Magnetic Resonance Imaging 57 (2019) 254–258

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.elsevier.com/locate/mri

Original contribution

MRI based texture analysis to classify low grade gliomas into astrocytoma and 1p/19q codeleted oligodendroglioma

Shun Zhang[a,b], Gloria Chia-Yi Chiang[b], Rajiv S. Magge[c], Howard Alan Fine[c], Rohan Ramakrishna[d], Eileen Wang Chang[b], Tejas Pulisetty[e], Yi Wang[b,f], Wenzhen Zhu[a,*], Ilhami Kovanlikaya[b,**]

[a] Department of Radiology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[b] Department of Radiology, Weill Cornell Medicine, New York, NY, USA
[c] Department of Neurology, Weill Cornell Medicine, New York, NY, USA
[d] Department of Neurological Surgery, Weill Cornell Medicine, New York, NY, USA
[e] Department of Radiology, Saint Louis University, Saint Louis, MO, USA
[f] Department of Biomedical Engineering, Cornell University, Ithaca, NY, USA

ARTICLE INFO

Keywords:
Texture analysis
Low grade glioma
Astrocytoma
Oligodendroglioma

ABSTRACT

Purpose: Texture analysis performed on MR images can detect quantitative features that are imperceptible to human visual assessment. The purpose of this study was to evaluate the feasibility of texture analysis on preoperative conventional MRI to discriminate between histological subtypes in low-grade gliomas (LGGs), and to determine the utility of texture analysis compared to histogram analysis alone.

Methods: A total of 41 patients with LGG, 21 astrocytoma and 20 1p/19q codeleted oligodendroglioma were included in this study. Patients were randomly divided into training (60%) and testing (40%) sets. Texture analysis was performed on conventional MRI sequences to obtain the most discriminant factor (MDF) values for both the training and testing data. Receiver operating characteristic (ROC) curve analyses were then performed using the MDF values and 9 histogram parameters in the training data to obtain cut-off values for determining the correct rate of discriminating between astrocytoma and oligodendroglioma in the testing data.

Results: The ROC analyses using MDF values resulted in an area under the curve (AUC) of 0.91 (sensitivity 86%, specificity 87%) for T2w FLAIR, 0.94 (87%, 89%) for ADC, 0.98 (93%, 95%) for T1w, and 0.88 (78%, 86%) for T1w + Gd sequences. Using the best cut-off values, MDF correctly discriminated between the two groups in 94%, 82%, 100%, and 88% of cases in the testing data, respectively. The MDF outperformed all 9 of the histogram parameters.

Conclusion: Texture analysis performed on conventional preoperative MRI images can accurately predict histological subtype of LGGs, which would have an impact on clinical management.

1. Introduction

WHO grade II tumors are considered low grade gliomas (LGG) because they typically have a better prognosis than high grade gliomas [1]. LGG can be classified as astrocytoma and oligodendroglioma based on 1p/19q co-deletion and isocitrate dehydrogenase (IDH) mutational status, according to the 2016 WHO tumor classification [2]. Oligodendroglioma has reported to have longer survival than astrocytoma [3], and 1p/19q co-deletion is also associated with longer survival and is a predictive marker for response to chemotherapy [4–6]. Because of the improved prognosis of oligodendroglioma, differentiation between astrocytoma and oligodendroglioma is important for clinical management.

Clinically, it is difficult for neuroradiologists to accurately discriminate between astrocytoma and oligodendroglioma based on visual assessment, although features such as “indistinct borders,” T2-FLAIR mismatch, and calcifications have been described [7,8]. Furthermore, clinical assessment is often qualitative and subjective, which can result in marked variability depending on radiologists' experience and expertise. MRI images are digital, composed of a series of two dimensional pixels, and contain different image features, which refer to the appearance, structure and arrangement of the parts of an object within an

* Corresponding author at: W. Zhu, Department of Radiology, Tongji Hospital, 1095# Jiefang Avenue, Wuhan 430030, China.
** Corresponding author at: I. Kovanlikaya, Department of Radiology, Weill Cornell Medicine, 407 E 61st Street Suite 107, New York, NY 10065, USA.
E-mail addresses: zhuwenzhen8612@163.com (W. Zhu), ilk2002@med.cornell.edu (I. Kovanlikaya).

https://doi.org/10.1016/j.mri.2018.11.008
Received 19 July 2018; Received in revised form 24 October 2018; Accepted 17 November 2018

image [9]. Texture analysis is in principle a quantitative technique for evaluating the position and intensity of signal features in MRI images. Textural features are, in fact, mathematical parameters computed from the distribution of pixels, which characterize the texture type and thus the underlying structure of the objects shown within an image, including six main categories: histogram, gradient, run-length matrix (RLM), co-occurrence matrix (COM), auto-regressive model (ALM), and wavelets [9]. Although some of the features can be evaluated qualitatively, most of them remain imperceptible to human visual assessment. Histogram analysis alone can represent a gray level distribution without spatial information and is a preferable quantitative ROI analysis method in previous clinical studies in describing tumor heterogeneity, guiding tumor classification and assessing progression [10–12]. Recently, texture analysis has been widely used in different fields and has shown promising results in differentiating brain glioma grading [13–15], tumor phenotype and overall survival prediction [16–20]. We hypothesized that textural parameters could be useful in identifying different pathological subtypes of glioma using conventional MRI images.

The purpose of this study was to evaluate the feasibility of a clinically implementable texture analysis on preoperative MRI conventional images (T2w FLAIR, ADC, T1w and post-gadolinium T1w (T1w + Gd)) to discriminate between astrocytoma and 1p/19q codeleted oligodendroglioma. We further compared the accuracy of this texture analysis to histogram analysis alone.

2. Material and methods

2.1. Patient selection

This retrospective study was approved by our local institutional review board, which waived written informed consent. 95 patients with low grade glioma were consecutively identified from June 2000 to December 2017. The inclusion criteria were: (1) Pathologically-proven (after resection or biopsy) grade II astrocytoma or oligodendroglioma, based on morphologic and genetic analysis regarding IDH and 1p/19q codeletion status, according to the 2016 WHO tumor classification [2]; (2) a pre-operative MRI scan that included T2w FLAIR, ADC, T1w or T1w + Gd sequences.

54 patients were excluded either because of genetic testing unavailable (n = 37) or lacking sufficient preoperative MRI images for analysis (n = 17). Finally, 41 LGG patients [21 astrocytomas (16 IDH-mutant, 5 IDH-wildtype) and 20 oligodendrogliomas (19 IDH-mutant, 1 IDH-wildtype and all 1p/19q codeleted)] (Fig. 1) were included in this study (Table 1).

2.2. MRI protocol

All brain MRIs were performed on our clinical scanners (GE Signa HDxt 1.5 T and 3.0 T, GE SIGNA EXCITE 1.5 T). Parameters for T2w FLAIR are: field of view = 24 cm, TR = 10,000 ms, TE = 162 ms, TI = 2200 ms, flip angle = 90°, slice thickness = 3–5 mm, matrix = 256 × 192, pixel Bandwidth = 163. ADC maps were reconstructed from the DWI sequence, whose parameters are as follows: field of view = 24 cm, TR = 10,500 ms, TE = 102 ms, flip angle = 90°, slice thickness = 5 mm, matrix = 128 × 128, pixel Bandwidth = 1421, *b*-values = 0, 1000 s/mm^2. Image parameters for T1w and T1w + Gd are: field of view = 24 cm, TR = 367 ms, TE = 15 ms, flip angle = 90°, slice thickness = 3–5 mm, matrix = 288 × 192, pixel Bandwidth = 61.

2.3. Texture analysis

Texture analysis was performed using open source MaZda software (version 4.6.0, Institute of Electronics, Technical University of Lodz, Lodz, Poland, http://www.eletel.p.lodz.pl/programy/mazda/) [21,22]. Patients were randomly divided into training (60%) and testing sets (40%). A flowchart about patient grouping and the texture analysis procedure is shown in Fig. S1.

Tumors were manually segmented on each image slice of the entire tumor on T2w FLAIR images by a neuroradiologist (six years of experience) and reassessed by another senior neuroradiologist (20 years of experience), then overlaid onto the other co-registered images (ADC, T1w and T1w + Gd). Any cystic or necrotic parts of the tumor were excluded. All image analyses were performed on preoperative MRI images. The number of image slices within the tumor ranged from 2 to 14 (mean 7.7).

2.3.1. Training data set

All segmented ROIs for each image slice on T2w FLAIR, ADC, T1w and T1w + Gd images were loaded into the MaZda package to perform texture analysis; as many as 279 features were generated within each ROI. These texture features were derived from 6 different statistical image descriptors: histogram features, gradient features, run-length matrix (RLM), co-occurrence matrix (COM), autoregressive model (AR),

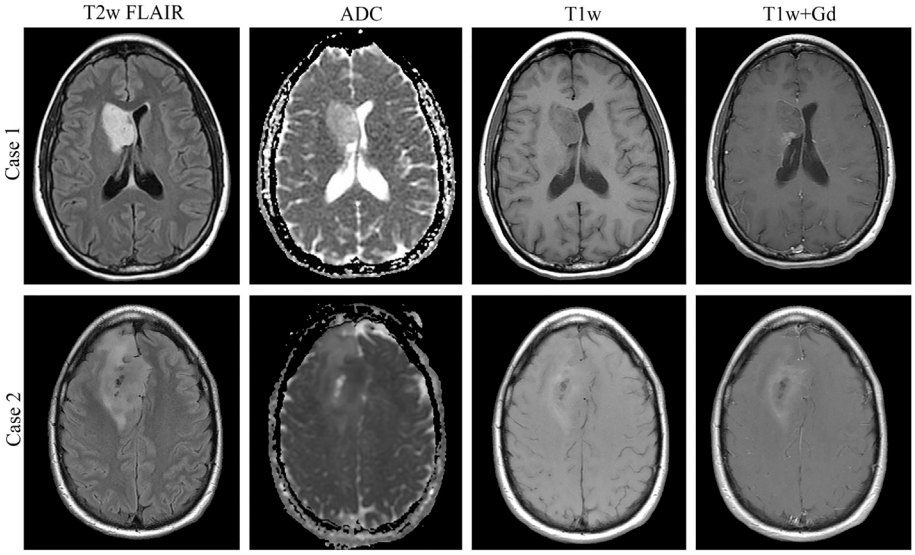

Fig. 1. Case 1 (top row): A 36-year-old female patient with astrocytoma (WHO grade II, IDH-mutant, 1p/19q intact) centered in the right caudate head. Case 2 (bottom row): 28-year-old female patient with oligodendroglioma centered in the right frontal lobe (WHO grade II, IDH mutant, 1p/19q codeleted).

Table 1
Patient characteristics and demographics.

	Astrocytoma	1p/19q Codeleted oligodendroglioma
Number of subjects with each sequence (T2w FLAIR/ADC/T1w/T1w + Gd)	21 (21/17/13/21)	20 (20/10/9/20)
Gender (M/F)	9/12	10/10
Age (years, mean ± SD)	36.33 ± 18.19	40.15 ± 12.04
IDH status (Mutant/Wildtype)	16/5	19/1

and wavelet transform. A detailed description of these textural features can be found in previous literature [22]. Before texture analysis, image intensities were normalized between μ ± 3σ (μ indicates the mean value of the gray levels within the ROI; σ the standard deviation); the range obtained was quantized to 6 bits/pixel. This procedure, used by previous studies [23–26], has proven to reduce brightness and contrast variations, and minimize the influence of inter-scanner as well as field strength differences, in order to generate ideal classifications. Since analyses on all 279 textures features are clinically impractical, the MaZda software provides three feature reduction algorithms: mutual information (MI), Fisher coefficient (F), and classification error probability and average correlation coefficients (POE + ACC, PA). Each algorithm determined 10 best distinguishable texture features resulting in a combined total of up to 30 top-ranked features for further analysis. These 30 features were then loaded into the statistical B11 texture analysis package; a linear discriminant analysis (LDA) model with the lowest misclassification rate was selected to obtain the most discriminant factor (MDF) values [27]. The values of the 9 histogram parameters (mean, variance, skewness, kurtosis, 1st percentile, 10th percentile, 50th percentile, 90th percentile, and 99th percentiles) were separately saved as histogram features (one of 6 different statistical image descriptors used for texture analysis), in order to compare with texture analysis.

Receiver operating characteristic (ROC) curves were performed on the generated MDF values and the 9 histogram parameters for each image slice using SPSS for Windows (version 19.0, Chicago, IL). The area under the curve (AUC) and the optimal cutoff values from the maximum Youden index, as well as the corresponding sensitivities and specificities were obtained from ROC curve analysis. The MDF values of the two groups were compared using independent sample *t*-tests, and a $p < 0.05$ was recognized as significant.

2.3.2. Testing data set

ROIs for T2w FLAIR, ADC, T1w and T1w + Gd images in the testing data were loaded into the MaZda software and processed in the same way as the training data in order to generate the 279 features. None of the images from the training data set were used in the testing data analysis. The same 30 features as in the training data were selected and loaded into the B11 analysis package, and the same LDA model was used to generate the MDF values for each image slice. The MDF values and 9 histogram parameters were used to classify the testing samples into a specified group (astrocytoma or 1p/19q codeleted oligodendroglioma) based on the optimal cutoff value predefined in the training data. A correct rate of discriminating two groups was consequently determined. Using the equation below, as in a previous study [27], the computed weighed values of MDF and histogram parameters on multiple image slices for each tumor were also tested on the predefined cutoff value to define an accuracy of discriminating two groups.

$$\bar{x} = \frac{w_1x_1 + w_2x_2 + \ldots + w_nx_n}{w_1 + w_2 + \ldots + w_n}$$

where $\bar{x}$ is the overall weighted mean value for each parameter, w_1 is the area of the first ROI, x_1 is the mean value of the first ROI, w_2 is the area of the second ROI, x_2 is the mean value of the second ROI, and so forth.

Post hoc, an exploratory analysis was performed to determine whether combining MR sequences, i.e. ADC and T1w, could further improve accuracy of the texture analysis.

3. Results

Detailed group information for the T2w FLAIR, ADC, T1w and T1w + Gd sequences is shown in Fig. S1 flowchart.

In the training data set, the MDF values generated from the LDA model when performing B11 analysis were significantly different between astrocytoma and 1p/19q codeleted oligodendroglioma (all $p < 0.001$). The ROC analyses on these MDF values resulted in an AUC of 0.91 (95% CI, 0.87–0.96) for T2w FLAIR, 0.94 (95% CI, 0.90–0.97) for ADC, 0.98 (95% CI, 0.95–1.00) for T1w, 0.88 (95% CI, 0.83–0.93) for T1w + Gd., and with corresponding high sensitivities and specificities. The MDF from texture analysis outperformed all the other histogram parameters, which had lower AUC, sensitivity, and specificity. In the testing data set, using the same cutoff MDF value generated in the training data set, we found high accuracies for both individual MDF on each image slice and weighted MDF on all image slices for the whole volume. These results also had higher accuracies than histogram parameters (Fig. 2, Table 2, and S1–S4).

An exploratory analysis combining the ADC and T1w sequences (Fig. S2, Table S5), did not significantly improve the performance of the texture analysis. The MDF value resulted in an AUC of 0.82 (95% CI, 0.76–0.87, sensitivity75%, specificity72%). In the testing data set, the accuracy was 77% (123/159) for individual image slices, and 70% (14/20) for the weighted MDF value of the whole tumor.

4. Discussion

Our study demonstrated that texture analysis performed on conventional preoperative MRI images has high sensitivity, specificity, and accuracy in discriminating between astrocytoma and 1p/19q codeleted oligodendroglioma. Texture analysis also outperformed all of the histogram parameters. In summary, it can predict underlying pathology and aid in clinical decision-making.

Texture analysis is becoming a significant contributor to image quantification for more accurate, reliable and objective medical diagnoses. It enables the quantification of gray level patterns, pixel interrelationships, and description of the variation in intensity within a specific area, as most of these features remain imperceptible to visual assessment [9,28]. In this current study, we performed texture analysis based on an overall discriminator MDF by analyzing the 30 top ranked features, instead of each individual feature. The texture analysis-based MDF, which provides a more comprehensive evaluation of MRI images, obtained better results than every histogram parameter, which has been used as a quantitative method in various glioma studies [10,12,29,30]. Although MRI exams of the patient cohort were performed on different scanners, we used a normalized procedure to reduce the variations in brightness and contrast, which could minimize the influence of inter-scanner and field strength differences.

In clinical radiological practice, astrocytomas are usually associated with the presence of moderate to extensive peri-tumoral edema, a lack of ventricular distortion, and a T1w isointense or hyperintense signal, while oligodendroglioma tends to be T1w hypointense, more common to have ventricular distortion, calcification, and has more possibility to locate in cortical or subcortical areas [31]. Additionally, in contrast to

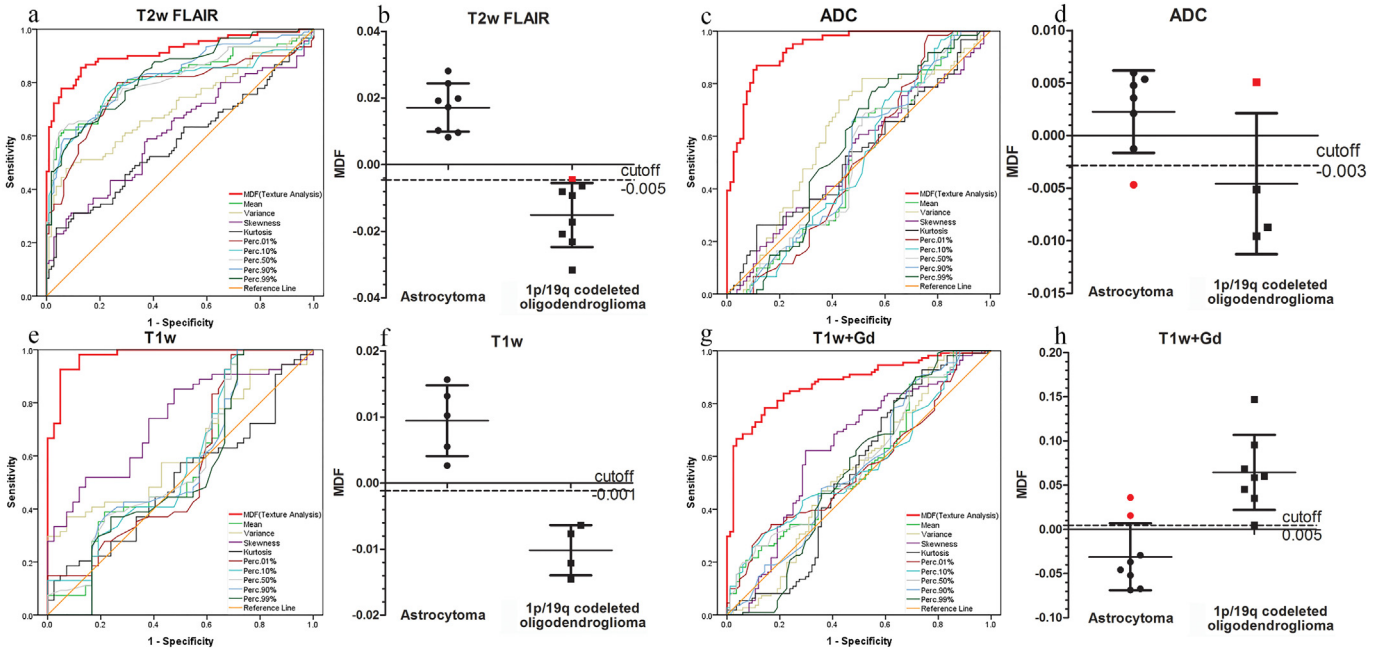

Fig. 2. a, c, e, g: ROC curves performed on texture analysis-based MDF and 9 histogram parameters (mean, variance, skewness, kurtosis, 1st percentile, 10th percentile, 50th percentile, 90th percentile, and 99th percentile) of different MRI sequences to discriminate between astrocytoma and 1p/19q codeleted oligodendroglioma. The area under the curve (AUC) of MDF (red solid line) outperformed the other 9 parameters (dotted lines). b, d, f, h: The results of using MDF cutoff values obtained from ROC analysis on training data to test the weighed value within each tumor in the testing data set. 1 out of 16 cases using T2w FLAIR, 2 out of 11 cases using ADC, 2 out of 16 cases using T1w + Gd, which are showed in red, were misclassified, and all the cases were correctly classified using T1w, using the same training set cutoff value for differentiating between astrocytoma and 1p/19q codeleted oligodendroglioma. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

astrocytomas, minimal enhancement and moderately increased perfusion is seen in oligodendrogliomas. Recent studies have also shown that 1p/19q co-deletion status has discriminative MRI features; for example 1p/19q codeleted oligodendroglioma has poorly circumscribed borders and is heterogeneous in signal intensity [7,8]. However, marked variability exists between observers [7,31–33]. The promising results of this quantitative texture analysis suggests that it can serve as an additional imaging biomarker for predicting the histological subtypes of LGG. Our results show that texture analysis based on T1w images acquired a relatively higher AUC than the other three sequences. This implies that T1w images contain even more potentially valuable information within an image. This could be explained by the fact that T1 relaxation times have the largest range in different tissue types, providing the best contrast resolution, and, with the help of texture analysis, more informative data can be extracted from them. T1w + Gd, which is valuable for evaluation of tumor enhancement, had the lowest AUC. For LGGs, both astrocytoma and oligodendroglioma usually have no or mild enhancement, so the injection of gadolinium may reduce the internal intrinsic contrast within the tumor. However, this needs to be further elucidated. While a prior study suggested that ADC could not differentiate between WHO Grade II astrocytomas and oligodendrogliomas [34], in our texture analysis, ADC was found to have one of the highest AUC values (0.94) and provide 82% accuracy using weighed MDF values. This may be due to texture analysis using more "features" of ADC, rather than just a single mean ADC value.

In general, texture analysis provides us with an effective way to predict the histological subtypes of LGG, which is not only of diagnostic but also predictive of therapeutic response and prognostic for survival. Furthermore, MaZda is a web based free-available texture analysis software package compiled for PC computers, which can be easily implemented in the clinic without additional professional technical input. Consequently, this may serve as an alternative method in routine clinical surveillance of LGG, particularly since molecular testing of glioma remains costly and not yet routinely available around the world.

Several limitations in our study deserve mention. First, texture analysis was performed based on individual image slice rather than the whole volume analysis, due to small sample size. Future studies including more cases and performing three dimensional volume analysis, which might reflects the features of entire tumor heterogeneity, will improve the reliability of texture analysis. Second, our texture analysis is based on a retrospectively collected data, future studies evaluated in a prospective way would enhance our findings.

In conclusion, texture analysis performed on conventional preoperative MRI images can accurately predict the histological subtypes of LGG, which may guide the clinical decision making.

Table 2
ROC results of texture analysis based MDF to discriminate between astrocytoma and 1p/19q codeleted oligodendroglioma.

MDF	Astrocytoma	Oligodendroglioma	AUC	Sensitivity	Specificity	Accuracy on testing data*	Accuracy on testing data**
T2w FLAIR	$(2.52 \pm 2.97) \times 10^{-2}$	$(-2.08 \pm 1.64) \times 10^{-2}$	0.91(0.87–0.96)	86%	87%	84%, 113/134	94%, 15/16
ADC	$(8.72 \pm 0.01) \times 10^{-3}$	$(-0.11 \pm 8.22) \times 10^{-3}$	0.94(0.90–0.97)	87%	89%	88%, 70/80	82%, 9/11
T1w	$(3.19 \pm 2.36) \times 10^{-2}$	$(-4.10 \pm 2.70) \times 10^{-2}$	0.98(0.95–1.00)	93%	95%	92%, 73/79	100%, 9/9
T1w + Gd	$(-1.25 \pm 1.27) \times 10^{-1}$	$(0.80 \pm 1.41) \times 10^{-1}$	0.88(0.83–0.93)	78%	86%	81%, 106/131	88%, 14/16

*, Accuracy evaluated on individual image slices of testing data using the cutoff value generated from the training data; **, Accuracy evaluated on the weighted value of all image slices for the whole volume of each tumor. AUC: area under the curve.

Funding

This work was supported by the National Institutes of Health of United States (R01 NS095562, R01 NS090464) and National Natural Science Foundation of China (81730049, 81801666).

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mri.2018.11.008.

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