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Histogram Analysis of ADC in Brain Tumor Patients

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ABSTRACT

At various stage of progression, most brain tumors are not homogenous. In this presentation, we retrospectively studied the distribution of ADC values inside tumor volume during the course of tumor treatment and progression for a selective group of patients who underwent an anti-VEGF trial. Complete MRI studies were obtained for this selected group of patients including pre- and multiple follow-up, post-treatment imaging studies. In each MRI imaging study, multiple scan series were obtained as a standard protocol which includes T1, T2, T1-post contrast, FLAIR and DTI derived images (ADC, FA etc.) for each visit. All scan series (T1, T2, FLAIR, post-contrast T1) were registered to the corresponding DTI scan at patient's first visit. Conventionally, hyper-intensity regions on T1-post contrast images are believed to represent the core tumor region while regions highlighted by FLAIR may overestimate tumor size. Thus we annotated tumor regions on the T1-post contrast scans and ADC intensity values for pixels were extracted inside tumor regions as defined on T1-post scans. We fit a mixture Gaussian (MG) model for the extracted pixels using the Expectation-Maximization (EM) algorithm, which produced a set of parameters (mean, various and mixture coefficients) for the MG model. This procedure was performed for each visits resulting in a series of GM parameters. We studied the parameters fitted for ADC and see if they can be used as indicators for tumor progression. Additionally, we studied the ADC characteristics in the peri-tumoral region as identified by hyper-intensity on FLAIR scans. The results show that ADC histogram analysis of the tumor region supports the two compartment model that suggests the low ADC value sub-region corresponding to densely packed cancer cell while the higher ADC value region corresponding to a mixture of viable and necrotic cells with superimposed edema. Careful studies of the composition and relative volume of the two compartments in tumor region may provide some insights in the early assessment of tumor response to therapy for recurrence brain cancer patients.

Keywords: ADC, Tumor, Progression, Compartment, Gaussian

1. INTRODUCTION

Glioblastoma multiforme (GBM) is the most aggressive and deadliest primary brain tumor. It is the highest grade glioma tumor and is the most malignant form of astrocytomas. Excepting the brainstem gliomas, glioblastoma has the worst prognosis of any CNS malignancy. Anti-VEGF therapy has shown to improve response to therapy in some recurrent GBM patients but not all. Therefore, it would be very valuable to identify those who may or may not responsd to therapy early in the treatment process. In this study, we studied the histogram of ADC in brain tumor region to see if it can be used as a potential indicator for tumor responsiveness.

It has been suggested from a previous study that the ADC may be useful for predicting the degree of malignancy of brain tumors [1, 2]. The ADC was measured by manually placing regions of interest in tumor regions on the ADC map. In patients with contrast-enhanced tumors, regions of interest were placed at the site of enhanced lesions on contrast-enhanced T1-weighted MR images. In patients with weakly enhancing or nonenhancing tumors, regions of interest were chosen after identifying the tumor area as an area of hyperintensity on FLAIR images. Cystic components were differentiated as both areas of hyperintensity on T2-weighted MR images and areas of hypointensity on FLAIR MR images [1].

2. METHODOLOGY

2.1 Data Preparation

Brain tumor patients underwent multiple visits over the time span of approximately two years. A total of seventeen patients' data was included in this study. At each visit, patients underwent multi-sequence MR imaging study

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including FLAIR, T1-weighted, post-contrast T1-weighted, T2-weighted, and DTI. For each DTI scan, five scalar images were derived (ADC, FA, Max, Min and Middle Eigenvalue) yielding 10 image series for each imaging study. The interval between two visits was approximately one to two months. All series were co-registered to the corresponding DTI series at the first visit. Annotated normal and tumor regions were then overlaid to other registered MRI slices at the same visit.

2.2 Registration

For a particular visit, all imaging series were first rigidly registered to the T1 scan of that visit to remove any intra-visit misalignment of imaging planes. This process was repeated for all visits. In order to remove inter-visit misalignment, only the T1 scan from each subsequent visit was rigidly registered to the T1 scan from the first visit. As a post processing step, for all registrations, the brain was automatically extracted from the T1 reference scan (using the Brain Extraction Tool (BET)) so that only the brain was aligned during the registration process. Due to the multimodal nature of the registration task, Normalized Mutual Information was the similarity measure chosen. All registrations were performed using the freeware vtkCISG registration toolkit, developed at King's College London [3]. By combining the registration transforms from the intra- and inter-subject registration results, we have the ability to align every series from every visit to a visit and series of our choice. For this work, we chose to align every series from every visit to the DTI scan at the first visit. It is not necessary to separately register all the derived DTI series (FA, ADC, Max, Min and Middle Eigen value) since they can be aligned by utilizing transforms resulting from the original DTI registrations. Fig. 1 shows sample registered MRI images with a defined ROI.

2.3 Probability Distribution Estimation

It is well known that the intensity value distribution inside tumor volume is not uniform and we assume it follow a Gaussian mixture (GM) with two modes based on a two-compartment model. To study the ADC histogram distribution inside the tumor region, we outlined the tumor region as the hyper-intensity areas on post contrast T1 images and overlay the regions on the corresponding ADC images (Fig. 2a). We then apply the Expectation-Maximization (EM) algorithm [4] to estimate the relative intensities and mean values of the two modes in the histogram analysis. The EM algorithm produces mean and variance for each of the two modes and the mixture coefficients (Fig. 2b). We repeated the above exercises for each visit and plot the GM parameters vs. time as shown in Fig. 3 for one patient. We also measured the peri-tumoral region based on hyper-intensity areas on FLAIR scan (Fig. 4a) by excluding the tumor region as defined by T1-POST scan (Fig. 2a), and fitted a GM model for ADC pixels (Fig. 4b).

3. RESULTS

ADC histogram of tumor region defined based T1-post scan shows supportive evidence for two-compartment model. Preliminary data suggested that changes in the relative proportion of the two components correlate with responsiveness to Anti-VEGF therapy. Figures 2-13 illustrate the same.

4. DISCUSSION

A recent study of the histogram analysis in brain tumor patients suggested a two compartment model in the tumor region [2]. It hypothesized that some areas of tumor may have densely packed cells and little edema, resulting lower ADC values, whereas other areas in the tumor are consists of a mixture of viable and necrotic cells with edema, which would have higher ADC values. Our studies have confirmed the suggestion of two-compartment model. However, changes in hyper-intensity areas on T1-post contrast images and the mass-effects that are often associated with the treatment and reduction of edema in brain tumors can further complicate voxel-based longitudinal studies of therapeutic response.

5. CONCLUSION

Our study confirmed the suggestion of a two compartment model and more consistent and automated techniques of contouring tumor volume throughout the entire treatment process are needed.

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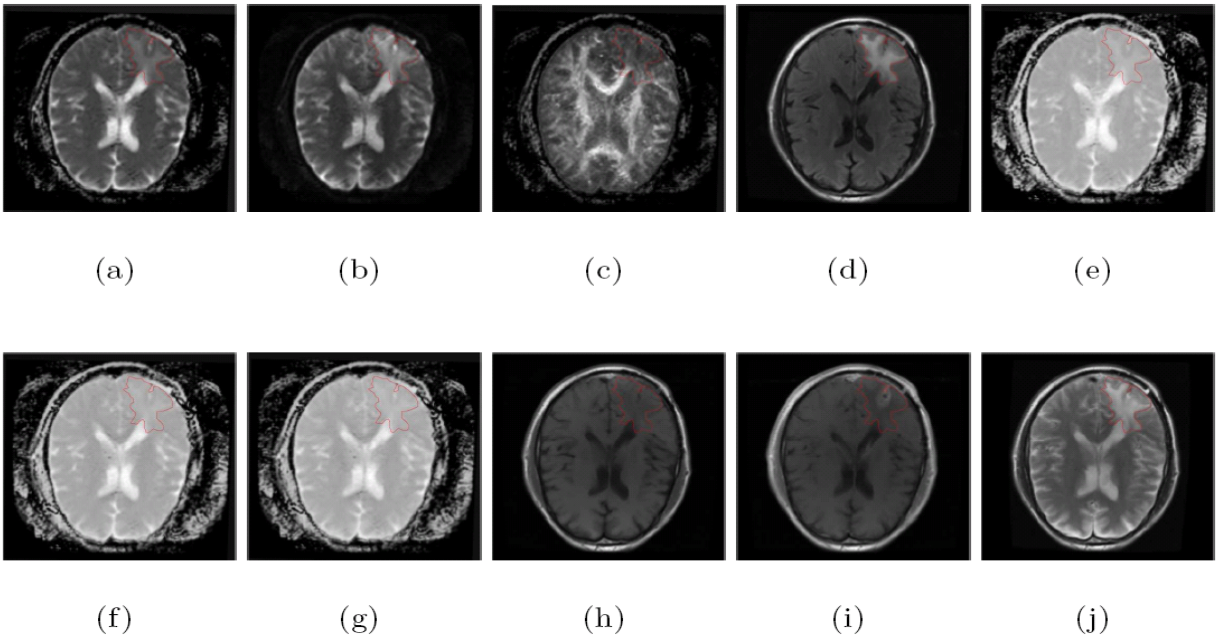


Figure 1. ROI overlaid across the ten co-registered MRI series. (a) ADC. (b) bo image in DTI series. (c) FA. (d) FLAIR. (e) MAX. (f) MID. (g) MIN. (h) T1-weighted. (i) post-contrast T1-weighted. (j) T2-weighted. As shown, ROI contour is drawn on FLAIR slices and then copied on to other registered scan series.

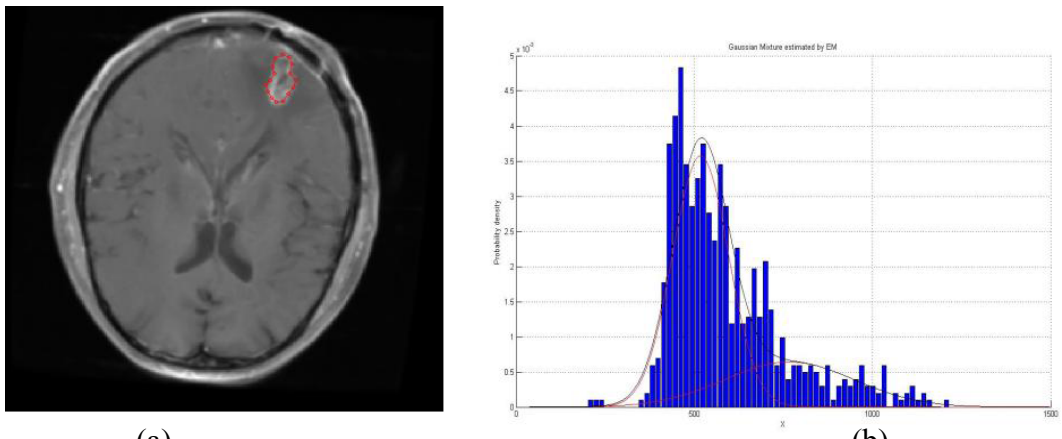
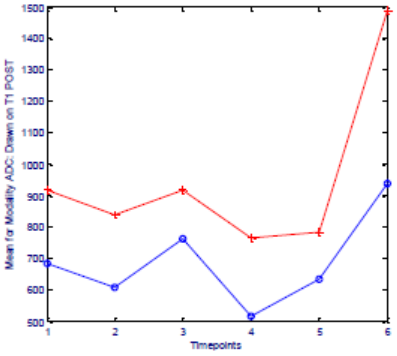
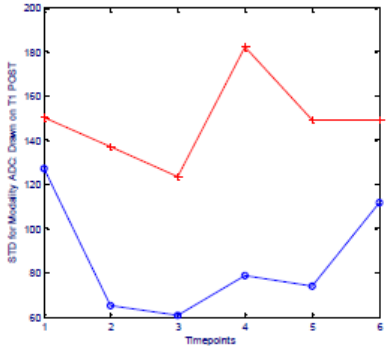
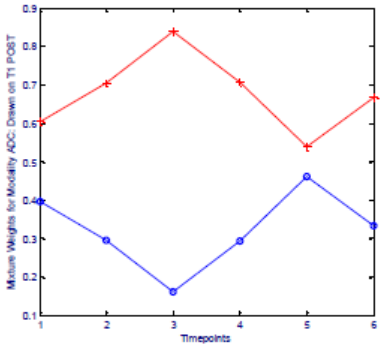
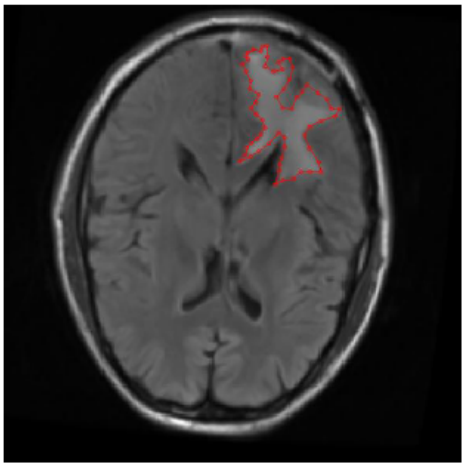


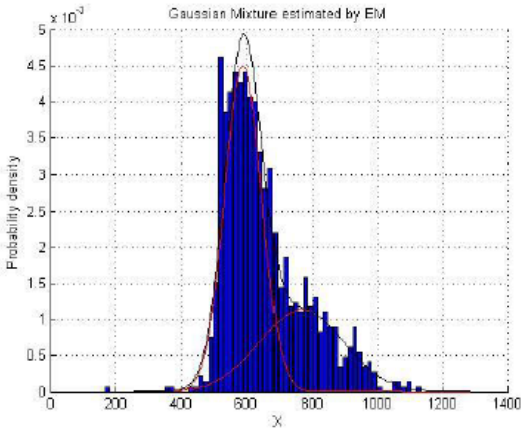
Figure 2. (a) Tumor region defined on T1-post scan and (b) Estimated Gaussian mixture for the ADC pixels inside the tumor region

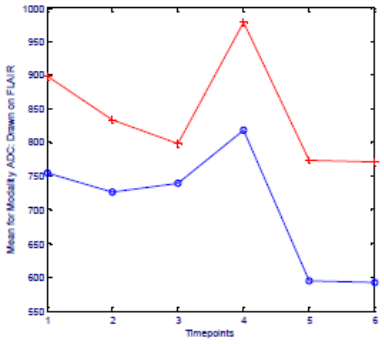


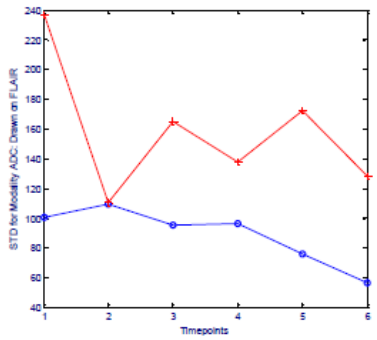


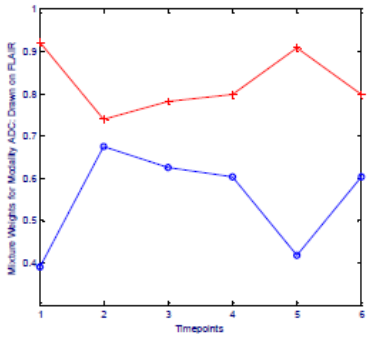


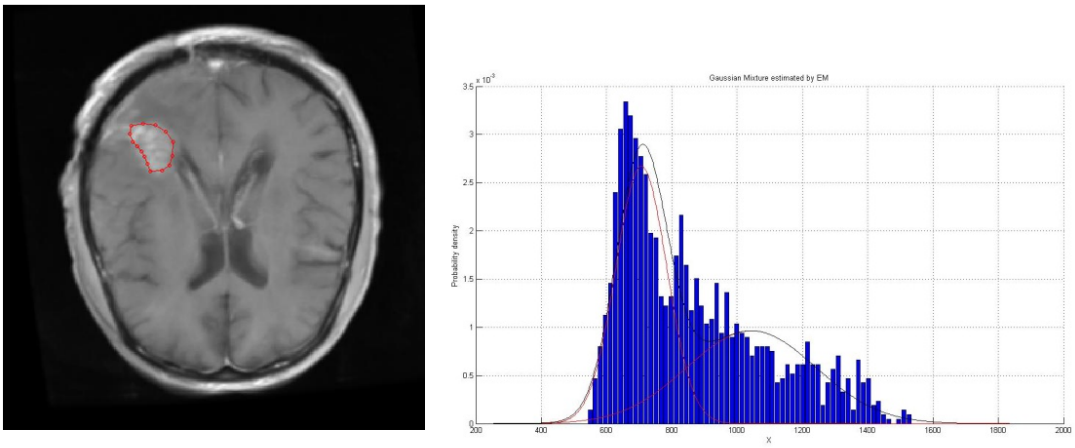






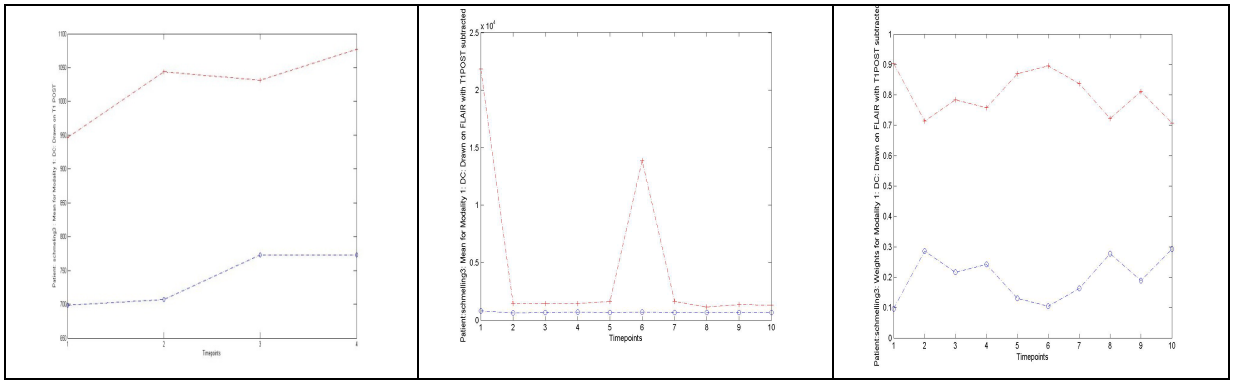






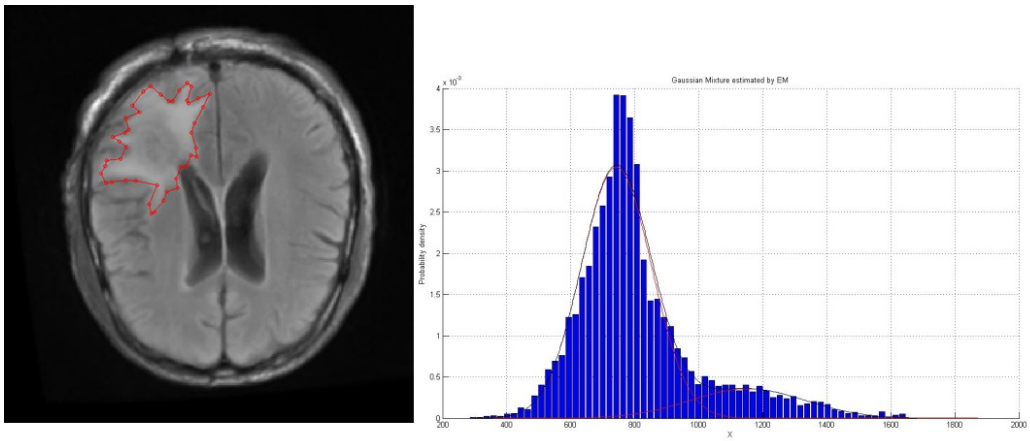
(a) (b)

Figure 6. (a) Tumor region defined on T1-post scan and (b) Estimated Gaussian mixture for the ADC pixels inside the tumor region for another patient.



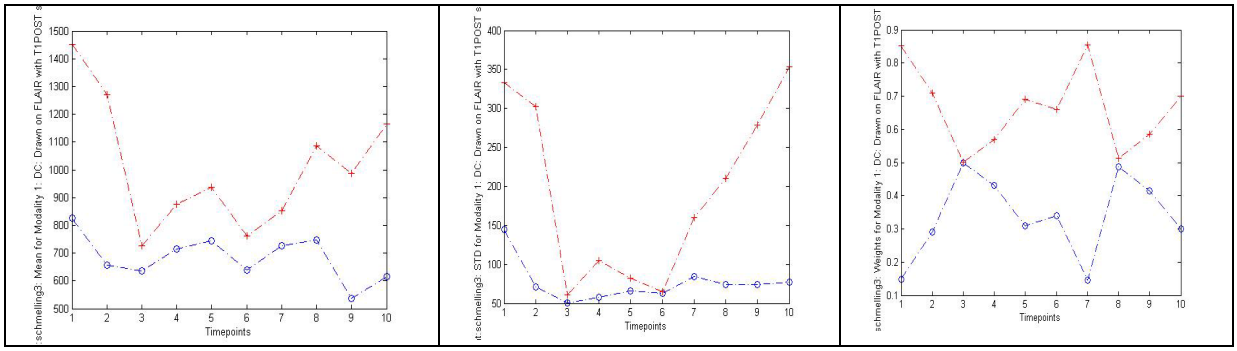
(a) (b) (c)

Figure 7. Parameters of the two mode-mixture Gaussian fitted to ADC pixels inside the tumor region. (a) Mean, (b) standard deviation (STD) and (c) mixture weights.



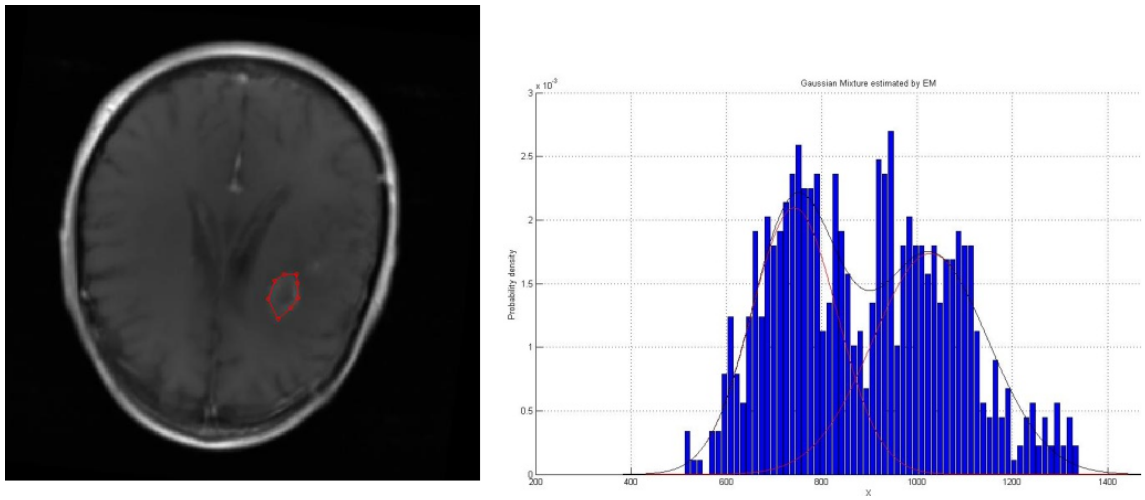
(a) (b)

Figure 8. (a) Tumor region defined on FLAIR scan and (b) Estimated Gaussian mixture for the ADC pixels inside the tumor region defined by FLAIR with the region defined in Figure 6 excluded.



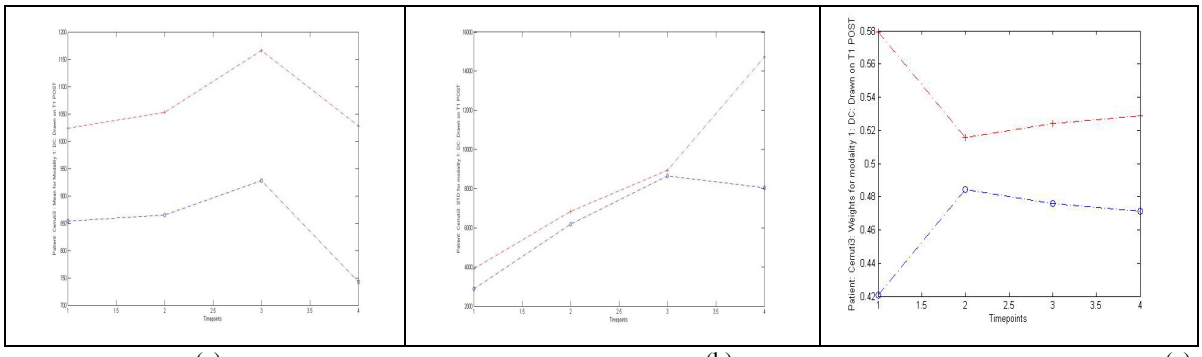
(a) (b) (c)

Figure 9. Parameters of the two mode-mixture Gaussian fitted to ADC pixels inside the peri-tumoral region defined in Figure 8 excluding tumor core region defined in Fig. 6. (a) Mean, (b) standard deviation (STD) and (c) mixture weights.



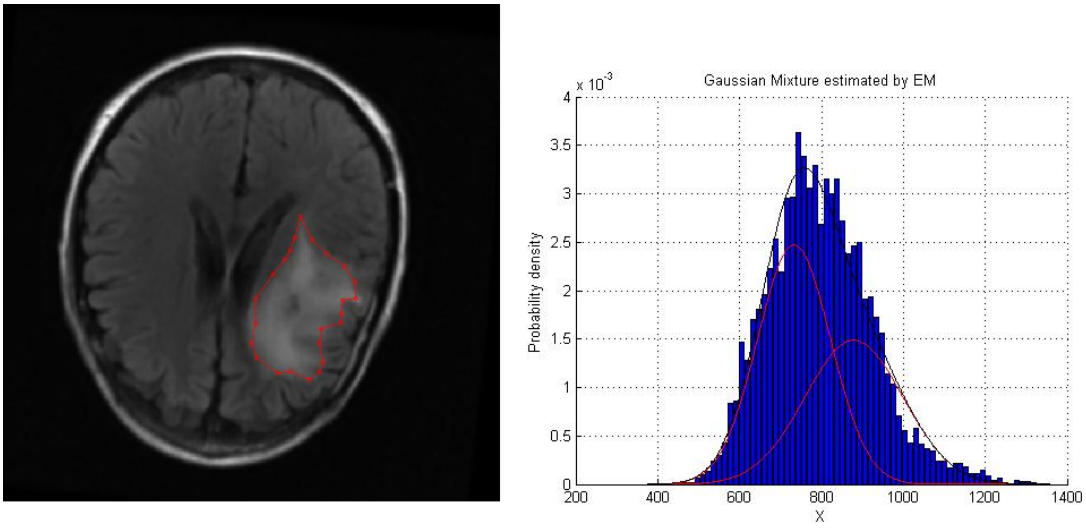
(a) (b)

Figure 10. (a) Tumor region defined on T1-post scan for another patient and (b) Estimated Gaussian mixture for the ADC pixels inside the tumor region for another patient.



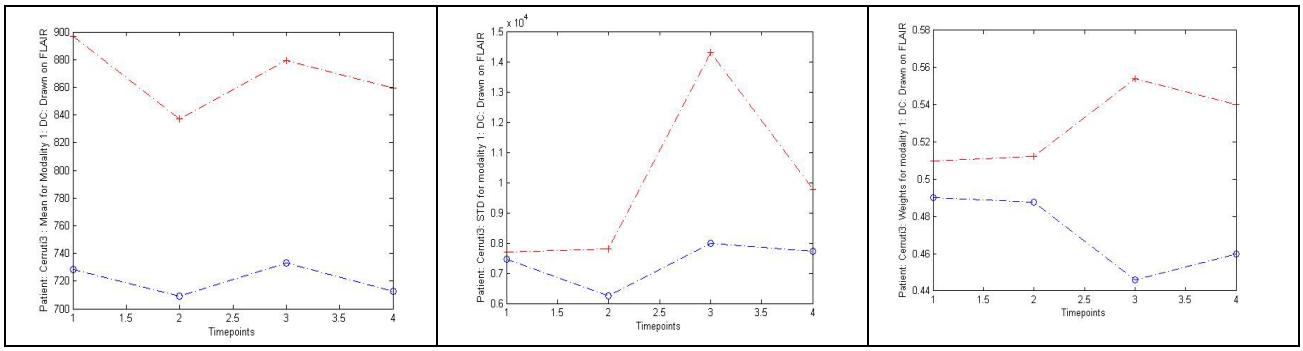
(a) (b) (c)

Figure 11. Parameters of the two mode-mixture Gaussian fitted to ADC pixels inside the tumor region. (a) Mean, (b) standard deviation (STD) and (c) mixture weights



(a) (b)

Figure12. (a) Tumor region defined on FLAIR scan for the patient in Figure 10 and (b) Estimated Gaussian mixture for the ADC pixels inside the tumor region defined by FLAIR with the region defined in Figure 10 excluded.



(a) (b) (c)

Figure 13. Parameters of the two mode-mixture Gaussian fitted to ADC pixels inside the peri-tumoral region defined in Figure 12 excluding tumor core region defined in Fig. 10. (a) Mean, (b) standard deviation (STD) and (c) mixture weights.