

Heterogeneity of T3 stage esophageal squamous cell carcinoma in different parts based on enhanced CT radiomics

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Abstract

Esophageal cancer is a common malignant tumor of the digestive system with a high incidence and a poor prognosis. At the present, CT-based radiomics is providing more and more valuable information. However, the heterogeneity of the study and the poor repeatability of the texture feature parameters have limited its wider clinical application. In the present study, we focused on comparing the differences in the texture features of T3 stage esophageal squamous cell carcinoma at different locations and normal esophageal wall, aiming to provide some pieces of useful information for future research on esophageal squamous cell carcinoma.

Fifty seven cases with throat CT imaging, including esophageal cancer contrast enhanced CT and conventional CT of healthy control group. The texture characteristics in control group and tumor group among different parts were compared. Using Univariable analysis, we compared the difference and conducted receiver-operator curve analysis to evaluate the performance of tumor grade diagnosis model.

53 radiomic features were significantly different in control group and so as 93 features for tumor group. The upper section was the mostly different from the other 2 sections. Run-length matrix (RLM) features in tumor group accounted for the highest proportion, only Surface Volume Ratio was different.

There are differences in the texture features of the tube wall in different parts of the esophagus of healthy adults, and this difference is more obvious in pT3 stage esophageal squamous cell carcinoma. In the future radiomics study of esophageal squamous cell carcinoma, we need to pay attention to this to avoid affecting the accuracy of the results.

Abbreviations: 18F-FDG = 18F-fluorodeoxyglucose, CT = computed tomography, EUS = endoscopic ultrasound, GSI = Gemstone Spectral Imaging, PET-CT = positron emission tomography-computed tomography, RLM = Run-Length Matrix, TNM = Tumor, Node, and Metastasis.

Keywords: computed tomography, esophageal squamous cell carcinoma, heterogeneity, radiomics, stage

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The protocols of this study were reviewed and approved by the Ethics Committee of our hospital. The patients have given their written informed consent.

The authors have no conflicts of interest to declare.

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

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1. Introduction

Esophageal cancer is a common malignant tumor of the digestive system. Although its incidence has been gradually decreased in the recent years, its mortality rate is still quite high^[1] and its prognosis is poor.^[2] Squamous cell carcinoma is the main histological type of esophageal cancer in China, accounting for about 80% to 90% of total esophageal cancer.^[3,4] The clinical examination methods commonly used in the diagnosis and treatment of esophageal cancer include endoscopic or endoscopic ultrasound (EUS), chest contrast enhanced computed tomography (CT), barium esophageal angiography, and 18F-fluorodeoxyglucose (18F-FDG) and positron emission tomography-computed tomography (PET-CT). However, each of them has certain limitations.^[5–8] Surgery, radiotherapy and/or chemotherapy are currently the main treatment methods for esophageal squamous cell carcinoma. However, the heterogeneity of malignant tumors results in large differences in curative effect after chemotherapy.^[9] Thus, how to accurately evaluate the curative effect on esophageal squamous cell carcinoma early by using imaging method and to provide valuable information for selecting appropriate treatment approaches is a common and important concern of clinicians and clinical researchers.

Currently, enhanced CT is the most commonly used method for pre-operative staging, diagnosis and post-operative evaluation of

esophageal squamous cell carcinoma. It can be used to evaluate the stage and efficacy of lesions based on the shape of the lesion, enhanced features and boundary conditions. However, its accuracy is poor. Due to the rapid development of new radiological technology, Lambin et al.^[10] first proposed the concept of radiomics in 2012, which reflects the heterogeneity of tumors, that is, automatic or semi-automatic analysis methods are used to extract a large number of features from medical images with high-throughput and transform imaging data. Currently, radiomics is an area of great interest in various malignant tumors and has drawn the attention of more and more researchers. Radiomics had been explored and applied in the evaluation and identification of tumor heterogeneity. For example, it was reported to improve the accuracy as compared with conventional diagnostic methods.^[11] It also plays a certain role in PET-CT as compared with the conventional index SUV_{max} .^[12] There is a growing body of evidence suggesting that radiomics may provide incremental value for staging, predicting treatment response and survival in esophageal cancer, for which, the current work-up has substantial limitations. Furthermore, there have been relatively rare reports on the analysis of the texture features of the esophagus in normal people and the texture features of different lesions in different parts of esophagus.

For the same type and same staging of malignant tumor, whether there are any differences in radiomics features between different disease locations still remain unclear. The question why do the patients with the same Tumor, Node, and Metastasis (TNM) stage of esophageal squamous cell carcinoma have different outcomes has not been addressed and clearly answered yet. Thus, in the present study, we attempted to compare the differences in texture feature between different parts of the esophagus of healthy people and patients with esophageal cancer. We also attempted to find out the reasons why the texture analysis of esophageal cancer is poorly reproducible.

2. Materials and methods

2.1. General information about the participating subjects

A total of 57 participants with throat enhanced CT imaging available from August 2017 to July 2018 were included in this retrospective study. Among them, 27 were carcinoma patients with lesions located at different regions and 30 were patients had a normal esophagus. The including criteria for carcinoma patients were as follows: esophageal squamous cell carcinoma patients with pT3N0-2M0 and the including criteria for control participants were normal healthy medical volunteers confirmed by gastroscopy. The staging of esophageal cancer was conducted based on the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC)s eighth edition esophagus and esophagogastric junction cancer TNM staging. All the patients underwent surgical resection to obtain pathological results. The patients ranged in age from 48 to 85 years, (median age 67); males: females = 22:5. All the patients were not given other treatments, such as radiotherapy and chemotherapy or targeted therapy before surgery. The protocols of this study were reviewed and approved by the Ethics Committee of our hospital.

2.2. CT imaging

GE Revolution Gemstone Spectral Imaging (GSI) multi-slice spiral CT was used to acquire CT imaging: patient was in supine position, hands were raised on the top of the head, matrix

512×512 ; layer thickness was 5 mm, layer spacing was 5 mm, 120 Kv; B31f reconstruction function, respectively, scanning arterial and venous phase. The lung window and the mediastinum window image were reconstructed; the mediastinum window image was WW: 350 and WL: 40.

2.3. Segmentation

The edge of the lesion ROI was manually delineated from the arterial phase image using ITK-SNAP (Version 3.4.0) software. For the carcinoma group, the tumors were manually segmented by 2 experienced radiologists (X.F. Li and C.Y. Liu) to avoid the subjective bias. X.F. Li draw the margins of the lesion slice by slice to acquire the 3D-Region of Interest (3DROI) covering the whole volume of the tumor using ITK-SNAP software. C.Y. Liu checked the ROIs to ensure that the segmentation was right. When they had different opinions, they discussed to make the final decision. Finally, the tumors were divided into 3 groups^[13] according to their locations: i.e., upper, middle, and lower thoracic esophagus (the upper section was from sternal notch to azygos vein; the middle section was from azygos vein to inferior pulmonary vein, and the lower section was from inferior pulmonary vein to EGJ).

For each patient in the control group, 3 ROIs corresponding to the upper, middle, and lower regions were segmented. The segmentation was conducted by the same radiologists mentioned above with the same procedure of tumor segmentation. The whole volume of each section as ROI was used in further analysis.

2.4. Feature extraction

The radiomics features were extracted using A.K software (Analysis Kit)(GE Healthcare, Chicago, IL, USA). A total of 396 features consisting of 42 first-order features, 20 geometry features and 334 texture features (based on GLCM, GLSZM, and RLM) were included. The details of these features were presented in Table 1.

2.5. Feature analysis

Firstly, we compared the radiomics features from different sections of normal tissues. The univariable analysis was conducted to judge whether the feature was different between groups; then, we used the post hoc test to find out the sources where the difference came from and decided which 2 groups had larger difference. After the univariable analysis, each feature had a *P* value representing the significant level and $P < .05$ was regarded as statistically significant. We calculated the percentage of significant features in different types, i.e., first-order, geometry,

Table 1

The features with significant difference among 3 regions in normal tissues group and tumor group.

| Category | Normal | | Patients | |
|-----------|----------|-----------------------|----------|-----------------------|
| | Count | Lowest <i>P</i> value | Count | Lowest <i>P</i> value |
| Histogram | 7 (40) | .0002 | 6 (40) | .0345 |
| Texture | 7 (54) | .0061 | 2 (54) | .0193 |
| GLCM | 14 (100) | .0002 | 3 (100) | .0017 |
| RLM | 20 (180) | .0029 | 80 (180) | .0001 |
| GLSZM | 1 (11) | .0033 | 1 (11) | .0224 |
| Shape | 5 (11) | .0001 | 1 (11) | .0059 |
| Total | 54 | - | 93 | - |

and texture features. With 396 P values, we also plotted a P value distribution histogram to evaluate the overall difference, to exclude the distribution of P values that were not random, we simulated 1000 features and each feature had 300 values and randomly divided into 3 groups. The simulated features were used to obtain a reference p -value distribution. Secondly, the tumor features were also compared between different sections by the same procedure as that used for normal tissues. The tumors were divided into 4 grades, grades 1-2 were treated as low grade while grades 3-4 were treated as high grade. We used the machine-learning-based radiomics analysis method to discriminate the different grades. First, we used all the features, and then used the features without differences between different sections.

2.6. Statistical analysis

All the statistical analyses were performed in R software (version 3.5.0, www.Rproject.org). Univariable analysis was used to compare the difference among 3 regions; receiver-operator curve analysis was conducted to evaluate the performance of tumor grade diagnosis model. $P < .05$ was regarded as statistically significant.

3. Results

As shown in Table 1, a total of 53 radiomic features were found to be significantly different in normal tissue group using single-factor ANOVA. RLM features accounted for the highest proportion (20/54). Shape features had the lowest P value. Additionally, we also found that the upper section was the one that is the mostly different from the other 2 sections. For tumor group, a total of 93 features were significantly different among 3 regions. Same as the normal tissue group, RLM features in tumor group accounted for the highest proportion (80/93), only 1 shape feature (SurfaceVolumeRatio) was different.

By comparing the P value distribution with the randomized P value distribution (Fig. 1), we found that the number of P value $< .05$ were higher than that of the random P values both in normal tissue group (Fig. 1a) and tumor group (Fig. 1b).

In radiomics feature analysis, the multivariable logistic regression classifier of discriminating the lower grade tumor from higher grade tumor was constructed. The formula was as follows:

$$\text{Radscore} = 0.108766458491728 - 2.02644694506608 * \text{Cluster Prominence_angle135_offset4} + 0.686907053346072 * \text{sumAverage}$$

The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were shown in Table 2. The performance of the classifier was evaluated with ROC analysis, the AUC was 0.8 (Fig. 2).

Finally, we checked the features in final model, and found that no significantly different features were included.

4. Discussion

It has been widely understood that the heterogeneity of tumors is not only related to the degree of invasion, but also determines the clinical treatment plan, which has a profound impact on the prognosis of patients. In the past, in the radiomics-based esophageal cancer research, different parts of esophageal cancer are treated as a whole, ignoring whether there are any differences in the characteristics of radiomics among different parts. The results obtained in the present study confirm that there are indeed

some differences in the radiomics characteristics of different parts of both healthy adults and patients with esophageal cancer. This observation suggests that when we compare the radiomics characteristics of normal esophageal and esophageal cancer lesions in future studies, we need to select the data of the unified parts, otherwise, it would cause errors and the accuracy would be affected.

In this study, we observed

1. differences in the radiomics characteristics between the upper thoracic and the middle thoracic segments and between the upper thoracic segment and the lower thoracic segment of normal adults;
2. a statistically significant difference in the imaging features between the upper thoracic esophagus and the lower thoracic esophagus and between the upper thoracic esophageal and the middle thoracic esophagus ($P = .0003$ and $P = .0075$, respectively).

The possible reasons for the differences can be speculated as follows: **Firstly**, the image acquisition features of this group are acquired from 64 rows of CT scan images, and the thickness of image layer is 5mm. Therefore, the CT image itself has limitations, and the soft tissue resolution is not high enough to clearly show the esophageal wall, especially in the CT transverse transposition image of the upper esophageal wall, frequently due to the sudden widening of the human body from the neck to the thoracic entrance and the formation of artifacts caused by high-density vertebral bodies behind the esophagus, which is difficult to avoid. The lower thoracic esophagus may also cause a difference between the upper thoracic segment and the middle thoracic segment and the lower thoracic segment due to the proximity to the esophagogastric junction. **Secondly**, the esophagus itself is a muscular cavity organ and there is a peristaltic wave under normal physiological state, thus, in the CT scan, it will show that a certain lumen is in an expanded state while a certain lumen is in a contracted state. Fan et al^[14] also reported that the thickness of the wall of the esophageal wall varied under different expansion and contraction conditions, which may also cause differences in the imaging ensemble characteristics of the esophageal wall at different sites. From a physiological point of view, the smooth muscle cells of the esophagus have a basic electrical rhythm and they have slow and irregular automatic rhythm, thus the different parts of the image acquired at the same time are different in the diastolic phase, resulting in differences in their radiomics characteristics. Because there are 7 to 10 longitudinal folds on the surface of the esophageal cavity, it is precisely due to the slow and irregular contraction of the esophageal cavity that causes the loose or denser arrangement of folds, which may also lead to differences in the radiomics characteristics of the esophageal. **Thirdly**, the esophagus is composed of mucosa, submucosa, and muscular. The anatomical distribution of the esophageal muscle layer is inconsistent, showing that the proximal 1/3 is skeletal muscle, the middle 1/3 is skeletal muscle which is interlaced with smooth muscle and the lower 1/3 of skeletal muscle is smooth muscle which is basically consistent with the demarcation of esophageal thoracic segment boundary, therefore it can also explain why there are differences in esophageal radiomics characteristics. Although the patients were all pT3 squamous cell carcinoma patients, there were 12 patients with pN1 stage, including 7 cases in the middle thoracic region and 5 cases in the lower thoracic segment, accounting for 44.4%. There were also 4 patients with

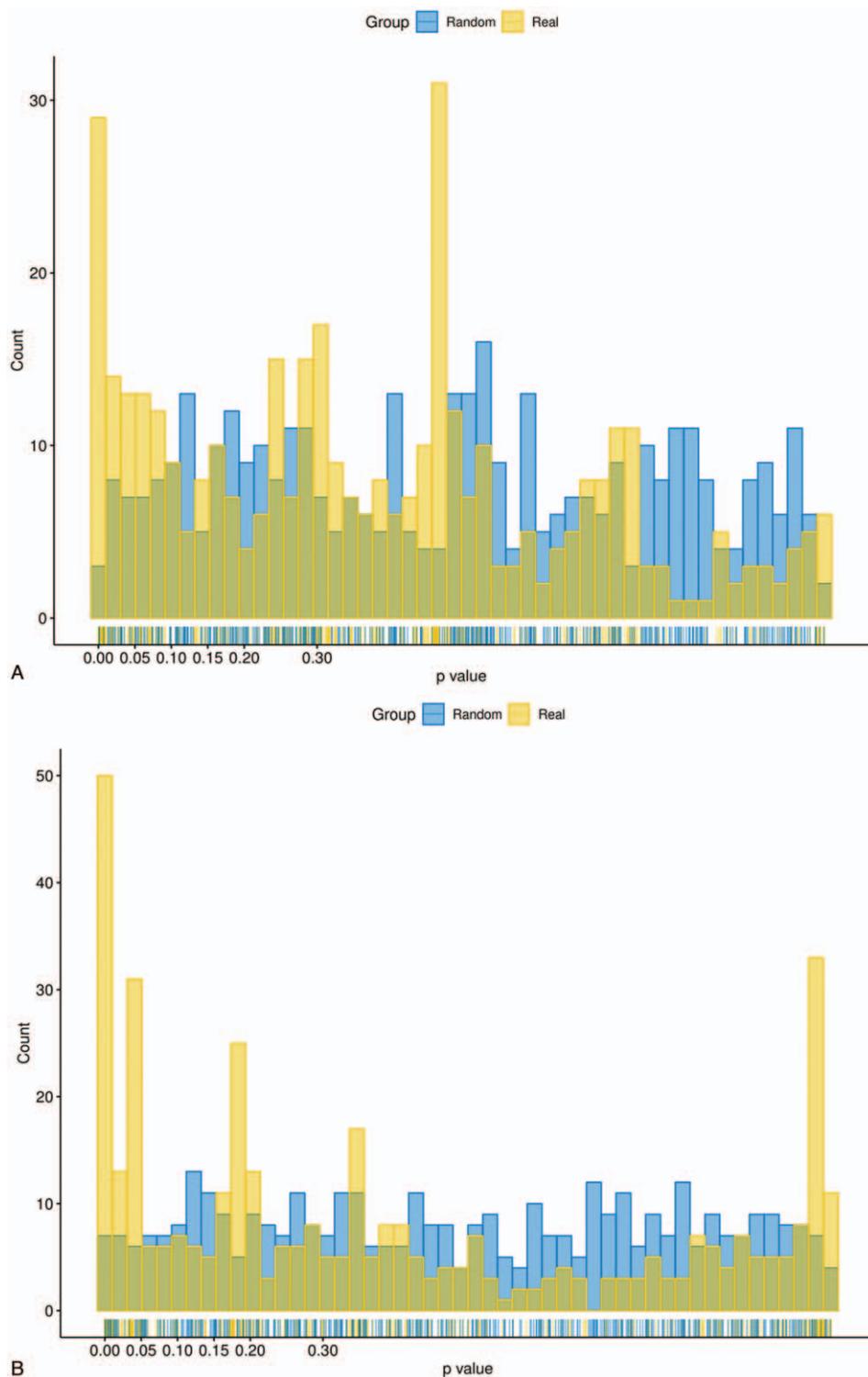


Figure 1. The *P* value distribution of normal tissue group (a) and tumor group (b).

Table 2

The measured parameters of the tumor grade diagnosis model.

| Cutoff | Accuracy (95%CI) | Sensitivity | Specificity | Positive Pred value | Negative Pred value |
|--------|---------------------|-------------|-------------|---------------------|---------------------|
| 0.454 | 0.815 (0.619–0.937) | 0.727 | 0.875 | 0.800 | 0.824 |

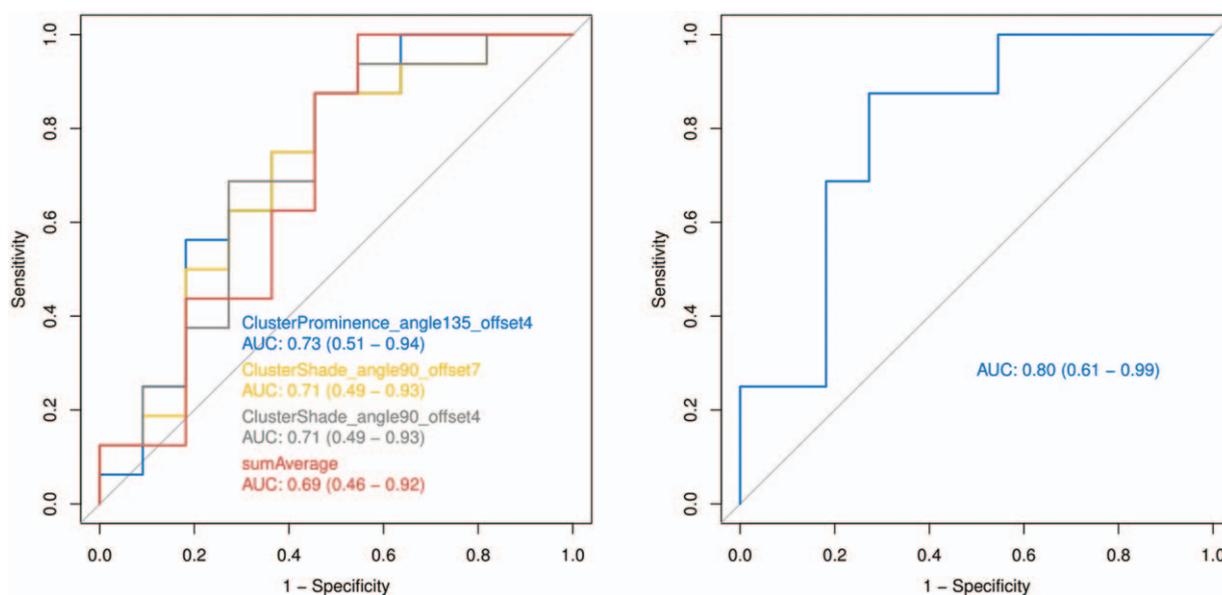


Figure 2. The receiver operator curves of 4 most discriminative features and the tumor grade diagnosis model.

pN2 staging, accounting for 14.8%. There were 3 cases in the middle thoracic and 1 case in the lower thoracic segment. No lymph node metastasis was found in the upper thoracic esophageal cancer patients, indicating that lymph node metastasis is more likely to occur in the middle and lower thoracic esophageal cancer. Thus, we speculate that the difference in imaging histology between upper thoracic esophageal cancer with middle and lower thoracic esophageal cancer may be related to lymph node metastasis. Moreover, in the 27 patients with esophageal cancer, the CT values of the upper thoracic esophageal cancer in the enhanced CT arterial phase were in the range of 50 to 70 HU while the CT values in the venous phase ranged 40 to 55HU; The CT value of the middle thoracic esophageal cancer in the enhanced CT arterial phase and in the venous phase were about 60 to 80 HU and about 55 to 70 HU, respectively. The CT values of the lower thoracic esophageal cancer in the enhanced CT arterial phase and in the venous phase were about 70 to 90 HU and 60 to 75 HU, respectively. There were significant differences between the upper thoracic esophageal cancer lesions and the lower thoracic segment ($P = .0231$). Therefore, we speculate that the differences in imaging histology may be related to the degree of enhancement and CT values. Last but not least, while they are both pT3 squamous cell carcinoma patients, the degree of differentiation is inconsistent and in this group of cases, we also found that the upper thoracic esophageal cancer was mainly based on the centripetal thickening of the esophageal wall, while the middle and lower thoracic esophageal segments are often eccentrically thickened. It is presumed that the formation of the mass is related to these factors.

Although we found differences in texture features in the same parts of the normal esophageal wall and esophageal cancer lesions, there are several limitations in this study. First, the sample size is insufficient, and we will continue to expand the sample size in the next study. Second, the study of esophageal cancer in this study was based on a 5 mm layer thickness. Zhao et al^[15] proposed that the texture features obtained on CT thin layer images (1.25mm) could more accurately describe the

heterogeneity of the lesion than the thick layer image of 5 mm. Finally, because the healthy control group in this group considered the medical cost and they used the conventional scan instead of the contrast enhanced scan, our study lacked the comparative study between the control group enhanced scan and the case group enhanced scan.

5. Conclusions

In summary, based on the above results, we suggest that the radiomics of the same location should be compared when we perform the radiomics analysis of the esophagus. It is believed that the radiomics will play an important role in the preoperative staging of esophageal cancer, prognosis, and efficacy evaluation.

Author contributions

Contributions:

- (I) Conception and design: Cai-yun LIU, Shao-feng Duan, Xiao feng LI
- (II) Administrative support: Qiang Wang, Xiao feng LI;
- (III) Provision of study materials or patients : Biao Yao, Cai-yun LIU, Xiao feng LI;
- (IV) Collection and assembly of data: Biao Yao, Cai-yun LIU, Xiao feng LI;
- (V) Data analysis and interpretation: Cai-yun LIU, Shao-feng Duan, Xiao feng LI;
- (VI) Manuscript writing: All authors;
- (VII) Final approval of manuscript: All authors.

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