

Application of Multiple-Quantum-Filtered ^{23}Na MRI to Monitor Chemotherapeutic Response in RIF-1 Tumors

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Introduction

It has been demonstrated that chemotherapy of subcutaneously- (sc-) implanted radiation-induced fibrosarcoma (RIF-1) tumors with cyclophosphamide (Cp) and intracranial 9L glioma with BCNU increases both water apparent diffusion coefficient (ADC) and ^{23}Na signal intensity (SI) (1,2). Histology and destructive chemical analysis show that these effects were largely due to an increase in extracellular space. However, we have shown that both water ADC and ^{23}Na SI in sc-implanted 9L glioma increase with untreated growth, and that these increases are arrested by chemotherapy with BCNU. Thus, it remains unclear if the changes in water ADC or ^{23}Na SI after chemotherapy are general phenomena or if they depend on the tumor model and chemotherapeutic drug. In addition, the possible contribution of changes in intracellular $[\text{Na}^+]$ to ^{23}Na SI after chemotherapy has not been evaluated. In this study, the effects of 5-fluorouracil (5FU), which inhibits thymidylate synthetase (the key enzyme for DNA synthesis), were monitored in RIF-1 tumors using *in vivo* ^1H and ^{23}Na MRI and positron emission tomography (PET) to evaluate water ADC, tissue and intracellular $[\text{Na}^+]$ and 2-[F-18]Fluoro-2-deoxy-D-glucose (FDG) uptake in the tumor.

Methods

Single quantum (SQ) and triple-quantum-filtered (TQF) ^{23}Na MRI, ^1H diffusion imaging, and FDG PET imaging were performed on untreated control and 5FU-treated C3H mice with sc-implanted RIF-1 tumors. MR images were acquired with a Varian 9.4 Tesla, 31-cm horizontal bore system. Each animal (n = 6 control, 7 treated) was examined before 5FU injection (150 mg/kg, ip) and daily for three days following treatment. 3D transaxial ^{23}Na MR images of the tumor were obtained using a gradient-echo imaging sequence. The following imaging parameters were used: 100 μs non-selective excitation RF pulse, 50 ms repetition time (TR), 10 ms echo time (TE), and 64 x 32 x 8 data points over a 40 x 40 x 36 mm field of view (FOV). TQF ^{23}Na pulse sequence parameters were: 90-100 ms 90° excitation RF pulse, 120 ms TR, 10 ms TE, and 64 x 32 x 8 data points over a 40 x 40 x 36 mm FOV. Water ADC in the tumor was measured using a multi-slice diffusion-weighted imaging (DWI) sequence. The following imaging parameters were used: 1,100 ms TR, 60 ms TE, 256 x 128 data points over a 40 x 40 FOV, 2.0 mm slice thickness, and 0.6 mm slice gap. Four interleaved b-factors (b = 0, 236, 945 and 1,679 s/mm^2) were used. H&E histology was performed after the last MR measurement. FDG PET (n = 5 control, 5 treated) was performed before 5FU injection and three days after treatment.

Results and Discussions

Tumor volumes were significantly lower in 5FU-treated animals two and three days post-treatment (Fig. 1A). At the same time points, *in vivo* MRI experiments showed a significant increase in water ADC (Fig. 1B) in treated tumors from (in $\times 10^{-4} \text{ mm}^2/\text{sec}$) 5.20 ± 0.28 (before treatment) to 6.13 ± 0.15 (day 2 after treatment) and 6.48 ± 0.32 (day 3 after treatment). In the control group, water ADC values did not change significantly during the experimental period. Similar to water ADC changes, tumor SQ ^{23}Na SI relative to the reference increased at days 2 and 3 after treatment (Fig. 1C) and was significantly higher compared to the mostly unchanged control values. However, TQF ^{23}Na SI increased in control tumors but not in treated tumors (Fig. 1D). Unchanged TQF ^{23}Na SI in treated tumors suggests that the increase in SQ ^{23}Na SI was caused mostly by the increase in extracellular space due to cell death following effective chemotherapy. Although changes in water ADC and SQ ^{23}Na SI were different in sc-implanted RIF-1 compared to sc-implanted 9L glioma (3), the changes in TQF ^{23}Na MRI signal intensities were similar in the two tumor models. FDG distribution in PET experiments showed a decrease in glucose metabolism after 5FU treatment (Fig. 2).

H&E histology showed some reasonable correlation between regions with low cellular density and high water ADC and SQ ^{23}Na SI. Usually both water ADC maps and ^{23}Na images had some verifiable heterogeneity in sc-implanted RIF-1 tumors. In some regions, when SQ ^{23}Na signal intensity was high, water ADC was not dramatically high. Histology showed that although these regions had a large extracellular space, it was filled with collagen caseous material that restricted water motion and decreased water ADC.

Conclusion

The increase in both water ADC and SQ ^{23}Na SI 2-3 days after effective chemotherapy earlier reported for Cp treatment (1) was also observed after 5FU treatment of sc-implanted RIF-1 tumors and appears to be largely related to an increase in extracellular space. The lower TQF ^{23}Na SI and FDG uptake in treated tumors compared with controls may result from a shift in metabolism from glycolysis to oxidation and/or a decrease in cell density. Unlike water ADC and SQ ^{23}Na SI, changes in TQF ^{23}Na MRI SI during untreated growth and with chemotherapy appear to be independent of the tumor model.

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References

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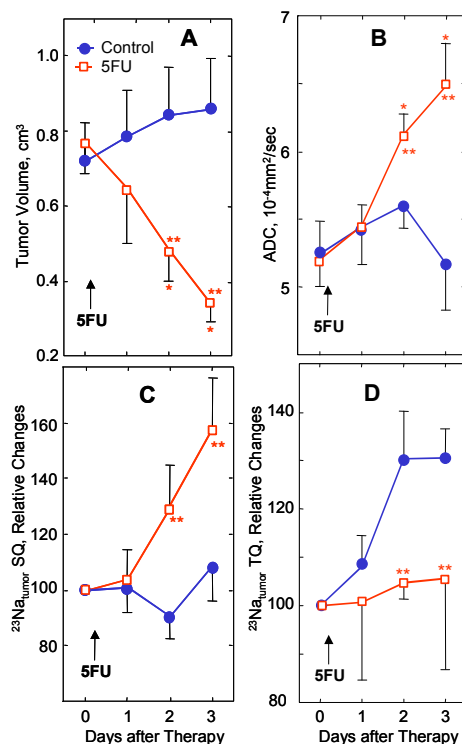


Figure 1.

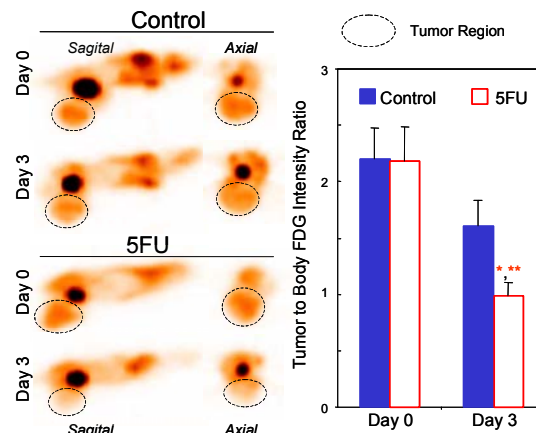


Figure 2.