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The Role of [^{18}F]FDG PET/CT in Monitoring of Therapy Response in Lung Cancer

Akinwale Ayeni, MBChB, MMed,*,‡,§ Osayande Evbuomwan, MBBS, PhD,† and Mboyo-Di-Tamba Willy Vangu, MD, PhD*

Lung cancer remains a leading cause of cancer deaths worldwide, with an all stage 5-year relative survival rate of less than 30%. Multiple treatment strategies are available and continue to evolve, with therapy primarily tailored to the type and stage of the disease. Accurate monitoring of therapy response is crucial for optimizing treatment outcomes. PET/CT imaging with [^{18}F]FDG has become the standard of care across various phases of lung cancer management due to its ability to assess metabolic activity. This review underscores the pivotal role of [^{18}F]FDG PET/CT in evaluating therapy response in lung cancer, particularly in non-small cell lung cancer (NSCLC). It examines conventional response criteria and their adaptations in the era of immunotherapy, highlighting the value of integrating metabolic imaging with established criteria to improve treatment assessment and guide clinical decisions. The potential of non-[^{18}F]FDG PET tracers targeting diverse biological pathways to provide deeper insights into tumor biology, therapy response and predictive outcomes is also explored. Additionally, the emerging role of radiomics in enhancing treatment efficacy assessment and improving patient management is briefly highlighted. Despite the challenges in the routine clinical application of various metabolic response criteria, [^{18}F]FDG PET/CT remains a crucial tool in monitoring therapy response in lung cancer. Ongoing advancements in therapeutic strategies, radiopharmaceuticals, and imaging techniques continue to drive progress in lung cancer management, promising improved patient outcomes.

Introduction

Lung cancer is the second most common cancer diagnosed worldwide. Despite numerous advances in the genetics and risk factors of the disease, as well as innovation in new therapeutic modalities, lung cancer remains the leading cause of cancer deaths. There were 2,408,616 new cases of lung cancer globally in 2022, affecting mainly high-income countries.[1] However, a country-specific report will provide a better understanding of the burden and impact of lung cancer locally.[2] The risk of developing lung cancer increases after the age of 40 years, but the disease is commonly diagnosed among individuals aged 50-70 years.[3] Lung cancer comprises two main histological types that include non-small cell lung cancer (NSCLC), accounting for 85% of all cases, and small cell lung cancer (SCLC). Common NSCLC types include adenocarcinoma (39% of all lung cancers) and squamous cell carcinoma (20%). SCLC is particularly known for fast, aggressive growth and difficulty in treating. It accounts for 15% of all lung cancers and has neuroendocrine characteristics. Relative survival at five years is between 22.9% and 26.5% and generally depends on the histology type and stage of the disease. The 5-year survival rate for localized disease is

*Division of Nuclear Medicine, Department of Radiation Sciences, Faculty of Health Sciences, University of The Witwatersrand, Johannesburg, South Africa.
†Department of Nuclear Medicine, Faculty of Health Sciences, University of The Free State, Bloemfontein, South Africa.
‡Nuclear Medicine, Klerksdorp/Tshepong Hospital Complex, Klerksdorp, North West Province, South Africa.
§Division of Nuclear Medicine, Department of Radiation Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.
Address reprint requests to Akinwale Ayeni, MBChB, MMed, Division of Nuclear Medicine, Department of Radiation Sciences, Faculty of Health Sciences, University of the Witwatersrand, Wits Health Sciences Campus, 7, York Rd, Parktown, Johannesburg 2193, South Africa. E-mail: akinwale.ayeni@wits.ac.za

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61.2% (64% for NSCLC, 29% for SCLC), 33.5% for locoregional disease (37% for NSCLC, 18% for SCLC) and 7% for distant spread (26% for NSCLC, 3% for SCLC).[4–6] Lung cancer treatments usually include surgery, radiation therapy, radiofrequency ablation, chemotherapy, targeted therapy and immunotherapy. It becomes critical to emphasize that early detection of lung cancer can improve the outcome of an appropriate treatment. Constant advancement in innovative and novel therapy approaches will ensure continual improvement in existing techniques with the emergence of new evolving options.[7]

The role of Fluorine-18 fluorodeoxyglucose ([^{18}F] FDG) PET/CT imaging in lung cancer is well established in staging, radiotherapy planning, evaluating treatment response, detecting recurrence and assessing risk to predict prognosis.[2,8–10]

Traditionally, different criteria have been used to assess cancer treatment response with several iterations and modifications that eventually incorporated metabolic imaging.[11,12]

The advancement of treatment options for lung cancer makes the evolution of imaging criteria for appropriate assessment of response to these therapies a crucial aspect of its overall management. Emerging promising radiopharmaceuticals other than [^{18}F]FDG have also entered the clinical space in lung cancer management.[13,14]

In this review, we will present the different criteria in treatment response assessment in lung cancer, focusing on the role of [^{18}F] FDG PET/CT in both NSCLC and SCLC.

Therapy Modalities in Lung Cancer

Similar to the management of most malignancies, therapy modalities in lung cancer are varied and largely depend on the type and stage of the disease.

Available treatment strategies include surgical resection, chemotherapy, radiation therapy, immunotherapy, molecular targeted therapy, ablative therapy, photodynamic therapy, and best supportive care only.[15]

As no single therapy is best for everyone, the ultimate decision of choice and sequence of these therapy modalities are multifactorial and should ideally rest with a multidisciplinary board comprising relevant medical professionals, also considering the patient's preference in a well-rounded personalized medicine approach.

NSCLC: Early and Locally Advanced

Primary treatment includes surgery, radiation therapy, and chemoradiation for early (Stage 1) and locally advanced (Stages 2 and 3) lung cancers.[16,17]

Surgery is a standard primary treatment for Stages 1, 2, and 3 (up to Stage 3B). If surgery is not an option, radiation therapy or chemoradiation may be used for primary treatment instead.

Definitive radiation therapy (curative intent) can be a mode of primary treatment up to stage 2B. However, definitive chemoradiation becomes the viable option from stage 2B with either N1 disease or T3 with invasive growth with no nodal disease.

Surgical approaches generally involve one of the following: wedge resection, segmentectomy, lobectomy, sleeve lobectomy, or pneumonectomy.

Even when resectable, NSCLC may include a bi- or multimodality approach. Systemic therapy is often used in conjunction with surgery in this instance, and these perioperative therapy options include platinum-doublet chemotherapy, immune checkpoint inhibitors, targeted therapy, chemoimmunotherapy, chemoradiation and sometimes radiation therapy.[16,17] Radiation therapy, apart from being used as main/primary therapy, can be used as part of concurrent or sequential chemoradiation or as adjuvant therapy. External Beam Radiation therapy (EBRT) is the most common method, with stereotactic ablative radiotherapy (SABR) preferred for early and intensity-modulated radiotherapy IMRT for locally advanced stages.

Consolidation treatment with immunotherapy or targeted therapy may be given after definitive sequential chemoradiation to improve the chances of a cure.

NSCLC: Advanced/Metastatic

Targeted therapy is used for advanced/metastatic NSCLC, depending on the driver mutations identified. These include kinase inhibitors, antibody therapy and antibody-drug conjugate, typically against genes such as EGFR, KRAS ALK, ROS1, BRAF V600E, NTRK, MET, RET and HER2.

Many immune checkpoint inhibitors, a type of immunotherapy, exist, and the one chosen for treatment will be based on the level of PD-L1 and type of NSCLS, either squamous cell carcinoma or adenocarcinoma (including other rare cell types). The options generally include PD-1 inhibitors such as Pembrolizumab, PD-L1 inhibitors such as Atezolizumab, and CTLA-4 inhibitors such as Ipilimumab.

Some advanced NSCLCs with high PD-L1 are only treated with immune checkpoint inhibitors. Combining this type of immunotherapy with chemotherapy is also an option, even in cases with low PD-L1. After combination therapy, continuation maintenance therapy with first-line immune checkpoint inhibitors may prolong remission.[18]

Treatment of metastatic NSCLC without treatable biomarkers partly depends on the patient's performance status. Patients with ECOG 0-2 are treated with systemic therapy, while supportive care is generally recommended in ECOG 3 and 4.

It is worth noting that, even without driver alterations, immune checkpoint inhibitors as first- and second-line therapy for patients with stage IV NSCLC have been found to extend both progression-free and overall survival.[19–22] Its use has, therefore, been recommended in international clinical practice guidelines.[23]

General first-line options for these patients are chemoimmunotherapy, chemotherapy alone, or chemotherapy with Bevacizumab, a monoclonal antibody type of targeted

therapy. Chemotherapy may be a "platinum-doublet" or a single agent, of which there are several options.

Maintenance therapy at the end of treatment may either be continuation maintenance (one of the first-line agents) or switch maintenance (changing to an agent not part of the first line).

Second-line therapy in the case of relapse will include immune checkpoint inhibitors, which are preferred if not part of the first-line regimen. Other options include Docetaxel with a VEGF antibody such as Ramucirumab or single-agent chemotherapy.

SCLC

Chemotherapy is the classic treatment for SCLC. SCLC is usually classified as either limited or extensive disease for treatment purposes.

Limited-stage SCLC includes TNM Stages 1-3 that can be treated with a single radiation therapy field. Surgery, typically lobectomy, will only be an option for very few patients (Stages 1 or 2A) even with limited-stage SCLC; therefore, treatment is principally a combination of chemo- and radiation therapy (including SABR) in the form of concurrent chemoradiation with curative intent.[24] Sequential chemoradiation or chemotherapy alone may also be an option, depending on the performance status and TNM stage.

Extensive-stage SCLC comprises all scenarios where a single radiotherapy field cannot be used to treat with curative intent. The goal of treatment in this instance is mainly system control rather than cure.[24]

The addition of immunotherapy has improved treatment outcomes of extensive-stage SCLC in recent years; thus, chemoimmunotherapy is the preferred treatment. Platinum-doublet chemotherapy with an immune checkpoint inhibitor is advocated. After chemoimmunotherapy, maintenance of immune checkpoint inhibitors may prove beneficial.

In addition to systemic therapy, radiation therapy may be beneficial for local symptom control. Whole-brain radiation therapy is usually used for the treatment of brain metastases, which may be initiated even before symptoms develop. Relapse is common in SCLC, and treatment options include varied chemotherapy agents and sometimes immunotherapy, depending on performance status and the timeframe of relapse.[25-27]

It is important to note that, for both NSCLC and SCLC, immunotherapy may not be safe to administer in some patients, even if they would have been otherwise eligible.

Monitoring Therapy Response

NSCLC: [18F]FDG PET/CT in Assessing Therapy Response at the End of Systemic Therapy (Excluding Immunotherapy)

Depending on the type of therapy, there are several qualitative and quantitative/semiquantitative methods of assessing treatment response with [18F]FDG PET/CT imaging of patients with NSCLC. Treatment response assessment with [18F]FDG PET/CT is preferably performed at 12 weeks after radiation or chemoradiation therapy and as early as four weeks after chemotherapy or surgery. This is because post-therapy-related inflammatory uptake is less and subsides within a short time, except if there are related complications associated with wound healing.[28] Some have also advocated that [18F]FDG PET/CT imaging can be performed as early as 10 days after chemotherapy, 6 weeks after surgery and 6-8 weeks after radiofrequency ablation.[29]

Quantitative/Semiquantitative Methods

The response evaluation criteria in solid tumor (RECIST) introduced in 2000 and revised in 2009 (RECIST 1.1) have, over the years, been used as a standardized tumor response assessment tool.[30] However, being an anatomical imaging criterion, important limitations have been observed with this method, most notably concerning reproducibility.[11,30,31] Tumors might also have anatomically nonmeasurable lesions, such as malignant pleural effusions, ascites and bone metastases, which cannot be assessed with this criteria.[31]

Most of these limitations have been addressed by assessment criteria using [18F]FDG PET/CT imaging.

The European Organization for Research and the Treatment of Cancer (EORTC) PET criteria introduced in 1999 (Table 1) was the initial standardized response assessment criteria using [18F]FDG PET. This response assessment was further refined by introducing the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST 1.0) in 2009 (Table 1).[32]

The PERCIST 1.0 response assessment has shown several advantages over the RECIST 1.1 criteria, most especially in predicting treatment response much earlier, as changes in glucose metabolism precede changes in tumor size.[33] It is thus currently being used to predict treatment response and clinical outcomes in many solid tumors.[34]

A few studies in the literature have compared these interpretation criteria in the treatment of NSCLC. One of them compared RECIST 1.1, PERCIST 1.0 and EORTC in evaluating the early therapeutic response of patients with advanced NSCLC after chemotherapy. This was a prospective study with 35 NSCLC patients who received standard chemotherapy and underwent [18F]FDG PET/CT scans before and after treatment. The study concluded that the EORTC criteria and PERCIST 1.0 were more sensitive and accurate than the RECIST 1.1 for detecting an early therapeutic response.[35]

Most other available studies in the literature only compared RECIST 1.1 and PERCIST 1.0, evaluating therapy response after chemotherapy or tyrosine kinase inhibitors (TKI).[36–42] These studies showed a significantly increased sensitivity of PERCIST 1.0 in detecting partial response and a relatively equal sensitivity in detecting progressive disease (Table 2). An example is the retrospective study conducted by Ding et al.,[37] where 44 patients with NSCLC who received chemotherapy and no surgery had their therapeutic response assessed using both the PERCIST 1.0 and RECIST 1.1. This was after using 2 or 4-6 cycles of cisplatin-based combination therapy. The authors concluded that both criteria have good

Table 1 Evaluation Criteria for EORTC and RECIST

Response Categories	EORTC	PERCIST 1.0
Complete metabolic response	Complete resolution of ^{18}F FDG uptake within tumor volume, indistinguishable from surrounding normal tissue.	Complete resolution of ^{18}F-FDG uptake within measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood-pool levels, with disappearance of all other lesions to background blood pool levels
Partial metabolic response	Reduction of minimum of 15% ± 25% in tumor ^{18}F-FDG SUV after one cycle of chemotherapy, and >25% after more than one treatment cycle	Reduction of at least 30% in SUL peak and an absolute drop of 0.8 SUL peak units
Progressive metabolic disease	Increase in ^{18}F-FDG tumor SUV of >25% within tumor region defined on baseline scan **or** appearance of new ^{18}F-FDG uptake in metastatic lesions.	Increase of at least 30% in SUL peak and an absolute increase of 0.8 SUL peak units **or** 75% increase in TLG, with no decrease in SUL **or** appearance of new ^{18}F-FDG-avid lesions typical of cancer and not related to inflammation or infection
Stable metabolic disease	FDG uptake increase by <25% and decrease by <15% and no visible increase in the extent of the FDG uptake	Neither PMR nor PMD

consistency; however, the PERSIST criteria is more sensitive in detecting complete remission and disease progression.

Studies where TKIs have been used to treat NSCLC have also shown the superiority of ^{18}F-FDG PET/CT imaging using PERCIST 1.0 for assessing treatment response. An example is the study conducted by Kerner et al.,[38] which analyzed the data of 13 patients with NSCLC treated with crizotinib. Their findings showed that PET could detect 45% of the progressive cases earlier than CT. Another study performed by Stefano et al.,[40] evaluating erlotinib therapy in patients with NSCLC, showed a significant difference between RECIST 1.1 and PERCIST 1.0 in assessing treatment response. Significant superiority in detecting partial response to therapy was noted with PERCIST 1.0. However, both PERCIST and RECIST were significant prognostic factors in predicting disease-free and overall survival. The summary of these findings and those of similar studies are shown in Table 2.

Outside the strict criteria of PERCIST 1.0 and EORTC, there are quantitative metabolic parameters that certain groups have used to assess treatment response in patients with NSCLC.[43] These were highlighted in an earlier review by Marcus et al.,[43] where they looked at the utility of Standard uptake value maximum (SUVmax), SUV peak, metabolic tumor volume (MTV) and tumor lesion glycolysis (TLG). In a prospective study by Horn et al.,[44] changes in SUVpeak and MTV were shown to be better predictors of treatment response following chemoradiation. Cerfolio et al.[45] reported $a > 80\%$ decrease in SUVmax following neoadjuvant therapy correlated significantly with pathological tumors, compared to changes in CT tumor volume. Moon et al.[46] reported that a 50% decrease in TLG could predict treatment response with a 100% sensitivity after chemotherapy, and this was better than MTV and RECIST, with sensitivities of 83% and 75%, respectively.

Qualitative Methods

There are various qualitative response assessment criteria currently being used for several malignancies. However, to date, none are known to be specific for lung cancer. Instead, validation of some of these criteria is being attempted in the treatment response of lung cancers.[43]

Table 2 Summary of the Findings of Studies Comparing RECIST 1.1 and PERCIST 1.0 in the Assessment of Treatment Response in Patients With NSCLC

Authors	N	Study Type/Year	Treatment	PR Rate PERCIST (%)	PR Rate RECIST (%)	PD Rate PERCIST (%)	PD Rate RECIST (%)
Zing et al.	44	Retrospective/2014	Chemotherapy	66	55	16	2
Tauhardt et al.	18	Retrospective/2014	Chemotherapy	88	46	11	11
Ordu et al.	30	Retrospective/2015	Chemotherapy	47	16	-	-
Stefano et al.	20	Prospective/2016	TKI	88	46	11	11
Shang et al.	35	Prospective/2016	Chemotherapy	60	20	23	23
Zwitter et al.	38	Prospective/2016	TKI	80	79	16	3
Kerner et al.	13	Retrospective/2016	TKI	78	60	11	20

One of these is Hopkin's criteria, initially for assessing treatment response in head and neck malignancies. It is a PET-based qualitative response criteria with good inter-reader agreement employed in assessing the treatment response of NSCLC with [18F]FDG PET/CT imaging 7-8 weeks after completion of treatment. This qualitative assessment scoring method, which uses a 5-point scale, was shown to have a high accuracy and could significantly predict patient survival.[28] Sheikhbahaei et al.[47] validated these response criteria in 2016 when they evaluated 201 patients with biopsy-proven lung cancer who underwent therapy response assessment with [18F]FDG PET/CT within 6 months of completing therapy. They concluded that using Hopkin's criteria for therapy response in lung cancer was associated with substantial interpreter agreement, accuracy and could significantly predict survival in lung cancer.

This 5-point scale was defined according to the intensity and pattern of [18F]FDG uptake, using the mediastinal blood pool and liver as reference points.

Score 1—Focal uptake less than or equal to that of the mediastinal blood pool.

Score 2—Focal uptake more than that of the mediastinal blood pool but less than the liver.

Score 3—Diffuse uptake more than mediastinal blood pool or liver.

Score 4—Focal uptake greater than liver.

Score 5—Focal and intense uptake greater than the liver.

Scores 1 and 2 were regarded as complete response, while Score 3 was considered to be likely in keeping with inflammatory changes, and Scores 4 and 5 were in keeping with residual disease.[28] Similar scoring systems, including the Deauville criteria, have also been employed in assessing treatment response of NSCLC, with some of them outperforming CT assessment.[43] Compared to the more complex methods involved with semiquantitative assessment, the qualitative response assessment has been shown to perform equally well.[48]

NSCLC: [18F]FDG PET/CT in Assessing Therapy Response Following Radiotherapy

Metabolic imaging with [18F]FDG PET/CT can be complicated with acute or chronic radiation-induced effects, with radiation-induced pneumonitis typically occurring 4-12 weeks after therapy, a common finding. Therefore, the general consensus is that 18F-FDG PET/CT should be delayed up to 12 weeks after radiation therapy to minimize false positive findings.[49]

It is important to remember that these radiation effects are more frequent and long-lasting following stereotactic body radiotherapy SBRT.[50] Assessing treatment response of NSCLC following SBRT with [18F]FDG PET/CT has been associated with a high risk of false positive findings, even up to over 12 months following treatment, with SUVmax values of >2.5.[51–53] It is thus being advised that residual or recurrent disease should not be diagnosed convincingly with only [18F]FDG PET/CT imaging[49] but rather with diffusion-weighted MRI.[29] However, despite these shortcomings, [18F]FDG PET/CT still outperforms anatomical imaging as size alone cannot accurately differentiate viable tumor from postradiation inflammatory changes.[52]

Evidence in the literature supports using [18F]FDG PET/CT in assessing treatment response in NSCLC patients post-radiotherapy. A robust prospective study by MacManus et al.[54] evaluated 73 patients with NSCLC who underwent [18F]FDG PET/CT before and approximately 70 days after radical radiotherapy. They used a similar qualitative interpretation criterion to the Hopkins' criteria and concluded that [18F]FDG PET/CT outperformed CT as a better predictor of survivor. Turgeon et al.[55] also demonstrated that assessing treatment response with [18F]FDG PET/CT after 90 days following radiotherapy was strongly associated with survival and identifying complete responders. It is important to note that in this study, they compared EORTC, PERCIST 1.0, Deauville score and Peter Mac score and found out that the visual qualitative interpretation criteria (Deauville and Peter Mac scoring systems) were better able to identify responders and showed less inter-reader variability. Even in the setting of chemoradiation therapy [18F]FDG PET/CT also has a role to play in assessing treatment response. In their prospective study with 37 patients, Huang et al.[56] showed that SUV and MTV changes from two serial [18F]FDG PET/CT (before and after chemoradiotherapy) allowed for the prediction of treatment response in advanced NSCLC.

NSCLC: [18F]FDG PET/CT in Assessing Therapy Response to Immunotherapy

Response Criteria for Immunotherapy

Immunotherapy has truly changed the landscape of therapy in lung cancer.[57]

Its uniqueness lies in boosting the host immunity to be primed to fight cancer while removing the breaks in the inhibition that permit tumor growth. With their distinct mechanisms of action, these therapies have led to atypical responses not observed with conventional treatments. Existing response criteria, such as WHO, RECIST 1.1, EORTC, and PERCIST, do not fully capture these effects.

The unique pattern of responses has been summarized[58,59] and includes *Pseudoprogression*, an objective response after having an initial increased in tumor burden—i.e. "apparent disease progression" before response; *Hyperprogression*, paradoxical acceleration of tumour growth kinetics, i.e. patients whose disease seems to grow faster after initiating immunotherapy; *Dissociated response*, decrease or stabilisation in some tumour sites with a concomitant increase in other sites, analogous to mixed responses seen with conventional chemotherapy; and *Durable response*, a concept that refers to patients achieving a long-lasting tumour response that can be maintained several years even after stopping immunotherapy.

These novel response patterns were mostly observed in patients treated with immune-checkpoint inhibitors, especially those against Cytotoxic T-lymphocyte-associated

protein 4 (CTLA-4).[60] It is pertinent to note that these early observations were initially made on melanoma patients using Ipilimumab (anti-CTLA-4 mAb) specifically but have been noted to also occur with other immune checkpoint inhibitors such as anti-PD-1 mAb Pembrolizumab and anti-PD-L1 mAb Nivolumab in patients with NSCLC, albeit to a lesser degree.[58]

However, in a pooled analysis of phase III trials done by Pons-Tostivint et al,[61] it was observed that durable responses were more frequent in patients treated with anti-PD-1/PD-L1 agents than in patients treated with anti-CTLA-4 agents (28% vs. 18%).

This has led to the development of new response criteria, essentially adaptations of the preceding traditional ones, designed to address their limitations and account for the unique characteristics of immunotherapy.

Morphologic Response Criteria

irRC (immune-related response criteria) was first described in patients with melanoma in 2009 by Wolchok et al.[62] based on the WHO criteria. Lesion progression required follow-up imaging confirmation to confer progressive disease. *irRECIST* (immune-related RECIST), proposed in 2013 by Nishino and colleagues, was meant to improve the shortcomings of *irRC* by using unidimensional measurements based on RECIST criteria.[63]

iRECIST (immune RECIST) was published by the RECIST working group in 2017 in an attempt to harmonise the immunotherapy-related modifications, thus introducing the concept of unconfirmed progressive disease (iUPD) to be confirmed at specified time points with further imaging.[64] Shortly after, *imRECIST* (immune-modified RECIST) was introduced in 2018 by Hodi et al.,[65] particularly redefining progression-free survival (imPFS).

Metabolic Response Criteria

PECRIT (PET/CT Criteria for Early Prediction of Response to Immune Checkpoint Inhibitor Therapy), *PERCIMT* (PET Response Evaluation Criteria for Immunotherapy), and *imPERCIST5* (immunotherapy-modified PERCIST5) are all forms of adaptations to RECIST 1.1 and PERCIST and were initially described using a population of patients with melanoma.

All these metabolic response criteria use [^{18}F]FDG for PET/CT imaging. According to Cho et al.,[66] PECRIT showed 95% accuracy in predicting early tumor response. Sachpekidis et al.[67] demonstrated the superior performance of PERCIMT in predicting tumor response when compared to EORTC with sensitivity, specificity, and accuracy of 94%, 70%, and 88%, respectively. A retrospective study by Ito et al.[68] concluded that changing the definition of PMD using imPERCIST5 further improved the prognostic value of ^{18}F-FDG PET/CT.

However, *iPERCIST* (immune PERCIST) was based on patients with NSCLC, first described in another retrospective study.[69] The criteria are based on PERCIST with the introduction of follow-up imaging to confirm progressive metabolic disease (PMD), comparable to the concept in iRECIST.

A comparison of the metabolic response criteria can be found in Table 3.

While all these criteria have shown promise, there is no consensus on the most preferred at different time points in immunotherapy. This is primarily due to a lack of evidence of long-term outcomes in well-designed prospective clinical trials for validation.[70,71] This complicates their formal inclusion in clinical guidelines, even though they are recognized, making harmonization and comparison of studies more challenging.[59] It is also worth noting that the routine use of these criteria in clinical practice may be limited by their time-consuming nature and the required use of specialized software in some instances.

The core principle unifying these modified criteria in response to immunotherapy is that imaging specialists must exercise caution when defining progressive disease. This will prevent the premature exclusion of patients from beneficial therapy. Confirmatory follow-up imaging should be performed in doubtful cases and is typically recommended between 4 and 8 weeks after initial post-treatment evaluation.[59] Indeed, recently proposed criteria that underscore this "wait and see" strategy is referred to as the *wsPERCIST*.[72]

Figures 1 and 2 show [^{18}F]FDG PET/CT images of a patient with PD-L1 positive NSCLC who had both chemotherapy and immune checkpoint inhibitor therapy. Complete metabolic response after initial therapy may be predictive of potential long-term response as suggested in this case.

PET Metrics for Therapy Assessment

SUVmax has been overwhelmingly used as the metric to measure metabolic activity, mainly due to its reproducibility. PERCIST favored SUVpeak, which was subsequently adopted by its immune-related criteria variants described above. While SUVmax predicts response and correlates with PD-L1 expression, it may not be the best predictor of overall survival.[73,74]

Other PET metrics, such as MTV (metabolic tumor volume) and TLG (total lesion glycolysis), have been found to be useful adjuncts.[75] Hashimoto et al.[74] studied patients with NSCLC treated with anti-PD-L1 mAb. They used multivariate analysis to demonstrate that tumour metabolic activity, measured by TLG and MTV, was an independent prognostic factor for predicting outcomes after anti-PD-1 antibody therapy, whereas SUVmax was not. A recent prospective study by Tricarico et al.[76] on 100 metastatic NSCLC patients demonstrated that total MTV (TMTV) is a strong prognostic marker for nonresponding patients according to PERCIST criteria. In fact, a report by the European Association of Nuclear Medicine (EANM) in 2019 recommended the routine inclusion of MTV and TLG as part of imaging results where feasible.[60]

Immune-Related Adverse Effects

Immune-related adverse effects (irAEs) are common in immune checkpoint inhibitor therapies. Most are self-limiting, but some are potentially life-threatening.[77,78] These inflammatory processes can also be monitored on [^{18}F]FDG

Table 3 Comparison of Metabolic Response Criteria for Immunotherapy

Criteria	PECRIT	PERCIMT	iPERCIST	imPERCIST5	wsPERCIST
Year	2017	2018	2019	2019	2024
Reference	Cho et al.[66]	Sachpekidis et al.[67]	Goldfarb et al.[69]	Ito et al.[68]	Masse et al.[72]
Tumor	Melanoma	Melanoma	NSCLC	Melanoma	NSCLC
Treatment	Immune checkpoint inhibitors (anti-PD-1, anti-CTLA-4)	Immune checkpoint inhibitors (anti-CTLA-4)	Immune checkpoint inhibitors (anti-PD-1)	Immune checkpoint inhibitors (anti-PD-1)	Immune checkpoint inhibitors (anti-PD-1, anti-PD-L1)
Modality	CT and [^{18}F]FDG PET	CT and [^{18}F]FDG PET	F[^{18}F]FDG PET	[^{18}F]FDG PET	[^{18}F]FDG PET
Delay for confirmation 'of PMD	3-4 wk	3 mo	2 mo	3 mo	4-8 wk
Target lesions	RECIST 1.1 PERCIST 1.0	Size (metabolically active lesion) $>$1.0 or 1.5 cm, $\leq$5 target lesions/patient	Minimum tumor SUL 1.5 $\times$ mean SUL liver, $\leq$5 target lesions/patient	Minimum tumor SUL 1.5 $\times$ mean SUL liver, $\leq$5 target lesions/patient	PERCIST 1.0
New lesions	Progression	Metabolic progressive disease (PMD)	Immune unconfirmed metabolic progressive disease (iuPMD)	Need to be included in the sum of SULpeak, PMD if $>$30% increase in the sum of SULpeak	To be confirmed on $PET_{interim}2$
Complete metabolic response (CMR)	Disappearance of all lesions	Disappearance of all metabolically active lesions	Disappearance of any uptake in target lesion	Disappearance of all metabolically active lesions	Complete resolution of uptake in target lesion. No new lesion typical of cancer.
Partial metabolic response (PMR)	$\geq$30% decrease from baseline	Disappearance of some metabolically active lesions without any new lesions	Reduction in SULpeak in target lesions $\geq$30%	Reduction in the sum of SULpeak in target lesions $\geq$ 30% and absolute drop in SUL by $\geq$ 0.8 SUL units	Reduction $>$30% of the sum of SULpeak of target lesions and absolute drop in SUL $>$ 0.8 SUL units.
Stable metabolic disease (SMD)	Neither PD, PR, nor CR evaluation of change in SUL peak of the hottest lesion: $>$15.5% (clinical benefit), $\leq$15.5% (no clinical benefit)	Neither PMD, PMR, nor CMR	Neither PMD, PMR, nor CMR	Neither PMD, PMR, nor CMR	Not CMR, PMR, or PMD.
Progressive metabolic disease (PMD)	$\geq$20% increase in the nadir of the sum of target lesions ($>$5 mm)	$\geq$4 new lesions of $<$1 cm or $\geq$3 new lesions of $>$1 cm or $\geq$2 new lesions of $>$1.5 cm	$\geq$30% increase in SULpeak or new metabolically active lesions: immune unconfirmed PMD (iuPMD)	$>$30% increase in SULpeak, with $>$ 0.8 SUL unit increase in tumor SULpeak	$>$30% increase in the sum of the SULpeak of target lesions or new ^{18}FDG-avid lesion(s) that are typical of cancer and not related to the treatment effect or infection
Confirmed PMD (cPMD)	n/a	n/a	PET at 4-8 wk: confirmed PMD	n/a	PET at 4-8 wk: confirmed PMD

n/a, not applicable.

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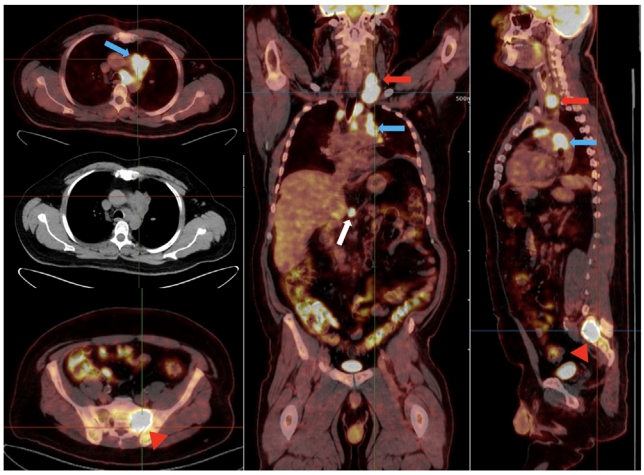

Figure 1 Baseline [^{18}F]FDG PET/CT images of a 47-year-old male with PD-L1 positive NSCLC. Baseline [^{18}F]FDG PET/CT images demonstrate neoplastic adenopathy in the neck (red arrows), intrathoracic (blue arrows), and abdominal nodes (white arrow); with left sacrum lytic osseous metastases (red arrowhead). There is non-avid atelectasis in the left lower lobe (not highlighted) but no [^{18}F]FDG-avid lesion is seen in the lung parenchyma.

PET imaging.[79] Apart from the obvious clinical implication of differentiating these reactions from disease progression, they are valuable for predicting the eventual clinical benefit of treatment.[59,71,78]

SCLC: [^{18}F]FDG PET/CT in Assessing Therapy Response

Small cell lung cancer has a biological behavior and runs a clinical course that is more aggressive than NSCLC. It has a doubling time of about 33 days, which is faster by a factor of 3 than NSCLC.[80] The initial response rate to treatment is high; however, the majority of patients relapse shortly after the end of therapy.[81–88] Even with this high initial response rate, there is still a chemoresistance group that will present with disease progression with worse outcomes.[85]

Therefore, there is a need for effective early assessment of treatment response. Especially in today's setting of newer and more effective treatment modalities, early prediction of therapeutic response could potentially identify patients who might need more effective therapy and thus prevent unnecessary side effects from ineffective therapies. In the early 2000s, a few studies had already been conducted, with [^{18}F]FDG PET and not PET/CT, that showed the potential use of glucose metabolic imaging in assessing the treatment response of patients with SCLC.[80,89] In 2003, Kamel et al.[89] studied 20 SCLC patients who had restaging [^{18}F]FDG PET. They

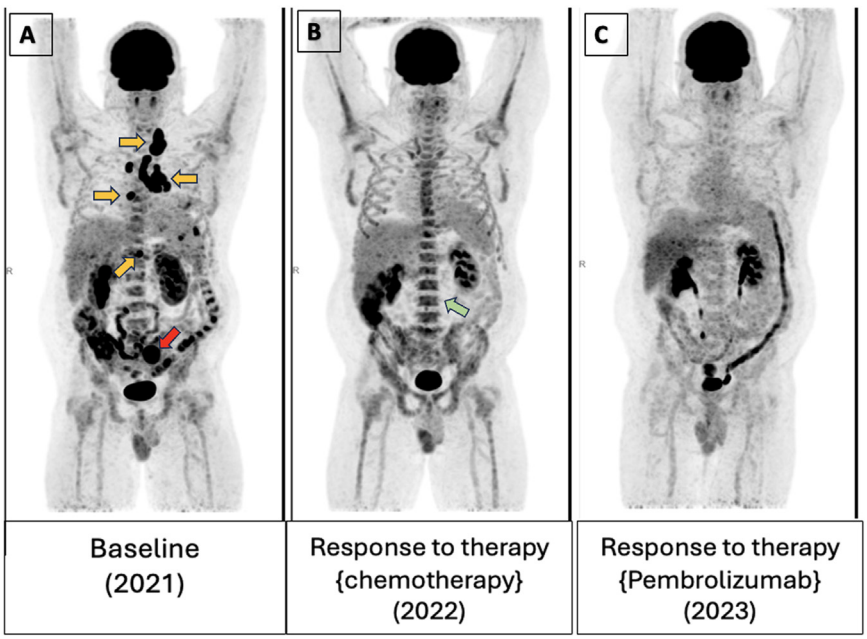

Figure 2 47-year-old male with PD-L1 positive NSCLC. Comparison of [^{18}F]FDG PET MIP images at Baseline (A), end-of-chemotherapy (B), and on immunotherapy (C). Baseline MIP image shows neoplastic adenopathy in the neck, thorax and abdomen (orange arrows), and skeletal metastases in left sacrum (red arrow) on baseline images. He completed six cycles of chemotherapy. Three weeks later, a PET/CT scan was done to evaluate response to chemotherapy which showed no evidence of metabolic activity in previously identified lesions, indicating complete metabolic response to therapy. Diffuse uptake noted in the spine was attributable to bone marrow response to recent chemotherapy (green arrow). Patient received anti PD-1 therapy (Pembrolizumab) and on follow-up imaging, MIP image (C) showed no evidence of active disease on immunotherapy.

reported that PET was able to correctly identify all five patients with complete remission, 11 of 12 patients with residual disease and all three patients with progressive disease. The increasing amount of evidence on the value of [18F]FDG PET/CT in therapy response assessment of NSCLC and few retrospective studies highlighting potential benefits for SCLC gave rise to prospective studies evaluating [18F]FDG PET/CT therapy response assessment in SCLC. Fischer et al.[82] evaluated 20 patients with SCLC with [18F]FDG PET/CT for early and final (end of therapy) response. Scans were analyzed qualitatively using the MacManus visual scoring criteria.

They concluded that response evaluation of SCLC with [18F]-FDG PET/CT was possible.

However, both early and end-of-therapy assessments did not seem to add any benefit over the RECIST criteria. A few studies have tried to evaluate the prognostic value of post-treatment [18F]-FDG PET/CT imaging of SCLC. A retrospective study conducted by Onitilo et al.[83] investigated the prognostic value of post-therapy [18F]FDG PET/CT in 22 patients with SCLC. Progression-free survival was significantly longer in PET-negative patients (10.5 months) than in PET-positive patients (4.3 months). Ziai et al.[90] also evaluated 29 patients retrospectively, with perfect concordance between EORTC and PERCIST criteria in response assessment. Eight patients had CMR, 9 had PMR, 5 had SMD, and 7 had PMD. They concluded that progression-free survival was significantly longer in all patients with CMR. Theirs was the first study to use standardised criteria (EORTC and PERCIST 1.0) in assessing the therapy response of SCLC patients with [18F]FDG PET/CT. The retrospective study on 59 SCLC patients by Kim et al.[85] evaluated survival analysis using multiple PET parameters, including SUVpeak, SUVmax, TLG and MTV. They reported that the percentage change in SUVpeak from pre- and post [18F]FDG PET/CT was an independent prognostic factor for overall survival. At the same time, MTV was an independent prognostic factor for progression-free survival.

In summary, several studies,[28,80,81] including a meta-analysis,[82] have confirmed the high diagnostic performance of [18F]FDG PET/CT in the setting of metabolic response assessment of lung cancer, with a better prediction of survival and complete response compared to CT. Figure 3 shows an example of complete metabolic response following chemo-radiation for a patient with SCLC, evaluated with [18F]FDG PET/CT.

To the best of our knowledge, there are still no official clinical practice guidelines recommending the routine use of [18F]FDG PET/CT in assessing the treatment response of patients with SCLC. We think it is high time this modality is incorporated into this space as enough evidence supports its use.

Interim [18F]FDG PET/CT Imaging in Assessing Therapy Response of Lung Cancer

Unlike lymphoma, with a standardized recognized role for interim [18F]FDG PET/CT imaging, at present, the same cannot be said for lung cancer. However, some encouraging results in the literature might support the use of interim PET/CT imaging in predicting early response to therapy and also offering prognostic information. In a prospective study involving 12 participants with SCLC, a 20% reduction in SUVmax after the first cycle of chemotherapy was a good predictor for therapy response.[91] An earlier study by Fischer et al.[92] demonstrated that the majority of SCLC patients who responded to treatment had about a 63% decrease in SUVmax after the first cycle of chemotherapy. Looking at interim response following TKI, the study conducted by Shao et al.[93] involving 78 patients newly diagnosed with Stage IIIB/IV EGFR-mutant NSCLC is a good example of the efficacy of interim [18F]FDG PET/CT in this setting. In that study, interim PET/CT imaging was performed 4-6 weeks following first-line EGFR-TKI therapy. They found that a reduction in interim PET SUVmax and SUVmean were independent risk factors for predicting progression-free survival (PFS).

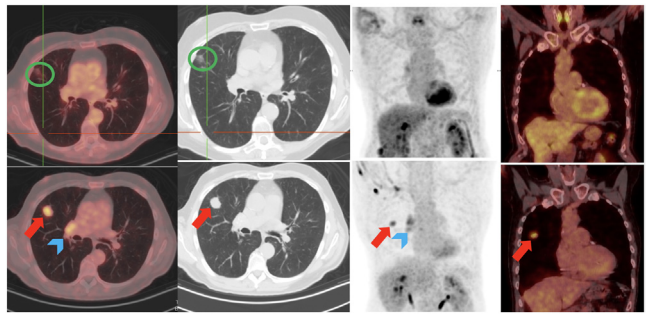

Figure 3 74-year-old diagnosed with small cell lung cancer on biopsy of right lung mass. Comparison of [18F]FDG PET/CT images at Baseline (bottom row) and end-of-therapy (top row). Baseline [18F]FDG PET/CT imaging (bottom row) showed avid mass in right lung (red arrow) and an ipsilateral active hilar node (blue arrowhead). After completion of chemo-radiation, [18F]FDG PET/CT imaging (top row) was done to assess therapy response. No evidence of FDG avid neoplastic disease. Previously seen right lung primary tumour is now a scar (green circle). Previous hilar node now calcified and inert. Overall findings was consistent with complete metabolic response.

Other PET Tracers in Therapy Response Assessment

Well-known pitfalls and limitations of 18F-FDG imaging have been documented.[94] Newer radiopharmaceuticals, which target various biological pathways involved in forming, growing and maintaining cancer cells beyond glucose metabolism, continue to emerge.[95]

Harnessing different aspects of lung cancer biology, many of these PET tracers have been investigated for staging. As a result, it is logical to evaluate their effectiveness in assessing treatment response.[96]

DNA Synthesis: [^{18}F]FLT

FLT (fluorothymidine) tracers target cell proliferation via DNA synthesis. The amount of FLT concentration in lung cancer cells reflects the activity of the proliferation-dependent enzyme thymidine kinase, which is selectively upregulated during DNA synthesis and phosphorylates [^{18}F]FLT to 3-fluorothymidine monophosphate, leading to trapping of the tracer in the cells.[96]

Results of studies evaluating the role of [^{18}F]FLT in assessing treatment response have been somewhat mixed, with some showing no clear advantage over [^{18}F]FDG while others indicate a favourable impact.[97–104]

[^{18}F]FLT has been found to correlate well with progression-free survival in patients undergoing radio- or chemoradiotherapy.[105] This radiotracer particularly looks especially promising for assessing early response to targeted therapies in preliminary results.[106,107]

Amino Acid Metabolism: [^{11}C]MET/[^{18}F]FET/[^{18}F]FMT

Amino acid metabolism is generally increased in malignant processes due to increased tumor development and cell proliferation. Tyrosine and methionine are the essential amino acids most commonly used for PET imaging in the form of L-methyl-^{11}C-methionine (MET) and ^{18}F-fluoeoethyl L-tyrosine (FET), respectively.

Due to logistical considerations, ^{18}F labeled with methionine has been favored in recent times. Only a handful of studies have evaluated treatment response assessment in lung cancer with radiotracers targeting amino acid metabolism. In nine patients who underwent stereotactic radiotherapy, [^{18}F]FET provided no additional information over [^{18}F]FDG when both were compared in a study by Ishimori and colleagues.[108] Using L-[3-^{18}F]-α-methyl tyrosine (^{18}F-FMT) in 18 patients, Kaira et al.[109] concluded that [^{18}F]FMT is a promising PET tracer for monitoring response to chemoradiotherapy and predicting the prognosis of patients with lung cancer.

Tumor Hypoxia: [^{18}F]FMISO/[^{18}F]FAZA/[^{64}Cu]-ATSM

Tumor hypoxia leads to poor prognosis owing to its promotion of angiogenesis, tumour aggressiveness and its association with resistance to radio- and chemotherapy.

It is, therefore, a target for tumor imaging of several cancers, and many radiopharmaceuticals have been investigated for various indications, including the evaluation of therapeutic outcomes. [^{18}F]FMISO has been the most studied under this category and serves as a reference for relatively newer radiotracers such as [^{18}F]FAZA, [^{18}F]FETNIM, and [^{64}Cu]ATSM (or [^{60}Cu]ATSM).

Among these, [^{64}Cu]ATSM seems promising as a prognostic factor in predicting treatment response after chemoradiotherapy, potentially playing a role in treatment planning in advanced stages and in monitoring treatment response in lung cancer.[26,96,110]

Angiogenesis: [^{18}F]alfatide [/^{18}F]Galacto-RGD/[^{64}Cu] VEGF

Angiogenesis, a vital characteristic of cancer, is a process coordinated by an intricate interplay of tumour stroma cells and associated proteins, receptors, and cytokines.

Integrins are key players in this regard, and radiopharmaceuticals targeting these transmembrane glycoproteins, particularly the arginine–glycine–aspartic acid (RGD) sequence, have been developed. RGD radiotracers seem to be complementary imaging agents to [^{18}F]FDG in predicting therapy response, assisting in treatment planning and monitoring in patients receiving antiangiogenic therapies.[98,111–113] However, its overall added clinical value in lung cancer management warrants further research.[96] VEGFR tracers do not yet play any clinical role in the molecular imaging of lung cancer.[114]

Cancer-Associated Fibroblasts: [^{68}Ga]FAPI/[^{18}F]FAPI

Cancer-associated fibroblasts play an important role in the tumour microenvironment. Fibroblast activation protein (FAP) is overexpressed in more than 90% of epithelial malignancies; hence FAP imaging continues to hold promise in the field of oncology due to its pan-cancer status, similar to FDG. While there are ongoing studies on its impact on staging and potential role in radiotherapy planning in lung cancer, not much has been studied in the area of therapy response assessment.[115–117]

Recently, Mittal et al.[118] assessed early response in 15 patients with non-small cell lung cancer by prospectively comparing [^{68}Ga]FAPI and [^{18}F]FDG PET/CT imaging after three cycles of chemotherapy. [^{18}F]FDG PET/CT and [^{68}Ga]FAPI PET/CT showed substantial agreement (kappa = 0.615, $P < 0.05$) in categorizing patients as responders and nonresponders, thus suggesting that ^{68}Ga-FAPI has a role to play in response assessment in NSCLC.

Somatostatin receptors: ^{68}Ga-DOTA-peptides

Pulmonary neuroendocrine tumors (NETs), including SCLC, account for approximately 20%-25% of primary lung neoplasms.[96,119,120]

Somatostatin receptors (SSTR) are generally overexpressed on NETs, particularly SSTR-2.

Somatostatin analogues (such as DOTANOC, DOTATOC, and DOTATATE) radiolabeled with ^{68}Ga have an established role in managing NETs in general, including lung carcinoids.

Therefore, SSTR imaging will be best suited for lung carcinoids (especially typical carcinoids), and the theranostic potentials make therapy response assessment in this category a prospective area to study if approved for this indication.[121]

On the other hand, SCLC, or large cell neuroendocrine carcinomas (LCNEC), are an aggressive form of neuroendocrine neoplasm with high glucose metabolism, making imaging with [^{18}F]FDG the preferred tracer in these tumors. However, given their usually poor prognosis, SSTR imaging and therapy have also been explored.[122,123]

Future Directions

In the era of artificial intelligence, there has been interest in radiomics, a rapidly evolving field of research concerned

with extracting quantitative metrics in medical images using mathematical algorithms.[124–126] Different studies have demonstrated the promise of this field.[127–130] In 2020, Verlentinuzzi et al. found iRADIOMICS superior to current standards using PET metrics such as MTV and TLG of both baseline and follow-up imaging in metastatic NSCLC patients treated with antiPD-1 mAb Pembrolizumab. Notably, the most predictive features were baseline radiomics, which may prove effective in prognosticating response patterns.[128] Ventura et al.[129] also showed that PET-CT-based radiomics may provide parameters with predictive value for response to first-line immune checkpoint inhibitor-based treatment in patients with advanced NSCLC.

A robust review conducted by Manafi-Farid et al.[126] highlighted the potential role radiomics might play in the staging, prognosis and prediction of treatment response before surgery, radiotherapy, chemotherapy, immunotherapy and TKI therapy of NSCLC. In a recent study by Liu et al.,[131] 106 NSCLC patients were evaluated for prediction of therapy response to neoadjuvant therapy using 2016 PET-based and 2016 CT-based extracted radiomic features. They concluded that [18F]FDG PET/CT-based radiomics, in addition to clinicopathological information, was an optimal method for predicting complete response to neoadjuvant therapy in patients with NSCLC. We believe that [18F]FDG PET/CT radiomics should also be explored and might prove useful in the interim and after-therapy assessment settings.

Finally, there are emerging radiopharmaceuticals, such as labeled anti-PD-L1 and anti-PD-1, which have the potential to improve treatment selection and assessment of response to immune checkpoint inhibitors. Examples are the first in-human trials reported with ^{89}Zr-Nivolumab or ^{89}Zr-Atezolizumab.[132,133] Another tracer was studied by Neeta Pandit-Taskar et al.[134] by labelling activated CD8+ lymphocytes with the same ^{89}Zirconium, with potential use in treatment response, particularly to differentiate actual progressive disease from an immune response.

There is no doubt that immunotherapy treatment of NSCLC is here to stay. Therefore, more specific tools for predicting and assessing its response will prove valuable in this setting, as demonstrated by few preclinical and clinical studies.[135–138]

While further research is required to validate their role in assessing treatment response to immunotherapy, we strongly believe they will become clinically valuable tools for both predicting and evaluating treatment response in this context.

Conclusion

[18F]FDG PET/CT plays a vital role in monitoring therapy response in lung cancer, particularly in non-small cell lung cancer (NSCLC). Its significance has grown even further with the development of adapted response criteria in the era of immunotherapy. By integrating metabolic imaging with established criteria, [18F]FDG PET/CT improves the ability to predict treatment outcomes and guide clinical decisions, highlighting the importance of interpreting imaging results in the context of evolving therapeutic strategies.

Beyond the traditional SUVmax, other PET metrics such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have gained attention for their ability to provide a more comprehensive assessment of tumor burden and metabolic activity. These metrics show promise in offering additional prognostic value and may better capture treatment responses in the context of immunotherapy where atypical response patterns are observed.

In addition, the emergence of non-[18F]FDG PET tracers targeting diverse biological pathways offers new opportunities for more tailored assessments. These tracers have the potential to provide deeper insights into tumor biology and therapy response, and their future integration into clinical practice could further enhance the precision of therapy monitoring and the personalization of lung cancer management.

The role of [18F]FDG PET/CT in monitoring therapy response continues to expand, with emerging evidence indicating its potential for predicting early treatment responses and providing valuable prognostic insights. Furthermore, advancements in novel radiopharmaceuticals and imaging techniques, such as radiomics, hold promise for enhancing treatment efficacy assessment and improving patient management in lung cancer.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Akinwale Ayeni: Project administration, Visualization, Writing – original draft, Writing – review & editing. **Osayande Evbuomwan:** Visualization, Writing – original draft, Writing – review & editing. **Mboyo-Di-Tamba Willy Vangu:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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