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CT-Based multiscale and multiphase Imaging Signature for the Quantitative Assessment of Patients With Carcinoma of the Esophagogastric Junction: Initial Differentiation between Squamous Cell Carcinoma and Adenocarcinoma

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Abstract

BACKGROUND

The biological behavior of carcinoma of the esophagogastric junction (CEGJ) is different from that of gastric or esophageal cancer. Differentiating squamous cell carcinoma of the esophagogastric junction (SCCEG) from adenocarcinoma of the esophagogastric junction (AEG) can indicate Siewert staging and indicate whether the surgical route for patients with CEGJ is transthoracic or transabdominal, as well as aiding in determining the extent of lymph node dissection. With the development of neoadjuvant therapy, preoperative determination of pathological type can help in the selection of neoadjuvant radiotherapy and chemotherapy regimens.

AIM

This study aimed to establish and evaluate CT-based multiscale and multiphase radiomics model to distinguish SCCEG and AEG preoperatively.

METHODS

We retrospectively analyzed the preoperative contrasted-enhanced CT imaging of single-center patients with pathologically confirmed SCCEG (n = 130) and AEG (n = 130). It was divided into training (n = 182) and test group (n = 78) at a ratio of 7:3. 1409 radiomics features were separately extracted from 2D or 3D ROIs in arterial and venous phases. Intra-/inter-observer consistency analysis, correlation analysis, univariate analysis, LASSO regression and backward stepwise logical regression were applied for feature selection. Totally, 6 Logistic regression models were established based on 2D and 3D multi-phase features. The ROC analysis, the continuous net reclassification improvement (NRI) and the integrated discrimination improvement (IDI) were used for assessing model discrimination performance. Calibration and decision curves were used to assess the calibration and the clinical usefulness of the model respectively.

RESULTS

The 2D-venous model (5 features, AUC: 0.849) performed better than 2D-arterial (5 features, AUC: 0.808). The 2D-arterial-venous combined model could further enhance the performance (AUC: 0.869). The 3D-venous model (7 features, AUC: 0.877) performed better than 3D-arterial (10 features, AUC: 0.876). And the 3D-arterial-venous combined model (AUC: 0.904) outperformed other single-phase-based models. The venous model showed a positive improvement compared with the arterial model (NRI > 0, IDI > 0), and the 3D-venous and combined model showed a significant positive improvement compared with the 2D-venous and combined model (P<0.05). The DCA curves showed that combined 3D-arterial-venous model and 3D-venous model had a higher net clinical benefit within the same threshold probability range in the test group.

CONCLUSION

The combined arterial-venous CT radiomics model based on 3D segmentation can improve the performance in differentiating EGJ squamous cell carcinoma from adenocarcinoma.

Key Words: Esophagogastric junction; Squamous cell carcinoma; Adenocarcinoma; X-ray computed tomography; Radiomics

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Core Tip: In this study, the multiscale and multiphase CT-based radiomics models were constructed and evaluated to discriminate squamous cell carcinoma and adenocarcinoma of the esophagogastric junction (CEGJ) before operation. The results demonstrated that the combination of multiphase 3D CT radiomics features could improve the differentiation performance than 2D CT radiomics or single-phase-based radiomics. Therefore, radiomics method could help open up a new field for noninvasive diagnosis and personalized management of CEGJ.

INTRODUCTION

Carcinoma of the esophagogastric junction (CEGJ) is defined as a carcinoma whose center is located within 5 cm above and below the esophagogastric anatomical junction and crosses the esophagogastric junction (EGJ). Due to the short and narrow EGJ site and the up-and-down invasive nature of the CEGJ, the biological behavior is different from that of gastric or esophageal cancer [1-3]. The Siewert staging, which is widely accepted in academia, classifies CEGJ into type I, II and III based on the distance between the tumor center and the EGJ [4]. Because of the infiltrative growth pattern of the tumor, the distance between the tumor center and the EGJ in CEGJ is difficult to measure accurately, and Siewert staging is often not easy to determine directly. Squamous cell carcinoma of the esophagogastric junction (SCCEG) has different clinicopathological features from adenocarcinoma of the esophagogastric junction (AEG). Based on the results from previous research, mediastinal lymph node metastases are more likely to occur in SCCEG above the EGJ, whereas metastases from the AEG under the EGJ probably appear in the abdomen [5-6]. Differentiating SCCEG from AEG can indicate Siewert staging and indicate whether the surgical route for patients with CEGJ is transthoracic or transabdominal, as well as aiding in determining the extent of lymph node dissection. With the development of neoadjuvant therapy, preoperative determination of pathological type can help in the selection of neoadjuvant radiotherapy and chemotherapy regimens.

Clinically, medical imaging plays a supporting role in pathological classification and tumor staging. Conventional computed tomography (CT), magnetic resonance imaging and positron emission tomography rely primarily on the visual assessment of the imaging physician and have limitations in early identification of the pathological type of CEGJ. Although histological biopsies are commonly used in clinical practice, some patients have contraindications or low tolerance, and the biopsy sample is limited to the mucosal surface, which may provide an inadequate assessment of the entire tumor status [7]. Therefore, it is important to explore a reliable, practical and non-invasive

preoperative histological staging method for CEGJ, which is clinically important for neoadjuvant radiotherapy, surgical approach selection and lymph node dissection in CEGJ patients. Radiomics technique uses a combined medical-industrial approach to transform traditional images into digital quantitative features, which are potential for digging the potential biological characteristics and heterogeneity of tumor images and has been widely and non-invasively used in the diagnosis, differential diagnosis and disease evaluation [8-12]. Radiomics technique has also been studied in the differential diagnosis of squamous lung cancer and adenocarcinoma [13-14]. However, it is still unclear whether radiomics features extracted from CT images would be useful in predicting pathological type in patients with CEGJ.

Both of two-dimensional (2D) cross section or three-dimensional (3D) volume in CT images could be delineated for radiomics feature extraction. The reported radiomics-based gastric cancer studies have either utilized 2D- or 3D segmentation [12, 15]. However, it remains unclear whether to apply 2D or 3D regions of interest (ROIs) for pathological typing. The selection of 2D or 3D ROIs for outlining can influence radiomics feature values, feature stability, feature screening, and discriminative model performance [16-18]. And the controversy still existed for the performance of diagnosis or prognosis between 2D and 3D radiomics in tumor [16-18].

Therefore, in the current study, we aim to construct and evaluate the multiscale and multiphase CT-based radiomics to discriminate SCCEG and AEG. The developed CT-based model might provide assistance in the personalized and precise treatment of clinical CEGJ patients, especially in the selection of surgical approach and determination of the extent of lymph node dissection.

MATERIALS AND METHODS

Patient Selection

With institutional review board approval (the ethical approval number is 2021-ky-1070-002) and waiver of the written informed consent, we retrospectively collected patients with SCCEG confirmed by gastroscopy and surgical pathology at the First Affiliated

Hospital of Zhengzhou University from January 2010 to June 2021. The patient enrollment criteria included: 1) CT-enhanced abdominal examination within 30 d before surgery ; 2) complete clinicopathological data available ; 3) the lesion covers at least 3 slices on CT cross section, and the maximum plane diameter is not less than 2cm ; 4) no neoadjuvant chemoradiotherapy prior to CT examination. Exclusion criteria included: 1) patient's history of other malignant tumors in combination ; 2) poor CT image quality or lack of raw DICOM data ; 3) combined heart, lung and other important organ dysfunction which could not be performed with CT examination. Finally, 130 patients with SCCEG were included, 87 males and 43 females, aged 38-89 (65.72 ± 8.84) years, with a disease duration of 5 days to 4 years and main symptoms of dysphagia, obstructive sensation of eating and abdominal pain. One patient with AEG was randomly selected according to the month of diagnosis of each SCCEG patient and matched with them according to the above inclusion and exclusion criteria. 130 patients with AEG were included, 93 males and 37 females, aged 31-83 (62.95 ± 9.91) years.

CT Image Acquisition

Informed consent forms were signed before all patients underwent contrast-enhanced CT scans. CT scans were acquired using a 64-row CT scanner (GE Healthcare, Discovery CT 750 HD, United States) or 256-row CT scanner (GE Healthcare, Revolution CT, United States). Preparation for the examination: fasting for more than 8 h before the examination, intramuscular injection of scopolamine 10-20 mg 15-20 min before the examination to reduce gastrointestinal motility (Hangzhou Minsheng Pharmaceutical PG Roup Co.,Ltd. Specifications: 10 mg/mL), and perform breath-holding exercises. Drink 800-1 000 mL of warm water 10 to 15 min before the examination. Scanning parameters: tube voltage 120 kV, tube current using automatic milliampere second technology, pitch 1.375/1.1; field of view (FOV) of 500 mm; 512 x 512 mm matrix, scan thickness 0.625mm to 5 mm, scan spacing 0.625mm to 5mm. Scan area: at least encompasses the lower esophagus to the lower border of both kidneys. Enhancement scan: 90-100 mL of non-ionic contrast agent was injected through the

elbow vein using a high-pressure syringe (GE Medical Systems, iopromide, 370 mg/mL).

Image processing and segmentation

The arterial- and venous-phase CT images were isotropically resampled with a voxel size of 1 mm × 1 mm × 1 mm by using the trilinear interpolation in the Artificial Intelligence Kit software (A.K, version: 3.3.0.R, GE Healthcare, USA), in order to minimize the effect of different scanning protocols or equipment on quantitative inhomogeneity of histological features [19]. 2D ROIs was outlined along the largest cross-sectional area in the axial plane of CT images. After delineating the tumor cross-sectional area slice-by- slice in the axial plane, 3D ROIs was finally merged in to volume of interest (VOI) (**Figure.1-2**). Care should be taken to avoid the gastric cavity and stomach contents, fatty tissue around the stomach wall and blood vessels when segmenting. The2D ROI or 3D VOI delineation was conducted by a radiologist (C.YJ, 6 years experience in imaging diagnosis). In order to ensure the reliability and reproducibility of the radiomics features, 30 patients were randomly selected to be segmented in 2D and 3D manner. For inter-observer agreement analysis, during the radiologist (C.YJ) conducted the first-time whole-dataset segmentation, the radiologist (H.WP, 7 years experience in imaging diagnosis) delineated the selected 30 patients at the same period. For intra-observer agreement analysis, the radiologist (C.YJ) repeatedly conducted the segmentation one month after the first-time delineation.

Radiomics Feature Extraction

The 2D or 3D radiomics features were extracted by open-source Python package Pyradiomics [20]. There were respectively 1409 radiomics features extracted from 2D or 3D ROIs in arterial or venous phases. The original images and the transformed images based on different filters were mainly used for feature extraction. A total of 107 features were extracted from the original images, including: 18 intensity statistical and 14 shape-based features. There were75 textural features extracted from Gray Level Cooccurrence

Matrix (GLCM), Gray Level Run Length Matrix (GLRLM), Gray Level Size Zone Matrix (GLSZM), Gray Level Dependence Matrix (GLDM) and Neighboring Gray Tone Difference Matrix (NGTDM). In addition, the same number of first-order grayscale statistical features and texture features are extracted based on different transformed images. A total of 744 features are extracted based on wavelet decomposition images with 8 filter channels, 279 features are extracted based on Laplacian of Gaussian (LoG) transform images (sigma parameters selected as 1.0mm, 3.0mm and 5.0mm), and 279 features are extracted based on Local Binary Pattern (LBP) filtered images (2nd order spherical harmonic function, spherical neighborhood operator with radius 1.0 and fine fraction 1) [20]. The features are extracted by discretizing the CT values within the ROIs based on a fixed interval width (bin width = 25 HU). The 2D and 3D radiomics features extracted from the randomly selected patients were used to calculate the intra-/inter-class correlation coefficient (ICCs). 2D or 3D features with intra- and inter-observer ICCs values simultaneously greater than 0.75 were retained, which meant the features with good repeatability were involved in the further analysis [18, 21].

Feature Selection and Model Construction

The 260 cases of data were divided into a training group and an internal test group by randomly stratified sampling at the ratio of 7:3. The training group was mainly used for preprocess parameter determination, feature screening and modeling, and the same treatment process, parameters and model were applied to the test group for internal test. The same method was used for feature preprocessing and feature screening in the arterial and venous phase training samples, and independent arterial and venous radiomics models were established. The feature selection and final modeling procedure was performed as follows. The features were firstly preprocessed by excluding features with variance < 1.0, filling missing values with the median and Z-score normalization, and excluding collinear features with cut-value of correlation coefficients larger than 0.7. Then the Mann-Whitney U test or t-test was used to select features with significant difference between two classes (P<0.05). The least absolute shrinkage and selection

operator (LASSO) logistic regression (minimum binomial deviance) with 10-fold cross validation was conducted to avoid overfitting and the features with non-zero cofficients were retained [22]. Finally, the retained features were inputted into backward stepwise logistic regression with minimum Akaike Information Criterion (AIC) to develop the regression radiomics model. The "Radscore" of each patient was calculated according to the formula (Radscore = $\beta_0 + \sum \beta_i x_i$, β_0 is a constant term and βi is the regression coefficient of the feature $x i$).

Four independent radiomics models were constructed, including: 2D arterial-phase model ($Radscore^{AP\_2D}$), 2D venous-phase model ($Radscore^{VP\_2D}$), 3D arterial-phase model ($Radscore^{AP\_3D}$) and 3D venous-phase model ($Radscore^{VP\_3D}$). Two combined models were derived based on the established independent model Radscore according to the regression formula (Radscore = $\beta_0 + \sum \beta_i x_i$, β_0 is a constant term and βi is the logistic regression coefficient of the model score $x i$). And the 2D arterial-venous combined model ($Radscore^{AP\_VP\_2D}$) and 3D arterial-venous combined model ($Radscore^{AP\_VP\_3D}$) were established.

Evaluation of Model Predictive Performance

The performance of the model was evaluated by using the receiver operating characteristic curve (ROC) analysis to obtain the area under the ROC curve (AUC). The sensitivity, accuracy, negative predictive value and positive predictive value were calculated from the cut-off values corresponding to the maximum of the Youden index to evaluate the discrimination performance of the model. The cut-off value the training group are applied to the test group to obtain their corresponding ROC parameters in the test group. The calibration curve analysis and the Hosmer-Lemeshow test were used for evaluating model calibration and the goodness of fit (P>0.05 indicates a good model fit). Delong's test was used to compare the AUC between paired models. Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to assess ability of the model in improving the

classification effectiveness [18]. The decision curve analysis (DCA) was used to assess the net clinical benefit or clinical utility of each model at different threshold probabilities.

Statistical Analyses

R software (version 3.6.3, http://www.r-project.org) was applied for statistical analyses in the current study. Radiomics features and Radscore were continuous variables, and data normality was tested using kurtosis and skewness values, and comparisons between two groups were made using independent samples t-test (for data with a normal distribution) or Mann-Whitney *U* test (for data without normal distribution). Categorical variables were tested by chi-square test or Fisher's exact test. A two-sided $P<0.05$ was considered as statistically significant level. The optimism of the prediction accuracy of the model was validated using 1000-times Bootstrap in the training group. The following R packages were applied: "icc" for intra-/inter-class correlation coefficient; "glmnet" for logistic regression; "pROC" for ROC analysis; "rmda" for DCA; calibration function in the "rms" package for calibration analysis, and the "PredictABEL" package for NRI and IDI analysis.

RESULTS

Feature screening and model construction

Arterial Phase Model Based on 2D ROI

There were 175 radiomics features (ICCs>0.75) were retained among 1409 features. There were 61 and 6 features retained rafter variance and correlation analysis respectively. Among 6 features screened by univariate analysis and 10-folds cross validation LASSO regression (**Figure.3A-3B**), 5 radiomics features were further selected by stepwise logistic regression analysis. The $Radscore^{AP\_2D}$ was summarized in **Supplementary Equation 1**(**S1**). The results of ICCs for individual features were shown in **Table S1** and the multivariable logistic regression result of features involved in the model was summarized in **Table S2**. ROC curves for single 2D arterial features to identify SCCEG and AEG were shown in **Figure.S1A-S1B**. The 2D arterial model

radiomics features and the differences of Rad-score^{AP_2D} in the training and test groups were shown in **Table S3**.

Venous Phase Model Based on 2D ROI

A total of 275 radiomics features (ICCs>0.75) were retained among 1409 features. There were 124 and 12 features kept after variance and correlation analysis respectively. Among 6 features screened by univariate analysis and 10-folds cross validation LASSO regression (**Figure.3C-3D**), 5 radiomics features were kept by stepwise logistic regression analysis. The Radscore^{VP_2D} was summarized in **Supplementary Equation 2**(**S2**). The results of ICCs for individual features were shown in **Table S4** and the multivariable logistic regression result of features involved in the model was summarized in **Table S5**. ROC curves for single 2D venous features to identify SCCEG and AEG were illustrated in **Figure.S1C-S1D**. The 2D venous model radiomics features and the differences of Rad-score^{VP_2D} in the training and test groups were shown in **Table S6**.

Arterial Phase Model Based on 3D ROI

A total of 714 radiomics features (ICCs>0.75) were retained among 1409 features. There were 358 and 27 features kept after variance and correlation analysis respectively. Among 15 features screened by univariate analysis and 10-folds cross validation LASSO regression (**Figure.3E-3F**), 10 radiomics features were kept by stepwise logistic regression analysis. The Radscore^{AP_3D} was summarized in **Supplementary Equation 3** (**S3**). The ICCs for individual features were shown in **Table S7** and the multivariable logistic regression result of features involved in the model was summarized in **Table S8**. ROC curves for single 3D arterial features to identify SCCEG and AEG are shown in **Figure.S1E-S1F**. The 3D arterial model radiomics features and the differences of Rad-score^{AP_3D} in the training and test groups were summarized in **Table S9**.

Venous Phase Model Based on 3D ROI

774 radiomics features (ICCs>0.75) were retained among 1409 features. There were 355 and 23 features kept after variance and correlation analysis respectively. Among 8 features screened by univariate analysis and 10-folds cross validation LASSO regression (**Figure.3G-3H**), 7 radiomics features were kept by stepwise logistic regression analysis, and the $Radscore^{VP\_3D}$ was summarized in **Supplementary Equation 2** (**S4**). The ICCs result for individual features were shown in **Table S10** and the multivariable logistic regression result of features involved in the model was summarized in **Table S11**. ROC curves for single 3D venous features to identify SCCEG and AEG are shown in **Figure.S1G-S1H**. The 3D venous model radiomics features and the differences of $Radscore^{VP\_3D}$ in the training and test groups were summarized in **Table S12**.

2D Arterial-Venous Combined Model

By combining $Radscore^{AP\_2D}$ and $Radscore^{VP\_2D}$, the 2D Arterial-Venous combined model was derived and the $Radscor^{AP\_VP\_2D}$ was described in **Supplementary Equation 5** (**S5**).

3D Arterial-Venous Combined Model

By combining $Radscore^{AP\_3D}$ and $Radscore^{VP\_3D}$, the 3D Arterial-Venous combined model was derived and the $Radscor^{AP\_VP\_3D}$ was summarized in **Supplementary Equation 6** (**S6**).

In this study, a total of 10 candidate radiomics feature parameters were screened out in 2D arterial and venous phase images, mostly first-order features and texture features extracted based on LoG transform or wavelet transform images, and the main categories included 4 first-order features, 2 GLRLM features, 2 GLSZM 7features,1 GLDM feature, and 1 NGTDM feature. More features were screened out in the 3D arterial phase and venous phase images—17 in total, and the main categories included 6 first-order features, 4 GLDM features, 4 NGTDM features, 1 GLRLM feature, 1 GLSZM feature, and 1 GLCM feature.

Radiomics Model Performance

The AUC values, specificity, sensitivity, accuracy, positive predictive value and negative predictive value of the 6 models developed in this study to discriminate SCCEG from AEG in the training and test groups were summarized in **Table 1**, and the ROC curves were shown in **Figure.3**. The model optimism was assessed by 1000-times bootstrap as shown in **Table 2**. It indicated that the 2D-arterial, 2D-venous, 3D-arterial and 3D-venous model presented a degree of optimism less than 0.1 during repeated sampling. The Delong test in the training and test groups were shown in **Table S13**. In the 2D model, the AUC was greater than 0.800 in the test group, except for the arterial model, which had an AUC of 0.752 in the test group. The AUC values of the venous model were higher than that of the arterial model (0.849 vs. 0.808 and 0.831 vs. 0.752) in both the training and test groups. In the 3D model, the AUC values were higher in the venous model than in the arterial model. In the combined model, both of 3D and 2D model were higher than their independent phase model both in the training and test groups. When comparing the performance between 2D and 3D models, the result showed that no matter for the independent phase model or the multi-phase-combined model, 3D models performed with higher AUC than 2D models. Among all the models, the 3D-arterial-venous combined model had the highest AUC values of 0.904 and 0.901 in the training and test groups. As some statistical significance was not obvious during Delong test, continuous NRI and IDI analyses were supplemented to evaluate the ability of each model for improving the classification and the results were shown in **Table S14**. In both the training and test groups, the venous model demonstrated a positive improvement in discrimination over the arterial model (NRI > 0, IDI > 0), the 3D-venous model demonstrated a significant positive improvement in discrimination over the 2D-venous model ($P < 0.05$), both in the 3D model and in the 2D model, the combined model demonstrated a significant positive improvement in discrimination over the arterial model ($P < 0.05$); the 3D combined model reflected a significant positive improvement in discrimination compared with the 2D combined model ($P < 0.05$). In addition, the calibration curve (**Figure 4**) and the results of the Hosmer-Lemeshow test (**Table S15**) indicate that the 6 models had good calibration. The clinical

utility of the model was confirmed by the decision curve (**Figure 5**), in which the 3D-arterial-venous combined model and the 3D-venous model had higher net benefits in the test group within a threshold probability interval of 0.3-1.

DISCUSSION

In the current study, the multiscale and multiphase CT-based radiomics method was used to preoperatively discriminate squamous cell carcinoma and adenocarcinoma of carcinoma of the esophagogastric junction (CEGJ). The results showed that the combination of multiphase 3D CT radiomics features could improve the differentiation performance. Therefore, radiomics method could help open up a new field for noninvasive diagnosis and personalized management of CEGJ. Histopathology biopsy was a commonly used clinical method, and these radiomics features were considered to be complementary to histology biopsy but not a complete substitute for histopathology at this time. Repeat biopsy or endoscopic ultrasound deeper biopsies should be recommended if upper endoscopic biopsies were inconclusive or if it conflicts with the results suggested by radiomics features. Radiomics can provide an adequate reference if the patient has contraindications and low tolerance to endoscopic biopsy.

Previous studies have focused on the quantitative parameters of spectral CT, Zhou *et al* [23] found that the normalized iodine concentration, the $K_{40\text{-}70\ keV}$, and the effective atomic number in the arterial phase could identify SCCEG and AEG, The AUC values were 0.720, 0.730, and 0.706, respectively. Radiomics uses mathematically describable imaging features to comprehensively analyze tumor heterogeneity [24], and has not been validated for identifying SCCEG from AEG. Therefore, we tried use radiomics features to identify the pathological type of CEGJ by comprehensively considering the effectiveness of different phases and segmentation method. In this study, more features were screened out in the 3D models of different phases than in the 2D models, which is related to the fact that the 3D ROIs contains the lesion as a whole and the extracted features have a larger distribution. The results showed that the efficacy of the venous features was higher than that of the arterial in identifying SCCEG from AEG.

Pathologically, squamous carcinoma grows faster and tends to grow in a swelling superposition with denser tissue structure, while adenocarcinoma mostly grows in an appendicular pattern with looser tissue structure [25]. With the prolongation of scanning time, the contrast agent continuously penetrates into the interstitial space of tumor cells, and more textural features appear in the venous phase, which better reflects the heterogeneous characteristics of squamous carcinoma. Tumor vascularization is a kind of biological behavior that reconstructs nutrition connection and promotes tumor development. Pathologic types, tumor origin, and structure of the microvasculature affect the enhancement pattern and radiomics-based parameters.

We found that among the features retained in the venous model, Dependence variance (GLDM) and Large dependence high gray level emphasis (GLDM) had larger weight in the 3D and 2D models, respectively. GLDM mainly describes the degree of dependence between voxel gray levels, and the SCCEG group reflects the high "Dependence variance" of 3D gray levels and the "Large dependence high gray level emphasis" of 2D gray levels, which reflects the large gray level heterogeneity of squamous cancer tissue in 3D features and the high gray level distribution in 2D features from texture features. The uneven distribution of tumor vessels in squamous carcinoma lesions is prone to tumor cell degeneration and necrosis, and it is speculated that the grayscale distribution of squamous carcinoma lesions has some complexity in different transformed images. In addition, features prevalent in the arterial and venous models are Busyness (NGTDM), Dependence variance (GLDM), first order grayscale features. NGTDM features can also represent a certain degree of grayscale distribution inhomogeneity. NGTDM describes the difference between adjacent grayscale values and average grayscale values within the quantized distance of the adjacent grayscale difference matrix, and the squamous carcinoma exhibits a high "Busyness", representing rapid intensity changes between pixels and their neighbors, reflecting the heterogeneous nature of the tissue. In addition, the first-order statistical gray value features calculated based on different dimensions and different phases of images were selected into each model simultaneously, indicating that the images of SCCEG group in

different phases and dimensions have lower gray values, which may be attributed to the histopathological inhomogeneity of microvessels within squamous carcinoma, less blood supply than adenocarcinoma, and lower gray statistical values in squamous carcinoma than adenocarcinoma.

For both of 2D and 3D models, the AUC difference was statistically significant between arterial-venous combined model and the independent arterial model, while not significant between arterial-venous combined model and the independent venous model. It suggested that the venous phase might contribute more predictive information compared with arterial phase. Combining the NRI and IDI index results, the venous model showed a positive improvement in discrimination compared to the arterial model, and the 3D model showed a significant positive improvement in discrimination compared to the 2D model as well.

Most previous radiomics studies varied in the utilization of 2D or 3D segmentation. However, different delineation methods may result in different feature values and predicting performance. The study of different dimensional outlining approaches and the corresponding model performance can guide radiomics practice in related disease areas. Zhao *et al* [15] develop a dual-energy CT–based nomogram for noninvasive identification of the status of HER2 expression in gastric cancer, both 2D and 3D radiomics nomogram performed well. Huang *et al* [18] found that the efficacy of the 3D model was superior to the 2D model when they developed 2D and 3D radiomics models to predict the aggressiveness of pancreatic solid pseudopapillary tumors. This study shows that in the discrimination of SCCEG and AEG, the use of 3D radiomics-based on CT images will be beneficial to improve the discrimination, but the time required for 3D segmentation is significantly higher than that of 2D, so it is also necessary to consider the improvement and optimization of automatic 3D lesion segmentation.

This study still has some limitations. Firstly, the lesion morphology of CEGJ is not fixed, and manual segmentation methods are required. While the lesion travels along the gastric and esophageal walls in a tortuous manner, and the consistency and stability

of the annotation will affect the efficacy of the model. In this study, features with ICCs > 0.75 were used for subsequent analysis, which ensured the robustness of the radiomics features to some extent. More candidate semi-automatic or automatic segmentation algorithm would be welcomed to improve clinical efficiency. Secondly, our study was previously reported to include data on squamous cell carcinoma of the cardia or distal esophagus, but it is still a single-center retrospective study with a small sample size, especially for SCCEG, which inevitably generates selectivity bias when paired with a larger number of AEGs. Future multicenter, prospective, large sample studies are needed to further improve and validate the diagnosing efficacy and generalization ability of the model. In addition, the main purpose of the current study was to evaluate the usefulness of 2D- or 3D-based radiomics methods and clinical data or laboratory test indicators were not included. There is much room for improvement of model reliability, which will be further collected in future studies in order to obtain a more comprehensive understanding.

CONCLUSION

In conclusion, multi-scale and multi-phase radiomics models based on CT imaging data was developed and validated for differentiating SCCEG from AEG before the operation in our study. The 3D radiomics model combining arterial and venous phase showed encouraging performance than that for corresponding 2D model. These models require further validation as decision support tools to guide clinical practice and develop individualized treatment plans for CEGJ patients. Currently, histopathological biopsy is still the common method of diagnosis.

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PRIMARY SOURCES

1	Yue Zhou, Ping Hou, Kaiji Zha, Dan Liu, Feng Wang, Kun Zhou, Jianbo Gao. "Spectral Computed Tomography for the Quantitative Assessment of Patients With Carcinoma of the Gastroesophageal Junction", Journal of Computer Assisted Tomography, 2019 Crossref	123 words — 2%
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