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# What does radiomics do in PD-L1 blockade therapy of NSCLC patients?

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## Abstract

With the in-depth understanding of programmed cell death 1 ligand 1 (PD-L1) in non-small cell lung cancer (NSCLC), PD-L1 has become a vital immunotherapy target and a significant biomarker. The clinical utility of detecting PD-L1 by immunohistochemistry or next-generation sequencing has been written into guidelines. However, the application of these methods is limited in some circumstances where the biopsy size is small or not accessible, or a dynamic monitor is needed. Radiomics can noninvasively, in real-time, and quantitatively analyze medical images to reflect deeper information about diseases. Since radiomics was proposed in 2012, it has been widely used in disease diagnosis and differential diagnosis, tumor staging and grading, gene and protein phenotype prediction, treatment plan decision-making, efficacy evaluation, and prognosis prediction. To explore the feasibility of the clinical application of radiomics in predicting PD-L1 expression, immunotherapy response, and long-term prognosis, we comprehensively reviewed and summarized recently published works in NSCLC. In conclusion, radiomics is expected to be a companion to the whole immunotherapy process.

**KEYWORDS**
features, non-small cell lung cancer, prediction, programmed cell death 1 ligand 1, radiomics

## INTRODUCTION

According to data released by the World Health Organization (WHO), lung cancer is the most common cause of cancer-related death, and it is reported that 1.8 million people will die of lung cancer worldwide in 2021. Non-small cell lung cancer (NSCLC) accounts for more than 85% of lung cancers and is a fundamental social health problem.[1]

As an essential therapeutic drug, immune checkpoint inhibitors (ICIs) have significantly improved the prognosis of NSCLC patients after Food and Drug Administration (FDA) approval. Especially in some tumor patients with negative targeted driver mutations (EGFR, ALK, etc.), PD-1/PD-L1 inhibitors have become the first-line treatment of choice.[2–5] In advanced NSCLC, the 5-year overall survival (OS) rate has been reported to be 32% for patients in the pembrolizumab arm compared to 16% in the chemotherapy arm.[6] It also indicates that treatment goals for advanced patients have changed from short-term control and short-term remission to long-term treatment.

It is believed that in the process of tumor immunity, PD-1 is expressed on tumor-infiltrating immune cells, and PD-L1 is mainly expressed on tumor cells and antigen-presenting cells.[7,8] The interaction of PD-L1 with PD-1 induces a conformational change in PD-1, which leads to the phosphorylation of cytoplasmic immunoreceptor tyrosine-based inhibitory motif (ITIM) and immunoreceptor tyrosine-based switch motif (ITSM) by Src family kinases.[9–11] When these tyrosine motifs are phosphorylated, SHP-2 and SHP-1 protein tyrosine phosphatases are recruited to attenuate T cell activation signals.[11–14] The binding of PD-L1 to PD-1 alters T cell activity in multiple ways, inhibiting T cell proliferation, survival, cytokine production, and other effector functions.[15–19]

However, not all patients are suitable for PD-L1 targeted therapy, and pathological detection and immunohistochemistry are the gold standards for testing.[20,21] Many studies have shown that PD-L1 expression in NSCLC patients is related to the prognosis of patients, and it may become a biomarker for predicting the prognosis of patients.[22–26] PD-L1 expression has been evaluated according to tumor proportion score (TPS), tumor cells (TC), tumor-infiltrating immune cells (IC) and combined positive score (CPS). Although there are various scoring methods, they all semi-quantitatively calculate the expression of PD-L1. Among them, TPS is widely used. It is generally believed that TPS <1% is negative for expression and unsuitable for treatment with anti-PD-L1 antibodies.[27] In a randomized controlled trial based on KEYNOTE-042, it was found that patients with TPS ≥1% can also benefit, and in 2019, the FDA approved the indication for the use of TPS ≥ 1%.[28] Before this, PD-L1 blockade therapy was only recommended for patients with TPS ≥50%.[29] Therefore, evaluating PD-L1 expression is particularly critical in the treatment process.[27,30]

In the course of clinical studies, it has been found that found that some patients showed a certain initial sensitivity to anti-PD-L1 antibodies at first and then developed drug resistance, which increased the economic burden of patients and contiiued disease progression. Ren et al. have summarized the possible mechanisms: (1) T cell dysfunction, (2) impairment of antigen recognition, (3) T cell activation disorder, (4) reduced T cell infiltration, (5) T cell exhaustion, and (6) changes in PD-L1 expression.[31–38]

In the process of PD-L1 blockade therapy, whether it is to evaluate indications or reveal possible drug resistance mechanisms, PD-L1 expression has a certain status. Many studies have shown that patients with high PD-L1 expression predict better prognosis, so the dynamic assessment of PD-L1 expression is critical.[6,39] Although pathological detection and immunohistochemistry are the gold standards for diagnosis, their invasive shortcomings are also evident. Partial specimens obtained by surgery for immunohistochemistry cannot fully reflect the tumor, resulting in inaccurate diagnosis. Liquid biopsy can be considered impermanent monitoring, but it cannot assess information such as overall tumor size and location.[40,41] Therefore, there is an urgent need for a noninvasive diagnostic method that can wholly and dynamically assess PD-L1 expression.

## ADVANTAGES OF RADIOMICS IN NONINVASIVE AND REAL-TIME DIAGNOSIS

### The process of radiomics

The development of high-throughput computing allows us to obtain a large amount of digitized information from imaging data such as computed tomography (CT), positron emission computed tomography (PET), and single-photon emission computed tomography (SPECT). The process of extracting and mining data from it is called radiomics. With the help of radiomics, we can discover the potential of reflecting biological processes from high-dimensional data of medical images, which is very different from traditional manual reading. Therefore, radiomics proposes that images are not just pictures but data.[42] Since tumor patients almost always have one or more imaging examinations, the application scope of radiomics in tumor diagnosis has also been expanded. The analysis process of radiomics mainly includes the following aspects: acquiring images, identifying region of interest (ROI), computer-aided segmentation, extracting features, and mining the relationship between features and biological behavior. In the mining process, joint analysis can be carried out with clinical information, genomic information, etc., and displayed from multiple dimensions.[43,44]

### Classification of radiomic features

The features extracted after segmentation can be divided into the following categories: (1) Morphological features: describe size features such as volume, diameter, etc. (2) First-order grayscale histogram features: obtain relevant statistical features, such as maximum value, minimum value, standard deviation, etc., according to the different grayscale frequency distributions in the segmented ROI. (3) Second-order and higher-order texture features: describe the relationship between gray value and spatial distribution in an image, such as absolute gradient, gray-level cooccurrence matrix (GLCM), gray-level run-length matrix (GLRLM), gray-level size zone matrix (GLSZM) and gray-level distance zone matrix (GLDZM), neighborhood gray-tone difference matrix (NGTDM), neighborhood gray-level dependence matrix (NGLDM). (4) Other features based on filtering and morphing.[45,46]

### Application of radiomics in lung cancer diagnosis

The earliest application of radiomics in lung tumors was mainly used to distinguish benign from malignant and identify diseased tissue.[47] For example, Maldonado et al. used high-resolution CT to identify pulmonary nodules by radiomics.[48] Later, it was gradually applied to predict tumor staging. Zhou et al. conducted a retrospective analysis of 348 patients with lung cancer and extracted 485 features employing CT radiomics to predict the presence of distant metastasis. The model was established with clinical characteristics, and the AUC could reach 89.09%.[49] With the wide application of targeted therapy, radiomics has also been used to diagnose molecular protein levels. We will discuss the application of radiomics in PD-L1 blockade therapy in this part.

## Applications of radiomics concerning PD-L1

To gain a more comprehensive understanding of the current application of radiomics in assessing PD-L1 expression in NSCLC and in NSCLC patients receiving PD-L1 blockade therapy, PubMed, web of science, Embase, clinicaltrials.gov and the Cochrane library were searched for available studies. A total of 39 relevant studies were retrieved after checking for duplication (Figure 1). According to the content, they are divided into the following categories.

## Prediction of PD-L1 expression by CT radiomics

As mentioned above, the pathological gold standard uses TPS calculated after immunohistochemistry as an indication for PD-L1 blockade therapy. This part of the study mainly uses CT imaging to extract features and predict the expression of PD-L1. We collected a total of 11 studies through the search, of which four set TPS = 50% as the cutoff value for prediction, two set TPS = 1% as the cutoff value for prediction, and three both performed TPS = 1% and TPS = 50%, and the other two did not specify TPS in the article (Table 1).

### TPS cutoff was 50%

Three of these were modeled solely using CT radiomics features. Yoon et al. extracted 58 features from CT imaging data from 153 NSCLC patients and screened four for establishing a model. The AUC was 0.661, the sensitivity was 0.528, and the specificity was 0.760.[50] Wen et al. extracted 462 features from the CT data set of 120 NSCLC patients. After screening, five features were used for modeling. The AUC was 0.839, the sensitivity was 0.917, and the specificity was 0.481.[51] From this, there is heterogeneity in the prediction effect of radiomics. There are apparent differences in the number of features extracted by different institutions for the same issue, and there are also significant differences in the bias of the prediction results. Similar problems exist in the subsequent analysis. After discussion, we believe that there are several factors: (1) Data standardization: The parameters of the imaging instrument manufacturers, the manually segmented ROI, and the operating software used in each center are different. (2) Statistical methods are different in the modeling process. This study can corroborate the second of these points, Shiinoki et al. extracted 1130 features from CT data of 203 NSCLC patients. After screening, three machine learning methods were used for modeling (LightGBM, SVM: Support vector machine and LR: Logistic regression), of which LightGBM had a better effect, the training set AUC was 0.95, and the test set was 0.79. The effect of SVM was the worst; the AUC in the training set was only 0.50.[52]

In the other studies with PD-L1 expression as the cutoff value of 50%, further information was included in addition to radiomics information to form a combined model. Bracci et al. extracted a total of 48 features from CT of 72 NSCLC patients and screened four features combined with clinical data to construct a prediction model jointly. The model had an AUC of 0.811 in the training set and 0.789 in the validation set, with a sensitivity of 83% and a specificity of 75%.[53] Also a study that combined clinical information by Sun et al. extracted 200 features from the CT imaging data of 390 patients. They selected nine features and combined them with clinical information to build and train the model. The training set AUC was 0.829, validation set AUC was

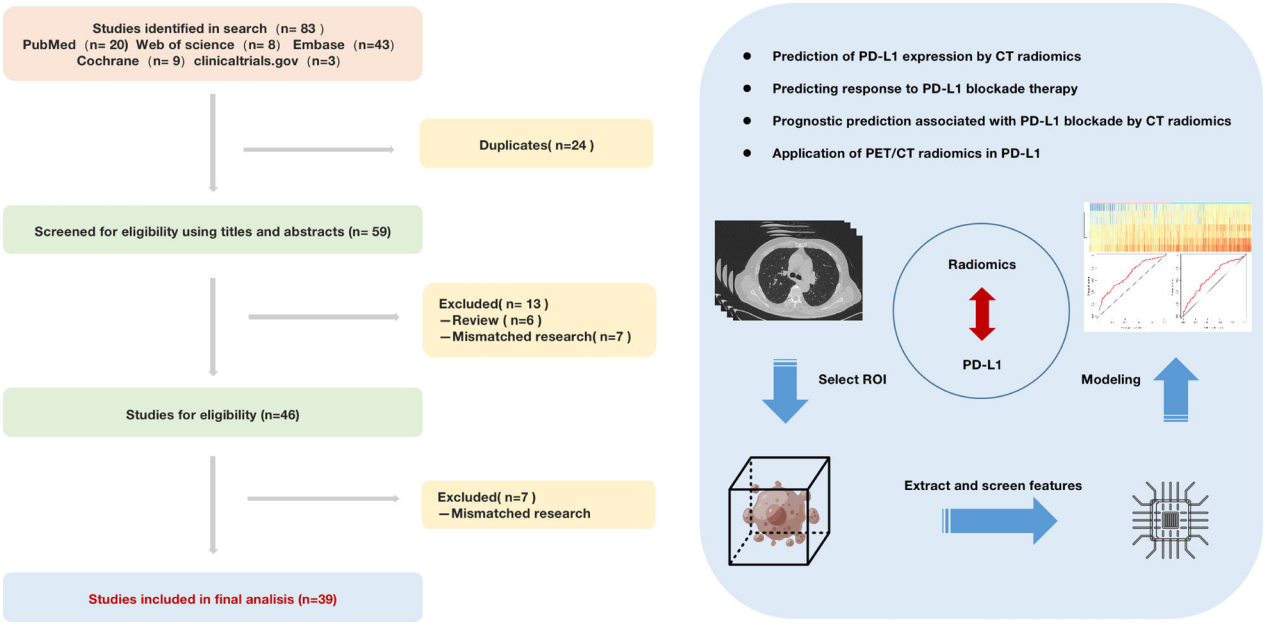


**FIGURE 1** Screening process and key points of studies included. A total of 83 articles were included through the retrieval of the above five databases. Finally, 39 papers were screened to meet the requirements. They all use radiomics to process imaging data to guide various aspects of immunotherapy

**TABLE 1** Ten studies on PD-L1 expression prediction (CT)

| Year | Authors | NSCLC stage | Sample size | Radiomics features in final model | PD-L1 TPS cutoff | Clinical question |
|---|---|---|---|---|---|---|
| 2017 | Wen et al. | NA | 96 | 8 | NA | Predict PD-L1, CD8 + TILs and Foxp3 + TILs expression |
| 2020 | Yoon et al. | IIIB–IVC | 153 | 4 | 50% | Predict PD-L1 expression |
| 2020 | Sun et al. | I–IV | 390 | 9 | 50% | Predict PD-L1 expression |
| 2021 | Bracci et al. | IIIA–IV | 72 | Six features for TPS ≥1%; 4 features for TPS ≥50% | 1% & 50% | Predict PD-L1 expression |
| 2021 | Jiang et al. | Tis–III | 125 | 9 | 1% | Predict PD-L1 expression |
| 2021 | Shiinoki et al. | NA | 203 | NA | 1% & 50% | Predict PD-L1 expression |
| 2021 | Wang et al. | I–IV | 1262(EGFR & PD-L1) | NA | NA | Predict EGFR and PD-L1 expression |
| 2021 | Wen et al. | III–IV | 120 | 6 | 50% | Predict PD-L1 expression and TMB |
| 2022 | Wang et al. | I–IV | 3816(EGFR & PD-L1) | 100-dimensional features | 1% & 50% | Predict EGFR and PD-L1 expression |
| 2022 | Wang et al. | I–IV | 1135 | NA | 1% & 50% | Predict PD-L1 expression and OS |

Abbreviations: OS, overall survival; TMB, tumor mutational burden.

0.848, sensitivity was 0.833, and specificity was 0.724.[54] Wang et al. combined the deep learning part. They collected 873 cases of NSCLC patients, extracted 1247 radiomics features from their chest CT, and divided the final model into multiple parts (including deep learning, radiomics and combinatorial part) for the classification task of EGFR and PD-L1 expression status, respectively. In the radiomics module, the AUC of the training set was 0.819, AUC of the validation set was 0.795, sensitivity was 0.795, and specificity was 0.716.[55]

## TPS = 1% used as cutoff value

Bracci et al. also rescreened the 48 previously extracted features in the study mentioned above and combined the clinical data with the six screened features for modeling. The AUC in the training set was 0.763, and the validation was 0.806. The sensitivity was 100%, and the specificity was 58.8%.[53] Wang et al. also screened and modeled from the 1247 features extracted above. In the radiomic module, the AUC on the training set was 0.884, the validation set was 0.836, the sensitivity was 0.744, and the specificity was 0.917.[55] Shiinoki et al. rescreened 1130 features for modeling, and LightGBM performed the best among the three modeling methods, with an AUC of 0.98 on the training set and 0.76 on the validation set.[52] Jiang et al. collected chest CT data of 125 patients with NSCLC, extracted 1287 features from it with the help of ITK-SNAP software, used Ridge regression to screen for potential features, and finally selected nine features for modeling, which are on the training set. The AUC was 0.96, the validation set was 0.85, the sensitivity was 0.913, and the specificity was 0.6364.[56] Few studies have taken 1% of PD-L1 expression alone, which may be related to the therapeutic effect of ICIs. The KEYNOTE-042 experiment demonstrated that patients with PD-L1 expression greater than 1% might benefit from using the corresponding blocker, but patients with PD-L1 expression greater than 50% may benefit significantly.[28]

In order to simultaneously construct a prediction model of PD-L1 expression and prognosis, Wang et al. also used radiomics combined with 3D ResNet to construct a PD-L1ES model based on the information of 1135 patients to complete the three-classification task and prognosis prediction. Its AUCs for PD-L1ES <1%, 1%–49%, and ≥50% in the prediction validation cohort were 0.950, 0.934, and 0.946, respectively.[57]

In addition, there are two studies in which the cutoff value for evaluating PD-L1 expression by immunohistochemical staining of pathological tissues of NSCLC patients was not noted. Wang et al. combined traditional radiomic methods with convolutional neural networks to simultaneously predict PD-L1 and EGFR expression to complete the four-classification task. Modeled on retrospective data from 1262 NSCLC patients, the AUC was 0.96 in the training and 0.8 in the validation set, with a sensitivity of 0.48 and a specificity of 0.84.[58] Wen et al. extracted 127 features from CT of 96 NSCLC patients and finally screened eight for modeling with a validation set AUC of 0.628.[59]

From the results of the above reports, radiomics is a potential method to predict the expression status of PD-L1 in NSCLC patients, but the accuracy of the prediction effect is not consistent among different centers. The results of multiple studies also suggest that comodeling of radiomic data with other dimensional data may achieve better results. For example, combining patients' clinical information or radiomics and artificial intelligence methods can significantly improve the AUC, sensitivity and specificity.[51,53–55]

**TABLE 2** Ten studies to predict response to PD-L1 blockade therapy (CT)

| Year | Authors | NSCLC stage | Sample size | Radiomics features in final model | Clinical question |
|---|---|---|---|---|---|
| 2017 | Tunali et al. | NA | 214 | 3 | Predict patients at risk of HPD |
| 2017 | Tunali et al. | III–IV | 71 | Three models (2/4/1) | distinguish PD and PR or CR (PD vs. PR/CR) |
| 2018 | Tang et al. | NA | 290 | 4 | Identify responders and nonresponders and predict prognosis |
| 2019 | Tunali et al. | NA | 228 | 4 for TTP <2 months vs. TTP ≥2 months 1 for HPD vs. non-HPD | Predict rapid disease progression |
| 2020 | Chen et al. | NA | 82 | 7 | Distinguishing pneumonitis from radiation therapy or ICIs |
| 2020 | Vaidya, et al. | I–IV | 109 | 3 | Predict patients at risk of HPD |
| 2021 | Alilou et al. | NA | 80 | 4 | Predict response and OS |
| 2021 | Yang et al. | IIIB and IV | 200 | 107 dimensions features | Identify immunotherapy responders and nonresponders |
| 2022 | Cheng et al. | NA | 73 | 3 kinds of features | Differentiate between CIP and RP |
| 2022 | Gong et al. | III-IV | 224 | 7 (preradiomics model); 4(delta-radiomics model) | Predict response to immunotherapy and PFS and OS |

Abbreviations: CIP, immune checkpoint inhibitor-related pneumonitis; CR, complete response; HPD, hyperprogressive disease; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RP, radiation pneumonitis.

## Predicting response to PD-L1 blockade therapy

The studies on the application of radiomics during PD-L1 blockade therapy can be roughly divided into three categories (Table 2). The first is to predict whether hyperprogression occurs. Hyperprogression here refers to the paradoxical phenomenon of accelerated disease progression after initiation of immunotherapy. This is undoubtedly a fatal blow for cancer patients. According to the available reports, among patients receiving immunotherapy, the proportion of this phenomenon fluctuated from 8% to 25.7%.[60–63] The pathophysiological mechanism of this phenomenon is still unclear. Therefore, if it can be identified, the worse situation may be avoided. Here, we have collected two related studies. Tunali et al. retrospectively collected data from 214 NSCLC patients receiving PD-1/PD-L1 blockade therapy. The three CT radiomics features were screened from it. Combined with the clinical information on age, its AUC reached 0.70.[64] Also, Tunali et al. analyzed the phenotype of rapidly progressive disease by time to progression (TTP) and/or tumor growth rate (TGR) based on information from 228 patients treated with PD-1/PD-L1 blockade. In conclusion, the AUROC derived from the clinical-radiological model for TTP <2 months and TTP ≥ 2 months was 0.804. The AUROC score for the clinical-radiological hyperprogressive disease (HPD) versus non-HPD models was 0.865.[65] Vaidya et al. extracted 198 features to model and identified hyperprogression with an AUC of 0.85 on the training set and 0.96 on the validation set.[63]

The second category is to predict the response to PD-L1 blockade therapy. A total of four studies used CT radiomics to predict the therapeutic effect of PD-L1 blockade therapy. The impact of a malignant tumor on the patient itself and the aggravation of the economic burden on the patient's family are obvious. Ineffective immunotherapy can exacerbate this burden, so some researchers have focused on predicting response to PD-L1 blockade therapy. Tunali et al. collected before immunotherapy data of patients with stage III/IV NSCLC who received PD-1/PD-L1 from 13 different institutions. They finally screened four radiomic features to establish a model to distinguish progressive disease (PD) and patients with partial response (PR) or (complete response CR), PD vs PR/CR. The ROC curve was drawn, and the calculated AUC was 0.79.[66] Yang et al. combined radiomics and deep learning to predict immunotherapy responders and nonresponders with an AUC of 0.80 on data from 200 patients with advanced NSCLC treated with PD-1/PD-L1. At the same time, the model was used to divide the patients into two groups according to the risk score.[67] Different from other radiomics methods, Alilou et al. collected CT imaging data of 80 patients who received PD-1/PD-L1 blockade therapy and performed airway reconstruction preprocessing to extract airway features. They screened four out of 14 features for modeling to distinguish responders from nonresponders, with an AUC of 0.63 in the test set.[68]

Since studies have reported that lung tumor evolution during immunotherapy reflects the efficacy of immune-related drugs, Gong et al. hypothesized that changes in intratumoral CT radiomics features during short-term immunotherapy may improve predictive performance.[69,70] They retrospectively collected CT data before and after ICIs in 224 patients with stage III or IV NSCLC from two centers, and defined PR and CR as the "responder group", stable disease (SD) and PD as "nonresponders". In particular,

**TABLE 3** Seven studies for prognostic prediction (CT)

| Year | Authors | NSCLC stage | Sample size | Radiomics features in final model | Clinical question |
|---|---|---|---|---|---|
| 2018 | Mazzaschi et al. | NA | 60 | NA | Predict OS |
| 2018 | Patil et al. | I–II | 166 | 3 | Predict risk of recurrence and OS |
| 2019 | Ackermann et al. | IIIB/IV | 16 | 5 for best overall response; 3 for OS | Predict response and survival |
| 2019 | Mazzaschi et al. | NA | 100 | 13 | Predict OS and DFS |
| 2020 | He et al. | III–IV | 327 | 1020 | Distinguish high TMB from low TMB |
| 2021 | Tonneau et al. | Advanced | 299 | NA | Predict ORR, PFS at 6 months, OS at 1 year |
| 2022 | Jazieh et al. | III | 133 | NA | Predict PFS and OS |

Abbreviations: DFS, disease-free survival; OS, overall survival; PFS: progression-free survival; TMB, tumor mutational burden.

Delta radiomics features, that is, changes in CT radiomics features before and after treatment, are proposed. The AUC of the model built from the delta radiomics features was significantly higher than that built with the preimmunotherapy radiomics features, from 0.64 and 0.52 to 0.82 and 0.87 in the two validation cohorts, respectively. The model also has predictive significance for prognosis.[70]

The third is to predict whether complications will occur during treatment. For cancer patients, the response of their immune system is different from that of normal people, and some patients have received a variety of treatments. They may develop fatal complications such as pneumonia during treatment. Chen et al. collected CT imaging data of 82 NSCLC patients who received radiotherapy, immunotherapy or both. After screening, seven features were included in the modeling to distinguish whether it was pneumonia caused by radiotherapy or immune checkpoint inhibitors. The AUC on the training set was 0.79. The validation set's accuracy was 77%, and the AUC was 0.84.[71]

Immunotherapy after radiotherapy is currently the standard for patients with stage III unresectable NSCLC. However, it is difficult for clinicians to differentiate between immune checkpoint inhibitor-related pneumonitis (CIP) and radiation pneumonitis (RP).[72,73] Cheng et al. retrospectively collected CT images and clinical data of pneumonia patients treated with ICIs alone (28 cases), radiotherapy (RT) patients (31 cases), and ICIs + RT patients (14 cases). Three features were screened to establish models, respectively, and the one with the best effect was selected to distinguish CIP from RP. The AUC, in its verification, can reach 0.896.[74]

For patients ready to receive ICIs, several questions need to be answered when making predictions: (1) Will the patient respond to ICIs and accelerate disease progression? (2) Are there possible adverse reactions during the treatment? Based on the advantages of radiomics being noninvasive and not increasing the financial burden of patients, it may be more acceptable to evaluate patients before treatment. The application of radiomics in treating PD-L1 is still in its infancy, and there are few related studies.

## Prognostic prediction associated with PD-L1 blockade by CT radiomics

Approving immune checkpoint inhibitors for treating patients with NSCLC is a milestone. In particular, for some patients whose tumors cannot be surgically removed, receiving ICIs can improve the prognosis.[75,76] However, how long has the patient's prognosis improved based on this part? What is the quantitative benefit of receiving immune checkpoint inhibitor therapy? How long to live? Individualized answers to these questions are not yet available. A literature search found that studies in this area related to radiomics can be divided into the following categories (Table 3).

First, for patients treated with PD-L1 blockade therapy, prognostic indicators such as OS, objective response rate (ORR), and progression-free survival (PFS) were predicted from their CT data. Tonneau et al. collected CT information of 299 patients before receiving immunotherapy and combined it with their clinical baseline characteristics to build a multivariate model. The results also showed improved predictive power for prognosis when combined with radiomic information.[77] Jazieh et al. included 133 patients who received PD-L1 blockade therapy after chemoradiotherapy (CRT), extracted and screened their CT, and finally established a risk score by Cox regression to predict PFS and OS.[78] Ackermann et al. collected 16 histologically confirmed TPS ≥ 50% stage IIIB/IV NSCLC patients treated with pembrolizumab. With the help of PyRadiomics, 47 features were extracted, and LASSO screened five features for predicting the overall response, and its AUC was 0.83. Three features were screened for predicting OS by Cox regression.[22]

With the advent of next-generation sequencing technology, tumor mutational burden (TMB) is a hot spot in tumor immunity. Currently, TMB is able to predict the response to PD-1/PD-L1 blockade in NSCLC patients.[79,80] He et al. collected two datasets, TMB ($n$ = 327) and immunotherapy dataset ($n$ = 123), and developed and validated the TMB radiomic biomarker (TMBRB) through convolutional neural networks. The results showed that the immunotherapy dataset could be divided into two groups based on TMBRB. There were significant differences in OS (HR: 0.54, 95% CI:

**TABLE 4** Twelve studies for application of PET/CT radiomics in PD-L1

| Year | Authors | NSCLC stage | Sample size | Radiomics features in final model | Clinical question |
|---|---|---|---|---|---|
| 2020 | Mu et al. | IIIB–IV | 400 | NA | Predict DCB, PFS, OS |
| 2020 | Mu et al. | IIIB–IV | 146 | 5 | Predict irSAEs |
| 2020 | Jiang et al. | I–IV | 399 | 24 (models based on CT-, PET-, PET/CT-derived) | Predict the expression of PD-L1 (1% & 50%) |
| 2020 | Mu et al. | IIIB–IV | 194 | 8 | Predict DCB |
| 2021 | Li et al. | I–IV | 255 | for 1%: 12(PET) + 6(CT) for 50%: 3(PET) + 4(CT) | Predict the expression of PD-L1 (1% and 50%) |
| 2021 | Zeng et al. | IIB–IIIB | 45 | NA | Predict patient prognosis (OS, PFS, LRC) |
| 2021 | Mu et al. | I–IV | 697 | NA | Predict PD-L1 expression, DCB, PFS and OS |
| 2021 | Mu et al. | NA | 837 | NA | Predict the expression of PD-L1 and EGFR |
| 2021 | Zhou et al. | I-IV | 103 | 3(PET) + 1(CT) | Predict tumor microenvironment immune types |
| 2021 | Mu et al. | IIIB and IV | 210 | 9 | Predict risk of cachexia, DCB, PFS and OS |
| 2022 | Forouzannezhad et al. | IIB–IIIB | 45 | Various | Predict patient prognosis |
| 2022 | Monaco et al. | I–IV | 265 | 3 | Predict the expression of PD-L1 (50%) |

Abbreviations: DCB, durable clinical benefit; irSAEs, immune-related adverse events; LRC, locoregional control; OS, overall survival; PFS, progression-free survival.

0.31 to 0.95; $p = 0.030$) and PFS (HR: 1.78, 95% CI: 1.07 to 2.95; $p = 0.023$) between the two groups.[81]

Second, the PD-L1-related radiomics features were used to predict the prognosis of patients, such as OS and recurrence. Mazzaschi et al. analyzed 60 NSCLC patients who received surgical treatment and constructed a model based on the postoperative pathological tumor microenvironment (TME), including PD-L1 expression and 841 features extracted by 3D slicer, which can be used to predict patient prognosis.[82] In addition to the above studies, Mazzaschi et al. in another study, combined histological tumor immune microenvironment analysis with radiomics. In this study, TME was classified according to PD-L1 and tumor-infiltrating lymphocytes (TILs) levels and was further defined as hot, intermediate, or cold according to the relative contribution of effector and inhibitory phenotypes. Additionally, a model was constructed to predict patient survival.[83] Tang et al. proposed a model that predicts CD3 counts and percent PD-L1 expression with the help of radiomics signatures and predicts patient outcomes.[84]

For tumors at an early stage, in addition to paying attention to survival, clinicians are more concerned about the recurrence of postoperative patients who have undergone surgical treatment. Patil et al. collected 166 patients with stage 1 and 2 NSCLC who underwent surgery. A total of 248 features were extracted. Through screening the features associated with PD-L1, a prediction model was established, which can predict whether a patient has recurrence (AUC = 0.73), overall survival ($p < 0.001$) and recurrence-free survival ($p < 0.001$).[85] CT data is clinical information that almost all cancer patients will have. It is easier to accept if radiomics can effectively predict survival and prognosis guidance.

## Application of PET/CT radiomics in PD-L1

As one of the most commonly used methods in tumor imaging, $^{18}$F-FDG-PET/CT can reflect the relevant characteristics of the tumor microenvironment utilizing glucose metabolism pathways.[86,87] Radiomics is a new modality focused on quantitatively extracting and analyzing medical images. Our literature search also found 12 studies using radiomics to analyze the PD-L1 association in tumors by PET/CT (Table 4). Similar to the CT methods analyzed previously, they are mainly divided into three categories.

The first category has more studies than the other two, using PET/CT to predict the expression of PD-L1. Zeng et al. collected 45 patients with unresectable NSCLC who received chemotherapy and demonstrated that PD-L1 expression was correlated with the number of features based on their PET/CT-extracted features ($p = 0.017$).[88] Mu et al. retrospectively included 837 NSCLC patients and divided them into training, validation, and test sets. A prediction model was constructed by an artificial intelligence algorithm using PET/CT images and clinical information, and the AUC was 0.89, 0.84 and 0.82, respectively.[89] CD8+ tumor-infiltrating lymphocytes are also critical throughout the PD-1/PD-L1 axis. Zhou et al. analyzed 103 NSCLC patients divided into four groups according to the expression of pathological PD-L1 and CD8+ tumor-infiltrating lymphocytes. The prediction effect of the composite model combined with clinical information has improved. In the training set, the AUC increased from 0.800 to 0.838; in the validation set, the AUC increased from 0.794 to 0.811.[90] Li et al. extracted 80 features from the PET/CT of 255 NSCLC patients and combined them with clinical information. The results showed that when PD-L1 expression was more than 1% and 50% predicted using radiomics alone, the AUC was 0.754 and 0.762, respectively. The AUC for predicting PD-L1 expression above 1% and 50% after incorporating clinical informative features were 0.762 and 0.814, respectively.[91] Mu et al. divided 697 NSCLC patients into three cohorts, two retrospective cohorts for model building and training and a prospective cohort for external validation. Based on PET/CT and clinical information combined with a

convolutional neural network, a deep learning score was constructed to evaluate the expression of PD-L1 and predict patients' clinical benefit and survival. In all three cohorts, the negative and positive expressions of PD-L1 could be significantly distinguished, and the AUCs were all greater than 0.82.[92] Monaco et al. extracted 527 features from 86 NSCLC patients' PET/CT. Three radiomics features were screened for modeling. The AUC of PD-L1 expression greater than 50% was predicted to be 0.84.[93]

While exploring this issue, Jiang et al. discussed the predictive performance of separate and combined modeling of PET and CT features. Twenty-four (PET and CT features) features related to PD-L1 expression were extracted from PET/CT. Three models were established respectively: one based on CT features, one based on PET features, and the third incorporating both features. The prediction effects of the three in predicting PD-L1 expression exceeding 1% and 50% were discussed, and all results were positive. The interesting point is that the prediction effect of adding PET features to the mixed model is not as good as the prediction effect of the model that simply uses CT features.[94]

The second category predicts patient prognosis by analyzing PD-L1-related radiomic features. Forouzannezhad et al. prospectively collected FDG-PET, CT and SPECT examination information at various treatment time points in 45 patients with unresectable NSCLC. They were treated with radiotherapy and PD-L1 blockade. Models were constructed to predict survival from three imaging tests. In the results, FDG-PET information alone was the best predictor of OS (c-index = 0.71). It is worth noting that the model prediction effect was not improved after the multitask combination.[95] Mu et al. combined their self-established PD-L1 deep learning scoring system, PET and CT multiparametric radiomic model and basic clinical information to construct a Cox multivariate regression model for predicting patients' PFS and OS. Validation was performed in an externally validated set of 48 patients, and its conclusions were mentioned to provide individualized clinical decision support.[96] The effect of immunotherapy is often related to patient prognosis. Mu et al. collected 194 patients with histologically confirmed stage IIIB–IV NSCLC with PET/CT images before ICIs. According to its modeling prediction of durable clinical benefit (DCB), the AUC in the training, validation and test sets were 0.86, 0.83 and 0.81, respectively. Also, in these three cohorts, nomogram models achieved C-indices of 0.74, 0.74, and 0.77 to predict PFS, and C-indices of 0.83, 0.83 and 0.80 to predict OS.[97]

The third category predicts whether adverse reactions will occur during ICIs treatment. According to current reports, the incidence of immune-related adverse events (irAEs) is between 7% and 43%.[98–100] Their appearance delays tumor treatment and worsens the patient's condition. Similarly, Mu et al. used the method mentioned above to build a model of the five PET/CT-related features screened out. The AUC in the training set, internal test, and external prospective validation set were 0.92, 0.92, and 0.88, respectively.[100] Cachexia, a complex metabolic syndrome in which the body's tissues are depleted, occurs in approximately 50% of cancer patients and accounts for 20% of cancer-related deaths. However, early identification of possible patients and intervention can reduce cachexia.[101–103] A retrospective analysis of PET/CT and clinical data before immunotherapy in 210 NSCLC patients from two institutions was performed. Using PET/CT images to predict the occurrence of cachexia, AUC was ≥ 0.74 in the training set, test and external test cohorts.[104]

Given the unique imaging principle of PET/CT, $^{18}$F-FDG can detect the energy metabolism of tumor cells and other cells in the tumor microenvironment. Although the molecular mechanism between glucose metabolism and PD-L1 has not been revealed, multiple studies have shown that the different expression distribution of PD-L1 in tumor tissues may lead to different metabolic distributions.[105,106] Therefore, models based on PET may predict better.

## LIMITATIONS AND CHALLENGES

Although the development of radiomics has achieved certain progression in the diagnosis, prognosis, and therapy response prediction of NSCLC patients, some general problems are arising. One of the recognized challenges is the stability and reliability of the constructed models. As in the studies we mentioned above, there are obvious differences in models' construction across different centers, even for the same aim. In this regard, we summarized the potential challenges of applying radiomics in further clinical practice.

First, during the medical image collection process, heterogeneous images can lead to irreproducible results.[107,108] There are many parameters during image acquisition including pixel pitch, slice thickness, reconstruction kernel and application of contrast agent, etc. Intra- and interscanner parameter heterogeneity may exist between different centers or different instruments at the same center. The solution to this pain point is to develop a normalization protocol for images.[109,110] Second, during the region of interest (ROI) selection and segmentation, in most cases, this part of the work is done by experienced radiologists who have done an excellent job of identifying and "indexing" lesions. However, studies have shown that manual segmentation leads to intraobservable variation and consumes much time.[111] Kalpathy-Cramer et al. showed that semi- or fully automated segmentation can make the process repeatable and improve robustness.[112] Third, in the feature extraction process, many software, terminology, and algorithms are available to assist, which is also a cause of heterogeneity. The image biomarker standardization initiative (IBSI) is an international collaborative initiative dedicated to standardizing the extraction of image biomarkers.[113] Part of the interoperability issue is addressed by providing image biomarker nomenclature and definitions, benchmark datasets and benchmark values to validate image processing. Fourth, feature selection, model training and validation. A very high number of radiomic features are extracted from medical

images and improper modeling can lead to overfitting.[114] Ideally, multiple modeling approaches should be tested to choose the best one.[115] In terms of validation, multiple replicate cross-validation should be considered if performed on cohorts from a single institution. However, utilizing multicenter and prospectively collected datasets is the best way to verify and avoid spurious results.[107]

In addition, with the advancement of computer technology, the emerging method of artificial intelligence has attracted much attention. Because of its high efficiency and automation advantages, there is a strong trend in the medical field to address visual information. However, it is not comparable to radiomics in terms of model interpretability. These AI systems are like a "black box" that lacks transparency on how various tasks are performed. Users may never understand how these networks work, and AI may identify patterns humans cannot explain. Although some scholars believe that a highly accurate opaque model is better than a less accurate transparent model. But interpretability is important when considering the use of AI imaging biomarkers to optimize clinical decision-making.[116,117]

In conclusion, we believe that applying radiomics in PD-L1-related imaging in NSCLC patients is promising. Radiomics features obtained by various imaging methods (CT, PET, SPECT, etc.) can predict PD-L1 expression, predict prognosis through PD-L1-related features, and assist in guiding immunotherapy and monitoring adverse reactions. To realize this vision faster, we must solve several problems, including the standardization of high-quality data and image data, the effective combination of multiple imaging methods, and the problem of prospective verification. Based on the well-established diagnostic utility, radiomics will promote personalized medical services and blaze a unique path in precise diagnosis and treatment.

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## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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