only ($p<0.001$). Boxplots for the ***q*** values are shown in **Fig 1**, and sample ***q*** and ***FA*** images with corresponding ROI's in **Fig 2**.

Discussion: The literature has conflicting reports on the precise value of DTI parameters in tumour studies. For example, previous research have shown that mean diffusivity (p) was either useful **(1,2)**, or not useful **(3,4)**. Similarly studies have shown FA was useful **(4,7)**, and not useful **(1,2,3).** 4 previous studies **(6)** have shown that q may be useful. Herein, the mean ***q*** value not being different in metastases to normal brain tissue was surprising. It suggests that anisotropy in metastases is equal to that in normal brain perhaps due to white matter compaction. ROC curve analyses showed significant overlap of both *q* and FA values between GBM and metastases. The MD and FA results are largely in agreement with previous studies. The **p** and **q** in GBM are also both in agreement with previous studies. The significant difference of the ***q*** value in the peritumoural margin between the two groups may suggest that DTI can detect tumour infiltration. To our knowledge, there has been no previous results of ***q*** in metastases.

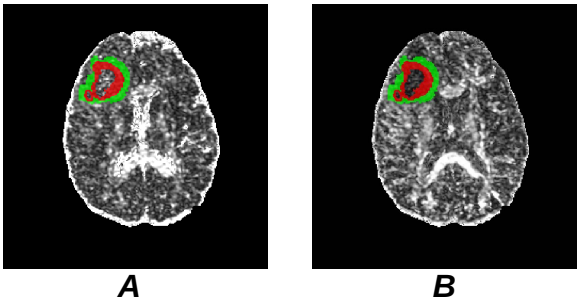
Conclusion Diffusion tensor imaging, and especially the anisotropic component of diffusion (***q***), can be used to differentiate, to some extent, between glioblastoma multiforme and metastatic brain tumour. A difference in ***q*** between the tumours can be seen in the gross tumour and the peritumoural margin, which theoretically is highly infiltrated by tumour cells. This leads to the inference that DTI can detect tumour cells that have infiltrated into the surrounding brain. Further research is required to refine the applicability of DTI, but its potential is evident.



Box-plot of mean *q* value showing from left to right: GBM gross tumour (G1), peritumoural oedema (G2) and margin (G3), and adjacent NAWM (G4); metastases gross tumour (M1), peritumoural oedema (M2) and margin (M3), and adjacent NAWM (M4); and normal brain compiled from all regions (N). Also shown are outliers: mild outliers by ○ and extreme outliers by ★.

Fig 1

References: **1:** Sinha, S., et al., AJNR Am J Neuroradiol, 2002. **23**(4): p. 520-7. **2:** Lu, S., et al., AJNR Am J Neuroradiol, 2003. **24**(5):p 937-41. **3**: van Westen, D., et al., Acta Radiol, 2006. **47**(3): p. 311-9. **4:** Provenzale, J.M., et al., Radiology, 2004. **232**(2): p. 451-60. **5**: Price, S.J., et al., Br J Neurosurg, 2004. **18**(4): p. 391-5. **6:** Price, S.J., et al.,. Eur Radiol, 2007. **7:** Toh, C.H., et al., Neuroradiology, 2007.



Axial processed images from DTI sequence. Image ***A*** the *q* map with two ROIs: tumour (with necrotic/haemorrhagic core excluded) in red and peritumoural margin in green. Image ***B*** shows an FA map with the same ROIs as image ***A***.

Fig 2