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CT-based radiomics signature for differentiating solitary granulomatous nodules from solid lung adenocarcinoma

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ABSTRACT

Objectives: Pulmonary granulomatous nodule (GN) with spiculated or lobulated appearance are indistinguishable from solid lung adenocarcinoma (SADC) based on CT morphological features, and partial false-positive findings on PET/CT. The objective of this study was to investigate the ability of quantitative CT radiomics for preoperatively differentiating solitary atypical GN from SADC.

Methods: 302 eligible patients (SADC = 209, GN = 93) were evaluated in this retrospective study and were divided into training (n = 211) and validation cohorts (n = 91). Radiomics features were extracted from plain and vein-phase CT images. The L1 regularized logistic regression model was used to identify the optimal radiomics features for construction of a radiomics model in differentiate solitary GN from SADC. The performance of the constructed radiomics model was evaluated using the area under curve (AUC) of receiver operating characteristic curve (ROC).

Results: 16.7% (35/209) of SADC were misdiagnosed as GN and 24.7% (23/93) of GN were misdiagnosed as lung cancer before surgery. The AUCs of combined radiomics and clinical risk factors were 0.935, 0.902, and 0.923 in the training cohort of plain radiomics(PR), vein radiomics, and plain and vein radiomics, and were 0.817, 0835, and 0.841 in the validation cohort of three models, respectively. PR combined with clinical risk factors (PRC) performed better than simple radiomics models ($p < 0.05$). The diagnostic accuracy of PRC in the total cohorts was similar to our radiologists ($p \geq 0.05$).

Conclusions: As a noninvasive method, PRC has the ability to identify SADC and GN with spiculation or lobulation.

1. Introduction

A solitary pulmonary nodule (SPN) is defined as a rounded lesion measuring less than 3 cm in diameter that is completely surrounded by pulmonary parenchyma and without other pulmonary abnormalities [1]. In clinical practice, the vast majority of malignant peripheral SPN are lung adenocarcinomas, and some solitary granulomas with spiculated or lobulated appearance on CT are indistinguishable from lung cancers [2,3]. PET-CT using 18 fluorine-fluorodeoxy glucose (^{18}F-FDG) can give false-positive results in the assessment of pulmonary granulomas [4]. It has been reported that more than 26% of the suspicious pulmonary nodules biopsied or resected are identified as benign, translating to nearly $600 M being spent annually on unnecessary and invasive surgical procedures in the USA [5,6]. However, patients with benign SPN do not require surgical resection, and prompt resection in patients with early-stage malignant SPN usually ensures a better prognosis. Thus, the development of a noninvasive and repeatable quantitative method would be of significant help in identifying indeterminate solid SPN before surgery in clinical practice.

Radiomics refers to the extraction of sub-visual, yet quantitative, imaging features with the intent of creating mineable databases from radiological images, which has attracted increasing attention of

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radiologists and clinicians. Radiomics uses a large number of automated data characterization algorithms to transform image data from a region of interest into the quantitative high-throughput feature space [7,8]. Radiomics can reflect biological information regarding the tumor such as cell morphology, and molecular and gene expression, which can provide noninvasive information regarding diagnosis, evaluation of prognosis, and prediction of treatment response [9–12].

To the best of our knowledge, a few investigators [13,14] have attempted to distinguish granulomas from malignancies using quantitative radiomics or computerized feature-based analysis. However, these studies were limited by a small sample size and incomplete normalized CT imaging data. The primary objective of our study, based on a relatively large sample and normalized CT data, was to investigate the ability of a CT-based radiomics signature for preoperatively differentiating solitary granulomatous nodules (GN) from solid adenocarcinomas (SADC) with spiculation or lobulation on CT.

2. Materials and methods

2.1. Patients

This retrospective study was approved by our institutional review board. Medical record review was performed in accordance with institutional ethics review board guidelines.

The inclusion criteria were as follows: (1) Patients were proven lung granulomatous lesion (tuberculous or fungal granulomas) and adenocarcinoma by surgical resection or image-guided biopsy pathology; (2) all patients underwent routine and contrast-enhanced CT of the entire thorax using the same CT machine with normalized reconstruction algorithm (B30) and thickness (2 mm), within two weeks of surgery; (3) solitary solid SPN did not display calcification or fat, measured between 7 and 30 mm with spiculation, lobulation, pleural indentation and without associated atelectasis or enlarged lymph nodes; (4) laboratory analysis of routine tumor markers were detected within a week before surgery, including CEA, CA125, and CA153. The positive threshold values for CEA, CA125, and CA153, were > 5 ng/ml, > 35 ng/ml, and > 25 ng/ml, respectively, according to the normal ranges used at our institution.

Exclusion criteria were as follows: (1) Patients with nodules that were highly suspected as benign lesions, such as a tuberculosis ball with caseous necrosis, or cryptococcus with the signature halo sign; (2) those with a history of other malignancies or combined malignancies; (3) those in whom the CT imaging was reconstructed using different algorithms or thicknesses or if the reconstruction was performed on a different CT machine; (4) those in whom the nodule segmentation failed to meet the standard leading to inaccurately extracted radiomics parameters.

Based on the above mentioned inclusion criteria, we enrolled patients between January 2016 and December 2017 at our hospital. A total of 302 patients (167 male and 135 female; mean age, 56.25 ± 12.51 years; age range, 22–87 years) were included, including 93 GN (67 fungal granulomas and 26 tuberculous granulomas)and 209 solid adenocarcinomas. We randomized the patients into two groups with a ratio of 7:3 (211 and 91 patients in the training and validation group respectively). The patients' selection process is shown in Fig. 1.

2.2. CT image acquisition

All patients underwent plain and vein phase contrast-enhanced CT of the entire thorax, in a multi-detector CT system (Definition AS + 128-Slice; Siemens Healthcare, Germany). CT scan parameters were as follows: tube voltage, 120 kV; automatic tube current modulation ; pitch, 0.9; field of view, 180 mm × 180 mm; matrix, 512 × 512; reconstructed slice thickness and slice increment, both 2 mm. After plain CT, vein-phase contrast-enhanced scans started 35 s after the contrast media reached 100 HU. Contrast medium (300 mg/mL, iopamidol injection, Bracco) was administered at a dose of 2 mL/kg body weight and rate of 3.0 or 3.5 mL/s. All images were exported in DICOM format for image feature extraction.

Two thoracic radiologists (YBG and XGY, with 10 and 20 years' experience in chest image interpretation, respectively) independently reviewed all the CT images on our PACS, and consensus was reached by discussion in case of disagreement. CT scans were reviewed as lung window images (window width = 1200 HU; window level = −500 HU) and mediastinal window images (window width = 450 HU; window level = 50 HU). Lesion size, spiculation, lobulation, and pleural indentation were evaluated as CT morphological features. Lesion size was defined as the maximum diameter of the tumor on axial images. Spiculation was defined as presence of linear strands extending from the nodule or mass margin into the lung parenchyma without reaching the pleural surface. Lobulation was defined as a portion of the surface of a lesion showing a shallow, wavy configuration, with the exception of the regions abutting the pleura. Pleural indentation was defined as the tumor with linear structure originating from the tumor and extending to the pleural surface.

2.3. Lesion segmentation and radiomics features extraction

For nodule segmentation, we employed a 3D U-net model [15,16], trained with lung image database consortium (LIDC) datasets. To evaluate the stability and robustness of nodule automated segmentation, we compared our nodule segmentation result with four radiologist labels (Supplementary Fig. S1). A total of 94 radiomics features (Supplementary Table S1) were extracted from plain-phase and vein-phase CT images using Pyradiomics(https://pyradiomics.readthedocs.io/en/latest/), an open-source python package for the extraction of Radiomics features from clinical images.

2.4. Statistical analysis

Clinical characteristics were analyzed between GN and SADC groups by using Fisher's exact test or the χ^2 test for nominal categorical variables and the independent *t*-test or Mann–Whitney U test for continuous variables. AUCs of the models were compared using T-test. A two-sided P-value < 0.05 was considered significant.

The L1 regularized logistic regression model was used in our study to identify the optimal radiomics features to differentiate solitary GN from SADC. The advantage of L1 regularization is that it can push feature coefficients to 0, creating a method for feature selection. This model is widely used for many classification problems, particularly ones with many features. We used 10-folder cross validation on our training cohort to choose the optimal L1 regularization strength.

As the L1 regularization penalty is comprised of the sum of the absolute value of the coefficients, we normalized our data in order to allow all the coefficients to be based on the same scale. In order to deal with the imbalanced data (65 GN vs. 146 SADC in the training cohort), we set different weights for the GN and solid adenocarcinomas group on model training by 1.6231 and 0.7128, respectively.

We trained six models on six different datasets separately; these included simple models [plain radiomics(PR); vein radiomics(VR); plain radiomics & vein radiomics (PVR)] and combined models [plain radiomics and clinical risk factors(PRC), vein radiomics and clinical risk factors(VRC), and plain & vein radiomics and clinical risk factors (PVRC)]. To ensure a fair comparison of these 6 datasets, we kept the hyperparameters of our L1 regularized logistic regression model to the same as those for the 6 datasets.

All model training and statistical tests were performed using Python 2.7 (https://www.python.org/). We used the "sklearn" package to perform the L1 regularized logistic regression model analysis and calculate AUCs. The ROC curves and the plots of optimal regularization strength were plotted using "matplotlib" package. The t-test was performed using the "scipy" package.