# Reproducibility Study of Prediction of Brain Tumors Response to Bevacizumab Treatment

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***Abstract*—Glioblastoma Multiform (GBM) is the most common cause of cancer death in both men and women. Bevacizumab is a recent therapy for stopping the tumor growth. The purpose of this paper is to present our reproducibility study of predicting response of the brain tumors to Bevacizumab treatment. This method allows physicians to select most effective treatment plans. We take two image series of patients before and after the treatment. After constructing Eigen images, we extract their statistical histogram features and then use regression analysis to develop a predictive model. Predictive models of response are developed with large regression coefficients (maximum R2=0.8). This method is dependent on the operator. To decrease the operator's role, this method is repeated four times for each patient. Then, the average of the achieved results is used for regression analysis. As a result, the regression coefficient increases (maximum $R^2$=0.86). The result of this approach is compared to that of a previous work at the University of Tehran showing excellent reproducibility of the proposed method.**

***Index Terms*—histogram analysis, glioblastoma multiform, bevacizumab, prediction, eigen image, statistical features, repeatability**

## I. Introduction

Brain tumor is one of the most threatening diseases in the world. Glioblastoma Multiform (GBM) tumors are aggressive primary brain cancers that are characterized by extensive infiltration into the brain and are highly resistant to treatment. Despite aggressive management with surgery, radiation and chemotherapy, the prognosis for patients with glioblastoma remains poor. Median survival is typically less than a year with little change in several decades.

Tumor cells like other living tissues require a constant source of blood for oxygen and nutrition. Tumor cells require more oxygen and nutrition for growing than normal cells. So they send a message to growth factor and cause triggering of new blood vessels construction which is known as angiogenesis process. Among these factors, vascular endothelial growth factor (VEGF) is most important. In 2004 Bevacizumab was presented against VEGF and prevented cancer cells from growth.

The purpose of this paper is to investigate the images of new patients treated with Bevacizumab for predicting the result of treatment. If the prediction result is that it does not have a significant impact on the tumor, we can think of other methods for treatment. Conversely, in the case of an appropriate prediction result, the treatment can continue. A.D. Norden et al [1] retrospectively reviewed 55 consecutive patients with recurrent malignant gliomas who received bevacizumab and chemotherapy to determine efficacy, toxicity, and patterns of recurrence and using a blinded, standardized imaging review and quantitative volumetric analysis, the recurrence patterns of patients treated with bevacizumab were compared to recurrence patterns of 19 patients treated with chemotherapy alone. Guaray D. Shah et al [2] used the response evaluation criteria in solid tumors, or RECIST criteria to measure response in tumors. They compared linear and volumetric measurements in adult high-grade supratentorial enhancing gliomas to determine the agreement between measurements in defining response and in their subsequent relation to survival. R. G. Blasberg [3] demonstrated that positron emission tomography (PET) as an imaging biomarker could be used for prediction of brain tumor therapy. Mardor et al. [4] addressed this problem using two parameters of Diffusion weighted imaging (ADC and $R_D$) in pre-treatment images and showed that these parameters were correlated with the response (relative change in the tumor size). M. Najafi [5] established relationships between multi-parametric MRI images acquired pre-treatment and the amount of reduction in the size of GD-enhanced are due to Bevacizumab treatment and developed a predictive model for the level of response. The purpose of this paper is to do a reproducibility study of M. Najafi's method of predicting brain tumors response to Bevacizumab treatment.

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The rest of paper is organized as follows. In section 2, the method and materials are explained. In section 3, the results of the experiments and the analysis are presented. Section 4 discusses the results and presents conclusions and future works.

## II. Materials and Methods

15 patients (11 male and 4 female) with GD-enhanced areas in their brain tumors were chosen as the data for the study. The ages ranged from 36 to 66 years with an average of 53. Two series of MR images were acquired from them before the treatment and 1-4 months after the treatment (Henry Ford Health System, Detroit, MI, USA). These images were acquired using a 3 Tesla GE system and included multi-parametric images with an image matrix of 512 × 512: T1-weighted (TR= 3000ms, TE= 6ms, TI= 1238ms), T1-post (TR= 3000ms, TE= 6ms, TI= 1238ms), T2-weighted (TR= 3000ms, TE= 103ms) and FLAIR (TR= 10000ms, TE= 120ms, TI=2250 ms). The images were high quality and co-registered, so no noise reduction or registration step was applied to the data.

First, using T1-post contrast images, we determine the slices that contained GD-enhanced areas of the tumors for a volume analysis. To perform this work, we need to extract GD-enhanced areas accurately. To this, we subtract the T1-post image from the T1-weighted image pixel by pixel and threshold the result. All of the selected slices of each patient are aligned to one of the slices. This work is performed by FSL. Then, the selected slices pass the skull removal step using Eigentool image analysis software (Henry Ford Health System). Then, Gram-Schmidt Orthogonalization is applied to the resultant sub-images from the previous step. This approach decomposes the multi parametric MRI data into white matter (WM), gray matter (GM), cerebrospinal fluid (CSF), and reminder (orthogonal) composite images [6].

We select the central slice (i.e., the slice with minimum effect of partial volume averaging [7]) for each patient for performing the analysis and feature extraction. The volume of the GD-enhancement area is computed for the first and second series of the images. Then, we compute the relative change in the volume of the GD-enhanced as a measure of response.

We select some samples of each region to be segmented as desired tissue pattern and the pixels from other regions are regarded as undesired tissue patterns.

Each composite image is constructed using a weighting vector that projects the original multi-dimensional vectors defined using the original MR images to a specific subspace:

$$EI_{jk} = \sum_{i=1}^{4} w_i . v_{jki} = \vec{W} . \vec{V}_{jk} \quad (1)$$

In this equation, $EI_{jk}$ is the intensity of $(j, k)^{th}$ pixel in the composite image, $\vec{W}$ is the weighting vector, and $\vec{V}_{jk}$ is the intensity vector of $(j, k)^{th}$ pixel in the original four MR images.

The weighting vector must maximize the SNR and the inner product of this vector with the other tissue patterns must be zero. Under this condition, the weighting vector equals to:

$$\vec{w} = \vec{t}_d \_ \vec{t}_d{}^p \quad (2)$$

where $\vec{t}_d$ is the desired tissue is vector and $\vec{t}_d{}^p$ is the projection of $\vec{t}_d$ onto the undesired tissue vectors. The latter can be calculated using the Gram-Schmidt orthogonalization procedure [7].

In this step, the GD-enhanced area is projected onto the composite images (WM, GM, and CSF) and their histograms are calculated using Eigentool. Then, a normalization step is applied on them to compensate for the effect of the size of the ROI.

Four histogram features (Mean, Standard deviation, Skewness, Kurtosis) are extracted using MATLAB™. Mean and Standard deviation represent average and dispersion of the histogram, respectively. Skewness is a measure of the asymmetry of the histogram and kurtosis reflects sharpness of the peak of a histogram.

This approach has been performed at the University of Tehran. We have repeated this method and our results agree with theirs. We show that the GM component include significant features for the prediction equations are derived from multiple-regression analyses with their corresponding regression coefficients.

This method is however dependent on the operator. To decrease the operator's role, this method is repeated four times for each patient. Then, the average of the achieved results is used for regression analysis. As a result, the regression coefficient increases (maximum $R^2$=0.86).

## III. Results

Table I shows changes in tumor enhancement size that is calculated by (v1-v2)/v1 as a measure of response, so that changes more than 50% consider as positive response and lower than 50% as negative response. Also this table represents the length of the time trial between two images acquisitions. Next, the histograms of the GD-enhancement region of each patient in the composite images were acquired.

The shape of histogram in patients that respond and not respond to treatment is different. Fig. 1 presents histogram of GM and WM of patients that responded or not responded to treatment. The histogram in patients that responded the treatment was more compressed. As a result, we extract four histogram features described in previous section from WM, GM, CSF composite images from central slice.

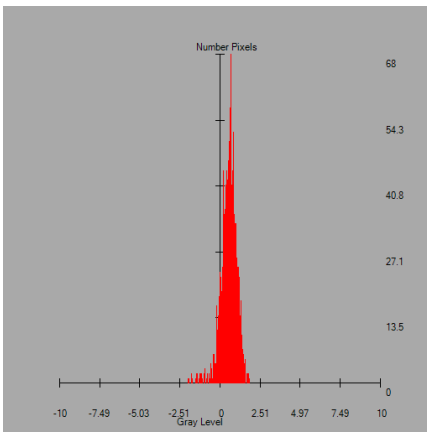
In case of single-regression analysis after repeated four times, standard deviation of GM is more effective in prediction ($P$<0.0002, $R$=-0.83).

Fig. 2 shows the regression line and prediction equation for this feature. Our results of multi-regression based on four repetitions are presented in Table II. The best coefficient of regression in this case is better than the

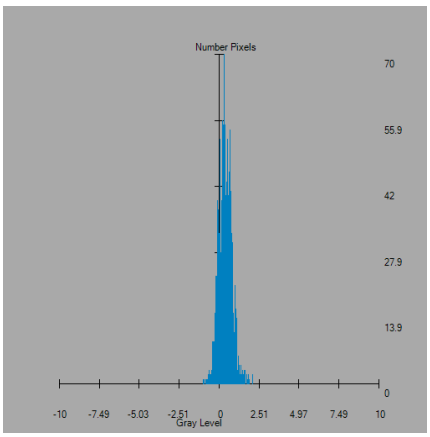
single-regression case. Table III represents Mr. Najafi's multi-regression result.

TABLE I. EXTENT OF RESPONSE IN PATIENTS AND TIME INTERVAL BETWEEN TWO IMAGE ACQUISITIONS

| patient | Relative change in tumor volume (%) | Time between two acquisitions (days) |
|---|---|---|
| 1 | 66.9 | 75 |
| 2 | 33.5 | 50 |
| 3 | 56.3 | 40 |
| 4 | 23.3 | 52 |
| 5 | 63.7 | 41 |
| 6 | 71.9 | 43 |
| 7 | 27.9 | 118 |
| 8 | 54.8 | 83 |
| 9 | 55.1 | 58 |
| 10 | 78.1 | 41 |
| 11 | 75.1 | 52 |
| 12 | 66.1 | 119 |
| 13 | 41.7 | 42 |
| 14 | 39.9 | 54 |
| 15 | 81.8 | 48 |




a

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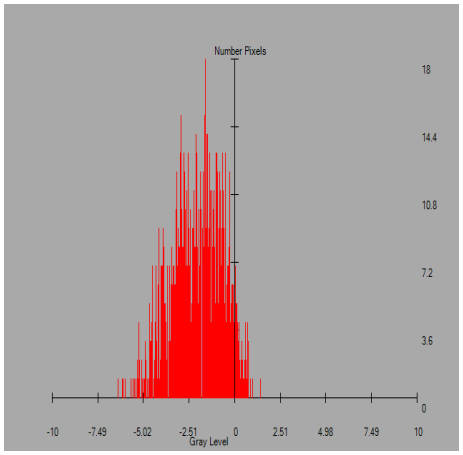


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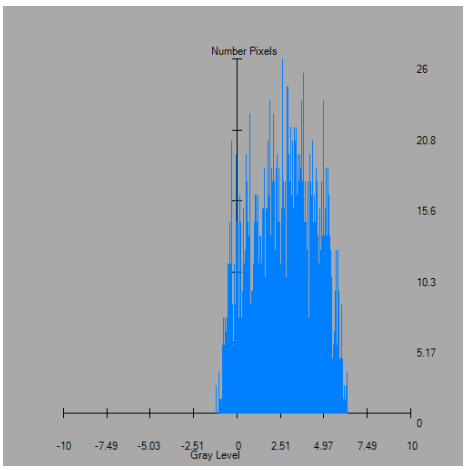


d

Figure 1. Image histogram of a responder (above row) and non-responder (below row). (a, c) GM histogram; (b, d) WM histogram.

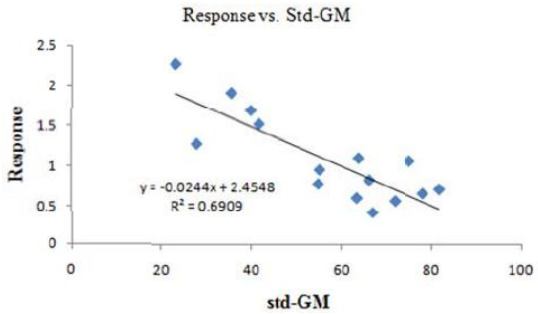


Figure 2. Response (relative decrease in the volume of the GD-enhanced area) as a function of the standard deviation of the pre-treatment GM composite image.

## IV. DISCUSSION AND CONCLUSION

In this study, reproducibility of prediction of brain tumor response by structural MR images for GBM with Gd-enhancement and treated with Bevacizumab is considered.

Gram-Schmidt orthogonalization analysis was used in this study because it generates more robust features than the conventional methods of feature extraction in MRI [8]. Since in this analysis, the gray levels of the resulting composite images are always distributed around 1

regardless of the intensities of the original images, there is no need for the standardization of the original images.

Comparison between two Tables (II, III) shows reproducibility of this method. Table IV represents reproducibility coefficient [9] between the extracted features. These results show reproducibility of this method.

In conclusion, this study illustrates that it is possible to predict the response of brain tumor patients to the therapy by Bevacizumab before treatment. Such a prediction system is vital for cancer patients because it can help with the choice of treatment.

This study confirms Mr. Najafi's approach that uses multi-parametric structural MR-images and their histogram features for the prediction of the response of the brain tumor patients to therapy. It also shows that this method can be reproducible. In the future, we intend to extract other features from the Gd-enhanced region of the tumor and show that there is a relationship between the level of response to treatment and image histogram.

TABLE II. THE RESULTS OF MULTIPLE- REGRESSION ANALYSIS FOR THE PREDICTION OF THE RESPONSE (Y).

| Features | Prediction equation | Regression coefficient ($R^2$) | Significance F |
|---|---|---|---|
| $Std_{GM}$ + $Std_{WM}$ | Y= -0.36 ($Std_{GM}$) + 0.017 ($Std_{WM}$) + 0.84 | 0.698 | 0.0007 |
| $Std_{GM}$ + $Kurt_{GM}$ | Y= -0.21 ($Std_{GM}$) + 0.06 ($Kurt_{GM}$)+ 0.61 | 0.779 | 0.0001 |
| $Std_{GM}$ + $Kurt_{GM}$ + $Std_{WM}$ + $Std_{CSF}$ | Y= -0.278 ($Std_{GM}$) + 0.147 ($Std_{WM}$) + 0.059 ($Kurt_{GM}$) + 0.114 ($Std_{CSF}$)+ 0.596 | 0.862 | 0.0002 |

TABLE III. MR. NAJAFI'S RESULTS OF MULTIPLE- REGRESSION ANALYSIS FOR THE PREDICTION OF THE RESPONSE (Y).

| Features | Prediction equation | Regression coefficient ($R^2$) | Significance F |
|---|---|---|---|
| $Std_{GM}$ + $Std_{WM}$ | Y= -0.62 ($Std_{GM}$) + 0.31 ($Std_{WM}$) + 0.93 | 0.67 | 0.003 |
| $Std_{GM}$ + $Skew_{GM}$ + $Kurt_{GM}$ | Y= -0.36 ($Std_{GM}$) + 0.11 ($Skew_{GM}$) + 0.11 ($Kurt_{GM}$)+ 0.63 | 0.82 | 0.0005 |

TABLE IV. REPRODUCIBILITY COEFFICIENT OF THE FEATURES USED IN

| Features | Correlation |
|---|---|
| $Std_{GM}$ | 0.8912 |
| $Kurt_{GM}$ | 0.9189 |
| $Skew_{GM}$ | 0.8734 |
| $Std_{WM}$ | 0.8918 |
| $Kurt_{WM}$ | 0.95925 |
| $Skew_{WM}$ | 0.8456 |

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