Repeated Split Sample Validation to Assess Logistic Regression Model of DTI in Differentiating Glioblastomas from Brain Metastases

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Introduction

Differentiation between glioblastomas and brain metastases remains challenging when patients present with a solid enhancing mass as both of them may exhibit ring-enhancement and extensive edema. Most of the previous DTI studies have used small sample population with mixed result[1-2]. Our previous study[3] with 63 patients showed that DTI metrics including mean diffusivity (MD) and anisotropy measures can differentiate glioblastomas from metastases with high sensitivity (92%) and specificity (100%). However, this result needs to be validated in a large sample. In this study, we reported the validation of this method in 203 patients.

Materials and Methods

Patients with enhancing lesions (n = 203) were included in this study. Histopathologic analysis of the resected tissue confirmed the diagnosis of glioblastoma in 129 patients (79M/50F, age 24-90) and brain metastasis in 74 patients (38M/36F, age 44-88). Of the 74 metastases, the primary sites for cancer include lung (47), breast (10), melanoma (7), colon (3), renal (2), sarcoma (2), parotid (1), esophageal (1) and ductal (1). All patients underwent MR examination before surgery on a 3T Siemens Tim Trio scanner with a 12-channel phased-array head coil. DTI data was acquired using a single shot, spin echo EPI sequence with parallel imaging using GRAPPA and acceleration factor of 2. 55 patients (40 glioblastomas, 15 metastases) were acquired with 12 diffusion weighting directions (TR/TE = 4900/83, NEX = 6) and remaining 148 patients were acquired with 30 directions (TR/TE = 5000/86, NEX = 3). Other sequence parameters were as follows: FOV = 22 x 22 cm^2, b = 0, 1000 s/mm^2, slice thickness 3 mm. It is assumed that there is no significant difference in MD and fractional anisotropy (FA) between 12 and 30 direction DTI data, as shown in other work[4]. DTI post processing was performed off-line using in house software. Contrast-enhanced T1 weighted images, FLAIR, FA and MD maps were coregistered and the tumor was segmented semi-automatically using IDL routines. DTI metrics from the enhancing (ER) and immediate peritumoral regions (IPR) were measured and compared between glioblastomas and brain metastases using an unpaired t-test. A multivariate logistic regression analysis was employed to determine the best model for classification. The full dataset was split randomly into a training set (70%) and validation set (30%). Sample splitting was repeated 10 times and AUC and regression coefficients were computed at each time.

Table 1: DTI metrics from the enhancing (ER) and immediate peritumoral regions (IPR) between glioblastomas and brain metastases

Subject	ER		IPR	
	MD ($10^{-3}mm^2/s$)	FA	MD ($10^{-3}mm^2/s$)	FA
Glioblastomas (n=129)	1.08±0.21	0.16±0.04	1.09±0.21	0.20±0.05
Metastases (n=74)	1.10±0.24	0.11±0.03*	1.16±0.22	0.16±0.05*

*indicates statistically significant difference ($p< 0.01$)

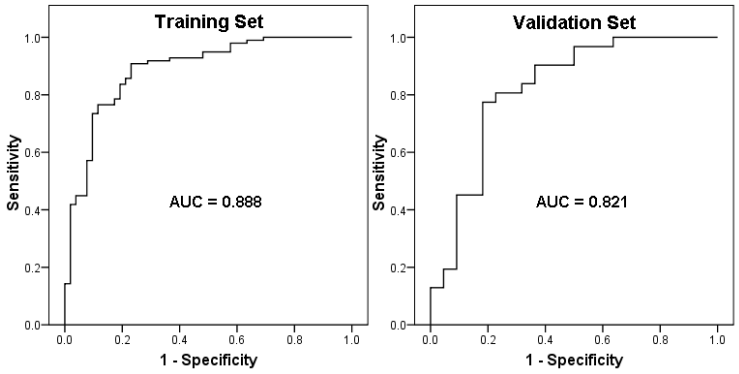

Fig.1 Representative receiver operative characteristic (ROC) curves from the enhancing (ER) and immediate peritumoral region (IPR) of the tumor for logistic regression model in the training and validation set. FA and MD from the ER and FA from the IPR is the best model for classification.

Results

DTI metrics from the ER and IPR of the tumor are shown in Table 1. FA values from ER and IPR for glioblastomas were significantly higher than those for brain metastases ($p< 0.01$). MD from both regions didn't show any significant difference.

The logistic regression analysis indicated that the best model using the ER included FA and MD. The best classifier using the IPR was FA. As shown in Table 2, DTI metrics from the ER differentiated two tumor types better than those of the IPR. When we combined both regions together, the best model included FA and MD from ER and FA from the IPR. Representative ROC curve for the training and validation set are shown in Fig.1. The results for repeated split sample validation are shown in Table 2.

Table 2: Mean ± SD of ten times split sample validations

Region	AUC		Regression Coefficient			
	Training	Validation	Constant	MD_{ER}	FA_{ER}	FA_{IPR}
ER	0.86±0.01	0.86±0.04	-7.75±0.67	2276±412	43.79±4.05	
IPR	0.69±0.03	0.70±0.07	-2.01±0.46			14.44±2.80
ER+IPR	0.87±0.02	0.85±0.03	-6.60±1.11	1797±626	54.18±7.15	-10.98±3.87

Discussion

Our prior studies in a small sample population have shown that FA and MD from the enhancing part are very useful for differentiating glioblastomas from brain metastases. Results from the present study confirmed that FA and MD from the enhancing part is a robust model for the distinction between glioblastomas and brain metastases. It has been reported that cells of glioblastoma produce large amounts of tumor-specific extracellular matrix (ECM) components, which serve as a substrate for adhesion and subsequent migration of the tumor cells through the enlarged extracellular space[5]. High FA value observed in glioblastomas may be due to the orientation of overproduced ECM.

Reference

1. Lu S, et al. AJNR 2003;24:937. 2. Tsuchiya K, et al. Br J Radiol 2005;78:533. 3. Wang S, et al. Neuroimage 2009; 44:653. 4. Landman BA, et al. Neuroimage 2007;36:1123. 5. Zamecnik J. Acta Neuropathol 2005; 110:435