GRADIENT ECHO SIGNAL DECAYS IN GYNECOLOGICAL CANCERS REQUIRE A GAUSSIAN AUGMENTATION OF THE MONO-EXPONENTIAL (GAME) MODEL: PRELIMINARY EVALUATION POST EXTERNAL BEAM RADIATION THERAPY AT 3T

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Introduction: Hypoxia within tumors increases treatment resistance and metastatic potential, and is associated with poor patient outcomes [1-6]. Non-invasive MRI attempts to detect hypoxia in cervical cancer via R_2^* ($1/T_2^*$) measurements using multiple gradient echo (GRE) signals with a standard **M**ono-**E**xponential (ME) decay model have been reported [7]. In this work, we evaluated this in gynecologic cancers post External Beam Radiation Therapy (EBRT), and report that proper characterization of GRE signals requires a **G**aussian **A**ugmentation of the **M**ono-**E**xponential (GAME) decay model, as recently shown in the brain [8].

Theory: GRE signal decay with echo time (TE) is generally assumed to follow a ME decay model: $S = \rho\, e^{-R_2^* TE}$, where $R_2^* = R_2 + R_2'$ is the sum of irreversible (R_2) and reversible (R_2') decay rates, R_2' being the half-width-at-half-maximum (HWHM) of a Lorentzian intra-voxel frequency distribution and ρ the pseudo-spin density [9]. However, if the intra-voxel frequency distributions are better characterized with Gaussian rather than Lorentzian functions, then S vs. TE follows a GAME decay model: $S = \rho\, e^{-R_2 TE} e^{-(\sigma TE)^2/2}$, where the Gaussian HWHM is $\sigma\sqrt{2ln2}$ [8].

Methods: Nineteen patients with gynecologic cancers presenting for High Dose Rate (HDR) brachytherapy following EBRT (ages: 54 ± 16 years, 12 cervical, 3 recurrent endometrial, 3 vaginal, 1 bladder neck/urethral tumors, stages: IA-IVA, volumes: 31.9 ± 30.1 cm^3) and 3 healthy volunteers (ages: 25 ± 2.5 years) participated in this IRB-approved study. Imaging was performed at 3T (Verio, Siemens, Erlangen, Germany) using body and spine matrix coils. The protocol included T2-weighted turbo-spin-echo (TSE, TE/TR=102/5190ms, flip=140, FOV=22x22cm, 256x320 matrix, 4mm slices) and 2D multi-slice multi-echo GRE imaging (TE= 3, 9, 18, 27, 36, and 45ms, TR=289ms, flip=24, FOV=30x30cm, 192x192 matrix, 4mm slices, breath-held). Data were acquired with patients intubated for brachytherapy and with volunteers wearing non-rebreather masks, while breathing a mixture of Oxygen and air (100% to 30% O_2 in expired air). Tumor (in patients), uterus (in volunteers), and muscle regions of interest (ROIs) were delineated on T2-TSE images. GRE signal decay, averaged over a neighborhood of 3x3 pixels, was fitted to both models using Matlab (Mathworks, Natick MA). For the ME model, ρ and R_2^* were extracted. For the GAME model, ρ, R_2 and σ were extracted. Unpaired t-tests were performed to compare data across oxygenation levels. F-tests were performed to test whether improvements (going from GAME to ME) were statistically significant.

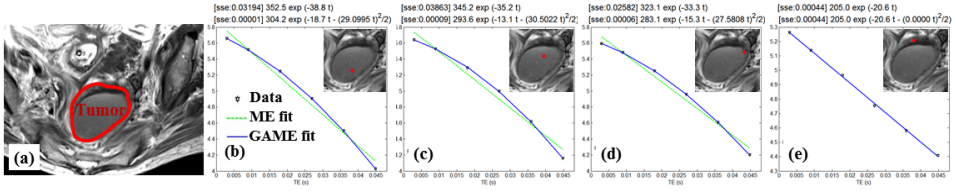

Figure 1: Anatomy, data ($log(S)$ vs. TE, black) and fits, for the same subject as Figure 3a (a) T2-TSE, with the tumor outlined (b-d) GAME (blue) outperforms ME (green) (e) As $\sigma \rightarrow 0$ and $R_2 \rightarrow R_2^*$, the models become equivalent (Red dots: location, SSE: sum of squared errors).

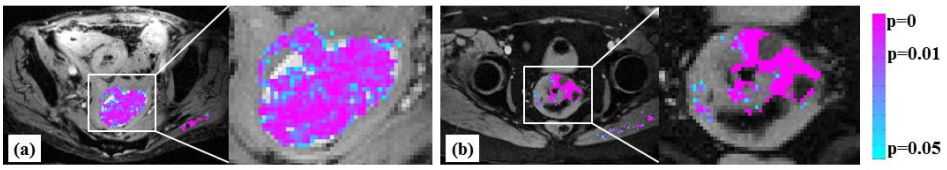

Figure 2: GAME statistically significantly improved fits over ME (p<0.05). F-test p-values of two different subjects are shown (a-b) Highly significant improvements were seen across the entire tumor.

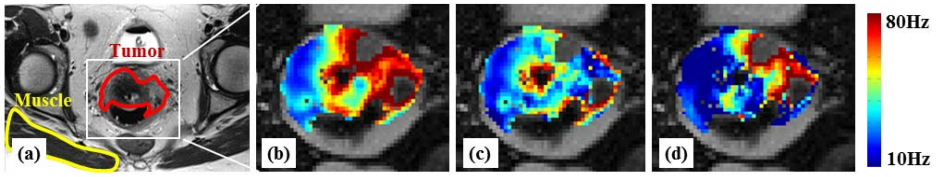

Figure 3: Anatomy and ME vs. GAME model fitting results, for the same subject as Figure 3b (a) T2-TSE, with muscle and tumor contours, along with maps of (b) ME R_2* (c) GAME R_2 (d) GAME σ.

Results: GAME characterized signal decays better than or equivalent to ME (Figure 1). GAME performed significantly better (p<0.05) in 25% of all tumor ROIs, and highly significantly better (p<0.005) in 15% of all tumor ROIs (Figure 2). GAME significant (p<0.05) improved 27% of cervical cancer ROIs, 24% of recurrent endometrial cancer ROIs, 14% of vaginal cancer ROIs, and 8% of the bladder neck ROI. Significant (p<0.05) improvements with GAME were limited to 12% of the ROIs in the healthy uterus. GAME performed significantly better (p<0.05) in 27% of muscle ROIs and highly significantly better (p<0.005) in 17% of muscle ROIs. Parameters did not change significantly across different gas mixtures in muscle, uterus or tumor ROIs (p>0.05). Parametric maps from the ME and GAME model fits are shown in Figure 3 for a typical case. Note that high R_2^* values observed with ME model fits may have different proportions of irreversible and reversible relaxation rate contributions, which are distinctly separated by the GAME model fit.

Discussion: In the previous cervical cancer hypoxia study, R_2^* values were directly estimated from GRE decays using a ME decay model, and high R_2^* values were assumed to be indicative of hypoxic regions within tumors [7]. Many factors besides oxygenation can influence the shape and rate of GRE signal decay in the pelvis, including air/tissue and air/bone interfaces (e.g. rectum, pubis), blood products (e.g. hemosiderin), calcifications, temperature, etc. The ME model appears inadequate, due to the distinct curvature on semi-log plots observed in both normal and cancerous tissue (Figure 1, b-d). It is likely that, increased susceptibility induced gradients from air/tissue and air/bone interfaces at 3T, in combination with realistic, Gaussian-like, slice profiles, are responsible for this curvature [10]. In this case, direct modeling of these effects [10] may be required to recover intrinsic R_2^* values.

Conclusion: Appropriate characterization of signal decay curves is essential for their use in quantitative MR studies. Better fit of the data are obtained in post EBRT gynecological cancers with the GAME vs. the ME model at 3T. The degree to which R_2 or σ values correlate with hypoxia remains unknown. However, improved characterization of GRE signal decay curves improves the potential for determining correlates of the fit parameters with biomarkers of e.g. oxygenation status. A hypoxia biomarker, as an indicator of cancer aggressiveness, could improve targeting of radiation into tumor regions while minimizing treatment morbidity.

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