Radiomic signatures for the non-invasive prediction of EGFR mutation status in brain metastases of lung adenocarcinoma

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Abstract

The epidermal growth factor receptor (EGFR) mutation exists in approximately 50% of patients with lung adenocarcinoma and is crucial for predicting response to targeted therapies. An increasing number of patients with lung adenocarcinoma have brain metastases (BMs) at diagnosis or later develop BMs. The study aimed to establish a non-invasive radiomics model for distinguishing EGFR mutation status in BMs and investigating the predictive performance of four MR sequences. 122 patients diagnosed with BMs of lung adenocarcinoma (57 mutant EGFR patients and 65 wild-type EGFR patients) were enrolled in the study. 960 features were extracted from contrast-enhanced T1-weighted imaging (CE-T1WI), fluid-attenuated inversion recovery (FLAIR), Diffusion Weighted Imaging (DWI), and contrast-enhanced susceptibility-weighted imaging (CE-SWI) sequences separately. 27 key radiomics features were selected after feature selection. The prediction performance of different machine learning models was evaluated and the model of four MR sequences was constructed using the SVM classifier. Accuracy, sensitivity, specificity, and AUC were used to evaluate our model performance. Our CE-T1WI + FLAIR + DWI + CE-SWI sequence model achieved the best performance with ACC reaching 0.9167, AUC reaching 0.9720, Sensitivity reaching 0.9167, and Specificity reaching 0.9015. It was significantly higher than the CE-T1WI model (ACC:0.7917, AUC:0.8631), CE-T1WI + FLAIR model (ACC:0.9167, AUC:0.9231) and CE-T1WI + FLAIR + DWI model (ACC:0.8333, AUC:0.9371) in the testing set. Our CE-T1WI + FLAIR + DWI + CE-SWI model can serve as an effective tool to predict the EGFR mutation status in BMs of lung adenocarcinoma and be conducive to guiding patient treatment strategies.

1. Introduction

Lung adenocarcinoma is the most common type of non-small cell lung cancer (NSCLC), which accounts for 35–40% of lung cancer cases [1]. Many patients with adenocarcinoma present at initial diagnosis with brain metastasis (BMs) from the primary tumor lesion and later develop BMs, with a prevalence of 20–30% [2]. Patients with BMs have a median survival of 4–8 months without treatments [3, 4]. In recent years, treatment strategies for patients with lung adenocarcinoma have improved significantly.

Epidermal growth factor receptor (EGFR) mutations are common in patients with lung adenocarcinoma. Tyrosine kinase inhibitors (TKIs) have achieved favorable results in patients with BMs of mutant-EGFR advanced lung adenocarcinoma [5], and alterations in some pathogenic genes of EGFR would have a good prognosis due to sensitivity to TKIs [6], such as the deletion of exon 19 and the point mutation in exon 21. Studies have shown that mutant EGFR patients with BMs of lung cancer have a higher survival rate than those with wild-type EGFR because of higher response rates to some treatments, such as whole-brain radiation therapy and specific chemotherapy medications [19]. Relevant research demonstrated significant differences in tumor microenvironment composition between patients with mutant EGFR and wild-type EGFR [6]. Some mutant EGFR patients with lung adenocarcinoma have a poorer response to anti-PD1 / PD-L1 immunotherapy [6]. Therefore, timely identification of EGFR mutation status is essential for predicting treatment outcomes and determining individual treatment strategies.

Currently, the standard procedure to confirm EGFR mutation status is still the pathological examination. However, due to its aggressiveness obtaining tissue specimens from primary tumors or BMs is not always practical and carries the risk of complications. In recent years, some research demonstrates that plasma circulating tumor DNA (ctDNA) has the potential to identify mutation status [7, 8, 9] which always requires high detection technology. Magnetic resonance imaging (MRI) is the most widely used non-invasive method for the detection and assessment of BMs, which could reveal many features [10, 11], including lesion size, intra-tumoral necrosis, peritumor edema, intra-tumoral microbleeds and the extent of imaging signal, but there are still no specific markers to assist radiologists to determine EGFR mutation status based on MRI images [12]. Therefore, it's urgent to develop an accurate and effective method to help identify EGFR mutation status, especially for synchronous BM patients with adenocarcinoma, which benefits timely diagnosis and prognosis evaluation.

High-throughput features extracted from medical images with radiomics methods can quantify tumor phenotypic differences and microenvironment-related information in imaging data, with applications in tumor classification, genotyping, and prognosis prediction [13, 14, 15, 20]. Many studies have demonstrated the clinical potential of brain MRI-based imaging methods for the detection of mutations in primary brain tumors and the assessment of outcomes [16, 17], and the ability to capture features associated with EGFR mutations from MRI images of BMs by radiomics [18, 19, 21, 22]. Wang et al [12] extracted features from
the whole tumor area and built the prediction model to distinguish EGFR status in BMs. However, some radiomics methods for predicting EGFR mutation status in patients with BMs of lung adenocarcinoma remain limited and few studies have involved multiple brain MRI sequences, especially the CE-SWI sequence.

Therefore, this study first involved the CE-SWI sequence, aiming to establish a reliable non-invasive approach for distinguishing EGFR mutation status in BMs of lung adenocarcinoma based on clinical data from patients of lung adenocarcinoma with synchronous BMs and imaging data from multiple brain MRI sequences: contrast-enhanced T1-weighted imaging (CE-T1WI), fluid-attenuated inversion recovery (FLAIR), Diffusion Weighted Imaging (DWI), contrast-enhanced Susceptibility-weighted imaging (CE-SWI), and analyze the predictive performance of the four MR sequences.

2. Materials and methods

2.1. Patients

This study was approved by the institutional review boards (IRBs) and the requirement for informed consent was waived. Inclusion criteria were as follows: (a) lung adenocarcinoma was diagnosed; (b) patients have presented BMs; (c) EGFR mutation status was confirmed; (d) all MRI examinations (CE-T1WI, FLAIR, DWI, and CE-SWI sequence) were completed before initiating treatment for the BMs. Exclusion criteria were as follows: (a) low MR image quality, such as image artifacts; (b) a history of other CNS diseases. The baseline characteristics included age, sex, and BM lesion number. 122 patients were randomly divided into the training and testing set according to the ratio of 4:1. Detailed information on the inclusion and exclusion of patients was shown in Supplementary Fig. 1. The pipeline of our study was in Fig. 1.

2.2. MRI acquisition and Tumor ROI segmentation

Patients were examined using an MRI scanner when initially diagnosed with brain metastases and scan parameters were in Supplementary Table 1. Paired BMs on CE-T1WI and CE-SWI sequences were manually delineated around the lesions slice-by-slice in the axial view by an experienced neuroradiologist using the ITK-SNAP (version 3.2) software. The segmented regions of interest (ROI) were confirmed by a senior neuroradiologist and refined if necessary. The whole ROI mask was the combination of these two masks and merged for subsequent feature extraction.

2.3. MRI preprocessing

Firstly, the N4 Bias Field Correction [23] was performed to reduce the nonuniformity of the low-frequency intensity. All sequences acquired during the same session were registered to the T1 sequence using ANTsPy (https://github.com/ANTsX/ANTsPy) package [24]. In order to guarantee the physical space consistency in different MRI, all images were resampled to 1×1×1 mm³ voxel size using the Simple Insight Segmentation And Registration Toolkit (SimpleITK, https://github.com/SimpleITK/SimpleITK) package [25]. To reduce the effect of differences in image intensity, intensity normalization was applied to all MRI images with the Z-score normalization method [26].

2.4. Feature extraction

According to the .yaml file that set up the image processing method, three kinds of radiomics features from each MR sequences would be extracted, including the first-order features, shape-based (3D, 2D) features, and high-order texture features, which included the gray-level co-occurrence matrix (GLCM), gray-level dependence matrix (GLDM), gray-level run length matrix (GLRLM), gray-level size zone matrix (GLSZM). For the LoG filter, the sigma values were set to 3.0 and 5.0 mm. For the wavelet transform, each image was filtered in the x, y, and z directions using a low and high bandpass filter. Finally, 960 features were obtained from each MR sequence which contained 14 shape-based features, 198 first-order features, and 748 high-order texture features. Table 1 presented the number distribution of features extracted in different image types.
Table 1
The number distribution of radiomics features extracted in different image types.

<table>
<thead>
<tr>
<th>Image Type</th>
<th>Shape Feature</th>
<th>First-Order Feature</th>
<th>High-Order Texture Feature</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original images</td>
<td>14</td>
<td>18</td>
<td>68</td>
<td>100</td>
</tr>
<tr>
<td>LoG-sigma-transformed images</td>
<td>0</td>
<td>36</td>
<td>136</td>
<td>172</td>
</tr>
<tr>
<td>Wavelet-transformed images</td>
<td>0</td>
<td>144</td>
<td>544</td>
<td>688</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>198</td>
<td>748</td>
<td>960</td>
</tr>
</tbody>
</table>

2.5. Feature selection and model construction

Before feature selection, uniformly converting the magnitudes of all extracted features into the same magnitude was to ensure consistency. For each feature vector, calculating the mean and standard deviation in the training set, and then subtracting each feature vector from the mean followed by division by the standard deviation. Features’ correlation was calculated using Pearson correlation.

The extracted radiomics features contained some redundant and irrelevant features. Feature selection could identify these and select the most informative radiomics features and avoid over-fitting issues. In our work, the Mann-Whitney U test was implemented to choose features with statistical differences (p-value < 0.05) and removed the feature with worse predictive power. Then the initially selected features were further filtered using the Least Absolute Shrinkage and Selection (LASSO) [27].

The selected features were used as the input of several machine learning (ML) models, including Extreme Gradient Tree (XGBoost) [28], logistic regression (LR) [29], Random Forest (RF) [30], Support Vector Machine [31] with the radial basis function kernel (SVM-RBF).

During the training process, we applied the Grid Search method and 5-fold cross-validation to optimize several models. The performance of each model was evaluated in our testing set. Hyperparameter values of each best model used in the prediction task was shown in Table 2. We implemented feature selection and ML algorithms using the SciPy library (https://scipy.org/) and Scikit-learn Machine Learning library (https://scikit-learn.org/stable/).

Table 2
Hyperparameter values of each model used in the prediction task.

<table>
<thead>
<tr>
<th>Model</th>
<th>Hyperparameter values</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>penalty='l1', solver='liblinear', max_iter = 1000</td>
</tr>
<tr>
<td>RF</td>
<td>n_estimators = 74</td>
</tr>
<tr>
<td>SVM-RBF</td>
<td>kernel='rbf', C = 1024, gamma = 0.0006, probability = True</td>
</tr>
<tr>
<td>XGBoost</td>
<td>n_estimators = 28, objective='binary: hinge', use_label_encoder = False</td>
</tr>
</tbody>
</table>

2.6. Statistical analysis

The statistical analysis was performed using SciPy library (https://scipy.org/) and SPSS (version 25.0; IBM Corp). Univariate analysis was used to evaluate the relationship between EGFR mutation status and patient features, including clinical characteristics and radiomics features. Accuracy (ACC), Sensitivity (SEN), Specificity (SPE), the receiver operating characteristic curve (ROC) and the area under the receiver operating characteristic curve (AUC) were used for assessing the ability of the prediction model.

3. Results

3.1. Clinical characteristics
Table 3 summarized the clinical characteristics of the 122 patients (65 patients with wild-type EGFR, and 57 patients with mutant EGFR). It was clear that there were no significant differences in terms of sex and age between wild-type EGFR and mutant EGFR patients whether in our training or testing set.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Training(n = 98)</th>
<th>p-value</th>
<th>Testing(n = 24)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wild (n = 52)</td>
<td></td>
<td>Wild (n = 13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mutant (n = 46)</td>
<td></td>
<td>Mutant (n = 11)</td>
<td></td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51.9(%)</td>
<td>0.207</td>
<td>53.8(%)</td>
<td>0.683</td>
</tr>
<tr>
<td>Female</td>
<td>48.1(%)</td>
<td></td>
<td>46.2(%)</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD years)</td>
<td>59.78±1.03</td>
<td>0.437</td>
<td>61.129±1.90</td>
<td>0.172</td>
</tr>
<tr>
<td></td>
<td>57.48±10.54</td>
<td></td>
<td>63.15±2.85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>62.37±9.15</td>
<td></td>
<td>59.09±2.77</td>
<td></td>
</tr>
<tr>
<td>Lesion number</td>
<td>7.21±11.82</td>
<td>0.9884</td>
<td>5/69±1.76</td>
<td>0.320</td>
</tr>
<tr>
<td></td>
<td>10.54±24.55</td>
<td></td>
<td>2.91±0.86</td>
<td></td>
</tr>
</tbody>
</table>

Note: SD: standard deviation. *p < 0.05.

### 3.2. Feature selection and signature construction

The process of LASSO feature selection was shown in Supplementary Fig. 2. We finally selected the 9 most important features on CE-T1WI, 10 features on FLAIR, 6 features on DWI, and 2 features on CE-SWI sequence, and the optimal alpha in LASSO was set 0.0509, 0.0285, 0.0231, and 0.0221 respectively according to the mean-square error (MSE) in the training process. The statistical analysis of the selected features was shown in Supplementary Table 2.

Then we visualized features extracted on each MRI sequence in the bar chart and the results were shown in Supplementary Fig. 3. The heatmap of the feature correlation coefficient after feature selection was shown in Fig. 2, with higher color saturation resulting in stronger inter-feature correlations and lower color saturation resulting in lower inter-feature correlations.

### 3.3. Model performance

Table 4 gave the prediction performance in the testing set of different MRI sequence models with different sets of features. It could be seen that incorporating the clinical features slightly improved the predictive performance of the model. The confusion matrix of each machine learning model when predicting on the validation set is shown in Fig. 3. The best prediction performance was achieved using the SVM model, with ACC reaching 0.9167, AUC reaching 0.9660, SEN reaching 0.9167 and SPE reaching 0.9015. The ROC curves and AUCs of these four different machine learning models in the testing set before and after incorporating the clinical features was presented in Fig. 4. It was clear that the ROC curve of each machine learning model moved to the upper left corner after incorporating the clinical features.

Considering the specificity of different MRI sequences, the T1 model, T1 + FLAIR model, T1 + FLAIR + DWI model, and T1 + FLAIR + DWI + SWI model were constructed by combining features extracted from MRI different sequences. The ROC curves of different MRI sequence models in the testing set were shown in Fig. 5. Figure 6 showed the heatmap of ACC, AUC, SEN, and SPE of four sequence models in the testing set. The prediction model performed better discrimination in the testing set after adding the features extracted from the SWI sequence.
Table 4
The predictive performance of EGFR status in the validation set.

<table>
<thead>
<tr>
<th>Model</th>
<th>27 radiomics features</th>
<th>27 radiomics features + 3 clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACC</td>
<td>AUC</td>
</tr>
<tr>
<td>SVM</td>
<td>0.9167</td>
<td>0.9650</td>
</tr>
<tr>
<td></td>
<td>(1.0000,0.8182)</td>
<td>(0.8182,1.0000)</td>
</tr>
<tr>
<td>RF</td>
<td>0.8333</td>
<td>0.9371</td>
</tr>
<tr>
<td></td>
<td>(0.9231,0.7273)</td>
<td>(0.7273,0.9231)</td>
</tr>
<tr>
<td>LR</td>
<td>0.8750</td>
<td>0.9580</td>
</tr>
<tr>
<td></td>
<td>(0.9231,0.8182)</td>
<td>(0.8182,0.9231)</td>
</tr>
<tr>
<td>XGB</td>
<td>0.7083</td>
<td>0.6958</td>
</tr>
<tr>
<td></td>
<td>(0.8462,0.5455)</td>
<td>(0.5455,0.8462)</td>
</tr>
</tbody>
</table>

Note: XGB = XGBoost. The values in the first row of the SEN and SPE columns are the weighted values of the predicted results on the two EGFR types, and the values in the second row in parentheses indicate the predicted results for the wild type and mutant respectively.

4. Discussion
In this present study, we analyzed brain MR images from four sequences in 122 patients with BMs of lung adenocarcinoma. 960 radiomics features were extracted from each normalized CE-T1WI, FLAIR, DWI, and CE-SWI sequence, and then were reduced to 27 key features (9 from CE-T1WI, 10 from FLAIR, 6 from DWI, and 2 from CE-SWI) by the LASSO selection method. We built machine-learning models to predict EGFR mutation status from selected features on the training set and evaluated the predictive ability of models on the testing set. We found that radiomics features from CE-T1WI, FLAIR, DWI, and CE-SWI sequences of brain MR could differentiate wild-type and mutant EGFR in BMs of lung adenocarcinoma.

Relevant research suggested that the age distribution of EGFR mutations status may count on different types [32, 33]. In this study, no statistical differences in EGFR mutation status were found by statistical analysis for gender and age, which may be due to the limitation of sample size in our study. The number of BM lesions characterized by statistical analysis was statistically different in terms of EGFR mutation status.

We extracted 960 imaging radiomics features from each MRI sequence, and selected 27 statistically significant radiomics features after Mann-Whitney U-test and LASSO feature selection. We visualized the feature importance of the extracted features on each sequence in the form of a bar chart and performed feature correlation analysis, showing the correlation between the features in the form of a heat map. From Fig. 2, it could be seen that most of the color blocks have low color saturation, the correlation between features was low and most of the redundant features have been removed.

The CE-T1WI + FLAIR + DWI + CE-SWI model showed excellent performance which yielded an ACC of 0.9167, AUC of 0.9720, Sensitivity of 0.9167, and Specificity of 0.9015 on our testing set, which was much higher than that of the CE-T1WI model (ACC: 0.7917, AUC:0.8531), CE-T1WI + FLAIR model (ACC:0.9167, AUC:0.9231), and CE-T1WI + FLAIR + DWI model (ACC: 0.8333, AUC:0.9371).

According to previous studies, radiomics has been used to assess the mutation status of distant metastases in primary cancers. Related studies have assessed the ability to identify the mutation status based on the radiomics features from primary lung cancer CT images [34–36]. However, with the advancement of imaging technology, a growing number of small brain metastases can be detected in some asymptomatic patients before the primary lung cancer is diagnosed. It is essential to build new radiomics models for rapid identification of mutation status rather than models based on primary tumor images. Furthermore, it is impractical to build radiomics models by extracting features from primary tumor lesions in patients who have received...
appropriate treatment (e.g., radiotherapy, chemotherapy, or surgical resection). Therefore, there is a need to develop an effective method based on conventional brain MRI from patients with BMs of lung adenocarcinoma, which will facilitate the development of personal treatment strategies. Recently, Wang et al. [12] built a radiomics signature with the logistic regression based on T2-FLAIR sequence to predict EGFR mutation status, yielding an AUC of 0.987 and an accuracy of 0.991 in their validation set. Ahn et al. [37] explored radiomics features from brain CE-T1WI images to predict EGFR mutation status in patients of BMs with primary lung cancer and the highest diagnostic performance was reaching an AUC of 0.8681 in the test set. Li et al. [38] used radiomics analysis to differentiate the EGFR and ALK gene mutations and their T2-FLAIR model achieved an AUC of 0.950. However, few studies have used all CE-T1WI, FLAIR, DWI, and CE-SWI sequences from BMs of lung adenocarcinoma to identify EGFR mutation status. As far as we know, our work is the first study involving the CE-SWI sequence and directly uses four brain MRI sequences (CE-T1WI + FLAIR + DWI + CE-SWI) to distinguish EGFR mutation status in BMs of lung adenocarcinoma. Our model can integrate multimodal complementary information to achieve more accurate prediction accuracy.

Our study remained some limitations. First of all, it was a retrospective study based on a single center and more prospective multi-center validation will have to be done in the future. Furthermore, due to the insufficient sample size, only wild-type and mutant EGFR mutation status were distinguished in this study, and more data will have to be collected to subdivide the mutation types and develop a radiomics signature to distinguish common EGFR mutations from rare mutations.

In conclusion, MRI sequence-based radiomics features are valuable in distinguishing the mutant EGFR and wild-type EGFR in patients with BMs of lung adenocarcinoma, especially features from the CE-SWI sequence, and our CE-T1WI + FLAIR + DWI + CE-SWI model achieved the best prediction result, which can serve as a non-invasive method to assist radiologists in judging EGFR mutation status.

5. Conclusion

In brief, we proposed and verified a radiomics pipeline based on CE-T1WI, FLAIR, DWI, and CE-SWI brain MR sequences to distinguish the EGFR mutation status in BMs of lung adenocarcinoma. Compared with those mainly focusing on single or two MR sequences, our CE-T1WI + FLAIR + DWI + CE-SWI sequence model achieved the best prediction result attributed to integrating multi-modality complementary information. Our developed radiomics model can provide a non-invasive and rapid identification of EGFR mutation status in BMs of lung adenocarcinoma, which can be effective for individual treatment planning.

Declarations

Funding

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Administrative support and provision of study materials or patients were performed by Linlin Sun, Li Zhu. Data analysis and interpretation were performed by LH Yu, ZK Yu. The first draft of the manuscript was written by LH Yu. All authors read and approved the final manuscript.

Data Availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Ethics approval**

The present study was approved by the local hospital. The requirement for written informed consent was waived.

**Consent to participate**

The present study was approved by the local hospital. The requirement for written informed consent was waived.

**Consent to publish**

The identifying information of all participants is not covered in this paper.

**References**


**Figures**

**Figure 1**

The pipeline of our study, including six parts.
Figure 2

The heatmap of feature correlation coefficient after feature selection.
Figure 3

Confusion matrix of four different models in the testing set. Wild means the wild-type EGFR, mutant means the mutant EGFR. (a) LR, (b) SVM, (c) RF, (d) XGBoost.
Figure 4

ROC curves of four machine learning models in the testing set. (a) only using radiomics features. (b) radiomics + clinical features.
Figure 5

ROC curves of different MRI sequences models in the testing set. (a) CE-T1WI model, (b) CE-T1WI+FLAIR model, (c) CE-T1WI+FLAIR+DWI model, (d) CE-T1WI+FLAIR+DWI+ CE-SWI model.
Figure 6

The heatmap of ACC, AUC, SEN, and SPE of different MRI sequence models in the testing set.

Supplementary Files

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- supplementary.docx