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Pseudo Progression Identification of Glioblastoma with Dictionary Learning

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Abstract

Objective—Although the use of temozolomide in chemoradiotherapy is effective, the challenging clinical problem of pseudo progression has been raised in brain tumor treatment. This study aims to distinguish pseudo progression from true progression.

Materials and Methods—Between 2000 and 2012, a total of 161 patients with glioblastoma multiforme (GBM) were treated with chemoradiotherapy at our hospital. Among the patients, 79 had their diffusion tensor imaging (DTI) data acquired at the earliest diagnosed date of pseudo progression or true progression, and 23 had both DTI data and genomic data. Clinical records of all patients were kept in good condition. Volumetric fractional anisotropy (FA) images obtained from the DTI data were decomposed into a sequence of sparse representations. Then, a feature selection algorithm was applied to extract the critical features from the feature matrix to reduce the size of the feature matrix and to improve the classification accuracy.

Results—The proposed approach was validated using the 79 samples with clinical DTI data. Satisfactory results were obtained under different experimental conditions. The area under the receiver operating characteristic (ROC) curve (AUC) was 0.87 for a given dictionary with 1024 atoms. For the subgroup of 23 samples, genomics data analysis was also performed. Results implied further perspective on pseudo progression classification.

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Conclusions—The proposed method can determine pseudo progression and true progression with improved accuracy. Laboring segmentation is no longer necessary because this skillfully designed method is not sensitive to tumor location.

Keywords

Pseudo progression; Glioblastoma multiforme; Dictionary Learning; Genomics analysis; Fractional anisotropy (FA); Diffusion tensor imaging (DTI)

1. Introduction

Glioblastoma multiforme (GBM) is a highly invasive disease, and its recurrence at sites distant from the core of tumors is the main cause of its high mortality. The current standard of care is surgical resection, followed by radiation therapy (RT) and concomitant and adjuvant temozolomide (TMZ) chemotherapy [1].

Pseudo progression (PsP) is a phenomenon showing changes of subacute imaging data in human glioma subsequent to chemoradiotherapy suggestive of progression [2]. The incidence of tumor PsP ranges from 28% to 66% in all GBM patients undergoing chemoradiation and typically occurs within three months after the completion of concurrent radiation and TMZ chemotherapy [3]. PsP has been associated with a variety of nontumoral processes, such as treatment-related inflammation [1], postsurgical changes, ischemia, and radiation necrosis [4, 5].

PsP is detected by magnetic resonance imaging (MRI) as contrast-enhanced regions that can mimic early tumor progression. However, PsP is difficult to identify by conventional MRI and morphologic MRI features [1, 6, 7]. Currently, the only method to distinguish PsP from early progression is by follow-up examinations on patients [2]. Differentiation between PsP and tumor progression is critical because PsP is an indication of that the current therapy is effective and should be continued, in which group the patients have a better chance of survival, whereas tumor progression indicates that the current therapy is not effective and should be altered if possible. Developing advanced sequence beforehand, but this step is labor intensive and introduces much ambiguity. A more complicated tumor growth model was developed as the metric of therapy response [14]. A score called Days Gained was computed by this model to distinguish PsP from true progression. This approach requires follow up of image data of patients. Segmentation cannot be avoided either. Generally, improvements to these approaches are greatly needed, particularly with the use of advanced analysis.

This study focuses on DTI sequence and uses extracted volumetric FA images as the key measurement. The dictionary learning (DL) approach is applied to the image sequence to obtain sparse representations. DL is a powerful image analysis method based on sparse representation techniques. DL methods have various forms derived from different application problems, such as image denoising [15], image in-painting [16], and image compression [17, 18]. However, most of these attempts are based on two-dimensional (2D) images. In the present study, we extend this approach to discriminate volumetric subjects. ROI segmentation is no longer needed in the DL approach. Therefore, the proposed method

is more efficient and accurate. Then, the feature matrix is composed by the sparse representation with a specially designed permutation, which could solve the location divergence of tumors. Finally, a small group of features is selected from the feature matrix, and the subjects are classified using the SVM approach.

2. Material and Methods

Between 2000 and 2012, a total of 161 patients [19] with GBM were treated with chemoradiotherapy after surgical resection at Wake Forest Baptist Medical Center. Along with chemoradiotherapy, the patients underwent MRI/DTI scans every two or three months after each stage of therapy for monitoring. MRI/DTI data; treatment schemes, such as date of surgery, type of surgery, RT dose, concurrent chemotherapy, concurrent chemotherapy agents, and patient information, such as date of birth, date of death, ethnicity, and gender, were fully available. Different treatment schemes could lead to different therapy results, including PsP, which could be identified by the proposed image analysis approach. However, the image analysis approach itself is essentially irrelevant to the treatment schemes. The doctor's diagnosis of PsP was made on the basis of clinical and imaging data and the clinical experience of the treating physician. Biopsy could be performed when necessary. For each patient, we selected the DTI sequence that was obtained when the patient was first diagnosed with PsP or true progression. Both PsP and true progression were assumed to have just occurred, and the time was the earliest for diagnosis by using imaging. Under this condition, 79 samples with qualified DTI data were selected and used, including 23 pseudo and 56 true progression samples, which were all collected after 2005. Among 79 samples, 23 samples possessed genomic data. The composition of the two datasets is shown in Table 1. The study protocol was approved by the Wake Forest Baptist Medical Center review board.

2.1. Pre-processing

The DTI data sequences were processed with MRICron [20] and FSL [21, 22]. Each DTI sequence of the DICOM images was transformed into a 4D image with the gradient information using the MRICron. Then, the FSL software was used to correct for eddy current-induced distortions and subject movements. Afterwards, non-brain tissue such as skin was removed [23]. The FA value of each voxel was computed by the FSL. Each reconstructed brain volume was linearly registered to the standard brain template FMRI58 [24]. As a result, all the registered volumetric FA images had the same number of slices and the same resolution. Thus, the same voxels across different patients were properly registered to one another. Figure 1 shows two randomly selected samples with one slice of the DTI raw data, the FA image, and the registered FA image, respectively. The figure also shows that the position and head shape are registered accurately.

2.2. Dictionary Learning and Sparse Representation

A dictionary is a matrix $D \in R^{N \times K}$, where R is the real space, and N and K are integers. One column of D is called an atom, which is an N dimensional vector, denoted as $d_k \in R^{N \times 1}$ ($k = 1, \dots, K$). The dictionary is redundant or over-complete if $N \ll K$. Let us express an $\sqrt{N} \times \sqrt{N}$ image patch by a vector $x \in R^{N \times 1}$, where each element is equal to the gray value

of one pixel of the patch. Given a dictionary D , we suppose a sparse linear combination of the atoms d_k that can represent the image patch x . Hence, we have

$$\|x - D\alpha\|_2^2 \leq \varepsilon \quad (1)$$

where $\varepsilon > 0$ is a small error bound. $\alpha \in R^{K \times 1}$ is the representation vector and possesses few nonzero entries. We have $\|\alpha\|_0 \ll N \ll K$, with $\|\cdot\|_0$ being the l_0 -norm. The number of atoms is larger than the length of an atom.

Suppose a training set of Q samples with S patches of each sample. Then a total of $S \times Q = M$ training patches were available. The goal of dictionary learning algorithm is to find a dictionary D that established training patches that are sparsely represented by the atoms in D . Let us denote the given training patch set as matrix $X \in R^{N \times M}$, a column vector of which is an image patch $x_s = R^{N \times 1}$ ($s=1, \dots, M$). The corresponding sparse representation vector can be denoted as matrix $\alpha \in R^{K \times M}$, a column vector of which is the sparse representation $\alpha_s \in R^{K \times 1}$ of the patch $x_s = R^{N \times 1}$ ($s=1, \dots, M$). Thereafter, the dictionary learning approach solves

$$\min_{D, \alpha} \sum_{s=1}^{S \times Q} (\|x_s - D\alpha_s\|_2^2 + v_s \|\alpha_s\|_0), \quad (2)$$

where v is the Lagrange multiplier. Several algorithms are available for dictionary learning, such as the fast online learning technique and the classical K-SVD method.

With the trained dictionary D and the obtained sparse representation, one image patch x can be successfully expressed as a sparse linear combination of the atoms in D and its corresponding sparse expression α as shown in Figure 2D. For each patient, the collection of sparse representation is a matrix $\{\alpha_s\}_{s=1}^S$. Clearly, each α_s indicates the pattern of the corresponding image patch x_s , and thus carries the attributes of the corresponding brain tissue.

2.3. Feature Matrix

As each image patch relates to a certain area of the brain tissue, the direct comparison of the sparse representations of each patch among patients actually involves location information. We developed the following method illustrated in Figure 3 to reshape the sparse representation matrix and compose the feature matrix, which are free from the location information. For each patient, the sparse representation matrix $\{\alpha_s\}_{s=1}^S$ can also be denoted as $(\{\beta_k\}_{k=1}^K)^T$, where β_k^T is a row in matrix $\{\alpha_s\}$ and represents the sparse coefficients that correspond to the same atom d_k in D for different image patches. Then, each β_k is sorted by the value and yields a new vector γ_k . We obtain the new matrix $(\{\gamma_k\}_{k=1}^K)^T$. In γ_k , the first element has the highest value among all the coefficients according to d_k . This order is based on the contribution of atom d_k to each image patch and successfully discards the location

information. Finally, the matrix is transformed into a vector $[\gamma_1^T, \gamma_2^T, \dots, \gamma_K^T]^T$. The whole process is summarized as follows:

- $$[\alpha_1, \alpha_2, \dots, \alpha_S]_{K \times S} = \begin{pmatrix} \beta_1^T \\ \beta_2^T \\ \dots \\ \beta_K^T \end{pmatrix}_{K \times S}$$
- Step 1: $\{\alpha_s\}_{s=1}^S = (\{\beta_k\}_{k=1}^K)^T$, i.e.,
- Step 2: $(\{\beta_k\}_{k=1}^K)^T = > (\{\gamma_k\}_{k=1}^K)^T$, where $\gamma_k = \text{sort}(\beta_k)$, which sorts β_k by value.
- Step 3: $(\{\gamma_k\}_{k=1}^K)^T = > [\gamma_1^T, \gamma_2^T, \dots, \gamma_K^T]^T$ Combining the vectors of all patients, we obtained the feature matrix $F \in R^{U \times Q}$, where $U = K \times S$ and $Q = Q_p + Q_t$ (Figure 2E). Each row in the feature matrix F serves as one feature, which represents the same rank of contribution that an atom d_k made in different patients. For example, the feature that is composed of the second-highest value in γ_k of each patient holds the second-highest contribution that d_k has made to each patient, and it can be associated with different image patches. Each atom d_k stands for a certain character, as atoms are considered to carry the fundamental information of brain tissue. For example, a certain d_k is mainly used for the constitution of image patches in the ROI of PsP. The corresponding sparse representation should be high in these image patches. The absolute value could vary in different patients. However, for each patient, the image patches falling under the ROI of PsP must relate more to the higher coefficients of d_k than the patches of other tissues. By sorting the coefficients β_k , we arranged the patches of each patient by how likely they contain pseudo progressive symptoms.

2.4. Feature Selection and Classification

The length of column, $K \times S$, is a huge number. Aside from the high computational cost, too many features can introduce noise and decrease the accuracy. Therefore, we need to reduce the dimensionality of F using a feature selection scheme called the index-based approach, proposed by [25]. In this approach, an index (DX score), which can be considered as a type of signal-to-noise ratio, is used to evaluate the discriminating capability of each feature. A top-ranking subset of these features was selected to build the SVM classifier. DX is defined as follows:

$$DX = \frac{(m_p - m_t)^2}{d_p^2 + d_t^2}, \quad (3)$$

where m_p and m_t are the mean value of the selected features in the pseudo progression and true progression groups, and d_p and d_t are the standard deviation of the selected features in the two groups, respectively. We selected the set of top-ranking features that give the highest

prediction accuracy. The index score is equal to the feature score (scaled by a constant) given by the feature selection tool of LIBSVM. The feature selection result obtained by this index score is comparable with the SVM-RFE (recursive feature elimination) algorithm. This approach is more advanced than the SVM-RFE in computational complexity and is especially suitable for the project because of the large feature size.

3. Experiments and Results

The DTI data of 79 patients were studied in this experiment. The volumetric FA image of each patient was extracted, and then registered to a standard volumetric space with a dimension of $182 \times 218 \times 182$. Two examples are given in Figure 1. The resolution of each slice was 182×218 . Each registered volumetric image had 182 slices. We selected 1 every 4 slices because it was dense enough. Thus, 46 slices were selected for every patient. Each slice was cut into 128×160 because the object was located centrally.

3.1. Performance of DL

In the DL step, 8×8 image patches were extracted from each slice. Each image patch was represented by a 64×1 vector, the elements of which were the gray scale of the pixels. The number of atoms K was set to 512. Therefore, the dimension of D was 64×512 . Corresponding to one image patch, the dimension of sparse representation α was 512×1 . A total of 512 atoms had a size of 64×1 , which indicates an 8×8 image patch. An image patch from the slices could be expressed as the linear combination of the 512 atoms, as shown in Figure 2D. Each slice was decomposed into 18513 patches by using the sliding mode with a gap of 1 pixel. Each volumetric image was decomposed into 851598 patches. As the large number, 29440 patches were randomly selected from each patient at the same position to train the dictionary D . Consequently, for one sample, the dimension of the sparse expression matrix was 512×851598 . The dimension was reshaped to form the $(\{\gamma_k\}_{k=1}^K)^T$ matrix, in which only the top 100 values were used in each row. Then, the dimension was converted to compose the feature matrix, which had a size of 51200×79 .

We applied our Index-based feature selection [25] approach to the feature matrix F . We finally selected the top 37 features that gave the highest prediction accuracy. The values of the 37 features are shown in Figure 4(a). Each column represents one patient, and each row represents a feature. The first 23 columns are the patients with pseudo progression. The other 56 columns are patients with true progression. The features corresponding to pseudo progression and true progression groups, respectively, had values in different scales. This finding demonstrates that PsP patients corresponded to a certain range of FA values [26]. Based on the difference, the features could classify the two symptoms.

The clinical information of the 79 patients is presented in Figure 4(a). The gray bar gives the diagnosis of the patients concerning pseudo progression. The Dark gray bar indicates that the patient has pseudo progression. The light gray bar indicates the patient has true progression. The yellow bar indicates whether the patient died of GBM. The dark yellow bar indicates that the patient did not die of GBM, whereas the light yellow means that the patient died of GBM. With respect to the yellow bar, only a few patients in the pseudo progression

group died of GBM, consistent with the current observation that PsP is the signal that the patient responds to the chemoradiotherapy. Thus, the mortality rate was lower in this group. Figure 4(a) clearly demonstrates that the performance of DL is consistent with the clinical information.

3.2. Classification Accuracy

5-fold cross-validation was applied to validate the classification performance. We randomly selected 80% of the samples of both types as the training set, and the remaining 20% samples was indicated as the testing dataset. The SVM classifier was built with the selected top features. The features in the testing set with the same order number as the top selected features were extracted. The classification result of the testing set was recorded in Table 2. The process was repeated 10, 30, and 100 times. The DL-based SVM classifier was shown to be stable. The receiver operating characteristic (ROC) and the precision recall (PR) analysis based on the 79 samples are shown in Figures 5(a) and 5(b). The area under the ROC curve (AUC) was 0.84.

3.3. Experiments with Different Dictionary Sizes

The number of atoms in the dictionary can be given according to the required accuracy and efficiency. Generally a large number of atoms would provide better accuracy but more time consuming. A trade-off between the accuracy and efficiency should be made. We have applied the method with different dictionary size other than $K = 512$.

Let K be equal to 1024, the dimension of D is 64×1024 . The sparse representation matrix is 1024×851598 when each volumetric image is decomposed to 851598 image patches. The formed feature matrix F is $102,400 \times 79$.

With the Index-based feature selection approach, the top 25 features, which indicate the highest prediction accuracy, are selected from the feature matrix. The values of the 25 features are visualized in Figure 4(b). The 23 columns on the left correspond to the patients with PsP. The pattern of features is the same as in Figure 4(b). 5-fold cross-validation has been applied as well. With $K = 1024$, the ROC and PR curve of 79 samples are shown in Figures 5(c) and 5(d) respectively. The AUC is 0.87 comparing 0.80 in [14]. The classification accuracy is reported in Table 2. The relationship between the size of the dictionary and the AUC of ROC and PR curves is shown in Figure 6. The experimental results show that the AUC increased when the size of dictionary increase, and the DL approach is stable when K is large enough, given that similar results are obtained when $K = 512$ and $K = 1024$. We prefer $K = 1024$ in our project.

4. Discussion

4.1. Association Study

The samples in Dataset 1 provide another perspective to further explore the problem of diagnosing PsP, as these samples have genomics data aside from image data. Sample 1 – 9 in Dataset 2 are PsP samples in Dataset 1. Sample 24–37 in Dataset 2 are true progression samples in Dataset 1. In the previous experiments, sample 1 and 4, which are in Dataset 1 as

well, were usually misclassified, the features of which were slightly different from most of other PsP samples shown in Figure 4. We excluded the misclassified samples in the image analysis, and used the rest patients for the genomics analysis. We obtained 189 differentially expressed genes (DEGs) with a p -value < 0.005 using the Limma [27] package. Like image feature, gene expression level can reflect the dynamic and physiologic interplay of cells [28]. To assess the association of the image features with gene expression, we calculated the Pearson's correlation coefficients (PCC). For the top 25 image features shown in Figure 4(b), we calculated the PCC to DEGs and used the corresponding p -values less than 0.05. The image-gene feature pairs with strong correlation (PCC of above 0.7) were selected to be informative of image feature. We found 21 genes that are associated with 11 image features. For example, image feature V1 is correlated with six genes, including ERCC1, which are important in DNA nucleotide excision repair [29]. Glioma patients present significantly different genotype of ERCC1, which may increase the risk in comparison with normal controls [29, 30]. However, patient groups are difficult to distinguish by basing only on one image feature and the correlated gene set. Figure 7 shows that the combination of features V1 and V18 are more powerful for clustering. Features V1 and V18 are discriminative coefficients with the corresponding atoms between the two symptoms. Specifically, among the non-zero coefficients of the two corresponding patches, features V1 and V18 are the unique selected features, respectively. Furthermore, corresponding patches that are identified by selected features V1 and V18 are located in the pathological area. Therefore, the intensity (that is, FA value) differences between two symptoms can be reconstructed by the identified V1 and V18 with their corresponding atoms. The image features are outlined on top in Figure 7, and the expression patterns of the corresponding gene sets are distinguished. These gene sets can reveal the physiologic basis of image features and act as potential biomarkers.

4.2. Comparison with Recent Approaches

As PsP is a challenging clinical problem in GBM, researchers have shown intensive interest in this area. Two methods can represent the trends of studies and report better results. The first method [9] uses SVM to classify PsP and tumor recurrence. In this study, eight modalities of the MRI sequence were used: contrast-enhanced T1, T2, FLAIR, PD, ADC, rCBF, rCBV, and MTT. The features were extracted from each voxel in an ROI. The features were processed (e.g., normalization), and the feature vector was formed for each voxel. SVM was then applied to identify the PsP. This approach requires eight modalities of MRI for all patients, which improves the patients' medicare cost and takes a long time to scan. Furthermore, this approach requests segmentation of the ROI, which is a time-consuming task. Eight sequences have to be segmented for one patient. This step not only exponentially increases the burden but also requires reliable registration across eight sequences. Although this application has an AUC of 0.94, it is not really practical in clinical application.

The second method [14] is an advanced version of the aforementioned approach. A model was developed to calculate the Days Gained score, which estimates the amount of time a given therapy delays tumor growth. As PsP increases the survival rate, the Days Gained score is significantly different in terms of the true progression and PsP cohorts. Therefore, the score can be used to identify PsP from true progression. Compared with the first method, the second method reduced the data complexity using the T1 and T2 sequences only.

However, segmentation could not be avoided in this study. Overall, the AUC of this method is 0.8, which is lower than that in the present study. Another obvious shortcoming is that the score cannot aid in diagnosis at the earliest time because the classification depends on the survival time.

5. Conclusions

In this study, we developed and validated a new method to evaluate true brain tumor progression in contrast to PsP. This method was helpful in clinical decision making. DTI, as a promising method for characterizing microstructural changes or differences in neuropathology and treatment, was used in this approach. FA was extracted as the key measurement of PsP. PsP of patients were successfully identified using the proposed image analysis approach. The labor-intensive and time-consuming segmentation of the ROI was no longer needed. Furthermore, the proposed approach solved the location restriction with a skillfully composed feature matrix. We also explained the misclassified samples and the features.

In future works, we will consider involving more measurements extracted from DTI data, such as the mean diffusivity, axial diffusivity, and radial diffusivity values. This additional information describes the different properties of the DTI data and provides more diagnostic value.

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References

1. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *The lancet oncology*. 2008; 9(5):453–461. [PubMed: 18452856]
2. da Cruz LH, Rodriguez I, Domingues R, Gasparetto E, Sorensen A. Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. *American Journal of Neuroradiology*. 2011; 32(11):1978–1985. [PubMed: 21393407]
3. DeWit M, De Bruin H, Eijkenboom W, Smitt PS, Van Den Bent M. Immediate post-radiotherapy changes in malignant glioma can mimic tumor progression. *Neurology*. 2004; 63(3):535–537. [PubMed: 15304589]
4. Kumar AJ, Leeds NE, Fuller GN, Van Tassel P, Maor MH, Sawaya RE, Levin VA. Malignant gliomas: Mr imaging spectrum of radiation therapy-and chemotherapy-induced necrosis of the brain after treatment 1. *Radiology*. 2000; 217(2):377–384. [PubMed: 11058631]
5. Ulmer S, Braga T, Barker F, Lev M, Gonzalez R, Henson J. Clinical and radiographic features of peritumoral infarction following resection of glioblastoma. *Neurology*. 2006; 67(9):1668–1670. [PubMed: 17101902]
6. Henson J, Ulmer S, Harris G. Brain tumor imaging in clinical trials. *American Journal of Neuroradiology*. 2008; 29(3):419–424. [PubMed: 18272557]
7. Mehta AI, Kanaly CW, Friedman AH, Bigner DD, Sampson JH. Monitoring radiographic brain tumor progression. *Toxins*. 2011; 3(3):191–200. [PubMed: 22069705]
8. Sundgren PC, Fan X, Weybright P, Welsh RC, Carlos RC, Petrou M, McKeever PE, Chenevert TL. Differentiation of recurrent brain tumor versus radiation injury using diffusion tensor imaging in patients with new contrast-enhancing lesions. *Magnetic resonance imaging*. 2006; 24(9):1131–1142. [PubMed: 17071335]

9. Hu X, Wong KK, Young GS, Guo L, Wong ST. Support vector machine multiparametric mri identification of pseudoprogression from tumor recurrence in patients with resected glioblastoma. *Journal of Magnetic Resonance Imaging*. 2011; 33(2):296–305. [PubMed: 21274970]
10. Feldman HM, Yeatman JD, Lee ES, Barde LH, Gaman-Bean S. Diffusion tensor imaging: a review for pediatric researchers and clinicians. *Journal of developmental and behavioral pediatrics: JDBP*. 2010; 31(4):346. [PubMed: 20453582]
11. Agarwal A, Kumar S, Narang J, Schultz L, Mikkelsen T, Wang S, Siddiqui S, Poptani H, Jain R. Morphologic mri features, diffusion tensor imaging and radiation dosimetric analysis to differentiate pseudo-progression from early tumor progression. *Journal of neuro-oncology*. 2013; 112(3):413–420. [PubMed: 23417357]
12. Schölkopf, B.; Smola, AJ. *Learning with kernels: Support vector machines, regularization, optimization, and beyond*. MIT press; 2002.
13. Zacharaki EI, Kanas VG, Davatzikos C. Investigating machine learning techniques for mri-based classification of brain neoplasms. *International journal of computer assisted radiology and surgery*. 2011; 6(6):821–828. [PubMed: 21516321]
14. Neal ML, Trister AD, Ahn S, Baldock A, Bridge CA, Guyman L, Lange J, Sodt R, Cloke T, Lai A, et al. Response classification based on a minimal model of glioblastoma growth is prognostic for clinical outcomes and distinguishes progression from pseudoprogression. *Cancer research*. 2013; 73(10):2976–2986. [PubMed: 23400596]
15. Elad M, Aharon M. Image denoising via sparse and redundant representations over learned dictionaries. *Image Processing, IEEE Transactions on*. 2006; 15(12):3736–3745.
16. Mairal J, Elad M, Sapiro G. Sparse representation for color image restoration. *Image Processing, IEEE Transactions on*. 2008; 17(1):53–69.
17. Bryt, O.; Elad, M. Improving the k-svd facial image compression using a linear deblocking method. *Electrical and Electronics Engineers in Israel, 2008. IEEEI 2008. IEEE 25th Convention of; IEEE; 2008*. p. 533–537.
18. Bryt O, Elad M. Compression of facial images using the k-svd algorithm. *Journal of Visual Communication and Image Representation*. 2008; 19(4):270–282.
19. Chan MD, Tatter SB, Lesser G, Shaw EG. Radiation oncology in brain tumors: current approaches and clinical trials in progress. *Neuroimaging clinics of North America*. 2010; 20(3):401–408. [PubMed: 20708554]
20. Rorden, C.; Karnath, H.; Bonilha, L. Mricron dicom to nifti converter. *Neuroimaging Informatics Tools and Resources Clearinghouse (NITRC)*;
21. Woolrich MW, Jbabdi S, Patenaude B, Chappell M, Makni S, Behrens T, Beckmann C, Jenkinson M, Smith SM. Bayesian analysis of neuroimaging data in fsl. *Neuroimage*. 2009; 45(1):S173–S186. [PubMed: 19059349]
22. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. Fsl. *Neuroimage*. 2012; 62(2):782–790. [PubMed: 21979382]
23. Smith SM. Fast robust automated brain extraction. *Human brain mapping*. 2002; 17(3):143–155. [PubMed: 12391568]
24. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. *Medical image analysis*. 2001; 5(2):143–156. [PubMed: 11516708]
25. Tan H, Bao J, Zhou X. A novel missense-mutation-related feature extraction scheme for drivermutation identification. *Bioinformatics*. 2012; 28(22):2948–2955. [PubMed: 23044540]
26. Fink J, Born D, Chamberlain MC. Pseudoprogression: relevance with respect to treatment of high-grade gliomas. *Current treatment options in oncology*. 2011; 12(3):240–252. [PubMed: 21594589]
27. Smyth GK, Michaud J, Scott HS. Use of within-array replicate spots for assessing differential expression in microarray experiments. *Bioinformatics*. 2005; 21(9):2067–2075. [PubMed: 15657102]
28. Segal E, Sirlin CB, Ooi C, Adler AS, Gollub J, Chen X, Chan BK, Matcuk GR, Barry CT, Chang HY, et al. Decoding global gene expression programs in liver cancer by noninvasive imaging. *Nature biotechnology*. 2007; 25(6):675–680.

29. Wrensch M, Kelsey KT, Liu M, Miike R, Moghadassi M, Sison JD, Aldape K, McMillan A, Wiemels J, Wiencke JK. Ercc1 and ercc2 polymorphisms and adult glioma. *Neuro-Oncology*. 2005; 7(4):495–507. [PubMed: 16212814]
30. Ji G, Gu A, Xia Y, Lu C, Liang J, Wang S, Ma J, Peng Y, Wang X. Ercc1 and ercc2 polymorphisms and risk of idiopathic azoospermia in a chinese population. *Reproductive biomedicine online*. 2008; 17(1):36–41. [PubMed: 18616887]

Figure 1.

Pre-processing of the DTI data. Left column: One slice of DTI; Middle column: One slice of FA image; Right column: Registered FA image. Two samples are given, and they are aligned to the same head space from their original shape.

Figure 2.
Flowchart of dictionary learning.

Figure 3.

Reshaping the sparse representation. The element with darker background has the larger value.

Figure 4. Image features and clinical information of 79 patients in total. Dark gray: pseudo progression, Light gray: true progression; Dark yellow: Did not die of GBM; Light yellow: Died of GBM.

Figure 5.
ROC and PR curves of the classification when $K = 512$ and $K = 1024$.

Figure 6. AUC of PR and AUC of ROC change with the dictionary size K . Solid line: AUC of PR; Dashed line: AUC of ROC.

Figure 7.
The association map of image features and gene features with the 23 patients in Dataset 1. The image features are shown on top. The gene expression pattern distinguished by image features are shown on bottom.

Table 1

Structure of the two datasets. Dataset 1 consists of patients with both genomics and imaging data. Dataset 2 consists of patients with imaging data. Dataset 1 is a subset of Dataset 2.

	Dataset 1	Dataset 2
Number of Samples	23	79
Number of Pseudo progression	9	23
Number of True progression	14	56

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Table 2

Performance of 5-fold cross-validation with Dataset 2.

	<i>K</i> = 512	<i>K</i> = 1024
10 times	83.13%	82.18%
30 times	82.34%	83.69%
100 times	82.50%	83.42%

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