

# The Emerging Role of Radiomics in COPD and Lung Cancer

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# The Emerging Role of Radiomics in COPD and Lung Cancer

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## Keywords

Radiomics · Chronic obstructive pulmonary disease · Lung cancer

## Abstract

Medical imaging plays a key role in evaluating and monitoring lung diseases such as chronic obstructive pulmonary disease (COPD) and lung cancer. The application of artificial intelligence in medical imaging has transformed medical images into mineable data, by extracting and correlating quantitative imaging features with patients' outcomes and tumor phenotype – a process termed radiomics. While this process has already been widely researched in lung oncology, the evaluation of COPD in this fashion remains in its infancy. Here we outline the main applications of radiomics in lung cancer and briefly review the workflow from image acquisition to the evaluation of model performance. Finally, we discuss the current assessments of COPD and the potential application of radiomics in COPD.

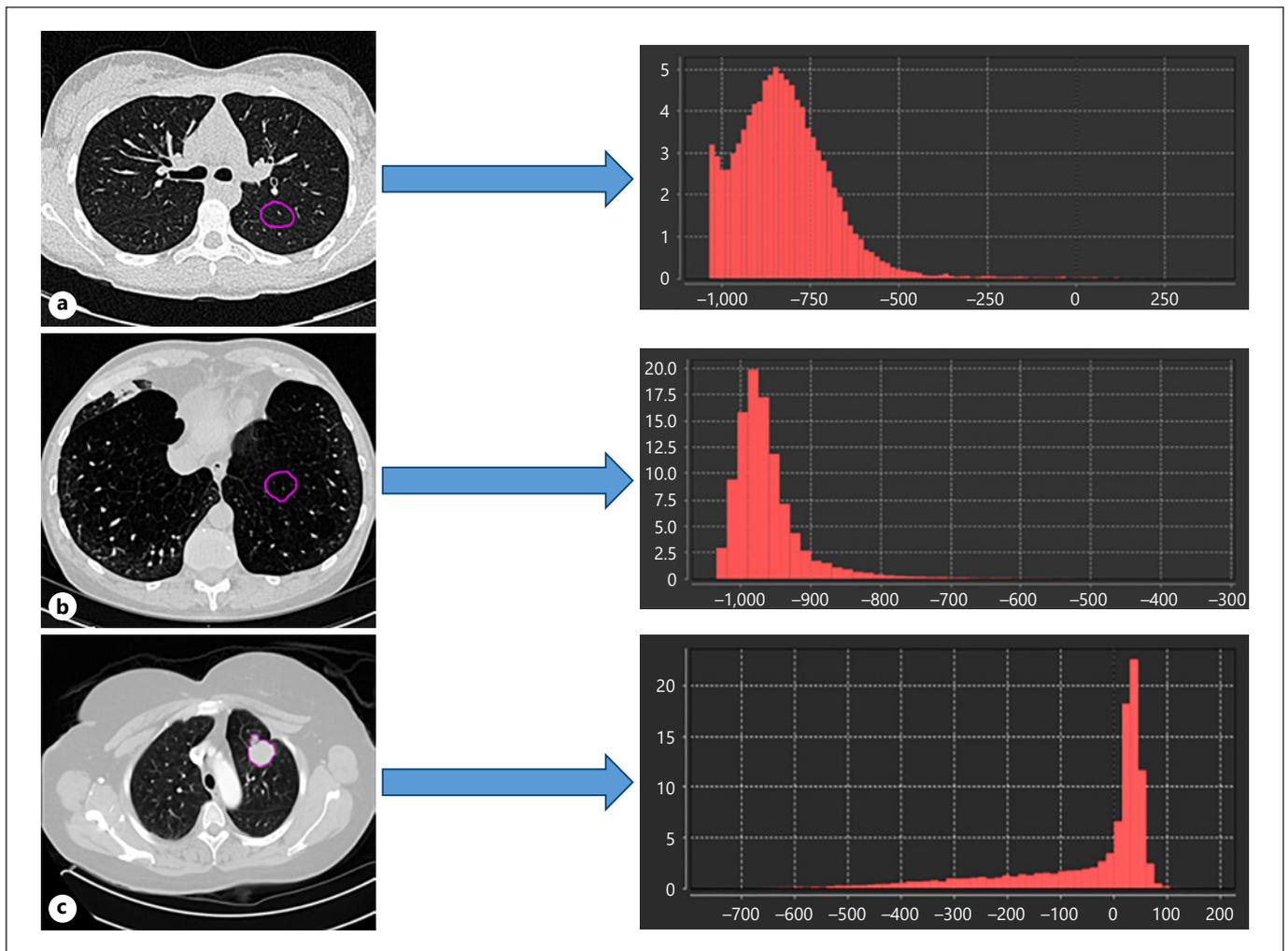
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## Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent lung diseases, with an estimated 328 million people worldwide being affected, and in two decades it is expected to become the leading cause of death globally [1]. COPD is characterized by the limitation of airflow, which can be measured using spirometry. It is not completely reversible and is often caused by exposure to noxious particles or gas (e.g., cigarette smoking) which creates an inflammatory response in the lung [2, 3]. COPD is a multicomponent disease comprising a combination of bronchiolitis, emphysema, and extrapulmonary effects [4]. While spirometry can measure airflow limitation, the contributions of large and small airway involvement and the extent and contribution of parenchy-

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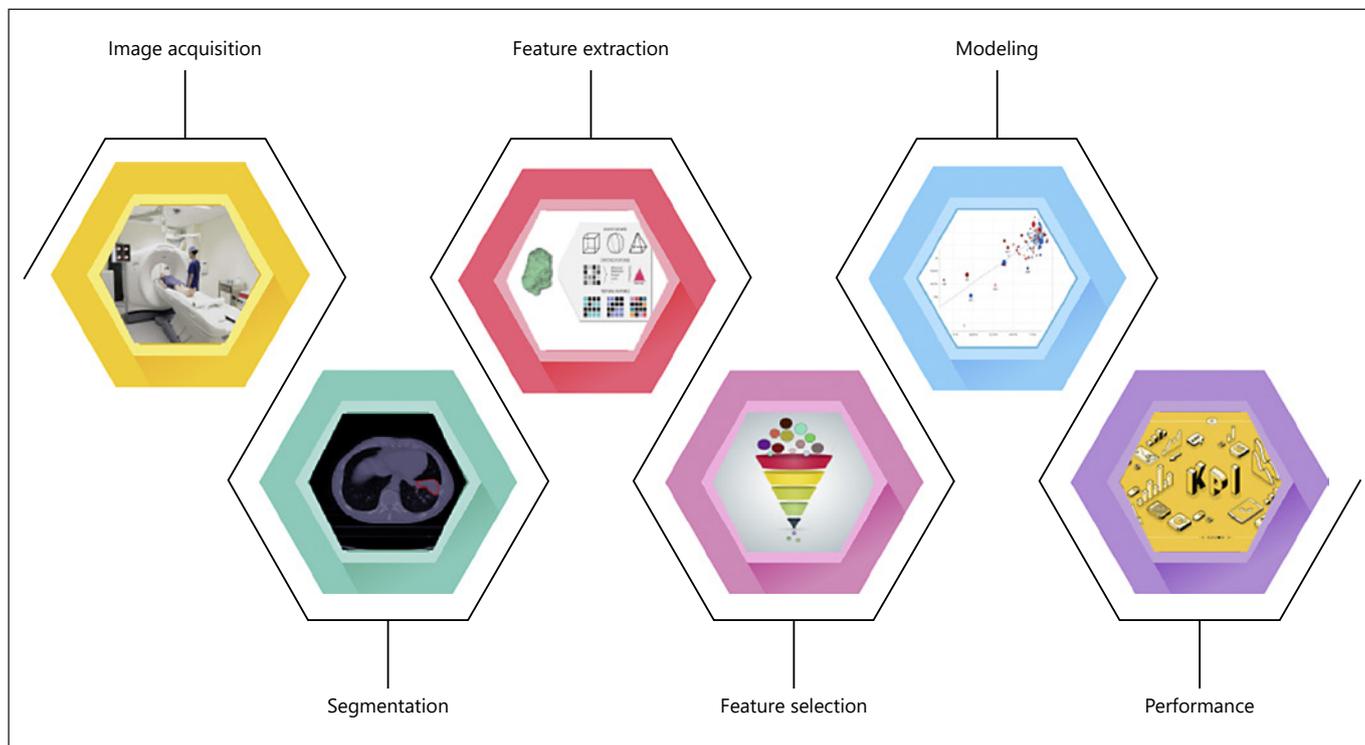


**Fig. 1.** Different distributions of HU values extracted from the ROI (purple outline) for normal tissue (a), COPD tissue (b), and lung tumor (c).

ma destruction cannot be assessed [5]. Imaging by means of computed tomography (CT) has an increasing role in the evaluation of COPD since CT features can suggest the presence and severity of COPD. These features can be assessed visually [6], but research is in advanced stages to automate the quantification of emphysema extent and distribution [7–10], airway wall thickness [11], and small airways disease [12].

Lung cancer is the other predominant lung disease, being one of the world's most prevalent cancers [13–16]. Globally, lung cancer is the most commonly diagnosed cancer (around 11% of all cancers in both sexes), and the world's leading cause of cancer-related mortality (around 18% of total cancer-related mortality) [17]. Lung cancers

can be divided into two broad groups, small cell lung cancer and non-small cell lung cancer (NSCLC) [18]. NSCLC can be further divided into subgroups according to histopathology into squamous cell carcinoma and adenocarcinoma [19]. COPD has been shown to be a major additional risk factor for the development of lung cancer, specifically squamous cell carcinoma [20, 21]. Discovering the link between COPD and lung cancer has drawn significant attention in recent years [22]. It has been shown that COPD and lung cancer share similar pathological processes [23], while smoking cigarettes is one important common factor that causes both COPD and lung cancer [20], and patients with COPD and NSCLC have poor survival outcomes compared to NSCLC patients without



**Fig. 2.** Graphic depiction of the radiomics workflow.

COPD [24]. The link of pathophysiological mechanisms between COPD and lung cancer is still not well understood (Fig. 1) [25].

The treatment of patients suffering from either disease would be greatly improved by personalized approaches, where patients are treated based on their and their diseases' individual characteristics rather than subpopulation statistics gained from clinical trials. Which role artificial intelligence will play on the path to this paradigm shift towards individualized treatment selection is being extensively investigated [26]. For example, biopsies are used in clinical practice to phenotype the tumor, but the heterogeneous nature of cancer cells limits the biopsy's capacity to fully capture its condition [27, 28]. Medical imaging, on the other hand, has the potential to noninvasively assess the phenotypic differences of tumors in three dimensions [29] and has recently experienced great advances in the field of artificial intelligence [30, 31]. In particular, radiomics or quantitative image analysis – the high-throughput extraction of quantitative features from medical images and their correlation with diagnostic and prognostic outcomes – has been researched to decode tumor phenotypes from a number of modalities such as CT,

magnetic resonance imaging, and positron emission tomography (PET). Thousands of quantitative radiomic features can be extracted from each region of interest (ROI) and further analyzed using machine learning tools to investigate correlations with biological and clinical endpoints [32–37]. Therefore, the application of radiomics to both COPD and lung cancer may improve the clinical workflow in diagnosing, managing, and following up the patients. It can provide noninvasive, reliable, and cost-effective clinical decision support systems, decreasing the need for invasive procedures.

### The Workflow of Radiomics

The process of handcrafted radiomics consists of several steps (Fig. 2): (1) collection of medical imaging (e.g., CT, magnetic resonance, PET/CT) for the target population; (2) segmentation of the ROI to be investigated; (3) extraction of radiomic features from the ROI; (4) the selection of radiomic features that best correlate with the outcome of interest; (5) building the radiomics signature, and (6) evaluation of the model performance on various

data sets using different metrics such as the receiver-operating characteristic, area under the curve, and the precision-recall curve. The workflow has been previously described in detail [30, 37, 38].

### *Quality of Radiomics Studies*

Despite the potential of radiomics to facilitate precision medicine as highlighted in numerous publications, a number of obstacles still limits the generalizability of radiomics signatures, and thus their translation to clinical applications. The most important and widely known limitation is the lack of reproducibility for radiomics biomarkers [39–41]. Several studies have investigated the stability of radiomic features with test-retest experiments [42–44] and reported that a considerable percentage of features is not reproducible in test-retest settings, i.e. using the same acquisition and reconstruction parameters on the same vendor for acquiring the scan. A study by Zhovannic et al. [45] demonstrated that 62 of radiomic features are sensitive to differences in acquisition and reconstruction parameters using the same imaging vendor. Other studies investigated the sensitivity of radiomic features to differences in segmentations, or what is known as interobserver variability [46].

As such, efforts must be made to unify image acquisition and reconstruction across different centers to facilitate quantitative imaging analysis research and integrate these methods into clinical decision support systems.

Several guidelines have been proposed to ensure that radiomic studies are methodologically sound and reproducible. Clear reporting in radiomics research is required to minimize bias and enhance the general application of prediction models. For instance, the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) initiative has established several recommendations in terms of reporting of the methodology of prediction models [47]. The Radiomics Quality Score is, however, established specifically for radiomics research [38]; it is a checklist that contains 16 elements to evaluate the design and reporting of a radiomics study. The Radiomics Quality Score guidelines include robust segmentation, the stability of test-retest, description of imaging protocol used, and internal/external validation. Due to the fast pace of advancement in this field, further improvement in the standardization of this score is required to ensure a high-quality workflow. Furthermore, the Image Biomarker Standardization Initiative (IBSI) is a newly formed guideline to address the standardization of feature calculation and image pre-processing [48].

## **Role of Radiomics in Lung Cancer**

### *Diagnosis*

Several studies have explored the use of radiomics in the screening of lung cancer. The advent of low-dose CT (LDCT) has altered the landscape of lung cancer screening. Studies indicate that LDCT imaging, unlike molecular markers in blood, sputum, and bronchial brushings, detects many tumors at early stages. For instance, the National Lung Screening Trial (NLST) in the USA demonstrated in a large population of 53,454 participants at a high risk for lung cancer a 20% relative reduction in mortality when participants underwent three annual screening (LDCT) scans instead of single-view posterior-anterior chest radiography [49]. Kumar et al. [50] used a LIDC-IDRI data set in order to differentiate between benign and malignant lesions, resulting in sensitivity and specificity of 79.06 and 76.11%, respectively. Other publications have already shown promising results in the diagnosis of lung cancer [51–53].

### *Staging*

Tumor/node/metastasis (TNM) staging of lung cancer is also important for cancer treatment. Several studies showed the added value of radiomic features in lung cancer staging. A study by Aerts et al. [54] that included 1,019 patients to extract 440 CT radiomics per patient reported that radiomic features were associated with the overall stage (TNM) of lung cancer. A study by Wu et al. [55] that used radiomic characteristics extracted from PET/CT to predict the early stage of distant metastasis (DM) in 101 early-stage NSCLC patients showed that PET radiomic features correlated with DM and had added value in M staging. Coroller et al. [35] applied radiomics on 182 lung adenocarcinomas in order to predict DM showing that radiomics performed well on M staging.

### *Genetics and Histopathology*

Besides diagnosing and staging lung cancer, the use of radiomics has been extended to predict gene mutation or different pathology types of lung cancer. A study by Zhang et al. [56] that included 298 patients found a correlation between epidermal growth factor receptor mutation and CT radiomics features. Liu et al. [57, 58] achieved the same results. Rios Velasquez et al. [59] developed a radiomic model that classifies mutations in patients with lung adenocarcinoma. The research found that the radiomic signature based on CT images can predict epidermal growth factor receptor status effectively. Wu et al.

[52] used two NSCLC cohorts from the Netherlands to predict the histological types of lung cancer (adenocarcinoma, squamous cell carcinoma).

### *Response to Therapy*

The use of radiomics signatures could be used to predict the response of patients to a particular therapy. In a study by Aerts et al. [60], it was reported that radiomics features obtained from CT images before treatment were able to predict the mutation status of epidermal growth factor receptor in NSCLC and correlated with gefitinib response. Coroller et al. [61] showed that radiomic features-based CT images acquired prior to treatment could predict the pathological response to chemoradiation in NSCLC patients. Mattonen et al. [62, 63] predicted the recurrence of lung cancer following receiving stereotactic ablative radiation therapy using radiomics. Another study that utilized  $\delta$ -radiomics, a method of analyzing the difference of radiomic features obtained from longitudinal scans, in stage III NSCLC patients to predict the outcome during radiation therapy, reported that the change in radiomic features values might be linked to the tumor response due to exposure to radiation [64]. Hao et al. [65] used radiomic characteristics of peritumoral tissue derived from PET images to study its correlation with distant failure in NSCLC and cervical cancer. The results showed a relationship between tumor boundaries and distant failure, suggesting that such an approach might be useful in predicting early response to radiotherapy in NSCLC and cervical cancer patients. In a recent study by Khorramin et al. [66], CT-based radiomic features were extracted from peri- and intratumoral lung adenocarcinoma tissue and shown to have the potential to predict the response to chemotherapy, and this correlated with both time to progression and overall survival for patients with NSCLC.

### *Prognosis*

Several studies investigated the prognosis of lung cancer using a radiomics approach. Coroller et al. [35] found a prognostic relation between radiomics features and DM and survival in patients with lung cancer. Aerts et al. [54] found an association between the prognosis of lung cancer and radiomics features. Balagurunathan et al. [42] showed a correlation between the prognosis of lung cancer and radiomic features. Song et al. [67] showed a connection between features extracted from CT images and overall survival in NSCLC patients.

## **Potential Translation of Radiomics in COPD**

The heterogeneous nature of COPD makes diagnosis challenging. However, it is crucial to unravel this variety of presentations to achieve an accurate diagnosis in early stages and help improve patients' outcomes [5]. Different COPD assessments are used in clinical practice, including pulmonary function test and quantitative CT (QCT). Pulmonary function tests are essential to diagnose and classify COPD. A commonly used pulmonary function test is spirometry, which is used to measure the forced expiratory volume in 1 s (FEV1) and the forced vital capacity (FVC) as the primary parameters [68]. However, spirometry alone does not provide any locational information regarding emphysema [68]. QCT is a promising approach that is able to quantify emphysema, airways abnormalities, and air trapping [5]. QCT has already demonstrated the capacity to evaluate the existence and degree of emphysema [69–75]. For example, CT densitometry parameters such as relative low-attenuation area [76–81] and percentile of the frequency-attenuation distribution [9, 82–84] are usually used to assess the degree of emphysema. Airways abnormalities are commonly measured by the calculation of the square root at an internal perimeter of 10 mm using linear regression [85–88]. It is considered the gold standard tool and has already demonstrated a significant correlation with the histological measurement of small airways [89]. Air trapping appears as decreased attenuation on expiratory CT images [90], making it the best way to evaluate air trapping in COPD [87]. The measurements of gas trapping using CT are highly correlated with pulmonary function tests in COPD patients [91].

Despite the ability of QCT to quantify COPD, the interpretation of QCT is still time-consuming, qualitative, requires experts, and is prone to variability in the diagnosis between experts. The CT image metric (radiomics) approach could potentially quantify COPD and uncover the disease's hidden mechanism and the link between lung cancer and COPD in a better nuanced and more powerful phenotypic classification. A radiomics signature would be easier to apply as a clinical decision support system and less time consuming compared to the currently used QCT. Therefore, several potential applications for radiomic features in COPD are suggested. Texture analysis for example has shown its effectiveness in assessing the degree of emphysema. A study by Ginsburg et al. [92] demonstrated the effectiveness of a texture-based approach in classifying between the lungs of never-smokers, smokers without emphysema, and smokers with emphysema, indicating that an early stage of smoking-related

lung injury could potentially be identified before emphysema develops. Another study by Castadi et al. [93] used a local histogram-based technique to quantify the distinct emphysema pattern using CT scans from 9,313 smoker subjects in the COPODGene study. The results of the study suggest that information extracted from CT patterns of emphysema were more predictive than threshold-based emphysema measurements such as “low attenuation area less than  $-950$ ”. As described above, the applications of radiomics in the screening of lung cancer showed interesting results. Automated screening of routine chest CT to diagnose COPD is therefore one possible use, with the ability to detect suspected sarcopenia not only in the lung, but also in the muscle tissue. Detection and differentiation between COPD stages and phenotypes, especially in early stages, will allow for the early and suitable treatment for the patient. In a study by Lafata et al. [94], the authors reported on the potential of radiomic features extracted from CT images to quantify the changes in lung function and associated with a spirometry test. The same approach using radiomics could be extended to investigate its relationship with other gold standard COPD markers such as waking exams, FEV/FVC ratio (Tiffeneau index) or the frequency of exacerbations associated with COPD patients, enabling an accurate diagnosis of COPD severity. In addition, the use of radiomics could improve the performance of the existing multifactorial models (nomograms) by adding radiomics features to existing clinical factors (age, sex, number of pack-years, current smoking, performance score, wheezing) as already shown in a previous publication [95].  $\delta$ -radiomics has already demonstrated its ability to predict the response to therapy in lung cancer. Therefore, such a technique could be used to identify quantitatively the evolution of the disease and the effect of (new) treatment. Additionally,  $\delta$ -radiomics could be applied to assess the difference between inspiration and expiration scans and to explore hidden information that could help in evaluating the extent and severity of pulmonary emphysema, air trapping, and airway abnormalities. The use of radiomics could potentially be used to predict whether the patient will respond to certain interventions, such as endoscopic lung volume reduction and inhalation steroids.

## Conclusion

The field of radiomics is rapidly growing and has already shown its potential in assessing lung cancers in terms of detection, treatment response, and prognosis.

Different QCT measurements have been used to quantify COPD abnormalities such as emphysema, air trapping, and airway remodeling. Applying radiomics in COPD has not been extensively investigated yet. We show examples of the potential use of radiomics in the diagnosis, treatment, and the follow-up of COPD and future directions for further research.

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