R E V I E W

Advances in Multimodal Imaging Techniques for Evaluating and Predicting the Efficacy of Immunotherapy for NSCLC

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Abstract: Immunotherapy has emerged as a transformative treatment for non-small cell lung cancer (NSCLC), yet its clinical benefits remain variable among patients. Early and accurate evaluation of treatment response is critical to guide therapeutic adjustments and improve outcomes. This review synthesizes recent advancements in multimodal imaging techniques—computed tomography (CT), positron emission tomography (PET)/CT, magnetic resonance imaging (MRI), and radiomics—for evaluating and predicting immunotherapy efficacy in NSCLC. We analyze the strengths and limitations of conventional morphological criteria (eg, RECIST, iRECIST) and highlight emerging quantitative biomarkers, including CT texture analysis, metabolic parameters (MTV, TLG), and diffusion-weighted MRI metrics. Notably, radiomics demonstrates promise in decoding tumor heterogeneity, PD-L1 expression, and immune microenvironment features, while immuno-PET probes targeting immune checkpoints offer novel insights into immune activity in vivo. Challenges such as pseudo-progression, nodal immune flare, and discrepancies between imaging responses and pathological responses are critically discussed. By integrating morphological, metabolic, and microenvironmental data, multimodal imaging enhances precision in patient stratification and therapeutic monitoring. Future research should prioritize multicenter, AI-driven radiomics validation and targeted tracer development to optimize NSCLC immunotherapy management. This review provides clinicians and researchers with new directions for utilizing multimodal imaging techniques in developing personalized treatment strategies.

Keywords: non-small cell lung cancer, immunotherapy, efficacy prediction, CT, PET, MRI

Introduction

Lung cancer is one of the most common malignancies in the world. According to the American Cancer Society, approximately 234,580 new lung cancer cases (116,310 in men and 118,270 in women) and 125,070 lung cancer-related deaths (65,790 in men and 59,280 in women) were reported in 2024.[1] Lung cancer is broadly classified into two major histological subtypes: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). SCLC, accounting for approximately 10–15% of cases, is characterized by rapid progression, early metastasis, and a strong association with smoking; in contrast, NSCLC constitutes 80–85% of all lung cancer diagnoses and encompasses distinct histological subtypes, including adenocarcinoma (the most prevalent subtype, arising from peripheral lung glands), squamous cell carcinoma (originating in central bronchial epithelial cells), and large cell carcinoma (a less common, poorly differentiated variant).[2,3] The clinical and molecular heterogeneity of NSCLC highlights the critical need for advanced multimodal imaging techniques to evaluate and predict immunotherapy efficacy, address its biological diversity, and improve patient stratification. Surgery remains the primary and most effective treatment for primary lung tumors, while chemotherapy, radiation therapy, immunotherapy, targeted therapy, or their combination are often used for advanced-

stage cancer.[4,5] Over recent years, the treatment of lung cancer has evolved profoundly owing to the advent of immune checkpoint inhibitors, including antibodies targeting programmed cell death protein 1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4).[6–11] For instance, in PD-L1-positive (tumor proportion score (TPS)≥50%) advanced NSCLC, pembrolizumab monotherapy achieved a 31.9% 5-year overall survival (OS) rate, compared to 5% with chemotherapy; similarly, nivolumab demonstrated a 14% 4-year OS rate in previously treated NSCLC patients.[12,13] Immunotherapy can block or inhibit ligand-receptor interactions,[14,15] thereby overcoming T-cell exhaustion, enhancing immune activity, and exerting anti-tumor effects.[16] However, the efficacy of immunotherapy varies from patient to patient.[17] For example, a US study has discovered that the difference between people who do and do not respond to immunotherapy may have to do with an immune cell known as CD5$^+$ dendritic cells (DCs).[18] CD5$^+$ DCs, a subset of conventional DCs, play a critical role in enhancing T-cell priming and effector function. Specifically, CD5$^+$ DCs promote the activation of CD5^{lo}CD4$^+$ helper T cells and neoantigen-specific CD8$^+$ cytotoxic T cells, which are essential for anti-tumor immunity. Their density in tumor-draining lymph nodes correlates with improved survival outcomes in NSCLC patients. In addition to CD5$^+$ DCs, multiple factors contribute to the variability in immunotherapy response in NSCLC patients, including tumor microenvironment components such as PD-L1 expression (high PD-L1 expression is associated with improved response to PD-1/PD-L1 inhibitors),[19] tumor-infiltrating lympho-cytes (high densities of CD8$^+$ T cells correlate with better outcomes),[20] and tumor mutational burden (TMB) (higher TMB predicts improved response to immunotherapy);[21] host factors such as gut microbiome (specific gut bacteria modulate systemic immunity via the gut-lung axis)[22] and inflammatory status (elevated systemic inflammation is linked to poor response and increased toxicity).[23] These factors collectively underscore the complexity of immunotherapy response and emphasize the need for multimodal tools to predict patient outcomes. Therefore, early evaluation and prediction of immunotherapy efficacy in NSCLC patients is crucial.

Imaging examinations remain an important method for diagnosis, efficacy evaluation, and prediction of lung cancer.[24] Traditional imaging is based on morphological structures for diagnosing and evaluating diseases. However, with the advent of the era of precision medicine and individualized therapy, functional imaging has been developing rapidly; it offers the possibility to detect microscopic alterations earlier than morphological changes of tumors,[25] thereby facilitating early identification of treatment response, enabling timely therapeutic strategy adjustments, and contributing to the optimization of clinical decision-making in NSCLC immunotherapy. Such clinical detection through imaging techniques enhances the accuracy of tumor biological assessment and supports personalized interventions that may influence patient outcomes by addressing therapeutic efficacy at a critical stage prior to overt morphological changes.[26] In this study, we discuss multimodal imaging techniques (CT, PET/CT, MRI) and radiomics (a method that extracts a large number of features from medical images using data-characterization algorithms) in evaluating and predicting the efficacy of immunotherapy in NSCLC patients. The advantages and shortcomings of various techniques and indicators mentioned above are also noted. We also discuss new directions for future research, which may provide new ideas for the selection of imaging methods for clinical evaluation and prediction of the efficacy of immunotherapy in NSCLC patients. The multimodal imaging techniques and indicators mentioned in this study are summarized in Figure 1.

Imaging Techniques to Evaluate the Efficacy of Immunotherapy in NSCLC Patients

Computed Tomography (CT)

CT is one of the most commonly used methods for examining lung tumors. A CT scan of the chest is the cornerstone of lung cancer imaging, based on which further management is decided. It possesses high density and spatial resolution and has a good observation effect on the morphology and size of lesions. NSCLC can be centrally located masses, invading the peripherally situated lesions or mediastinal structures that invade the chest wall.[27]

Conventional NSCLC treatments, such as radiotherapy and chemotherapy, mainly rely on cytotoxic drugs used to induce apoptosis or directly kill tumor cells, and their efficacy is mainly reflected in the tumor size change.[27] The Response Evaluation Criteria in Solid Tumors (RECIST)[28] and RECIST 1.1 published in the European Journal of Cancer[29] use the change in tumor size before and after treatment as the tumor burden to evaluate the efficacy of treatment. The schematic
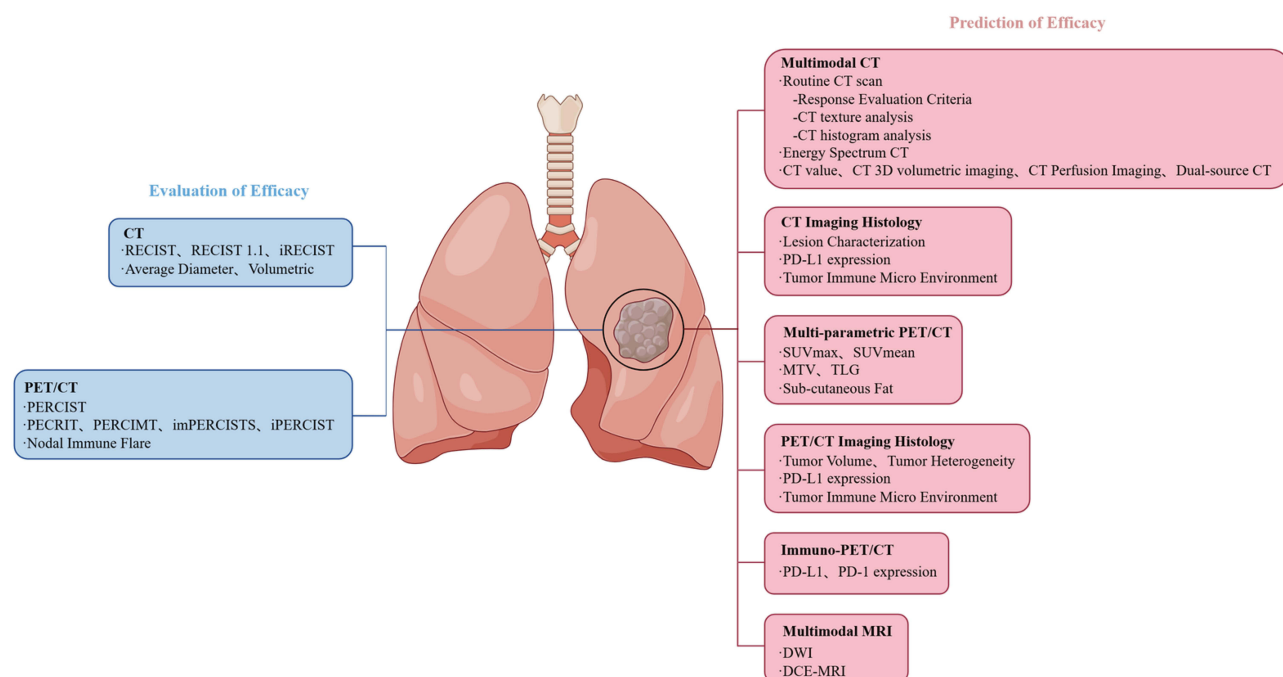
Figure 1 Multimodal imaging technology approach for evaluation and prediction of NSCLC immunotherapy efficacy. Source: Original illustrations created using Figdraw.com (License ID. YllSlefef2).

diagram of non-contrast CT based on the RECIST 1.1 standard for immunotherapy efficacy evaluation is shown in Figure 2. Measurable lesions are defined as lesions not on the non-measurable list below and having the longest diameter of ≥10 mm on spiral CT with 5 mm reconstructed section thickness in the axial plane (not the sagittal or coronal planes in CT
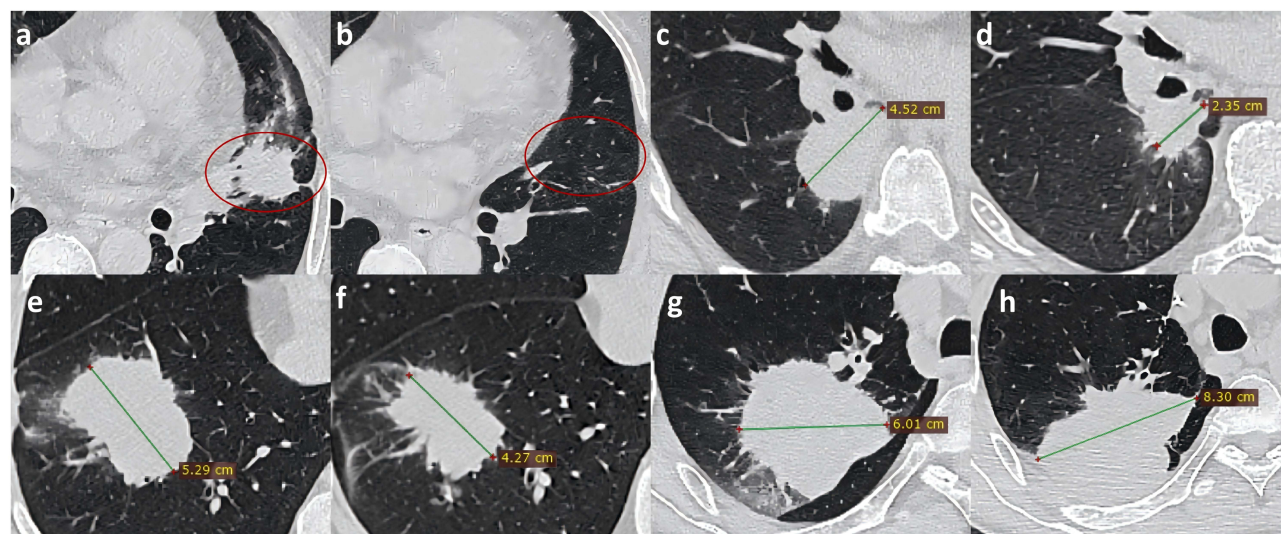
Figure 2 Schematic diagram of non-contrast CT based on the RECIST 1.1 standard for immunotherapy efficacy evaluation. (**a**) showed a mass in the upper lobe of the left lung (red circle), which was pathologically diagnosed as squamous cell carcinoma. Subsequently, the patient received two cycles of immunotherapy, and preoperative CT (**b**) showed disappearance of the tumor lesion (red circle), which was evaluated to achieve CR. (**c**) showed a mass in the lower lobe of the right lung, which was pathologically diagnosed as adenocarcinoma. Subsequently, the patient received two cycles of immunotherapy, and preoperative CT (**d**) showed a significantly reduced lesion, which was evaluated to achieve PR. (**e**) showed a mass in the lower lobe of the right lung, which was pathologically diagnosed as squamous cell carcinoma. Subsequently, the patient received three cycles of immunotherapy, and preoperative CT (**f**) showed a slightly reduced lesion, which was evaluated to achieve SD. (**g**) showed a mass in the upper lobe of the right lung, which was pathologically diagnosed as squamous cell carcinoma. Subsequently, the patient received two cycles of immunotherapy, and preoperative CT (**h**) showed an enlarged tumor, which was evaluated to achieve PD. All imaging cases were entirely original and approved by the institutional review board, with the ethical approval number sjtky11-1x-2022(35).

imaging).[28] The detailed classification and definition of the assessment criteria are summarized in Table 1. However, imaging findings of tumors treated with immunotherapy are distinct from those treated with conventional systemic therapy, and various rule sets have been published. Eg, some immunotherapy patients present with specific response patterns, such as pseudo-progression, dissociated response and hyper-progression of the disease, pseudo-progression is defined as a temporary increase in tumor size followed by shrinkage, mostly due to immune cell infiltration or therapy-related necrosis and edema; dissociated response is defined as concurrent growth and regression of different lesions; hyper-progression is defined as the acceleration growth of tumor after immunotherapy.[26,30] The schematic diagram of special response patterns after immunotherapy for NSCLC is shown in Figure 3. In the CheckMate-159 trial (NCT02259621), a pilot study evaluating neoadjuvant nivolumab in 21 patients with resectable stage I, II, or IIIA NSCLC, 20 patients underwent complete tumor resection. Among these, 9 patients (45%) achieved major pathological response (MPR), defined as ≤10% residual viable tumor cells in the resected specimen. Notably, while the objective response rate assessed by RECIST criteria was only 10%, this discrepancy highlights that MPR—a histopathological endpoint indicative of profound tumor regression—may capture the effects of immunotherapy not fully detectable by imaging alone.[31] Although the small sample size (n=21) limits the generalizability of these findings, they underscore the potential value of integrating pathological assessments with imaging-based criteria to comprehensively evaluate treatment responses in early-stage NSCLC. More evidence indicates that some patients with MPR cannot achieve objective remission by RECIST criteria alone, as pathological regression and radiographic response may exhibit substantial discrepancies due to tumor hetero-geneity and immune-related inflammatory changes.[32] Moreover, Luo et al pointed out that progression-free survival (PFS) varies greatly within the stable disease (SD) range, showing heterogeneity among SD subgroups; the RECIST criteria define "SD" as more responsive to the rate of tumor proliferation than to the tumor response to immunotherapy and patients with PFS > 6 months and no tumor growth as "SD responders".[33] This conclusion further supports the inconsistencies in the evaluation of imaging efficacy and prognosis of immunotherapy patients. The possible reasons are necrosis, inflammatory infiltration, mesenchymal formation, and fibrosis, which appear after traditional NSCLC treatment is applied.[34] After immunotherapy, some NSCLC lesions also show special pathological signs such as cholesterol cleft, a large number of lymphocytes aggregation and tertiary lymphoid structure based on the above pathological changes,[35] which makes diagnosis challenging. Thus, in early 2017, the Immune Response Evaluation Criteria in Solid Tumors (iRECIST) has been proposed.[36] This criteria introduced two new concepts—unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD)—which provisionally assesses the RECIST 1.1 criteria for progressive disease (PD) as iUPD

Table 1 Morphology and Metabolic Response Evaluation Criteria

	RECIST	RECIST 1.1	iRECIST	PERCIST
Imaging modalities	CT	CT	CT	FDG PET
Complete response (CR)	Disappearance of all lesions	Same as RECIST	Same as RECIST 1.1	Disappearance of all lesions or indistinguishable from the surrounding blood pool background in all lesions.
Partial response (PR)	≥30% decrease from baseline	Same as RECIST	Same as RECIST 1.1	≥30% decrease in SULpeak in the target lesion and ≥ 0.8 SUL
Stable disease (SD)	Neither PR nor PD	Same as RECIST	Same as RECIST 1.1	Neither PR nor PD
Progressive disease (PD)	≥20% increase in the sum of longest diameters	≥20% increase in the sum of longest diameters with an absolute increase of ≥5 mm	iUPD: Same as RECIST 1.1 iCPD: Re-evaluation in 4–6 weeks	≥30% increase in SULpeak in the target lesion and ≥ 0.8 SUL, or visible increase in extent of tumor uptake.
New lesions	PD	PD	iUPD	PD

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; iUPD, unconfirmed progressive disease; iCPD, confirmed progressive disease; SUL, standardized uptake value adjusted for lean body mass; RECIST, Response Evaluation Criteria in Solid Tumor; iRECIST, immune RECIST; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors.
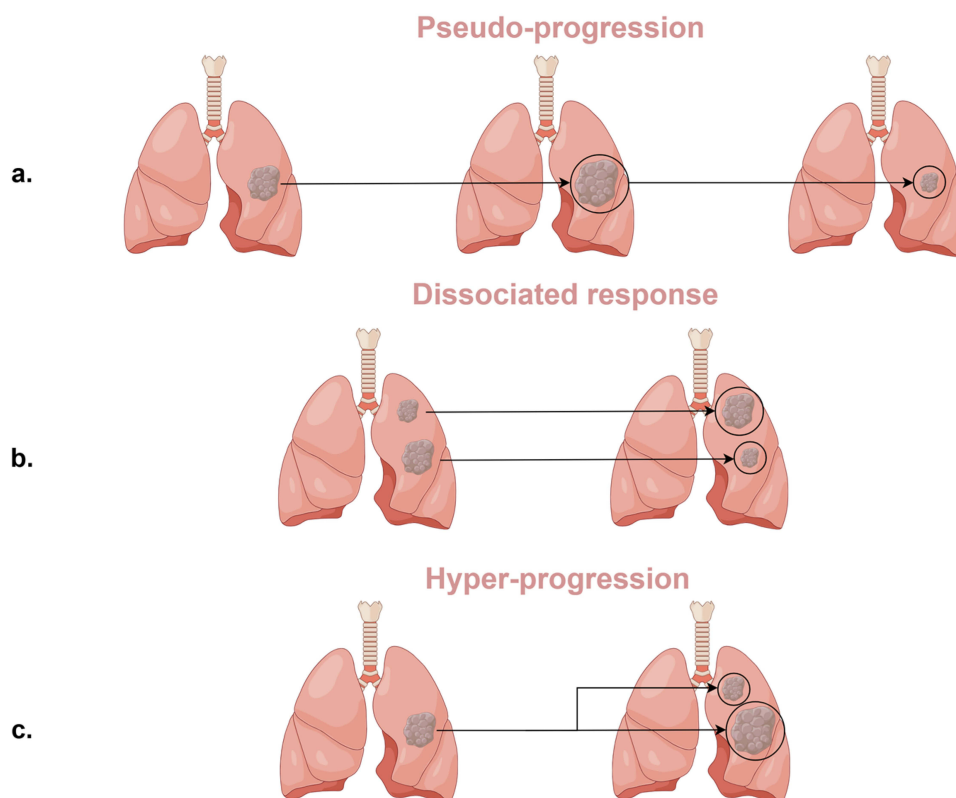
Figure 3 Schematic diagram of special response patterns after immunotherapy for NSCLC. (**a**) Pseudo-progression: initial increase in tumor size followed by shrinkage. (**b**) dissociated response: some tumors shrink while others grow during immunotherapy. (**c**) hyper–progression: rapid and significant tumor growth and metastasis. Source: Original illustrations created using Figdraw.com (License ID. TWTTYc24cb).

and require re-evaluation after 4–6 weeks to confirm iCPD. If the tumor evaluated as iUPD does not change during subsequent treatment, it is redefined as iUPD at the next evaluation. Although this criterion defines the delayed effect of tumor immunotherapy, it evaluates the efficacy by measuring the diameter of the tumor lesion before and after treatment; however, it cannot predict the degree of tumor response to immunotherapy. The detailed classification and definition of the assessment criteria are summarized in Table 1.

Currently, most of the efficacy evaluation criteria use a single long diameter of the largest cross-section to measure the change in tumor size, often ignoring the asymmetry of some tumor changes. The 2017 Fleischner Society guidelines recommend measuring pulmonary nodule size using the average of the long and short axes of the largest cross-section, as outlined in their management criteria for incidentally detected solid and subsolid nodules.[37] In addition, gross tumor volume (GTV) is more representative of changes in tumor size on a three-dimensional level, but its measurement method is more complex than tumor diameter measurement. In the future, it may be possible to provide a more accurate description of lesion size based on mean tumor diameter or GTV and thus evaluate the efficacy of the treatment.

Positron Emission Tomography (PET/CT)

PET/CT plays a dual pivotal role in the management of NSCLC. First, as a standard imaging modality for clinical staging (recommended by guidelines such as National Comprehensive Cancer Network), PET/CT integrates ^{18}F-FDG metabolic activity with anatomical CT features to accurately delineate primary tumors, lymph node metastases, and distant metastases, thereby critically guiding therapeutic strategies.[38,39] Second, its quantitative metabolic parameters (eg, maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG)) reflect tumor microenvironment heterogeneity and serve as key biomarkers for predicting immunotherapy responses.[40] Thus, PET/CT not only serves as a cornerstone for staging and response assessment but also provides a potential tool for tailoring individualized immunotherapy regimens. In 1999, the European Organization for Research and Treatment of Cancer (EORTC) introduced the first criteria

for tumor assessment based on ^{18}F-FDG PET/CT.[41] A few years later, the EORTC criteria were replaced by the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) criteria[42] for evaluating the efficacy of solid tumors using ^{18}F-FDG tracer (as shown in Table 1). In the following years, a number of PET/CT evaluation criteria for evaluating tumor response to immunotherapy have been proposed, including PECRIT criteria, PERCIMT criteria, imPERCISTS criteria, and iPERCIST criteria;[43–46] however, a majority of studies have focused on evaluating patients with melanoma, and there is limited research data on the application of these criteria in patients with NSCLC. Also, Cascone's analysis of the NEOSTAR trial identified a "nodal immune flare" (NIF) phenomenon,[47] where 16% (7/44) of NSCLC patients treated with neoadjuvant immunotherapy demonstrate radiologically abnormal nodes post-therapy that upon pathological evaluation are devoid of cancer and demonstrate de novo non-caseating granulomas, this phenomenon was not observed in patients after neoadjuvant chemotherapy (0% (0/28)); NIF is characterized by abnormally enlarged lymph nodes on imaging and high ^{18}F-FDG uptake on PET/CT. However, no significant changes in tumor size (p=0.089) and SUVmax (p=0.142) values were found between NIF and No-NIF patients after neoadjuvant immunotherapy, making it impossible to differentiate NIF from actual disease progression on imaging. Therefore, this phenomenon may be misinterpreted as tumor progression, and further examination should be performed if abnormal lymph nodes suspected of disease progression are detected after treatment. NIF should be differentiated from tumor infiltration in conjunction with pathology.

Imaging Techniques to Predict the Efficacy of Immunotherapy in NSCLC Patients

Multimodal CT Examination

Routine CT Scan

Conventional CT scans are used to predict the prognosis of immunotherapy by measuring the diameter of tumor lesions based on RECIST and its derived criteria. Tazdait et al[48] compared the predictive value of the RECIST 1.1, irRECIST,[49] and iRECIST criteria for evaluating the efficacy of immunotherapy in patients with NSCLC. Based on survival analyses, the authors concluded that RECIST 1.1 criteria underestimated the benefit of PD-1 or PD-L1 inhibitors in approximately 11% of the evaluated population, suggesting that the irRECIST and iRECIST criteria are more accurate compared to RECIST 1.1 criteria.[48]

Prior studies have demonstrated that CT texture analysis (CTTA) can differentiate genetic mutations and tumor grades in certain tumors, including lung cancer.[50] CTTA can quantify the pixel values inside the lesion, obtain the distribution characteristics and patterns of the pixel values, and provide microscopic information that is not easily accessible to the naked eye, thus evaluating the intra-tumor heterogeneity. A retrospective study of 54 NSCLC patients demonstrated CTTA as a new independent predictor of survival.[51] Cox analysis showed coarse-texture CTTA (filter=2.5) was the strongest survival predictor (OR=56.4, 95% CI=4.79–665, P=0.001), surpassing PET stage (OR=3.85, P=0.002) and SUVmax (P=0.076). Patients with low CTTA uniformity (≤0.624) had 100% 30-month mortality versus 53% survival in high-uniformity group (P<0.0014), highlighting CTTA's potential for enhancing NSCLC risk stratification. Shen et al[52] extracted texture features of pre-immunotherapy enhanced CT images of NSCLC patients, including histogram, absolute gradient, tour matrix, grayscale covariance matrix, autoregressive model, and wavelet transform, and analyzed each texture feature. The results showed that the pre-immunotherapy enhanced CTTA could predict the efficacy of immunotherapy for NSCLC with a sensitivity and specificity of 88.2% and 76.3% (AUC = 0.812; 95% CI: 0.706–0.919).[52] In addition, a Zerunian study proposed that the mean value of positive pixels, a CTTA parameter, was significantly associated with lower OS and PFS (P < 0.0035), which could be used as a predictive imaging biomarker for OS and PFS in patients with NSCLC treated with first line immunotherapy.[53] CT histogram analysis (CTHA) consists of algorithms for extracting numerical parameters from diagnostic images and analyzing the distribution of CT values within regions of interest. In a multicenter retrospective study of 104 platinum-refractory NSCLC patients treated with nivolumab (median age: 67 years; 66.4% male; 72.1% non-squamous histology), Ravanelli et al demonstrated that CTHA using spatial scale filters (SSF) could stratify survival outcomes. Coarse-texture kurtosis at SSF=4 mm inversely correlated with OS (adjusted HR=0.476, 95% CI: 0.29–0.77; P=0.0028), while kurtosis at SSF=6 mm predicted shorter PFS (HR=0.556, 95% CI: 0.36–0.86; P=0.0088). These findings underscore the prognostic value of baseline CTHA in identifying high-risk subgroups among immunotherapy-treated NSCLC patients.[54]

Energy Spectrum CT

The energy spectrum CT technique includes single-energy imaging, material separation, and effective atomic number, which can acquire a wide range of parameters that provide value in lesion efficacy assessment. In a prospective single-arm Phase II trial (NCT04326153) involving 20 patients with potentially resectable stage IIIA/IIIB NSCLC (90% squamous carcinoma), Sun et al conducted a comparative analysis of single-source dual-energy CT (ssDECT) and postoperative pathology. Among patients achieving pathological complete response (pCR) after neoadjuvant chemoim-munotherapy (8/20, 40%), ssDECT demonstrated reductions in average iodine values (ΔAP=−3.17%; ΔAP=−6.61%) and normalized iodine concentration (ΔAP=−6.09%; ΔAP=−20.25%) compared to baseline. Notably, ssDECT accurately differentiated residual necrotic/reparative tissue from viable tumor in pCR patients, outperforming conventional CT, which misclassified 62.5% (5/8) of pCR cases as stable disease. This highlights ssDECT' s potential for resolving discrepancies between imaging and pathological responses in immunotherapy-treated NSCLC.[55]

Possible Future Directions

The CT value can quantitatively measure the absorption rate of X-rays by different tissues. Necrosis, fibrosis, and special pathological signs, which often appear in tumor lesions after treatment, lead to corresponding changes in the CT values of the lesions.[56] CT three-dimensional volumetric imaging can identify the tumor lesion and the surrounding adjacent tissues, thus providing a more intuitive description of the morphology and structure of the tumor lesion. Also, three-dimensional volume measurement is more accurate than the RECIST standard measurement.[57,58] Moreover, CT perfusion imaging provides information about the blood supply inside the tumor and has some predictive value for the outcome of NSCLC patients after treatment.[58] Dual-source CT demonstrates high sensitivity in detecting intratumoral hemorrhage, as evidenced by its ability to identify hemorrhagic response in 14% (4/29) of solid and lymph node target lesions in NSCLC patients undergoing anti-angiogenic therapy. By utilizing virtual non-enhanced images and iodine-enhanced material decomposition, this modality accurately differentiates post-treatment lesion enlargement caused by hemorrhage (eg, attenuation >50 hU on virtual nonenhanced images) from true tumor progression, thereby providing reliable net tumor enhancement measurements without additional radiation exposure.[59]

In conclusion, all of the above multiple CT imaging tests have different values in predicting the efficacy of NSCLC immunotherapy. However, these methods are still in the exploratory stage, and detailed research data and in-depth research are required.

CT Radiomics

Radiomics is a rapidly evolving field of research concerned with extracting quantitative metrics, ie, advanced quantitative imaging features with high throughput from CT, PET or MRI images.[60] Its key advantage is that it can capture microscopic tumor features typically unobservable to the naked eye. Radiomics data can be used to construct models that correlate image features with clinical and biological endpoints, thereby characterizing or predicting the onset, progression, and clinical outcome of disease from the three-dimensional level of the lesion.[61]

CT Radiomics Based on Lesion Characterization

Trebeschi et al performed radiomics-based characterization of each lesion on preprocessed contrast-enhanced CT imaging data and developed and validated a non-invasive machine-learning capable of distinguishing between immu-notherapy response and non-response biomarkers.[62] Their data suggest that radiomics characterization of lesions can serve as a noninvasive biomarker of response to immunotherapy, which was significant in predicting the efficacy of immunotherapy for NSCLC (AUC=0.83, p<0.001), and may show utility in improving patient stratification in neoadju-vant and palliative settings.

CT Radiomics Based on PD-L1 Expression

Tumor cell expression of PD-L1 is approved as a diagnostic biomarker for immunotherapy in NSCLC patients. Tian et al developed a CT-based deep learning model to predict PD-L1 expression (cutoff ≥50%) in NSCLC patients, stratifying patients into high PD-L1 expression signature (PD-L1ES) score and low PD-L1ES score groups. The low PD-L1ES score group demonstrated significantly improved PFS (median PFS: 363 days, 95% CI: 363~) compared to the high PD-L1ES

score group (median PFS: 183 days, 95% CI: 122~257), with a hazard ratio (HR) of 2.57 (95% CI: 1.22~5.44; P = 0.010).[63] Furthermore, integrating this model with clinical variables (age, sex, smoking history, and family history) enhanced prognostic stratification capabilities (combined model HR: 3.53, 95% CI: 1.86~6.72; P < 0.001).

CT Radiomics Based on Tumor Immune Micro Environment Phenotypes

Immune cells in the tumor immune microenvironment (TIME) have an important role in tumor resistance.[64] Studies have shown that CD8^{+} T cell infiltration within tumors correlates with the efficacy and survival of immunotherapy.[65] TIME can be classified into three immune phenotypes: immune-inflamed, immune-excluded, and immune-desert.[66] The immunoinflammatory phenotype has a considerable CD8 cell infiltration and often responds to immunotherapy,[67] which is opposite to the characteristics seen in the immune-desert tumor (less CD8 cell infiltration); in the latter case, transforming growth factor-β, activation of myeloid-derived suppressor cells, and angiogenesis prevent T-cell infiltration within the tumor.[68] Thus, the TIME phenotype may influence the efficacy of immunotherapy. Sun et al developed and validated a biomarker for tumor-infiltrating CD8 cells based on enhanced CT radiomics. This new radiomics profile was able to classify tumors with high and low CD8 infiltration abundance (AUC=0.74), predict gene expression of CD8 cells (AUC=0.67), and classify the tumor immunophenotype (AUC=0.76); the median survival of patients with a high radiomics score (24.3 months) was significantly greater than that of patients with a null predictor (11.5 months) at 6 months post-immunotherapy (P=0.0081, HR=0.58).[69]

Multi-Parametric PET/CT

Routine PET/CT Parameters

PET/CT parameters include SUVmax, mean standardized uptake value (SUVmean), MTV, and TLG. MTV and TLG are more often used to predict efficacy.[70] Monaco et al[71] analyzed 92 patients with NSCLC treated with nivolumab, pembrolizumab, or atezolizumab and showed that the median MTV was significantly lower in those who achieved disease control (complete response (CR), partial response (PR), SD) than in those who did not achieve disease control (PD)(77 vs.160.2, P=0.039). Also, patients with MTV and TLG values below median values had longer OS (P=0.03 and 0.05).[71] Moreover, Bauckneht et al analyzed 45 patients with imaging evaluations of PD during treatment with nivolumab. They found that MTV was an independent predictor of OS (HR=1.001; 95% CI: 1.001–1.002) and could identify patients responding well to immunotherapy.[72] In addition, a retrospective study analyzing 57 patients with NSCLC undergoing immunotherapy found that MTV (P=0.028) and TLG (P=0.035) were significantly associated with disease progression, whereas SUVmax was not significantly correlated with disease progression and prognosis.[73] In addition, Ling et al systematically evaluated 13 related studies and found that baseline MTV may be highly predictive of survival while baseline TLG only predicts OS in a small proportion of patients; they also concluded that baseline SUVmax and SUVmean are unsuitable for use as prognostic indicators for patients with advanced or metastatic NSCLC who receive immunotherapy.[74] This phenomenon may be related to the activation of the TIME. Immunotherapy induces an increase in the in-flow and activity of immune cells, such as T-lymphocytes, in the TIME, which, in turn, increases the uptake of ^{18}F-FDG by the lesion; this condition masks the actual therapeutic response and may even lead to the generation of false-positive results.[75–77] Therefore, although SUVmax and SUVmean are commonly used semi-quantitative parameters for PET/CT, whether they can be used as predictors of prognosis in patients undergoing immunotherapy remains controversial.

Special PET/CT Parameters

In addition to the above commonly used PET/CT parameters, Popinat et al analyzed lean body mass, fat body mass, muscle body mass, visceral fat mass and sub-cutaneous fat (SCFM) parameters and discovered that patients with low SCFM (<5.69 kg/m^2) had a poorer prognosis (P=0.04). Also, SCFM resulted as an important prognostic factor in stage IV NSCLC treated with nivolumab.[78]

PET/CT Radiomics
PET/CT Radiomics Based on Lesion Characterization

PET/CT imaging is still in a rapid development stage. Polverari et al evaluated the value of imaging radiomics based on baseline ^{18}F-FDG PET/CT images of primary foci in predicting the efficacy of immunotherapy, where patients with high tumor volume (P=0.035), high TLG values (P=0.037) and heterogeneity expressed by "skewness" (P=0.032) and "kurtosis" (P=0.046) had a higher probability of poor immunotherapy outcome. Volume and heterogeneity were considered to be associated with disease progression.[73]

PET/CT Radiomics Based on PD-L1 Expression

PET/CT imaging histologic features have some value in predicting PD-L1 expression status.[79] Valentinuzzi et al analyzed immunotherapy [18F] FDG PET radiomics signature (iRADIOMICS) and compared them with the PD-L1 TPS and iRECIST criteria in predicting prognosis, finding that iRADIOMICS (AUC=0.90; 95% CI: 0.78–1.00) had better predictive power than the PD-L1 TPS (AUC=0.60; 95% CI: 0.37–0.83) and iRECIST criteria (month 4) (AUC=0.86; 95% CI: 0.72–1.00).[80]

PET/CT Radiomics Based on Tumor Immune Micro Environmental Profiles

Tong et al used a machine learning model based on PET/CT radiomics and clinical features to predict the TIME profiles of NSCLC and found that CD8 cell expression could represent the temporal profile of NSCLC. Also, combined PET/CT imaging histology-clinical model (AUC = 0.932) was superior to the PET/CT imaging histology model (AUC = 0.907, P = 0.0326) and the clinical model (AUC = 0.868, P = 0.0036) in predicting higher immune scores and more immune-activated pathways in the high CD8 cell group than in the low CD8 cell group (P = 0.0421).[81] Thus, the authors suggested that a combined ^{18}F-FDG PET/CT radiomics-clinical model could be a clinical noninvasive method for detecting the immune status of NSCLC tumors and predicting the efficacy of immunotherapy.

Immuno-PET Imaging

In recent years, immuno-PET/CT imaging has developed rapidly. Today, novel radiopharmaceuticals can identify specific immune system targets and are under investigation in pre-clinical and clinical settings. For example, several radiolabeled ^{18}F, [89]Zr, and ^{64}Cu have been tested against the expression of tumor-infiltrating lymphocytes at the PD-1/PD-L1 checkpoints and the aggregation of CD8$^+$ T cells.[82–84] Niemeijer et al used the ^{18}F-BMS-986192 and [89]Zr-nivolumab tracers for the first time in humans and demonstrated the feasibility of non-invasive quantitative analysis of PD-L1 and PD-1 with both tracers.[85] Moreover, Smit et al used [89]Zr-durvalumab to detect PD-L1 in 13 patients. The tracer detected a higher number of tumor foci; also, tumor uptake of the tracer was higher in patients with treatment response or stable disease than in patients with disease progression, but the difference was not statistically significant (median SUVpeak, 4.9 vs 2.4; P=0.06)).[86] The reason for this may be the small sample size, which needs to be expanded for more in-depth studies in the future.

Liu et al evaluated the feasibility of the PET tracer [^{68}Ga] Ga-NOTA-Nb 109 for PD-L1 immuno-PET imaging in patient-derived xenografts (PDX) (nude mice) with lung adenocarcinoma and squamous cell carcinoma, showing that [^{68}Ga] Ga-NOTA-Nb 109 could accurately and sensitively assess PD-L1 expression in NSCLC PDX models.[87] New molecular probe binding sites, such as tracers targeting binding to granzyme B and tumor-associated macrophages have been demonstrated to have a good ability to assess the early response to immunotherapy in mouse cancer models.[88–90] This type of study is important for screening patients who may respond to immunotherapy and guiding the development of appropriate therapeutic strategies for such patients. Further in-depth clinical studies based on large sample sizes of NSCLC patients are awaited in the future.

Multimodal MRI

Diffusion-weighted imaging (DWI) MRI is widely used to evaluate and predict the efficacy of NSCLC immunotherapy.[91] This imaging approach is based on detecting the Brownian motion of water molecules in the tissues, which enables the assessment of the tumor cell and tissue microstructure. Its parameters, including real diffusion coefficient (D) value,

macroscopic diffusion kurtosis (Kapp), and apparent diffusion coefficient (ADC) values, can be used to predict the efficacy of treatment. Bao et al predicted the efficacy of neoadjuvant chemo-immunotherapy (NCIT) in resectable NSCLC patients by predictive value of intravoxel incoherent motion (IVIM) DWI and diffusion kurtosis imaging (DKI) and found that the post-NCIT ADC, ΔADC, and ΔD value changes were significantly higher in the pCR group (mean value=0.982, 0.162, and 0.129) than in the non-pCR group (mean value=0.834, 0.014, and −0.110), whereas the pre-NCIT D, post-NCIT Kapp, and ΔKapp in the pCR group (mean value=0.721, 0.846, and −0.005) were significantly lower than those in the non-pCR group (mean value=0.845, 1.028, and 0.168). Also, the multivariate logistic regression analysis showed that the pre-NCIT D and post-NCIT Kapp values were the independent predictors for response and that the combined predictive model consisting of IVIM-DWI and DKI had the best predictive efficacy (AUC=0.889).[92] Furthermore, Karayama et al assessed the efficacy of immunotherapy using IVIM-MRI, showing that an increase in ADC at 8 weeks, decreased in ADCkurt (kurtosis of ADC) and ΔADCkurt at 4 weeks after immunotherapy are associated with longer PFS, a decreased ΔADCskew (skewness of ADC) at 4 weeks was associated with longer PFS and OS. This study suggests that changes in ADC histograms can help predict long-term efficacy after immunotherapy.[93] In addition, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), which can show information on intra-tissue perfusion and tumor heterogeneity, has been used to identify benign and malignant nodules in the lungs; however, this method has been less frequently used in NSCLC immunotherapy studies.[94]

Summary and Prospect

Within the landscape of NSCLC immunotherapy, multimodal imaging techniques have emerged as pivotal tools for evaluating treatment response and predicting clinical outcomes, fulfilling the critical clinical need for early identification of non-responders to facilitate timely therapeutic modifications. CT remains the cornerstone for morphological assessment, with quantitative analyses (eg, volumetric measurements, texture/radiomics features) providing deeper insights into tumor heterogeneity that surpass traditional size-based criteria such as RECIST, which frequently misclassifies immune-related responses including pseudo-progression. PET/CT integrates metabolic information, with parameters such as MTV and TLG demonstrating prognostic value, although challenges remain in differentiating immune-induced inflammation (eg, nodal immune flare) from true progression. Immuno-PET/CT demonstrates potential for non-invasive detection of immune checkpoint expression (eg, PD-L1/PD-1); however, clinical translation remains constrained by limited cohort sizes and challenges in tracer specificity. MRI, particularly DWI, delivers microstructural insights into tumor response but remains constrained by motion artifacts and restricted clinical availability when compared with CT and PET.

This review elucidates how multimodal imaging—through capturing morphological, metabolic, and microenvironmental features—augments histopathological evaluation, allowing refined stratification of NSCLC patients undergoing continued immunotherapy. However, persisting challenges encompass heterogeneity in radiomics feature extraction across studies and the difficulty in differentiating immune-related phenomena (eg, inflammatory changes versus true progression) with single-modality assessments. Future investigations should emphasize multicenter validation of multimodal imaging-pathology integration, development of AI-driven algorithms to decipher complex radiomics signatures, and exploration of targeted immuno-PET tracers to optimize patient stratification and therapeutic monitoring. By addressing these limitations, multimodal imaging could advance precision immunotherapy through enabling earlier identification of treatment-responsive cohorts and refining clinical decision-making to ameliorate NSCLC prognosis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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