**PhD Thesis Title:** Intravoxel Incoherent Motion (IVIM) and Multi-parametric MRI Analysis for Chemotherapy Response Evaluation in Bone Tumor

**Author:** Dr. Esha Baidya Kayal
**Email:** eshab101@gmail.com
**Institution:** Centre for Biomedical Engineering, Indian Institute of Technology Delhi, India
**Research collaboration:** Department of Radiodiagnosis, All India Institute of Medical Sciences, New Delhi, India and
Department of Medical Oncology, Dr. B.R. Ambedkar Institute-Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India
**Supervisor:** Dr. Amit Mehndiratta
**Co-supervisor:** Dr. Devasenathipathy Kandasamy
**Advisors:** Dr. Sameer Bakhshi, Dr. Kedar Khare, and Dr. Raju Sharma
**Graduation Date:** 14.10.2020
**Available Online:** N/A

**ABSTRACT:**

Osteosarcoma is the most common bone sarcoma and the third most common malignancy in children and adolescents with high morbidity and mortality. Early evaluation of chemotherapy response may help to prevent the patients from undergoing ineffective chemotherapy regimens, reducing side-effects, saving treatment time, cost and may improve patient management through personalized therapeutic options. The goal of this PhD thesis was to investigate the role of non-invasive imaging-based markers for monitoring and evaluating early therapeutic response in patients with osteosarcoma receiving neoadjuvant chemotherapy using Intravoxel incoherent motion (IVIM) and multi-parametric MRI analysis. Existing challenges in the literature regarding anticancer therapeutic response evaluation in the bone tumors were attempted to be addressed in this PhD research work.

The first objective of this thesis was to develop the methodology for reliable and reproducible IVIM parameter estimation as the existing widely used IVIM analysis methodologies, viz bi-exponential (BE) model and segmented BE techniques, evaluate IVIM parameters at each voxel independently, overlooking the spatial context in tissue which may lead to unreliable noisy solutions. To achieve this goal, two gradient-based adaptive penalty functions, Total Variation (TV) and Huber penalty function (HPF) were incorporated into the non-linear least-square (NLLS) optimization of standard BE model and two novel IVIM analysis methodologies: 1) BE model with Total Variation Penalty function (BE+TV), and 2) BE model with Huber Penalty function (BE+HPF) were developed. Proposed BE+TV and BE+HPF methods, adaptively adjust the NNLS error and reduce the non-physiological spatial inhomogeneity and noise in parameter estimation by using TV/HPF penalty reduction at each iteration of NNLS optimization to produce reliable and reproducible parametric images. Experimental results using simulation and empirical clinical datasets showed quantitatively and qualitatively improved IVIM parameter estimation by proposed BE+TV and BE+HPF methodologies than the existing BE and segmented BE techniques. The performance of the two developed methodologies was similar.

The second objective was to assess the potential of quantitative IVIM analysis for characterizing and evaluating early chemotherapeutic response in patients with osteosarcoma. IVIM parameters such as diffusion coefficient (*D*), perfusion coefficient (*D**), and perfusion fraction (*f*) were evaluated using state-of-the-art IVIM analysis methodology BE+TV along with apparent diffusion coefficient (*ADC*), and histogram analysis was performed for these parameters. Experimental results demonstrated the potential of IVIM analysis for evaluating chemotherapy response in osteosarcoma with correlation to both the radiological and the histopathological response evaluation measurements as the reference standards. IVIM perfusion-related

parameters (*D*, f*) and their histogram parameters - standard-deviation, energy, and entropy were effective to be used as surrogate markers for characterizing heterogeneity in tumor micro-vasculature and its changes during chemotherapy in osteosarcoma.

The third objective was to develop a robust and novel automated methodology to delineate, visualize and quantify the proportion of necrosis and viable tissue present within the tumor and eventually evaluate the chemotherapeutic response using multi-parametric MRI. To achieve this goal, Simple linear iterative clustering supervoxel (SLICs) and Otsu multi-thresholding (Mth) were combined to develop the proposed SLICs+MTh methodology; while the former technique clusters the voxels with similar intensity levels in close proximity and the latter technique selects and combines the clusters to sub-segment the targeted pathological region within the tumor. The proposed methodology SLICs+MTh is non-invasive, and imaging-based and uses diffusion-weighted image (DWI), T2 weighted fat-saturated image, and *ADC* parametric map. SLICs+MTh was applied to the tumor before and after the chemotherapy regimen and it produced a reliable approximation of the amount of macro-necrosis and viable tumor volume in osteosarcoma which was in satisfactory agreement with the estimated histopathological necrosis after surgery.

The fourth objective was to assess the efficacy of multi-parametric 3D statistical texture analysis in characterizing tumor microstructure and its changes during chemotherapy in osteosarcoma and evaluating early therapeutic response. To meet the purpose, textural features based on Gray-level co-occurrence matrix (GLCM), Neighborhood gray-tone difference matrix (NGTDM) and Run length matrix (RLM) were evaluated on T1W, T2W & DWI images and *ADC, D, D** & *f* parametric maps. A linear discriminant analysis was performed to find the potential surrogate markers for tumor aggressiveness and responsiveness to chemotherapy. NGTDM features coarseness, busyness and strength for *D, D** & *f* and T1W, T2W images, acquired even before the start of the chemotherapy; they were found to be useful markers for predicting tumor aggressiveness and prognosis. GLCM features contrast, correlation; NGTDM features contrast, complexity and RLM features short run low gray-level emphasis; for *D, D** & *f* and the T2W image, were found to be effective markers for chemotherapy response early in the course of treatment.

This PhD research work developed methodologies for reliable quantitative IVIM parameter estimation and identified imaging-based markers for monitoring and evaluating the chemotherapeutic response in osteosarcoma by applying various analyses using IVIM and multi-parametric MRI. The research findings of this thesis might help the oncologist and radiologists in performing early prediction and evaluation of the chemotherapy response in patients with osteosarcoma and therefore might be beneficial for the patients by enabling a personalized treatment regime.

**References to author publications that relate specifically to the dissertation**:


1. **Baidya Kayal E.**, Kandasamy D., Khare K., Alampally J.T., Bakhshi S., Sharma R., Mehndiratta, A. ***Quantitative Analysis of Intravoxel Incoherent Motion (IVIM) Diffusion MRI using Total Variation and Huber Penalty Function***. *Medical Physics*. 2017;44(11):5849-5858. doi: 10.1002/mp.12520.
2. **Baidya Kayal E.**, Kandasamy D., Khare K., Bakhshi S., Sharma R., Mehndiratta, A. ***Intravoxel Incoherent Motion (IVIM) for Response Assessment in Patients with Osteosarcoma undergoing Neoadjuvant Chemotherapy.*** *European Journal of Radiology.* 2019;119:108635. doi: 10.1016/j.ejrad.2019.08.004.
3. **Baidya Kayal E.**, Kandasamy D., Sharma R., Sharma MC., Bakhshi S., Mehndiratta, A. ***SLIC-Supervoxels-based Response Evaluation of Osteosarcoma treated with Neoadjuvant Chemotherapy using Multi-parametric MR Imaging****. European Radiology.* 2020;30(6):3125-3136. doi: 10.1007/s00330-019-06647-1.
4. **Baidya Kayal E.**, Kandasamy D., Sharma R., Bakhshi S., Mehndiratta, A. ***Segmentation of Osteosarcoma Tumor using Diffusion Weighted MRI: A Comparative Study using Nine Segmentation Algorithms****. Signal, Image and Video Processing*. 2019;14(4):727-735. doi: 10.1007/s11760-019-01599-x.

5. **Baidya Kayal E.**, Kandasamy D., Khare K., Bakhshi S., Sharma R., Mehndiratta, A. ***Texture Analysis for Chemotherapy Response Evaluation in Osteosarcoma using MR Imaging.*** *NMR in Biomedicine.* 2021;34(2):e4426**.** doi: 10.1002/nbm.4426.
6. **Baidya Kayal E.**, Kandasamy D., Yadav R., Bakhshi S., Sharma R., Mehndiratta, A. ***Automatic segmentation and RECIST score evaluation in osteosarcoma using diffusion MRI: A computer aided system process.*** *European Journal of Radiology.* 2020;133:109359. doi: 10.1016/j.ejrad.2020.109359.