Dual Na/ADC Biomarker Assessment of Rat Glioma during BCNU Chemotherapy

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Introduction

Monitoring of tumor response to anti-cancer drug therapy using a dual sodium/proton biomarker was tested in this project. The central hypothesis of this project purports that during efficacious anti-cancer therapy there is a correlation between Na MRI and proton diffusion of tumors whereby both methods can predict outcome before visible tumor shrinkage. Dual modality proton/sodium MRI provides unique insight for monitoring of heterogeneous alterations of malignant cells and supports use of ADC as an indicator of changes in tumor cellularity during cancer therapy [1].

Materials and Methods

Male Fischer 344 rats were implanted with 9L gliosarcoma cells (n=10). Seventeen days after the tumor implantation, treated group (n=5) received 1,3-bis (2-chloroethyl)-1-nitrosourea (BCNU) chemotherapy as a single dose injection (26.6 mg/kg). Three additional normal rats served as a second control. Sodium MRI was performed on 9.4 T Varian scanner using 3D back-projection pulse sequence with an echo time of 500 μs. The other parameters were: readout gradient 1.3 G/cm, FOV 64x64x64 mm, acquisition matrix 32x32x32, TR = 0.1 s and scan time = 30 min. Duration of the 90 pulse was ~50 μs. Proton ADC maps were acquired by spin echo pulse sequence, FOV 30x30 mm, matrix 128x128, 13 slices, slice thickness = 1 mm, interleave multi-slice acquisition with inter-slice distance of 1.5 mm, TR = 3 s and TE = 60 ms. Isotropic diffusion weighted images at two b-factors were acquired for calculation of ADC map: "high-b" (b = 1082 s/mm^2) and "low-b" (b = 117 s/mm^2). All measurements were repeated every few days for several weeks after BCNU administration. Proton ADC and sodium images were reconstructed, co-registered before correlation between tumor ADC and sodium content were performed on voxel by voxel mode in Matlab. Animal experiments were conducted according to the protocols approved by the University LARC.

Results

Chemotherapy increased Na concentration in the tumor especially at the edges which is correlated with a large increase in tumor ADC values (Fig.1). Regions of necrosis were observed on both sodium and proton ADC images. Dual biomarker assessments of rat brains in untreated and treated animals showed a large distribution of tumor Na concentration (Fig. 2). A sharp increase in ADC of untreated tumors started only at high tumor sodium content. In treated animal (Fig.2, blue) the ADC values correlated well with the growth of tumor Na content.

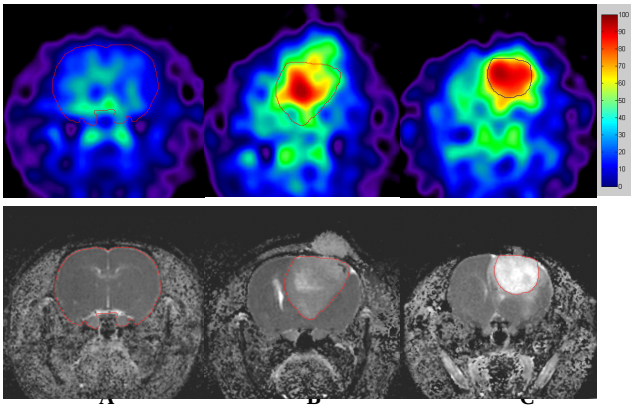

Fig. 1. Na MRI (upper row) and ADC maps (bottom) for three different rodents acquired at the same day: normal (A); non-treated 9L rat glioma (B) and BCNU treated animal (7 days after single dose BCNU injection); both (B) and C) are at day 24 after tumor implantation.

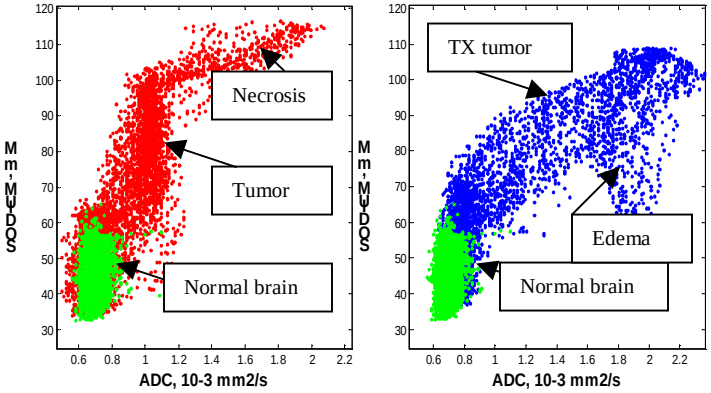

Fig. 2. Voxel by voxel dual sodium/proton biomarker assessment of a whole brain slice for two tumor bearing rodents: non-treated (red) and BCNU treated (blue), performed at day 24 after 9L tumor implantation and 7 days after start of treatment. Green color represents a normal brain.

Discussion

Heterogeneity of the tumor can be seen in both Na and proton ADC. Even with a large tumor size, distribution of the Na signals and ADC map remained heterogeneous, thus the therapeutic response of tumor cells is also expected to be heterogeneous. It is important to notice that the rim of the non-treated tumor had the lowest Na concentration; high tumor Na concentration reflects tumor necrosis. As a result of chemotherapy, an intense increase in Na concentration in all areas of the tumor was observed including the rim. Correspondingly, the largest increase in ADC of water in the tumor was detected during chemotherapy. Voxel by voxel dual sodium/proton biomarker evaluation of tumor treatment reflects a variety of tumor responses in different regions of the tumor which is valuable for evaluation of the cancer therapies.

Conclusion

During treatment of rat glioma by BCNU chemotherapy, a correlation of tumor ADC and tumor Na was found which supports the hypothesis of changes in tumor cellularity during successful cancer therapy. Both Na/ADC modalities are capable to predict tumor shrinking in advance. Results of this study yield a broad assessment of the more advanced ADC biomarker and together with other studies [2-5] contribute to evaluation of sodium MRI applied to oncology. Integration of Na MRI with ADC mapping provide a comprehensive view and quantification of heterogeneous processes in tumor cells and can help in guiding tumor therapy.

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