Mouse models of human cancer: noninvasive phenotyping with MRI

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Target audience: Scientists using MRI for preclinical studies of cancer therapeutics or diagnostics in mouse models.

Purpose: What can noninvasive imaging reveal about the underlying biology of cancer**?** There is a critical need for development of new diagnostic and therapeutic strategies to improve outcomes for cancer patients. Mouse models are often used to address these goals in a preclinical setting[1]. An important step in the validation of mouse models is to determine how well they resemble human disease; imaging can be a useful technique to accomplish this. *In vivo* imaging reveals not only tumor location and size, but also important biological and physiological processes including vascularity, metabolism and proliferation. Mouse models of human cancer are often characterized histologically and molecularly, but not with an *in vivo* image-based characterization. Our goal was to establish a clinically relevant framework for MRI-based characterization of two distinct cancers in mice, and to compare with human disease.

Methods: We used over 250 mice representing a diversity of mouse models - from commonly used xenografts to advanced GEMMs wherein key molecular pathways relevant to human high grade brain astrocytoma (Rb, Ras, PTEN) and breast cancer (Rb, p53, BRCA1) are genetically altered. We developed a new high-resolution radiologic-pathologic correlation technique to accurately co-register even the earliest stages of cancer (~100 microns). To facilitate clinical applicability, a key element of our approach was to acquire and analyze murine MRI data analogously to human data. Pulse sequences at 3T (Philips Achieva) were obtained, including T_1 weighted FFE, T_2 weighted TSE and dynamic contrast enhanced MRI (DCEMRI) for extraction of pharmacokinetic parameters K^{trans} and k_{ep}. We took the novel step of adapting two clinical MRI lexicons for application in mice: the BIRADS and VASARI descriptors developed for breast and brain MRI, respectively.

Results: We found that from both a morphologic (BIRADS and VASARI analysis) and physiologic (K^{trans} and k_{ep} analysis) perspective, GEMMs and allograft models recapitulated the heterogeneity of the human MRI phenotype more than xenograft models. However, several interesting discrepancies emerged: (i) although the vast majority of human high grade astrocytomas (HGA) present with a thick enhancing margin on MRI, in mice this was rare (Figure 1), and (ii) in humans, contrast media is needed to visualize early stage preinvasive breast cancers, but we found this was not the case in mice (Figure 2).

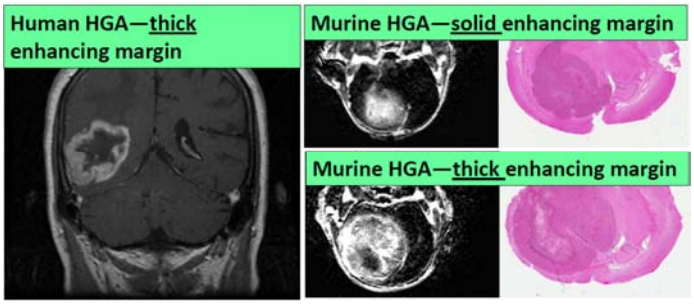

Figure 1: Contrast enhanced T_1 imaging of human (at 1.5T) and murine (at 3T) high grade astrocytoma (HGA). 93% of human HGAs present with a ***thick*** enhancing margin according to VASARI analysis. Less than 3% of murine HGAS exhibit this phenotype. Most murine HGAs have ***solid*** enhancing margins.

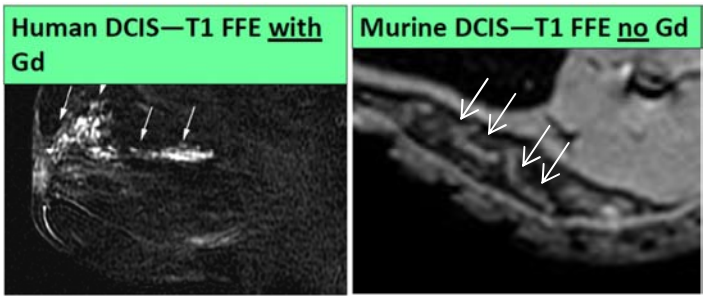

Figure 2: T_1 3D FFE of human (at 1.5T) and murine (at 3T) preinvasive breast cancer, ductal carcinoma *in situ* (DCIS). In humans, injection of a contrast medium (a Gd chelate) is needed to detect DCIS reliably. But using the same MR acquisition, murine DCIS can be detected with over 90% sensitivity ***without*** contrast media administration.

Discussion: We have developed a framework for performing a clinically motivated MRI-based characterization of mouse models of breast and brain cancer. This includes qualitative analysis (based on the human VASARI and BIRADS lexicons) and quantitative physiologic imaging of vascular permeability. In doing so we found that, unlike xenografts, GEMM and allografts recapitulated the heterogeneity of the human MRI phenotype. This study establishes a new strategy for image-based characterization of cancer in mouse models, including acquisition, analysis and pathologic correlation. With this framework, we can embark on further investigation into the biological underpinnings of image-based features. Specifically, in mouse models the genetic and molecular signaling pathways of cancers can be easily manipulated. Our next step is to determine how different genetic and molecular alterations affect the imaging phenotype of a diversity of mouse models.

The MRI data included in this study is obtainable online at the National Biomedical Imaging Archive: https://imaging.nci.nih.gov/.

References: 1.Holland EC. Nat Rev Genet. 2001.