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FULL PAPER

A quantitative study of shape descriptors from glioblastoma multiforme phenotypes for predicting survival outcome

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Objective: Predicting the survival outcome of patients with glioblastoma multiforme (GBM) is of key importance to clinicians for selecting the optimal course of treatment. The goal of this study was to evaluate the usefulness of geometric shape features, extracted from MR images, as a potential non-invasive way to characterize GBM tumours and predict the overall survival times of patients with GBM.

Methods: The data of 40 patients with GBM were obtained from the Cancer Genome Atlas and Cancer Imaging Archive. The T_1 weighted post-contrast and fluid-attenuated inversion-recovery volumes of patients were co-registered and segmented into delineate regions corresponding to three GBM phenotypes: necrosis, active tumour and oedema/invasion. A set of two-dimensional shape features were then extracted slice-wise from each phenotype region and combined over slices to describe the three-dimensional shape of these phenotypes. Thereafter, a Kruskal-Wallis test was employed to identify shape features with significantly different distributions across phenotypes. Moreover, a Kaplan-Meier analysis was performed to find features strongly associated with GBM survival. Finally, a multivariate analysis based on the random forest model was used for predicting the survival group of patients with GBM.

Results: Our analysis using the Kruskal-Wallis test showed that all but one shape feature had statistically significant

differences across phenotypes, with p -value < 0.05 , following Holm-Bonferroni correction, justifying the analysis of GBM tumour shapes on a per-phenotype basis. Furthermore, the survival analysis based on the Kaplan-Meier estimator identified three features derived from necrotic regions (*i.e.* Eccentricity, Extent and Solidity) that were significantly correlated with overall survival (corrected p -value < 0.05 ; hazard ratios between 1.68 and 1.87). In the multivariate analysis, features from necrotic regions gave the highest accuracy in predicting the survival group of patients, with a mean area under the receiver-operating characteristic curve (AUC) of 63.85%. Combining the features of all three phenotypes increased the mean AUC to 66.99%, suggesting that shape features from different phenotypes can be used in a synergic manner to predict GBM survival.

Conclusion: Results show that shape features, in particular those extracted from necrotic regions, can be used effectively to characterize GBM tumours and predict the overall survival of patients with GBM.

Advances in knowledge: Simple volumetric features have been largely used to characterize the different phenotypes of a GBM tumour (*i.e.* active tumour, oedema and necrosis). This study extends previous work by considering a wide range of shape features, extracted in different phenotypes, for the prediction of survival in patients with GBM.

INTRODUCTION

Glioblastoma multiforme (GBM) is one of the most common and aggressive primary human brain cancers.¹ The expected time to mortality for patients with GBM following initial diagnosis is 2 years, owing to the resistance of GBMs to conventional therapies.² A recent study reports a median survival time of 12.6 months.³ Despite a range of surgical and oncological treatment options, the prognosis of patients with GBM remains poor.

During aggressive proliferation, the morphological appearance of GBM tumours in MRI is affected by their degree of invasiveness. Owing to the GBM proliferation process, in which the tumour separates into clusters of cells forming sub-tumours, a higher degree of invasiveness will typically result in more irregular tumour shapes.⁴ The growth of these cell clusters is also heavily dependent on fluctuations in local oxygen and nutrient supply at a macroscopic scale.^{4,5} Moreover, GBM tumours generally grow

anisotropically along the white matter and, less commonly, along the edge of cerebrospinal fluid-filled regions.⁶ Resulting tumour shapes are thus irregular and highly variable.⁷

Several shape-based methods have been proposed in the literature for analyzing GBM tumours. In the study of Goldberg-Zimring et al,⁸ spherical harmonics were used to approximate the three-dimensional (3D) shape of brain tumours, toward the goal of obtaining accurate measurements of tumour volume. Morphological features, such as area, eccentricity and equivalent diameter, were also proposed to discriminate GBM tumours from solitary metastasis, based on structural⁹ or diffusion^{10,11} MRI data. Most shape analysis methods need to apply a segmentation technique as a pre-processing step to delineate the tumour boundary in volumetric data. This segmentation technique can be fully automatic¹² or require manual input from an expert.¹³

Predicting the survival of patients with GBM has also been the subject of significant interest. In the studies of Lacroix et al¹⁴ and Park et al,¹⁵ clinical descriptors like the Karnofsky Performance Status, age and gross total resection were shown to be correlated with survival time in patients with GBM. Studies have also demonstrated the link between gene expression data and the response of patients with GBM to aggressive therapy.^{16,17} Genomic data were also used to predict the prognosis group of patients with GBM.¹⁸ Various studies have also considered imaging features as potential predictors of survival time in patients with GBM. In study of Park et al,¹⁵ the volume and location of tumours were used in conjunction with various demographic and clinical variables to predict survival time after surgery for recurrent GBM. The presence of contrast enhancement, oedema or lesions also showed them to be statistically significant prognostic indicators.^{19–22} In addition to their features, methods proposed for predicting GBM survival can also be distinguished by their predictive model, which can be based on statistical techniques like Cox proportional hazards regression,¹⁵ or data mining approaches like decision trees²³ and support vector machines.²⁴

Currently, the application of shape features for characterizing GBM phenotypes (*i.e.* necrosis, active tumour and oedema/invasion) and predicting patient survival is still limited. To the best of our knowledge, this is the first study to use automatically extracted shape features for these important tasks. We hypothesize that such morphological features capture significant properties of GBM phenotypes, including shape irregularities, which can be analyzed to study the overall survival of patients with GBM.

METHODS AND MATERIALS

Figure 1 shows a flowchart of the proposed project. First, raw imaging data are acquired in the form of T_1 weighted (T1W) images and fluid-attenuated inversion-recovery (FLAIR) scans. Afterwards, segmentation (labelling) is performed from registered image pairs in order to delineate regions corresponding to the three GBM phenotypes. Owing to imaging characteristics, shape features of active tumour and necrotic tissues are extracted from T1W images (these regions have a higher contrast in T1W

imaging than in FLAIR) and oedema regions from FLAIR images (oedema regions have a higher contrast in FLAIR than in T1W imaging). Various shape descriptors (features) are then computed slice by slice, for each phenotype. A slice-wise analysis is used to benefit from the wider range of two-dimensional shape features, many of which can be combined over region slices to obtain 3D shape features (*e.g.* region volume is directly related to the sum of region areas in corresponding slices). Such an analysis is also justified by the fact that GBM tumour patterns are typically orientation-invariant. Once extracted, these shape features are used to conduct three different analyses. In the first analysis, a Kruskal–Wallis test is applied to evaluate the significance of each shape feature in distinguishing between GBM phenotypes. Likewise, the second analysis uses the Kaplan–Meier estimator and log-rank test to predict the survival of the patient with GBM based on individual features. Finally, a multivariate analysis using a random forest (RF) model is employed to classify patients with GBM into short and long survival groups.

Patient population and data

Our patient population consists of 40 patients with GBM (17 females, 23 males; age range from 18 to 80 years; median age 61 years; mean age 59 years) from The Cancer Genome Atlas (<http://cancergenome.nih.gov/>), the data for which were acquired prior to treatment. Although more patient data are available in this database, most have modalities obtained with significantly different acquisition parameters (*e.g.* sampling resolution), making the registration of these modalities prone to errors. In turn, these registration errors hinder the segmentation of GBM phenotypes. To avoid this confounding factor in our analysis, we thus limited our investigation to a subset of data of 40 patients (from a total of 262 patients), for which the registration and segmentation were validated qualitatively by experts. Supplementary Table A lists the case identities of the patient data used in our study. It can be noted that all these cases exhibit all three GBM phenotypes (*i.e.* necrosis, active tumour and oedema).

The patient data were downloaded from The Cancer Imaging Archive (<http://cancerimagingarchive.net/>), an online sharing resource housing images acquired from several institutions.²⁵ These data have been previously deidentified by The Cancer Genome Atlas and are publicly available for download; thus, no institutional review board approval was required. For each patient, two MRI sequences were available: (1) post-contrast T1W imaging and (2) T_2 weighted FLAIR. All images were acquired at a resolution of 512×512 pixels, each subject with a possibly different number of slices.

Data pre-processing

For each patient, T1W and FLAIR images were spatially registered with a rigid transform model, using the 3D Slicer software version 4.3.1 (www.slicer.org).²⁶ Registration is required because the FLAIR and T1W images were acquired with different slice parameters, angles and voxel thickness. In cases where the voxel size for corresponding FLAIR and T1W images was not equivalent, FLAIR images were resampled to match the T1W image voxel size prior to registration. This volume-to-volume registration process took an average of 42.5 s per patient data.

Figure 1. (a) A processing diagram of the proposed method and analyses; (b) an example of phenotype regions extracted from post-contrast T_1 weighted (T1W) and fluid-attenuated inversion-recovery (FLAIR) images; (c) identification of features with significant differences across phenotypes using the Kruskal–Wallis test; and (d) survival analysis based on the Kaplan–Meier estimator. GBM, glioblastoma multiforme; RF, random forest.

Following registration, images were segmented slice by slice to extract regions corresponding to the three GBM phenotypes. This segmentation step was performed manually by a first radiologist (researcher with 5 years' experience in quantitative imaging) and then validated and refined by a second radiologist (researcher with 7 years' experience in quantitative imaging). Necrosis and active tumour phenotypes were determined from T1W images, in which active tumour regions correspond to the contrast-enhancing portion of the tumour and necrotic regions are typically low-intensity voxels located inside the active tumour. On the other hand, oedema regions were obtained from FLAIR images. It can be noted that a cross-subject normalization of volume intensities is not required in our case because the segmentation was performed manually and shape features are insensitive to relative differences in intensity.

Shape feature extraction

Shape features were extracted slice by slice, for each phenotype, using the Region Properties tool of MATLAB® (MathWorks®,

Natick, MA).²⁷ As mentioned previously, two-dimensional shape features were considered instead of 3D ones owing to their greater availability, and because they can be combined to obtain features characterizing a 3D volume. A total of 11 features were chosen for their ability to describe the geometrical characteristics of GBM phenotypes: Area (f_1), Eccentricity (f_2), Equivalent diameter (f_3), Filled area (f_4), Extent (f_5), Major (f_6) and Minor (f_7) Axis lengths, Orientation (f_8), Perimeter (f_9), Solidity (f_{10}) and Convexity (f_{11}). A description of these features is provided in Table 1.

For each phenotype, features extracted in the slices containing this phenotype were combined by taking their cross-slice average. Using this strategy, we thus obtained a total of 33 shape features (11 features $\times$ 3 phenotypes) for each patient with GBM. Finally, the resulting features were normalized to zero mean and unit variance, using z score normalization, thereby reducing the effects of bias and variance on the analysis.

Table 1. Description of shape features

Feature	Description
Area	Number of pixels in the region
Eccentricity	Ratio of the distance between the foci and the major axis length of an ellipse with same second moments as the region. Values range between 0 (in case of a circle) and 1 (in case of a line segment)
Equivalent diameter	Diameter (in pixels) of a circle with the same area as the region
Filled area	Number of pixels in the region with all holes filled in
Extent	Ratio between the region area and the area of the region bounding the box (<i>i.e.</i> the smallest rectangle containing it)
Major axis length	Length (in pixels) of the major axis of an ellipse with same normalized second central moments as the region
Minor axis length	Length (in pixels) of the minor axis of an ellipse with the same normalized second central moments as the region
Orientation	Angle (from -90° to $+90^\circ$) between the horizontal image axis and the major axis of an ellipse with the same normalized second central moments as the region
Perimeter	Distance (in pixels) around the region boundary
Solidity	Ratio between the region area and the area of its convex hull
Convexity	Ratio between the region perimeter and the perimeter of its convex hull

Statistical analyses

A Kruskal–Wallis test was first applied on the shape features to find statistically significant differences among the three GBM phenotypes. This non-parametric method measures the probability that different groups have the same median.²⁸ To account for the multiple comparisons (33 tests, 1 for each feature), *p*-values were then corrected using the Holm–Bonferroni

method.²⁹ Features with corrected *p*-value < 0.05 were considered significant.

For the survival analysis of patients with GBM, we considered the median of each shape feature as a cut-off value to part patients in two groups. As in the study of Kleinbaum and Klein,³⁰ the time-to-event (*i.e.* number of days until death) distributions of the two groups were estimated using the Kaplan–Meier estimator and compared using the log-rank test. Once again, the statistical significance of features was assessed at *p*-value < 0.05 , following Holm–Bonferroni correction.

For a multivariate analysis, we used all 11 features as input to an RF model,³¹ for the classification of patients with GBM in two classes representing short survival (*i.e.* survival time less than the median survival time) and long survival (*i.e.* survival time greater or equal to the median survival time).³² Based on prior experiments, the number of RF decision trees was set to 100. A fivefold cross-validation strategy was used to evaluate the performance of the model, in which the 40 patients were randomly divided into 5 even-sized groups. Each group was then used, in turn, as a test set for computing the area under the receiver-operating characteristic curve (AUC)³³ of the RF model trained with the remaining patient data. The overall performance of the model was measured as the average AUC obtained over all five folds. The MATLAB Statistical Toolbox was used for all statistical calculations.

RESULTS

Feature analysis

Table 2 gives the mean and standard deviation of normalized feature values computed in the three GBM phenotypes. Corrected *p*-values of the Kruskal–Wallis tests, showing whether the distribution of features differs across phenotypes, are also reported. Except for Orientation, all shape features exhibited statistically significance differences, with *p*-value < 0.05 , following Holm–Bonferroni correction. This suggests that the

Table 2. Distribution (mean $\pm$ standard deviation) of unnormalized feature values in the three glioblastoma multiforme phenotypes

Feature	Necrosis	Active tumour	Oedema	<i>p</i> -value ^a
Area	695.9 $\pm$ 650.5	1182.0 $\pm$ 752.7	1672.1 $\pm$ 1011.7	6.42×10^{-6}
Eccentricity	2.8 $\pm$ 1.6	1.1 $\pm$ 0.4	1.9 $\pm$ 0.6	3.13×10^{-10}
Equivalent diameter	35.9 $\pm$ 17.7	38.3 $\pm$ 13.3	54.5 $\pm$ 19.6	3.45×10^{-5}
Filled area	701.2 $\pm$ 655.2	1687.7 $\pm$ 1144.8	1716.8 $\pm$ 1040.6	2.28×10^{-6}
Extent	2.3 $\pm$ 1.4	0.9 $\pm$ 0.3	1.2 $\pm$ 0.4	1.32×10^{-9}
Major axis length	53.8 $\pm$ 26.5	61.9 $\pm$ 24.8	99.2 $\pm$ 38.0	4.00×10^{-8}
Minor axis length	30.7 $\pm$ 15.3	41.7 $\pm$ 17.1	48.0 $\pm$ 18.3	9.22×10^{-5}
Orientation	11.0 $\pm$ 48.7	3.9 $\pm$ 40.1	-5.1 $\pm$ 47.4	0.342
Perimeter	164.9 $\pm$ 94.5	186.0 $\pm$ 85.2	325.8 $\pm$ 135.9	3.01×10^{-8}
Solidity	3.2 $\pm$ 1.9	1.1 $\pm$ 0.4	1.8 $\pm$ 0.6	3.13×10^{-10}
Convexity	901.3 $\pm$ 802.0	1956.4 $\pm$ 1384.7	2781.3 $\pm$ 1851.0	1.70×10^{-7}

^aFollowing Holm–Bonferroni Correction.

characteristics of GBM phenotypes are captured by a heterogeneous set of shape features.

The differences in feature values observed across phenotypes are further illustrated in the box plots of Figure 2. Based on pairwise Wilcoxon rank-sum tests with significance level 0.01, oedema regions have statistically higher values than the other two phenotypes for features corresponding to Eccentricity and Perimeter and statistically lower values for Solidity. Likewise, compared with other phenotypes, necrosis regions show statistically lower values for Area, Equivalent diameter, Filled area, Major/Minor axis length, Orientation, Perimeter and Convexity.

To analyze the relationship between pairs of shape features extracted in different phenotypes, a heatmap of feature correlation is shown in Figure 3. For all phenotypes, we see that features corresponding to Area, Equivalent diameter, Filled area, Major/Minor axis length, Perimeter and Convexity are highly correlated ($\rho > 0.7$). This result is not surprising since all these features encode properties related to region size. Likewise, Extent and Solidity show a high correlation. More interestingly, we notice a low correlation between features extracted from different phenotypes, implying that these phenotypes have distinct morphological characteristics.

Survival analysis

The results of our survival analysis are summarized in Table 3, which gives the cut-off value (*i.e.* median) of each feature used

to divide patients into two groups (below and above the cut-off), the median survival time of patients in these groups and the Holm–Bonferroni corrected p -values of the log-rank test measuring whether the survival distributions in the two groups are equal. We observe that the features of Eccentricity, Extent and Solidity extracted from necrosis regions are statistically significant in predicting the overall survival time of patients with GBM. Remaining shape features derived from necrosis, active tumour and oedema regions were not found to be significant, following Holm–Bonferroni correction. The impact of these features on survival outcome can also be assessed by considering the survival curves of patients below and above the cut-off values (Figure 4). It can be seen that necrosis regions with low Eccentricity lead to a higher chance of survival (hazard ratio of 1.87). Likewise, a smaller Extent or greater Solidity in necrosis regions is associated with a better survival outcome (hazard ratio of 1.68 and 1.72, respectively).

For the multivariate analysis, Figure 5 gives the mean receiver-operating characteristic curve and AUC values obtained with shape features extracted from each phenotype (11 features), for predicting whether the survival time of a patient with GBM is below or above the median survival time. Comparing phenotypes, we observe that features from necrosis regions lead to the highest prediction accuracy (mean AUC of 63.85%), followed by features from oedema regions (mean AUC of 61.77%). In contrast, shape features from active tumour regions show a poor predictive ability (mean AUC of 52.99%). Combining the

Figure 2. Box plot of shape features derived from active tumour (vAT), oedema (vE) and necrosis (vN) regions. Midlines give the median feature value and whiskers give the interquartile range.

Figure 3. Heatmap of correlation coefficients between shape features [Area (f_1), Eccentricity (f_2), Equivalent diameter (f_3), Filled area (f_4), Extent (f_5), Major (f_6) and Minor (f_7) Axis lengths, Orientation (f_8), Perimeter (f_9), Solidity (f_{10}) and Convexity (f_{11})] derived from active tumour (vAT), oedema (vE) and necrosis (vN) regions.

features of all 3 phenotypes (total of 33 features) increases the mean AUC to 66.99%, suggesting that morphological characteristics of different phenotypes provide complementary information for GBM prognosis.

DISCUSSION

We used shape features derived from MRI to identify morphological differences in GBM phenotypes (*i.e.* necrosis, active tumour and oedema). Except for Orientation, all shape features

showed statistically significant differences when compared across phenotypes (Figure 2 and Table 2). These findings are consistent with previous work in the literature, which found morphological features to be strong predictors for the diagnosis of GBMs vs solitary metastasis.^{10,11}

We also evaluated the usefulness of these shape features for predicting survival group of patients with GBM. Our analysis based on the Kaplan–Meier estimator identified three significant

Table 3. Kaplan–Meier analysis of glioblastoma multiforme phenotypes: necrosis (vN), active tumour (vAT) and oedema (vE)

Feature	Cut-off (median)			Median survival (days)						p -value ^a		
				Above cut-off			Below cut-off					
	vN	vAT	vE	vN	vAT	vE	vN	vAT	vE	vN	vAT	vE
Area	535.5	1059.0	1654.0	328	315	291	274	317	328	0.198	1.998	3.030
Eccentricity	2.0	0.8	1.7	268	285	317	333	322	317	0.003	2.632	2.441
Equivalent diameter	37.9	40.3	55.2	323	291	285	315	317	322	0.603	3.212	3.030
Filled area	538.5	1502.0	1679.0	328	328	291	274	317	325	0.197	1.266	3.191
Extent	1.7	0.6	0.9	268	291	316	333	317	317	0.031	3.465	2.495
Major axis length	52.6	62.6	99.9	322	316	291	317	317	317	0.722	1.266	1.333
Minor axis length	31.1	42.9	50.2	328	328	291	315	315	317	0.614	1.517	1.413
Orientation	13.6	13.0	12.2	328	317	317	279	315	291	0.326	3.313	1.517
Perimeter	164.0	181.0	332.8	322	315	291	317	317	322	1.589	3.465	1.998
Solidity	2.3	0.8	1.4	268	316	316	331	317	317	0.019	2.564	1.724
Convexity	752.0	1771.0	2620.0	328	315	291	274	317	317	0.173	1.469	0.294

^aFollowing Holm–Bonferroni correction (corrected values above 1 were left as such).

Figure 4. Kaplan–Meier survival curves for patients above and below the median value of three necrosis shape features: Eccentricity (f_2), Extent (f_5) and Solidity (f_{10}).

features derived from necrotic regions (*i.e.* Eccentricity, Extent and Solidity), which were associated with the overall survival of patients with GBM (Table 3). These features were shown to be good indicators of GBM outcome, with hazard ratios ranging from 1.68 to 1.87 (Figure 4). The usefulness of shape features from necrosis regions was also confirmed by our multivariate analysis, where using these features as an input to an RF model led to the highest prediction accuracy (Figure 5). Results of our survival analysis are in agreement with the findings of Gevaert et al.,³⁴ Mazurowski et al and Chaddad and Tanougast,^{22,35} which showed the proportion of necrosis (or equivalently, the proportion of enhancing tumour) to be a good predictor for GBM survival. These results, obtained using shape features, are also complementary to previous studies, suggesting a link between phenotype texture and the survival of patients with GBM.^{22,35–37}

Figure 5. Mean accuracy obtained by the random forest model for predicting the survival group (above or below the median survival time) of patients. Receiver-operating characteristic (ROC) curves and area under the ROC curve (AUC) values are reported for shape features derived from necrosis (vN), active tumour (vAT) and oedema (vE) regions, as well as features from all three phenotypes (Combined).

This study is also related to recent work establishing a link between image features, based on spatial habitats³⁸ and texture (*i.e.* fractal texture analysis, histogram of oriented gradients, run length, local binary patterns and Haralick features)³⁹ and the 12-month survival status of patients with GBM. In comparison with these studies, our analysis focuses on the morphological characteristics of GBM tumours occurring in regions corresponding to necrosis, oedema and active tumour. Our primary motivation for this approach is that shape features can effectively capture the irregularity of GBM tumours during their progression, which may ultimately result from different levels of cellular heterogeneity within developing tumours. Also, shape features are intuitive and can be used to quantify aspects of GBM shape that may not be easily observable by the human eye.

Our study also has some limitations, the most important being the limited number of patients with GBM ($n = 40$). Having a larger patient cohort would help to better quantify the variability of GBM tumour shapes and their link to prognosis. A cross-site study including data from multiple medical centres would be an important step towards this goal.

CONCLUSION

This study proposed the use of shape features for characterizing three GBM phenotypes (*i.e.* oedema, active tumour and necrosis) and predicting the survival group of patients with GBM. Such features capture significant properties of GBM tumours, including shape irregularities, which are linked to cellular abnormalities in developing tumours. Three shape features computed from the necrotic region, *i.e.* Eccentricity, Extent and Solidity, were shown to be statistically related to the overall survival of patients with GBM, with respective hazard ratios of 1.87, 1.68 and 1.72. In a multivariate analysis based on the RF classifier, features from necrotic regions also gave the highest accuracy in predicting the survival group of patients, with a mean AUC of 63.85%. However, combining the features of all three phenotypes led to a 3% increase in mean AUC, suggesting that shape features from different phenotypes can be used in a synergic manner to predict GBM survival. Future work will include validating the proposed approach on a larger cohort of

patients, analyzing the evolution of tumour shapes from longitudinal data and combining the shape descriptors used in this study with other types of features.

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