Radiomic model for differentiating parotid pleomorphic adenoma from parotid adenolymphoma based on MRI images

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Abstract

Background: Magnetic resonance imaging (MRI) is used routinely in the clinical management, and we explored the diagnostic value of radiomic signatures based on MRI to distinguish parotid pleomorphic adenoma from parotid adenolymphoma.

Methods: The clinical characteristics and images data were retrospectively collected from 252 cases (126 cases in training cohort and 76 patients in verification cohort) in this study. And 429 radiomic features of T1-weighted imaging (T1WI) sequence and 414 radiomic features of T2-weighted imaging (T2WI) were extracted from MRI images. We selected the radiomic features from three sequences (T1WI, T2WI and T1-2WI) by univariate analysis, lasso correlation and spearman correlation. Then we built six quantitative radiological models based on the selected radiomic features using two machine learning methods (multivariable logistic regression, MLR and support vector machine, SVM). We assessed the performance of the six radiomic models, and an ideal radiomic signature was chosen to compare its diagnosis efficacy with that of the clinical model.

Results: The radiomic model based on features of T1-2WI sequence by MLR showed optimal discriminatory (accuracy = 0.87 and 0.86, F-1score = 0.88 and 0.86, Sensitivity= 0.90 and 0.88, Specificity=0.82 and 0.80 positive predictive value=0.86 and 0.84, negative predictive value=0.86 and 0.84 in training and validation cohorts, respectively) and its good calibration was also observed ($p>0.05$). The area under the receiver operating characteristic curve (AUC) of the T1-2WI radiomic model was significantly better than that of the clinical model for both the training (0.95 vs. 0.74, $p=0.000$) and validation (0.90 vs. 0.73, $p=0.001$) cohorts.

Conclusions: The radiomic model based on MRI in our study is complementary to the current

knowledge of differential diagnosis for parotid pleomorphic adenoma and parotid adenolymphoma.

Keywords: Parotid pleomorphic adenoma, Parotid adenolymphoma, Radiomics, Diagnosis

Background

The morbidity of salivary gland tumors has progressively increased year by year, and nearly 80% cases occurred in the parotid gland [1]. As the two most common parotid tumors, parotid pleomorphic adenoma (PPA) is quite different from parotid adenolymphoma (PA) in terms of biological behavior [2], for the former shows higher potential of malignant change while the latter is more likely to grow with multifocal [3]. Therefore, precise differential diagnosis between PPA and PA is crucial to provide clinical guidance for the individualized treatment.

Medical imaging has the advantages of assessing and monitoring tumor temporally and spatially, which provide diagnostic information for diseases and thereby reduce the need for investigative surgery or other risky of patient care as much as possible [4,5]. More and more studies indicate the details of the radiographic imaging influence the accuracy of the diagnosis and reveal more characteristics of tumor even biological behavior [6,7]. However, by naked-eye, it is inevitable to loss some unreadable information of the radiographic imaging, which inappropriately interfere the clinical decision at some extent. In the field of medical imaging, the advances in artificial intelligence opened up a new frontier called radiomics, which integrates radiology, oncology, and machine learning algorithms. [8-9]. Compared with the traditional medical imaging method based on the visual interpretation, radiomics could mine the deep and subtle information of imaging through converting radiographic images into the quantitative features including descriptors of shape, size, and textural patterns [10].

The application of radiomics has made great strides in tumor diagnosis, treatment response assessment and prognosis [11-12]. In head-neck cancers patients, computed tomography (CT) and positron emission tomography (PET) radiomics signatures predict not only the HPV (p16) status in oropharyngeal squamous cell carcinoma [13] but also the hypoxia status [14], as well as distinguish the oropharyngeal and hypopharyngeal cancer [15]. Moreover, MRI radiomics signatures also have been recognized as the non-invasively and preoperatively independent prognostic factors for head and neck squamous cell carcinoma (HNSCC) and nasopharynx cancer (NPC) in clinical practice [16-17]. In parotid tumors, MRI is used routinely in the clinical management, but rarely few studies revealed the role of MRI radiomics model on distinguishing PPA from PA.

The purpose of this article is to complement current knowledge of differential diagnosis for PPA and PA by converting the image information into an radiomics model. Thus, we delineated the region of interest (ROI) of PPA and PA patients who underwent MRI scanning and selected the radiomics features from both T1WI and T2WI sequence. Further, we constructed radiomics models based on the selected features, and compared the diagnosis efficacy between the radiomics model and the clinical feature model.

Methods

Patients

This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Henan University of Science and Technology, and all procedures were in accordance with the principles of the Helsinki Declaration. In the primary screening period, we retrospectively enrolled four hundred twelve patients with parotid tumor undergoing MRI examination in the First

Affiliated Hospital of Henan University of Science and Technology between 2013 and 2019. And the further inclusion criteria are as follows: 1) there was no treatment for patients before examination; 2) T1WI and T2WI sequences of MRI scanning were complete included; 3) images were clear without artifacts; 4) definite pathological diagnosis by surgery and pathology were provided for patients. Finally, 112 PA patients and 140 PPA patients were collected in this study.

The clinical features of the 252 subjects are listed in Table 1. Among the PA patients, the average age was 55.57±1.29 (range: 23-77years) and the gender ratio (M/F) 1.38:1. Among the PPA patients, the average age was 47.81 ±1.473 (range: 15- 81 years) and the gender ratio (M/F) 0.67:1. The 252 subjects in the study were randomly separated into training (70% of the total) and verification (30% of the total) cohorts. Therefore, 176 cases were assigned to the training cohort (PA/PPA = 78/98) and the other 76 patients were assigned to the verification cohort (PA/ PPA = 34/42). The flow chart of the procedure is given in Fig.1.

Image acquisitions

All subjects underwent routine 1.5 Tesla MRI scans (GE Signa HDX 1.5 T; GE Healthcare, Milwaukee, WI) and Head-neck coil. The scanning sequence were acquired including the fast spin echo T1WI and the fast spin echo T2WI with fat saturation. The corresponding parameters of T1WI showed as following: TR 700.0 ms, TE 8.9 ms, matrix 320×192 mm, 24cm×24cm, slice thickness 5 mm, spacing 1 mm. The corresponding parameters of T2WI showed as following: TR 3900.0 ms, TE 100.0 ms, matrix 320×256, FSE 24 cm×24 cm, slice thickness 5 mm, slice spacing 1 mm in axial images; TR 3300.0 ms, TE 100.0 ms, matrix 320×224, FSE 24 cm× 24 cm, slice thickness 5 mm, slice spacing 1 mm in coronal images.

Tumor segmentation and radiomics feature extraction

MRI image data came from our organization's image archiving and communication system (PACS). Two board-certified senior radiologists (readers 1 and 2, with 8 and 13 years of clinical experience in head and neck diagnosis, respectively) independently interpreted MRI images including T1WI and T2WI sequence scanning on the PACS of the radiology department (Fig.2 a-b). The two radiologists manually delineated the ROI by using MATLAB (2014b, Mathworks, Nafick, MA,USA) and an open source program software, Imaging Biomarker Explorer (IBEX,http://bit.ly/ IBEX_MD Anderson). And the extracted feature included intensity histogram, gray co-occurrence matrix (GLCM), gray run length matrix (GLRLM) and shape. The reader 1 extracted features twice with the same procedure, and twice collected features data were used to measure the intra-observer consistency. At the same time, the reader 2 extracted features independently, and the features data collected by reader 2 were compared with that by reader 1 to evaluate inter-observer consistency. Intraclass correlation coefficient (ICC) was used to calculate the consistency, and the features with robust consistency (ICC> 0.75 both in intra-observer and inter-observer) would be remained for next selection.

Dimensionality reduction and radiomics feature selection

After z-score normalization, the extracted features (ICC>0.75) of T1WI and T2WI sequence were examined by independent sample t-test (continuity variable) or Mann-Whitney U test (classified variable). Here, the selected features of T1WI and T2WI sequence ($p<0.05$) were combined as the T1-2WI features, and all the retained T1WI, T2WI and T1-2WI features ($p<0.05$) were processed to the dimensionality reduction procedure as following.

First the patients were randomly allocated to the training cohorts and validation cohorts at the ratio of 7:3 according to the published report. Second, in order to improve the accuracy and fitting

degree of the modeling, LASSO method was carried out on the training cohort to further screen the significant features [18]. The 1-standard error of the minimum criteria was used in this study. Third, correlation coefficient values of the radiological features were assessed by spearman analysis, and the radiological features with high linear correlation (correlation coefficient values of 0.90-1.00) were excluded.

Construction of radiomics models

After the dimensionality reduction procedure, the important and independent T1WI, T2WI and T1-2WI features were respectively used to construct radiomics models based on two machine learning methods, the MLR and SVM. The discriminatory performance of the models were quantified and evaluated in training and validation cohorts according to AUC, accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), F-1score. The calibration of radiomics model was calculated by the Hosmer-Lemeshow test. The independent clinical feature model was established with the clinical features by MLR. And then the diagnosis efficacy of the radiomics model was compared with that of the clinical feature model on both the training cohort and the verification cohort.

Statistical analysis

Use R (version 3.4.1, https://www.r-project.org/) was used to the statistical analysis. The normality of the distribution and the homogeneity of variance were respectively evaluated by shapiro-wilk test and Bartlett test. Continuous variables were compared by independent t-test or wilcoxon rank sum test while categorical variables were compared by chi-square tests or Fisher's exact tests. LASSO regression was carried out using "glmnet" package with the multivariate binary logistic regression. The correlation coefficient matrix was visualized by "ggplot2" and "ggcorrplot"

package. SVM models and ROC curves were generated with “e1071” and “pROC” packages, respectively. And the AUCs were compared using the ‘DeLong’ test in both the MLR and SVM model. And p-value<0.05 indicated statistical difference.

Results

Clinical characteristics

The baseline characteristics of the patients in this study are summarized in Table 1. In the both training cohort and validation cohort, there was no significant difference in the proportion (p=0.951) but significant differences in sex, age and smoking behavior (p<0.05) of PA patients and PPA patients. PPA is more common in young adults, while PA is more common in elderly men with smoking history [19]. And the clinical features are following used to construct the clinical models.

Intra- and inter-observer variability assessment of feature extraction

A total of 429 radiomics features of T1WI sequence were extracted by ROI (intra-observer mean ICC=0.843708, inter-observer mean ICC=0.7079306). And 174 radiomics features of T1WI sequence (ICC<0.75) were excluded, among which 100 did not reach the inter-observer reproducibility as well as 74 not in both intra-observer and inter-observer (Fig.2c-d). The remaining 255 features of T1WI sequence were included in the follow-up analysis. A total of 414 radiomics features of T2WI sequence were extracted by ROI (inter-observer mean ICC=0.8031534, intra-observer mean ICC=0.8989001). And 148 radiomics features of T2WI sequence (ICC<0.75) were excluded, among which 106 did not reach the inter-observer reproducibility as well as 42 not in both intra-observer and inter-observer (Fig.2c-d). The remaining 266 features of T2WI sequence were included in the follow-up analysis.

Feature selection and radiomics feature building

207 features of T1WI sequence (T1WI features) and 239 features of T2WI sequence (T2WI features) with significant differences were selected using T test or Mann-Whitney U test ($p<0.05$). Then the 207 T1WI features and 239 T2WI features were combined as T1-2WI radiomics features. Further, three feature groups, T1WI features (n=7) and T2WI features (n=8) as well as T1-2WI features (n=8), were respectively extracted by LASSO regression under the 1-SE criteria by 10-fold cross-validation (Fig.3 a-f). And there were none pairs of features that showed a very strong positive correlation in any of the three feature group by spearman correlation coefficient (Fig.3 g-i). Thus, the radiomics features of above three groups were respectively used to construct diagnostic models to distinguish PPA from PA.

Construction of the radiomics model

The models were built with MLR and SVM analysis, and the discriminatory performance of the six models were depicted by AUC, accuracy, sensitivity, specificity, PPV, NPV, F-1score (Table 2). T1-2WI features model was more robust when compared with the T1WI features model and T2WI features model by both MLR and SVM analysis. Subsequently, we constructed individual clinical feature model for further evaluating the discriminatory performance of T1-2WI features model (Table 3). And the DeLong test showed that the AUC of T1-2WI feature model was significantly better than that of the clinical model both in the training cohort ($p=0.000$) and verification cohort ($p=0.001$) (Fig.4a-b). And we further visualized such results by the decision curve (Fig.4c). Additionally, the calibration of T1-2WI features model was also reliable for the p-value of the Hosmer-Lemeshow test was unsignificant ($P>0.05$) (Fig.4d) [20].

Discussion

The diagnostic analysis of traditional imaging methods depended crucially on some subjective factors as well as the specific knowledge and experience of radiographers and radiologists. With the increasing amount of image data, artificial intelligence and methodologies, radiomics as the newly post-processing technique have gradually shown its advantage in the objectivity, quantification and repeatability of diagnostic analysis, which advance the precision medicine and individualized therapy in the future [21].

In this study, we provided a non-invasive and individualized radiomics diagnosis signature for distinguish the PPA from PA. We extracted features of ROI on both T1WI and T2WI sequence of MRI. We further selected the important and independent features of T1WI sequence and T2WI sequence by univariate analysis, LASSO correlation and spearman correlation. In addition, after the features of T1WI sequence and T2WI sequence had been underwent the selection by univariate analysis, we combined these features as T1-2WI features and further selected them by LASSO correlation and spearman correlation. Subsequently, we constructed and validated quantitative radiological models respectively based on the three features groups (T1WI features n=7; T2WI features, n=8; T1-2WI features, n=8). Finally, we also constructed the clinical feature model based on the clinical data from patients with PPA and PA.

The results showed, among the mentioned six radiomics models, the T1-2WI features model was the most robust in verification cohorts whenever constructed by MLR or SVM machine learning methods. The reasons is that the imaging model based on the combination of features from T1WI and T2WI sequence might provide more information than the model built by features from any single sequence. Moreover, in this study, 10-fold cross-validation is used to avoid the risk of modeling deviation and over-fitting as much as possible [22]. However, the model constructed by

MLR performed better than that constructed by SVM based on the T1WI features (n=7) and T2WI features (n=8). We inferred the possible reason may be that, compared with the model constructed by MLR, the model constructed by SVM is too complex to avoid over-fitting [23].

Given above results, the T1-2WI features radiomics constructed by MLR was chose as the representative radiomics model to compare its discrimination efficacy with that of clinical model. For equal comparison, we also used MLR to construct the clinical model. Significantly, T1-2WI features radiomics were better than clinical features model in terms of the AUC, accuracy, sensitivity, specificity, PPV, NPV, F-1score, and decision curve for differential diagnosis of parotid lymphoma and parotid pleomorphic adenoma in both training cohort and verification cohort. Besides, the calibration of T1-2WI features radiomics model was further validated by Hosmer-Lemeshow good of fit test. Our results further indicated that the radiomics model could improve the diagnosis efficacy for it might objectively and quantitatively provide the information of intra-tumor heterogeneity and inter-tumor microenvironment hidden behind the image [24, 25].

Our research also had the limitations. One is that we did not apply the multicenter cases. The other is the lack of the results on the combination of radiological features with tumor molecular markers or genomic information [26, 27]. In the future, we will further explore the relationship between radiomics and genomics, and such multi-omics might conducive to the precise diagnosis.

Conclusions

Our study constructed six radiomics models based on three feature radiomics sequences of MRI (T1WI, T2WI and T1-2WI) and two machine learning methods (MLR and SVM) in order to increase the accuracy of differential diagnosis between PPA and PA. The radiomics model based on features of T1-2WI not only showed optimal discriminatory among six radiomics models

but also significantly performed better than clinical model on both the training and validation cohorts. We hope the radiomics model based on MRI in our study could be helpful for distinguishing PPA from PA.

Abbreviations

AUC: Area under the concentration-time curve; MRI: Magnetic resonance imaging; T1WI features: features from T1-weighted imaging; T2WI features: features from T2-weighted imaging; T1-2WI features: features from T1-weighted imaging and T2-weighted imaging; ICC: intraclass correlation coefficient; LASSO: Least absolute shrinkage and selection operator; GLCM: gray co-occurrence matrix; GLRLM: gray run length matrix; ROC: Receiver operating characteristic; ROI: Region of interest; SVM: Support vector machine; MLR: multivariable logistic regression; PPV: positive predictive value; NPV: negative predictive value;

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Authors' Contributions

DSC and LNS proposed the study. LLS and SJC performed research, analyzed the data and wrote the first draft. WC, ZS, XDW collected the data. All authors contributed to the interpretation of the study and to further drafts. All authors read and approved the final manuscript.

Availability of data and materials

The data and material are available through the corresponding authors.

Ethics approval and consent to participate

This retrospective study was approved by the First Affiliated Hospital of Henan University of Science and Technology. Written informed consent was provided by all participants.

Consent for publication

All authors gave consent for the publication of this paper.

Competing interests

The authors declare that they have no competing interests.

Legend

Fig. 1 The flow chart of patient recruitment and model construction were showed in this study. LASSO, least absolute shrinkage and selection operator; T1WI, T1-weighted imaging; T2WI, T2-weighted imaging;

Fig.2 (a-b) The ROI of PPA (red) and PA (green) were delineated manually on head-neck MRI image, including T1WI (a) and T2WI (b) sequence. (c-d) The stability of features from T1WI (c, d) and T2WI (e,f) sequences was evaluated for both inter-observer (c,e) and intra-observer (d,f) agreement by the ICC. And the features with satisfactory agreement (ICCs of > 0.75) were showed above the red cutoff line. PPA, parotid pleomorphic adenoma; PA, parotid adenolymphoma T1WI, T1-weighted imaging; T2WI, T2-weighted imaging; ROI, region of interest; ICC, interclass correlation coefficient

Fig.3 (a-f) LASSO regression was used for feature selection. The deviance curve was plotted and parameter (λ) selection was tuned using 10-fold cross-validation. Dotted lines denoted the minimum criterion (right) and 1-SE of the minimum criteria (left). The 1-SE criterion was applied and there were respectively 7 features of T1WI sequence (a,b) with non-zero coefficients (the

optimal value of λ =0.07543); 8 features of T2WI sequence (c,d) with non-zero coefficients (the optimal value of λ =0.03457); 8 of T1-2WI sequence (e,f) with non-zero coefficients (the optimal value of λ = 0.06485). (g-i) Spearman correlation coefficients were calculated for the features of T1WI,T2WI and T1-2WI sequence. No pair of features showed extremely strong positive correlations among there feature groups (0.90~1.00). LASSO, least absolute shrinkage and selection operator; 1-SE, 1-standard error criterion .

Fig.4. (a-b) ROC curves comparing the radiomics model based on TW1-2 sequence and clinical model for the training cohort (a) and the validation cohort (b); (c-d) The discrimination and calibration of radiomics model based on TW1-2 were validated by the decision curve and Hosmer-Lemeshow.

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