Evaluation of Intratumoral Virus Delivery in Brain Tumor Oncolytic Virus Therapy Using Diffusion Tensor Imaging

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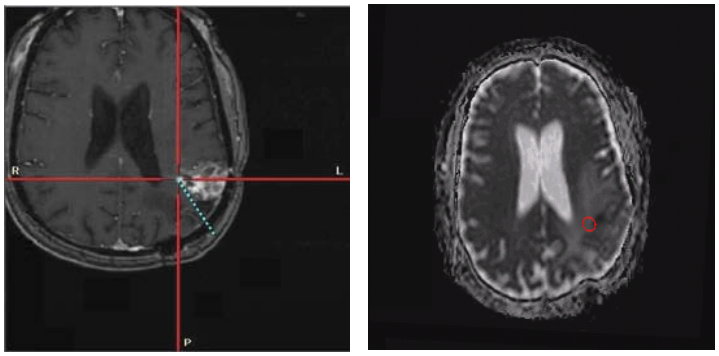
INTRODUCITON

Oncolytic virus therapy is a novel technique to treat malignant brain tumors, which uses a genetically engineered virus to replicate in, and kill cancer cells while sparing normal cells[1]. The therapy requires intratumoral injection of virus vectors, but arbitrarily selected injection sites may result in limited distribution of agents or uneven saturation of tumor. It is necessary to develop a noninvasive method to assess the effect of virus delivery on treatment outcome. Magnetic resonance diffusion tensor imaging (DTI) has been used to evaluate overall response of oncolytic virus therapy, and an inverse correlation between tumor cell density and mean diffusivity (MD) was reported[2]. However, to evaluate efficacy of each individual injection, the information from whole tumor is not as useful as that from local injection sites because of the lack of sensitivity of changes in mean MD values in the presence of significant cellular heterogeneity with the tumor mass. Therefore, in the current study, instead of correlating the variations of MD values to cell density within whole tumor area, we investigate this correlation within areas adjacent to each injection site, and evaluate local treatment response. By doing so, we assess each injection site retrospectively, and this facilitates the development of a strategy to optimize injection sites, and hence, improve current virus therapy protocols.

MATERIALS and METHODS

Two patients with clinically diagnosed glioblastoma multiforme (GBM) were enrolled. For each patient, a genetically modified herpes simplex virus, G207[1], was administered stereotactically into five enhancing areas of tumor. Diffusion tensor images were acquired before the inoculation of virus, and longitudinally, at 4 weeks and 12 weeks after the inoculation. For diffusion tensor imaging, a single-shot EPI sequence was run on a 3T Philips MRI scanner with following parameters: 15 diffusion gradient directions, b value=1000s/mm^2, TR/TE=3250ms/88ms, FOV=230mm, slice thickness=4mm, 24 slices, reconstruction matrix=256x256, and total imaging time 157 seconds. Diffusion tensor calculations were performed using custom-written MATLAB (Mathworks, Natick, MA) programs, and MD maps were generated. A circular region of interest (ROI) with radius of 5 pixels centered on injection site was defined for each injection on post contrast T1 weighted image, and used on MD maps (Figure 1). Mean MD was calculated for each ROI. All studies were approved by the UAB Institutional Review Board (IRB).



a b

Figure 1. (a) The T1 post contrast image indicating the location of injection site 1 of patient A, (b) The MD map indicating the circular ROI with radius of 5 pixels defined for that site.

RESULTS and DISCUSSION

Figure 2 shows longitudinal changes in mean MDs of injection site ROIs of patient A and B. Four Injection sites (1, 2, 4, and 5) from patient A and three injection sites (1, 2, and 5) from patient B demonstrated an initial drop of mean MD at 4 weeks and then an increase at 12 weeks. The transient decrease in mean MD may be induced by inflammatory reaction after the injection of viral vectors[3]. With the migration of inflammatory cells into the tumor site, the cell density increased within tumor, resulting in a decrease in mean MD. The escalation of mean MD after the initial drop suggests decreased tumor cell density after tumor cell death induced by virus therapy. This was corroborated by the clinical responses of the subjects, which were partial (more than 50% shrinkage of tumor) and stable (tumor size reduced but less than 50% change) responses for patient A and B, respectively. We conclude that these sites were optimally positioned. Also, injection site 4 from patient B was effective, even though its mean MD increased across the studies without initial decrease, probably because there was a minor or no inflammation at this site.

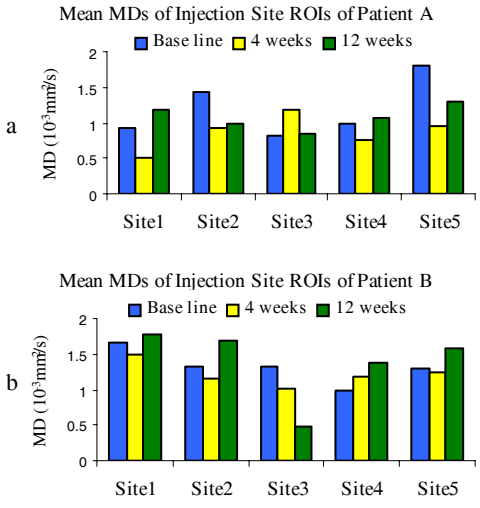


Figure 2. Longitudinal changes in mean MDs of injection site ROIs of patient A (a) and B (b).

However, not all local injection areas followed the same variation trend for mean MD as those mentioned above. The mean MD of the injection 3 of patient A increased at 4 weeks and then decreased at 12 weeks. The initial escalation of mean MD may be induced by the presence of traumatic edema around the injection site 3. Traumatic edema caused by the injection needle increases water content within extracellular space, resulting in an increase in mean MD. The mean MD of injection 3 from patient B decreased suggesting that tumor cell density kept increasing and the injection was failure.

CONCLUSIONS

The overall response of oncolytic virus therapy in malignant brain tumors could mask underlying heterogeneous responses among local injection areas. Localization of response as measured by DTI can provide critical information related to selection of inoculation sites.

REFERENCES

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ACKNOLEDGEMENT

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