Quantitative Glioma Grading Using Transformed Gray-Scale Invariant Textures of MRI

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Abstract

Background: A computer-aided diagnosis (CAD) system based on intensity-invariant magnetic resonance (MR) imaging features was proposed to grade gliomas for general application to various scanning systems and settings.

Method: In total, 34 glioblastomas and 73 lower-grade gliomas comprised the image database to evaluate the proposed CAD system. For each case, the local texture on MR images was transformed into a local binary pattern (LBP) which was intensity-invariant. From the LBP, quantitative image features, including the histogram moment and textures, were extracted and combined in a logistic regression classifier to establish a malignancy prediction model. The performance was compared to conventional texture features to demonstrate the improvement.

Results: The performance of the CAD system based on LBP features achieved an accuracy of 93% (100/107), a sensitivity of 97% (33/34), a negative predictive value of 99% (67/68), and an area under the receiver operating characteristic curve (Az) of 0.94, which were significantly better than the conventional texture features: an accuracy of 84% (90/107), a sensitivity of 76% (26/34), a negative predictive value of 89% (64/72), and an Az of 0.89 with respective p values of 0.0303, 0.0122, 0.0201, and 0.0334.

Conclusions: More-robust texture features were extracted from MR images and combined into a significantly better CAD system for distinguishing glioblastomas from lower-grade gliomas. The proposed CAD system would be more practical in clinical use with various imaging systems and settings.

Keywords: brain tumor; glioma; computer-aided diagnosis; local binary pattern; magnetic resonance imaging

Introduction

According to the World Health Organization tumor classification of the central nervous system (CNS), diffuse gliomas can be subdivided into grades II (low malignancy) to IV (high malignancy) according to their degree of malignancy [1, 2]. Grade II and III tumors are lower-grade gliomas (LGGs) with more-favorable outcomes [3]. Although there are several different subgroups among them, they still share many common histopathological and molecular signatures [2, 4]. In contrast, glioblastomas (GBMs) are the most malignant tumor type with a dismal prognosis despite advances in different therapeutic managements [5]. Conventionally, several pathological features, including mitotic activity, cytological atypia, neoangiogenesis, and tumor necrosis, are used to determine tumor grades. However, some of the criteria are not precise enough to prevent ambiguity in glioma grading [6, 7]. In addition, misgrading was reported in up to 30% of cases of diffuse gliomas, which resulted from heterogeneous expressions of aggressive cellular features with unguided surgical biopsies [7-11].

Magnetic resonance (MR) imaging (MRI) is the imaging method of choice for depicting tumors of the CNS. It can provide clear tissue contrasts and help estimate the malignancy of brain tumors [12-14]. In addition to conventional sequences, several physiological MRI techniques including diffusion-weighted imaging, MR spectroscopy, and perfusion-weighted imaging, have also been applied to differentiate LGGs from GBMs [15-18]. To avoid unnecessary operations and to facilitate more-accurate grading of diffuse gliomas in the CNS, the role of MRI cannot be overemphasized. Ryu et al. [15] performed a texture analysis on the corresponding apparent diffusion coefficient maps of MR diffusion-weighted images. Diffusion-weighted imaging is an imaging technique that uses

diffusion of water molecules (Brownian motion) to generate signals. Therefore, it is not anatomical imaging, and several important pieces of information related to gliomas, such as tumor necrosis, the blood-tumor-barrier, and angiogenesis, cannot be depicted by it. Kinoshita et al. [14] presented correlations between T2-weighted images and the genetic status of LGGs. However, biological features of glioma represented by T2-weighted images are limited and still underexplored.

With the development of image-processing techniques, computer-aided diagnosis (CAD) systems were proposed to quantify tumor characteristics on MR images and combine them with artificial intelligence classifiers. Then, CAD systems can estimate tumor types and grades [19-21] by means of a probability model. The efficient procedures and consistent results can provide reliable suggestions to radiologists. Errors due to overlooking certain aspects may be reduced during clinical examinations. However, most textural features used in distinguishing tissue differences are based on gray-scale pixel values on MR images [22]. In practical use, different MRI systems and settings generate images with various brightness distributions. Intensity variations affect texture analyses and result in different performances [21]. A previous study used multiple feature sets together to distinguish tumor types of glioblastomas [23]. Rather than using numerous features, this study proposed extracting textural features after intensity-invariant transformation to strengthen the ability to distinguish textural features. A local binary pattern (LBP) [24] was proposed to transform inherent gray-scale pixel values into binary values according to the local textural composition. The transformed LBP map takes relative correlations between adjacent pixels into consideration and therefore becomes intensity-invariant. The transformed textural features extracted from the LBP map can then be

compared to original textural features to show the improvement and the promising use in clinical examinations with various MRI systems and settings.

Materials and Methods

Patient information

The Cancer Genome Atlas (TCGA) and the Cancer Imaging Archive (TCIA)

The collected MRI datasets, including 34 GBM and 73 LGG patients, were from TCIA (http://cancerimagingarchive.net/) of the National Cancer Institute, a portal containing images of TCGA patients for image analysis. The materials and data provided by TCGA were used in compliance with all applicable laws, regulations, and policies for the protection of human subjects. All necessary approvals, authorizations, human subject assurances, informed consent documents, and approvals of institutional review boards were obtained [25]. All MR images used in this study were provided from three institutes: Henry Ford Hospital, Case Western Hospital, and Thomas Jefferson University Hospital.

In total, 34 GBMs (grade IV) and 73 LGGs (grades II and III) were included in the study. For LGGs, 33 oligodendrogliomas, 16 oligoastrocytomas, and 24 astrocytomas were included. Nineteen oligodendrogliomas were classified as grade II, and 14 cases were classified as grade III. Seven cases of oligoastrocytoma were classified as grade II, and nine cases were classified as grade III. For astrocytomas, four cases were classified as grade II, and 20 cases were classified as grade III. As a result, we had totals of 30 grade II and 43 grade III gliomas in the LGG group. More-detailed demographic features of the LGG and GBM groups are given in table 1.

Image analysis

Contrast-enhanced axial T1-weighted images were selected for analysis in this study. A board-certified neuroradiologist (K.H., with 12 years of experience), who was blinded to the clinical and histopathological information, selected the most representative 2D image of each tumor. Contour delineation of tumors was then manually performed using OsiriX in the selected contrast-enhanced T1WI. Pixels inside the defined tumor area were used for further feature analysis.

LBP features

Textural features are widely used in CAD systems to discriminate between benign and malignant tumors [26]. However, most texture analyses of image patterns based on the original gray-scale values are system-dependent [21]. The classification can only perform well when a specific scanning system is used. Different MRI scanning systems have various settings which may result in images with different brightness compositions. The brightness variability influences the reliability of textures interpreted by the gray-scales. It was not surprising that the 34 GBMs and 73 LGGs used in this experiment had various gray-scale distributions in image brightness (Fig. 1), because they were collected from three institutes: Henry Ford, Thomas Jefferson University, and Case Western Hospitals. To extract more-robust textural features, LBP transformation [24] was performed prior to texture extraction in the experiment.

Because medical images or natural images may have various intensity distributions due to various illuminance or machine settings, the brightness variability thus influences the reliability of textures interpreted by the gray-scales. LBP is an efficient operator to

describe local image patterns. The 1st order derivative between the central and its neighboring pixels is transformed as a binary representation. Depending on the computational efficiency, various textural features can be obtained in real-time for clinical diagnoses. This is the advantage of LBP compared to other methods such as the Gabor filter and wavelet transformation [27]. The LBP algorithm uses local contrast for an intensity-invariant transformation. That is, regardless of the kind of resolution an image has, as long as contrast (the difference between adjacent pixels) exists, a relative correlation can be calculated. Therefore, LBP is appropriate for application to images for intensity-invariant features. In the LBP transformation, an image pattern is defined in a local 3×3 mask with gray-scales of nine image pixels. To achieve invariance with respect to shifts in brightness, the processed pixel (central) is compared to the eight surrounding neighbors by subtraction (Fig. 2). If a neighbor pixel is greater than the central pixel, one is assigned. Otherwise, a zero value is assigned. Consequently, the neighborhoods are thresholded by the central pixel value into a binary pattern. Signed differences rather than the original gray-scale are not influenced by shifts in brightness and therefore are intensity-invariant.

Assigning different weights to neighbors with different orientations generates a representative value indicating different binary patterns using the following formula:

$$\mathrm{LBP} = \sum_{i=1}^{8} C \times 2^{i-1}; \qquad (1)$$

where *C* is the comparison result (1/0) between the central pixel and neighboring pixels, and *i* corresponds to the orientation in Fig. 2. After the LBP transformation, the resulting image (Fig. 3) is regarded as intensity-invariant. Therefore, extracting image features from it can be variation resistant.

LBP intensities inside the tumor area are regarded as a probability function and are shown as a histogram. The histogram moment [28, 29] was then used to characterize the histogram shape for comparisons between LGGs and GBMs. The quantitative moment features included the first, second, third, and fourth order central moments of the histogram, i.e., the mean, variance, skewness, and kurtosis:

$$\text{Mean} = \frac{1}{N}\sum_{i=1}^{N} P_i, \quad (2)$$

$$\text{Variance} = \frac{1}{N}\sum_{i=1}^{N}(P_i - Mean)^2, \quad (3)$$

$$\text{Skewness} = \frac{1}{N}\sum_{i=1}^{N}(P_i - Mean)^3, \text{ and} \quad (4)$$

$$\text{Kurtosis} = \frac{1}{N}\sum_{i=1}^{N}(P_i - Mean)^4, \quad (5)$$

where P_i is the intensity value, and N is the number of pixels. The mean is the distribution center obtained by summarizing all intensities and dividing the sum by the number of pixels. Variance measures the level of spread of the intensity values, while skewness calculates the symmetricity of a distribution to determine whether it is biased to one side. Kurtosis is a metric describing a single-peak shape with heavy weight in the tails by comparison to a normal distribution. In addition to moment features, textural features describing correlations between adjacent pixel values were also extracted from the LBP for tumor characterization. The textures based on the gray-level co-occurrence matrix (GLCM) are described below.

GLCM Textures

Various CAD systems have used GLCM textures to describe image patterns for tumor classification. The matrix formulates co-occurrence frequencies of two adjacent pixels (i and j) to present correlations at different distances, d, and directions, θ [30, 31].

Establishing a matrix from an image G with reduced intensity bins reduces the computational complexity. In the experiment, a distance d=1 and four directions of θ=0°, 45°, 90°, and 135° were used to take all combinations together into consideration. Co-occurrence in the GLCM indicates whether two adjacent pixels have a correlation between them. Consequently, four directions are enough to express all conditions. For example, 0° of a pixel can be regarded as 180° of the other pixel. The following formulas are the GLCM textural features proposed in this study:

Autocorrelation = $$\sum_i \sum_j (p_x - \mu_x)(p_y - \mu_y) \Big/ \sigma_x \sigma_y \quad (6)$$

Contrast = $$\sum_n n^2 \left\{ \sum_i \sum_j p\,(i,j) \right\}, |i-j| = n \quad (7)$$

Correlation = $$\frac{\sum_i \sum_j (i-\mu_x)(j-\mu_y) p(i,j)}{\sigma_x \sigma_y} \quad (8)$$

Cluster prominence = $$\sum_i \sum_j (i + j - \mu_x - \mu_y)^4 p(i,j) \quad (9)$$

Cluster shade = $$\sum_i \sum_j (i + j - \mu_x - \mu_y)^3 p(i,j) \quad (10)$$

Dissimilarity = $$\sum_i \sum_j p(i,j)|i-j| \quad (11)$$

Energy = $$\sum_i \sum_j p(i,j)^2 \quad (12)$$

Entropy = $$-\sum_i \sum_j p(i,j) \log(p(i,j)) \quad (13)$$

Homogeneity = $$-\sum_i \sum_j \frac{1}{1+i-j} p(i,j) \quad (14)$$

Difference variance = $$\sum_i i^2 p_{x-y}(i) \quad (15)$$

Difference entropy = $$-\sum_i p_{x+y}(i) \log(p_{x+y}(i)) \quad (16)$$

Information measure of correlation = $$\frac{HXY - HXY1}{max\{HX, HY\}}$$
$$HXY = (8),$$
$$HXY1 = -\sum_i \sum_j p(i,j) \log(p_x(i) p_y(j))$$
$$HX = entropy\ of\ p_x, \quad (17)$$

$HY = entropy\ of\ p_y$

Inverse difference normalized = $$\sum_i \sum_j \frac{1}{1+|i-j|} p(i,j) \quad (18)$$

Inverse difference moment = $$\sum_i \sum_j \frac{1}{1+(i-j)^2} p(i,j) \quad (19)$$

where μ_x, μ_y, σ_x and σ_y are the mean and standard deviation (SD) of the marginal distributions of $p(i,j|d,\theta)$.

$$\mu_x = \sum_i i \sum_j p(i,j), \mu_y = \sum_j j \sum_i p(i,j) \quad (20)$$

$$\sigma_x^2 = \sum_i (i-u_x)^2 \sum_j p(i,j), \sigma_y^2 = \sum_j (j-u_y)^2 \sum_i p(i,j) \quad (21)$$

Statistical analysis

The proposed LBP features were individually tested to verify whether they could be used to distinguish between LGG and GBM tumors. The Kolmogorov-Smirnov test [32] was first used to determine their normalities. Student's *t*-test [32] was then used to evaluate features with normal distributions, while others were evaluated by the Mann-Whitney U-test [32]. Significant features were those with p values of < 0.05.

With respect to the ability to combine LBP features, a binary logistic regression was used as the classifier. Taking the biopsy-proven pathology as the gold standard, backward elimination evaluated the relevance of features so that redundant features could be excluded. Feature selection ceased when the smallest error rate was achieved. The generalizability of the selected features was validated via leave-one-out [32]. In each validation iteration, one case was picked from the acquired cases and used to test the trained model based on the remaining n-1 cases. After classification, each case was given a probability as the likelihood of being a GBM. A case with a probability of ≥ 0.5 was considered to be a GBM in the experiment.

Performances of LBP features were compared to conventional GLCM features on five performance indices: accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). With different thresholds, the corresponding sensitivities and specificities were calculated and illustrated using a receiver operating characteristic (ROC) curve. Az, the area under the ROC curve, was calculated to evaluate the overall performance using ROCKIT software (C. Metz, University of Chicago, Chicago, IL, USA). A Chi-squared test in SPSS software (vers. 16 for Windows; SPSS, Chicago, IL, USA) was used to compare performance indices.

Results

Table 2 shows the significant LBP features tested by either Student's *t*-test (with a normal distribution) or the Mann-Whitney U-test (with a non-normal distribution) and the corresponding *p* values. After combining relevant features in a classifier, the performance of LBP features achieved an accuracy of 93% (100/107), a sensitivity of 97% (33/34), a specificity of 92% (67/73), and an Az of 0.94. All performance indices were better than conventional GLCM features (Table 3). The performance results were generated by the logistic regression classifier after feature selection using backward elimination. In particular, differences in accuracy, sensitivity, NPV, and Az were statistically significant (all p values < 0.05). A comparison of ROC curves is illustrated in Fig. 4. Especially for sensitivity, eight GBMs misclassified by conventional GLCM features were correctly classified by LBP features. Taking the grade 4 case in Fig. 1d as an example, using LBP features, the malignancy estimation improved from 2% to 100%.

Discussion

A biopsy is the gold standard of clinical cancer diagnoses. However, the invasive procedure is not appropriate for some kinds of tumors such as brain tumors. Up to 30% of diffuse gliomas can be misgraded, which is caused by the heterogeneous composition of aggressive cellular tissues. To avoid unnecessary operations and provide more-accurate grading of diffuse gliomas, the role of MR images cannot be depreciated. The gray-scale brightness and contrast of image pixels are helpful in distinguishing different tissues and estimating the malignancy of brain tumors. The assistance provided by CAD systems can also improve the accuracy and efficiency of diagnoses. However, textural features which are widely used in CAD systems are easily affected by brightness variations caused by imaging parameters.

Previously, after LBP transformation, texture descriptors were used to describe images of brain MR volumes for an image retrieval system [33]. LBP features are also used to represent salient micro-patterns in mammographic mass detection [34]. Rather than using LBP descriptors introduced in the previous literature, this study extracted GLCM features from LBP-transformed images and compared them to pure GLCM features. The results showed that LBP transformation is useful in combination with other texture calculation to extract intensity-invariant features. The LBP transformation uses relative differences between a pixel and its adjacent neighbors. Therefore, the local texture of MR images can be expressed in an intensity-invariant form. Quantitative image features, including the histogram moment and textures, were then extracted from the LBP to reduce intensity variations caused by different scanning settings. As shown in Table 2, nine features obtained a statistically significant difference in distinguishing LGGs and GBMs.

Benefitting from the complementary power of various features, the prediction model established by the logistic regression classifier achieved an accuracy of 93% (100/107) and an Az of 0.94, which were both significantly better than conventional features (an accuracy of 84% (90/107) and an Az of 0.89) with respective *p* values of 0.0303 and 0.0334 (Table 3). The previous literature showed that a CAD system based on intensity histograms and GLCM features obtained accuracies of 87%~89% in classifying different types of brain tumors [23] from two hospitals. In this study, the accuracy of conventional GLCM features achieved an accuracy of 84% which is close to that reported in the previous literature. However, the collected database was from three hospitals with various MRI systems and settings as shown in Table 4, and thus would be a greater challenge to classify.

By means of an LBP transformation, LBP features improved the accuracy from 84% to 93%. This improvement was significant (p = 0.0303) and can deal with various combinations of settings for generating images. To the best of our knowledge, this is the first study using LBPs for glioma grading. Results in the previous literature [23] using multiple MRI textural features for tumor extents in glioblastoma were compared to that of the proposed method as shown in Table 5. The success of the LBP may be due to its methodology using relative pixel value differences rather than absolute pixel values. This behavior imitates what radiologists do on clinical examinations. Each time, a radiologist only focuses on one image without considering other cases, thus the observation depends on the relative presentation of image pixels in the tumor area. Whether CAD systems can be practically applied to clinical use, their diagnostic performances as verified by cases from multiple sources such as multiple centers are relevant and need to be considered.

A previous study used multiple feature sets together to distinguish brain tumor types [23]. Time-consuming computations were involved, and the dimensions of the feature space needed to be further reduced. This study proposed a more-efficient way to enhance features. LBP transformation was proposed to enhance relative correlations between adjacent pixels to became intensity-invariant. The texture features extracted with LBPs were then strengthened to achieve an accuracy of 93% with a limited number of 107 cases.

Intensity variations that exist between images obtained from different scan settings can thus be reduced via the LBP transformation, and textural features thus had a better performance. The limitation of the experiment is that too many different settings existed among images obtained from the three hospitals. We can only verify the effect of individual settings on textures in future experiments. Another aspect for a future study is that more-complete MR sequences would be helpful in predicting tumor grades. This study only used contrast-enhanced T1WIs which have a weakness of peritumoral edema not possibly being clearly demonstrated. However, necrosis and/or angiogenesis are key histopathological determinants for differentiating grade II and III from grade IV gliomas. Necrosis is an area of a unenhanced region within the tumor with a signal resembling that of cerebrospinal fluid and can always be clearly depicted in contrast-enhanced T1WIs [13]. In addition, the activity of the angiogenesis module within the tumor was proven to be associated with the degree of contrast enhancement [35, 36]. Therefore, we believe that measurements of signal intensities on contrast-enhanced T1-weighted images can be key determinants for differentiating GBMs from LGGs. However, further investigations of the role of other MRI sequences like fluid-attenuated inversion recovery, diffusion-weighted imaging, perfusion-weighted imaging, and MR spectroscopy are warranted. Also, whether LBPs can be

successfully applied to these images to obtain intensity-invariant textural features needs to be explored. The methods of MR image reconstruction would also be helpful in extracting more quantitative features from the three-dimensional volume for subsequent classification.

Conclusions

The LBP was introduced in this study to transform local textures in MR images into intensity-invariant ones. Compared to directly extracting textural features, features extracted with the LBP achieved a significantly improved accuracy from 84% to 93% in distinguishing LGGs and GBMs. Further validation of the proposed malignancy estimation model based on LBP features in different clinical cohorts is warranted.

Conflicts of Interest

The authors have no relevant conflicts of interest to disclose.

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Figure Captions

Fig. 1. Collected low-grade gliomas (a, b) and glioblastomas (c, d) with various gray-scale distributions in image brightness. (http://cancerimagingarchive.net/ - "License", the CC BY license (https://creativecommons.org/licenses/by/3.0/).

Fig. 2. A local binary pattern (LBP) was created by making comparisons between the processed pixel and its adjacent neighbors.

Fig. 3. Local binary pattern (LBP) transformation of (a) the tumor area in Fig. 1a and (b) the corresponding LBP. (http://cancerimagingarchive.net/ - "License" and the CC BY license (https://creativecommons.org/licenses/by/3.0/, tumor areas in this figure were extracted from original images).

Fig. 4. Comparison of receiver operating characteristic (ROC) curves illustrating trade-offs between the sensitivity and specificity of local binary pattern (LBP) features and conventional gray-level co-occurrence matrix (GLCM) features.

Table 1. Demographic features of low-grade glioma (LGG) and glioblastoma GBM) groups

	Age (years)	Gender	Tumor laterality	Tumor location	Histopathological subtypes
LGG	46.9 ± 12.7	Female: 44 Male: 39	Right: 43 Midline: 1 Left: 39	Frontal: 41 Temporal: 25 Parietal: 7	Oligodendrogliomas: 33 Oligoastrocytomas: 16 Astrocytomas: 24
GBM	64.2 ± 12.4	Female: 14 Male: 20	Right: 19 Left: 15	Frontal: 12 Temporal: 15 Parietal: 4 Occipital: 3	All GBMs

Table 2. Significant image features obtained from local binary pattern (LBP) transformation and corresponding *p* values generated by Student's *t*-test (normal distribution) or the Mann-Whitney U-test (non-normal distribution)

Feature	Low-grade gliomas		Glioblastomas		*p* value
	Mean±SD	Median	Mean±SD	Median	
Autocorrelation	1.61±0.42		1.43±0.28		< 0.05*
Correlation		0.84		0.71	< 0.001*
Cluster prominence	262.69±168.19		177.06±111.74		< 0.01*
Cluster shade	21.31±13.81		14.84±9.43		< 0.01*
Information measure of correlation	-0.58±0.07		-0.50±0.04		< 0.001*

Mean		11.24		3.87	< 0.001*
Variance		780.30		81.31	< 0.001*
Skewness		3.24		4.14	< 0.01*
Kurtosis		15.60		28.19	< 0.01*

* A *p* value of < 0.05 indicates a statistically significant difference.

Table 3. Performance comparisons between local binary pattern (LBP) features and conventional gray-level co-occurrence matrix (GLCM) features in distinguishing between low-grade gliomas and glioblastomas

	LBP	GLCM	*p* value
Accuracy	93% (100/107	84% (90/107)	0.0303*
Sensitivity	97% (33/34)	76% (26/34)	0.0122*
Specificity	92% (67/73)	88% (64/73)	0.4135
PPV	85% (33/39)	74% (26/35)	0.2698
NPV	99% (67/68)	89% (64/72)	0.0201*
Az	0.94	0.89	0.0334*

* A *p* value of < 0.05 indicates a statistically significant difference.

PPV, positive predictive value; NPV, negative predictive value; Az, area under the receiver operating characteristic curve.

Table 4. Representative magnetic resonance imaging (MRI) systems and settings of the collected database from three hospitals

	Henry Ford Hospital	Case Western Hospital	Thomas Jefferson University
MRI system	GE Signa HDxt	Siemens Avanto	Siemens Magnetom Vision
Magnetic field strength (T)	1.5	1.5	1.5
TE (ms)	13	2.81	3.5
TR (ms)	500	2160	7.6

Slice thickness (mm)	2.5	1	1.5
Flip angle	90	15	15
Field of view (mm)	240	250	280
Matrix	256×192	256×256	512×256
Contrast medium	Gadolinium-based contrast medium	Gadolinium-based contrast medium	Gadolinium-based contrast medium

Table 5. Performances of local binary pattern (LBP) and gray-level co-occurrence matrix (GLCM) features compared to those in the glioma-related literature

	LBP	GLCM	L.S. Hu [23]
Accuracy	93%	84%	85%
Sensitivity	97%	76%	85%
Specificity	92%	88%	85%
PPV	85%	74%	82%
NPV	99%	89%	88%

PPV, positive predictive value; NPV, negative predictive value.