Prediction of the degree of pathological differentiation in tongue squamous cell carcinoma based on radiomics analysis of magnetic resonance images

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Abstract

Background: To explore the value of radiomics based on magnetic resonance fat-suppressed T2-weighted images in predicting the degree of pathological differentiation of tongue squamous cell carcinoma (TSCC).

Methods: Retrospective analysis of 87 TSCC patients who were randomly divided into a primary cohort and a test cohort. The tumour regions were manually labelled in fat-suppressed T2-weighted imaging (FS-T2WI) and PyRadiomics was used to extract radiomics features. The radiomics features were then selected by the least absolute shrinkage and selection operator (LASSO) method. The model was established by the logistic regression classifier using a 5-fold cross-validation method, applied to the set and evaluated using the area under the receiver operating characteristic curve (AUC), accuracy, sensitivity and specificity.

Results: In total, 1132 features were extracted, and seven features were selected for modelling. The AUC in the logistic regression model for well-differentiated TSCC was 0.90 with specificity and precision values of 0.92 and 0.78, respectively, and the sensitivity for poorly differentiated TSCC was 0.74.

Conclusion: In this model, there was a significant relationship between radiomics characteristics and the degree of pathological differentiation, and the degree can be predicted from MRI features using machine learning.

Advances in knowledge: Texture analysis and prediction of the differentiation degree of TSCC by MRI are not only a breakthrough and innovation in the diagnosis of TSCC but are also of significance in clinical diagnosis and treatment.

Background

Tongue squamous cell carcinoma (TSCC) is one of the most difficult malignancies to control [1], which displays particularly aggressive behaviour even at an early stage [2] and, despite significant advances in cancer therapeutics over the past 30 years [3], the five-year survival rate is still unsatisfactory [4]. One reason for this dismal outlook could be the biological propensity for local invasion and the high incidence of cervical lymph node metastasis at the time of diagnosis (40%) [5]. Another reason is that, without consideration of individual differences in genetic and biological behaviour, it potentially results in ineffective treatment in some patients and unnecessary overtreatment in others. Therefore, it is important to understand the clinical behaviour and outcome of TSCC and focus on individually tailored treatment. Although histological assessment of biopsy or surgical specimens is still the gold standard method [6], rapid histological biopsy before surgery may not allow for the evaluation of the characteristics of the entire tumour, which is required for diagnosis of TSCC.

Cross-sectional magnetic resonance imaging (MRI) can reveal the extent of locoregional tumour spread, depth of invasion, extent of lymphadenopathy, and occult metastasis in exquisite anatomical detail [7], so there may be a degree of correlation between the biological heterogeneity of a malignant tumour and the heterogeneity of its image texture. Recent research has shown that some histopathological parameters can be evaluated preoperatively with an MRI [8] or a satisfactory diagnostic biopsy [9]. The degree of pathological differentiation reflects the extent of the malignancy [10]. The poorer the differentiation, the more disordered the tissue and vascular structure and the higher the risk of cancer cells invading the surrounding tissues [11]. Given that biomarkers seen on an MRI may reflect the heterogeneity of cancerous tissue, texture analysis of a single biomarker may have increased sensitivity and specificity [12].

Texture analysis is a branch of radiomics that is based on imaging features and uses a computer algorithm to provide the spatial distribution features of the grey level in an area to quantify the heterogeneity of a tumour [13, 14]. MRI based on imaging radiomics analysis can not only detect and locate the focus but also monitor disease progression and the response to curative treatment. It can also provide information that a biopsy cannot, that is, the overall heterogeneity of the tumour and the effects of long-term treatment [15, 16]. In recent years, radiomics analysis has playing an increasing bigger role in cancer research, particularly in the identification of imaging biomarkers and clinical management, including classification and staging, evaluation of efficacy, and prediction of the prognosis of brain, breast, prostate, and lung tumours [17–21]. An increasing number of imaging characteristics have been reported to be highly predictive of the degree of pathological differentiation of tumours and to have diagnostic value [22].

In this study, FS-T2WI data and a series of machine learning algorithms were used to build a prediction model, identify imaging markers that could potentially predict the degree of pathological differentiation of TSCC, quantify and visualise the radiomics features extracted from MRI scans, and develop a diagnostic model to guide the selection of individualised diagnostic and treatment methods and improve the outcomes for patients.

Materials And Methods

Patients

Retrospective analysis of 87 TSCC patients who were randomly divided into a primary cohort (72 patients; 23 well-differentiated, 28 moderately differentiated and 21 poorly differentiated) and a test cohort (15 patients; 5 cases of each differentiation degree), including 68 men, 19 women, mean age 58.6 (range 38–75) years, with biopsy-proven TSCC for which preoperative MRI scans acquired between June 2016 and October 2019 were available and from which the degree of pathological differentiation could be determined. The clinical characteristics of this study's cohort are shown in Table 1. The inclusion criteria were to have a case of biopsy-proven TSCC with complete clinical data and absence of concomitant disease, and the ability to cooperate with an MRI examination. The exclusion criteria were as follows: no definitive postoperative information on pathological characteristics, local or systemic treatment before surgery, a minimum tumour diameter < 5 mm (not amenable to placement of a region of interest [ROI]), and poor MRI quality for post-processing due to artefact.

Table 1

Patient characteristics in the primary and test set (n = 87). Notes: A P-value < 0.05 was considered to indicate a statistically significant difference. *age's test^ independent-samples t-test, others 's test^chi-square test.

	Pathological differentiation degree of TSCC							
	Primary set				Test set			
	Poorly differentiated (n = 23)	Moderately differentiated (n = 28)	Well differentiated (n = 21)	P-value	Poorly differentiated (n = 5)	Moderately differentiated (n = 5)	Well differentiated (n = 5)	P-value
Sex	21	24	17	0.610	3	3	4	0.741
Male	2	4	4		2	2	1	
Female								
Age, years	39–75	43–75	38–75	0.514	47–68	53–72	34–62	0.495
Range	56.8	59.0	59.8		55.4	61.2	49.8	
Average								
Localization of tumor	9	8	1	0.094	1	2	1	0.864
Tip	9	10	12		3	2	2	
Body	5	10	8		1	1	2	
Root								
Pain	18	20	20	0.691	4	3	1	0.153
Yes	5	8	1		1	2	4	
No								
Margin	8	8	3	0.094	1	2	4	0.153
Well-circumscribed	15	20	18		4	3	1	
Ill-defined								
Cystic degeneration	14	13	14	0.330	3	2	1	0.435
Yes	9	15	7		2	3	4	
No								
Sublingual gland duct dilatation	10	12	6	0.514	1	2	0	0.287
	13	16	15		4	3	5	
Yes								
No								
Lymphatic metastasis	12	6	4	0.021	3	1	1	0.092
Yes	11	23	17		2	4	4	
No								

MRI and texture analysis

All the MRI examinations were performed using a 1.5-T Avanto scanner (Siemens Healthineers, Erlangen, Germany) with an 8-channel phased-array neck coil. The patient's head was secured using a relaxing cushion, ensuring that the shoulders were in contact with the

lower part of the coil. Non-contrast axial FS-T2WI sequence acquired in multiple breath-holds were obtained using the following parameters: a repetition/echo time of 5080/87 ms, a slice thickness/interslice gap of 4.0/0.4 mm, 20 slices, and a matrix of 256 × 320. This study used the Dr Wise Multimodal Research Platform (<https://keyan.deepwise.com>) (Beijing Deepwise & League of PHD Technology Co., Ltd, Beijing, China) for texture analysis, including image annotation. For the extraction of features, an open-source python package called PyRadiomics (2.1.0), a platform that supports feature extraction in both two and three dimensions and can be used to calculate single values per feature for an ROI ("segment-based") or generate feature maps ("voxel-based"), was used. The steps in the texture analysis are shown in Fig. 1.

Delineation of tumour ROI

All scans were retrospectively reviewed, loaded and processed in the original DICOM format and then transmitted to the post-processing workstation. The tumour regions in the primary dataset were labelled manually by two experts. In the case of discordance, the opinion of a third radiologist was requested, and consensus was reached through discussion. Finally, the volume of interest was obtained for feature extraction and quantification. An axial FS-T2WI scan was selected as the labelling image. It was possible to classify the tumour tissue based on the principle of not exceeding the tumour boundary.

Extracting features from MRI scans

The high-pass or low-pass wavelet filter and Laplacian of Gaussian filter with different λ parameters were used to pre-process the original images. Each stage of wavelet filtering generated eight decompositions, and all possible combinations of high-pass or low-pass filters (wavelet_LLH, wavelet_LHL, wavelet_LHH, wavelet_HLL, wavelet_HLH, wavelet_HHL, wavelet_HHH, and wavelet_LLL) and four Laplacian of Gaussian filters ($\lambda = 2, 3, 4, 5$) were applied in all three dimensions for pre-processing. The features extracted from the original images included their first-order features based on the pixel value, the shape features of the tumour and the internal and surface texture features extracted from each ROI, including the grey level co-occurrence matrix (GLCM), grey level run length matrix (GLRLM), grey level size zone matrix (GLSZM), and grey level dependence matrix (GLDM). In total, 1132 radiomics features were extracted from each ROI, and a standardised Z-score was then obtained by subtracting the average value and dividing by the standard deviation. Features showing poor consistency between different groups were removed by calculating the intraclass correlation coefficient (ICC); features with an ICC > 0.75 were selected and modelled. Finally, the least absolute shrinkage and selection operator (LASSO) algorithm was used for feature reduction and selection. The most important feature with a coefficient that was not zero was identified for modelling and improving the performance of the model. The LASSO method uses a shrinking (regularisation) process whereby it penalises the coefficients of the regression variables, shrinking some of them to zero. Variables that still have a non-zero coefficient after the shrinking process are selected to be part of the model. The goal of this process was to minimise prediction error.

Establishment of the model

Using the logistic regression (LR) classifier to establish the model by the 5-fold cross-validation method, whereby all the data were divided into five parts, four of which were used for model training, the other one was used to evaluate the effectiveness of the model, and finally all the data were used in a training set and a testing set. After all training and testing, the performance of the model was evaluated by the average value of five tests. In this study, the generalisation properties of the learning algorithm were focused on for multiclass classification problems and the confusion matrix of each classifier was used as a measure of its quality. A confusion matrix is useful for evaluating the ability of classifiers to classify multiclass objects in addition to receiver operating characteristic (ROC) curves. The accuracy score, the ratio of the correctly classified samples to all samples, was also used to evaluate the predictive performance of the model. Finally, a model was computed by using selected features.

Statistical analysis

The classification model was built using the Scikit-learn software package (version 0.20.3). Matplotlib (version 3.1.0) was used to draw the ROC curves. The statistical analysis of general data was performed using SPSS for Windows version 16.0 (IBM Corp., Armonk, NY, USA). Chi-square tests were used to detect differences in the categorical variables between groups. Group differences in quantitative variables were examined using independent-samples *t*-tests. A *P* value < .05 was considered statistically significant.

Results

Patients and radiomics features

The characteristics of the 87 study participants are summarised in Table 1. There was a significant difference in the rate of lymphatic metastasis ($P < 0.05$), based on the degree of pathological differentiation of TSCC in the primary set. There was no significant difference in sex, age, localisation of the tumour, pain, margin, cystic degeneration, or sublingual gland duct dilatation, based on the degree of pathological differentiation. A total of 1132 imaging features, including 234 first-order features, 14 shape features and 884 texture features, were extracted from the original images through wavelet and Laplacian of Gaussian filters and selected by the LASSO algorithm. The key relevant features were selected by the 10-fold cross-validation method, as shown in the mean square error(MSE) path of the LASSO algorithm (Fig. 2a). The best alpha value was 0.18484 and the $-\log(\alpha)$ value was 0.73320. The vertical axis of the path graph of the coefficient solution (Fig. 2b) represents the coefficients of each feature in the LASSO model, which change with the change in alpha value. Based on the best alpha value, the coefficients corresponding to the different features were identified, features with a coefficient that was not 0 were selected, and finally seven of the 1132 features were selected for modelling. The feature list and coefficient chart shows two first-order features (wavelet-LHH_first-order_maximum and log-sigma-2-0-mm-3D_first-order_maximum) and five texture features (wavelet-HHH_glrIm_LongRunHighGreyLevelEmphasis, log-sigma-3-0-mm-3D_glcM_Idmn, wavelet-HHL_glcM_MaximumProbability, wavelet-LHL_glszm_GreyLevelNonUniformityNormalised, and original_glcM_ClusterShade) (Fig. 2c). The intraobserver and interobserver consistency of the annotation images were good (Fig. 3). All features of the selected modelling had consistency > 0.75 .

Establishment and evaluation of the model

Performance evaluation of the prediction model in primary sets

The prediction model's performance was first assessed in the testing sets with the equilibrium of the class distribution and balanced data. The results are shown in Table 2. In terms of the accuracy of the classification, the confusion matrix results confirmed that there was consistency between the predicted and actual results, suggesting better performance of the model in the classification of multiclass objects (Fig. 4a). ROC curve analysis also verified that the model could predict and distinguish the degree of pathological differentiation of TSCC with a high accuracy of 0.81–0.90 (all AUC > 0.80). The diagnostic effect of this prediction model on differentiation was more than 80%. The micro-average AUC of the LR model in the 5-fold cross-validation of the primary dataset was 0.86, tending towards the upper left corner and far from the diagonal (Fig. 4b). Moreover, in the LR model, the AUC for well-differentiated TSCC was 0.90, suggesting that this model had the highest accuracy for predicting and distinguishing well-differentiated TSCC.

Table 2
The results of primary set and test set. F1-score = $2PR/(P + R)$ (P, precision; R, recall)

		Precision	Sensitivity	Specificity	F1-score	Support
Primary set	Poorly	0.68	0.74	0.84	0.71	23
	Moderately	0.66	0.68	0.77	0.67	28
	Well	0.78	0.67	0.92	0.72	21
	Accuracy				0.69	72
	Macro avg	0.70	0.69	0.84	0.70	72
	Weighted avg	0.70	0.69	0.84	0.69	72
Test set	Poorly	0.67	0.40	0.90	0.50	5
	Moderately	0.60	0.60	0.80	0.60	5
	Well	0.57	0.80	0.70	0.67	5
	Accuracy				0.73	15
	Macro avg	0.61	0.60	0.80	0.59	15
	Weighted avg	0.61	0.60	0.80	0.59	15

Performance evaluation of prediction model in an external validation set

In addition to the internal testing above, an external validation for the performance of the prediction model was also performed by using an external validation set without pre-processing or the equilibrium of the class distribution. The machine learning algorithms in the external validation were the same as those used in the primary set. In terms of classifier performance in the external validation set, confusion matrix and ROC curves both indicated a high classification accuracy of the model, with an AUC value of 0.72–0.86. ROC curves also revealed that the model could distinguish the degree of pathological differentiation of TSCC with high accuracy of at least 72% (Fig. 4c, d). Ultimately, the prediction model that used seven optimal characteristics was validated to be significantly effective in the prediction of the degree of pathological differentiation of TSCC.

Discussion

In this study, the texture features of 87 patients with biopsy-proven TSCC were extracted and analysed. Correlations were sought by comparing these features with histopathological features that were determined postoperatively. Tumour characteristics that suggest the degree of pathological differentiation are difficult to distinguish accurately by visual observation alone. We found that the imaging features extracted from MRI scans correlated with the degree of pathological differentiation in patients with TSCC. In general, classification models with AUC values of 1.00–0.90 and 0.90–0.80 are regarded as excellent and good, respectively [23]. The micro-average AUC values for the prediction models constructed by the LR in the 5-fold cross-validation of the primary dataset reached 0.86, the AUC and specificity values for well-differentiated tumours was better (>0.90), indicating that the diagnosis model can accurately distinguish well-differentiated TSCC; this model also had the highest sensitivity for diagnosis of poorly differentiated tumours. In terms of the external validation set, classifier performance indicated a high classification accuracy of the model. Therefore, the radiomics analysis described here has a strong ability to predict the degree of pathological differentiation of TSCC.

The most recent WHO guidelines [24] recommend use of cell differentiation to grade head and neck carcinomas. Lower tumour heterogeneity is likely associated with a lower histological grade [25]. Many studies have concluded that the degree of pathological differentiation is a strong histological feature that correlates with locoregional recurrence. In the present sample, most cases were classified as moderately differentiated, consistent with what other studies have observed for oral squamous cell carcinoma [26]. Moreover, similar to results reported by Jing et al. [27], poorly differentiated tumours showed a statistically significant relationship with recurrence ($P=.043$). Therefore, poor differentiation is a known risk factor for treatment failure in patients with tongue cancer [28], and it is important to determine the degree of pathological differentiation preoperatively to assess the prognosis. Fujima. et al. [29] studied the utility of the MRI histogram and texture analysis in head and neck malignancies; however, it is limited to the correlation analysis between first-order features and apparent dispersion coefficient(ADC) values, and no external verification was carried out. For TSCC, larger resections generally result in a worse functional outcome [30]. Early comprehensive treatment is needed for patients with poorly differentiated tumours to maximise the therapeutic ratio, avoid unnecessary extended resection and treatment and improve quality of life and the prognosis as much as possible.

Prognostic and predictive markers hold the promise of allowing more personalised treatment of TSCC in order to improve cure rates and minimise side effects. In patients followed closely for N0 disease, 20–30% will subsequently develop cervical lymph node metastases. A 40% incidence of micrometastatic disease was still found when elective neck dissection was performed in patients with T1 and T2 TSCC [32]; most of the patients were poorly differentiated. Therefore, these present findings have the potential to impact the clinical management of early TSCC. Excessive staging may lead to loss of the opportunity for effective surgical treatment and too low clinical staging may result in ineffective or even harmful therapy. However, accurate judgment of the degree of pathological differentiation before surgery may improve this situation. The performance of radiomics analysis varies depending on the MRI scanner, imaging parameters and tumour delineation method used [31, 32]. MRI scans acquired by one type of scanner and imaging parameters from the entire dataset were used to reduce the influence of these variations on performance [33]. However, in terms of delineation, the consistency within and between groups was analysed using the ICC to avoid interobserver and intraobserver differences. The results of independent verification suggested that reproducible radiomic features for observing delineation variability should be investigated to obtain high prediction performance in the case of using different datasets. In this study, rather than measuring the largest diameter of the tumour slice, the whole tumour volume was measured, which can extract tumour features more efficiently, thereby offering an opportunity to overcome the limitations of visual image interpretation and to refine the characteristics of different tumour regions [34].

In this study, an intensive search for non-invasive imaging biomarkers was undertaken and a prediction model that can not only detect imaging information hidden in the focus but can also distinguish the degree of differentiation of that focus, which has high clinical value, was used. At present, the research on texture analysis of head and neck tumours is relatively limited. Texture analysis and prediction of the differentiation degree of TSCC by MRI are not only a breakthrough and innovation in the diagnosis of TSCC, but also of significance

in clinical diagnosis and treatment. This study also had some limitations: the study data was limited and obtained from a single centre; the ROI still depends on a semiquantitative feature extraction method; the edge and contour of the tumour are affected by the experience of the evaluator; the diagnosis model still needs to be used in conjunction with other important diagnostic indicators, with the cases increasing.

Conclusion

In conclusion, although texture analysis and image features play an important role in the prediction of the degree of differentiation of TSCC, the path towards clinical application is long and challenging. This study sheds some light on TSCC research and demonstrated a consistent association between image features and specific clinical outcomes.

Abbreviations

TSCC: tongue squamous cell carcinoma

FS-T2WI: fat-suppressed T2-weighted imaging

LASSO: least absolute shrinkage and selection operator

MRI: magnetic resonance imaging

ROI: region of interest

GLCM: grey level co-occurrence matrix

ICC: intraclass correlation coefficient

LR: logistic regression

ROC: receiver operating characteristic

MSE: mean square error

ADC: apparent dispersion coefficient

Declarations

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of China-Japan Union Hospital of Jilin University.

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Conflict of Interests statement

All of the authors had no any personal, financial, commercial, or academic conflicts of interest separately.

Authors Contribution

Conception and design of the research: Yu BT and Ding J. Acquisition of data: Huang CC, Xu JX. Analysis and interpretation of the data: Liu S, Guan YY. Statistical analysis : Li T. Obtaining financing : None. Writing of the manuscript :Yu BT . Critical revision of the manuscript for intellectual content : Zheng XW.

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Figures

Figure 1

Flow chart of radiomics analysis. From left to right, manual segmentation to obtain voxel-based region of interest in a three-dimensional slice, extraction of radiomics features using Pyradiomics software, selection of features using LASSO regression, development of the model, and evaluation of diagnostic performance using ROC analysis.

Figure 2

(a) The MSE path in the LASSO algorithm. The dotted lines in different colors indicate each group of cross-validation samples corresponding to different $-\log(\alpha)$ with a different MSE. The black solid line is the mean value of five MSE groups. The best α is the value with the lowest MSE. Note: The optimization objectives of LASSO are as follows: (see Equation in the Supplemental Files) CV, LASSO, least absolute shrinkage and selection operator; MSE, mean square error (b) LASSO coefficient solution path for the seven features. (c) Coefficients in the LASSO model of the seven features. The vertical axis represents the seven key features for modeling. The transverse axis represents the relative weight of these features.

Figure 3

Intraobserver(a) and interobserver(b) consistency (ICC).

Figure 4

Performance assessment of prediction model in primary set and external validation set. Confusion matrix ROC curve analysis in primary set(a and b) and external validation set(c and d). The solid lines in different colors indicate that the ROC curve for each class of TSCC correspond to a different AUC, which represents the positive rate of prediction of the degree of pathological differentiation. The dotted lines in different colors indicate the ROC curves of the micro-average and macro-average. (Note: Numbers 1, 2, and 3, represent poorly, moderately, and well differentiated TSCC, respectively).

Supplementary Files

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- [Equation.jpg](#)