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An innovative mathematical analysis of routine MRI scans in patients with glioblastoma using DoctorEye

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Abstract—**Improving the initial diagnosis and the assessment of response to treatment in malignant gliomas, while avoiding invasive methods as much as justifiable, is one major aspect actual research is focusing on. Imaging studies are used to calculate tumor volume and define vital, necrotic and cystic areas within a tumor. Though the visual interpretation of magnetic resonance (MR) images is based on qualitative observation of variation in signal intensity, a correlation of signal intensities with histological features of a tumor is not possible. Better methods are needed for a reliable interpretation of follow-up studies in single patients. Histograms of signal intensities might serve as a method adding quantitative data to the description of a tumor. Using DoctorEye software, tumors can be easily rendered and histograms of the signal intensities within a tumor as well as mean and median signal intensities are possible to calculate. Our results in glioblastoma suggest that these histograms are an innovative method of gaining new tumor-specific information without performing additional investigations in a patient. It can be an additional diagnostic tool in differentiating various intracranial lesions from each other, as well as in assessing response to treatment or progression of malignant glioma.**

Keywords—MRI; DoctorEye; Signal intensities; histogram; glioblastoma; pseudoprogression

I. INTRODUCTION

Despite recent diagnostic and therapeutic achievements patients with glioblastoma have a dismal prognosis. Early diagnosis of tumor progression and better characterization of progressive disease (PD), radiation necrosis (RN) and pseudoprogression (PP) are most important for improving treatment and outcome [1]. It is believed that PP is caused by cytotoxic effects of chemotherapy and radiation resulting in a subacute inflammation with abnormal vessel permeability and edema [2]. Up to 20% of patients may develop PP with clinical symptoms that are not distinguishable from symptoms of PD [3]. RN can occur any time after irradiation and results in disruption of the blood-brain barrier with subsequent edema and mass effect [4].

Since 1990 the MacDonald criteria, based on measurable changes in contrast-enhancing lesions, have been the standard approach for measuring response in patients with malignant glial tumors [5]. Recently the Response Assessment in Neuro-Oncology (RANO) Working Group proposed new criteria that pointed out the limitations of the above-mentioned approach and also take into account nonenhancing tumors [6]. Nevertheless they still lack a high level of accuracy [7]. Thus the process of analyzing the individual follow-up of patients with malignant gliomas offers much potential for improvement.

There are different imaging modalities available, like Gadolinium MRI (Gd-MRI), magnetic resonance (MR) spectroscopy, diffusion weighted MRI (dw-MRI), 18fluorodeoxyglucose positron emission tomography (18F-FDG PET), and single photon emission CT (SPECT) that try to distinguish more or less accurate between PD, RN and PP with 18F-FDG PET scans are most important. 18F-FDG PET shows in RN and PP compared to PD a reduced glucose uptake [8]. RN is in addition characterized by a high apparent diffusion coefficient (ADC) and a high lactate and low choline peak in MR spectroscopy [4].

To the best of our knowledge there is no data available that uses histograms of signal intensities of MRI for the characterization of glioblastoma. With the described innovative mathematical method of analyzing routine MRI scans we are trying to reveal new tumor-specific information that helps to distinguish between PD and PP. This method is easily feasible in daily clinical care, it will give results without further imaging studies and is therefore more cost efficient.

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II. MATERIALS & METHOD

A. *Image acquisition*

MR Images from 33 patients with glioblastoma were analyzed at the time of diagnosis and during their individual follow-up including T1, T1 with gadolinium contrast and T2 modalities.

B. *Preprocessing*

Tumor volumes were calculated after rendering of the tumor using DoctorEye as an open source tool under the GNU General Public License [9], [10]. Suspected active tumor tissue, necrosis, edema and the cerebrospinal fluid "Fig. 1" were separately analyzed in all mentioned modalities. All segmentations were performed by manual rendering of the areas of interest. To ensure the highest grade of accuracy supervision was performed by an experienced neuroradiologist (WR). Signal intensities of the cerebrospinal fluid (CSF) were used as reference values for standardization purposes [11]. Up to now a quantitative analysis of signal intensities is not possible due to the variety of MR machines and the lack of standardization in producing MR-images.

C. *Measurements and Analysis*

DoctorEye provides the calculation of histograms of segmented areas and the corresponding mean and median values of signal intensities. The data of the histograms were uploaded to Microsoft Office Excel 2007 and further statistics done including normalization of the data. A comparison of the shape of the histograms, the mean and median values of signal intensities of different tumor areas were done for each modality at the time of diagnosis and during follow-up in individual patients and between them. In nine of the 33 Patients a complete follow-up could be analyzed, referring to DICOM data-sets at diagnosis, after surgery and after radio- and chemotherapy.

D. *Validation*

As in most patients no 18F-FDG PET scan, dw-MRI or SPECT were available, validation is only based on clinical and outcome data.

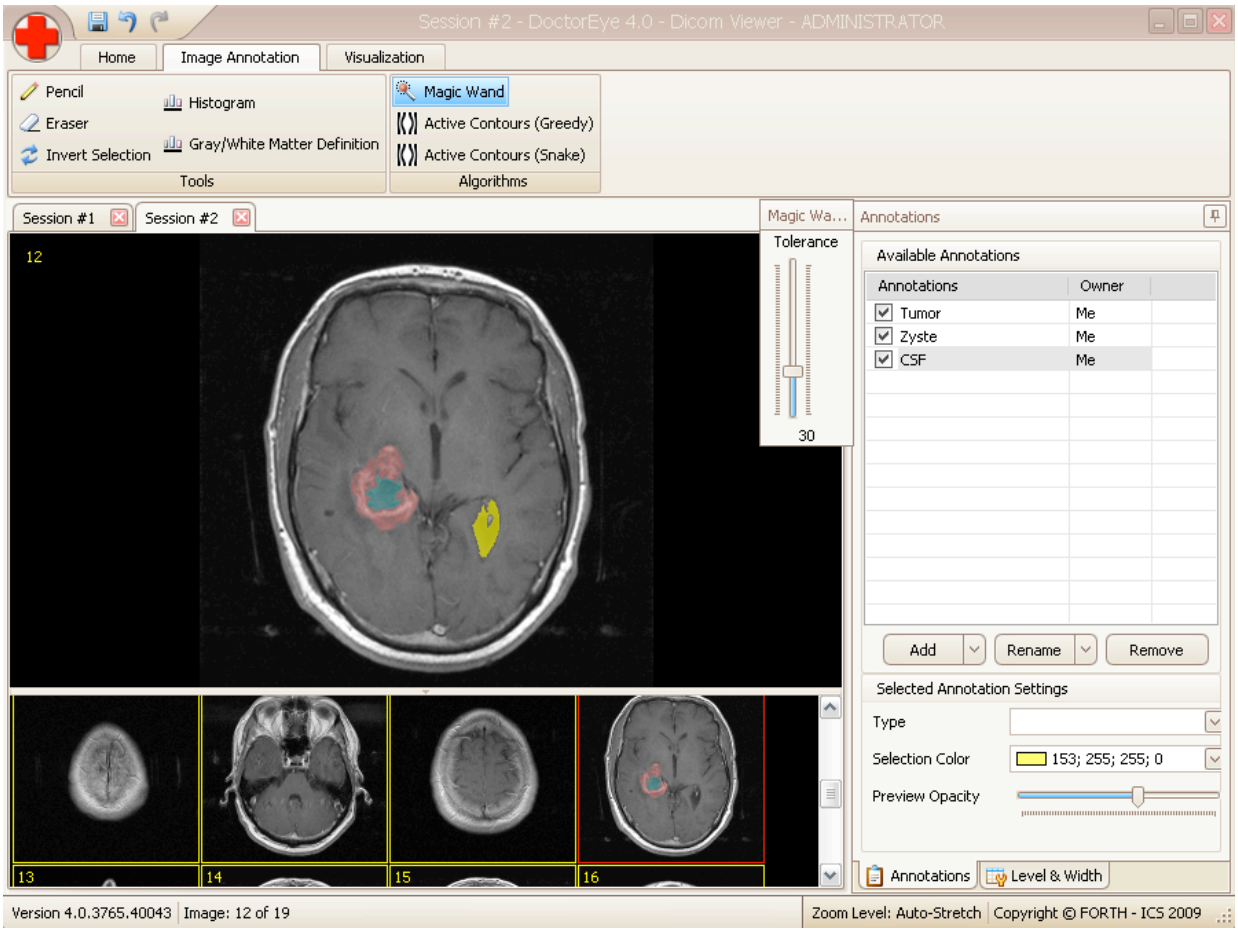

Figure 1. Segmentation of a glioblastoma using DoctorEye at the time of diagnosis. The contrast enhanced tumor in shown in red and the non-contrast area in green. Cerebrospinal fluid is marked in yellow (only part of the part the left side ventricle).

III. RESULTS

It is well known that different MR modalities show different shapes of a glioblastoma in a single patient at the same time "fig.2". By measuring volumes and segmenting the tumor in different modalities active tumor-tissue, necrotic areas and edema could be distinguished the best by using the histograms of the signal intensities. These are different within the tumor and vary significantly in all modalities.

At the time of diagnosis the histogram of all glioblastoma showed a bimodal distribution of signal intensities in T1 modality. "Fig. 3" displays the median distribution of these signal intensities of the tumor (green plus red) and of the CSF (yellow) of all patients at the time of diagnosis. Such similarities of the shape are seen during follow-up in individual patients as well. This is valid for the images after surgery, "after radio- and chemotherapy".

Using combinations of histograms from different modalities the tumor can be described in a much better way than by calculating solely the tumor volume. It is possible to define necrotic areas and vital tumor areas as shown in green and red in "Fig. 3". This allows the calculation of the volume of the vital tumor at any time. Standardizing the mean peak of signal intensities of the vital tumor area and of the necrotic tumor area by relating them to the mean peak of signal intensities of the CSF a significant difference ($p < 0.05$) between tumor and necrosis is found at all analyzed time points in T1, T1 with contrast enhancement and T2 "Tab. 1".

The more the standardized median and mean value of signal intensities in T1 with contrast enhancement are increasing during follow-up in a single patient the more likely the patient suffers from disease progression. If these values are going down the more likely a tumor response can be diagnosed "Tab. I".

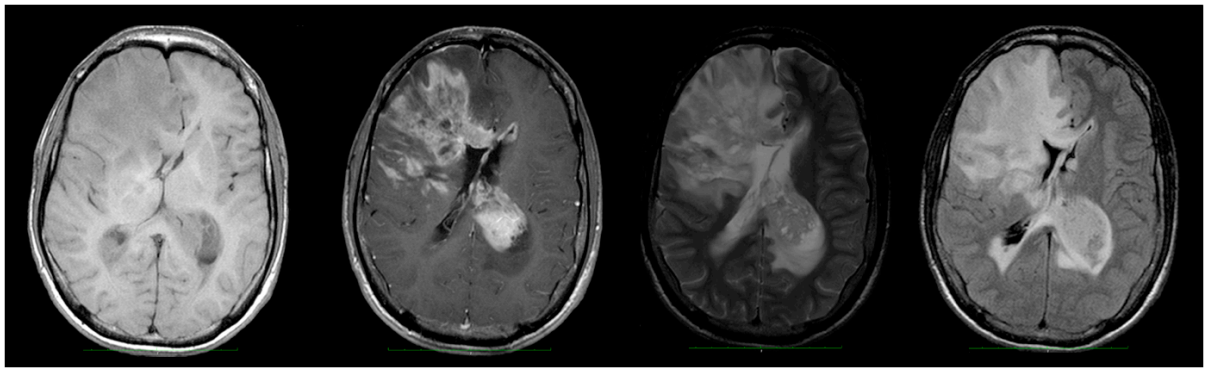

Figure 2. Different modalities of MR images in a single patient with glioblastoma at the time of diagnosis.

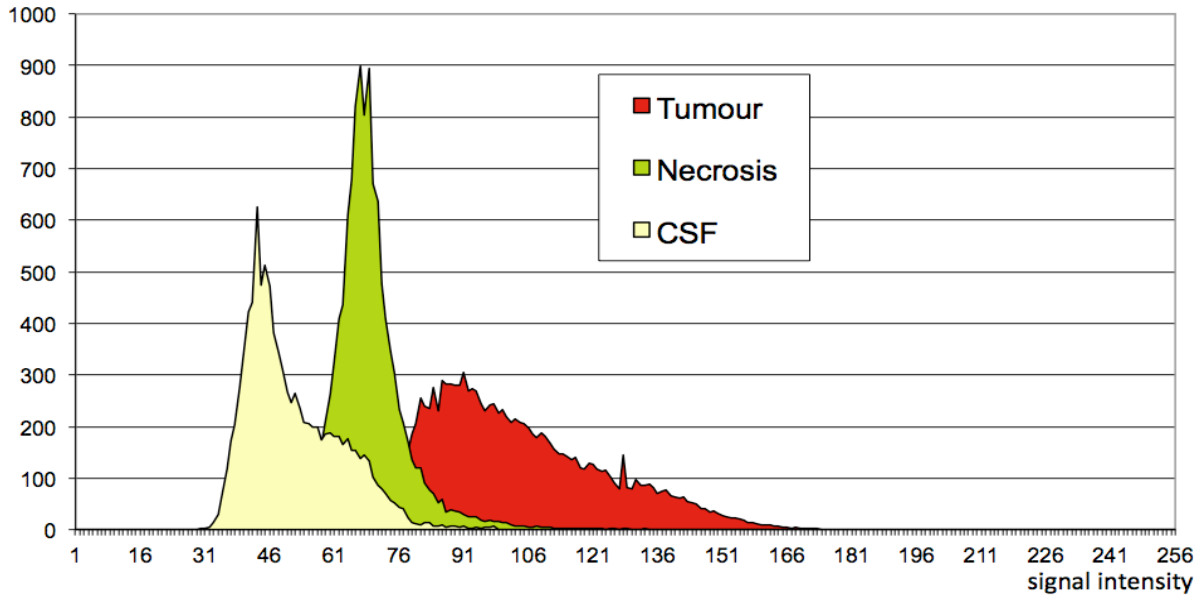

Figure 3. Mean signal intensity histogram of 33 patients with a glioblastoma at the time of diagnosis. *Y-axis: mean number of Voxels.*

TABLE I. STANDARDIZED MEAN SIGNAL INTENSITIES OF DIFFERENT MODALITIES AT DIFFERENT TIME POINTS CALCULATED FROM ALL PATIENTS OF THIS SERIES. *CE: CONTRAST ENHANCEMENT; TU: TUMOR; N: NECROSIS, W: WHOLE TUMOR (VITAL AND NECROTIC)*

T1	T1 + CE	T2		
2.3	2.4	0.89	Diagnosis	Tu
1.6	1.3	1.2		N
1.5	2.3	0.95	after Irradiation	Tu
0.7	0.9	0.9		N
1.5	2.7	0.79	at relapse	Tu
0.9	1.7	1.0		N
1.5	1.6	0.88	Diagnosis	W
1.2	1.5	0.89	after irradiation	W
1.3	2.1	0.88	at relapse	W

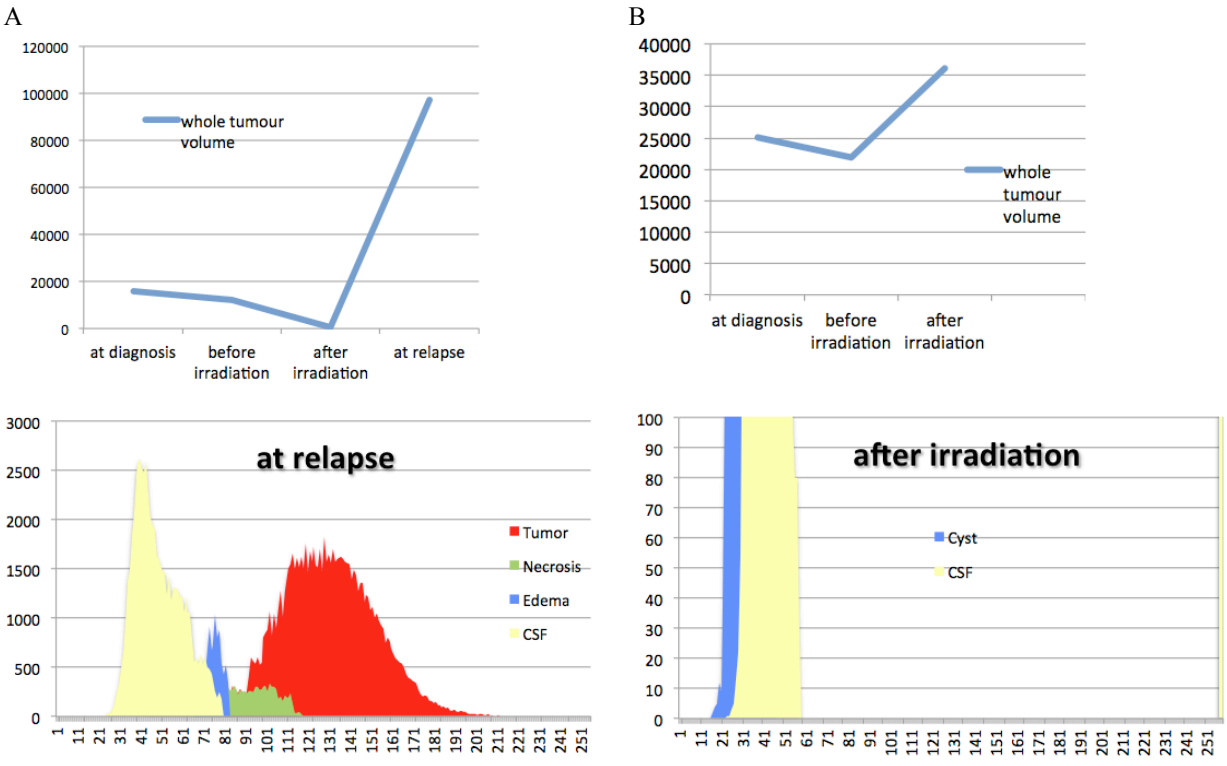

Figure 4. Progressive disease (A) and pseudoprogression (B) as shown in the histograms of signal intensities in T1 in the follow-up of 2 patients with glioblastoma. *green: necrotic tumor, red: vital tumor; yellow: CSF; blue cyst; blue line tumor volume*

In addition these histograms can distinguish between PD and PP/RN if one links the whole tumor volume with the volume of the necrotic and the vital part of the tumor that can be easily calculated "Fig. 4".

IV. DISCUSSION

Glioblastoma are treated today with surgery, irradiation and chemotherapy. Imaging studies are important for diagnosis of remission or recurrence of disease. Unfortunately the diagnosis of recurrence is not easily to distinguish from PP or RN [1]. "Tab. II" gives an overview of different imaging modalities to distinguish PP/RN from PD or recurrence including our data of the histogram of signal intensities.

TABLE II. CHARACTERISTICS OF PSEUDOPROGRESSION (PP)/ RADIATION NECROSIS (RN) AND RECURRENCE OR PROGRESSIVE DISEASE (PD. *CE: CONTRAST ENHANCEMENT*

Imaging	**PP/NR**	**PD**
MRI CE	↑	↑
^{18}F-FDG PET	↓	↑
Histogram		
Vital tumor	→↓	↑
Necrotic tumor	→↑	→↓

Besides us, up to now no other group did analyze histograms of signal intensities in T1, T1 with contrast enhancement or T2 modalities of MRI. The main reason is the missing standardization of MRI technologies. Only in case of diffusion weighted images reproducibility is easy to achieve and ADC values can be compared between different time points. In 2012 Pope et al. [12] showed by the analysis of histograms derived from such ADC analysis that this is a significant marker in the prediction of response to bevacizumab in glioblastoma.

Simulation models based on MR technologies for the prediction of tumor response in glioblastoma are investigated by few groups only [13], [14], [15]. Chen et al. could show in 2010, that such simulations are able to successfully predict the region of recurrence in glioblastoma [15]. Precise data from imaging studies are of utmost importance to gain such results in in silico oncology models. The better these data are the more accurate results can be predicted [16], [17]. For the validation of the models segmentation of the tumor at diagnosis and during follow-up is of utmost importance. A correlation between tumor texture and signal intensities in MRI expressed by histograms of signal intensities is a step forward in precisely calculating volumes of different tumor areas, e.g. necrotic and vital areas. The use of such histogram data in 'in silico oncology' models and the oncosimulator is under investigation in different EU funded projects (p-medicine [18], TUMOR [19]).

As glioblastoma shows a typical bimodal distribution of signal intensities it can be questioned, if other brain tumors show different shapes of the histogram of signal intensities. If so this method would help in better characterization of brain tumors by MRI.

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