A Radiomic analysis approach of multiparametric MRI for Glioma grading

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Aims and objectives

Gliomas are the most aggressive primary brain tumors, presenting poor survival rates, while the accurate preoperative grade classification is of main clinical importance, related to early prognosis and precise selection of the therapeutic approach. According to the World Health Organization (WHO) grading system [1], gliomas are subdivided into four categories considering their malignancy status, i.e. grades I, II (low grade) and grades III, IV (high grade).

To date, several studies have reported that MRI may supportively contribute in tumor heterogeneity assessment, overcoming sample-biopsy limitations, towards glioma grading. Most of these studies consider either conventional [2] or advanced MRI sequences [3] individually, which provide different perspectives of gliomas pathophysiology. Usually, the proposed methods are complemented by advanced image analysis techniques, such as shape and texture analysis, for increasing diagnostic accuracy through the quantitative assessment of the spatial information provided by MRI.

Even though the specific findings seem promising, the increased methodological variability of the current MRI unilateral evaluation approaches, consequently resulting into conflicting sensitivity and specificity reports, could lead to a misinterpretation of gliomas' biological heterogeneity mechanisms.

As it has been mentioned from certain research studies exploiting multiparametric MRI (mp-MRI) data [4-5], the combination of several MRI parameters representative of the underlying pathophysiology, may lead to a better understanding of tumor characteristics, and a more accurate grade classification. Furthermore, the recent advent of Radiomics, considering novel approaches including advanced quantification and classification methodologies, which facilitate the manipulation and evaluation of multidimensional imaging feature data, may serve as a sophisticated analysis framework [6], in performing various clinical data associations (e.g. imaging, genomics) [7]. Hence, it is evident that in the precision medicine era, a plethora of quantitative parameters should be taken into consideration for an accurate tumor characterization. However, there is still a demand for further investigation on the validation and utility of combining such techniques, in order to establish a powerful non-invasive tool in clinical practice.

The aim of this study was to comprehensively evaluate 3T multiparametric glioma MRI data utilizing radiomic analysis, to provide imaging biomarkers of increased prognostic value for glioma grading. To our knowledge, this study is one of the very few [8-9] to incorporate conventional MR data accompanied by all the advanced MR neuroimaging techniques used in brain tumor evaluation, within a robust radiomic analysis pipeline.
Methods and materials

Multiparametric-MRI acquisition and Data post-processing:

Forty patients initially diagnosed with Low- or High-Grade Gliomas (20 LGG & 20 HGG) underwent MRI performed on a 3-Tesla MR whole-body scanner, applying an advanced imaging examination protocol including, conventional MRI (T1W-C, T2W-FSE, T2W-FLAIR), MR Spectroscopy (1H-MRS), Diffusion Tensor Imaging (DTI) and Dynamic Susceptibility Contrast Enhanced MRI (DSCE), using a 4-channel birdcage and an 8-channel phased-array head coil. Prior to this retrospective study, Local Institutional Review Board approval and patient informed consent was obtained (Fig. 1).

FSL software, was utilized for parametric MR volumes co-registering, re-slicing into an isotropic voxel size, and applying bias field corrections. DTI data post-processing was performed with FSL, including Eddy Current distortions correction, brain tissue extraction, Diffusion Tensor estimation and Mean Diffusivity (MD), Fractional Anisotropy (FA), Pure Isotropy (p) and Pure Anisotropy (q) parametric maps calculation. In-vivo SV data analysis and calculation of metabolite ratios were performed with GE Functool software. Post-processing of the raw spectral data included baseline correction, frequency inversion and phase shift. Gaussian curves were fitted to NAA, Cho, Cr, lipid and lactate peaks for determination of peak area. Finally, metabolite ratios of NAA/Cr, Cho/Cr, ml/Cr and Lipids/Cr were calculated from the area under each metabolite peak for each patient ROI separately. The Functool software was utilized for processing DSCE data. CBV maps were calculated for tumors' representative slices and the mean rCBV measurements were extracted from ROIs placed in areas of maximum contrast enhancement and their contralateral areas. In addition, gadolinium uptake time curves were also obtained for identifying the volume of contrast agent maximum uptake for every patient, which was utilized for textural features extraction.

Volume of Interest (VOI) extraction:

A k-medians clustering segmentation method based on DTI parametric maps, reported in our previous study [10], was implemented in Matlab 2015b for classifying the brain voxels of each patient into groups with similar isotropic and anisotropic diffusion properties, accounting for normal and tumorous brain tissue diffusivities. Specifically, k-medians clustering (k=16) is applied on a 2D histogram of p (isotropic) and q (anisotropic) components of the diffusion tensor, derived from all patient cohort. Subsequently, RGB color mapping of clusters according to the relative magnitudes of p, q and T2 values of the cluster centroids and subsequent color assigning to each individual patient’s brain voxels according to their position in the p-q space, results in whole brain segmented maps (Fig.2). These color-coded maps are based on the contouring provided by diffusion properties, being robust in displaying tissue microarchitecture, thus healthy and tumorous brain tissues present distinctive boundaries.
Finally, tumor core segments highlighted by the clustering technique, were delineated on colormaps by an experienced radiologist, and stacked up to form tumor VOI masks. Subsequently, these VOI masks where applied on the various co-registered multiparametric images of our dataset, resulting in a set of 3D parametric representations of the gliomas.

Radiomic Feature extraction:

Histogram analysis have considered 12 statistical features (minimum, percentile-25%, median, percentile-75%, maximum, range, mean, standard deviation, skewness, kurtosis, entropy, uniformity) acquired from normalized data histograms with MATLAB 2015b. Texture analysis was implemented in MaZda ver.5 software, considering 11 Gray-Level Co-Occurrence Matrix-based (angular second moment, contrast, correlation, sum of squares, inverse difference moment, sum average, sum variance, sum entropy, entropy, difference variance, difference entropy) and 5 Gray-Level Run Length Matrix-based features (short run emphasis, long run emphasis, gray level non-uniformity, run length non-uniformity, fraction), both calculated on 8-bit quantized images, and averaged over the 13 3D image directions, to obtain directionality independence measurements [11]. In summary, the quantitative radiomic features extracted from the eight 3D tumor parametric VOIs, regarding p, q, MD, FA, T1W-C, T2W-FSE, T2W-FLAIR and maximum gadolinium uptake volumes of DSCE MRI, along with the four metabolic ratios of 1H-MRS (Ch/Cr, NAA/Cr, ml/Cr, Lipids/Cr) and mean rCBV values, resulted in a total of 581 distinct attributes for each subject.

Feature selection and classification:

The machine learning feature selection and classification processes were based on Support Vector Machines (SVM), implemented in Weka 3.8 software.

Radiomic features were imported in the Support Vector Machine-Recursive Feature Elimination (SVM-RFE) algorithm, which is a wrapping feature selection method [12]. More specifically, SVM-RFE iteratively eliminates a set of features by removing the least important one, according to the weighting vectors of an SVM classifier. Consequently, feature ranking in a descending order of discriminative importance is obtained, according to the elimination sequence.

Afterwards, the performance of a well-established linear SVM package (SMO) was evaluated with Receiver-Operator-Characteristic (ROC) analysis, on consecutively SVM-RFE top ranked feature subsets, to identify the optimal feature subset. More specifically, the classifier was repeatedly trained, starting with the 1 higher-ranked features with a stepwise of adding up 1 feature at each iteration, and tested with leave-one-out cross-validation. Further investigation through a grid search method aiming in accuracy maximization was utilized for optimizing the hyperparameters of the classification model.
Fig. 1: Radiomic analysis pipeline.

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Fig. 2: Whole brain segmented maps of a LGG (e) and a HGG (j) case, resulting from the k-medians clustering of the DTI isotropic (c, h), anisotropic (d, i) and T2-weighted components feature space (a, f). The different colors presented (k=16) correspond to distinct brain tissue diffusion properties, which facilitate the precise definition of healthy tissue, tumor core and peritumoral edema. The final delineation of tumor core (red outline) is the outcome of the further combination with T1-weighted post-contrast imaging (b, g).

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Results

The evaluation of different feature subsets with linear 'SMO', has nominated the adaptation of 21 SVM-RFE top ranked features, shown in Table 1, which provide the highest discriminating ability between LGGs and HGGs. Also, Lipids/Cr metabolic ratio was the highest ranked feature. As shown in Table 1, all MRI modalities/parameters have contributed in the final feature set, except for DTI's Fractional Anisotropy (FA). In addition, 8 features where histogram-based and 12 features where textural-based, while GLCM features were much more statistically significant than GLRLM (11vs1). Finally, a complexity parameter $c=10^3$ for the linear kernel 'SMO' have been determined by the grid search, demonstrating a classification performance with 95.5% Accuracy, 95% Sensitivity, 96% Specificity and 95.5% Area Under the ROC Curve.
### Table 1: SVM-RFE top-ranked feature subset selected for classification

<table>
<thead>
<tr>
<th>Rank</th>
<th>MRI modality</th>
<th>Parameter</th>
<th>Quantification Method</th>
<th>Radiomic Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1H-MRS</td>
<td>1H-MRS</td>
<td>-</td>
<td>Lipids/Cr</td>
</tr>
<tr>
<td>2</td>
<td>Conventional MRI</td>
<td>T1W-C</td>
<td>Histogram</td>
<td>Skewness</td>
</tr>
<tr>
<td>3</td>
<td>DTI</td>
<td>q</td>
<td>Histogram</td>
<td>Mean</td>
</tr>
<tr>
<td>4</td>
<td>Conventional MRI</td>
<td>T1W-C</td>
<td>Histogram</td>
<td>Variance</td>
</tr>
<tr>
<td>5</td>
<td>DTI</td>
<td>MD</td>
<td>GLCM</td>
<td>Inverse Difference Moment</td>
</tr>
<tr>
<td>6</td>
<td>DTI</td>
<td>q</td>
<td>GLCM</td>
<td>Sum of Squares</td>
</tr>
<tr>
<td>7</td>
<td>DSCE</td>
<td>raw</td>
<td>GLRLM</td>
<td>Run Length Non-Uniformity</td>
</tr>
<tr>
<td>8</td>
<td>Conventional MRI</td>
<td>T1W-C</td>
<td>GLCM</td>
<td>Angular Second Moment</td>
</tr>
<tr>
<td>9</td>
<td>Conventional MRI</td>
<td>T2W-FLAIR</td>
<td>GLCM</td>
<td>Difference Variance</td>
</tr>
<tr>
<td>10</td>
<td>DTI</td>
<td>q</td>
<td>GLCM</td>
<td>Correlation</td>
</tr>
<tr>
<td>11</td>
<td>DTI</td>
<td>MD</td>
<td>Histogram</td>
<td>Median</td>
</tr>
<tr>
<td>12</td>
<td>DTI</td>
<td>q</td>
<td>Histogram</td>
<td>Difference Entropy</td>
</tr>
<tr>
<td>13</td>
<td>Conventional MRI</td>
<td>T2W-FLAIR</td>
<td>Histogram</td>
<td>Variance</td>
</tr>
<tr>
<td>14</td>
<td>DSCE</td>
<td>rCBV</td>
<td>-</td>
<td>Mean</td>
</tr>
<tr>
<td>15</td>
<td>DTI</td>
<td>p</td>
<td>GLCM</td>
<td>Difference Entropy</td>
</tr>
<tr>
<td>16</td>
<td>Conventional MRI</td>
<td>T2W-FLAIR</td>
<td>GLCM</td>
<td>Sum Variance</td>
</tr>
<tr>
<td>17</td>
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<td>raw</td>
<td>Histogram</td>
<td>Minimum</td>
</tr>
<tr>
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<td>GLCM</td>
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</tr>
<tr>
<td>19</td>
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<td>T2W-FSE</td>
<td>Histogram</td>
<td>Entropy</td>
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<tr>
<td>20</td>
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<td>GLCM</td>
<td>Angular Second Moment</td>
</tr>
<tr>
<td>21</td>
<td>DTI</td>
<td>q</td>
<td>GLCM</td>
<td>Sum Entropy</td>
</tr>
</tbody>
</table>
Conclusion

In the present study, radiomic analysis on a 3T mp-MRI dataset was performed for glioma grade classification between low- and high-grade tumors, demonstrating 95.5% Accuracy and 95.5% AUC in predicting glioma grades, utilizing 21 mp-MRI radiomic features.

The justification for implementing the specific SVM feature selection and classification methods, is based on the predictive robustness indicated by similar studies regarding glioma grading in the past. In a computer-aided-diagnostic approach Chen et al. [14] utilized SVM-RFE for selecting textural features, derived from CNN-based segments of conventional MRI data, and XGBoost classification presenting 91.27% accuracy. Citak-Er et al. [8] have proposed a sophisticated SVM-RFE implementation, with different tumor ROIs mean values of an mp-MR dataset. Subsequently, they utilized the SVM-RFE outcome for training a linear SVM classifier with 93% classification accuracy. Our study exploiting a comparable patient sample size and MR sequences confirms the increased diagnostic ability provided by SVM-RFE and linear SVM classification of mp-MRI data. In addition, the higher accuracy value presented in our study demonstrates the potential role of utilizing radiomic features.

Tian et al. in a recent study [9], which was based on the same group’s initial research [13], proposed a mpMRI glioma grading classification scheme based on SVM-RFE and RBF kernelized SVM, showing 96% accuracy and 98% AUC values. Even though their study presents slightly better performance compared to our study, our model is achieving comparable results utilizing a smaller number of radiomic features (21 vs. 28), increasing its relative efficiency. Since the two studies follow similar feature extraction, selection and classification methodologies, it is obvious that our study’s good performance should be attributed to the addition of Diffusion Tensor and Spectroscopic imaging data utilized. As shown in Table 1, an important number of features extracted from these techniques, have shown high discriminative ability, as this is already investigated and confirmed [15].

More specifically, previous studies have reported the value of textural features of Apparent Diffusion Coefficient (ADC) as potential biomarkers for glioma grade differentiation [16]. In a recent study, Raja et al. [17] investigated the contribution of Diffusion Tensor and Diffusion Kurtosis Imaging in gliomas grading. Their texture-based features have shown significant differences regarding several DTI parameters, except for FA, which comes in agreement with the results of our study. However, we have found that the anisotropic diffusion tensor component, as expressed by the pure anisotropy (q) has proven to be of great importance (5 out of the 21 features were derived for q maps) and could play an essential role in glioma heterogeneity assessment.

In addition, MR spectroscopy is a powerful technique for evaluating brain tumor metabolic processes with an increased diagnostic impact. Previous studies support the potential of MRS metabolic ratios in brain pathology differentiation [18], especially when combined with other advanced techniques. Even though a statistically significant difference for
the specific ratios was not observed in our study, which might be expected since we are comparing gliomas, however the MRS derived Lipids/Cr ratio was the highest ranked feature. Consequently, the lipids concentration in glioma's tumor core, which is proportional to the extent of tumor's necrotic component, may serve as a robust imaging biomarker in differentiating between Low- and High-grade gliomas.

In conclusion, the recent technological advancements in the field of medical imaging have given rise to the incorporation of innovative methodologies regarding tumor phenotypic characteristics quantification and multiparametric data analysis which aid in improving the clinical decision support. The current study presents a comprehensive methodological perspective for evaluating MRI derived phenotypic characteristics for glioma grading, based on multiparametric MR neuroimaging data and state-of-the-art radiomic analysis methods. It shows that radiomic features derived from mp-MRI could be used for accurate glioma classification by exploiting the underlying pathophysiology.
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