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Advances in Radiomics for Individualized and Precision-Based Diagnosis and Treatment of Lung Cancer

Tongtong Liu[†], Fang Wang[†], Shuai Qie, Xuefeng Wang, Kuan Liu, Yang Li, Hongyun Shi*

Department of Radiotherapy, Affiliated Hospital of Hebei University, Baoding 071000, Hebei Province, China
[†]These authors contributed equally to this work and shared first authorship.

***Corresponding author:** Hongyun Shi, hyshi2015@163.com

Abstract: Lung cancer is among the most prevalent cancers and has the highest mortality rate globally. The diagnosis, pathohistological classification, and molecular testing of lung cancer primarily rely on tissue biopsy or surgical resection. These methods are invasive and associated with limitations, including sample quantity and quality, as well as patient tolerance. Radiomics, an emerging technology, enables the extraction of high-throughput quantitative information from medical images, providing radiomic features applicable to clinical diagnosis and treatment. Significant advancements have been made in the application of radiomics to the diagnosis, molecular detection, efficacy prediction, and prognosis of lung cancer. This review examines the progress in radiomics for individualized and precise diagnosis and treatment of lung cancer in recent years.

Keywords: Lung cancer; Non-small cell lung cancer; Small cell lung cancer; Radiomics

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1. Introduction

Lung cancer is one of the most common cancers globally and accounts for the highest mortality among all malignancies [1]. In 2020, an estimated 2.2 million new cases were reported, resulting in 1.8 million deaths, which represented 21% of all cancer-related fatalities [2]. Non-small cell lung cancer (NSCLC) accounts for 80–85% of cases [3], while small cell lung cancer (SCLC) comprises 10–15% [4]. Due to the non-specific nature of lung cancer symptoms, more than 70% of patients present with advanced disease (IASLC stage III or IV) at diagnosis [5]. According to the American Association for Cancer Research (AACR), as of July 2021, the five-year survival rate for lung cancer was 21.7% [6].

Early-stage lung cancer treatments include surgical resection, stereotactic body radiation therapy (SBRT), and percutaneous ablation. Conversely, the primary treatment options for advanced unresectable NSCLC are

radiotherapy, chemotherapy, targeted therapy, and immunotherapy. Current diagnostic methods for lung cancer, including pathological and radiomic characterization and the detection of driver genes and immune receptors (e.g., programmed cell death ligand 1 [PD-L1]), are largely dependent on histological sampling via percutaneous transthoracic needle biopsy (PTNB), bronchoscopic biopsy, or surgical resection [7]. However, these techniques are constrained by the localized nature of tissue sampling, which may not adequately represent the tumor's heterogeneity [8]. Moreover, as the expression of driver genes and immune receptors can change over time, repeated biopsies may be required. Tissue biopsy procedures are further influenced by patient tolerance, the risk of complications, and the quantity and quality of the obtained samples.

Medical imaging has become an indispensable tool in modern medicine due to its convenience, speed, and reproducibility. Radiomics, a relatively mature medical image informatics technology, employs artificial intelligence to extract high-throughput quantitative data from imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET/CT) [9]. This technology enables the mining of imaging features related to tumor heterogeneity, aiming to develop an individualized and interpretable analytical tool suitable for clinical use [10]. It is hypothesized that various medical imaging modalities can provide quantitative data correlating with tumor pathophysiology, gene and protein expression, and treatment outcomes, including the efficacy and prognosis of radiotherapy and other therapies [11].

A growing body of research in radiomics focuses on predicting tumor histology, driver mutations, treatment response, recurrence, and prognosis. These studies contribute to the advancement of precise and personalized diagnosis and treatment. This review highlights recent progress in radiomics, particularly its applications in the individualized and precise diagnosis and management of lung cancer.

2. Radiomics in lung cancer diagnosis

In contemporary clinical practice, the diagnosis of lung cancer remains reliant on puncture biopsy. While puncture biopsy is considered the gold standard for tumor diagnosis, it is an invasive procedure that may yield tissue samples that are not representative of the tumor's overall characteristics [8]. Additionally, the procedure is associated with potential risks of complications. Therefore, it is imperative to develop new, highly precise methods for accurately diagnosing tumors and determining the degree of tumor differentiation (DTD), lymph node metastasis (LNM), and pathological types [12].

Numerous studies have demonstrated the significant clinical value of radiomics in addressing these diagnostic challenges. Hendrix *et al.* [13] and Dennie *et al.* [14], in their respective studies, extracted texture features from CT images of malignant and benign pulmonary nodules and utilized them to develop high-sensitivity and high-specificity image-based modeling techniques. Their findings validated the effectiveness of such models in classifying pulmonary nodules.

Fan *et al.* [15] conducted a retrospective analysis aimed at predicting the pathological subtypes of lung nodules in 160 patients with lung adenocarcinoma using radiomics. The study concluded that radiomic features could differentiate between invasive adenocarcinomas and non-invasive lesions, demonstrating a high predictive capability for invasive adenocarcinomas. Similarly, Wang *et al.* [16] constructed a predictive model using three algorithms: Random Forest, Support Vector Machine, and Logistic Regression. The objective was to predict mediastinal lymph node metastasis in patients with NSCLC. The CT radiomic model developed using the Random Forest algorithm exhibited a high degree of accuracy, with an area under the curve (AUC) value of 0.909.

In another study, Zhu *et al.* [17] collected CT images from 129 lung cancer patients and developed a radiomics model to distinguish between lung adenocarcinoma (ADC) and lung squamous cell carcinoma (SCC). The AUCs for the training and validation sets were 0.905 and 0.893, respectively, with sensitivities of 83.00% and 82.80% and specificities of 92.90% and 90.00%. These results demonstrate that radiomics is a highly effective method for identifying the pathological types of lung cancer.

In conclusion, substantial evidence from multiple studies indicates that radiomics is an effective approach for predicting the degree of tumor differentiation, lymph node metastasis, and pathological types in lung cancer patients.

3. Radiomics in the detection of EGFR-mutated genes

Targeted therapy has become a pivotal component in the management of patients with NSCLC. Given that the *Epidermal Growth Factor Receptor* (*EGFR*) is a frequently utilized target gene in NSCLC, determining the mutation status and subtype of *EGFR* is crucial for the effective implementation of targeted therapy. Molecular testing remains the primary method for identifying *EGFR* mutation status. However, this approach has limitations due to the temporal and spatial heterogeneity of tumors, rendering it unsuitable for certain patients [18].

Radiomics has made significant progress in predicting *EGFR* mutations. In a study by Mei *et al.* [19], the CT imaging features of 296 NSCLC patients were analyzed and combined with clinical features to construct a predictive model. This model achieved AUC values of 0.655 for the *EGFR* exon 19 deletion mutation, 0.675 for the EGFR exon 21 L858R mutation, and 0.664 for the overall mutation status. These findings suggest that imaging characteristics may play a critical role in predicting *EGFR* status and indicate the potential of radiomic features as biomarkers for identifying *EGFR* mutation status and subtypes.

Cheng *et al.* [20] developed a gradient-enhanced decision tree model based on the ground-glass appearance of CT images in early-stage lung adenocarcinoma. The model identified *EGFR* mutation status with an AUC value of 0.822. This model was validated in patients with lung adenocarcinoma undergoing targeted therapy, demonstrating a significant improvement in the remission rate of *EGFR*-mutated patients, increasing from 25.9% to 53.8%.

In another study, Clay *et al.* [21] incorporated CT images of lung tissue with a 10-mm peri-tumor circumference into their analysis. The predictive model developed in this study achieved an AUC value of 0.72 for identifying *EGFR* mutation status.

In conclusion, substantial evidence demonstrates that CT-based radiomics has excellent predictive efficacy in determining the *EGFR* mutation status of NSCLC patients, thereby offering significant potential for enhancing targeted therapy strategies.

4. Radiomics in the assessment of lung cancer treatment efficacy

The current clinical treatments for lung cancer include chemotherapy, radiotherapy, targeted therapy, immunotherapy, and other modalities. However, the prognosis of individual patients may vary significantly depending on the treatment regimen employed. Moreover, there is a lack of reliable methods for accurately predicting and assessing treatment response [22]. In recent years, the use of imaging techniques, such as CT, PET/CT, and others, to predict the efficacy of lung cancer treatments has garnered increasing attention. The ability to predict therapeutic efficacy and prognostic outcomes using these techniques could substantially enhance their

clinical applications.

In a study by Yang *et al.* [23], a predictive model was developed using radiomic features extracted from pre-treatment chest CT images. This model successfully predicted the response of NSCLC to first-line chemotherapy, targeted therapy, or a combination of both, achieving an AUC of 0.746 (95% confidence interval [CI], 0.646–0.846). Zhang *et al.* [24] conducted a retrospective study of 122 NSCLC patients with EGFR mutation-positive status to investigate the efficacy of combining CT radiomics with cytokeratin 19 fragment levels in predicting the outcomes of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) therapy. The AUCs for the clinical model, the radiomics model, and the combined model in the training set were 0.686, 0.800, and 0.836, respectively; the AUCs in the validation set were 0.666, 0.774, and 0.837, respectively.

Regarding immunotherapy, the prediction of treatment response is currently based on the expression of biomarkers within the tumor immune microenvironment, such as PD-L1. Tian *et al.* [25] analyzed CT images from 143 NSCLC patients and constructed a CT radiomic nomogram by integrating clinical factors with radiomic features. This model demonstrated high efficacy in assessing PD-1 expression in NSCLC patients, with an AUC of 0.92.

To predict the efficacy of stereotactic body radiation therapy (SBRT) for NSCLC, Wang *et al.* [26] developed and validated a nomogram based on radiomic features extracted from pre-treatment CT images. The model exhibited high predictive performance, with an AUC value of 0.808 for the training set and 0.741 for the validation set.

The evidence from these studies demonstrates that radiomic features can effectively forecast treatment response in patients with NSCLC. This capability can assist clinicians in modifying, intensifying, or altering treatment plans at the earliest opportunity, thereby improving patient outcomes.

5. Radiomics in lung cancer regression

In the context of lung cancer regression, radiomics-based studies have proven to facilitate more precise survival predictions for lung cancer patients and support clinicians in selecting personalized treatment strategies. Several studies have demonstrated the efficacy of intra-tumor radiomic features in predicting overall survival (OS), tumor recurrence prognosis, and time to progression in lung cancer patients.

Sawayanagi *et al.* [27] developed a predictive model using clinical features derived from pre-treatment CT scans and radiomic features of the primary tumor. The predicted OS time (mean: 37.8 months) was found to closely align with the observed OS time (33.7 months), demonstrating the model's accuracy. Niu *et al.* [28] proposed a multi-omics model incorporating CT images, dosimetric features, and clinical characteristics of lung cancer patients. This model significantly enhanced the precision of radiation pneumonitis (RP) prediction, achieving AUC values of 0.94 and 0.92 in the test and validation sets, respectively. The study also revealed that patients with RP exhibited a longer OS compared to those without RP, particularly those with mild RP. The median OS was 31 months in the non-RP group and 49 months in the RP group (hazard ratio [HR] = 0.53, $P = 0.0022$). Among RP subgroups, the median OS was 57 months for patients with mild RP and 25 months for those with severe RP (HR = 3.72, $P < 0.0001$).

Huang *et al.* [29] utilized machine learning to analyze pre-treatment FDG-PET and lung cancer CT scans. Their integrated PET+CT model demonstrated high predictive accuracy for disease progression in NSCLC patients, achieving an accuracy of 0.790 and an AUC of 0.876. Zheng *et al.* [30] conducted a multicenter trial to predict

progression-free survival (PFS) using CT scan results for SCLC. The study also evaluated the incremental value of radiomic features alongside clinical risk factors for individual PFS estimation. Results indicated that radiomic features were significantly associated with PFS (HR = 4.531, 95% CI: 3.524–5.825, $P < 0.001$). Additionally, the radiomic nomogram demonstrated superior predictive performance for PFS (C-index 0.799) compared to the clinical nomogram (C-index 0.629).

Collectively, these studies underscore the efficacy of radiomics in predicting survival outcomes for patients with various forms of lung cancer. This approach holds significant promise for guiding the development of personalized treatment strategies, ultimately improving patient care and prognosis.

6. Limitations and future prospects

In the diagnosis and treatment of tumors, achieving accurate diagnosis and staging, administering standardized and individualized treatments, and predicting treatment response, recurrence, and prognosis are of paramount importance. Radiomics, an emerging medical imaging technology, enables the generation of descriptive data, the development of predictive models, and the correlation of quantitative imaging features with phenotypic or gene-protein characteristics. It contributes significantly to the detection, diagnosis, staging, treatment response prediction, and prognosis assessment of lung cancer, thereby playing an increasingly vital role in clinical decision-making.

However, several limitations persist in current radiomics research:

(1) Study design: Most studies in the field involve relatively small sample sizes and are retrospective, single-center investigations. These studies often lack external validation datasets and incorporate a limited range of clinical factors and radiomic features.

(2) Equipment dependence: High-quality, standardized imaging data are crucial for radiomics. Variations in imaging equipment and techniques across different institutions can affect the reliability and reproducibility of radiomic features, leading to inconsistent results.

(3) Standardization challenges: The radiomics process currently lacks standardized databases, research protocols, image reconstruction algorithms, pre-processing methods, and feature extraction algorithms. Additionally, the stability and reproducibility of studies require significant improvement to enable widespread clinical application.

(4) Resource requirements: The implementation of radiomics and artificial intelligence (AI) demands substantial investment in technology, expertise, and training. These requirements may pose challenges, particularly for smaller healthcare institutions or those with limited resources.

Addressing these challenges and limitations is critical to fully realizing the potential of radiomics in optimizing lung cancer diagnosis and treatment. Overcoming these obstacles is essential to advancing personalized medicine and enhancing clinical outcomes in lung cancer management.

Disclosure statement

The authors declare no conflict of interest.

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