Discrimination of mediastinal metastatic lymph nodes in NSCLC based on radiomic features in different phases of CT imaging

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Abstract

Background: We aimed to develop radiomic models based on different phases of computed tomography (CT) imaging and to investigate the efficacy of models for diagnosing mediastinal metastatic lymph nodes (LNs) in non-small cell lung cancer (NSCLC).

Methods: We selected 231 mediastinal LNs confirmed by pathology results as the subjects, which were divided into training (n=163) and validation cohorts (n=68). The regions of interest (ROIs) were delineated on CT scans in the plain phase, arterial phase and venous phase, respectively. Radiomic features were extracted from the CT images in each phase. A least absolute shrinkage and selection operator (LASSO) algorithm was used to select features, and multivariate logistic regression analysis was used to build models. We constructed six models (orders 1-6) based on the radiomic features of the single- and dual-phase CT images. The performance of the radiomic model was evaluated by the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV).

Results: A total of 846 features were extracted from each ROI, and 10, 9, 5, 2, 2, and 9 features were chosen to develop models 1-6, respectively. All of the models showed excellent discrimination, with AUCs greater than 0.8. The plain CT radiomic model, model 1, yielded the highest AUC, specificity, accuracy and PPV, which were 0.926 and 0.925; 0.860 and 0.769; 0.871 and 0.882; and 0.906 and 0.870 in the training and validation sets, respectively. When the plain and venous phase CT radiomic features were combined with the arterial phase CT images, the sensitivity increased from 0.879 and 0.919 to 0.949 and 0.979 and the NPV increased from 0.821 and 0.789 to 0.878 and 0.900 in the training group, respectively.

Conclusions: All of the CT radiomic models based on different phases all showed high accuracy and precision for the diagnosis of LN metastasis (LNM) in NSCLC patients. When combined with arterial phase CT, the sensitivity and NPV of the model was be further improved.

Background

Lung cancer is one of the most common malignancies and is associated with the highest cancer morbidity and mortality rates worldwide. Non-small cell lung cancer (NSCLC) accounts for
approximately 85% of all lung cancers [1]. Lymph node metastasis (LNM) is the most common type of tumor metastasis pathway of NSCLC and remains an essential prognostic factor and guide for adjuvant therapy. In clinical practice, comprehensive treatment that includes surgery, chemotherapy and radiotherapy is the standard treatment for stage I-IIIB NSCLC. However, the scope of lymph node (LN) LN dissection and the LN areas of LNs targeted by radiotherapy remain controversial among different medical centers. Currently, positron emission tomography (PET)/computed tomography (CT) is a relatively accurate imaging technique for the diagnosis of metastatic LNs, with a relatively high specificity for LN staging in patients with NSCLC [2,3]. However, the low prevalence and high cost of PET/CT equipment limit its clinical application. Additionally, CT has disadvantages for in the identification of metastatic LNs, in that high rates of false-positive and false-negative results occur when images are analyzed for judged according to morphological changes, including size, shape, necrosis, and external capsule invasion [4,5]. Hence, a great need exists for sensitive and accurate methods to preoperatively assess the status of LNs, which could help to decrease the rate improve the degree of radical surgery, select appropriate chemotherapy regimens, and delineate the radiotherapy target area.

Due to the emergence of personalized medicine and targeted therapy, the need for quantitative image analysis has increased with the rapid increase in the amount of the explosion of standard medical data. Radiomics provides promising opportunities in this regard, endowing medical imaging with to play an increasingly important role in analyzing tumor heterogeneity [6]. Previous studies have shown that objective and quantitative image features could potentially be used as prognostic or predictive biomarkers [7]. However, most studies have focused on single-phase CT images, which may not allow the best to obtain the best model to be obtained from a series of CT images. Therefore, in the present study, we investigated the accuracy of radiomic and delta -radiomic features between different CT phase scans different phases for in the preoperative discrimination of metastatic LNs in NSCLC patients to provide the best reference model for the clinical diagnosis of mediastinal lymph nodes.

Methods
**Patient information**

The Institutional Review Board approved the retrospective review of the medical records for this analysis. The inclusion criteria were as follows: (I) all patients underwent systematic LN dissection or sampling within two weeks after undergoing plain non-contrast and enhanced contrast CT scans; (II) no patients received any treatments before the scans were performed; the LNs status was confirmed by pathology results; and (III) LNM was confirmed by pathology results; and (IV) distant metastasis, multiple tumors and other manifestations were absent. The exclusion criteria were as follows: (I) clinical data were incomplete, or statistical analysis could not be performed; (II) patients received treatments before the scans were performed; (III) poor image quality affected the quantitative analysis; and (IV) CT images were reconstructed using different algorithms, thicknesses, or equipment.

**CT image acquisition**

All patients underwent routine and enhanced CT scanning, and a Philips scanner (Holland, CT Lightspeed 16) was used with the following an imaging protocol: of tube voltage 120 kV, cube current 300 mA, thickness 2 mm and in-plane resolution 0.97×0.97. The contrast medium was injected into the elbow vein at the an injection rate of 2.3~3.0 ml/second, and the maximum dose was 100 ml. An arterial phase scan was performed 25 to 30 seconds after contrast medium injection, and a venous phase scan was performed 90 seconds later. Plain, arterial and venous phase images were obtained. All images were exported in the Digital Imaging and Communications in Medicine (DICOM) format for image feature extraction.

**Radiomics workflow**

The radiomics workflow included: (1) image segmentation, (2) feature extraction, (3) feature selection, and (4) predictive model building.

**Lesion segmentation**

We performed manual segmentation on arterial-phase CT images using MIM Maestro version 6.8.2 (MIM software, Cleveland, OH)MIM Maestro software (MIM Software, Cleveland, OH), and pathologically confirmed LNs were defined as regions of interest (ROIs). Using the arterial-phase CT
image as the reference, plain and venous -phase CT images were corrected by the nonrigid registration method, and the contouring results were mapped to the plain and venous- phase images, respectively. The target images were delineated by two senior radiologists with 20 years of experience in chest CT diagnosis, and differences in the findings were resolved by a third high-ranking radiologist when disputes occurred. Figure 1 shows schematic diagrams of the ROIs on three CT images of in different phases.

Figure 1. CT images from a 56-year-old man with mediastinal LNM confirmed by pathology. PanelsPictures a, b and c show the ROIs on plain, arterial and venous phase CT images, respectively.

Feature extraction

Radiomic features were extracted from LNs using 3D Slicer software, an open-source Python package for the extraction of features from medical images (version 4.6, http://www.slicer.org) [8]. In total, 841 radiomic features were extracted and were organized into two categories: (I) based on original images; and (II) based on wavelet images. Eighteen first-order features derived from the tumor intensity histogram reflected the distribution of the values of individual voxels without concern for spatial relationships. Thirteen shape features provided the geometric tumor volume. Seventy-four texture features described the spatial arrangement of voxels, as calculated from different parent matrices, which included including the gray level dependence matrix (GLDM), the gray level co-occurrence matrix (GLCM), the gray level size zone matrix (GLSZM), the gray level run length matrix (GLRLM) and the neighborhood gray-tone difference matrix (NGTDM) [9]. In addition, 736 wavelet features derived from eight filtering modes were obtained.

Feature selection and development of radiomic models development

The A least absolute shrinkage and selection operator (LASSO) logistic regression algorithm was used to select significant features with nonzero coefficients to develop models. In this study, we constructed six models based on the radiomic features of single-phase imaging and joint two-phase imaging, which included models 1, 2, and 3 (based on the plain, arterial and venous phase radiomic features, respectively), and models 4, 5, and 6 (based on the delta radiomic features between plain and arterial phase imaging, plain and venous phase imaging, and arterial and venous phase imaging,
respectively). The above process was implemented in R software (version: 3.3.3, https://www.r-project.org). The classification performance of the radiomic models was quantified by the area under the receiver operator characteristic curve (AUC), sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) in both the training and validation cohorts.

Statistical analysis

The data analysis was performed using Statistical Package for Social Sciences (SPSS) software version 23.0 (SPSS, Chicago, IL, USA) and R software (version 3.4.0, https://www.r-project.org). We compared continuous values (age) between the training and verification groups by independent samples t tests, and the χ² test was used to compare the two classification characteristics (sex and pathological outcome) between the training and verification groups. P values less than 0.05 were considered statistically significant.

Results

Characteristics of patients in the training and validation cohorts

Participants were selected according to the inclusion and exclusion criteria and were limited to patients treated between January 2015 and June 2018 at our hospital. We divided the patients into two independent cohorts: 61 patients treated between January 2015 and June 2017 constituted the training cohort, and 25 patients treated between July 2017 and June 2018 constituted the validation cohort. The characteristics of patients in both the training and validation cohorts are displayed in Table 1. A total of 231 LNs in from eighty-six patients which has surgical-pathologic information diagnosed with NSCLC with mediastinal LNM were examined, including 58 males and 28 females aged 35–84 years (mean age 60±10 years). In the training cohort, 60.7% (99/163) of LNs were pathologically positive, and 39.3% (64/163) of LNs were pathologically negative. In the validation cohort, 61.8% (42/68) of LNs were pathologically positive, and 38.2% (26/68) of LNs were pathologically negative. No difference was observed in the patient age or LN pathological status between the two cohorts.

Table 1. Characteristics of patients in the training and validation cohorts
| Group          | LN status   | Age (Mean±sd) | Sex (n) |
|---------------|-------------|---------------|---------|
|               | N⁺          | N⁻            |         |
| Training      | 99          | 64            | 60±10   | 40   | 21 |
| Validation    | 42          | 26            | 60±10   | 18   | 7  |
| Test value    | 3.765⁺      | -0.049⁻       | 4.840⁺  |       |
| P value       | 0.052       | 0.961         | 0.028   |       |

Note: a: c² value; b: t value

Selection of features and the construction of radiomic models

A total of 841 features were extracted from each phase CT image of the training cohort. We screened these features and chose 10, 9, 5, 2, 2, and 9 features that had nonzero coefficients as potential predictors using the LASSO logistic regression model. Figure 2 depicts the process of feature selection. The weighted values of the nonzero characteristics selected to develop models were are summarized in a Supplementary file. The radiomic models all showed a favorable predictive efficacy for identifying mediastinal LNM in NSCLC patients, with AUC values higher than 0.830 in the training cohort (Figure 3).

Figure 2. The feature selection process. (a.) LASSO coefficient profiles of the 841 features. (b.) Tuning parameters (λ) selected in the LASSO model were used for applied 10-fold cross-validation via with the minimum criteria. The Y-axis indicates misclassification errors, and the lower X-axis indicates the average deviance ln(λ) values, which were -2.19, -2.44, -2.14, -1.61, -1.75, and -2.61 in models 1–6, respectively. The vertical lines through the red dots show the upper and lower limits of the deviances. Dotted vertical lines were drawn at the optimal values using the minimum criteria with 1 standard error (the 1-SE criteria). Numbers along the upper X-axis represent the average number of predictors.

Figure 3. ROC curves of the radiomic models. Panels Figure a-e correspond to models 1–6, respectively.

Analysis of models based on the single- and joint-phase CT

Based on three single-phase CT images and two joint-phase CT images, we constructed six models in this study. As shown in Table 2, model 1 yielded the highest AUC, specificity, accuracy and PPV, which were 0.926 VS and 0.925, 0.860 VS and 0.769, 0.871 VS and 0.882, and 0.906 VS and 0.870 in the
training and validation sets, respectively. However, the sensitivity and NPV of the arterial phase model were higher than those of the other single-phase models. We observed that the AUC value of the joint model was lower than that of the single-phase model, but the sensitivity and NPV of the training group were significantly improved higher. Compared with those of model 1, the sensitivity and NPV of model 4 increased from 0.879 and 0.821 to 0.949 and 0.878, respectively. Moreover, compared with those of model 3, the sensitivity and NPV of model 6 increased from 0.919 and 0.789 to 0.979 and 0.900, respectively. The sensitivity, specificity, accuracy, NPV, and PPV of each model are listed in Table 2.

Table 2. Efficacy of models for identifying mediastinal LNM in the training and validation groups

| Model | Group   | AUC | SEN  | SPE  | ACC  | PPV  | NPV  |
|-------|---------|-----|------|------|------|------|------|
| 1     | training| 0.926| 0.879| 0.860| 0.871| 0.906| 0.821|
|       | validation| 0.925| 0.952| 0.769| 0.882| 0.870| 0.909|
| 2     | training| 0.875| 0.929| 0.609| 0.804| 0.786| 0.848|
|       | validation| 0.876| 0.976| 0.423| 0.765| 0.732| 0.917|
| 3     | training| 0.857| 0.919| 0.469| 0.742| 0.728| 0.789|
|       | validation| 0.802| 0.905| 0.500| 0.750| 0.745| 0.765|
| 4     | training| 0.850| 0.949| 0.563| 0.798| 0.770| 0.878|
|       | validation| 0.813| 0.952| 0.423| 0.750| 0.727| 0.846|
| 5     | training| 0.831| 0.879| 0.594| 0.767| 0.770| 0.760|
|       | validation| 0.800| 0.952| 0.615| 0.824| 0.889| 0.889|
| 6     | training| 0.841| 0.979| 0.281| 0.706| 0.678| 0.900|
|       | validation| 0.702| 0.928| 0.192| 0.647| 0.650| 0.625|

Note: SEN: sensitivity; SPE: specificity; ACC: accuracy; PPV: positive predictive value; NPV: negative predictive value.

Discussion

The International Association for the Study of Lung Cancer (IASLC) showed that, based on a newly established large database, the 5-year survival rates for patients with LNM ranged from 26 to 53% [10]. The systematic dissection of LNs in lung cancer patients has been widely accepted, but the extent of LN dissection has remained a matter of debate due to the precise assessment of metastatic LNs [11,12]. LNM is an important factor that affects tumor and LN staging. Therefore, the noninvasive preoperative evaluation of the LN status is crucial for determining determination of the lung cancer
stage, surgical plan, and prognosis [13].

Currently, CT and PET/CT are the most routinely used noninvasive methods for the clinical diagnosis of LNs. The international standard for the diagnosis of metastatic LNs by CT in lung cancer is a short-axis LN diameter larger than 10 mm. However, due to the single diagnostic criterion, the accuracy of the diagnosis is limited to some extent. Also, PET/CT is a noninvasive method for staging cancer that has been increasingly employed by multidisciplinary lung cancer teams. Many studies have reviewed the diagnostic performance of PET/CT for LN staging in patients with NSCLC [14~16]. A systematic review showed that the summary sensitivity and specificity estimates for a maximum standard uptake volume (SUVmax) ≥2.5, which is the PET/CT positivity criterion, were 81.3% and 79.4%, respectively [17]. However, the low prevalence and high cost of PET/CT equipment have resulted in it being less commonly applied used than CT alone in preoperative examinations. If the accuracy of CT in the diagnosis of LNs lymph nodes could be improved, it would provide more important clinical guidance for identifying the delineation of radiotherapy targets and the selection of surgical range.

Recently, the development of radiomics has enabled medical images to be converted into high-throughput quantitative data, providing information that can be explored and used to guide clinical decision-making. In contrast to subjective descriptions of the volume and shape of lesions, radiomic features can more comprehensively describe the state of lesions, overcoming the disadvantages of traditional diagnostic methods [18~20]. Therefore, radiomics is expected to improve the accuracy of diagnosis based on CT images diagnosis. Moreover, studies have demonstrated the feasibility of using radiomic features to predict LNM in rectal, breast and esophageal cancers, providing theoretical support for this study [21~23].

In the present study, we constructed radiomic models based on pathological diagnostic results to facilitate the preoperative identification of metastatic LNs in NSCLC patients. The results showed that the diagnostic models based on different phases all exhibited favorable discrimination (AUC values greater than 0.8, a maximum sensitivity of 97.9%, and a maximum specificity of 86.0%), and model 1 (plain CT) yielded the highest AUC, specificity, accuracy and PPV. The underlying reason for the better
performance on non-contrast images may be that the biological heterogeneity within the LNs that can be described by radiomic features may be confounded by the intravenous injected contrast material, which may then lead to worse discrimination between malignant and benign LNs due to the existing intratumoral contrast material. On the other side, the result of this study showed that more texture features (10 texture features) were selected from non-contrast CT than contrast-enhanced CT (9 or 5 texture features), and the texture features from plain CT scan were found to be more significant in discriminating mediastinal metastatic lymph nodes. Moreover, previous researches have confirmed this interesting finding. He et al.[24] evaluated the effects of contrast-enhancement on the diagnostic performance of radiomics signatures in solitary pulmonary nodules (SPNs), which indicated that contrast-enhancement can affect the diagnostic performance of radiomics signatures in SPNs and that non-contrast CT is more informative. Similarly, Sui et al.[25] confirmed that the radiomics features of the non-contrast CT have a better predictive performance than those of contrast CT in anterior mediastinal lesion risk grading. In the research of classifying mediastinal LNM of NSCLC from $^{18}$F-FDG PET/CT images, Yao et al.[2426] summarized the PET/CT diagnostic results of 2543 NSCLC patients from 22 research centers and found that the overall sensitivity and specificity of PET/CT for identifying mediastinal LNM were 0.66 and 0.82, respectively. In addition, another study showed that the sensitivity and specificity of CT in for the diagnosis of mediastinal lymph node metastasis LNM were 0.79 and 0.72, respectively [275]. Compared to those in previous published studies, the methods proposed in this our study have the advantages of being quantitative and reproducible, with a higher sensitivity and specificity than the previously reported methods. Moreover, we, different from previous studies that only analyzed characteristics of single-phase CT images, this study extracted not only extracted radiomic features from plain, arterial, and venous phase CT images but also calculated delta radiomic feature values between different phase CT images in different phases. The arterial phase mainly reflects the tissue perfusion of the tumor, and the venous phase mainly reflects the clearing of the tissue blood flow, which is also an important imaging feature of tumor metastasis [286]. Dynamic CT texture analysis can assess temporal changes in tumor heterogeneity after the administration of contrast material and could provide another
dimension of physiologic tumor assessment [29]. The sensitivity and NPV of the model were significantly better when combined with arterial phase CT. The results revealed that the sensitivity and NPV of models 4 and 6 were significantly improved in our study, which may have been because temporal changes in texture features can potentially provide diagnostic and prognostic information and can increase the utility of contrast-enhanced CT. In clinical practice, for NSCLC patients treated with neoadjuvant therapy and routine radical surgery, false-positive LNs will not result in insufficient treatment or lead to treatment delay. However, the higher NPV of this approach means that negative LNs will be more accurately identified, which may change the clinical treatment plan [3027]. These findings suggest that the accuracy of models can be improved when combined with dual-phase models radiomic features in future clinical applications.

This method of integrating a large number of features in CT images that cannot be recognized or distinguished by the human eye has high accuracy and sensitivity in for diagnosing mediastinal LNM in NSCLC patients and is expected to improve the efficacy of treatments for NSCLC. However, there are still some limitations of this study. First, the data used in this study were obtained from the same center. Second, the diagnostic capacity of combined clinical and quantitative imaging features cannot could not be evaluated. Third, a minority of patients in our study underwenthad both CT and PET/CT before surgery because of the high cost of PET/CT and the high radiation exposure. We will add related cases in future studies and compare the study results with the PET/CT results, and the predictive accuracy might be further improved by automatically combining features determined by radiomic and deep learning. In summary, all of the CT radiomic models based on different phases all showed high accuracy and precision for in the diagnosis of LNM in NSCLC patients. The combination of plain and venous phase CT scans with arterial phase CT radiomic features can further improve the sensitivity and NPV negative predictive value of the model.

**Abbreviations**

NSCLC: Non-small cell lung cancer; LNM: Lymph node metastasis; PET/CT: Positron emission tomography/computed tomography; ROIs: Regions of interest; GLDM: Gray level dependence matrix; GLCM: Gray level co-occurrence matrix; GLSZM: Gray level size zone matrix; GLRLM: Gray level run
length matrix; NGTDM: Neighborhood gray-tone difference matrix; LASSO: least absolute shrinkage and selection operator; AUC: Area under the receiver operator characteristic curve; SEN: Sensitivity; SPE: Specificity; ACC: Accuracy; PPV: Positive predictive value; NPV: negative predictive value; SE: Standard error

Declarations

Ethics approval and consent to participate

The Ethics Committee (IRB) at Shandong Cancer Hospital and Institute Shandong Cancer Hospital Affiliated to Shandong University reviewed and discussed the protocol and other consent aspects of the trial. After the vote (Total: 11, Agree 11, Disagree: 0), the IRB agreed that the trial followed the guidelines of good clinical practice (GCP) and that the trial could be conducted at Shandong Cancer Hospital and Institute Shandong Cancer Hospital Affiliated to Shandong University (NO. 201805056). The need for informed consent of this retrospective study was waived.

Consent to publish

Consent for publication was provided for all data published here.

Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request (yinyongsd@126.com).

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

SX designed the study and wrote the initial draft of the manuscript. GZG and QQT contributed to the design of the study and the analysis and interpretation of data and assisted in the preparation of the manuscript. JHD, DWL, and YY contributed to data collection and interpretation, and critically reviewed the manuscript. All authors approved the final version of the manuscript and have agreed to
be accountable for all aspects of the work in and for ensuring that questions related to the accuracy
or integrity of any part of the work are appropriately investigated and resolved.

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Figures

Figure 1

CT images from a 56-year-old man with mediastinal LNM confirmed by pathology. Pictures a, b and c show the ROIs on plain, arterial and venous phase CT images, respectively.
The feature selection process. (a.) LASSO coefficient profiles of the 841 features. (b.) Tuning parameters ($\lambda$) selected in the LASSO model applied 10-fold cross-validation via the minimum criteria. The Y-axis indicates misclassification errors, and the lower X-axis indicates the average deviance $\ln(\lambda)$ values, which were -2.19, -2.44, -2.14, -1.61, -1.75, and -2.61 in models 1-6, respectively. The vertical lines through the red dots show the upper and lower limits of the deviances. Dotted vertical lines were drawn at the optimal values using the minimum criteria with 1 standard error (the 1-SE criteria). Numbers along the upper X-axis represent the average number of predictors.
Figure 3

ROC curves of the radiomic models. Figure a-e correspond to models 1-6, respectively.

Analysis of models based on the single- and joint-phase CT

Supplementary Files

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