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^{18}F-FDG PET/CT for Response Assessment in Lung Cancer

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Treatment response assessment in lung cancer is crucial in the management strategy and outcome of patients. Accurate treatment response assessment can guide the treating physicians and improve patient survival. Anatomic and metabolic tumor response assessments have been evaluated extensively, showing a positive impact in the management of these patients. ^{18}F-FDG PET/CT provides early and more specific treatment response assessments, preceding anatomic changes in these tumors. Familiarity with the different treatment response assessment algorithms, criteria, time intervals, imaging pitfalls is essential for treating physicians and nuclear radiologists to provide accurate response assessments. Artificial Intelligence is being more frequently explored for this purpose and can assist physicians in providing prompt and accurate treatment response assessments.
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Introduction

Cancers of the lung and bronchus are the second most common malignancy with an estimated 235,760 new cases in 2021 in the United States, accounting for 22% of all cancer deaths and a lifetime risk of 6.1%. Recent advances in the diagnosis and treatment have led to a steady decline in the death-rate related to these cancers over the past decade.[1] Histopathological and immunohistochemical evaluation play a crucial role in confirming the primary malignancy diagnosis and classifying these tumors which in turn has a significant impact on the treatment strategy and outcome. Majority of lung cancers (85%) are classified as non-small cell lung cancers (NSCLC), which are further classified as adenocarcinoma (39% of all lung cancers), squamous cell carcinoma (20%), large-cell carcinoma (3%) and other minor variants such as sarcomatoid cancers.[2,3] Small-cell lung cancer (SCLC) are more aggressive with neuroendocrine characteristics accounting for 15% of all lung cancers.[2]

Patient survival depends on the stage of the tumor with 5-year relative survival ranging from 60% in localized disease to 6% in patients with distant metastases. The corresponding rate for regional metastases is 22%. This highlights the importance of early diagnosis, accurate staging with prompt initiation of treatment, early treatment response assessment and determination of prognosis to improve patient survival and outcomes.[1] ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) Positron Emission Tomography/Computed Tomography (PET/CT) plays an important role in the staging, treatment planning, response assessment, detection of recurrent disease, follow-up and prediction of prognosis in these patients.[4-7]

Accurate treatment response assessment is critical to evaluate the effectiveness of current treatment strategy, identify residual or progressive disease to guide further management. However, appropriate timing of the PET/CT and knowledge of potential PET/CT interpretation pitfalls is important for the interpreting nuclear radiologist and the clinician to decrease false positive conclusions related to ^{18}F-FDG uptake in posttreatment inflammation. With the introduction of numerous immunotherapeutic agents in the recent past, differentiating true disease progression from inflammatory

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radiotracer uptake is a common imaging challenge in evaluating treatment response in these patients.[8,9]

This article will focus on the role of ^{18}F-FDG PET/CT in the treatment response assessment of lung cancers. The most used response criteria, potential pitfalls, with special focus on recent advances, especially in artificial intelligence in the treatment response assessment of lung cancers will be discussed.

Management of Lung Cancer

Management of NSCLC

Initial Surgical Treatment

Following the initial staging of NSCLC, management depends on the primary extent of the tumor (T), nodal disease (N) and the presence of distant metastatic disease (M). Detailed discussion of the treatment strategies is beyond the scope of this article. In patients without nodal disease and operable tumors, initial surgical exploration and resection with mediastinal nodal dissection or systemic lymph node sampling is the treatment of choice. In patients with possibly resectable tumors, neo-adjuvant preoperative concurrent chemoradiation or chemotherapy is given, and the tumors are reevaluated with chest CT with or without ^{18}F-FDG PET/CT and a surgical plan is made if the tumor is resectable. In patients with separate pulmonary nodules in the same lobe or ipsilateral non-primary lobe, surgery is preferred. Patients with contralateral lung nodules are treated as two primary lung tumors. Parenchymal sparing resection is recommended in solitary metachronous disease.

Adjuvant Treatment

In early stage (1A) disease with negative margins, observation without adjuvant treatment is recommended. In patients with early stages (IA-IIB) and positive margins, re-resection or radiation therapy with or without adjuvant chemotherapy is considered. In patients with stage 1B or IIA disease with negative margins, they can either be observed or treated with adjuvant chemotherapy and osimertinib in high-risk patients. In higher stages (IIB-IIIA), adjuvant chemotherapy and atezolizumab or osimertinib is preferred.

In patients with positive margins (IA-IIIB), reresection with or without chemotherapy or adjuvant radiation with or without chemotherapy or adjuvant sequential/concurrent chemoradiation is considered depending on the stage of the primary disease.

Definitive Radiation Therapy

In lower stage inoperable tumors without nodal disease (IA-IIB), definitive radiation therapy (RT), preferably stereotactic ablative radiotherapy is suggested, followed by surveillance or adjuvant chemotherapy for high-risk disease. Radiation therapy or image-guided thermal ablation can be considered in patients with metachronous disease as alternative treatment to parenchymal sparing surgical resection.

Definitive Chemotherapy or Chemoradiation

In patients with inoperable tumors, N2 or N3 disease, definitive concurrent chemoradiation therapy followed by adjuvant Durvalumab is recommended. In patients with N2 disease, alternative treatment strategy includes induction chemotherapy with or without RT followed by surgery or RT with or without chemotherapy, depending on response to induction therapy. In patients with inoperable metachronous tumors, palliative chemotherapy with or without local treatment can be considered.

Management of Metastatic Disease

In patients with metastatic disease, the management strategy depends on the extent of distant metastases, performance status and patient prognosis. A multidisciplinary approach to the treatment is crucial and treatment strategy includes a combination of antineoplastic systemic therapy along with palliative care. In patients with M1a disease, local therapy such as pleurodesis, catheter drainage or pericardial drainage is considered along with systemic therapy. In patients with M1b disease, molecular biomarker testing, brain MRI, ^{18}F-FDG PET/CT along with histopathological confirmation of metastatic disease, when possible is recommended. In patients with limited intracranial metastases, stereotactic radiosurgery or surgical resection followed by stereotactic radiosurgery or whole brain RT are options. Molecular biomarker status has an impact on the choice of systemic treatment which often include chemoimmunotherapy. For example, an EGFR tyrosine kinase inhibitor, afatinib is chosen in EGFR positive NSCLC.

Other Considerations

Patients with suspected multiple lung cancers with no disease outside the chest, the management depends on mediastinal nodal status. Observation can be considered in patients at low risk of being symptomatic. Otherwise, definite local therapy similar to the management of metachronous disease is recommended, as described above.[10]

Management of SCLC

In patients without nodal or distant metastases (stage I-IIA), lobectomy and mediastinal lymph node dissection or sampling is preferred in operable tumors. In tumors not amenable to surgery, stereotactic ablative radiotherapy or concurrent chemoradiation is considered. In higher stage disease (IIB-IIIC), systemic therapy with or without RT is considered depending on the performance status of the patient. Individualized treatment with supportive care is recommended in patients with poor performance status due to factors not related to the primary cancer diagnosis. Similar principles apply to extensive stage disease. Systemic therapy regimens in extensive stage disease often include immunotherapeutic agents such as atezolizumab or durvalumab. Additional local directed therapy may be necessary to prevent complications or to alleviate secondary effects. For example, patients with high risk of fracture secondary

to metastatic disease may require stabilization and external beam RT.[10]

Treatment Response Assessment in Lung Cancers

Early treatment response assessment in patients with lung cancer is crucial to identify non-responders in whom treatment plan may need to be altered to improve patient outcome. Imaging plays an important role in treatment response assessment. Evaluation with PET/CT offers the advantage of demonstrating pathologic response of the tumor, which often precedes anatomic changes seen on conventional imaging. Imaging treatment response is pertinent in patients receiving neoadjuvant therapy prior to definitive surgical resection. Tumors deemed unresectable may be treated with definitive chemoradiation. In these patients, chest CT with or without PET/CT is recommended.[10] Following definitive therapy, current practice guidelines have no clear recommendations for the frequency and appropriate time interval after completion of treatment for imaging evaluation of treatment response.[11] However, recurrent, or residual malignancy have been demonstrated in up to one-third of these patients.[12] PET/CT can be advantageous over conventional imaging for the evaluation of treatment response in lung cancer with a significant impact on patient outcome.[13,14] The timing of PET/CT often poses a challenge secondary to posttreatment inflammation and associated false positive assessments of treatment response. Factors to be considered are the treatment end point under assessment, responsiveness, and biology of the tumor type under evaluation, clinical treatment response assessment etc. In general, a time interval of 1-2 weeks after chemotherapy may be sufficient for evaluation, with the greatest response at 3-4 weeks after initiation.[15] However, following radiotherapy the optimal time point is often under debate and generally a 6-12 weeks interval is necessary to account for posttreatment related inflammation.[16]

Quantitative and Semiquantitative Assessment of Treatment Response in Lung Cancers

Imaging treatment response assessment in oncology can be assessed with measuring changes in the size or volume of tumor burden and/or measuring semiquantitative metabolic tumor markers assessed on PET/CT imaging. The most used criteria which incorporate PET/CT parameters for treatment response have been briefly discussed below

Response Evaluation Criteria in Solid Tumors (RECIST) Criteria

The most widely used objective quantitative anatomic response assessment is the RECIST criteria. The most recent RECIST 1.1 evaluates tumor burden with identifying total of five target lesions, up to two per organ and recording the sum of their longest diameters. Soft tissue lesions are considered measurable if they are greater than or equal to 10 mm in their long axes. Lymph nodes are considered measurable if they are equal to or greater than 15 mm in their short axes. Smaller lesions, skeletal metastases without a soft tissue component, ascites, pleural effusion, lymphangitic spread of tumor, leptomeningeal disease, cystic or necrotic lesions or lesions within an irradiated region are considered non-measurable but noted. Baseline measurements are recorded as close to the treatment initiation as possible (<4 weeks). Limitations of anatomic measurement accuracy exists. In real practice, interobserver variability is a challenge with misclassification in approximately 40% of patients.[17] In the updated criteria, PET/CT findings are included in the criteria for the detection of new lesions only (Fig. 1). Although only shown in a small cohort of patients, PET/CT resulted in change in categorization from stable to progressive disease in one-third of patients with new lesions detected on PET/CT. Response categories are assigned based on changes in the measurements as detailed in Table 1.[18,19]

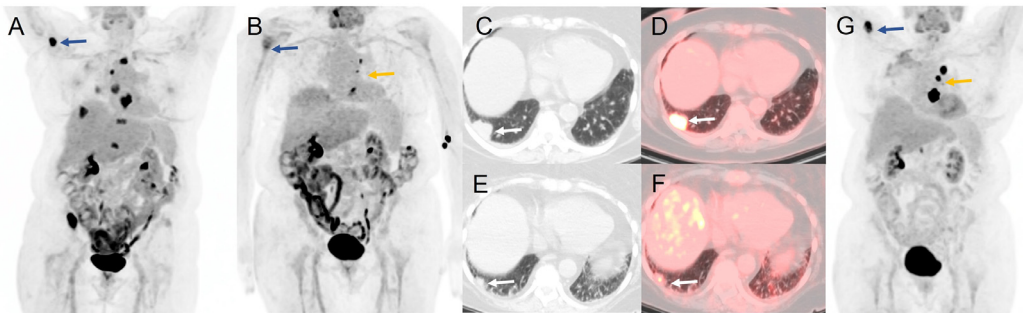

Figure 1 73-y-old woman with right lower lobe moderate to poorly differentiated adenocarcinoma. Coronal MIP (A), axial CT (C), axial fused PET/CT (D) of a staging PET/CT demonstrate a hypermetabolic right lower lobe mass (white arrows) consistent with known primary malignancy with hypermetabolic nodal, and osseous metastatic disease. Following three cycles of systemic chemotherapy, although there is significant improvement in the FDG uptake of previously seen lesions, as seen on the coronal MIP (B), axial CT (E) and axial fused PET/CT (F) of the follow-up PET/CT new FDG-avid lesions are noted in the left internal mammary nodal station (yellow arrows). Subsequent PET/CT (G) confirmed progressive disease in the new lesions with increasing uptake in a previously seen right humeral lesion (blue arrows).

Table 1 Quantitative and Semiquantitative Treatment Response Assessment Criteria

Treatment Response Categories	RECIST 1.1	PERCIST 1.0	EORTC
Complete Response (CR or CMR)	Disappearance of all target and non-target lesions*	Complete resolution of FDG uptake with the uptake less than the mean SUL of liver and indistinguishable from surrounding background	Complete resolution of the FDG uptake within the tumor, indistinguishable from the background.
Partial Response (PR or PMR)	At least a 30% decrease in sum of target diameters	A decrease of greater than 30% and an absolute decrease of 0.8 SUL units between the target lesions	Reduction in SUV by 15%-25% after 1 cycle of chemotherapy and greater than 25% in subsequent cycles
Progressive Disease (PD or PMD)	20% increase + 5-mm absolute increase in the sum of the target lesions**	An increase of greater than or equal to 30% and an absolute increase of 0.8 SUL units between the target lesions or development of one or more new lesions.	Increase in SUV by 25%, visible increase in the extent of FDG uptake (>20%) and/or appearance of new FDG avid lesions
Stable Disease (SD or SMD)	Neither PR nor PD	Neither PMR nor PMD	FDG uptake increase by <25% and decrease by <15% and no visible increase in the extent of the FDG uptake
Non-CR/Non-PD	Persistence of one or more non-target lesions		

CMR, complete metabolic response; PMD, progressive metabolic disease; PMR, partial metabolic response; SMD, stable metabolic disease
*All pathological lymph nodes must have reduction in size to short axis <10 mm
**Appearance of one or more new lesions is also considered disease progression; When there is overall increase in non-target tumor burden even with SD or PR in target disease is considered progression.

Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST)

PERCIST 1.0 was introduced in 2009 and was found to predict treatment response and clinical outcome in many different types of cancers.[20] It is important to note that the original criteria were proposed with semiquantitative standardized uptake value corrected for lean body mass (SUL) measurements in the tumor and background reference normal structures. The use of SUL instead of the most widely used SUV, corrected for body weight can eliminate semiquantitative measurement changes related to fluctuation in body weight. The authors also used SULpeak instead of single-pixel SUVmax to decrease variability related to noise and filtering. Background normal liver activity with SUL within a 3 cm volume of interest is measured. When the activity in the descending thoracic aorta is measured instead of the liver for background normal blood pool reference value, a 2 × 1 cm rectangular volume of interest is used. A visual inspection of the PET images is performed to identify metabolically active foci that are consistent with malignant lesions. The highest SULpeak is measured in the single hottest tumor within a 1mL spherical volume of interest. Important points to consider are for a lesion to be considered measurable the SULpeak must be greater than or equal to one and a half times the mean SUL for the reference liver plus two times the standard deviation. If the blood pool reference activity is used instead of the liver, the lesion should be at least two times the mean SUL plus two times its standard deviation, because the blood pool activity is typically less than that of the liver. It is to be noted that the target lesion may not necessarily be the same lesion between the two time points. The hottest lesion is chosen at each time point of evaluation[21] (Fig. 2).

European Organization for Research and Treatment of Cancer (EORTC) Criteria

The earliest of criteria established for the evaluation of treatment response in solid tumors was the criteria laid out by the EORTC PET study group. The SUV measurements used in this criterion were corrected for body surface area. The categories of treatment response were similar to the categories outlined in the previous criteria (Table 1).[16]

Studies comparing the different interpretation criteria are limited. A study comparing RECIST 1.1, PERCIST 1.0 and EORTC in patients with advanced NSCLC after chemotherapy showed that the sensitivity and accuracy of EORTC and PERCIST 1.0 was better than RECIST 1.1 for predicting treatment response with less discordant classifications between the response assessments by PERCIST and EORTC. One important limitation highlighted was some patients classified as stable disease anatomically by RECIST 1.1 demonstrated changes in metabolic parameters and were categorized as at least partial metabolic response by PET-based treatment response assessments, which in turn has impact on patient outcome and management strategy[22] (Fig. 3).

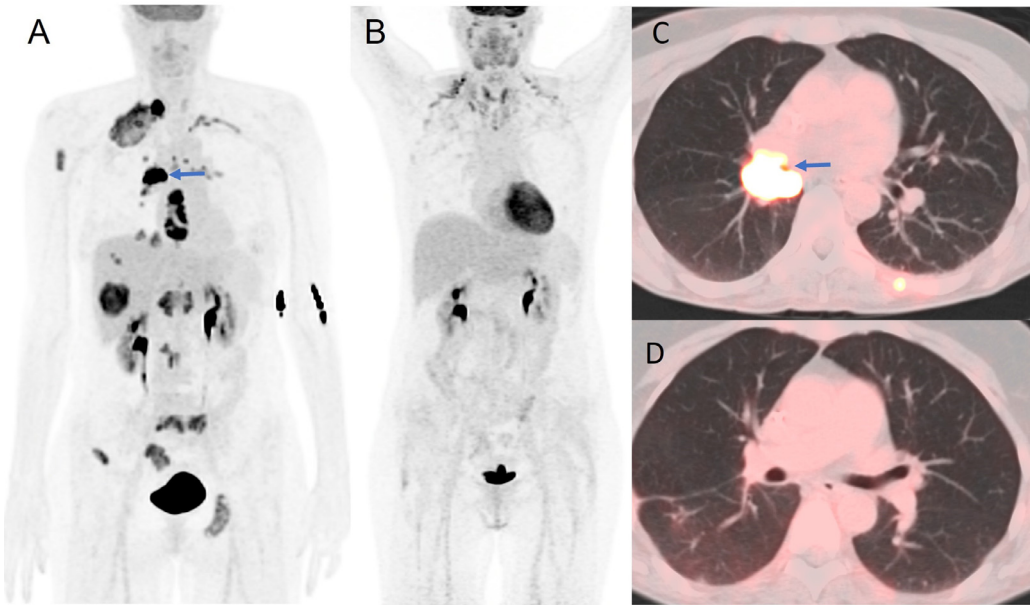

Figure 2 50-y-old female with metastatic poorly differentiated adenocarcinoma of the lung. Coronal MIP (A) of the staging PET/CT demonstrates hypermetabolic right hilar mass with metastatic disease involving the nodes, pleura, liver and bones. The hottest lesion was identified as the right hilar mass and shown on the axial fused PET/CT (C) (blue arrows) with peak SUVlbm of 24.4. She underwent radiation therapy to a few osseous lesions followed by systemic chemoimmunotherapy. A follow-up PET/CT performed approximately 2 mo after therapy shows complete metabolic response (PERCIST 1.1). Physiologic radiotracer uptake is noted in the brown fat within the soft tissues of the neck.

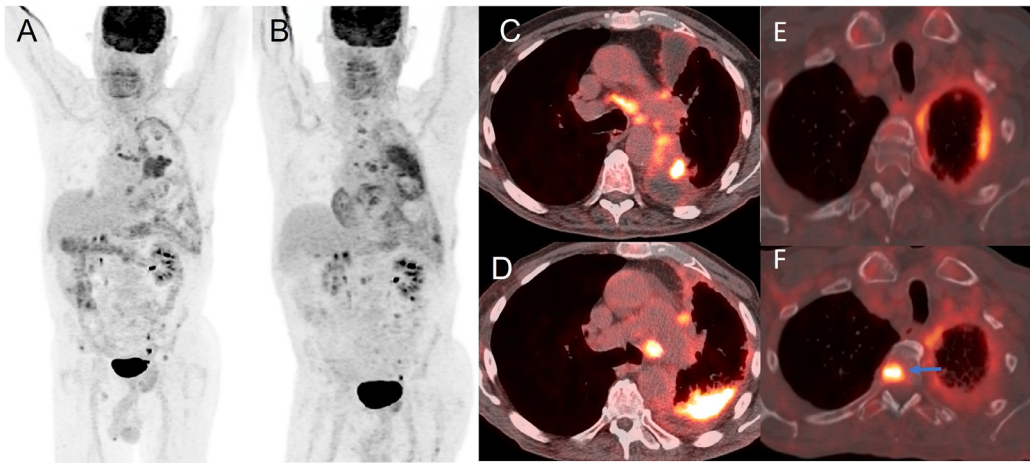

Figure 3 83-y-old man with metastatic left lower lobe adenocarcinoma. Coronal MIP (A), axial fused PET/CT (C, E) of a staging PET/CT demonstrates the left lower lobe mass with metastatic disease in the nodes, pleura, malignant pleural effusion. He was initially treated with chemoimmunotherapy. Coronal MIP (B), axial fused PET/CT images (D, F) of the re-staging PET/CT performed after four cycles followed by maintenance therapy demonstrated progressive disease with increase in the extent of the left lower lobe mass, pleural metastases, malignant pleural effusion and lymph nodes with new metabolically active foci in the bones (blue arrow), suggestive of progressive disease, requiring change in management plan.

Other Metabolic Tumor Assessments

Although the most used metabolic quantitative measurement for treatment response assessment and tumor burden is maximum standardized uptake value corrected for body weight (SUVmax) in routine clinical practice, which has limitations highlighted above. Prospective studies have shown change in SUVpeak and metabolic tumor volumes (MTV) as better predictors of response following chemoradiation.[23] For clinical utility purposes, an SUVmax reduction by at least 20% after chemotherapy, as early as the first cycle can predict response to treatment.[24] Following neoadjuvant therapy, a significant reduction in SUVmax (>80%

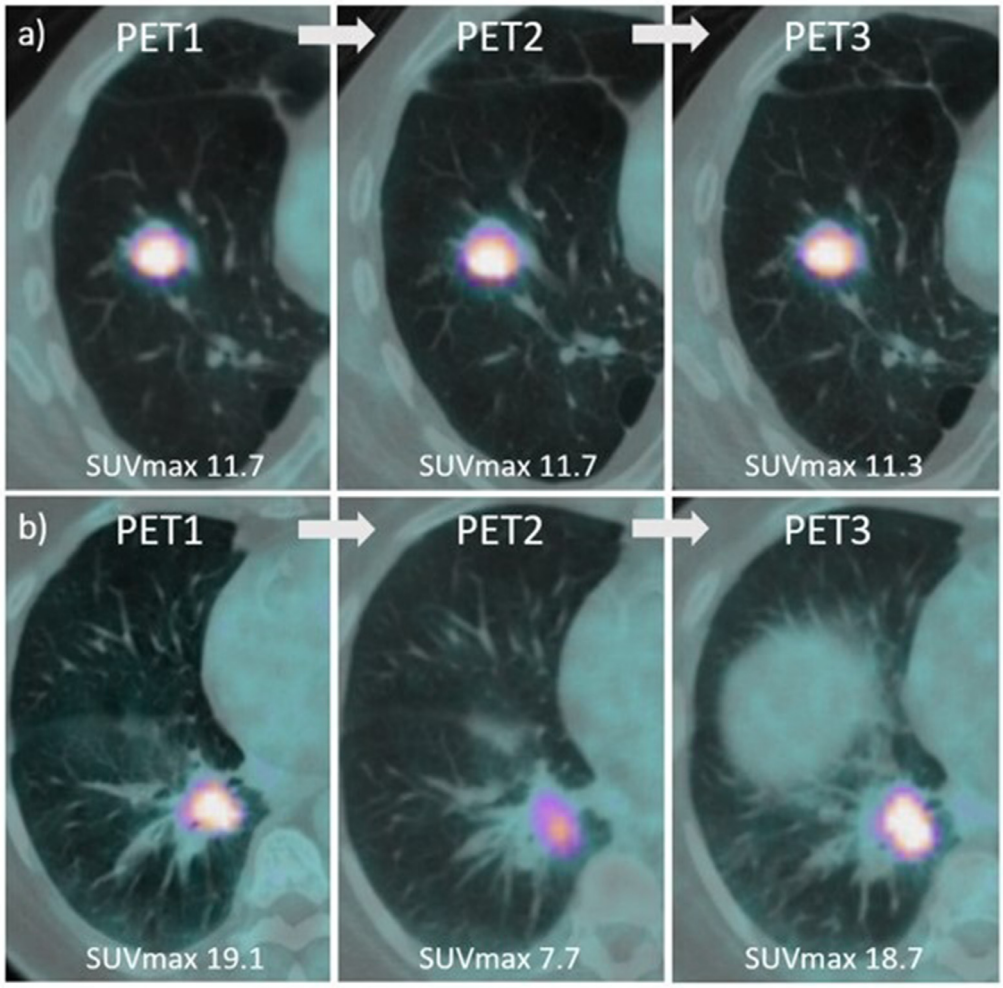

Figure 4 Representative PET/CT images from two patients illustrating relative metabolic stability (A) and dynamic changes in maximum SUV (B) over the course of treatment: (A) patient with early stage (T1b N0 M0) adenocarcinoma of the right lower lobe treated with SBRT alone; (B) patient with advanced (T3 N0 M1) lung adenocarcinoma, with progression at right lower lobe, treated with SBRT and concurrent carboplatin, pemetrexed and pembrolizumab.[28]

decrease) correlates significantly ($P < 0.001$) with pathologic tumor response, better than changes in CT tumor volume.[25] Although, comparison of absolute SUV parametric values may not accurately reflect the changes in tumor metabolic activity, it has been shown that there can be a significant difference in SUVmax after neoadjuvant chemoradiation in mediastinal nodes between responders and non-responders (2.5 vs 3.5; $P = 0.04$).[26] Other metabolic tumor markers such as tumor lesion glycolysis (TLG) can also be used to identify patients at risk of disease progression. A 50% decrease in TLG can predict treatment reponse with a high sensitivity (100%) and negative predictive value (100%) after chemotherapy, better than decrease in MTV (83%, 90%) and RECIST (75%, 89%), respectively, However, these parameters suffer from low specificity and positive predictive value[27]. Although there is constant debate on the timing of PET/CT following radiation therapy to avoid false positive findings related to inflammation, a small prospective study of 14 patients in patient receiving SBRT for lung cancer has shown that metabolic changes in the tumor during SBRT measured serially (2 weeks after treatment initiation, between fraction 1 and 2, and fractions 4 and 5) can predict disease progression. The authors reported distant failure in patients with progressive increase in the primary lesion SUVmax ($P = 0.025$). Similar correlation was demonstrated with SUVmax/SUVmean, SUVmean/liver SUVmean, MTV/GTV, SUVmax/mean coefficient of variation. PET variables without significant change during treatment did not predict local or distant failure[28] (Fig. 4).

Qualitative Criteria and Visual Assessment of Treatment Response

Multiple qualitative response assessment criteria have been introduced over the years to assist clinicians to determine PET/CT treatment response assessment with simple and time-efficient criteria using internal normal reference standards, most commonly the mediastinal blood pool and normal liver (Table 2).

Table 2 Qualitative Treatment Response Criteria in Lung Cancer

Hopkins Criteria[30]	Mac Manus Score[14]	Deauville Score[32]	Kremer Score[26]	Interpretation
Uptake < mediastinal blood pool	No tumor uptake or uptake = mediastinum (CR)	No tumor uptake	No pathological uptake (CR)	Negative
Uptake > mediastinal blood pool <liver		Mild uptake < mediastinal blood pool	Substantial decrease in area and intensity of uptake < mediastinum (Significant Response)	
Diffuse uptake > mediastinal blood pool or liver*		Uptake > mediastinum < liver		
	Reduction in intensity of uptake and/or tumor volume decrease + no disease progression at distant sites (PR)		Reduction in area and intensity but uptake > mediastinum (PR)	Positive
Focal uptake > liver	No appreciable change in uptake + no new sites (SD)	Uptake slightly to moderately higher than liver	No change (SD)	
Focal and intense uptake > liver	Appreciable increase in tumor uptake or volume + other thoracic or distant metastatic disease progression (PD)	Markedly increased uptake or any new lesion	Worsening of uptake with increase in uptake and/or appearance of new sites of disease (PD)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*Probable inflammation.

Although, many of these criteria were introduced in other primary cancers, attempts have been made to validate these criteria in the treatment response of lung cancers. For example, the Hopkins criteria, initially introduced for the treatment response assessment of head and neck cancers with promising results has been validated in lung cancer, performed approximately 7-8 weeks after treatment completion.[29] These studies demonstrated good inter-reader agreement for the visual interpretation with overall high sensitivity, positive predictive value, and accuracy. The reported sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 89%, 79%, 92%, 73%, 86% and, 89%, 80%, 93%, 71%, 87%, respectively in these two studies. These findings correlated with patient survival (hazard ratio 6.1, $P < 0.001$). These findings held true in NSCLC or SCLC, patients treated with primary surgical resection and in patients who underwent definitive chemotherapy or chemoradiation.[29,30] Mac Manus et al described a similar interpretation criterion in NSCLC patients prospectively and showed that posttreatment PET scans performed approximately 70 days after completion of radiotherapy was a strong predictor of time to survival, outperforming CT evaluation.[14] Similarly, Deauville criteria, one of the most popular qualitative PET treatment response criteria in solid tumors can be applied to lung cancers.[31] In a routine clinical setting, qualitative visual interpretation with promising results as above can be more practical and widely accepted. However, there are limited studies comparing the different treatment response criteria to help clinicians decide which one of these criteria may be advantageous over the other. Turgeon et al compared the EORTC,[16] PERCIST criteria,[20] Deauville score and Peter Mac score approximately 90 days after radiotherapy and showed that, although all four criteria were strongly associated with patient survival, visual qualitative interpretation criteria showed less inter-reader variability and were better able to identify complete responders.[32] Kremer et al described a similar visual five-point scoring system for assessing mediastinal nodal response to neoadjuvant chemoradiation in NSCLC patients comparing the uptake to mediastinal blood pool primarily with uptake less than the mediastinum considered negative. However, the exact time interval between the chemoradiation therapy and the PET/CT is unclear. The reported sensitivity, sensitivity, specificity, positive predictive value, negative predictive value and accuracy were 100%, 94%, 75%, 100% and 95%, respectively.[26]

Each of these criteria have their own benefits and limitations. In the clinical research setting, a more objective criteria for treatment response documentation may be favored. In routine clinical practice, qualitative response criteria may offer a fast, simple method to assess treatment response and provides the advantage of discriminating false positive findings such as posttreatment inflammation, changes in lung configuration and varied patterns of treatment response between patients (Fig. 5). However, these criteria can be

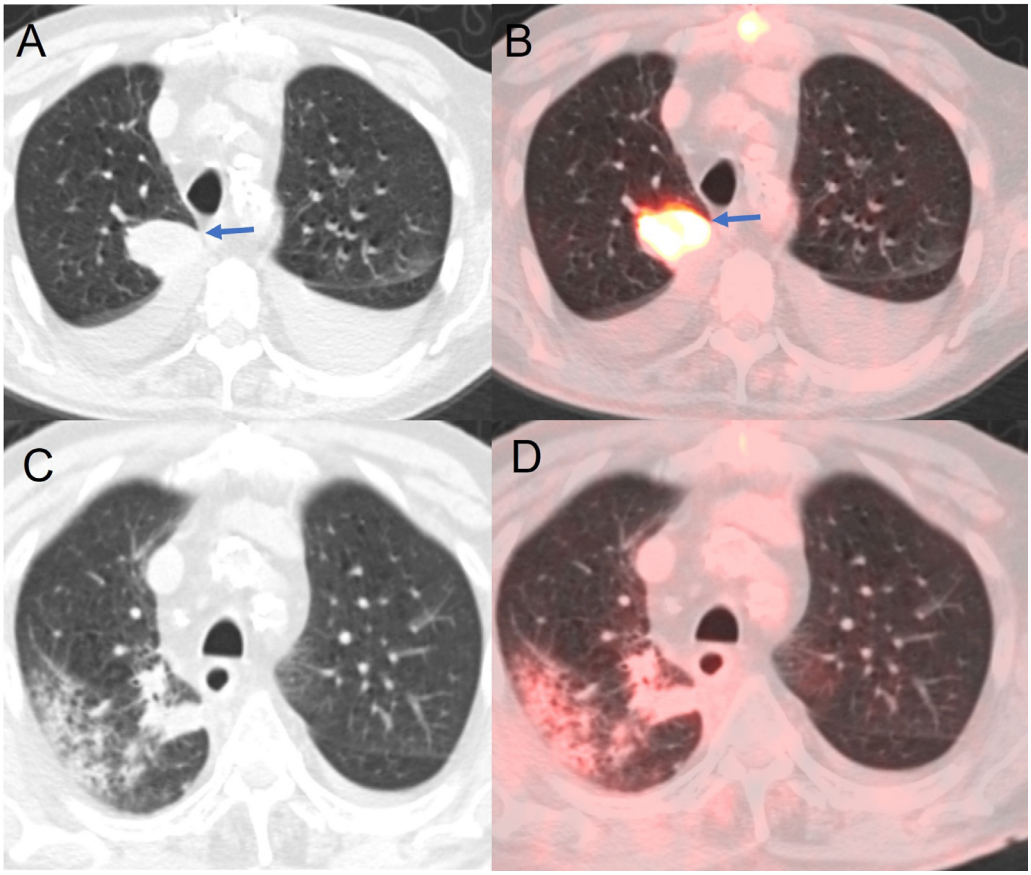

Figure 5 80-y-old man with T2N0 NSCLC of the right upper lobe. Axial CT (A), axial fused PET/CT (B) of the staging PET/CT demonstrates a hypermetabolic right upper lobe lung mass (blue arrows), consistent with the known primary. No other findings of locoregional or distant metastatic disease was identified. The patient underwent SBRT to the right upper lobe and the axial CT (C), axial fused PET/CT (D) of a posttreatment PET/CT demonstrates diffuse radiotracer avid parenchymal opacities in the right upper lobe without significant residual FDG-avid mass, consistent with radiation pneumonitis. Radiotracer uptake in the sternum is related to inflammatory radiotracer uptake from recent sternotomy for CABG.

subjective with some of these criteria lacking precise definition of each category which can lead to suboptimal interpretations without adequate training and prior experience with radiology-pathology correlation to the novice reader.

Other visual interpretations have been used to predict response without set criteria. Considering focal FDG uptake greater than background hilar or mediastinal uptake suspicious for disease, following post-induction therapy PET/CT response had better sensitivity ($P < 0.0001$) and accuracy ($P = 0.012$) compared to mediastinoscopy re-staging, likely related to posttreatment related changes that may be challenging to mediastinoscopy.[33]

Immunotherapy Treatment Response Assessment in Lung Cancer

Treatment strategies for many solid tumors currently include immunotherapy with the recent advances in immunotherapeutic agents. Lung cancer treatment often include an array of immune checkpoint inhibitors as described above. Changes in the metabolic activity and semiquantitative PET measurements can help problem solving with many of these tumors demonstrating immune response related morphologic changes which can be a challenge to the response assessment.[9,34,35] PET/CT also helps in predicting prognosis in these patients.[36] These findings led to the modification of some of the above-described response criteria to address atypical treatment related findings to different pseudoprogression from true disease progression.[37,38] Current treatment response assessment guidelines after immunotherapy are described in detail in the subsequent sections of this issue.

Prognostic Significance of Treatment Response Assessment

Patients who demonstrate a favorable response to treatment have better overall outcome in terms of overall survival, disease-free survival, event-free survival, risk of distant disease,

local disease control, morbidity, and mortality, across different treatment strategies and stages of disease ranging from neoadjuvant or definitive chemotherapy or chemoradiation, surgery, SBRT or a combination of the above.[39-44] PET/CT plays an important role in this assessment in comparison to conventional CT imaging assessments. In non-responders, in comparison to those with complete response, there was a significant difference in relative death rate (Hazard Ratio (HR) 4.4 ($P = 0.0003$) vs 3.4 ($P = 0.47$)). Adjusted for known prognostic factors such as performance status, stage of tumor, weight loss, CT response, PET response has been shown to be significantly associated with patient survival ($P < 0.0001$).[14] The different treatment response criteria mentioned earlier in this paper can provide valuable prognostic information. Treatment response assessed after chemotherapy, chemoradiation and/or surgical management with PERCIST,[45] EORTC[46] or Hopkins criteria[30] have all shown to predict patient outcome. PERCIST may be a better predictor of disease-free survival in comparison to RECIST.[47] A study has shown concordance in the treatment response assessment between PERCIST and EORTC with a significant correlation with overall survival.[48] A single comparison study of the different interpretation criteria showed a 2-year overall survival of 76% vs 51%; 76% vs 50%; 85% vs 44%; and 82% vs 45% for the EORTC, PERCIST, Mac Manus and Deauville criteria, respectively between patients categorized as complete responders vs those who were not.[32] NSCLC patients on definitive chemotherapy closely studied prospectively with changes in SUVmax weekly after initiation of therapy, demonstrated a positive outcome in patients with a negative regression slope showing decrease in tumor SUVmax over time compared to those who did not (median survival 20 weeks vs median survival was not reached in the group with decrease in uptake ($P = 0.0016$)).[15] In advanced NSCLC patients receiving neoadjuvant chemoradiation therapy, the decrease in FDG uptake is significantly associated with patient survival, as early as 2 weeks after induction chemotherapy and prior to radiation therapy. A 60% decrease in SUV was associated with better 5-year survival (60% vs 15%; $P = 0.0007$). The survival was significantly lower (<5%) when the SUV decrease was lower than 25%. This may be an indication to alter chemotherapy regimens in these patients to improve outcome. Important observations to note were that there was no significant change in the SUV measurements after radiotherapy in all tumor types except squamous cell carcinoma ($P = 0.006$). There was also a close correlation between SUVmax and SUVmean measurements.[49] In patients receiving definitive radiation therapy, a meta-analysis of five studies showed that the post radiation SUVmax correlated with overall survival (HR 1.3) and local disease control (HR 2.0). In patients receiving SBRT, a similar association was noted (HR 2.2).[50] Percentage decrease in TLG can independently predict overall survival and percentage decrease in MTV can predict progression-free survival. In comparison to RECIST, TLG was shown to be a better predictor of progression-free survival.[27]

Artificial Intelligence (AI) in PET/CT Treatment Response Assessment

Machine Learning

There is growing interest in the application of neural networks for machine-learning based image processing, computer assisted detection, computer assisted diagnosis, and response assessment within Radiology and Medicine as a whole. These efforts remain in their early stages and primarily so far have focused on predicting response to various therapeutic agents via pathologic and radiomic features on CT. Despite the important qualitative and quantitative role of FDG PET in response assessment, machine learning tools have yet to seriously scratch the surface by incorporating PET data. These are described in detail in a dedicated section in this issue.

AI Assisted Reconstruction

While direct use of the FDG PET/CT data in direct response assessment remains in its infancy, machine learning has already been incorporated into the imaging chain by both imaging equipment manufacturers as well as standalone software vendors. Canon,[51] United Imaging,[52] Siemens,[53] and Subtle Medical[54] all offer AI-assisted reconstructions as an evolution of iterative reconstruction which performs post-processing noise reduction to enhance imaging quality. These systems allow tweaks to the conceptual equation *Image Quality = scanner sensitivity x scan time x tracer dose* by allowing image quality to be preserved while significantly decreasing scan time (therefore increasing throughput) or decreasing radiation dose. These algorithms can provide image enhancement for whole-body exams,[55] but also may create image quality improvements in PET/CT image quality specifically helpful for pulmonary assessment by increasing lesion conspicuity[56] of small pulmonary nodules or lymph nodes. Aside from noise reduction, other uses of machine learning in image acquisition include respiratory motion correction to reduce blur and automated image acquisition protocol tailoring based on patient anatomy.

AI Augmented Response Assessment

Many of the current methods for response assessment require rigorous adherence to measurement protocols to properly derive the RECIST, PERCIST, or EORTC data while using a clinical PACS viewer. The groundwork is there for a futuristic software product that integrates a DICOM viewer (or plugs into an existing PACS product) and incorporates several disparate machine learning products to create an AI-Augmented Response Assessment system. By combining image segmentation networks with a system that can receive DICOM image data, such a system could automatically segment and track candidate lesions,[57] measure the appropriate quantitative parameters (eg. size, SUVmax, SULpeak), and perform multiple response assessments automatically (RECIST 1.1, PERCIST 1.0, and/or EORTC), ultimately reducing timepoint-to-timepoint variability and improving data accuracy.[58] This could be an iterative system that adds new models as they are developed and validated, such as automated whole-body

total lesion glycolysis as a mechanism for tracking tumor burden and response.[59] CT algorithms could also be included, such as any of the predictive lung cancer radiomics systems or morphometric analysis[60] for prediction of surgical outcomes[61] or tolerance of other therapeutic toxicities.[62]

Conclusion

Treatment response assessment in lung cancer is crucial in the management strategy and outcome of patients. Accurate treatment response assessment can guide the treating physicians and improve patient survival. Anatomic and metabolic tumor response assessments have been evaluated extensively, showing a positive impact in the management of these patients. PET/CT provides early and more specific treatment response assessments, preceding anatomic changes in these tumors. Familiarity with the different treatment response assessment algorithms, criteria, time intervals, imaging pitfalls is essential for treating physicians and nuclear radiologists to provide accurate response assessments. Artificial Intelligence is being more frequently explored for this purpose and can assist physicians in providing prompt and accurate treatment response assessments.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.semnuclmed.2022.04.001.

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