the three categories: PR, SD and PD, and reported 100% accuracy [22]. However, the threshold they used for classification was determined from a single dataset of 20 patients used for both training and testing, while in our experiments, a cross validation analysis was performed. In Moffat et al's study, they explored the assessment of fractionated radiation therapy for different types of brain tumors with 20 patients scanned on the same scanner [22]. However, in our study, we focused on the GBM brain tumors treated by anti-angiogenesis drugs, which suppress the blood supply for the tumor cells and may not directly decrease the tumor cellularity. The difference in accuracy may come from the different mechanism of treatment. Additionally, our dataset is from GBM drug trials across multiple sites, thus our preliminary study is an important contribution for exploring DWI as an early imaging biomarker in a real pharmaceutical drug trial. In future work, we will extract texture feature to include spatial information, and shape features will be extracted as well. By introducing a new richer feature set indicating more useful tumor information, we aim to include more information about tumors and further improve the performance of the classification system.

One limitation of this study is that we classified CR, PR and SD as responders for the ground truth to achieve a binary classification. Since SD and PR may have different patterns in terms of their ADC histogram change, a multi-category classification system will be explored in future work. Another limitation of the study is that we used the Macdonald criteria at the eighth or tenth week after treatment for determining treatment response. In future work, time-to-progression and survival time will be a better endpoint to classify treatment response. Another limitation comes from the 3D ROI mapping tool. This tool is more computationally efficient compared to the co-registration techniques, but it cannot correct for patient motion. Therefore, in our study, a board-certified radiologist's visually checked and edited all segmentation results as needed. In the future, a more sophisticated registration method with an image similarity measure may improve the accuracy of the tumor contours on ADC maps, and consequently improve the accuracy of the extracted features and the classifier performance.

ADC values obtained on pre-operative MRI scans are reported to be of prognostic value in patients with glioblastoma [25,42]. The term "prognosis" refers to predicting the likely outcome of treatment. ADC, reported to be inversely proportional to tumor cellularity, is gaining interest in predicting GBM tumor prognosis. Our proposed framework now uses changes in DW-MRI for early prediction of treatment response; however, the framework with feature extraction and machine learning technique could be generalized to pre-treatment DW-MRI for prognosis prediction.

In this study, we developed a CADrx framework with machine learning techniques to automatically predict tumor treatment response before the size change using DW-MRI. In our preliminary study, our major contributions are extracting statistical ADC histogram features, applying GMM to model the ADC histogram to interpret the competing effects of cellular density and edema, and applying machine learning techniques using all the extracted features. Cell density and edema may be reflected in ADC values before size changes are apparent on standard MRI sequences. Therefore, ADC holds promise as a biomarker, in determining both which tumors are more likely to respond to treatment and which tumors are actually responding.

In conclusion, this work shows that a CADrx system using quantitative ADC histogram features and a machine-learned classifier has better performance in treatment response assessment over conventional analysis using only a mean ADC value. This will have major implications for clinical trials. This work has potential clinical significance for early treatment response assessment in GBM.

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