DCE-MRI Perinecrotic Imaging Biomarker Signature and Observed Interpatient Heterogeneity

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Introduction: The use of imaging biomarkers to potentially accelerate the development process for new lines of cancer therapy and pharmaceuticals was discussed during an impromptu breakout meeting at the 2005 ISMRM meeting. Use of these imaging biomarkers has been proposed to generate more intermediate results during a trial, which, if significant, could improve cost-effectiveness of a study and/or speed up development of therapeutic techniques, when compared to traditional study endpoints [1]. We explore use of Dynamic Contrast Enhanced Magnetic Resonance Imaging, (DCE-MRI), as a means for defining regional descriptors of contrast uptake in tumors as predictive imaging biomarkers. Regions were grouped across similar levels of depth from the surface, and extending from the tumor's exterior to its interior. DCE-MRI regional tumor was investigated by evaluating:

1) If there a predictable regional uptake signature in the DCE-MRI studies that can be derived from the surface toward the interior of the tumor with high granularity in resolution via a three dimensional depth model?
2) To what spatial depth using DCE-MRI does a tumor biomarker provide a consistent signature before hypoxia/necrosis interferes with the perinecrotic model representation?
3) Are any DCE-MRI generated biomarker signatures consistent and quantifiable across patients?
4) What effect does radiation therapy treatment have on the perinecrotic imaging biomarkers?

To address these issues, we applied both standard relative signal measures, which are easiest to apply clinically and are understandable to most cancer care-givers; and pharmacokinetic models that potentially provide a higher level of quantification, but which can introduce complexity needed to more accurately adhere to underlying principles. For our evaluation, we rely on our long term experience with working in cervical cancer (10-year repository of DCE-MRI studies), and use these models to summarize the pattern of contrast uptake from ten cervical cancer patients [2].

Methods: Conventional relative signal intensity ratios, as well as pharmacokinetic models, were used to evaluate perfusion levels in tumors from ten stage III-IV cervical cancer patients. Three dimensional morphological operators were used to define a high resolution mask of the DCE-MRI data oriented from the exterior toward the interior of the tumor. Linear regression was used to fit, what appeared to be, a relatively low-noise linear regime up to 6-8 mm from surface depth. Tumors were delineated by an experienced, cancer-oriented radiologist. Following delineation, a map representing distance to the boundary was generated (figure C). Evaluations were performed at three different treatment time points: The first pre-radiation therapy; the second two weeks post-radiation therapy; and the third one month post-radiation therapy, to determine the ability to observe this regional signal variation.

Results: The data appears to fit a model that has at least two regimes: A) perinecrotic linear region (typically 6-8mm) depth followed by: B) a highly necrotic varying core regime (see figure E). Secondly, a sign based categorical analysis reveals ($P<0.004$) that 9 out of 10 patient tumors can be modeled using a decreasing slope. Finally, a multi-factor ANOVA across patients demonstrates that the slope parameters and intercepts are derived from different distributions ($p<0.001$). Slope variations between patients range from -1.2 to -10 in nine patients. In the tenth patient case there is a positive linear slope over a 1.5cm range; however when the fitting depth range was reduced from 1.25 cm, the regressed slope=-4.8 became negative. For this particular case, it is suspected that there is likely a higher amount of necrotic core that directly impacts the regression evaluation.

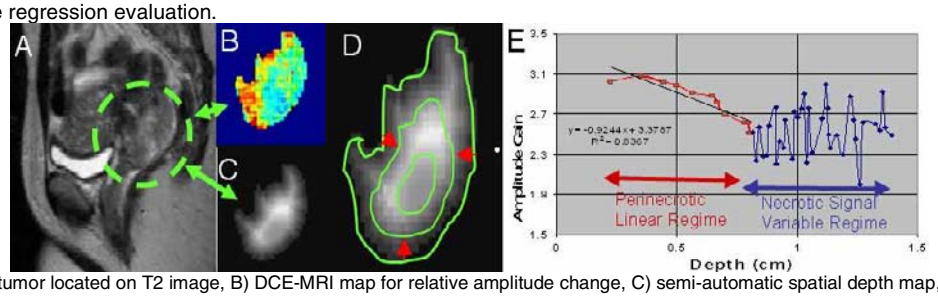

Figure 1: A) tumor located on T2 image, B) DCE-MRI map for relative amplitude change, C) semi-automatic spatial depth map, d) simplified illustration of level curves for clarification of the surface depth model, D) aggregated data demonstrates perinecrotic and necrotic regions.

Discussion: We demonstrate in this work that there is significant imaging-biomarker detail provided by high resolution, depth information in our measurement of signal differences aggregated over ring (mantle) regional evaluations from the perinecrotic outside toward the hypoxic/necrotic tumor core. These mantles can provide a response signature for the level of angiogenesis and/or tumor hypoxia. Structurally, a simple linear distribution seems to be a reasonable model for approximating the response of the tumor up to a depth of 6-8 mm, followed by a transitional signal variable regime up to 1.5 cm. The hypoxic/necrotic regime can be highly variable (Figure B). As shown in our results, this predictable linear depth model of decreasing linear response across tumors on a patient-by-patient basis is significant ($p<0.004$). This is followed at deeper depth by a value which appears to be random signal dominated by a necrotic region (possibly due to residual proteinaceous material or blood products). Between patients, however, the slope and intercepts appear to be highly variable. This variability indicates a strong need for critical observation between patients and provides potential evidence for the need of personal-health-care derived treatment plans. Finally, the results post-therapy show highly variable signal that we suspect to be influenced significantly by post radiation inflammatory response indicating that the pre-radiation treatment phase is potentially critical for planning in the patients diagnosis. In summary this research describes a newly developed imaging biomarker for identifying perinecrotic region used for the evaluation of cancerous processes. This work proposes the future need for development of targeting the treatment resistant perinecrotic region for development of potentially better cancer therapies.

References: 1) Smith JJ, Sorenson G, Thrall J, Radiology 2003; 227:633–638;
2) Mayr NA,, et al. JMRI 2000 Dec;12(6):1027-33.