PhD Thesis Title: Characterization of tumor microstructures with diffusion-weighted MRI

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Graduation Date: June 2020
Available Online: https://escholarship.mcgill.ca/concern/theses/6d5702105

ABSTRACT:

Cancerous tumors are often heterogenous in their cellular composition and morphology. The tumor subregions can differ in many properties including growth rate, ability to metastasize, immunological characteristics, and sensitivity to therapies. Characterizing the tumor microenvironment could be beneficial for cancer diagnosis and the development of targeted therapy. Diffusion-weighted magnetic resonance imaging (DW-MRI) is a powerful tool for the characterization of tumor microenvironment, due to its sensitivity to the Brownian motion of water molecules. By relating plausible models of the underlying tissue architecture to the acquired diffusion signal, microstructural information such as cell size and volume fraction can be obtained. The overall goal of this thesis was to develop novel DW-MRI based techniques to characterize tumor microenvironment. Our first aim was to characterize heterogeneity in the tumor microenvironment, by identifying different tumor habitats in soft tissue sarcoma. To this end, we developed a novel reference-tissue-based method for probabilistic classification of up to five tumor habitats, using maps of the apparent diffusion coefficient (ADC), T2 relaxation maps, and a calculated map representing high-b-value diffusion-weighted MRI. The classification method was demonstrated in soft-tissue sarcoma. The classification results were qualitatively consistent with histopathology. The second part of our work focused on further characterization of tumor microenvironment by extracting microstructural information on a cellular level, such as cell size and volume fractions. By building on the existing microstructure imaging framework which assumed a single cell population in the tumor, we developed microstructure mapping with two cell populations co-existing in the same space. It was found that for a minimum difference of 3 μm in radius between the large and small cell populations and a signal-to-noise ratio (SNR) of 50, the radii and volume fractions of both cell populations could be accurately estimated. To demonstrate the potential application of microstructure mapping in cancer treatment monitoring, the final component of this thesis focused on differentiating three potential post-treatment tumor microenvironments including necrosis, progression of disease, and infiltration of T-cells, all without a prior knowledge. This was achieved by developing a model selection method that chose the most suitable diffusion model to describe the tumor microenvironment. The method was evaluated with simulated diffusion data. Overall, this thesis introduced three novel DW-MRI based techniques for the characterization of tumor microenvironment.

References to author publications that relate specifically to the dissertation:

1. **Xing S** and Levesque IR, “A simulation study of cell size and volume fraction mapping for tissue with two underlying cell populations using diffusion weighted MRI.” Magnetic Resonance in Medicine. 86(2): 1029-1044 (2021). doi: 10.1002/mrm.28694

2. **Xing S**, Freeman CR, Jung S, Turcotte R, Levesque IR, “Probabilistic Classification of Tumour Habitats in Soft Tissue Sarcoma.” NMR in Biomedicine. 31(11): e4000 (2018). doi: 10.1002/nbm.4000