Grading of Gliomas by Contrast-Enhanced CT Radiomics Features

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ABSTRACT

Background: Gliomas, as Central Nervous System (CNS) tumors, are greatly common with 80% of malignancy. Treatment methods for gliomas, such as surgery, radiation therapy, and chemotherapy depend on the grade, size, location, and the patient's age.

Objective: This study aimed to quantify glioma based on the radiomics analysis and classify its grade into High-grade Glioma (HGG) or Low-grade Glioma (LGG) by various machine-learning methods using contrast-enhanced brain Computerized Tomography (CT) scans.

Material and Methods: This retrospective study involved acquiring and segmenting data, selecting and extracting features, classifying, analyzing, and evaluating classifiers. The study included a total of 62 patients (31 with LGG and 31 with HGG). The tumors were segmented by an experienced CT-scan technologist with 3D slicer software. A total of 14 shape features, 18 histogram-based features, and 75 texture-based features were computed. The Area Under the Curve (AUC) and Receiver Operating Characteristic Curve (ROC) were used to evaluate and compare classification models.

Results: A total of 13 out of 107 features were selected to differentiate between LGGs and HGGs and to perform various classifier algorithms with different cross-validations. The best classifier algorithm was linear-discriminant with 93.5% accuracy, 96.77% sensitivity, 90.3% specificity, and 0.98% AUC in the differentiation of LGGs and HGGs.

Conclusion: The proposed method can identify LGG and HGG with 93.5% accuracy, 96.77% sensitivity, 90.3% specificity, and 0.98% AUC, leading to the best treatment for glioma patients by using CT scans based on radiomics analysis.

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Keyword

Radiomics; CT Scan; Glioma; Cancer; Neoplasms; Tumor; Machine Learning

Introduction

Gliomas, as Central Nervous System (CNS) tumors, are greatly common with 80% of malignancy [1]. In the United States, gliomas were diagnosed in approximately 6 out of every 10,000 individuals from 2000 to 2013 [2]. According to molecular data, the World Health Organization (WHO) classifies gliomas into four grades: grades I & II as Low-grade Glioma (LGG) and III & IV as High-grade Glioma (HGG) [3, 4]. The most common glioma is glioblastoma (Grade IV) with 15.1% and 46.1% of all primary and malignant brain tumors,

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respectively. The relative and median survival of high-grade glioma patients, depending on their age, is less than 15 months; patients with LGG have long-term survival [1].

Treatment methods for gliomas, such as surgery, radiation therapy, and chemotherapy depend on the grade, size, location, and the patient's age, in which surgery as the first step of treatment to remove the tumor is usually followed by radiation therapy and chemotherapy, especially in high-grade gliomas [5]. The grading of gliomas determines the treatment planning and evaluates treatment response and the prognostic patients [6].

However, the grading of gliomas as a fundamental factor affects the treatment plan, Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) may not precisely predict the grading of gliomas [7, 8]. The histopathological analysis as the current gold standard for grading gliomas depends on tumor biopsy methods [4], including open biopsies and stereotactic needle biopsies, in which needles are used for deeper brain tumors. Stereotactic, an invasive and high-risk method, leads to bleeding, brain swelling, seizures, stroke, infection, blood clots, reaction to anesthesia and sample errors, and variability in interpretation [9, 10].

However, some advanced techniques of MRI, such as Diffusion Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS), and perfusion have been recently used for grading gliomas, no methods have been definitively approved yet by WHO [11-13]. In addition, a long scan time in MRI is known as a major disadvantage due to motion artifacts. Another non-invasive method to decode the characteristics of tumors is radiomics, extracting non-visible features to quantify the properties of tumors [14]. The extracted features are classified into three statistical groups: 1) the first-order statistical methods to describe the distribution of values of individual voxels without spatial relationship (e.g. mean, median, maximum, minimum, skewness, flatness, and kurtosis), 2) the second-order statistical methods to describe "texture" features and statistical interrelationships between voxels with similar (or dissimilar) contrast values; the Texture Analysis (TA) potentially provides a promising imaging biomarker to assess the heterogeneity of tumors, and 3) higher-order statistical methods to impose filter grids on the image and extract repetitive or nonrepetitive patterns [15, 16]. Moreover, radiomics studies consist of data acquisition, segmentation, extraction and qualification of the features, and data analysis [16].

However, CT scans have more advantages over MRIs, including less time, more availability, and the possibility for patients, who use implantable medical devices, most of the studies have been conducted on MRI in radiomics [17].

The current study aimed to quantify glioma based on the radiomics analysis and classify its grade into HGG or LGG. Therefore, the radiomics approach was combined with various machine-learning methods using contrast-enhanced brain CT scans.

Material and Methods

This retrospective study consists of data acquisition, segmentation, feature selection and extraction, classification, analysis, and evaluation of classifiers.

Patient Selection and Population

This study was approved by the Ethics Committee of the Faculty of Medical Science, Mashhad University of Medical Sciences, Mashhad, Iran, and examined 130 patients who performed stereotactic biopsies from 2013 to 2019 in Mashhad, Imam Reza Hospital, Iran. All patients, who participated in this study, signed the informed consent. Further, the inclusion criteria for patients were as follows: 1) histopathologic diagnosis of gliomas grouped into LGGs and HGGs according to the WHO criteria and 2) CT images without any beam-hardening artifacts in the Region of Interest (ROI). The lack of pathological information

and CT scan images led to the exclusion of 35 and 26 patients from the study, respectively. Also, 7 patients were excluded due to beam hardening artifacts in the tumor area. Finally, 62 patients were included with 31 LGG and 31 HGG patients.

Image data acquisition

All patients underwent a brain contrast-enhanced CT scan using a 16-slice multi-detector CT scanner (Neusoft Medical System Co., Ltd, Shenyang, China, www.neusoftmedical.com), with the acquisition parameters as follows: axial scan mode, 120 kV, 180 mAs, detector collimation, 4×0.75 mm^2, and matrix size 512×512. Contrast-enhanced CT was performed after 5-7 min following intravenous administration of 90 mL of iodinated contrast medium (Iodixanol 652 mg/mL; Visipaque 320 mg I/mL; GE Healthcare Biosciences, Little Chalfont, UK). All CT scan images were obtained with the same scanner and protocol to reduce the influence factors on image intensity variation.

Tumor segmentation

In this study, the segmented tumor was performed by a 25-year experienced CT-scan technologist using 3D slicer software (version 4.10.2) and used for delineating tumor core Volume of Interest (VOI) in each patient. Some quantitative histograms and textural features were calculated on the selected VOI of each patient.

Feature extraction

The current study aimed to extract high-dimension features to describe quantitative attributes of VOI (16) by an open-source software Pyradiomics (available at https://www.radiomics.io/pyradiomics.html). Further, 14 shape features (e.g., surface area, elongation, and minor axis length), 18 histogram-based features, and 75 texture-based features were computed. The histogram-based features (first-order features) describe the distribution of voxel intensity in medical images, such as mean, median, min, max range, skewness, and kurtosis. Furthermore, texture-based features illustrate statistical intercorrelation between voxels with similar (or dissimilar) contrasts, which measure intratumoral heterogeneity, like the Gray Level Co-occurrence Matrix (GLCM), Gray Level Size Zone (GLSZM), and Neighborhood Gray Level Dependence Matrix (NGLDM).

Feature Selection

Feature normalization prevents some features from a greater or lower weight. Accordingly, a z-score normalization for feature values was used to uniform the range of each feature. On the other hand, feature selection results in removing redundant features and keeping important features for the next step.

In the present study, 13 out of 107 features, including 3 and 10 histogram and texture-based features, respectively, without any shape features were selected by Least Absolute Shrinkage and Selection Operator (LASSO) or L1 regularization to design models for HGG and LGG differentiations.

Model building

A total of 13 out of 107 features were used to avoid data overfitting in designing machine-learning classification models. Five classification algorithms, including Decision Tree, Discriminant Analysis, Logistic Regression, Support Vector Machine (SVM), and the k-nearest Neighbor (KNN) were applied to differentiate between HGG and LGG. Furthermore, pathological grading was applied as a golden standard to train the proposed supervised classification technique, implemented on the MATLAB R2017 platform.

Performance evaluation

The Area Under the Curve (AUC) and Receiver Operating Characteristic (ROC) curve were employed to evaluate and compare the performance of the classification models. Two

different cross-validation values, including the 5- and 10-fold cross-validation were used to validate models. For example, in the 5-fold cross-validation, the entire dataset was randomly separated into five subsets so that one subset was used as a testing set, and the others were used as a training set. The training-testing procedures were also repeated five times until each sample in the dataset was used as a training and testing sample. The accuracy, sensitivity, specificity, AUC, ROC of the prediction models, and confusion matrix were also evaluated in the current study.

Results

The tumor area was identified by contrast-enhanced CT scans, and the histogram and textural features were then extracted, in which the top 13 features from the LASSO feature-selection algorithm were considered significant (Table 1). Algorithms were classified into 3 different cross-validations, and each performance value was computed based on mean different cross-validation results to determine the best classifier algorithms between LGG and HGG.

A total of 107 features were extracted from selected VOIs, and Z-score was used to normalize features inserted into the LASSO feature selection algorithm to avoid overfitting and removing redundant features. Finally, 13 out of 107 features were selected to differentiate between LGGs and HGGs and perform various classifier algorithms with different cross-validations. In this study, 3 of the best group classifiers were presented so that the best classifier algorithm was linear-discriminant with 93.5% accuracy, 96.77% sensitivity, 90.3% specificity, and 0.98% AUC in differentiation LGGs and HGGs (Figures 1 and 2). Table 2 shows the best three classifier algorithms with 5- and 10-k-fold cross-validations.

Discussion

According to the findings of the current study, the proposed method can be considered a diagnostic aid for identifying LGG and HGG, and treatment of gliomas depends on the grade, size, type, and location of the tumor. However, the biopsy is known as the gold standard to diagnose a brain tumor and determine its grade, it is an invasive and high-risk method, leading to problems, such as bleeding, seizures, and long queues. However, some MRI techniques: MRS, Diffusion-weighted Imaging (DWI), and perfusion not only are non-invasive but also evaluate the histopathological features of gliomas, and determine the tumor grading, they are not available to all patients. Thus, in the current study, CT scans and radiomics techniques were used to determine tumor grade. To the best of our knowledge, no study has been conducted on glioma grading by radiomics using the CT scan.

Zacharaki et al. used MRI textural and shape features to classify brain tumors with 0.878 and

Table 1: Top 13 significant features selected by Least Absolute Shrinkage and Selection Operator (LASSO)

Type of Features		
First-Order Features (Histogram)	**Second-order Features (Textural)**	
Median	glcm_Contrast	glrlm_LowGrayLevelRunEmphasis
Skewness	glcm_ClusterShade	ngtdm_Complexity
Interquartile Range	glcm_InverseVariance	glrlm_LongRunEmphasis
	glszm_GrayLevelVariance	glrlm_ShortRunLowGrayLevelEmphasis
	glszm_LargeAreaEmphasis	glszm_GrayLevelNonUniformityNormalized

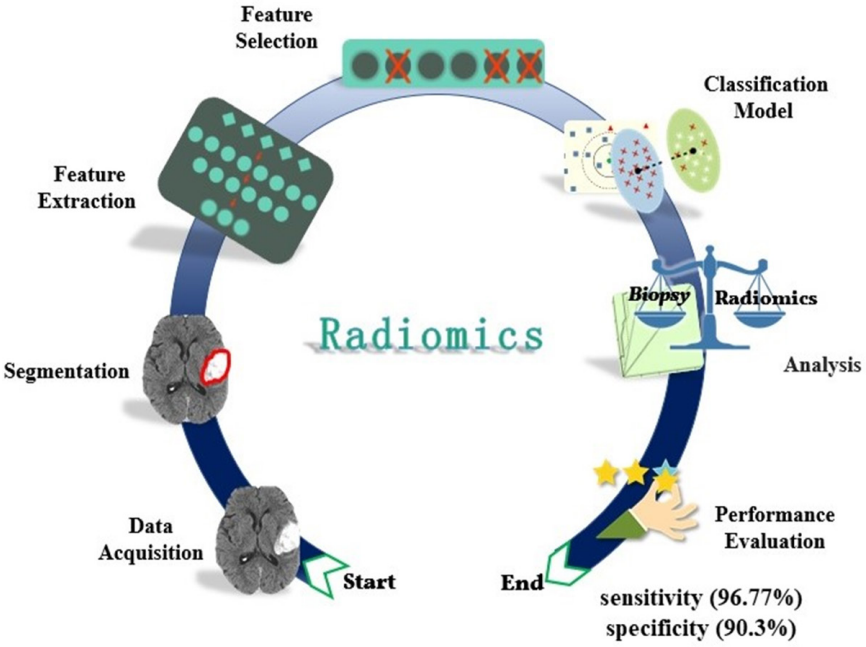

Figure 1: Workflow of study

0.896 accuracy and AUC, respectively, using SVM with a leave-one-out cross-validation, leading to overfitting while the current study reduced overfitting with various cross-validations [18]. Bonte et al. applied radiomics on structural MRI to differentiate between LGG and HGG with 84.5% accuracy on CT scan images obtained from different sources with various protocols, resulting in a high degree of noise in the ground-truth diagnosis [19]. In the present study, all CT scans were obtained from one medical imaging center with the same scan protocol. Ditmer et al. applied MRI texture analysis for glioma grading on 94 patients (14 LGGs and 80 HGGs) with 93% sensitivity, 86% specificity, and 0.90 AUC [15]; moreover, they studied two patient groups (14.8% and 85.2%) that this unbalanced data might lead to miss-diagnosis. In the present study, 2 groups of 31 patients were selected to avoid miss-diagnosis. Further, Zhang et al. classified HGG and LGG using radiomics features on DTI with an AUC of 0.93, 94% accuracy, 98% sensitivity, and 86% specificity by using SVM [20]. The textural features are the most common factor to classify glioma grading tumors using radiomics, considered in 77% of selected features of the present study.

The current study was conducted with some limitations, as follows: 1) the relatively small number of the patient; however, the cross-validation method was used to avoid overfitting, this study is still at risk of overfitting, 2) manual segmentation, which was time-consuming and susceptible to reader variability, and 3) the lack of CT-based radiomics study for glioma grading classification to compare the results.

Conclusion

According to the findings, the proposed radiomics-based technique with high sensitivity (96.77%) and specificity (90.3%) can provide a proper estimate of the tumor grade and also design a suitable treatment for patients who cannot undergo surgery. It is believed that the non-invasive radiomics method of CT imaging can be replaced by non-invasive

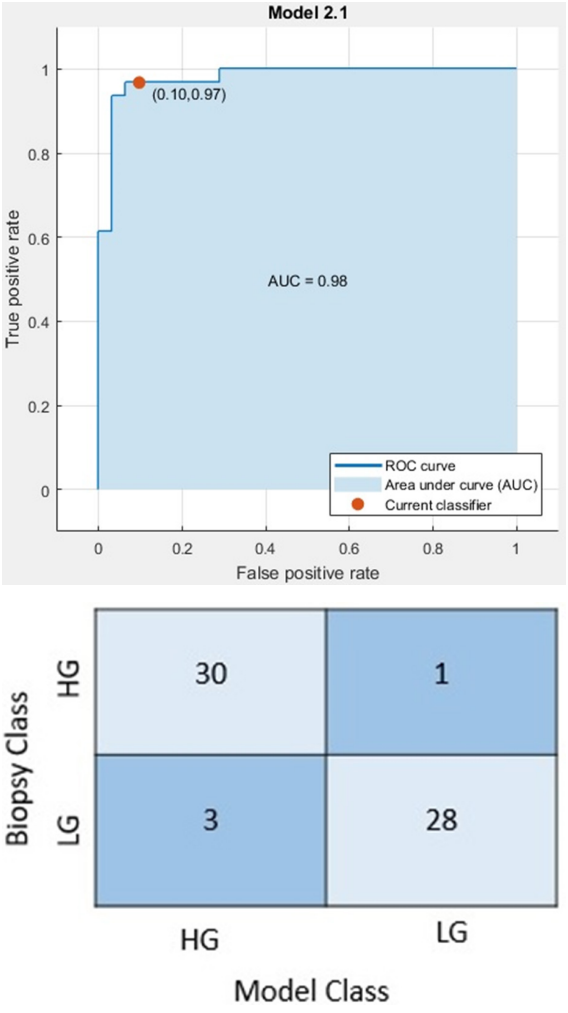

Figure 2: Linear discriminant classification confusion matrix and Receiver Operating Characteristic curve (ROC) curve with 5-fold cross-validation (High Grade (HG), Low Grade (LG))

methods in future studies.

Authors' Contribution

M. Maskani and A. Zamanpour did the study; H. Abdolahi analyzed the data; S. Abbasi wrote the article and checked the concept, H. Etemad-Rezae and A. Montazerabadi rechecked the whole of the study and analysis as supervisors. All the authors read, modified, and approved the final version of the manuscript.

Ethical Approval

This study was approved by the Mashhad Faculty of Medical Sciences with the code number: IR.MUMS.MEDICAL.REC.1399.055.

Informed Consent

All patients who participated in this study signed the informed consent.

Conflict of Interest

None

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Table 2: Classification of the performance

Model	k-fold	AUC	Accuracy	Sensitivity	Specificity
Linear Discriminant	5	0.98	93.5	90.9	96.5
	10	0.98	91.9	90.6	93.3
SVM	5	0.94	90.3	90.3	90.3
	10	0.98	88.7	85.2	92.8
KNN	5	0.87	87.1	87	87
		0.92	87.1	87.5	89.6

AUC: Area Under the Curve; SVM: Support Vector Machine; KNN: K-Nearest Neighbor

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