

Multiparametric MR mapping of Tissue Response to Photodynamic Therapy in an Intramuscular Model of Murine Squamous Cell Carcinoma

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Introduction

Photodynamic therapy (PDT) is a clinically approved treatment for cancer that involves activation of a tissue localized sensitizer by light which results in direct cytotoxicity, vascular damage, and induction of an inflammatory response. Magnetic resonance imaging (MRI) methods have previously been applied to monitor PDT in subcutaneous tumor models. In this study, we examined tissue response to PDT using T2-weighted (T2W) MRI and diffusion weighted MRI (DWI) in an intramuscular model of murine squamous cell carcinoma (SCC). Multiparametric MR mapping (T2W and DWI) was performed to compare photodynamic tissue damage following transcutaneous (TC) illumination or interstitial delivery (ID) of light to tumors in mice.

Methods

Experimental imaging studies were performed using intramuscular SCCVII tumors (n=15) established in female C3H mice. Approximately 7-8 days post implantation, PDT was carried out using 2-[hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH). Briefly, tumor-bearing mice were injected with 0.4 μ mol/kg HPPH (i.v.) ~24h prior to illumination of tumors (665 nm, 135J, 75mW) either by TC (n=5) or ID (n=4). Control tumors (n=6) received the sensitizer but were not illuminated. Studies were performed using a 4.7 T/33-cm horizontal bore magnet (GE NMR Instruments, Fremont, CA) incorporating AVANCE digital electronics (Bruker Medical Inc). Data acquisition consisted of scout images and coronal T2-weighted images ($TE_{eff} = 41ms$, $TR = 2424ms$, $FOV = 4.8 \times 3.2$ cm, matrix size = 256×192 , 21 slices, slice thickness 1mm) to visualize tumor growth. T2-relaxation rate measurements were performed using a multi-echo CPMG spin echo sequence ($TR = 2500$ ms, $TE = 15-300$ ms, $FOV 3.2 \times 3.2$, $MTX 192 \times 192$, 5 slices, slice thickness 1 mm, number of echoes = 20). Diffusion-weighted MRI was performed using a multi-slice diffusion-weighted SE sequence with the following parameters: $TE/TR = 30/1200ms$, matrix size = 128×128 , $FOV 3.2 \times 3.2$, diffusion gradient strength (four variable gradient strengths per acquisition) = 8, 128, 256, 420mT/M, diffusion B value = 2.9, 512, 2036, 5470 s/mm^2 , diffusion gradient duration = 6ms, diffusion gradients applied in X,Y, and Z directions, slice thickness = 1mm, 5 slices. T2W images were acquired at different times post implantation to assess tumor growth. T2 measurements and DWI were performed 24h post PDT to examine tumor response to treatment. T2 maps were calculated on a pixel-by-pixel basis in MATLAB and pseudo-colored using AnalyzeTM. Statistical significance ($p < 0.05$) was determined by performing an unpaired two-tailed student's *t* test.

Results

The panel of images shown in Figure 1 are calculated T2 (*upper panel*) and ADC (*lower panel*) maps of control and PDT-treated SCCVII tumors. Interstitial HPPH-PDT resulted in a marked change on T2 maps 24h post treatment compared to untreated controls or TC-PDT. Mean T2 values of ID-PDT tumors were higher ($p < 0.05$) compared to controls. Corresponding ADC maps also showed hyperintense areas in tumors following ID-PDT suggestive of effective photodynamic cell kill. In contrast, tumors treated with TC-PDT did not show a significant change in T2 values ($p > 0.05$) compared to controls. CD-31 immunostaining of tumor sections showed evidence of significant vascular damage with ID-PDT.

Conclusions

The findings of our study reveal the utility of multiparametric MRI as a non-invasive tool for mapping of early tissue response to PDT. The results suggest that ID of light is likely to be more effective than TC-PDT particularly with bulky, invasive, intramuscular SCC. Studies are currently underway to correlate changes detected on T2W and DWI with molecular and immunohistochemical markers of photodynamic cellular and vascular damage.

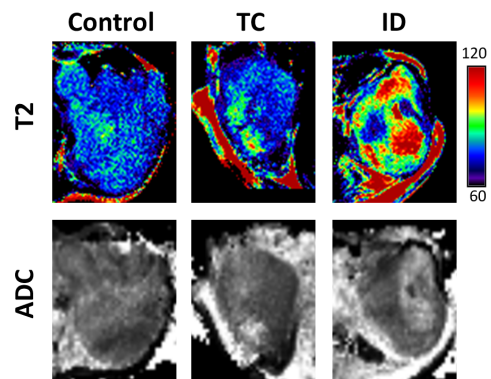


Figure 1. T2W MRI and DWI of intramuscular SCCVII response to HPPH-PDT