


Contrast-enhanced CT radiomics features to predict recurrence of locally advanced oesophageal squamous cell cancer within 2 years after trimodal therapy

A case-control study

Sun Tang, MS^{a,b}, Jing Ou, MS^a, Yu-Ping Wu, MS^a, Rui Li, MD^a, Tian-Wu Chen, MD^{a,*} , Xiao-Ming Zhang, MD^a

Abstract

Radiomics transforms the medical images into high-dimensional quantitative features and provides potential information about tumor phenotypes and heterogeneity. We conducted a retrospective analysis to explore and validate radiomics model based on contrast-enhanced computed tomography (CECT) to predict recurrence of locally advanced oesophageal squamous cell cancer (SCC) within 2 years after trimodal therapy. This study collected CECT and clinical data of consecutive 220 patients with pathology-confirmed locally advanced oesophageal SCC (154 in the training cohort and 66 in the validation cohort). Univariate statistical test and the least absolute shrinkage and selection operator method were performed to select the optimal radiomics features. Logistic regression was conducted to build radiomics model, clinical model, and combined model of both the radiomics and clinical features. Predictive performance was judged by the area under receiver operating characteristics curve (AUC), accuracy, and F1-score in the training and validation cohorts. Ten optimal radiomics features and/or 7 clinical features were selected to build radiomics model, clinical model, and the combined model. The integrated model of radiomics and clinical features was superior to radiomics model or clinical model in predicting recurrence of locally advanced oesophageal SCC within 2 years in the training (AUC: 0.879 vs 0.815 or 0.763; accuracy: 0.844 vs 0.773 or 0.740; and F1-score: 0.886 vs 0.839 or 0.815, respectively) and validation (AUC: 0.857 vs 0.720 or 0.750; accuracy: 0.788 vs 0.700 or 0.697; and F1-score: 0.851 vs 0.800 or 0.787, respectively) cohorts. The combined model of radiomics and clinical features shows better performance than the radiomics or clinical model to predict the recurrence of locally advanced oesophageal SCC within 2 years after trimodal therapy.

Abbreviations: ¹⁸FDG-PET CT = ¹⁸F-fluorodeoxyglucose-positron emission tomography CT, AUC = area under receiver operating characteristics curve, CECT = contrast-enhanced computed tomography, GLCM = gray-level co-occurrence matrix, GLRLM = gray-level run-length matrix, ICC = intra-class correlation coefficient, LASSO = least absolute shrinkage and selection operator, NCCN = National Comprehensive Cancer Network, NPV = negative predictive value, PPV = positive predictive value, ROC = receiver operating characteristic, ROI = regions of interest, SCC = squamous cell cancer.

Keywords: computed tomography, esophagus, recurrence, squamous cell cancer, therapy

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ST and JO contributed equally to this work.

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^a Sichuan Key Laboratory of Medical Imaging, Department of Radiology, Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, China, ^b Department of Radiology, Chongqing University Cancer Hospital/Chongqing Cancer Hospital, Chongqing, China.

* Correspondence: Tian-Wu Chen, Sichuan Key Laboratory of Medical Imaging, Department of Radiology, Affiliated Hospital of North Sichuan Medical College, 63# Wenhua Road, Nanchong 637000, Sichuan, China (e-mail: tianwuchen_nsmc@163.com).

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1. Introduction

Oesophageal cancer is one of the most aggressive malignant tumors in the digestive system and its predominant histopathological type is squamous cell cancer (SCC) in Asia and Eastern Europe.^[1,2] The locally advanced oesophageal SCC is defined as T2–T4 and/or lymph node-positive without distant metastasis.^[3] According to relevant literature reported, the 5-year survival rate of locally advanced oesophageal SCC is only about 30% to 50%, which implies a high rate of disease recurrence and poor survival.^[4–7] The published study shows that the survival rate after the recurrence of oesophageal cancer is extremely poor, with a median survival time of only 10.5 months.^[8] To lower disease recurrence and improve overall survival, trimodal therapy (including neoadjuvant chemotherapy, radiotherapy, and surgical resection) is presently considered the optimal therapy for patients with locally advanced oesophageal SCC.^[4,5,9,10]

As a traditional imaging tool, contrast-enhanced computed tomography (CECT) is often used to evaluate the preoperative staging of oesophageal SCC, including the degree of local invasion and lymph node metastasis for treatment decision making.^[11] However, CECT only demonstrates the external morphological characteristics of locally advanced oesophageal SCC, and it is limited to assess the intra-tumor heterogeneity. Radiomics has gradually received widespread attention for it transforms the medical images into high-dimensional quantitative features and provides potential information about tumor phenotypes and heterogeneity.^[12–14] At present, numerous studies based on radiomics have been conducted to predict the recurrence of various types of tumors, including hepatocellular carcinoma, lung cancer, bladder cancer, and breast cancer, and have proposed good performance.^[15–18] And radiomics has widely used in oesophageal cancer to predict the response to radiotherapy and chemotherapy, 3-year overall survival, and lymph node metastasis.^[19–21] To the best of our knowledge, there is no literature to date about whether radiomics features can predict recurrence of locally advanced oesophageal SCC after therapy. Therefore, the purpose of the present study was to explore and validate radiomics model based on CECT that can predict recurrence of locally advanced oesophageal SCC within 2 years after trimodal therapy.

2. Materials and methods

2.1. Study population

This retrospective study was conducted according to the approval of the institutional review board of our hospital with a waiver of patient informed consent.

From March 2014 to September 2018, a total of consecutive 246 patients with locally advanced oesophageal SCC were collected from our hospital. The enrolled patients needed to fulfill the following inclusion criteria: (1) patients underwent thoracoabdominal CECT examination within 2 weeks before receiving trimodal therapy, (2) patients did not undergo any tumor-related treatment (eg, chemotherapy or radiotherapy) before receiving the CT scans, (3) patients were pathologically confirmed locally advanced oesophageal SCC according to the current American Joint Committee on Cancer TNM Staging System Manual (8th edition),^[22] and (4) patients received trimodal therapy and were regularly followed up for at least 2 years after the treatments. In addition, trimodal therapy was a multimodality combination therapy of neoadjuvant chemother-

apy, radiotherapy, and surgical resection. The exclusion criteria for patients in this study were as follows: (1) lost to follow-up within 2 years (n=18) or (2) with incomplete clinical-pathological information (n=8). Therefore, a total of 220 patients were included in this study, and they were randomly divided into the training group and the validation group at a ratio of 7:3 according to the published report by an earlier investigation.^[23] The patient flowchart is shown in Figure 1.

The conventional baseline clinical variables, including gender, age, tumor location, histological grade, T stage, N stage, and TNM stage (Table 1) were extracted by reviewing the medical records. Similarly, with the pattern of clinical variables used in the published literature,^[24] the clinical variables of T stage, N stage, and TNM stage were all used in our study to build the clinical model. Tumor staging was determined by the latest American Joint Committee on Cancer guidelines.^[22]

2.2. Follow-up

According to the latest edition of National Comprehensive Cancer Network (NCCN) guidelines,^[25] the asymptomatic enrolled patients with oesophageal SCC received follow-up CT at 3 to 6 months intervals in the first 2 years, at 6–12 months intervals during the third to fifth years, and then annually after the fifth years. If the patient was suspected of recurrence, further clinical examinations such as endoscopy, and ¹⁸F-fluorodeoxyglucose-positron emission tomography CT (¹⁸FDG-PET CT) would be performed to confirm the recurrence.^[26] Based on the previous NCCN guidelines, all patients enrolled in our study were followed up for more than 2 years. Patients with suspected recurrent lesions underwent cervical and thoracoabdominal CT, cerebral CT, endoscopic biopsy, and even ¹⁸FDG-PET CT to confirm the recurrence.

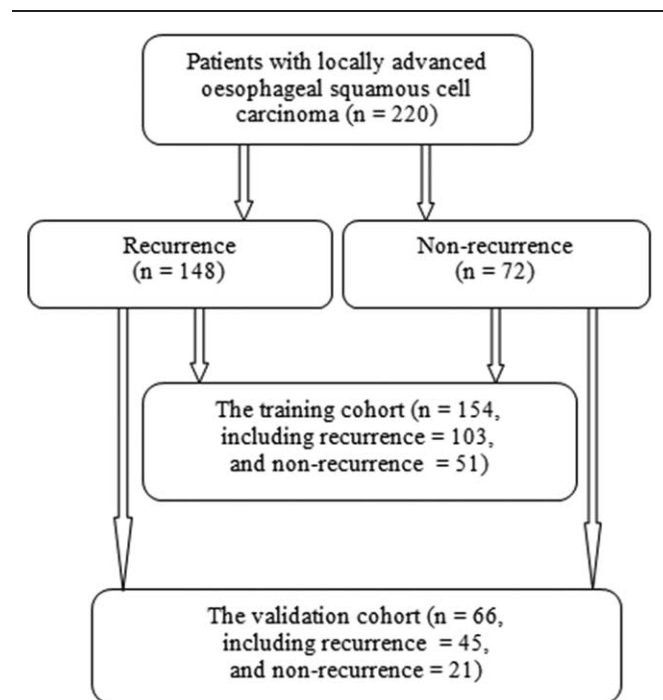


Figure 1. The flow chart for collecting patients.

Table 1
Clinical features of recurrence and non-recurrence cohorts.

Clinical features	Recurrence (n = 148)	Non-recurrence (n = 72)	P value	
Gender (%)	Male	108 (73)	45 (62.5)	.113
	Female	40 (27)	27 (37.5)	
Age (mean ± SD)		62.8 ± 8.0	63.0 ± 7.4	.594
Tumor location	Upper	11 (7.5)	11 (15.3)	.169
	Middle	101 (68.2)	47 (65.3)	
	Lower	36 (24.3)	14 (19.4)	
T stage (%)	T1	1 (0.7)	5 (6.9)	<.001*
	T2	35 (23.6)	32 (44.5)	
	T3	86 (58.1)	30 (41.7)	
	T4a	26 (17.6)	5 (6.9)	
N stage (%)	N0	71 (48)	59 (81.9)	<.001*
	N1	48 (32.4)	9 (12.5)	
	N2	23 (15.5)	4 (5.6)	
	N3	6 (4.1)	0 (0)	
Differentiation degree (%)	Low	65 (43.9)	44 (61.1)	.038*
	Middle	74 (50)	23 (32)	
	High	9 (6.1)	5 (6.9)	
TNM stage (%)	IB	15 (10.1)	13 (18.1)	<.001*
	IIA	43 (29.1)	42 (58.3)	
	IIB	4 (2.7)	3 (4.2)	
	IIIA	6 (4.1)	5 (6.9)	
	IIIB	68 (45.9)	8 (11.1)	
	IVA	12 (8.1)	1 (1.4)	

Numbers in parentheses are percentages; n=number, SD=standard deviation.

*Statistically significant at $P < .05$.

2.3. CT image acquisition and radiologic evaluation

All patients in our study underwent thoracoabdominal CECT scans using 128 multi-detector scanners (LightSpeed VCT, GE Medical Systems, USA). Before CT examination, all patients with oesophageal cancer drank 100 to 200 mL water as oral negative contrast material. During the CT scans, the patients were scanned in the supine position and held a breath for 10 to 15 seconds to obtain good quality images and avoid artifacts. After conventional CT scan without enhancement, CECT was performed a 25 to 30 seconds delay after intravenous injection of 1.5 mL/kg contrast material (Omnipaque, Iohexol, GE Healthcare, USA) at the rate of 3.0 mL/s with a pump injector (Vistron CT Injection System, Medrad, USA). The CT scanning parameters were given as follows: tube voltage of 120 kV, tube current of 200 mA, rotation time of 0.5 seconds, detector collimation of $64 \times 0.6 \text{ mm}^2$, pitch of 0.9, slice thickness of 5 mm, slice interval of 5 mm, and matrix of $512 \times 512 \text{ mm}^2$. The coverage of CT examination was from the inlet of the chest to the middle of the left kidney. All CECT image data used to extract radiomics features were transferred to the picture archiving and communication system.

2.4. Region-of-Interest segmentation and radiomic feature extraction

For delineating regions of interest (ROI) of oesophageal SCC (Figure 2), the CECT images were uploaded on IBEX ($\beta 1.0$, http://bit.ly/IBEX_MDAnderson).^[27] IBEX was an open-source software, which ran on 64-bit MATLAB 2013Ra (MathWorks Inc). Two readers in digestive radiology (readers 1 and 2, with 3 and 22 years of medical imaging experience, respectively) were responsible for tumor segmentation, with blinding to patients'

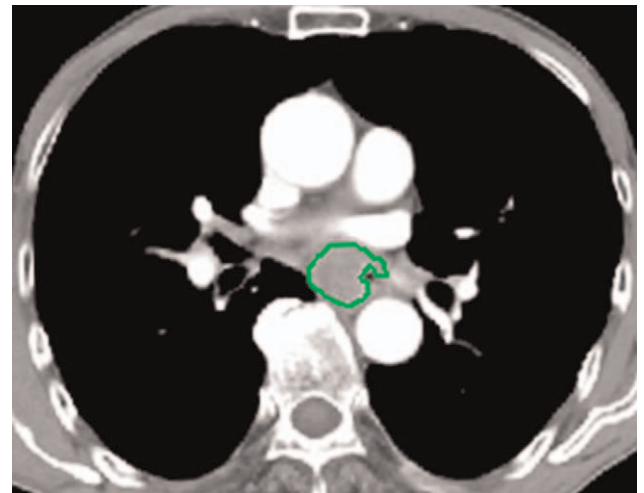


Figure 2. The outlines of oesophageal cancer manually drawn on contrast-enhanced CT data. CT=computed tomography.

pathological results. If disagreement arose, the consensus was reached through discussion and consultation. Each ROI of the lesion was manually outlined layer by layer avoiding adjacent structures of air, fat, blood vessels, and bone. Radiomics features were extracted from the IBEX, and included gray-level co-occurrence matrix (GLCM), gray-level run-length matrix (GLRLM), intensity histogram, and shape feature.

2.5. Intra- and inter-observer agreements

To improve the reproducibility of radiomics feature extraction, 60 consecutive samples of 220 patients with locally advanced oesophageal SCC were randomly selected for depicting the intra- and inter-observer agreements by the previous 2 radiologists. The intra-class correlation coefficient (ICC) was used as the evaluation indicators to measure the intra- and inter-observer agreements. An ICC score greater than or equal to 0.75 was considered consistent, suggesting the radiomics feature extraction was reproducible. To assess the ICC of intra-observer, reader 1 delineated the ROI twice following the same sketching steps. At the same time, reader 2 depicted the ROI independently to evaluate the inter-observer ICC by comparing the radiomics characteristics that reader 1 extracted from the first ROI depiction.

2.6. Dimensionality reduction and radiomics feature selection

To avoid the curse of dimensionality and reduce the bias from radiomics features during modeling,^[23] the radiomics features with good intra- and inter-observer agreements in the training cohort were further processed by following steps.

First, all selected radiomics features underwent z -score according to this formula: $X_{\text{norm}} = \frac{x - \mu}{\sigma}$, where x is the original feature value, μ is the mean value of this feature, and σ is the standard deviation.

Second, the Student t test or Mann–Whitney U test was further used to select the radiomics features with statistical significance (P value $< .05$).

Finally, the least absolute shrinkage and selection operator method (LASSO) performed variable selection and regularization on high-dimensional data, and it was used to select the core radiomics features to enhance the accuracy and interpretability of radiomics model.^[23,28] The 1-standard error of the minimum criteria (the 1-SE criteria, a simpler model) was used to adjust the regularization parameter (λ) for the select feature using 10-fold cross-validation.

2.7. Construction of the radiomics model

The final core radiomics features and clinical features were used to build 3 predictive models to predict recurrence of locally advanced oesophageal SCC within 2 years after trimodal therapy through logistic regression, including radiomics model, clinical model, and the combined model with radiomics and clinical features. The tuning of the optimal radiomics model followed the same procedures as those described above. The assessment of the optimal predictive model was judged mainly by the area under the receiver operating characteristic curve (AUC), accuracy, and F1-score. Other evaluation metrics, including positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity were also calculated.

2.8. Statistical analysis

All radiomics data was performed through R platform (version 3.4.1 <https://www.r-project.org/>). The “psych” package was performed to assess the intra- and inter-observer agreements of radiomics feature extraction. The “glmnet” and “foreach” packages were used to perform LASSO regression, and “pROC” package was used to draw receiver operating characteristic (ROC) curve. The AUCs among the above-mentioned 3 predictive models were compared using the “DeLong” test. Clinical characteristics were statistically analyzed based on the variable type using SPSS software (version 22). The normality of distribution was evaluated by Shapiro–Wilk test and the homogeneity of variance was tested by the Bartlett test. Continuous variables, represented as the mean or median, were compared by the Student *t* test or Mann–Whitney *U* test. The categorical variables were described in percentiles and compared using the Chi-square test or Fisher exact test. A *P* value was less than .05, suggesting there was a statistically significant difference.

3. Results

3.1. Clinical characteristics

Of our 220 locally advanced oesophageal SCC patients, 148 patients relapsed within 2 years, while the remaining 72 did not. Table 1 records the 7 clinical characteristics of locally advanced oesophageal SCC in both the recurrence and non-recurrence dataset. Four clinical feature including T stage, N stage, differentiation degree, and TNM stage indicated that there were statistical differences between the recurrence and non-recurrence of locally advanced oesophageal SCC (all *P* values <.05) whereas age, gender, and tumor location were not statistically significant (all *P* values >.05). The previous 7 basic clinical features were used to build a predictive model.

3.2. Inter- and intra-observer agreements

A total of 352 radiomics features were extracted from IBEX to fully describe the characteristics of the locally advanced oesophageal SCC. For intra-observer agreement, the consistency ratio of all 352 features reached 82.6% (mean ICC=0.870, ranging from 0.058 to 1, Figure 3A), and there were 291 extracted features with ICC greater than 0.75 whereas ICC was not greater than 0.75 for 61 features. In terms of the inter-observer agreement, the consistency ratio of all 352 features reached 78.9% (mean ICC=0.842, ranging from 0.033 to 1, Figure 3B), and there were 277 features with ICC greater than 0.75 while ICC was not greater than 0.75 for 75 features including the previous radiomics features with the intra-observer ICC of not greater than 0.75. Therefore, 75 features in total were excluded from our extracted features after evaluation. The remaining 277 features with both intra- and inter-observer ICC values of greater than 0.75 were selected for further dimensionality reduction analysis. All results were derived from the feature extraction by reader 1.

3.3. Dimensionality reduction and feature selection

The Student *t* test or Mann–Whitney *U* test showed that out of the remaining 277 features, 22 features were excluded as they were not significantly different (all *P* values >.05). Therefore, 255 features in total were used for LASSO regression, and 10 radiomics features were selected by LASSO (25.5:1 ratio) for further modeling, with the best-tuned regularization parameter λ of 0.039 under the 1-SE criteria found by 10-fold cross-validation

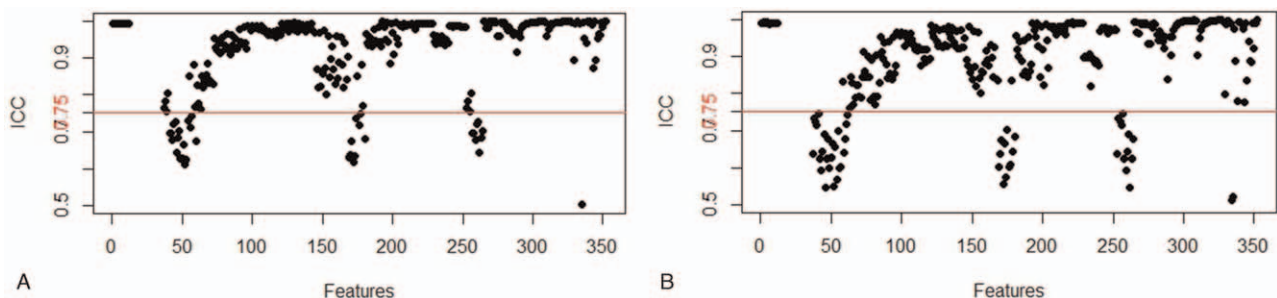


Figure 3. Stability evaluation of the extraction of CT radiomics features by intra- (A) and inter-observer and (B) intra-class correlation coefficient (ICC). CT = computed tomography.

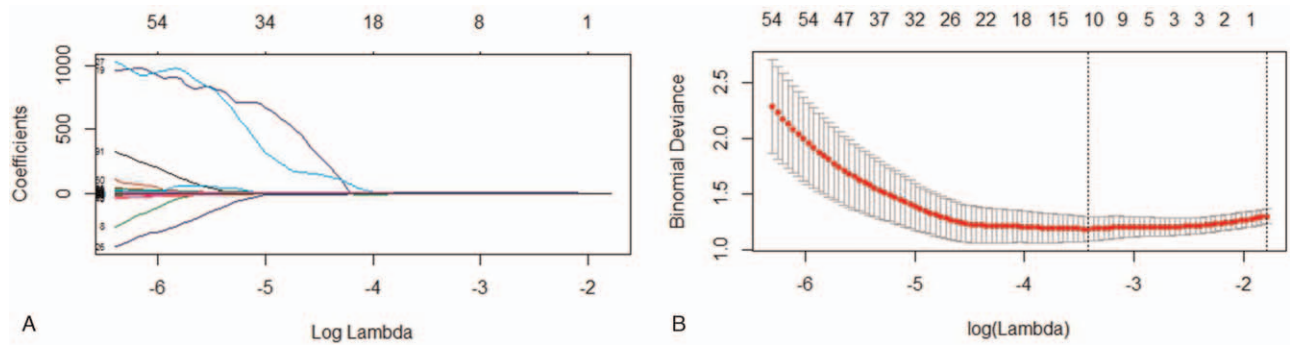


Figure 4. Feature selection using the LASSO regression. (A) Turning optimal parameter lambda (λ) using 10-fold cross-validation and minimum criterion in LASSO model. The left and right dashed lines represent the minimum criterion and the 1-SE criterion, respectively. The 1-SE criterion has been applied. (B) LASSO coefficient profiles of the 255 radiomics features. The picture shows the optimal λ value of 0.039. 10 features with non-zero coefficients have been selected. 1-SE = 1-standard error, LASSO = least absolute shrinkage and selection operator.

(Figure 4A and B). These 10 features are recorded in detail in Table 2.

3.4. Construction of the radiomics model

The 10 selected optimal radiomics features and 7 clinical features were used to construct 3 models to predict the recurrence of locally advanced oesophageal SCC within 2 years through logistic regression, including a radiomics model, a clinical model, and a model combined radiomics with clinical features. The most suitable model was selected by AUC, accuracy, and F-1 score as well as sensitivity, specificity, positive predictive value, and negative predictive value as shown in Table 3. The receiver operating characteristic curves (Figure 5A and B) visually showed that the integrated model of radiomics and clinical features was superior to radiomics model or clinical model in predicting recurrence of locally advanced oesophageal SCC within 2 years in the training cohort (AUC: 0.879 vs 0.815 or 0.763; accuracy: 0.844 vs 0.773 or 0.740; and F1-score: 0.886 vs 0.839 or 0.815, respectively) and in the validation cohort (AUC: 0.857 vs 0.720 or 0.750; accuracy: 0.788 vs 0.700 or 0.697; and F1-score: 0.851 vs 0.800 or 0.787, respectively). The DeLong test showed that the combined model of radiomics and clinical features was statistically better than either of the other 2 models in predicting the recurrence of locally advanced oesophageal SCC within 2 years (all P values $<.05$) whereas there was no statistical

difference between the radiomics model and the clinical model (P value $>.05$).

4. Discussion

Radiomics receives much more attention in cancer research in recent years, because it can mine a large number of quantitative features from traditional images such as CT, magnetic resonance imaging, and PET/CT in a high-throughput way.^[29] As a non-invasive, rapid, and low-cost new method, radiomics reflects the phenotypic characteristics of cancer and can help to predict the prognoses or factors associated with treatment strategies, such as survival time, recurrence, adverse events, and subtypes.^[30] In our study, we constructed and validated the CECT radiomic models for predicting the recurrence of locally advanced oesophageal SCC within 2 years after trimodal therapy.

Among 7 clinical features used to establish the clinical model of our study, T stage, N stage, TNM stage, and differentiation degree were independent clinical risk factors for the recurrence of locally advanced oesophageal SCC within 2 years, while age, gender, and tumor location had no certain correlation with the recurrence of this tumor. This is also consistent with previous research conclusions.^[31] Previously many published researches show infiltration depth, differentiation degree, status and the number of lymph node metastasis are valuable prognostic factors in predicting early death by recurrence. However, our study

Table 2
Selected features with descriptions.

Feature category		Features of recurrence vs non-recurrence
Texture features	GLCM	X45.4Correlation X90.1Correlation X0.1DifferenceEntropy X135.7InformationMeasureCorr1 X90.1InformationMeasureCorr2 X0ShortRunHighGrayLevelEmpha
Intensity histogram features	GLRLM	X0.975Quantile
Shape features	Intensity histogram Shape	Volume Max3DDiameter Roundness

GLCM = gray-level co-occurrence matrix and GLRLM = gray-level run-length matrix. GLCM features have been constructed by 4 directions ($\theta=0^\circ, 45^\circ, 90^\circ,$ and 135°) and 3 offsets ($d=1, 4, 7$); and GLRLM features have been constructed by 2 directions ($\theta=0^\circ$ and 90°) and one offset ($d=1$).

Table 3

The performance of the 3 constructed models to predict recurrence within 2 years of locally advanced oesophageal squamous cell carcinoma.

Models	Cohort	AUC	ACC	F1-score	Sen	Spe	PPV	NPV
Radiomics model	Training	0.815	0.773	0.839	0.892	0.538	0.791	0.718
	Validation	0.720	0.700	0.800	0.870	0.300	0.741	0.500
Clinical model	Training	0.763	0.740	0.815	0.863	0.500	0.772	0.650
	Validation	0.750	0.697	0.787	0.804	0.450	0.771	0.500
The combined model	Training	0.879	0.844	0.886	0.903	0.725	0.869	0.787
	Validation	0.857	0.788	0.851	0.889	0.710	0.816	0.706

ACC=accuracy, AUC=area under the receiver operating characteristic curve, NPV=negative predictive value, PPV=positive predictive value, Sen=sensitivity, Spe=specificity.

shows the use of clinical model built by these 7 clinical features is moderate in predicting the recurrence of locally advanced oesophageal SCC within 2 years after trimodal therapy, with the AUC value of 0.763 in the training cohort, and the AUC value of 0.750 in the test cohort.

In this study, 10 core radiomics features were selected from all the 352 extracted features to construct the radiomics model, including 6 texture features, 1 intensity histogram feature, and 3 shape features. X45.4Correlation, X90.1Correlation, X0.1DifferenceEntropy, X135.7InformationMeasureCorr1, and X90.1InformationMeasureCorr2 are texture features of gray-level co-occurrence matrix, which reflects the local heterogeneity variation by analyzing texture changes between adjacent pixels.^[32] X0ShortRunHighGrayLevelEmpha is the texture feature of GLRLM, which reflects regional heterogeneity because it analyzes texture changes throughout the entire length of the run.^[32] Tumor prognosis is closely related to local and regional heterogeneity of tumor. The intensity histogram feature of X0.975Quantile shows good repeatability in our study, which is similar to that in the reported research.^[33] Shape features of Volume, Max3DDiameter, and Roundness provide the external morphologic features about the contours of the tumor. Our study illustrates the CECT radiomics model performs well in both the training group and the validation group, with AUC values of 0.815 and 0.720, respectively. This also indicates the fact that radiomics model has a certain function in predicting the recurrence of locally advanced oesophageal SCC within 2 years after trimodal therapy.

By integrating high-dimensional radiomics features and clinical features, the predictive efficacy of the combined model was superior to that of the radiomics model and the clinical model, with the AUC value of 0.879 in the training cohort and 0.857 in the test cohort. This result reflects combined model can be a

quantitative tool for predicting recurrence of locally advanced oesophageal SCC within 2 years after trimodal therapy.

To guarantee the robustness of radiomics model, our study adopts the following steps. On the one hand, for selecting a feature and building models, each radiomics feature we used to build predictive models underwent screening of intra- and inter-observer agreements, univariate analysis, and LASSO to ensure optimization and repeatability. The robustness of the model was guaranteed by 10-fold cross-validation and stepwise regression.^[28] On the other hand, the validation cohort at a ratio of 7:3 was set up for internal verification of this study and achieved a satisfactory prediction result.^[23]

However, several limitations exist in our study. Firstly, our study is a single-center study. Despite this limitation, our study can provide a good predictive model for the recurrence of locally advanced oesophageal SCC within 2 years after trimodal therapy. We will perform an external validation of multicenter to further verification of our model. Secondly, the published studies have shown that genes such as CXCR-2 and Cyclin D1 are closely related to the prognosis of tumors.^[34,35] More studies are needed to demonstrate whether the gene characteristics can be considered in making radiomics models. Lastly, our study did not perform the correlation analysis of the radiomics features with the pathological data in this study. We will perform the relevant study in the future.

5. Conclusions

Our study showed that the radiomics features had great potential to predict the recurrence of locally advanced oesophageal SCC within 2 years after trimodal therapy, and the combined model of

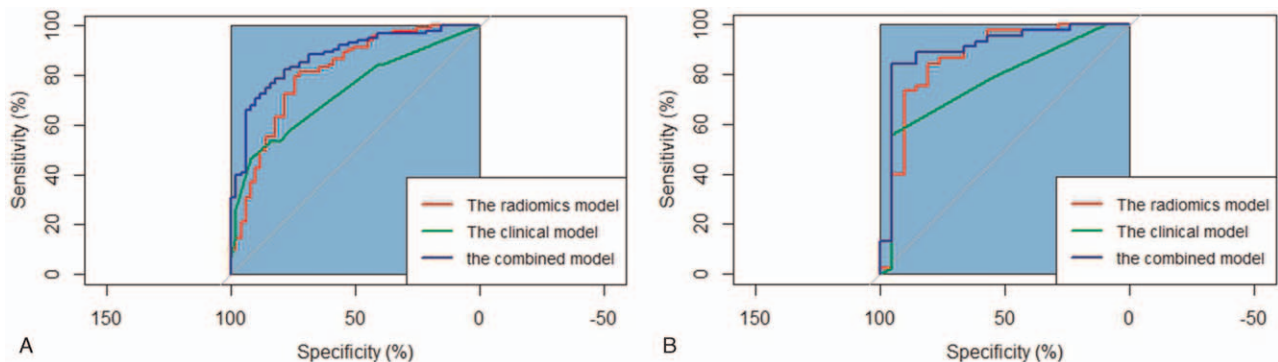


Figure 5. The ROC curves show the performance of the radiomics model, the clinical model, and the combined model of radiomics and clinical features to predict recurrence of locally advanced oesophageal squamous cell carcinoma within 2 years after trimodal therapy in (A) the training and (B) validation cohorts. ROC=receiver operating characteristic.

radiomics and clinical features showed better performance than either radiomics model or clinical model. We hope that our integrated model can be helpful for selecting the patients with a high risk of recurrence to undergo effective personalized therapy and rational surveillance to prevent recurrence of this cancer.

Author contributions

Conceptualization: Rui Li, Tian-Wu Chen, Xiao-Ming Zhang.

Data curation: Sun Tang.

Formal analysis: Sun Tang, Jing Ou.

Funding acquisition: Tian-Wu Chen.

Investigation: Sun Tang, Yu-Ping Wu.

Methodology: Jing Ou, Rui Li, Tian-Wu Chen, Xiao-Ming Zhang.

Project administration: Rui Li, Tian-Wu Chen.

Resources: Tian-Wu Chen.

Software: Tian-Wu Chen, Xiao-Ming Zhang.

Supervision: Rui Li, Tian-Wu Chen, Xiao-Ming Zhang.

Validation: Sun Tang, Jing Ou, Yu-Ping Wu.

Visualization: Sun Tang, Jing Ou, Yu-Ping Wu.

Writing – original draft: Sun Tang, Jing Ou, Yu-Ping Wu, Tian-Wu Chen.

Writing – review & editing: Sun Tang, Rui Li, Tian-Wu Chen, Xiao-Ming Zhang.

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