Thesis title: Quantitative DCE-MRI: On Development of Methodology and Evaluating its Applications in Glioma Grading

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ABSTRACT

This Ph.D. thesis is aimed at addressing some of the challenges towards reliable computation and standardization of quantitative dynamic-contrast-enhanced magnetic resonance imaging (DCE-MRI) parameters for glioma grading in a routine clinical setting. The scope of the research work presented in this thesis resulted in developing the protocol and methods for the DCE-MRI data acquisition and analysis, which can help clinicians in better diagnosis, prognosis, and treatment planning of glioma.

The first chapter starts with a discussion of glioma, its molecular characteristics, epidemiology, and state of art prognostic measures. Next, a basic introduction about underlying physics and image formation in MRI is provided. Overview of different tissue relaxation and basic concepts behind image acquisition with different tissue contrasts and basic pulse sequences are discussed. Next, this chapter discusses about conventional MRI protocols used for brain tumor patients. A brief overview of advanced imaging techniques for the quantitative evaluation of glioma and its application to glioma grading, tissue segmentation, and follow-up studies are also included in this chapter. This chapter then highlights the advantages of DCE-MRI over other advanced MRI techniques for glioma characterization. A description of the pipeline of state-of-art methods for quantitative DCE-MRI analysis and the application of DCE-MRI for glioma

characterization are also included in this section. Before identifying the research gap and forming the objectives, a literature review of currently available literature about different methods used for quantitation of DCE-MRI derived tracer-kinetic-parameters (TKPs), reliability and variability of TKPs estimation, and current challenges faced for the routine clinical application are included.

The purpose of the study mentioned in chapter-2 was to determine an optimum scan acceleration factor (R) to accelerate DCE-MRI data acquisition while achieving full brain coverage with an improved spatial resolution for the analysis of patients with glioma in a clinical setting. The performance of SENSE and Compressed-SENSE (CSENSE) based scan acceleration techniques have been evaluated. The quality of structural images (T_1-W, T_2-W) and computed precontrast T_1 maps (T_{10}) (at different CSENSE factors) were compared with SENSE acquisitions. Analysis was carried out on data from healthy volunteers and an in-house developed phantom to obtain an optimum acceleration factor for acquiring T_1-W, T_2-W, and 3D T_1-W FFE images. Error propagation to T_{10} estimation was also evaluated. The efficacy of quantitative DCE-MRI parameters in differentiating low-grade glioma (LGG) and high-grade glioma (HGG) using the optimized protocol (protocol-2) was evaluated and compared with the conventional protocol (protocol-1) used at our Centre.

Among the previously reported works of literature on the applications of Generalized-tracer-kinetic-model (GTKM) parameters, the accuracy of differentiation and classification using TKPs exhibit large discrepancies and variations. Also, the magnitude scales of parameter values reported in these studies are not consistent due to multiple factors mentioned earlier. One of the major factors that affect the magnitude scale of these parameters is the variations in arterial input function (AIF), which is important for fitting GTKM to concentration-time curves. So, the study presented in the chapter-3 consisted of three sub-objectives; (i) to develop an optimized subject-specific AIF estimation method, (ii) to comprehensively evaluate the sensitivity to noise and inter/intra-subject variability of TKPs in different tissue regions (contrast-enhancing (CE) tumor, non-enhancing tumor (NET), normal-appearing gray matter (GM) and white matter (WM) regions) of glioma patients mainly due to variations in AIF, and (iii) to evaluate the impact of different normalization techniques in mitigating the inter-subject variability of TKPs to corresponding values computed from healthy tissue regions. A reliable estimation of volume transfer constant (K^{trans}) and blood plasma volume fraction (v_p) are possible in normal-appearing and tumor tissue

regions. Normalization of K^{trans} and v_p in tumor regions to corresponding parameters in the normal-appearing tissue regions have mitigated the inter-subject and intra-subject variability and has improved the accuracy of differentiation of HGG and LGG.

In chapter-4, a tissue-specific hybrid two compartmental model (HTCM) for the blood-brain barrier (BBB) permeability assessment in glioma patients is proposed. GTKM and Patlak model (PM) are the widely accepted models in clinics for glioma characterization. PM is generally preferred for shorter durations (data less than 1 minutes) and GTKM is optimum for longer duration data (~4-10 minutes) in tumor regions. However, in healthy tissue regions, for longer duration data, GTKM derived leakage volume fraction (v_e) is not relevant since the BBB is intact. It was observed that the reliability and magnitude of v_e don't change in healthy tissue regions with data length. Hence, GTKM may over-fit the healthy tissue curves. On the other hand, PM leads to under-fitting since it assumes a unidirectional flow, which doesn't hold for medium (1-3 min) or long-duration data. To address this problem, this chapter discusses an optimized tissue-specific model, which acts as both GTKM and PM depending on the contrast agent transients of the tissue representing voxel. The hybrid two compartmental model (HTCM) has shown significant improvement in computation time (~40%). The parameters computed from HTCM and GTKM in CE regions have exhibited a high correlation for DCE-MRI data less than 2 minutes. One of the major advantages while fitting the HTCM is that the maximum number of parameter estimation is always two. However, it is possible to differentiate between K^{trans} depending on the underlying physiology of the representing voxel.

Cerebral blood volume (CBV) and cerebral blood flow (CBF) computed from the first-pass (FP) analysis of DCE-MRI data have shown wide potential in clinical applications such as initial grading and tumor sub-class segmentation. However, the estimation of these parameters is erroneous due to the leakage of the contrast agent in the tumor tissues with BBB breakdown. In CE tissues, a significant amount of leakage contribution is incorporated to CBV and CBF due to BBB leakage. However, in non-enhancing and healthy tissue regions, the contribution of leakage profile is due to multiple factors like elevated steady-state contrast agent (CA) concentration in the vasculature (AIF) after FP, and diffusion effect (shutter speed effect). Recently, compartmental tissue uptake model (CTUM) has been proposed for the simultaneous computation of leakage corrected CBV and CBF (it is coined as v_p and F_p in CTUM) from DCE-MRI. This model was

proposed and evaluated for DCE-MRI data with data length less than 4 minutes. So, in chapter-5, a method for leakage correction was implemented for both CBV and CBF (from first-pass), and it was compared with CTUM and PM parameters. Also, the efficacy of leakage corrected CBV and CBF were evaluated on application to glioma grading. Comparing the hemodynamic maps computed using first-pass analysis and CTUM, both CBV and CBF (with and without leakage corrected) maps were smoother than v_p and F_p maps. Even though absolute quantification of blood flow and blood volume were possible using both methods, leakage correction didn't improve the glioma grading for the data presented in the current study.

The research work presented in this thesis has been converted into a post-processing tool for quantitative DCE-MRI analysis of glioma. The author believes that the methods and post-processing tool presented in this thesis can help clinicians to improve the diagnosis and treatment planning of glioma and will also benefit the patients who are suffering from glioma and humankind in general.