Imaging of Novel Oncologic Treatments in Lung Cancer Part 1

Systemic Therapies

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Abstract: Thoracic tumors are a leading cause of cancer-related morbidity and mortality. In recent years, developments in oncologic treatments for these tumors have ushered in an era of targeted therapy, and, in many cases, these novel treatments have replaced conventional strategies to become standard therapeutic options, particularly in those with lung cancer. Targeted medical therapies for lung cancer now include angiogenesis inhibitors, tyrosine kinase inhibitors, and immunotherapeutic agents. Several novel ablative therapies have also gained widespread acceptance as alternatives to conventional surgical options in appropriately selected patients. Tumors treated with targeted medical therapies can respond to treatment differently when compared with conventional therapies. For example, pseudoprogression is a well-described phenomenon in patients receiving checkpoint inhibitor immunotherapy in which an initial increase in tumor burden is followed by a decrease in tumor burden and sometimes partial or complete response, while the frequent cavitating responses seen when antiangiogenic agents are used can be difficult to quantify using existing response assessment criteria. In some cases, novel response assessment criteria are needed to adequately capture response. In addition, numerous treatment-related side effects have been described, which are important to recognize, both to ensure appropriate treatment and to avoid misclassification as worsening tumor. Imaging plays a vital role in the assessment of patients receiving targeted medical therapy, and it is essential that thoracic radiologists are familiar with the rationale underpinning these treatments and the expected posttherapy findings.

Key Words: thoracic malignancy, lung cancer, response assessment, tyrosine kinase inhibitor, immunotherapy, antiangiogenesis

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LEARNING OBJECTIVES

After completing this CME activity, physicians should be better able to:

1. Assess the clinical background of targeted medical therapies in lung cancer.
2. Outline the novel patterns of treatment response observed in patients receiving targeted cancer therapies and why conventional response assessment tools such as RECIST 1.1 may not be applicable in these patients.
3. Analyze imaging finding of thoracic-related adverse events associated with targeted medical therapies.

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Thoracic malignancies, of which lung cancer is the most common, are a leading cause of cancer-related morbidity and mortality.[1] The advent of targeted therapy in oncology has dramatically changed the treatment of lung cancer. In addition to novel ablative therapies such as stereotactic body radiation therapy and image-guided percutaneous thermal ablation, numerous targeted medical agents have emerged as viable treatment options in patients with advanced lung cancer.

Historically, medical therapy for advanced lung cancer relied on the use of platinum doublets.[2] Recent drug development that focused on specific cell signaling pathways or oncogenic processes coupled with molecular characterization of tumor subtypes has led to the development of targeted drugs. These include agents that act on angiogenesis pathways,[3] agents that act on tumors with specific genetic mutations,[4] and those that cause immune-checkpoint inhibition, thus promoting an antitumor immune response.[5,6]

Imaging findings, when targeted medical and ablative therapies are used, can differ from those that are seen following the use of cytotoxic chemotherapy or conventional radiation and surgical techniques. It is, therefore, crucial that radiologists become familiar with these novel therapeutic options and are aware of the expected posttherapy imaging findings. We aim to review the clinical background of the most frequently used targeted medical treatments in lung cancer, to describe expected posttreatment radiologic findings, and to summarize novel approaches to radiologic response assessment.

MOLECULAR TARGETED THERAPY

Historically, medical treatments for cancer relied on drugs that targeted rapidly dividing cells and were nonspecific in killing both cancerous and noncancerous cells.[2] Targeted treatments that act on molecular signaling pathways crucial to cancer cell survival are in theory more specific in targeting tumors.[7,8] The nomenclature and classification of these agents can be complex, as numerous molecular pathways have been identified as targets for therapy. Broadly, the nomenclature reflects the site of action of the drug and can be divided into monoclonal antibodies acting on the cell surface or on circulating growth factors

(typically such agents end with the suffix -mab), or as small molecule inhibitors acting within the cell (typically such agents end with the suffix -nib).[9] Examples of cellular processes that are targeted by drugs currently approved for cancer treatment include hormonal pathways, signal transduction pathways, gene expression modulation, angiogenesis pathways, and antitumor immunologic pathways. This discussion will focus on the most common categories of agents currently used in thoracic oncology: those targeted at lung cancers with specific genetic mutations/rearrangements, antiangiogenic agents, and immune-checkpoint inhibitors.

Agents Targeted at Specific Genetic Aberrations

Overview of the Therapeutic Approach

There are numerous targeted therapies that act on non–small cell lung cancers (NSCLC) with specific genetic aberrations. The most commonly targeted NSCLCs are those with epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) rearrangements, and BRAF mutations.[10–15] The targeted agents used in these tumors are tyrosine kinase inhibitors (TKI). Tyrosine kinases are transmembrane molecules that, when activated, regulate intracellular metabolic pathways, which ultimately control cell growth and division.[16] Examples of Federal Drug Administration (FDA)-approved TKIs used in NSCLC are summarized in Table 1.

Response Assessment Using Imaging

Response assessment using radiologic size-based parameters underestimates clinical benefit in many lung cancer patients receiving TKIs. In the era of cytotoxic chemotherapy, stable disease (SD), as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, [17] was often a transient state and consequently not typically thought of as indicative of significant antitumor response. However, early clinical experience with EGFR-inhibiting TKIs led to the recognition that a long period of SD may be regarded as evidence of drug efficacy.[18] In a subset of patients receiving targeted therapy, even evidence of RECIST-defined progressive disease (PD) may be followed by long periods of clinical stability.[19] For example, this may occur in patients who develop small new lesions, which subsequently grow indolently over several cycles of treatment, but which technically meet the RECIST 1.1 definition of PD. In addition, this phenomenon can occur in patients who have a profound antitumor response and subsequent slow regrowth of tumor (Fig. 1).

This initial experience in patients with EGFR mutations was subsequently borne out in the context of TKIs directed at other genetically distinct lung cancers—for example, tumors with ALK rearrangements.[20] These patterns of indolent progression in the context of clinical stability highlight the limitations of existing size-based measurements for capturing clinical effect in the era of targeted therapy. For this reason, targeted therapy in lung cancer can occasionally be continued beyond the point of RECIST 1.1 PD, and some trials may rarely allow continued participation if RECIST 1.1-based PD occurs in the context of ongoing clinical benefit.[21,22] A recent study assessing treatment beyond progression in patients with EGFR-mutated lung cancer demonstrated that such a strategy is feasible and may delay time to salvage therapy.[21] A retrospective study assessing lung cancer patients with ALK rearrangements who were treated beyond RECIST-defined progression demonstrated that patients who continued treatment with the ALK inhibitor crizotinib had longer overall survival (OS) from the time of RECIST-defined PD than those who did not continue crizotinib (16.4 vs. 3.9 mo; hazard ratio: 0.27, 95% confidence interval [CI]: 0.17-0.42).[23]

^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) noninvasively assesses glucose metabolism in tumors, and ^{18}F-FDG is the most commonly used radiotracer in oncologic imaging as a surrogate of tumor

TABLE 1. FDA-approved Targeted Therapies for Non–Small Cell Lung Carcinoma

	Name	Trade Name	Manufacturer	Principle Molecular Target
Targeted medical therapy				
Tyrosine kinase inhibitors (TKI)	Osimertinib	Tagrisso	AstraZeneca	EGFR
	Erlotinib	Tarceva	Genentech	EGFR
	Gefitinib	Iressa	AstraZeneca	EGFR
	Afatanib	Gilotrif	Boehringer Ingelheim	EGFR
	Necitumumab*	Portrazza	Eli Lilly	EGFR
	Ceritinib	Zykadia	Novartis	ALK
	Crizotinib	Xalkori	Pfizer	ALK
	Alectinib	Alecensa	Genentech	ALK
	Lorlatinib	Lorbrena Alunbrig	Pfizer	ALK
	Brigatinib		Takeda	EGFR/ALK
Other protein kinase inhibitors	Trametinib	Mekinist	Novartis	MAPK kinase (MEK)
	Dabrafenib	Tafinlar	Novartis	BRAF
	Everolimus†	Afinitor	Novartis	mTOR
Angiogenesis inhibitors	Bevacizumab	Avastin	Genentech	VEGF
	Ramucirumab	Cyramza	Eli Lilly	VEGF
Immunotherapy				
Checkpoint inhibitors	Nivolumab†	Opdivo	Bristol-Myers Squibb	Anti-PD1
	Pembrolizumab	Keytruda	Merck	Anti-PD1
	Atezolizumab	Tecentriq	Genentech	Anti-PD-L1
	Durvalumab	Imtinzi	AstraZeneca	Anti-PD-L1

*FDA approved for squamous NSCLC only.
†FDA approved for small cell lung cancer.
MAPK indicates mitogen-activated protein kinase; mTOR, mammalian target of Rapallo; VEGR, vascular endothelial growth factor.

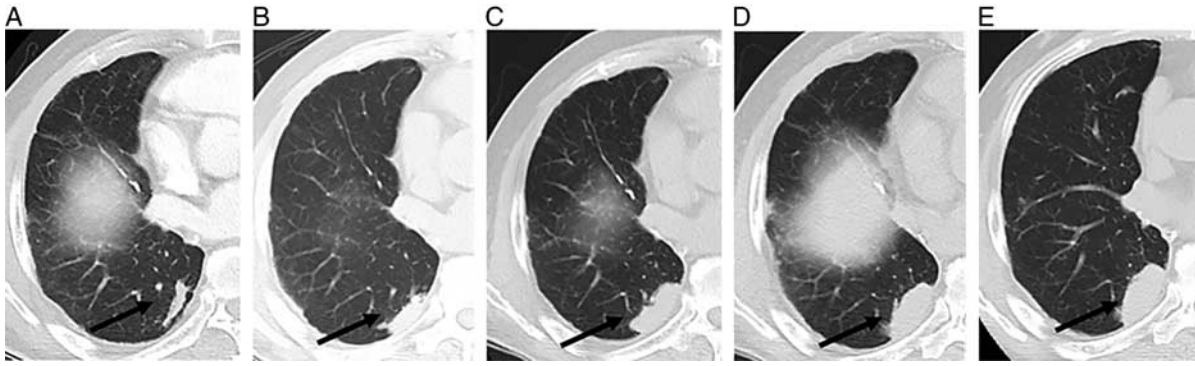

FIGURE 1. Slow progression of a metastatic NSCLC lung cancer lesion (arrow) in a patient receiving TKI therapy (Erlotinib). A, Baseline axial CT image of right lower lobe NSCLC before commencing TKI therapy with subsequent slow growth over 32 months on TKI therapy. B, CT 6 months after TKI therapy. C, CT 16 months after TKI therapy. D, CT 24 months after TKI therapy. E, CT 32 months after TKI therapy.

response. Despite considerable interinstitutional variability in PET imaging methodology, which has limited the ability to compare response assessment between studies,[24] several investigators have demonstrated the reproducibility of tumor metabolic assessments within a given institution.[25] Nevertheless, the routine use of PET/computed tomography (CT) is not currently recommended by the National Comprehensive Cancer Network for response assessment or for surveillance in patients with NSCLC.

In the context of targeted therapies, several studies have assessed the ability of ^{18}F-FDG PET to both evaluate response to treatment and to predict potential responders before treatment. For example, in one series of patients treated with Erlotinib, those with tumors with SUVmax <6.6 before treatment had significantly better OS than those with SUVmax >6.6 [16.3 mo (95% CI: 7.1-25.4) vs. 3.1 mo (95% CI: 0.6-5.5)].[26] Several studies assessing the utility of ^{18}F-FDG PET for response assessment in patients treated with TKIs demonstrate an association between changes in tumor metabolic activity and several clinical outcome measures including OS and progression-free survival (PFS).[27,28] For example, in a cohort of patients treated with Erlotinib and Bevacizumab for lung cancer, a >20% decrease in SUV on ^{18}F-FDG PET 3 weeks following the start of therapy was associated with a longer PFS compared with those without >20% decrease (9.7 mo [95% CI: 1.8-17.6] vs. 2.8 mo [95% CI: 2.0-3.5]).

In small studies of patients receiving TKIs for cancers with targetable mutations, novel PET radiotracers that are not in routine clinical use have shown some promise when used to predict responders at baseline. For example, ^{18}F-fluorothymidine, a marker of cell proliferation, has been used to predict response to Erlotinib in patients who have EGFR-mutant NSCLC.[26] Patients with low proliferation, as indicated by low uptake on FLT PET, had significantly longer survival (low FLT uptake, 10.3 mo [95% CI: 0-23.3 mo] vs. high FLT uptake, 3.4 mo [95% CI: 0-8.1 mo]).[26] The feasibility of performing PET/CT with ^{11}C-Erlotinib has been demonstrated in a small series of NSCLC patients.[29] A preclinical model using ^{18}F-fluoromisonidazole (FMISO), a marker of cellular hypoxia, has been used to detect hypoxic changes in response to treatment with Erlotinib.[30]

Imaging of Complications/Toxicities

Although relatively uncommon, TKI-associated pneumonitis is a clinically important phenomenon and has been reported with many of the TKIs used to treat lung cancer.[31–34] Pneumonitis is the most common cause for drug-related mortality in lung cancer patients receiving TKIs, accounting for up to 65% of toxicity-related deaths.[32]

The CT features of TKI-related pneumonitis vary considerably but include ground-glass opacities, airspace consolidation, centrilobular nodules, interlobular septal thickening, honeycombing, and traction bronchiectasis, the distribution of which tends to be multifocal and bilateral.[31] It is possible to classify the CT appearance according to the American Thoracic Society/European Respiratory Society (ATS/ERS) classifications of idiopathic interstitial pneumonias.[35] Using this classification system, several patterns have been described, including diffuse alveolar damage/acute interstitial pneumonia (DAD/AIP), bronchiolitis obliterans, hypersensitivity pneumonitis (HP), organizing pneumonia, nonspecific interstitial pneumonia, and usual interstitial pneumonia.[31] DAD corresponds to the clinical phenomenon of adult respiratory distress syndrome (ARDS) and is associated with worse clinical outcomes. For example, in a cohort of patients with Erlotinib-induced pneumonitis, those with a DAD pattern on CT had a mortality of 65% compared with those with a non-DAD pattern who had a mortality of 32%.[36]

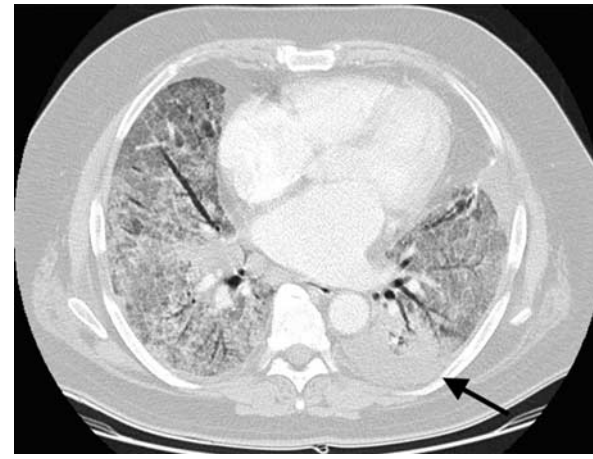

FIGURE 2. TKI-induced pneumonitis, diffuse alveolar damage pattern. Contrast-enhanced axial CT image shows diffuse ground-glass opacification with dependent dense consolidation (black arrow) in a patient receiving erlotinib.

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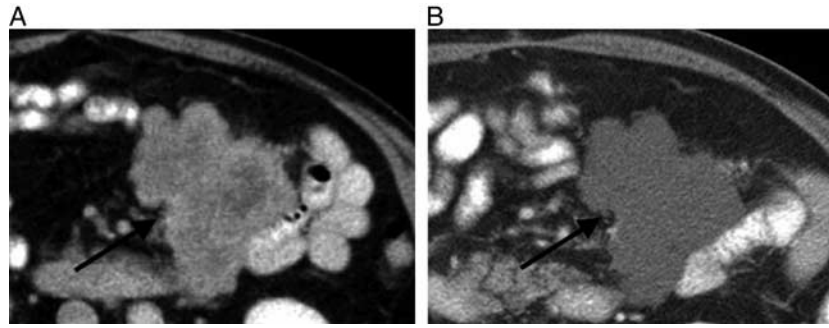

FIGURE 3. Choi criteria: gastrointestinal stromal tumor (GIST) and imatinib use. A, Baseline contrast-enhanced axial CT image shows mesenteric GIST (black arrow), which is heterogenously hyperattenuating before therapy. B, Follow-up contrast-enhanced axial CT image obtained after 4 months of imatinib shows no change in the size of lesion; however, the lesion is now homogenously hypoattenuating with marked reduction in attenuation from baseline, suggestive of internal necrosis and treatment response.

On CT, the typical appearance of DAD is diffuse bilateral ground-glass opacities with multiple foci of dense consolidation, particularly in dependent regions[35] (Fig. 2).

Antiangiogenic Agents

Overview of the Therapeutic Approach

Vascular endothelial growth factors (VEGFs) are a family of signaling proteins that play a key role in tumor angiogenesis.[37] The pathways they regulate have become targets for cancer treatments, leading to the development of several antiangiogenic agents in a variety of malignancies.[3,37,38] Antiangiogenic agents currently approved by the FDA for use in lung cancer are Bevacizumab and Ramucirumab. Bevacizumab is a monoclonal antibody targeted at circulating VEGF-A,[3] while Ramucirumab targets the VEGF receptor.[38]

Response Assessment Using Imaging

Early experience in the use of targeted anticancer therapies led to the recognition that RECIST 1.1-based assessments of tumor response may not adequately capture antitumor activity.[39] Purely size-based assessments fail to account for other morphological changes within the tumor such as necrosis and cavitation. This effect was noted in patients responding to treatment with imatinib, a TKI used to treat gastrointestinal stromal tumors, many of whom demonstrated modest reduction in tumor size but a profound reduction in tumor attenuation on CT (Fig. 3). Treatment response can be underestimated in this setting, and, consequently, the Choi criteria were developed for use in patients with gastrointestinal stromal tumors receiving imatinib. These novel criteria took both tumor size and tumor attenuation into account when assessing response, and Choi et al found that a reduction in tumor density of > 15% on CT, or a tumor size decrease of > 10%, better identified patients who responded to treatment (Choi demonstrated a sensitivity of 97% for detecting patients who had a metabolic response on PET/CT, compared with 52% for RECIST).

Similar challenges in response assessment are encountered in patients receiving antiangiogenic agents for lung cancer. Crabb et al[40] found that up to 24% of patients with NSCLC treated with the antiangiogenic agent cediranib had a cavitary response, compared with 0 patients in a control arm treated with carboplatin and paclitaxel. A pattern of cavitary response has been documented with other antiangiogenic agents including Bevacizumab[41] (Fig. 4), and can be seen in the dominant lung tumor or in nondominant pulmonary nodules (rarely in association with surrounding interstitial abnormalities).[42] Cavitation is hypothesized to occur because of intralesional central necrosis resulting from inhibition of angiogenic pathways. Importantly, the presence of cavitation has implications for response assessment.

The RECIST 1.1 criteria measure tumor size in its longest diameter and do not account for the necrotic, cystic, or cavitary change.[17] Modified RECIST criteria, which account for cavitary change within a lung mass, by subtracting cystic components from solid components, have been proposed for use in this context (Fig. 5).[40] Other modifications to the RECIST 1.1 criteria, which have been

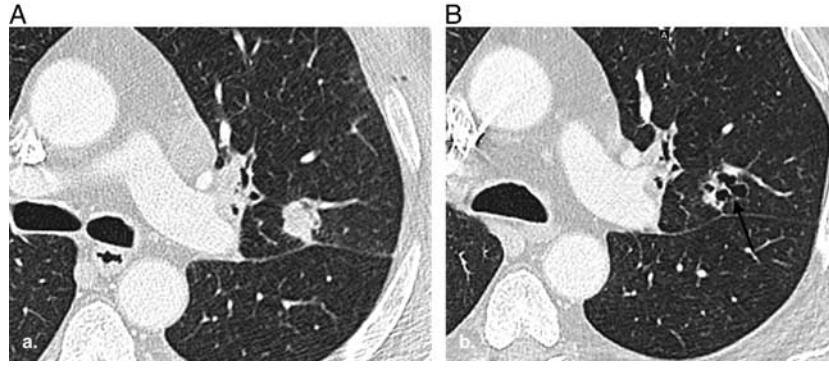

FIGURE 4. Cavitary response with the use of antiangiogenic agents. A, Baseline contrast-enhanced axial CT image shows a solid NSCLC in the left lung. B, Follow-up contrast-enhanced axial CT image obtained after 6 months of therapy with an antiangiogenic agent, demonstrating no significant overall change in size of lesion but new central cavitation (arrow).

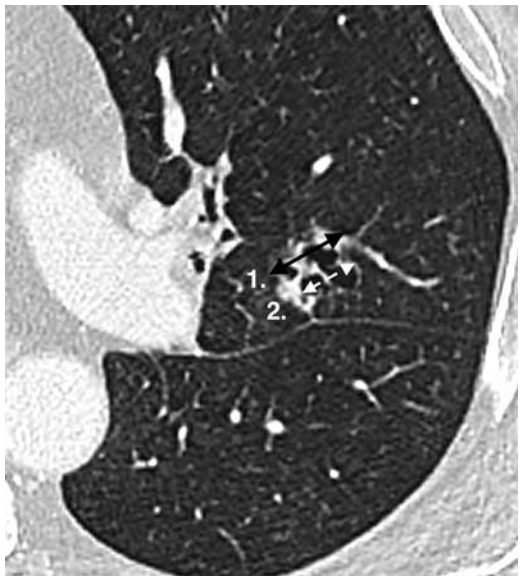

FIGURE 5. Modified RECIST response assessment of the cavitary lesion. The lesion in longest diameter is measured as per RECIST 1.1 criteria (measurement 1, solid black arrow). The cavitary component is then measured (measurement, dashed white arrow). The total tumor burden is calculated as measurement 2 subtracted from measurement 1.

proposed in the literature (but not by the RECIST 1.1 working group), use reduced tumor attenuation and increased ground-glass change within a tumor as markers of response. In a small cohort of patients with NSCLC receiving Bevacizumab, Lee and colleagues used a combination of size and tumor attenuation (a reduction in CT attenuation of $\geq$15% as part of the definition of partial response) and classified 54% of patients as having complete or partial response compared with 18% when RECIST 1.1 was used.[43] To date, none of these novel criteria are in routine clinical use for patients with thoracic malignancies.

Imaging of Complications/Toxicities

Bevacizumab-associated complications most likely to be encountered by the thoracic radiologist are hemorrhage and thromboembolic events. In early trials with Bevacizumab that included patients with squamous cell histology, the rate of serious pulmonary hemorrhage was high. Subsequent trials that excluded squamous cell histology had lower rates of pulmonary hemorrhage, ranging from 1% to 2%.[3,44] On CT, pulmonary hemorrhage can manifest as ground-glass or consolidative opacities, with or without interlobular septal thickening.

Patients receiving antiangiogenic agents are at increased risk for thromboembolic events, particularly arterial thromboembolism. Arterial thromboembolism has an incidence of 3% to 5% in patients treated with Bevacizumab, conferring a relative risk of 1.5 to 2.[45,46] Bevacizumab-associated tracheoesophageal fistula is a serious complication but rarely develops in patients who have not received radiation therapy.[47]

Immunotherapy

Overview of the Therapeutic Approach

Immunotherapy with checkpoint blockade is a novel oncologic treatment strategy that aims to provoke an antitumor response by activating the patient's immune system. As numerous trials have demonstrated the clinical benefit of this treatment strategy, there is now FDA approval for several checkpoint inhibitors in multiple cancer subtypes.[48] Checkpoint inhibitors are monoclonal antibodies that work by acting on cell receptors that regulate the T-cell immune response to cancer. The cell receptors targeted are cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD1) or its ligand programmed cell death ligand 1 (PD-L1). All play important roles as negative regulators of T-cell-mediated anticancer immunity. Drugs that target CTLA-4 or PD1/PD-L1 aim to switch off the inhibition of T-cell-mediated anticancer immunity, ultimately promoting an antitumor immune response.[49] Checkpoint inhibitors that are FDA approved for use in Lung Cancer are summarized in Table 1.

Response Assessment Using Imaging

During early clinical trials of ipilimumab in patients with melanoma, it was recognized that a subset of patients who responded to treatment did not demonstrate the patterns of tumor response classically seen with cytotoxic chemotherapy.[50] In a small number of patients, tumor burden initially increased after ipilimumab treatment was started (in some cases with new lesions developing), with a subsequent reduction in tumor burden, often followed by partial or complete response, as defined by the RECIST criteria.[50] This phenomenon probably reflects infiltration of the treated tumor by host immune cells and is termed pseudoprogression.[51] Another group of patients demonstrated long periods of RECIST-defined SD with an indolent reduction in tumor burden over many months or even years. In neither group was the antitumor response adequately captured by RECIST 1.1 assessment. Indeed, in the first group, assessment using RECIST 1.1 led to a designation of PD when in fact patients were benefiting from a potent antitumor effect.

In 2005, building on the above observations, a working group of oncologists outlined several of the key tenets of immunotherapy response assessment: (i) appearance of antitumor activity can take longer for immunotherapy compared with cytotoxic therapy; (ii) a response to immunotherapy can occur after RECIST 1.1-based PD; (iii) stopping immunotherapy may not be appropriate in a clinically stable patient unless PD is confirmed; (iv) allowance should be made for "clinically insignificant" PD (eg, the appearance of new small lesions in the presence of other responding lesions); and (v) durable SD may represent effective antitumor activity.[50]

Although uncommon, pseudoprogression (defined as an increase in tumor burden reaching the threshold for PD with a subsequent reduction in tumor size) presents a clinical challenge to radiologists and oncologists alike (Fig. 6). Occurring in 7% to 10% of melanoma patients,[50,52] pseudoprogression is less common in other malignancies.[53] In a cohort of NSCLC patients treated with anti-PD-1 therapy, 3 of 166 patients (2%) demonstrated radiologic pseudoprogression.[54] Pseudoprogression occurs most commonly early in the course of treatment, the majority of cases within the first 12 weeks of treatment[52]—for example, in the cohort of NSCLC patients reported by Katz and colleagues, all patients who were classified as having pseudoprogression demonstrated tumor burden increases in the first 3 months of therapy, with evidence of subsequent treatment response documented in all 3 cases after an additional 1 to 3 months of follow-up.[54] Importantly, in

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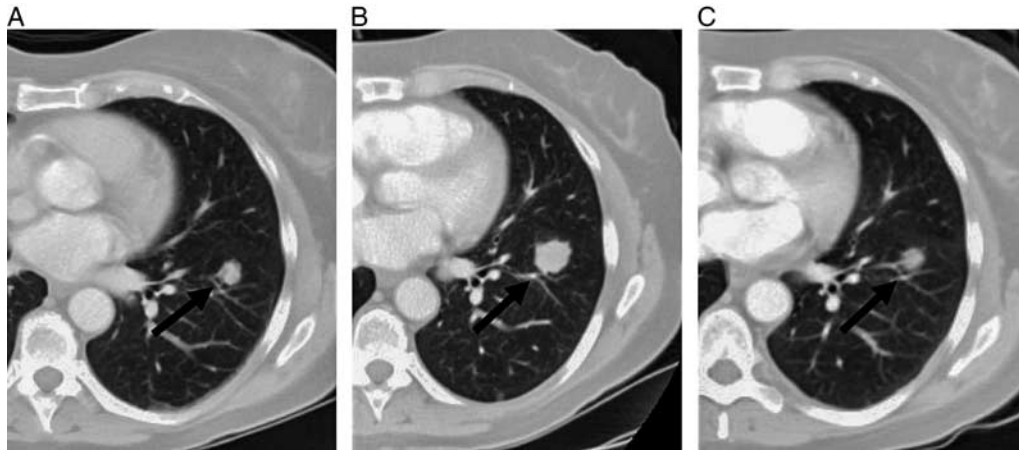

FIGURE 6. Pseudoprogression: an increase in tumor burden, initially after immunotherapy is commenced, with a subsequent reduction in tumor burden, often followed by a partial or complete response, as defined by the RECIST criteria. A, Baseline axial CT before commencing immunotherapy showing a left upper lobe tumor (arrow). B, Axial CT, 2 months after initiation of immunotherapy, shows increased size of the nodule, which, using RECIST 1:1 criteria, would be deemed progressive disease. C, Axial CT obtained 8 weeks later with the patient remaining on immunotherapy now demonstrates a reduction in size of the nodule, consistent with treatment response.

rare instances pseudoprogression occurring later in the time course of treatment can be encountered[52] and has been reported to occur after 2 or more consecutive scans demonstrating PD.[55] To date, pseudoprogression has been reported more commonly with anti-CTLA4 therapy than anti-PD1 therapy[56] and, in the context of melanoma, appears to occur more commonly in extranodal sites.[52] There is currently no reliable way to differentiate pseudoprogression from true progression on imaging grounds, and surveillance imaging protocols rely on the use of short-term imaging follow-up to assess whether the increase in tumor burden is transient.[57]

Because these atypical immune-modulated response patterns cannot be adequately captured by RECIST 1.1, new response assessment criteria were proposed, taking into account the possibility of an initial increase in tumor burden in patients responding to checkpoint inhibition. The first such criteria were termed the immune-related response criteria (irRC).[50] The most important change from existing RECIST 1.1 criteria was that new target lesions could be added to the total tumor burden measurement in contrast to the automatic designation of PD with the development of new lesions (which would be required under RECIST 1.1). In addition, irRC added the recommendation that, in the context of a clinically stable patient, radiologic PD should be confirmed with follow-up imaging in ~4 weeks to account for the possibility of pseudoprogression.[50] A modified version of the irRC, typically referred to as irRECIST, was subsequently proposed and is now widely used in clinical trials.[58–60] irRECIST is similar to irRC in its treatment of new lesions but is more closely aligned with the RECIST 1.1 criteria, as opposed to irRC, which is aligned with the WHO criteria. The most notable differences between irRC and iRECIST are that irRECIST uses unidimensional measurements and allows the selection of up to 5 target lesions, while irRC uses bidimensional measurements and allows the selection of up to 15 target lesions. Unidimensional measurements have demonstrated more reproducibility, with less measurement variability when compared with bidimensional measurements.[61]

Although irRECIST is widely used in clinical trials, the criteria were not developed in the context of a formal working group, and, as such, there have been concerns with regard to its standardized application from trial to trial.[57] In an attempt to standardize the collection of response data in clinical trials, a subcommittee of the RECIST working group was convened in 2016 and developed a detailed response assessment guideline for use in this setting, which they termed iRECIST. Similar to RECIST 1.1 in its scope and level of detail, iRECIST incorporates the principles outlined in irRC and irRECIST, thereby addressing potential pitfalls of what may constitute a possible premature conclusion of PD, versus confirmed PD with increasing tumor burden following a prior episode of pseudoprogression.[57] RECIST 1.1, irRC, irRECIST, and iRECIST are summarized in Table 2.

Interest in the potential utility of PET/CT as a predictive biomarker in patients receiving immunotherapy has resulted from its ability to assess tumor response and also to potentially identify patients who are more likely to respond to treatment. Most of the work to date has focused on the use of ^{18}F-FDG PET/CT in melanoma; however, there are additional novel PET tracers which, in preclinical models, hold promise for the noninvasive characterization of tumors treated with immunotherapy.[62]

^{18}F-FDG PET/CT has demonstrated some utility for response assessment. Using a modified version of the Positron Emission Tomography Response Criteria in Solid Tumors (imPERCIST), Ito and colleagues demonstrated that changes in tumor uptake after anti-CTLA therapy were strongly associated with OS in melanoma patients.[63] For example, patients classified as responders on the basis of imPERCIST had a 2-year OS of 66% versus 2-year OS of 29% in patients without a response on imPERCIST.[63] A more recent small prospective study assessing the potential utility of an early PET/CT, after 3 to 4 weeks of checkpoint inhibitor therapy for melanoma, demonstrated some utility for PET in predicting response to treatment; however, the accuracy of RECIST 1.1 was higher than that of PERCIST for predicting response.[64] In the same cohort, however, a combination of anatomic and functional response assessment outperformed RECIST 1.1 alone and PERCIST alone. An interesting subgroup of patients in this study demonstrated stable anatomic disease but increased

TABLE 2. Comparison Between the Response Assessment Criteria Commonly Used in Patients Receiving Immunotherapy, That is, RECIST 1.1, irRC, irRECIST, and iRECIST[21,50,55,56]

	RECIST 1.1	irRC	irRECIST	iRECIST
Type of measurement	Unidimensional (sum of diameters)	Bidimensional (sum of product of diameters [SPD])	Unidimensional (sum of diameters)	Unidimensional (sum of diameters)
Definition of target lesions	Non-nodal lesions: ≥10 mm in longest diameter Nodal lesions: ≥15 mm in shortest diameter	≥5×5 mm (no distinction made between nodal and non-nodal lesions)	Follow the definitions from RECIST 1.1	Follow the definitions from RECIST 1.1
No. target lesions	Up to 5 lesions Maximum of 2 per organ	Up to 10 visceral lesions and 5 cutaneous lesions	Follow the definitions from RECIST 1.1	Follow the definitions from RECIST 1.1
Definition of new target lesion	NA	≥5×5 mm Up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions	Follow the definitions of target lesion size and number from RECIST 1.1	Follow the definitions of target lesion size and number from RECIST 1.1
Definition of PD	≥20% increase in the sum of diameters New lesions Unequivocal progression of nontarget lesions	≥25% increase in SPD	≥20% increase in the sum of diameters Unequivocal progression of nontarget lesions Unequivocal progression of new nonmeasurable lesions	≥20% increase in the sum of diameters Unequivocal progression of nontarget lesions New target lesion New nontarget lesion
Definition of confirmed PD	NA	Recommend confirmation scan after a minimum of 4 wk, if clinically stable	Recommend confirmation scan after a minimum of 4 wk, if clinically stable	Recommend confirmation scan after 4-8 wk, if clinically stable See below for definitions of confirmed PD as per iRECIST*

*Using iRECIST, PD is confirmed on confirmation scan if the following are observed: increase in sum of diameters by ≥5 mm; any further increase in previously progressed nontarget lesions; Increase in new lesion sum of diameters by ≥5 mm; any further increase in new nontarget lesions; new progressive disease in any category outside the one in which the initial assessment of PD was made.

NA indicates not applicable.

^{18}F-FDG uptake at 4 weeks, and all eventually had tumor regression on additional follow-up scans. In addition, it was noted that the optimal PERCIST threshold value predictive of response was >15.5%.[64] These phenomena presumably reflect the inflammatory antitumor response underpinning checkpoint inhibitor immunotherapy.

Imaging of Complications/Toxicities

Because of its ability to promote immune system activation, immune checkpoint blockade can lead to a number of immune-mediated inflammatory side effects termed immune-related adverse events (irAEs). The irAEs most likely to be encountered by thoracic radiologists are pneumonitis, sarcoid-like reaction, thyroiditis, and myocarditis. These complications should be diagnosed appropriately and not attributed to disease progression.

Pneumonitis is a relatively uncommon but a potentially fatal irAE. A recent meta-analysis assessing the incidence of PD-1 inhibitor–related pneumonitis in patients with a variety of malignancies, demonstrated the overall incidence during PD-1 inhibitor monotherapy to be 2.7%, with a higher incidence in patients with NSCLC (4.1%) and renal cell cancer (4.1%) compared with those with melanoma (1.6%). In patients with melanoma who received combination PD-1 inhibitor therapy, the incidence of pneumonitis was higher (6.6%).[65] Clinically, the majority of patients develop low-grade pneumonitis, which responds to medical management, although in a small percentage of patients, a move severe and potentially fatal pneumonitis may develop.[66,67] In recent a series by Naidoo et al of 43 patients with anti-PD-1/PD-L1–related pneumonitis, 73% had grade 1 or 2 pneumonitis (either asymptomatic or with mild/moderate symptoms), 24% had grade 3 or 4 pneumonitis, and 1 patient died.[66]

On CT, ground glass and reticular opacities are the most common finding,[66,68] and diffuse involvement of multiple lung lobes is more common than focal involvement. For example, all lung lobes were involved in 75% of patients in a recently reported case series.[68] When pneumonitis is classified according to the ATS/ERS classification of idiopathic interstitial pneumonias,[35] a cryptogenic organizing pneumonia pattern is the most common (65% of patients), followed by a nonspecific interstitial pneumonia pattern (15%), an AIP/ARDS pattern (10%), and a hypersensitivity pneumonitis pattern (10%). The AIP and cryptogenic organizing pneumonia patterns are associated with the highest clinical grade of pneumonitis[68] (Fig. 7).

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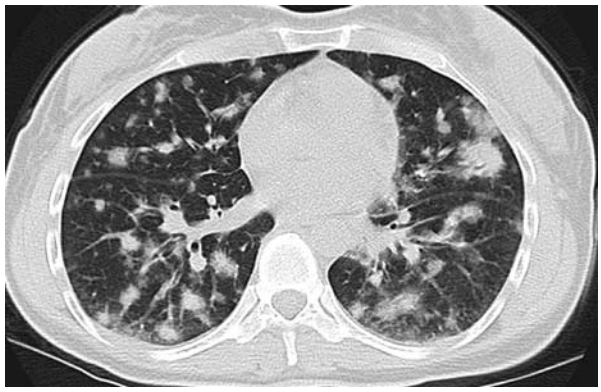

FIGURE 7. Immunotherapy-related pneumonitis. Contrast-enhanced axial CT image shows diffuse predominantly nodular consolidative opacities in a patient with lung cancer receiving checkpoint inhibitor immunotherapy. The opacities resolved following steroid therapy, consistent with immunotherapy-related pneumonitis (organizing pneumonia pattern).

A T-cell–mediated sarcoid-like reaction with the development of noncaseating granulomas has been reported in patients receiving checkpoint inhibition therapy. The most common presentation is with hilar and mediastinal adenopathy, typically bilateral and symmetrical, and which may be avid on ^{18}F-FDG PET imaging.[69] Sarcoid-like adenopathy has been reported to occur in up to 5%[70] of patients treated with ipilimumab for melanoma and can be particularly clinically challenging in the context of thoracic malignancy. Adenopathy may occur with or without parenchymal lung involvement. Recently, immunotherapy-induced sarcoid-like reaction involving the lung parenchyma without adenopathy has been described; in these cases, patients were reported to present with focal lung consolidation, which was often nodular or round.[71] Following checkpoint inhibitor therapy, new symmetric thoracic adenopathy and lung nodularity should be interpreted cautiously in order to avoid its attribution to metastatic disease. In some cases, a biopsy may be necessary to confirm the diagnosis (Fig. 8).

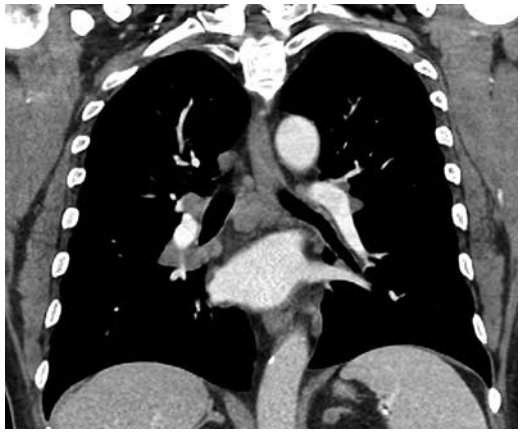

FIGURE 8. Immunotherapy-related sarcoid-like reaction. Contrast-enhanced coronal CT image shows new multistation mediastinal and hilar lymphadenopathy in a patient with melanoma receiving checkpoint inhibitor immunotherapy, subsequently biopsied and confirmed as granulomatous inflammation.

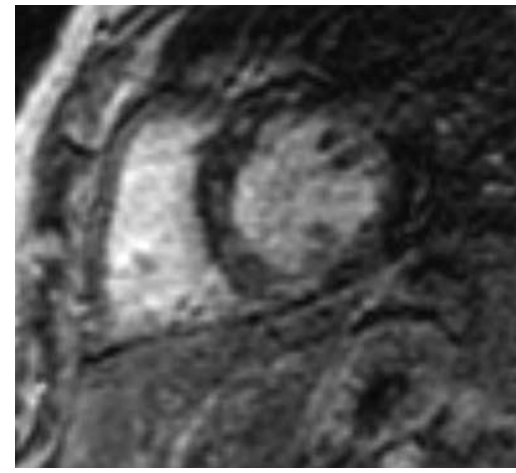

FIGURE 9. Immunotherapy-related myocarditis. Delayed post-contrast short-axis images through the left ventricle in a patient with melanoma receiving checkpoint inhibitor immunotherapy who presented with chest pain and elevated troponin. Patchy areas of high signal in a nonischemic distribution are suggestive of myocarditis in this context.

Immunotherapy-related myocarditis is a rare but increasingly recognized entity with a 0.3% reported incidence in patients treated with combination ipilimumab/nivolumab. Although in some cases the clinical course is indolent, there are several reported instances of severe myocarditis that can be fatal.[72] Cardiac magnetic resonance imaging is the imaging test of choice in characterizing myocarditis, with findings including regional wall motion abnormalities and increased T2 signal and delayed myocardial enhancement in a nonischemic distribution[73] (Fig. 9).

Interestingly, some studies have suggested that the development of irAEs is associated with an increased likelihood of an antitumor response. For example, in a cohort of patients with metastatic melanoma treated with anti–CTLA-4 antibody therapy, patients with radiologically detectable irAEs had a complete response rate of 25% compared with 3% in those without radiologically detectable adverse events.[74]

CONCLUSIONS

The role that targeted medical therapy and immunotherapy play in the treatment of thoracic malignancy continues to expand. Many of these treatments are associated with atypical imaging findings and novel response patterns that can complicate response assessment and clinical management. Imaging plays a vital role in the assessment of such patients, and it is essential that thoracic radiologists become familiar with these treatments, the expected posttherapy findings, the impact on response assessment, and therapy-related complications.

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SA-CME EXAMINATION QUESTIONS

[*]1. Which statement is ***true*** regarding Tyrosine Kinase inhibitors (TKIs)?
- A. Response assessment: using RECIST 1.1 reflects clinical benefit in all lung cancer patients receiving TKIs.
- B. Are associated with radiological pseudo-progression.
- C. ^{18}F FDG PET/CT is recommended for routine response assessment and surveillance in patients with NSCLC treated with Tyrosine Kinase inhibitors.
- D. Clinical benefit can be seen in the setting of indolent radiological progression.

[*]2. Which of the following statements is ***true*** regarding Tyrosine Kinase inhibitor associated pneumonitis:
- A. The clinical and imaging manifestations of pneumonitis are uniform between patients.
- B. Higher incidence in patients with pre-existing pulmonary fibrosis.
- C. Acute interstitial pneumonitis pattern on CT confers a better prognosis.
- D. Upon diagnosis, the target agent does not need to be discontinued.

[*]3. Regarding the use of anti-angiogenic agents in lung cancer, which of the following statements is ***true***?
- A. Have a cytocidal effect as opposed to cytostatic effect on tumors.
- B. A cavitary response is more common in patients treated with anti-angiogenic agents, than in patients treated with cytotoxic chemotherapy.
- C. Associated with a reduced risk of thromboembolic events.
- D. Bevacizumab associated pulmonary hemorrhage occurs more commonly in patients with adenocarcinoma histology.

[*]4. Which of the following statements is ***true*** regarding radiological pseudo-progression in patients receiving checkpoint inhibitor immunotherapy?
- A. Is distinguishable from true progression using radiological assessment.
- B. Is more common with anti-PD1 therapy than anti-CTLA4 therapy.
- C. Typically occurs between 9-12 months after immunotherapy is started.
- D. Is a rare response pattern in patients receiving checkpoint inhibitor immunotherapy.

[*]5. Regarding immune related adverse events, which of the following statements is ***true***?
- A. Development of radiological immune related adverse events is associated with reduced likelihood of antitumor response.
- B. Pneumonitis has been reported in up to 20% of patients with lung cancer receiving immunotherapy.
- C. T-cell mediated sarcoid like reaction is only associated with hilar and mediastinal adenopathy.
- D. Sarcoid-like reactive adenopathy can be avid on ^{18}F FDG PET