Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 8
MMTCS 2025

Advances in Immunotherapy of Biomarkers for Non-small Cell Lung Cancer Based on Radiomics

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Abstract. With the development of immunotherapy for non-small cell lung cancer (NSCLC), it has become increasingly crucial to evaluate the efficacy of immunotherapy and screen for the beneficiary population. However, how to use radiomics to screen suitable immune checkpoint markers and analyze immunotherapy prognosis is still lacking in-depth research. In this study, the basic concepts of radiomics were explored and biomarkers were analyzed in combination with computed tomography (CT) and positron emission tomography (PET/CT). Considering programmed death ligand 1 (PD-L1) expression status and tumor mutational load in patients receiving immunotherapeutic treatment, We developed a deep learning model that is non-invasive and analyzed relevant studies to screen for suitable biomarkers. In addition, we analyzed the effect of tumor immune microenvironment profile (TIME profile) on immune checkpoint inhibitors (ICIs) response, providing valuable parameters for cell cycle-dependent kinase inhibitor (CKI) therapy in advanced patients, and investigated the risk assessment for pneumonia linked to immune checkpoint inhibitors (ICIP). All things considered, radiomics can help support clinically tailored treatment and is very useful in forecasting the effectiveness and side effects of immunotherapy in patients with NSCLC.

Keywords: Radiomics; Non-small cell lung cancer; Biomarkers; Immunotherapy.

1. Introduction

NSCLC, which makes up 85% of all lung cancers(LC), is the most prevalent subtype of LC, which is a leading cause of cancer-related deaths globally [1]. Early-stage NSCLC patients typically undergo surgical resection, while advanced-stage NSCLC patients receive systemic therapy or immunotherapy. Although immunotherapy is currently widely applied in clinical practice, its effect is related to tumor heterogeneity, tumor immune microenvironment and other factors, and only a few patients can benefit from it, so there aren't many trustworthy prognostic indicators for immunotherapy [2]. At the same time, radiomics is a non-invasive, high-throughput and low-cost method, which can quantitatively analyze imaging data and generate models to determine the pathological type, malignant degree and prognosis of tumors. However, the traditional macroscopic medical imaging examination technology has not met the requirements of clinical diagnosis and treatment. Yang et al. recently analyzed the CT scans of 200 advanced NSCLC patients undergoing therapy with anti-PD-1 and PD-L1 medications by combining the multi-omics deep learning technique with the radiological aspects of CT, and showed that the prognostic evaluation of radiomics was better than the predictive power of baseline PD-L1 expression [3]. Therefore, it is necessary to use radiological methods to predict immune checkpoint markers as a quantifiable objective feature and combine with clinical factors to establish radiomics models in CT and PET/CT to early predict adverse reactions and determine whether patients need immunotherapy. The discussion of the above questions is of great significance for selecting appropriate biomarkers and predicting the pathological response and the effectiveness of immunotherapy in NSCLC patients, and promoting personalized treatment in clinical practice. This paper reviews the research progress of establishing an appropriate radiological model to select biomarkers, predict adverse reactions and immune efficacy in immunotherapy of NSCLC patients.

2. Basic Contents of Radiomics

Radiomics is a non-invasive and high-throughput radiology method, which extracts a large amount of quantitative information with the help of computer system, and can noninvasively and dynamically observe the pathological structure, biological information and microenvironment in and around the tumor, and extract the situation that can not be observed by naked body [4]. The application of radiomics in NSCLC includes the evaluation of the effect and response of immunotherapy, early non-invasive diagnosis, and prediction of later treatment results [5].

As shown in figure 1, generally speaking, applying medical imaging equipment to acquire and reconstruct medical pictures, segmenting regions of interest, extracting radiomic features, categorizing the features, and creating models and prediction models are all part of the imaging workflow [5].

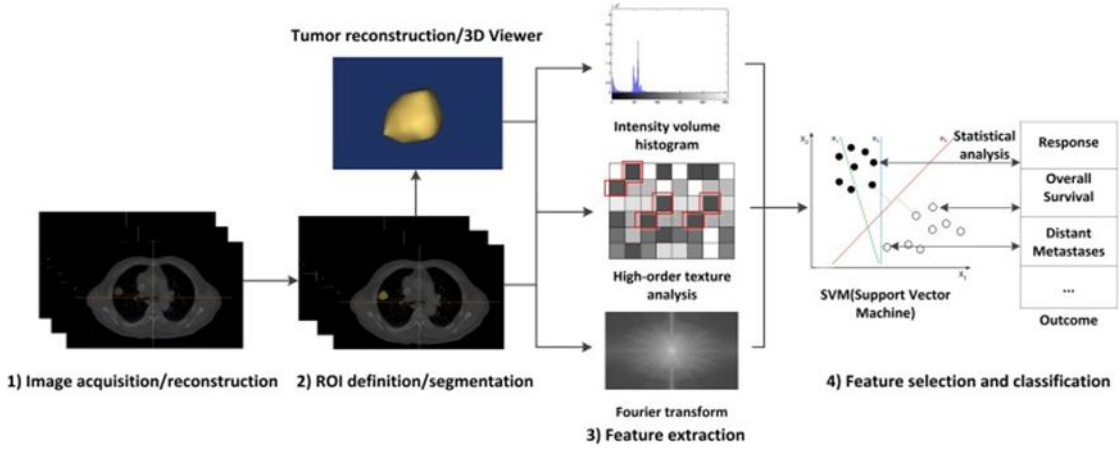

Fig. 1 The workflow of radiomics [5].

Although radiomics can provide accurate imaging information for the efficacy evaluation of NSCLC, the combination of radiomics with biomarkers can further improve the accuracy of imaging prediction.

3. To Explore the Appropriate Immune Checkpoint Markers

3.1. To Explore Immune Checkpoint Markers Based on CT Radiomics

Vaidya et al. found that receiving ICIs can improve the survival outcome of patients, but HPD phenomenon of the disease will also occur [6]. Biomarkers that predict HPD phenomena in clinical practice are still lacking. In order to identify hyperprogressive patients (HPs), responders, and non-responders, the intratumoral and peritumoral regions were manually segmented, and the texture and vascular tortuosity features in the intratumoral and from the pre-treatment CT scan pictures of NSCLC patients receiving PD-1 or PD-L1, peritumoral areas were removed, and the feature structure was analyzed by unsupervised clustering, and the radiomics model was constructed by the training team. Features were screened with five-fold cross validation, and the five classifiers were evaluated with indicators such as area under the curve (AUC) as a biomarker to predict HPD phenomenon in patients under ICIs treatment. At the same time, Li et al. [7] also pointed out that there is a lack of non-invasive and immediate prediction methods to predict atypical reactions such as false progression (PP) and HPD caused by ICIs treatment. Therefore, based on the enhanced CT scan data of NSCLC treated with ICIs, PECIST1.1 was used to evaluate the treatment response, and the region of interest was manually drawn. Support vector machine (SVM) and logistic regression (LR) algorithm were used to construct the radiomics model. AUC and the model's efficacy was assessed using other indicators, and it may be utilized as a non-invasive marker to predict PP and HPD in patients with NSCLC.

The study by Wang et al. used TMB as one of the predictive biomarkers in immunology [8]. In this study, NSCLC patients with the same cancer imaging profile database (TCIA) were selected as the training set, and then recruited according to the same CT image standard to distinguish between

patients who underwent targeted next-generation sequencing (NGS) and patients who received immunotherapy. Using the three-dimensional reconstruction function, the segmented two-dimensional region of interest (ROI) was reconstructed into three-dimensional state and four morphological features were extracted. Subsequently, whole exome (WES) sequencing was performed. Every patient was split into two groups: the high TMB cohort and the low TMB cohort. Obtaining TMB is one of the clinically actionable biomarkers. On the basis that TMB is the immune response of ICI in NSCLC, Yang et al. developed a prediction model to differentiate between high and low TMB after using radiomics techniques to assess patients' TMB status [9]. Combined with clinical data, including smoking room and pathological type, and CT imaging data, it was found that the nomogram constructed by combining clinical features and radiomics score had the best diagnostic effect and good performance in distinguishing high TMB status from low TMB status.

3.2. To Explore Immune Checkpoint Markers Based on (-2- [18 F]-Fluoro-2-deoxy-D-glucose)18F-FDG PET/CT Model

Currently, ICIs are mostly used for cancer treatment, but the prediction of PD-L1 expression only has certain clinical significance for LC and head and neck cancer. While 18F-FDG-PET is useful in the treatment monitoring of a variety of cancers, there are few studies on anti-PD-1 or PD-L1 antibody treatment monitoring [10]. According to Kaira et al., PD-L1 expression is strongly linked to 18F-FDG uptake, and elevated PD-L1 expression under hypoxia can encourage immune escape of tumor cells. Additionally, using PD-L1 inhibitors can alter glucose metabolism and 18F-FDG uptake of tumor cells [10]. In NCSLS, pretreatment 18F-FDG uptake has prognostic significance. When assessing response, 18F-FDG-PET measures total lesion glycolysis (TLG) and metabolic tumor volume (MTV) better than the maximum SUV(SUVmax). These measurements can also indicate partial pathological response. Norikane et al. found that PD-L1 expression can optimize the treatment plan, and PD-L1 expression may be predicted by 18F-FDG PET [11]. In this trial, Tumor percentage score (TPS) was used to categorize individuals who had PD-L1 immunohistochemistry positivity and an 18F-FDG PET/CT scan prior to therapy. SUVmax and 31 texture features were evaluated with the LIFEx software package. Six texture features were found to be more potential than SUVmax in predicting PD-L1 expression. Therefore, 18F-FDG PET texture features are expected to be reliable non-invasive biomarkers for PD-L1 expression in NCSLS patients.

The main treatment strategies for NSCLC patients are tyrosine kinase inhibitors (TKIs) and ICIs, and the appropriate treatment can be selected through the dynamic changes of heterogeneous biomarkers. Targeted therapy represents the evaluation of epidermal growth factor receptor (EGFR) mutation status as a treatment option for selecting EGFK-TKI or ICI. Wei et al. developed a classification of EGFR mutation status based on 18F-FDG PET/CT [12]. In patients receiving EGFK-TKI treatment, EGFR-DLS was discovered to be substantially favorably connected with a longer PFS. Thus, the well-established EGFR-DLS model may be employed as a biomarker for the identification of individuals who are responsive to EGFR-TKI in an invasive manner.

3.3. To Explore Immune Checkpoint Markers Based on CT and PET/CT

In order to predict the response to PD-1/PD-L1 treatment in patients who benefited from ICIs and advanced NCSLS, Sako et al. used traditional CT and PET/CT scans prior to treatment to gather real-world data (RWD) of patients in order to develop and validate radiomics biomarkers based on deep learning models [13]. Biomarker generalitability was evaluated using prospective clinical trial data, CT response scores (CTRS) and enhanced CTRS (eCTRS) were generated through a multi-stage process, PFS and overall survival (OS) were used to assess biomarker performance, and six-fold cross-validation was used to train and test the model.

4. Evaluation of Immune Efficacy and Outcome

4.1. Evaluation Based on CT Radiomics

According to the research results of Vaidya et al. [6], the established radiological model was used as a biomarker. Unsupervised clustering analysis showed that HPs clustered in the clustering based on the texture pattern and vascular tortuosity features in intra - and peritumoral tissues. The results showed that intratumoral and peritumoral related texture features and vascular tortuosity features could distinguish HPD from other patients, and radiomics could predict poor OS in HPs patients. Li et al. also drew a similar conclusion that in the PP group, the LR model had the best performance, and the training and test sets' respective AUCs were 0.95 and 0.88, respectively, which could effectively distinguish PP from other response modes. With an AUC of 0.97 in the training set and 0.87 in the test set, the SVM model performed best in the HPD group and was better able to differentiate HPD from PD [7]. The CT radiomics model constructed in this study has a good performance in predicting PP and HPD, but both studies lack PD-L1 expression data, which leads to limitations.

Flatness, autocorrelation, and minimization were chosen as the main radiomics properties based on Wang et al.'s study findings, and the multi-distance logic method was used to create the TMB prediction model [8]. The AUC in validation set 1 was 0.775, indicating high TMB classification capacity, and the results indicated that immunotherapy was more likely to be beneficial for patients with low TMB. It is employed to forecast immunotherapy's effectiveness. The radiomics model validates TMB as a predictive biomarker, corrects the overfitting problem, has good predictive performance and discrimination ability, and serves as an invasive and feasible rapid tool for the evaluation of immunotherapy approaches.

Wen et al. believed that the method of detecting TMB, an important predictive biomarker, had certain limitations, so the clinicopathological and CT morphological variables were collected for immunohistochemical staining and next-generation sequencing test, the region of interest was divided on the image and features were extracted, and the LASSO algorithm and logistic regression were used to construct the prediction model [14]. It was found that TMB status was related to stage, differentiation degree and vacuole sign. The AUC of radiomics features in predicting TMB was 0.759, and the combination of clinicopathological and CT morphologic factors had a better prediction effect, with an AUC of 0.818.

To find out how the degree of PD-L1 expression affects the model's capacity for prediction, Wen et al. [14] also constructed another radiomics model using the same methodology. The degree of differentiation, tumor morphology, and positive PD-L1 expression was shown to be linked to vascular convergence signs. PD-L1 expression was associated with pretreatment CT quantitative radiomics characteristics, which might be very helpful in guiding immunotherapy for NSCLC patients. The AUC of radiomics features in predicting PD-L1 was 0.730, and the AUC of combined model prediction was 0.839.

4.2. Evaluation Based on 18F-FDG PET/CT

The tumor immune microenvironment (TIME) phenotype will influence the effectiveness of immunotherapy, and 18F-FDG PET/CT is more frequently employed in the clinical diagnosis of LC than traditional medical imaging techniques. In order to verify the temporal distribution of NSCLC predicted by this machine learning model, Tong et al. [15] employed 18F-FDG PET/CT to create radiomics and paired it with clinical characteristics. In order to determine if CD8 expression could accurately reflect the temporal profile of NCSLS patients, RNA-seq data from 1145 samples from the TCGA dataset was chosen after radiomics analysis was completed on patients from the DPH and TCIA datasets. Subsequently, in the DPH cohort, 221 individuals had PET/CT examinations. and injected with 18F-FDG. After segmentation and feature extraction, it was combined with clinical factors such as age and gender. Three radiological models—PET/CT, CT, and PET radiological

models—were created in order to assess the diagnostic effectiveness of using ROC curves to predict the TIME spectrum of NSCLC. Concurrently, clinical characteristics were incorporated to create the combined PET/CT clinical model (AUC=0.920 in testing and AUC=0.932 in training). Compared to the radiomics model, it performed better (AUC=0.907, Z=2.1363, P=0.0326). In order to determine the tumor immune state of NSCLC, this combined radiation-clinical model can be employed as a non-invasive clinical technique.

Furthermore, PET/CT can provide more accurate formation location and more detailed surrounding structure, which has broader development prospects and application space than PET and CT alone.

The expression status of PD-L1 in patients with NSCLC may also be predicted using the 18F-FDG-based PET/CT model in addition to the CT model. Zhao et al. [16] separated them into positive and negative groups after detecting PD-L1 expression using immunohistochemistry (IHC). Two features were employed to construct a radiomics model, and the model's AUC in the training and validation groups was greater than the clinical model's (0.638 and 0.640, respectively) at 0.706 and 0.761. The combined model's AUC in the training and validation cohorts was 0.718 and 0.769 respectively, and did not differ substantially from the radiomics model's. The prediction performance of the nomogram based on the joint model was good.

In addition, Chardin et al. collected 18F-FDG PET/CT images before treatment, measured parameters such as SUVmax, SUVpeak, MTV and TLG, and recorded clinical and biological characteristics of patients [17]. After 6 months of follow-up, the relationship between each parameter and OS and the predictive value of early treatment discontinuation (ETD) were analyzed. In the future, patients can be stratified based on MTV. It has been discovered that high baseline MTV is a significant independent predictor and prognostic factor for advanced NSCLC patients prior to immunotherapy, which can predict ETD and poor OS. It may also help determine single or combination treatment regimens in clinical practice.

CKI therapy is not appropriate for all patients with advanced NSCLC. Patients who had an 18F-FDG PET/CT scan before therapy were chosen by Ventura et al.They evaluated the efficacy by contrast-enhanced CT after treatment, segmented the tumor volume on PET images and created a prediction model using logistic regression after transferring it to CT scans [18]. The two PET radiomics features of "PET-skewness" and "PET-median" had predictive value, and the AUC of "PET-skewness" was 0.69 when predicting treatment response. For predicting overall progression, the AUC for "PET-Median" was 0.75. Therefore, radiomics based on 18F-FDG PET/CT may provide predictive parameters for first-line treatment of CKI in advanced patients.

4.3. Joint Evaluation Based on CT and PET/CT

Sako et al. found that in the RWD test dataset B, CTRS could identify patients who might benefit from ICI treatment in the first-line ICI monotherapy cohort, with HR of PFS of 0.46 and HR of OS of 0.50. In clinical trial dataset C, the OS HR of CTRS was 0.33, but PFS did not reach statistical significance. eCTRS performed better in some cohorts, and both of them were superior to traditional imaging markers in predicting PFS and OS. Therefore, biomarkers established by this experiment can be used to evaluate ICIs response [13].

4.4. Evaluation of Immune Checkpoint Inhibitor Pneumonitis

ICIs can regulate the body's immune function, and immunotherapy is also widely used in clinical practice, but it can cause ICIP, which is a continuous immune-related additional event (irAE). ICIP has an incidence rate of up to 5%-19% in NSCLC patients, which may cause death of patients [19]. PD-1 and PD-L1 inhibitors can significantly prolong the survival of patients with advanced NSCLC, and are related to the high expression of tumor PD-L1 protein. PD-L1 expression is a commonly used biomarker to predict the efficacy, but it has limitations, and TMB can also be used as a potential indicator [20]. Ground-glass opacity is the most common imaging feature of pneumonia, which should be differentiated from ICI pneumonia [20]. Yang et al. [19] pointed out that radiomics can

also be used for feature extraction, prediction, diagnosis and prognostic analysis of ICIP. By screening the radiomics features of ICIP, traditional radiomics needs manual extraction, while deep learning radiomics uses deep neural network architecture (CNN) model and translator to enable ICIP differential and early diagnosis by transforming the verbal domain into the visual environment.

In order to predict treatment outcome and irAEs, relevant biomarkers are also needed, and Peng et al. calculated NLR and PNI by collecting clinical characteristics and baseline peripheral blood data of patients [21]. Drug efficacy was evaluated according to RECIST 1.1, and irAEs were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). PFS and OS were calculated using the Kaplan-Meier technique, the variables influencing PFS and OS were examined using the Cox regression model, and the relationship between peripheral blood indicators and irAEs was examined using the logistic regression model. The prognosis of patients with advanced NSCLC treated with PD-L1 inhibitors and irAEs may be linked to the identification and validation of relevant peripheral blood indicators (e.g., NLR, LDH, and PNI). This information helps guide clinical research on LC immunotherapy.

5. Conclusion

Radiomics, as a noninvasive, time-saving and dynamic observation method, can obtain intratumoral and peritumoral biological information in NSCLC, which has great potential in clinical development. In this review, CT-based radiomics model, 18F-FDG PET/CT and the combination of the two can be used as a suitable biomarker such as EGFR-DLS deep learning model or radiomics to select an appropriate biomarker such as TMB, which can predict the TIME spectrum and PD-L1 expression status, and effectively evaluate the PFS of the disease. HPD and OS were also used to predict the prognosis of ICIP. However, the number of literature in this study is small, and it only involves NSCLC cases, which has certain limitations. Since the research is affected by tumor heterogeneity and a variety of clinical factors, there is still a lack of more accurate and widely applicable models. In the future, the scope of research needs to be expanded, it is necessary to raise the standard of research, and a composite model can be constructed by combining with artificial intelligence. To achieve the clinical personalized treatment needs.

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