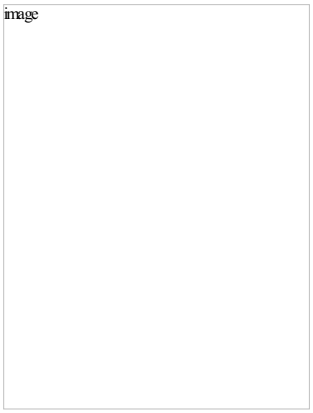

Immunotherapy in Lung Cancer and the Role of Imaging

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Immunotherapy in Lung Cancer and the Role of Imaging

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Abstract

Lung cancer is the leading cause of cancer-related mortality and accounts for more deaths than breast, prostate, and colon cancers combined. Traditionally, treatment options have included surgery, chemotherapy, and radiation therapy. Continual advances in the characterization of lung cancer have resulted in the development of effective immunotherapies. These agents help the immune system recognize tumors as foreign, stimulate the immune system, and relieve the inhibition that allows the growth and spread of cancer. Conventional response criteria such as the World Health Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumors (RECIST) have been used extensively in clinical trials; however, these guidelines have been optimized for use with traditional cytotoxic chemotherapy. Data from clinical trials employing immunotherapy has shown that unique

responses may be seen with these agents that are not fully captured by conventional response criteria. In response to these observations, several modified criteria have been developed for use with immunotherapy, including immune-related response criteria (irRC), immune-related RECIST (irRECIST), and immune RECIST (iRECIST). As the use of immunotherapy continues to grow, there is increasing recognition of immune-related adverse events, which may manifest on imaging examinations.

Introduction

Lung cancer is responsible for almost 1 in 4 cancer-related deaths, more than breast, prostate, and colon cancer combined (1). Approximately 222,500 new cases of lung cancer will be diagnosed and 155,870 deaths result from lung cancer in 2017, as estimated by the American Cancer Society (1). Traditionally, the treatment options for lung cancer have included surgery, chemotherapy, and radiation therapy. However, significant advances in the genetic and molecular characterization of lung cancer have led to the development of a wide variety of targeted therapies and immunotherapies.

Traditional chemotherapy is cytotoxic in nature and targets rapidly dividing cells. In contrast, immunotherapy helps the immune system recognize cancer as foreign, stimulates the immune system, and relieves the inhibition that allows cancer spread. Immunotherapy may be classified as active or passive depending on its effect on the immune system. Prior attempts at treating non-small cell lung cancer (NSCLC) with immunomodulatory agents such as interleukin 2 (IL-2), interferon, and Bacillus Calmette-Guerin (BCG) were unsuccessful (2). However, recent work has led to the creation of immunotherapies that relieve the suppression of anti-tumor

activity in some cases of advanced NSCLC, the first of which were approved by the U.S. Food and Drug Administration (FDA) in 2015 (3,4).

Conventional response criteria such as the World Health Organization (WHO) criteria and Response Evaluation Criteria in Solid Tumors (RECIST) have been used extensively in clinical trials for the assessment of treatment response (2). However, experience with immunotherapies such as ipilimumab, an immunomodulatory monoclonal antibody, has shown that unique responses may be seen with these agents that are not captured by traditional response criteria. In response to these observations and the limitations of conventional response criteria, several modified criteria have been developed to evaluate treatment response in patients treated with immunotherapy, including immune-related response criteria (irRC), immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), and immune RECIST (iRECIST) (2,5). With the growing utilization of immunotherapy, there is a better understanding of immune-related adverse related events and how these complications may manifest on imaging studies. Some of the most common immune-related adverse events such as pneumonitis and colitis can result in abnormalities on computed tomography (CT) and FDG positron emission tomography (PET)/CT (6,7).

In this article, the immunotherapeutics used for the treatment of lung cancer, the fundamentals of response criteria developed for use with immunotherapy, and imaging of immune-related adverse events are presented.

Immunotherapy

General Concepts

The immune system plays a crucial role in anti-tumor activity as it, under normal circumstances, identifies cancer cells and initiates an appropriate response to remove the cells after tumor-associated antigens are identified (8,9). However, cancer cells can avoid detection by the immune system and inhibit anti-tumor effects, resulting in the continued growth and potential spread of cancer in the body; thus, immunotherapy attempts to boost the immune system and allow it to mount a more effective response.

Immunotherapy has been described as active or passive in nature depending on its interaction with the host immune system and the type of response elicited. Active immune response involves humoral and/or cell-mediated immunity, and includes recombinant cytokines, biochemotherapy, cancer vaccines, and immunomodulatory monoclonal antibodies (10). In contrast, passive immune response requires no activation of the immune system, and is characterized by temporary anti-tumor activity achieved through the utilization of preformed target-specific monoclonal antibodies that bind to tumor-associated antigens and activate clearance of cancer cells by the immune system. Examples of passive immunotherapy include target-specific monoclonal antibodies, oncolytic viruses, and adoptive T-cell therapy.

Treatment of Lung Cancer

Immunomodulatory Monoclonal Antibodies

Immunomodulatory monoclonal antibodies are an active immunotherapy that modulate T-cell activity through interactions with cell surface targets including receptors and/or ligands and thus enhance the immune response (11,12). Several factors have been identified that regulate T-cell activation, including immune checkpoints (receptor-ligand pairs on the cell surface), inhibitor and co-stimulatory pathways (13,14). For example, specific targets include programmed death protein 1 (PD-1) / programmed death receptor ligand 1 (PD-L1), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and lymphocyte activation gene 3 (LAG-3) (12,15-20).

Several checkpoint inhibitors have been approved for the treatment of lung cancer, including nivolumab, pembrolizumab, and atezolizumab. Nivolumab and pembrolizumab have been approved by the FDA as single agents for second-line treatment of patients with advanced non-small cell lung cancer. Although the utilization of nivolumab does not require testing for PD-L1 expression, pembrolizumab is the first immunotherapeutic approved for first-line treatment of patients with metastatic non-small cell lung cancer whose tumors overexpress PD-L1. In March 2016, nivolumab was approved for the treatment of advanced squamous lung cancer refractory to chemotherapy, based on the results of several clinical trials, including two phase III trials, CheckMate 017 and Checkmate 057 (21-23). Pembrolizumab was approved in October 2015 for patients with NSCLC based on the results of the KEYNOTE-010 trial (24). Atezolizumab, an anti-PD-L1 agent, was approved in October 2016 for the treatment of metastatic NSCLC that has progressed during or after first-line platinum-based chemotherapy

based on the findings from the OAK and POPLAR clinical trials (25,26). For patients with epidermal growth factor receptor (*EGFR*) mutations or anaplastic lymphoma kinase (ALK) rearrangements, it is indicated for use after disease progression with an FDA-approved targeted therapy.

Target-Specific Monoclonal Antibodies

Target-specific monoclonal antibodies block receptor sites and inhibit signaling pathways, tag tumor-associated surface antigens to promote clearance of cancer cells, and activate antibody-dependent cell mediated cytotoxicity (8,9,27). Several of these agents have been approved for the treatment of lung cancer, including bevacizumab and ramucirumab. Bevacizumab is directed against vascular endothelial growth factor (VEGF) and blocks angiogenesis. It is administered in combination with carboplatin and paclitaxel for the initial systemic treatment of patients with unresectable, locally advanced, recurrent, or metastatic non-squamous cell non-small cell lung cancer. Ramucirumab is directed against the vascular endothelial growth factor receptor 2 (*VEGFR2*) and is approved for use with docetaxel to treat patients with metastatic non-small cell lung cancer with disease progression after treatment with chemotherapy, as well as non-small cell lung cancer with *EGFR* and/or *ALK* aberrations once disease progression has occurred with FDA-approved therapy.

Treatment Response Evaluation

General Concepts

Conventional response criteria such as the WHO criteria and RECIST have been used to evaluate the effectiveness of cytotoxic therapies such as chemotherapeutic agents. The WHO criteria were the first widely used response criteria but were limited by several shortcomings (28). RECIST 1.0 was developed by an international group of investigators to improve upon the WHO criteria and standardize the characterization of treatment efficacy in 2000 and was followed by revised RECIST criteria (RECIST 1.1) in in 2009 (29,30). These response criteria assume that an increase in tumor size and/or the appearance of new lesions reflects progressive disease (PD) and chemotherapy is usually discontinued.

A significant limitation of WHO and RECIST is that different patterns of response may be encountered when evaluating patients treated with immunotherapy that are not adequately recognized and captures. In response to this shortcoming, a large multidisciplinary group of experts presented and discussed their experiences with response evaluation in the context of immunotherapy. Based on their observations, it was recommended that existing response criteria be modified and irRC was created from the backbone of WHO. An analysis of 487 patients with unresectable stage III or IV melanoma treated with ipilimumab in 3 multicenter phase II clinical trials demonstrated 4 patterns of clinical responses. Two of these responses, including a response in baseline lesions evident by week 12 (and no new lesions), and stable disease followed by a slow, steady decline in disease, were evident by conventional response criteria. However, the two other response patterns were unique, including a response after an initial increase in total tumor burden (also known as pseudoprogression) and a reduction in

total disease during or after the appearance of new lesion(s) at time points later than week 12 (2). Several modified criteria have been designed for use with immunotherapy, including irRC, irRECIST, and iRECST (Table 1).

Immune-related Response Criteria (irRC)

irRC were adapted from the WHO criteria and designed for use in clinical trials involving immunotherapeutics, and differ from other response criteria such as RECIST in many ways. Two of the most significant differences from conventional response criteria include the recommendation that response assessment after the completion of treatment be made with two consecutive follow-up imaging studies at least 4 weeks apart because of a potentially delayed response to immunotherapy and that new or enlarging lesions are not necessarily considered PD and must be confirmed with follow-up imaging.

In contrast to RECIST 1.1, irRC does not specifically state which imaging modalities should be used to evaluate treatment response. In many clinical trials, anatomic modalities such as computed tomography (CT) and combined anatomic and metabolic modalities such as FDG positron emission tomography(PET)/CT are used interchangeably. However, irRC considers only anatomic measurements in the assessment of response. The tumor burden, defined as the sum of the products of the 2 largest perpendicular diameters (SPD) of all index lesions, is calculated at baseline. Lesions must measure ≥ 5 x 5 mm to be selected as target or index lesions, and up to 5 may be selected per organ (up to 10 visceral lesions and 5 cutaneous lesions). At subsequent time points, the SPD of all index lesions and the SPD of any new measurable lesions that are identified constitute the tumor burden. An overall response category, including complete response (irCR), partial response (irPR), stable disease (irSD), and

irPD, is assigned based on the change in tumor burden between time points. In contrast to conventional response criteria, the overall tumor burden must increase ≥ 25% and be confirmed by repeat imaging at a minimum of 4 weeks after initial documentation to constitute PD. This recommendation stems from the fact that new lesions or a perceived increase in tumor burden due to pseudoprogression can result from immune cell recruitment to sites of microscopic disease. Thus, all patients with irCR, irPR, and irPD must have repeat imaging performed at a minimum of 4 weeks later for confirmation.

Immune-related RECIST (irRECIST)

In contrast to irRC, irRECIST utilizes unidimensional measurements of lesions. Nishino and colleagues assessed the impact of reducing the number of target lesions and using unidimensional measurements in determining response to ipilimumab in melanoma patients. They found that unidimensional measurements provided highly concordant response assessment compared to the bidimensional irRC and were less variable (5). The group concluded that the number of target lesions in immune-related response assessment could be reduced to up to 2 per organ and up to 5 in total and proposed the use of unidimensional measurements to assess response (5).

The application of irRECIST is very similar to RECIST 1.1 in terms of recommended imaging modalities, definitions of measureable and unmeasurable disease, and criteria for selecting target and non-target lesions. Target lesions may include non-lymph node lesions measuring ≥ 10 mm in long-axis diameter or lymph nodes measuring ≥ 15 mm in short-axis diameter, and up to 5 total target lesions may be selected with a maximum of 2 per organ. The measurements of lesions selected as target lesions are recorded as the total measured tumor

burden (TMTB). Measurable lesions not selected as target lesions, sites of non-measurable disease, and abnormalities that may be difficult to reproducibly measure may be added as non-target lesions.

The incorporation of new lesions is one of the major differences between irRECIST, RECIST 1.1, and irRC. In RECIST 1.1, once new lesions are identified, the overall response is considered PD and therapy is typically discontinued and new lesions are not followed. In irRECIST, new lesions may be considered measurable or unmeasurable, and those selected as new target lesions must meet the same criteria for inclusion as the target lesions selected at baseline. Up to 5 new target lesions may be selected with a maximum of 2 per organ. New measurable lesions not selected as target lesions may be followed qualitatively as new non-measurable lesions. The longest diameters of existing non-nodal target and new non-lymph node target lesions and short-axis diameters of existing lymph node target and new lymph node target lesions constitute the TMTB. The overall response categories for irRECIST include irCR, irSD, irPR, and irPD, and are based on changes that occur over time in the TMTB of measured target lesions, non-target lesion assessment and new non-measurable lesions. Although confirmation of irPR and irPD are not necessary, confirmatory evaluation may be recommended for patients with a minimal TMTB percent increase over 20% particularly during the first 12 weeks of treatment.

Immune RECIST (iRECIST)

Recently, the RECIST working group created modified guidelines based on RECIST 1.1 for use with immunotherapeutics, referred to as iRECIST, to ensure consistent design and data collection (31). iRECIST is similar to RECIST 1.1 and irRECIST in terms of recommended modalities for imaging assessment, what constitutes measureable and unmeasurable disease, and the criteria for selecting target and non-target lesions (31). New lesions may be classified as target or non-target and are recorded separately. Categories for response assessment include iCR, iSD, iPR, unconfirmed progressive disease (iUPD), and confirmed progressive disease (iCPD); these allow for the improved characterization of atypical responses previously described (31). The iUPD category requires confirmation at the subsequent time point. In the case of new disease, these lesions result in iUPD; however, iCPD is only reached if additional new lesions are present on the subsequent time point or if there is an increase in size of new lesions (defined as ≥ 5 mm for the sum of new lesion target or any increase in new lesion non-target). If progression is not subsequently confirmed, and there is a decrease in tumor burden meeting the criteria for iCR, iPR, or iSD, then iUPD must be reached once again and confirmed at the subsequent time point assessment for iCPD to be achieved. If there is no significant change in tumor burden, then the time point response remains iUPD.

Recommended Use of Novel Response Criteria

It is currently recommended that novel response criteria such as irRC, irRECIST, and iRECIST be used alongside conventional response criteria such as RECIST in clinical trials. Hodi et al showed that implementation of irRC is useful to avoid premature termination of effective

treatment with immunotherapy when assessing response (32). They compared irRC and RECIST 1.1 in patients with advanced melanoma undergoing treatment with pembrolizumab and found that RECIST 1.1 underestimated the benefit of therapy (measured by overall survival) in 15% of patients. Therefore, they suggested that the use of modified criteria that permit treatment beyond initial progression per RECIST v1.1 might prevent premature cessation of treatment.

Immune-related Adverse Events

General Principles

Autoimmune-mediated complications may develop over the course of treatment and have been postulated to be the result of either induction of autoimmunity or of a proinflammatory state (33). These effects tend to resolve with discontinuation of immunotherapy, suggesting that these events are not truly autoimmune diseases and are simply due to general immunologic enhancement (6). The most common immune-related adverse event is dermatologic toxicity (6,7). Other complications include pneumonitis, enterocolitis, hepatitis, and endocrinopathies such as hypophysitis, thyroiditis, and adrenal insufficiency. Other adverse events such as sarcoid-like reaction, acute kidney injury, pancreatitis, neurotoxicity, cardiotoxicity, and ophthalmologic toxicity are less common. Opportunistic infections such as *Aspergillus* pneumonia, cytomegalovirus viremia and Fournier's gangrene have been reported (34).

Imaging of Adverse Events

Radiologists must be able to recognize the unique adverse events associated with immunotherapy to guide appropriate management and prevent misinterpretation. Several of the most common adverse events affecting the chest and abdomen that may be encountered by radiologists on CT or PET/CT performed for restaging and/or surveillance purposes will be described herein.

Pneumonitis is the most common complication affecting the chest. Naidoo and colleagues showed that several patterns of disease may be present, including 1) cryptogenic organizing pneumonia (COP)-like, 2) ground-glass opacities, 3) interstitial pattern, 4) hypersensitivity pneumonitis-like, and 5) pneumonitis not otherwise specified (Figure 1 and Figure 2) (35). Immune-related pneumonitis may evolve over time. For instance, in some cases the COP-like pattern may change to extensive ground-glass opacities. In some instances, nodular opacities may be present and should not be mistaken for recurrent disease. Sarcoid-like reaction is a rare immune-related adverse event that manifests with numerous small perilymphatic nodules with or without ground-glass opacities (36) (Figure 3). Mediastinal and hilar lymphadenopathy may be seen in combination with pulmonary abnormalities or in isolation (Figure 3). Immunotherapy may result in thyroiditis, manifesting with radiotracer uptake on iodine-123 thyroid scintigraphy and an enlarged and heterogeneous thyroid gland on ultrasound. Thyroiditis may also be identified on CT, producing enlargement and heterogeneous low attenuation of the thyroid gland, and FDG PET/CT, showing increased FDG uptake in an enlarged gland (Figure 4). Immune-related adverse events may affect the airways and result in wall thickening involving the trachea and/or bronchi. Complications of

immunotherapy may affect the cardiovascular structures and result in pericarditis, manifesting as a pericardial effusion and/or pericardial thickening and enhancement on CT (37). Constrictive physiology may develop and is best delineated with echocardiography and MR imaging (38,39).

Radiologists should be familiar with several important complications of immunotherapy that may arise in the abdomen and pelvis, the most common of which is colitis. Colitis is associated with the highest mortality of all immune-related adverse events and a delay in diagnosis is associated with poor outcomes (40). On CT, immune-related colitis results in wall thickening (which may be segmental or diffuse), mucosal enhancement, submucosal edema, air-fluid levels, infiltration of the pericolonic fat, and ascites. The CT findings of autoimmune pancreatitis are similar to those of acute pancreatitis unrelated to immunotherapy, and include enlargement and heterogeneity of a portion of the pancreas with adjacent inflammatory changes including fat stranding, edema, and free fluid (41) (Figure 6). Due to the inflammation, increased FDG uptake is typically present in the affected region of the pancreas (42). Other structures in the upper abdomen may be affected such as the liver, biliary tract, and adrenal glands.

Conclusions

As the role of immunotherapy in treating patients with lung cancer continues to expand, radiologists must understand and be able to appropriate use the modified response criteria used to evaluate these patients including irRC, irRECIST, and iRECIST. Additionally, as a wide variety of immune-related adverse events may impact patients treated with immunotherapy, the radiologist should be aware of the imaging findings of potential complications.

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Figure Legends

Figure 1. Pneumonitis. A. Contrast-enhanced axial CT of a 33-year-old woman with melanoma treated with immunotherapy demonstrates diffuse ground-glass opacities bilaterally. B. Contrast-enhanced axial CT of a 74-year-old woman with melanoma treated with immunotherapy shows ground-glass opacities superimposed on interlobular septal thickening resulting in a “crazy-paving” configuration. C. Unenhanced axial CT of a 57-year-old woman with lung cancer treated with immunotherapy demonstrates a cryptogenic organizing pneumonia–like appearance of immune-related pneumonitis in the left lower lobe with central ground-glass opacity and surrounding consolidation (arrow). Immune-related pneumonitis may manifest in several ways, including ground-glass opacities and a cryptogenic organizing pneumonia-like pattern.

Figure 2. Sarcoid-like Reaction. A. Contrast-enhanced axial CT of a 58-year-old man with melanoma treated with immunotherapy demonstrates numerous pulmonary nodules along the bronchovascular bundles in the right lung (arrow). B. and C. Unenhanced axial CT (B) and fused axial FDG PET/CT (C) of a 56-year-old woman with lung cancer treated with immunotherapy shows enlarged paratracheal lymph nodes (arrows, B) that are FDG-avid on PET/CT. These lymph nodes were biopsied with no evidence of malignancy and a diagnosis of sarcoid-like reaction was made.

Figure 3. Thyroiditis. A. Contrast-enhanced axial CT of a 40-year-old man with lung cancer treated with immunotherapy shows enlargement and slight heterogeneity of the thyroid gland. B. and C. Fused axial FDG PET/CT (B) and unenhanced axial CT (C) of a 32-year-old woman with

melanoma treated with immunotherapy demonstrates increased FDG uptake throughout the thyroid gland and diffuse low attenuation of the gland parenchyma. Immune-related thyroid toxicity most commonly manifests as thyroiditis, which can be identified on various studies, including CT and FDG PET/CT.

Figure 4. Pericarditis. Contrast-enhanced axial CT of a 74-year-old man with melanoma treated with immunotherapy demonstrates a small pericardial effusion and pericardial thickening and enhancement (arrow) consistent with pericarditis. A right pleural effusion is also present.

Figure 5. Colitis. A. Contrast-enhanced axial CT of a 40-year-old woman with lung cancer treated with immunotherapy demonstrates focal wall thickening involving the cecum (arrow) consistent with colitis. Adjacent inflammatory changes are present. B. Contrast-enhanced axial CT of a 43-year-old man with melanoma treated with immunotherapy shows diffuse thickening of the colon (black arrows). Inflammatory changes and ascites are present in the adjacent portions of the abdomen.

Figure 6. Pancreatitis. Contrast-enhanced axial CT of a 51-year-old man with melanoma treated with immunotherapy and presenting with abdominal pain demonstrates slight heterogeneity of the pancreatic head and inflammatory changes in the adjacent fat (arrow) consistent with immune-related pancreatitis.

	irRC	irRECIST	iRECIST
Imaging modalities	Not specifically mentioned[1]; CT, MRI, chest radiography, FDG PET/CT may be used	CT, MRI, chest radiography, FDG PET/CT	CT, MRI, chest radiography, FDG PET/CT
Target lesions	5 per organ, up to 10 visceral and 5 cutaneous	2 per organ, 5 total	2 per organ, 5 total
Measurable size	≥ 5 x 5 mm	≥ 10 mm long axis organ lesions; ≥ 15 mm short axis for lymph nodes	≥ 10 mm long axis organ lesions; ≥ 15 mm short axis for lymph nodes
Measurement parameters	Bidimensional measurement	Unidimensional measurement	Unidimensional measurement
Tumor burden	Sum of the products of the two largest perpendicular diameters of all target lesions (SPD)	Sum of the diameters of all target lesions	Sum of the diameters of all target lesions
Unmeasurable Lesions	Non-target lesions derived from irRC include: Lymphangitic carcinomatosis; skin involvement in breast cancer; abdominal masses that can be palpated but not measured	1. Measurable lesions not selected as target lesions at baseline 2. Unmeasurable disease: lesions too small to measure (< 10 mm long axis organ lesions or < 15 mm short axis for lymph nodes) 3. Other lesions difficult to measure in a reproducible manner: Bone metastases; leptomeningeal metastases; malignant ascites, pleural or pericardial effusions; inflammatory breast disease; lymphangitic carcinomatosis; cystic lesions; ill-defined abdominal masses; skin lesions	1. Measurable lesions not selected as target lesions at baseline 2. Unmeasurable disease: lesions too small to measure (< 10 mm long axis organ lesions or < 15 mm short axis for lymph nodes) 3. Other lesions difficult to measure in a reproducible manner: Bone metastases; leptomeningeal metastases; malignant ascites, pleural or pericardial effusions; inflammatory breast disease; lymphangitic carcinomatosis; cystic lesions; ill-defined abdominal masses; skin lesions

New Lesions	Incorporated into total tumor burden	Incorporated into total measured tumor burden	Result in iUPD[2]; iCPD[3] achieved if additional new lesions are present on subsequent time point or an increase in size of new lesions (≥ 5 mm for the sum of new lesion target or any increase in new lesion non-target)

[1] Cutaneous lesions are included in potential tumor burden, therefore clinical measurements may theoretically be allowed.

[2] immune Unconfirmed Progressive Disease (iUPD).

[3] immune Confirmed Progressive Disease (iCPD).

Table 1. Comparison of irRC, irRECIST and iRECIST.