

Imaging of Cancer Immunotherapy: Current Approaches and Future Directions

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M.N. and H.H. supported by the National Cancer Institute (grants R01CA203636 and U01CA209414).

Conflicts of interest are listed at the end of this article.

Radiology 2019; 290:9–22 • <https://doi.org/10.1148/radiol.2018181349> • Content codes: **BQ MI OI**

Cancer immunotherapy using immune-checkpoint inhibitors has emerged as an effective treatment option for a variety of advanced cancers in the past decade. Because of the distinct mechanisms of immunotherapy that activate the host immunity to treat cancers, unconventional immune-related phenomena are encountered in terms of tumor response and progression, as well as drug toxicity. Imaging plays an important role in objectively characterizing immune-related tumor responses and progression and in detecting and monitoring immune-related adverse events. Moreover, emerging data suggest a promise for molecular imaging that can visualize the specific target molecules involved in immune-checkpoint pathways. In this article, the background and current status of cancer immunotherapy are summarized, and the current methods for imaging evaluations of immune-related responses and toxicities are reviewed along with their limitations and pitfalls. Emerging approaches with molecular imaging are also discussed as a future direction to address unmet needs.

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Learning Objectives:

After reading the article and taking the test, the reader will be able to:

- Describe the mechanism of immune-checkpoint inhibitor therapy and its implications on image interpretation in patients treated with immune-checkpoint inhibitors
- Recognize the unconventional tumor response patterns at imaging of patients treated with immune-checkpoint inhibitors
- Describe the spectrum of imaging manifestations of immune-related adverse events in various organs

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The recent advances in cancer immunotherapy using immune-checkpoint blockade have brought a paradigm shift in advanced cancer treatments. The mechanism of cancer immune-checkpoint inhibitor therapy is through the blockade of tumor-mediated inhibition of immune responses, which can be associated with novel types of tumor response patterns and toxicities. Imaging plays a critical role for objectively defining tumor response and progression in patients treated with immunotherapy and for detecting and monitoring immune-related toxicities, which can involve various organs. Given the rapidly increasing use of cancer immunotherapy in the clinical setting, it is essential for radiologists to be familiar with the cutting-edge approaches to immune-related response and toxicity evaluations with imaging. This article provides an overview of the background and current status of cancer immunotherapy and summarizes the current imaging strategies for immunotherapy response and toxicity assessments. This article also reviews emerging approaches using molecular imaging that try to address the unmet needs in the rapidly evolving field of immuno-oncology.

Overview and Current Status of Cancer Immunotherapy

Cancer immunotherapy using immune-checkpoint inhibitors has emerged as a successful treatment option for the treatment of various types of advanced cancers in the past decade (1–6). The mechanism of anticancer activity of immune-checkpoint inhibitors is based on the blockade of immune inhibition by tumors rather than direct cytotoxic or targeted effects to tumor cells. It has become clearer that T cells have major roles in immune-mediated defense mechanisms against cancer (1–7). The stimulatory and inhibitory signals from the ligand-receptor pairs between tumor cells, T cells, dendritic cells, and macrophages in the tumor microenvironment are called “immune checkpoints.” These immune checkpoint molecules regulate T-cell activation specific to tumor cells as immune responses of the host against cancer (Fig 1) (1–8). Tumor cells are the major mediators of immune suppression in the interaction and facilitate their escape from T-cell-mediated host immune responses so that they can survive and proliferate (5,7,9,10). Immune-checkpoint

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Abbreviations

CTLA-4 = cytotoxic T-lymphocyte antigen 4, FDG = fluorine 18 fluorodeoxyglucose, irAE = immune-related adverse event, irRC = immune-related response criteria, irRECIST = immune-related RECIST, NSCLC = non-small cell lung cancer, OR = odds ratio, PD = progressive disease, PD-L1 = programmed cell death protein ligand 1, PD-1 = programmed cell death protein 1, RECIST = Response Evaluation Criteria in Solid Tumors, SCAD = segmental colitis associated with diverticulosis

Summary

Knowledge of cancer immunotherapy and unique manifestations of immune-related adverse events is essential for radiologists to accurately interpret imaging studies and to effectively communicate the results to the referring physicians.

Essentials

- Cancer immunotherapy using immune-checkpoint inhibitors has introduced a paradigm shift in the treatment of various types of advanced cancers in the past decade.
- Because of the distinctive biologic mechanisms of immune-checkpoint blockade that utilize host immunity to treat cancer, unconventional tumor response patterns have been noted in imaging studies of patients treated with immune-checkpoint inhibitors.
- Although pseudoprogression is increasingly recognized among referring physicians and radiologists and is often featured as a representative phenomenon of immune-related tumor response, the incidence of pseudoprogression among patients treated with immune-checkpoint inhibitors is actually low (<10%).
- The use of immune-checkpoint inhibition in cancer treatment is associated with unique toxicities, termed immune-related adverse events, which can involve various organs from head to toe and present a spectrum of imaging manifestations in each organ.
- Molecular-based imaging has shown promise to address unmet clinical needs in the field, and further studies are needed to translate the approach in the clinical setting for better selection and monitoring of patients to maximize the benefit of cancer immunotherapy.

inhibitors, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors and programmed cell death protein 1 (PD-1) and programmed cell death protein ligand 1 (PD-L1) inhibitors, can interfere with the interaction and block the T-cell immune inhibition by tumors, leading to the activation of the immune response against cancer (9–12).

In 2010, Hodi et al (13) reported the result of a phase III trial of the CTLA-4 inhibitor ipilimumab in advanced melanoma and demonstrated a significantly improved overall survival. The median overall survival was 10.0 months in patients treated with ipilimumab plus a glycoprotein 100 peptide vaccine (gp100), compared with 6.4 months among patients receiving gp100 alone as a control group (hazard ratio for death, 0.68; $P < .001$). The results of the study opened a new era of utilizing immune-checkpoint blockade for cancer therapy. Subsequent clinical trials have also studied PD-1/PD-L1 inhibitors, which showed promising activity in patients with various types of advanced cancers, leading to the regulatory approvals of these agents for a variety of indications (Table 1). Immune-checkpoint blockade has quickly become a mainstream treatment strategy for advanced cancers in the oncology clinic.

The unique mechanism of immune-checkpoint inhibitor therapy underlies a wide range of novel patterns of tumor responses and toxicities, which are often associated with specific imaging findings on treatment-monitoring studies in patients receiving immunotherapy. Given the rapidly increasing use of immunotherapeutic agents in the oncology practice, understanding the mechanism of action of these agents is essential for radiologists to accurately interpret the imaging studies and effectively communicate the results to the referring physicians.

Immune-related Response Assessment with Imaging

Because of the distinctive biologic mechanisms of immune-checkpoint blockade, unconventional tumor response patterns at imaging have been noted in patients treated with immune-checkpoint inhibitors. Well-recognized immune-related response patterns include response after an initial increase in tumor burden (Fig 2) or response during or after the appearance of new lesions (Fig 3). These phenomena are often termed “pseudoprogression,” because these patterns would be categorized as progression according to conventional tumor response criteria such as Response Evaluation Criteria in Solid Tumors (RECIST) at the time of the initial increase in or appearance of new lesions (4,8,15–17). The mechanism of pseudoprogression is thought to be the infiltration of T cells into tumors, resulting in an initial apparent increase in tumor burden rather than true proliferation of tumor cells (16).

Several modified criteria have been proposed to capture these atypical patterns in patients receiving cancer immunotherapy. This section will review (a) the evolution and current status of immune-related response evaluation strategies, (b) pitfalls of the current immune-response evaluations, and (c) emerging observations in immune-related tumor response dynamics.

Evolution and Current Status of Immune-related Response Evaluation Strategies

Conventionally, strategies for evaluation of tumor response to therapy include the World Health Organization criteria, which were introduced in 1979, and RECIST, which were introduced in 2000 and revised in 2009 (Table 2) (18–21). In the process of tumor response evaluations, target lesions are selected on baseline images, and measurements of these lesions are performed on serial follow-up images to quantify tumor burden changes and define response and progression according to the criteria described in Table 2.

On the basis of observations of immune-related response patterns, modifications of the conventional tumor response criteria have been proposed in an attempt to accurately characterize immune-related response patterns. These efforts resulted in a series of modified criteria and guidelines specifically designed for patients treated with immunotherapy (Table 2). The first set of criteria was the immune-related response criteria (irRC), which were developed in 2009 (16). There are two key features of irRC that introduced an important concept for immune-related response evaluations. First, irRC required confirmation of progression on two consecutive studies at least 4 weeks apart, rather than declaring progressive disease (PD)

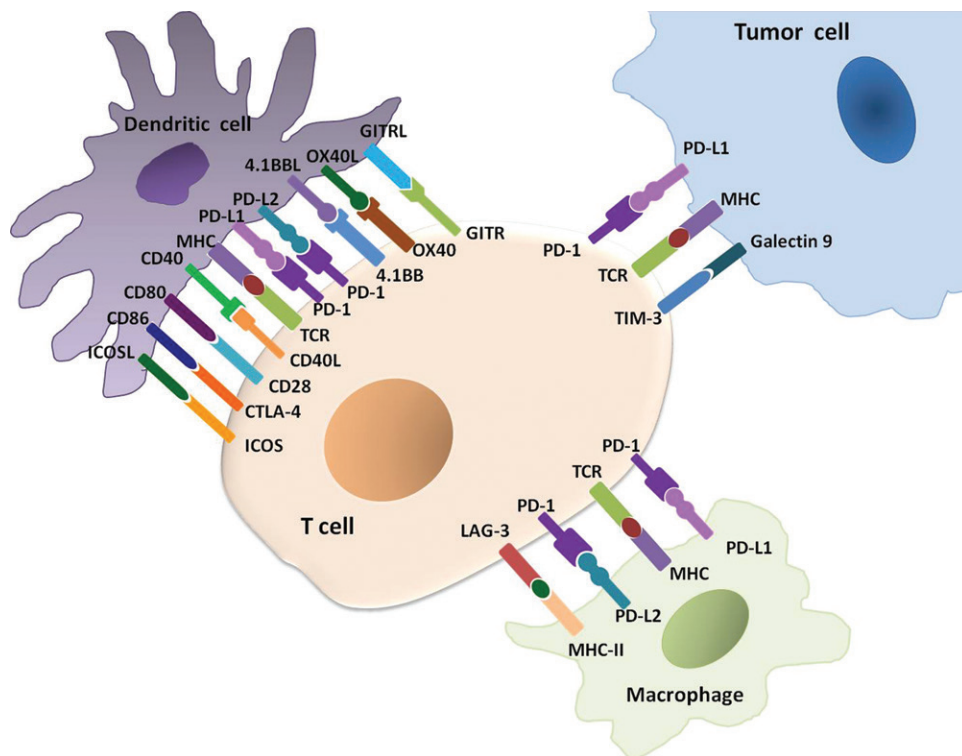


Figure 1: Immune-checkpoint molecules between tumor cells and immune cells in the tumor microenvironment. A number of inhibitory receptors and ligands are expressed on T cells, dendritic cells, macrophages, and tumor cells in the tumor microenvironment and serve as critical mediators of immune suppression by tumors. These receptor-ligand pairs, such as programmed cell death ligand 1 (*PD-1*)/programmed cell death protein ligand 1 (*PD-L1*) in the T cell and tumor cell interaction, are called “immune checkpoint” molecules. The blockade of these checkpoints using immune-checkpoint inhibitors such as *PD-1/PD-L1* inhibitors and cytotoxic T-lymphocyte antigen 4 (*CTLA-4*) inhibitors have emerged as successful treatment options for a variety of advanced cancers. (Modified from references 4 and 5.) *GITR* = glucocorticoid-induced tumor necrosis factor receptor-related protein, *GITRL* = *GITR* ligand, *ICOS* = inducible T-cell co-stimulator, *ICOSL* = *ICOS* ligand, *LAG* = lymphocyte activation gene, *MHC* = major histocompatibility complex, *TCR* = T-cell receptor, *TIM* = T-cell immunoglobulin and mucin domain.

immediately at the initial increase in tumor burden above the threshold. This is to capture instances of pseudoprogression, which may subsequently demonstrate tumor reduction (Fig 4) (8,16). Second, when new lesions appear, irRC includes the measurements of new lesions in the sum of the entire tumor burden for response assessment, rather than defining PD. This is because some patients may respond during or after the appearance of new lesions (Fig 3) (8,16). Subsequently, irRC were used in immunotherapy trials to define end points and was evaluated for its added value. In a study comparing irRC and RECIST 1.1 in 327 patients with advanced melanoma treated with pembrolizumab, 7% (24 of 327) of the patients demonstrated pseudoprogression (15). Patients assessed as having PD according to RECIST 1.1 but non-PD according to irRC had longer overall survival than patients with PD according to both RECIST 1.1 and irRC (median overall survival: 22.5 vs 8.4 months) (15), indicating an added value of irRC.

Although there is no doubt that irRC introduced an important concept for immune-related response evaluations and contributed to raise awareness of atypical response patterns during immunotherapy, there were a few issues in this approach, mostly related to the methods of tumor measurements. Notably, irRC was

based on World Health Organization criteria and thus utilized bidimensional measurements, multiplying the longest diameter and the longest perpendicular diameter to quantify tumor burden (18,21). However, most solid-tumor trials after 2000 utilized RECIST, which uses unidimensional single-diameter measurements for tumor response evaluation (19–21). The use of bidimensional measurements in irRC was problematic because the direct comparisons of the trial results were difficult when some investigators use RECIST with its unidimensional measurements and others use irRC with its bidimensional measurements. In addition, a number of previous studies demonstrated that bidimensional measurements have larger measurement variability and higher misclassification rates compared with RECIST-based unidimensional measurements (22–24).

To propose a unified direction for immune-related response evaluations that are aligned with RECIST, Nishino et al (25–27) performed a series of studies to optimize strategies and to develop a “common language” for immune-related response assessment (25–27). In 57 patients with advanced melanoma treated with ipilimumab, the results of response assessment by using the original irRC with bidimensional measurements were compared with those of response assessment by using unidimensional irRC that utilized RECIST-based single-diameter measurements while retaining the important features of irRC in terms of new lesions and confirmation of progression (26). Bidimensional and unidimensional irRC resulted in highly concordant response evaluations ($\kappa_w = 0.881$ for best immune-related response), with no evidence of a difference for time to progression (26). Measurement variability of the unidimensional approach was half of that of the bidimensional irRC (95% limits of agreement: -16.1% , 5.8% vs -31.3% , 19.7% , respectively) (26), confirming higher reproducibility of RECIST-based unidimensional methods. A subsequent study (25) demonstrated that RECIST 1.1 revisions, including a reduced number of target lesions and short-axis measurements in lymph nodes, are also feasible in immune-related response evaluations. These studies provided the scientific basis for a current direction toward RECIST-based assessment for immunotherapy, while keeping the important features of irRC. These response criteria

Table 1: Immune-Checkpoint Inhibitors and Their Approved Indications in Oncology Practice in the United States

Class of Agent and Agent	Approved Tumor Types in the United States
CTLA-4 inhibitor	
Ipilimumab*	Melanoma [†]
PD-1 inhibitor	
Nivolumab*	Melanoma [†] , NSCLC [†] , RCC [†] , Hodgkin lymphoma [†] , UCC [†] , head and neck sqCC [†] , dMMR and MSI-H colorectal cancer, hepatoma
Pembrolizumab	Melanoma [†] , NSCLC [†] , Hodgkin lymphoma [†] , UCC [†] , head and neck sqCC, MSI-H or dMMR solid tumors, gastric and gastroesophageal junction cancers, cervical cancer
PD-L1 inhibitor	
Atezolizumab	UCC [†] , NSCLC [†]
Durvalumab	UCC, NSCLC (as consolidation after chemoradiotherapy for stage III)

Note.—CTLA-4 = cytotoxic T-lymphocyte antigen 4, dMMR = mismatch repair deficient, MSI-H = microsatellite instability high, NSCLC = non–small cell lung cancer, PD-L1 = programmed cell death protein ligand 1, PD-1 = programmed cell death protein 1, RCC = renal cell carcinoma, sqCC = squamous cell carcinoma, UCC = urothelial cancer.

* Ipilimumab and nivolumab combination therapy is also approved for metastatic melanoma and advanced RCC and for dMMR and MSI-H colorectal cancer.

[†] The indications have also been approved in the European Union (14).

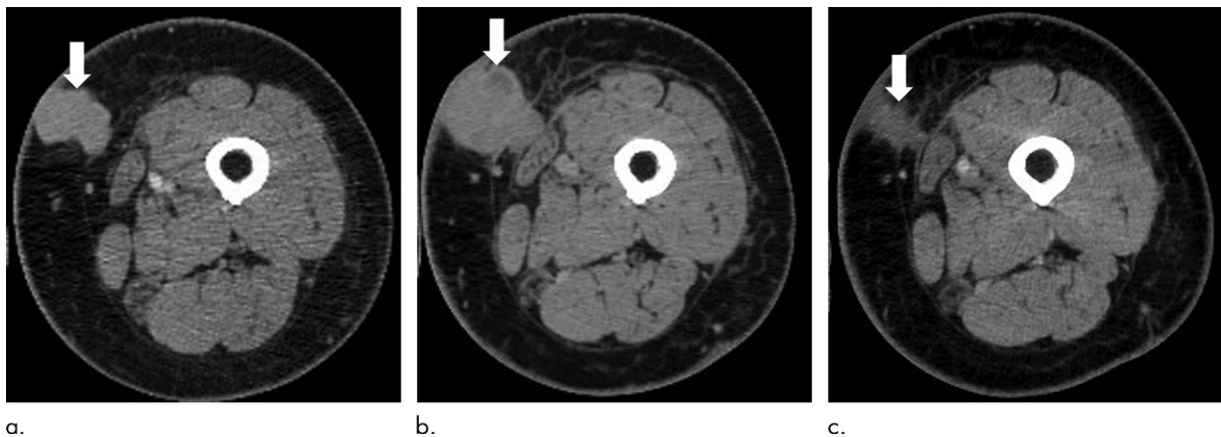


Figure 2: Pseudoprogression with initial increase in tumor burden followed by subsequent tumor shrinkage due to immune-related response in a 66-year-old woman with metastatic melanoma treated with nivolumab and ipilimumab. **(a)** Baseline contrast material-enhanced axial CT image obtained before therapy shows a metastatic nodule (arrow) in the left upper medial thigh measuring 4 cm in the longest diameter. **(b)** Follow-up axial CT image at 3 months of therapy shows an increase in the lesion, which now measures 5 cm (arrow), indicating progressive disease according to the Response Evaluation Criteria in Solid Tumors, or RECIST. **(c)** Further follow-up axial CT image at 6 months of therapy shows a decrease in size of the lesion, which now measures 2.5 cm (arrow), representing immune-related tumor response.

are referred to as immune-related RECIST (irRECIST) among investigators of immuno-oncology community and are used in trials of novel immunotherapeutic agents (4,25,26,28).

Another recent development is the introduction of iRECIST, updated criteria for immunotherapy trials (29). iRECIST follows the direction demonstrated by irRECIST in that it utilizes RECIST-based measurements and keeps important modifications to capture immune-related response patterns. Additionally, iRECIST introduced a concept of “unconfirmed PD” (iUPD), which indicates PD according to RECIST 1.1 that remains to be confirmed. iUPD can become “confirmed PD” (iCPD) if the next imaging study in 4–8 weeks shows further increase. The concept can be helpful for further delineation of response assessment results, because patients with initial tumor burden increase may not necessarily be reevaluated with a consecutive study for confirmation. Some patients may choose to

start the next systemic therapy without waiting for 4 weeks or more to have the confirmation study. Others may not tolerate immunotherapy any further because of side effects or cannot return for the follow-up study because of clinical deterioration. New lesion assessments were also updated per iRECIST, and instead of new lesion measurements being included in the sum of the entire tumor burden, new lesions are recorded and measured separately (29). iCPD can be assigned if additional new lesions or an increase in new lesions is noted at the next imaging study in 4–8 weeks (29). The value of iRECIST remains to be validated in prospective trials, and some details may need further clarification. Regardless, the introduction of iRECIST further ensures that a RECIST-based approach should be used for immune-related response evaluations and supplements the ongoing efforts to develop a common language for treatment response assessment for immunotherapy.

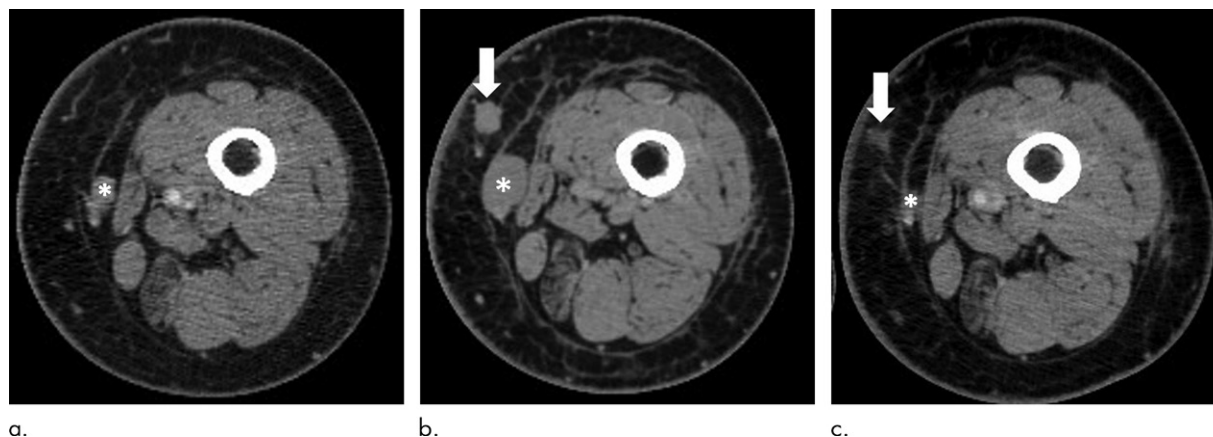


Figure 3: Pseudoprogession with appearance of a new lesion followed by subsequent immune-related response in a 66-year-old woman with metastatic melanoma treated with nivolumab and ipilimumab. Compared with **(a)** a baseline axial CT image obtained prior to the initiation of therapy, **(b)** a follow-up axial CT image obtained after 3 months of therapy shows a new subcutaneous lesion (arrow), indicating progressive disease according to the Response Evaluation Criteria in Solid Tumors, or RECIST; however, **(c)** a further follow-up axial CT image obtained after 6 months of therapy shows shrinkage of the new lesion (arrow), representing immune-related response. Note that another lesion in the deep subcutaneous tissue (*) increased at 3-month follow-up, followed by subsequent shrinkage of the lesion, also indicating immune-related response after initial increase in tumor burden.

Table 2: Summary of Conventional Tumor Response Criteria and Modified Strategies for Immune-related Response Evaluations

Type of Criteria and Criteria	Measurement	PR Criteria*	PD Criteria†	Confirmation of PD	New Lesion
Conventional tumor response criteria					
WHO (1979) (18)	Bidimensional (LD×LPD)	≥50% reduction	≥25% increase, new lesion, or nontarget PD	Not required	Defines PD
RECIST 1.0 (2000) (19)	Unidimensional (LD)	≥30% reduction	≥20% increase, new lesion, or nontarget PD	Not required	Defines PD
RECIST 1.1 (2009) (20)	Unidimensional (LD for nonnodal lesions; LPD for lymph nodes)	≥30% reduction	≥20% and ≥5 mm increase, new lesion, or nontarget PD	Not required	Defines PD
Modified strategies for immune-related response evaluation					
irRC (2009) (16)	Bidimensional (LD×LPD)	≥50% reduction	≥25% increase	Required on consecutive studies at least 4 weeks apart	Does not define PD; measurements of new lesions included in the total tumor burden
irRECIST (2013) (25–27,73)	Unidimensional (LD for nonnodal lesions; LPD for lymph nodes)	≥30% reduction	≥20% and ≥5 mm increase, new lesion, or nontarget PD	Required on a consecutive scan at least 4 weeks apart	Does not define PD; measurements of new lesions included in the total tumor burden
iRECIST (2017) (29)	Unidimensional (LD for nonnodal lesions; LPD for lymph nodes)	≥30% reduction	≥20% and ≥5 mm increase, new lesion, or nontarget PD	Required at the next assessment 4–8 weeks later	Defines unconfirmed PD; confirms PD if additional new lesions or size increase (≥5 mm for the sum of new target or any increase in new nontarget lesions) are noted on the next assessment

Note.—irRC = immune-related response criteria, irRECIST = immune-related RECIST, LD = longest diameter, LPD = longest perpendicular diameter, PD = progressive disease, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, WHO = World Health Organization.

* In reference to the baseline measurements.

† In reference to the nadir (the smallest measurement since the baseline).

Pitfalls of Current Immune-Response Evaluations

Pseudoprogession is increasingly recognized among referring physicians and radiologists and is often featured as a representative phenomenon of immune-related tumor response. However, it is also important to be aware that the incidence of pseudoprogession among patients treated with immune-checkpoint inhibitors is low (4,17,30). The incidence rate of pseudoprogession is up to 10% or often lower in melanoma (15,16,31,32), and was 5% in advanced non-small cell lung cancer (NSCLC) in a phase I nivolumab trial (33). A recent study (34) of advanced NSCLC treated with single-agent PD-1 inhibitor therapy as a part of standard care reported pseudoprogession in 0.6% (one of 160) of the patients, further indicating the rarity of the event.

In terms of the frequency of subsequent response in patients whose disease progresses initially, a phase I trial of pembrolizumab in ipilimumab-refractory advanced melanoma reported that three (5%) among 58 patients who initially progressed according to RECIST achieved immune-related partial response at 24 weeks (35).

Although further investigations are needed in various tumor types and different immunotherapeutic regimens, based on the accumulated data to date, tumor burden increase during immune-checkpoint inhibitor therapy indicates true progression in most patients rather than pseudoprogession. In this context, radiologists have an essential role in objectively assessing imaging findings in reference to the available data and having active dialogues with referring physicians about the details of specific cases, including the patient's symptoms and overall clinical status for optimal treatment.

Another shortcoming of the current strategy of immune-related response evaluations relates to the timeframe between pseudoprogession and subsequent tumor reduction. The current criteria define confirmed PD on the basis of the second consecutive study at 4–8 weeks later (16,25,26,29,36). However, these recommended time intervals are not based on scientific evidence, and further studies are needed to determine the optimal timeframe for confirmatory studies. Moreover, tumor reduction after pseudoprogession can occur after confirmed PD over the course of several months (Fig 4) (32,34). These observations indicate the limitation of the current methods and the need for further strategies

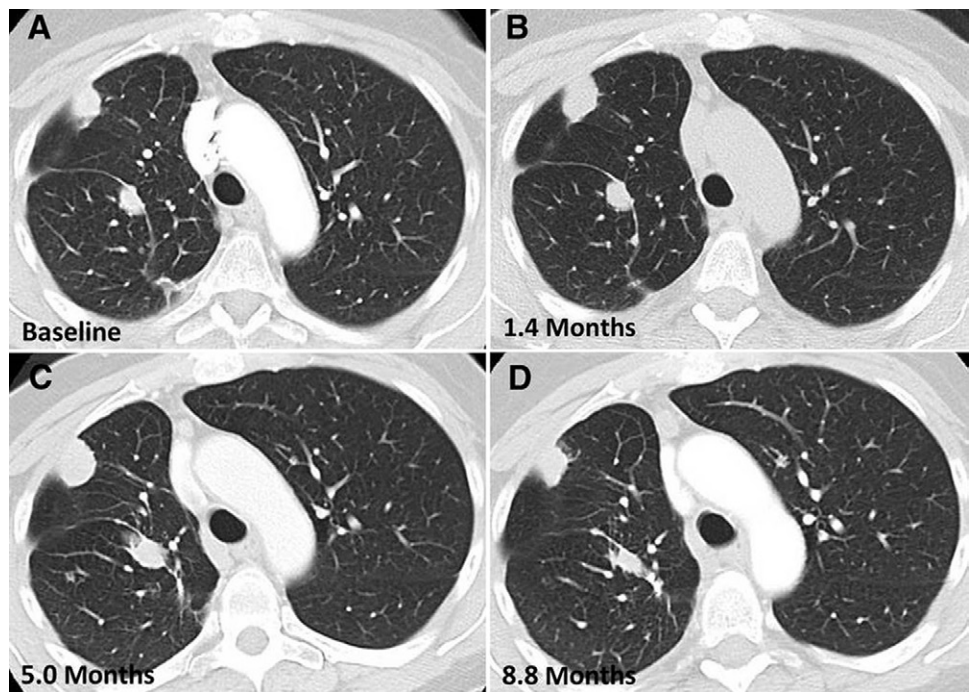


Figure 4: Axial chest CT images show pseudoprogession followed by subsequent tumor reduction noted after confirmation of progressive disease on consecutive images obtained over the course of several months in a 63-year-old woman with lung adenocarcinoma treated with nivolumab who experienced pseudoprogession. Comparing subsequent findings to, A, the baseline, the patient experienced tumor burden increase at, B, 1.4 months of therapy, meeting the criteria for progressive disease, which was confirmed on, C, a serial CT scan at 5.0 months of therapy. Subsequently, tumor regression was noted at, D, 8.8 months of therapy. (Reprinted, with permission, from reference 34).

for how to differentiate a small subset of patients with pseudoprogession from other patients to address this ongoing clinical dilemma.

In addition to tumor size changes, tumor density measured as CT attenuation can be a marker for response and outcome in patients with cancer, as demonstrated in gastrointestinal stromal tumors treated with antiangiogenic therapy (8,37). A prior study (38) evaluated CT attenuation changes in patients with advanced melanoma treated with ipilimumab plus the vascular endothelial growth factor inhibitor bevacizumab. One-third of the patients achieved a tumor density increase of 15% or greater, meeting the criteria for partial response according to CT attenuation criteria developed by Choi et al (37). However, attenuation changes were not associated with survival in these patients. The role of CT attenuation changes in evaluating response to immunotherapy remains to be further established (38). Similarly, the role of fluorine 18 fluorodeoxyglucose (FDG) PET in the response assessment of immunotherapy remains to be established.

Emerging Observations in Immune-related Tumor Response Dynamics

Although tumor response criteria are important for defining response and progression and for providing end points for clinical trials, emerging observations from recent studies indicate the importance of longitudinal tumor burden dynamics on serial imaging studies during immunotherapy.

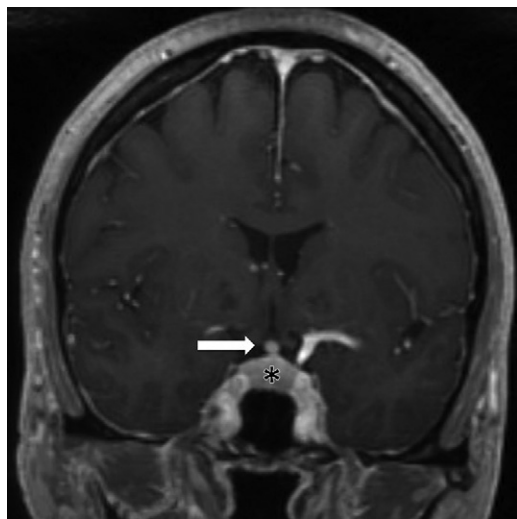


Figure 5: Immune-related hypophysitis in a 56-year-old woman with metastatic melanoma receiving ipilimumab and nivolumab and with headaches at presentation. Coronal MR image after 8 weeks of ipilimumab and nivolumab therapy shows an enlarged pituitary gland (*) and infundibular thickening (arrow), representing immune-related hypophysitis. The symptom and findings resolved after corticosteroid therapy.

In 96 patients with advanced melanoma treated with pembrolizumab monotherapy, a tumor burden increase of less than 20% from baseline during therapy according to irRECIST was noted in 55% of the patients and was associated with longer overall survival (32). Patients with a tumor burden increase of less than 20% throughout PD-1 therapy had significantly reduced hazards of death compared with those who experienced a tumor burden increase of 20% or greater (hazard ratio [HR] = 0.19 and $P < .0001$ at univariate analysis; HR = 0.18 and $P < .0001$ at multivariable analysis) (32). Another study in 160 patients with advanced NSCLC who were treated with nivolumab or pembrolizumab monotherapy (34) also showed a significantly prolonged overall survival in patients with a tumor burden increase of less than 20% throughout therapy compared with those who experienced a tumor burden increase of 20% or greater (HR = 0.24, Cox $P < .0001$ after adjusting for smoking [HR = 0.86, $P = .61$] and baseline tumor burden [HR = 1.55, $P = .062$]). These results propose a practical marker of treatment benefit of immune-checkpoint inhibitor therapy based on the longitudinal evaluations of CT scans to guide treatment decisions.

Additionally, a recent report by Champiat et al (39) described “hyperprogressive disease” as a novel aggressive pattern of immune-related tumor behavior. Hyperprogressive disease was defined as a RECIST progression at the first evaluation and a twofold or greater increase in the tumor growth rate after starting PD-1/PD-L1 inhibitor therapy compared with the period before starting PD-1/PD-L1 inhibitor therapy. Hyperprogressive disease was noted in 9% (12 of 131) of patients treated in phase I clinical trials of PD-1/PD-L1 inhibitor monotherapy for various tumor types and was associated with an older age ($P < .05$). The

frequency of hyperprogressive disease was 19% (seven of 36) in patients older than 65 years, as compared with 5% (five of 95) in patients younger than 64 years ($P = .018$) (39). These observations indicate a need for further studies to understand the mechanisms of rapid tumor progression and to refine strategies for patient selection for immunotherapy.

Immune-related Adverse Events and the Spectrum of Imaging Manifestations

The use of immune-checkpoint inhibition in cancer treatment is associated with unique toxicities, termed immune-related adverse events (irAEs), which can involve various organs from head to toe. The irAEs present a spectrum of imaging manifestations in an organ-specific manner (40–44). irAEs are newly recognized entities in the past few years of immuno-oncology practice, and thus the concept and knowledge of them are still evolving. The mechanism of irAEs is presumed to be autoimmune effects resulting from misdirected stimulation of the immune system during immunotherapy (45). With the rapidly increasing access to immunotherapeutic agents in the clinical setting, there are increasing demands for radiologists to be familiar with clinical and imaging manifestations of irAEs and to contribute to early diagnosis and optimal monitoring as a member of a multidisciplinary team for cancer care. We focus on a spectrum of clinical and radiographic manifestations of several organ-specific irAEs for which imaging plays critical roles in diagnosis and monitoring.

Hypophysitis

Hypophysitis is one of the most common immune-related endocrinopathies and has been increasingly recognized as an important irAE, noted in up to 10%–13% of patients with melanoma treated with ipilimumab (46–48). The diagnosis of immune-related hypophysitis is presumptive and is generally based on the development of new hypopituitarism and pituitary enlargement at imaging after initiation of immunotherapy without an alternative etiology (49). In a recent meta-analysis of the incidence of endocrine dysfunction in immunotherapy trials (50), patients with melanoma who were treated with PD-1 inhibitors had significantly less risk of hypophysitis (odds ratio [OR], 0.29; $P < .001$) compared with those treated with ipilimumab. Combination immunotherapy was also associated with significantly higher odds of developing hypophysitis (OR, 2.2; $P = .001$). Another study in patients with melanoma treated with ipilimumab reported that male sex and older age were risk factors for immune-related hypophysitis (47).

Clinical presentations of immune-related hypophysitis are commonly headache and fatigue or weakness, while visual defects are extremely rare, likely because the enlargement of the pituitary gland is usually mild compared with lymphocytic hypophysitis in other settings (49). The median onset of hypophysitis was 9 weeks after therapy initiation, with a range of 5–36 weeks, in an ipilimumab-treated cohort (48). New pituitary enlargement at imaging in patients undergoing immune-checkpoint blockade therapy is recognized as a sensitive and specific indicator of the entity (Fig 5) and may precede clinical symptoms or biochemical hypopituitarism (47,49). At MRI, enlarged pituitary

glands may demonstrate homogeneous or heterogeneous enhancement, and thickening of the pituitary stalk may also be noted (46,47,49). Treatment strategies include systemic high-dose corticosteroid administration, while hormone replacement for hypophysitis-related hormone deficiencies is also useful (46,47,49). Resolution of pituitary findings at MRI along with resolution of clinical symptoms is often noted during the course of immune-related hypophysitis, where MRI plays an important role for both detection and monitoring of this irAE (46,47,49,51).

Pneumonitis

Pneumonitis related to immune-checkpoint inhibitor therapy is of concern, especially in patients treated with PD-1/PD-L1 inhibitors. Although it is relatively rare, pneumonitis is a clinically serious and potentially life-threatening toxicity of immune-checkpoint blockade, resulting in pneumonitis-related deaths in early phase trials, and is recognized as an “event of special interest” (33,42,52–54). Initial reports of pneumonitis related to immune-checkpoint inhibitors have described a spectrum of radiologic manifestations with different morphologic patterns of interstitial pneumonias (54,55). The clinical courses also varied among patients; some patients required admission to the intensive care unit and sometimes even intubation, whereas others were successfully treated with oral corticosteroids and were able to restart PD-1 inhibitor therapy without experiencing recurrent pneumonitis (54,55). These initial observations prompted further systematic studies of pneumonitis related to immune-checkpoint inhibitors (Fig 6).

In terms of the incidence of pneumonitis, a prior meta-analysis of 20 clinical trials of PD-1 inhibitor therapy in melanoma, NSCLC, and renal cell carcinoma reported that the overall incidence was 2.7% for all-grade pneumonitis and 0.8% for pneumonitis of grade 3 or higher in patients treated with PD-1 inhibitor monotherapy (56). Higher odds of pneumonitis were noted in NSCLC for all-grade pneumonitis (OR, 1.43; $P = .05$) and for pneumonitis of grade 3 or higher (OR, 2.85; $P < .0001$) compared with melanoma. Combination immunotherapy had significantly higher odds than monotherapy for all-grade pneumonitis (OR, 2.04; $P < .0001$) and for pneumonitis of grade 3 or higher (OR, 2.86; P

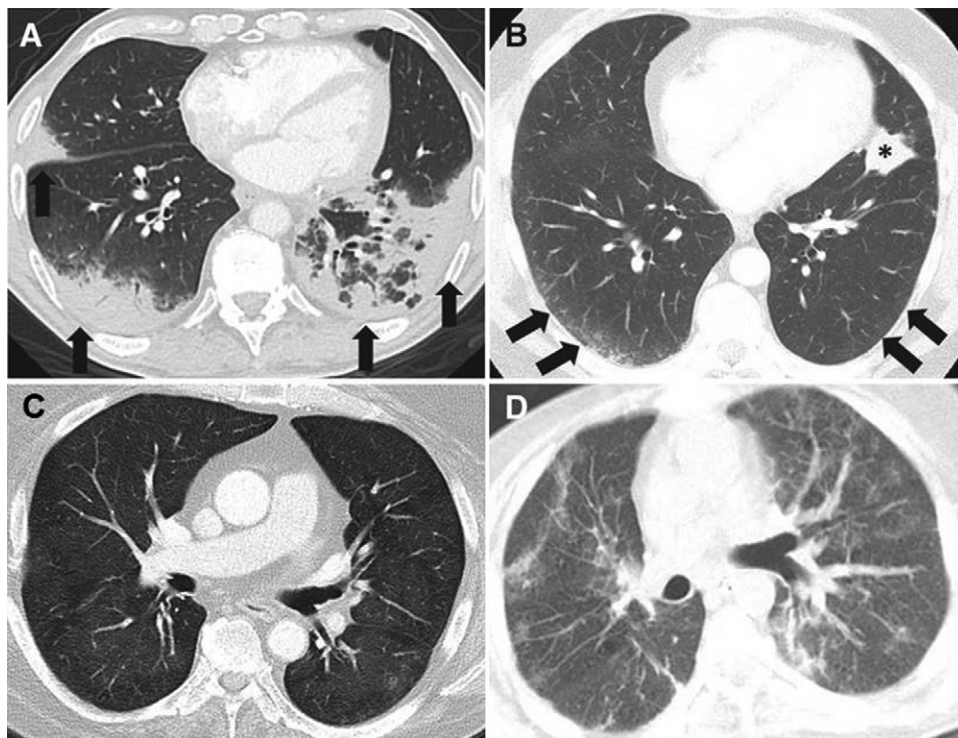


Figure 6: Axial chest CT images show the spectrum of radiographic patterns of immune-checkpoint inhibitor-related pneumonitis, which includes, *A*, the cryptogenic organizing pneumonia (COP) pattern, *B*, the nonspecific interstitial pneumonia (NSIP) pattern, *C*, the hypersensitivity pneumonitis (HP) pattern, and, *D*, the acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern. *A*, The COP pattern is characterized by multifocal bilateral parenchymal consolidations with peripheral and lower lung distribution, with ground-glass opacities (GGOs) and reticular opacities (arrows). *B*, The NSIP pattern demonstrates GGOs and reticular opacities predominantly in a peripheral and lower lung distribution (arrows). * = Lung tumor burden. *C*, The HP pattern demonstrates diffuse GGOs and centrilobular nodularities, with scattered areas of air trapping. *D*, The AIP/ARDS pattern is characterized by diffuse or multifocal GGOs or consolidations, along with lung volume loss and traction bronchiectasis. (Reprinted, with permission, from reference 66).

$< .0001$) (56). Another meta-analysis of 19 clinical trials investigating PD-1 inhibitors and PD-L1 inhibitors as single-agent therapy in NSCLC reported a higher incidence of pneumonitis for PD-1 inhibitors than for PD-L1 inhibitors (3.6% vs 1.3%, respectively; $P = .001$) (57). In a subanalysis of 550 patients with NSCLC treated with pembrolizumab in the phase I KEYNOTE-001 trial, the overall incidence of pneumonitis was 3.8% (21 of 550) (58). The incidence was higher in patients with a history of asthma or chronic obstructive pulmonary disease (5.3%) and in those with a history of thoracic radiation (6.0%) (58). While these studies provide important insights for the propensity of developing pneumonitis among different patient cohorts, many questions remain to be addressed, including biomarkers for pneumonitis, accurate diagnostic methods and monitoring strategies, and optimal treatment approaches.

From a radiology perspective, characterization of pneumonitis using the radiographic patterns according to the classification of interstitial pneumonias has been shown to be applicable in patients treated with novel precision therapies, including immunotherapy (42,59–66). A prior study characterized the spectrum of radiographic patterns of pneumonitis in correlation with clinical severity in 20 patients with melanoma, NSCLC, or lymphoma who developed pneumonitis during treatment with nivolumab

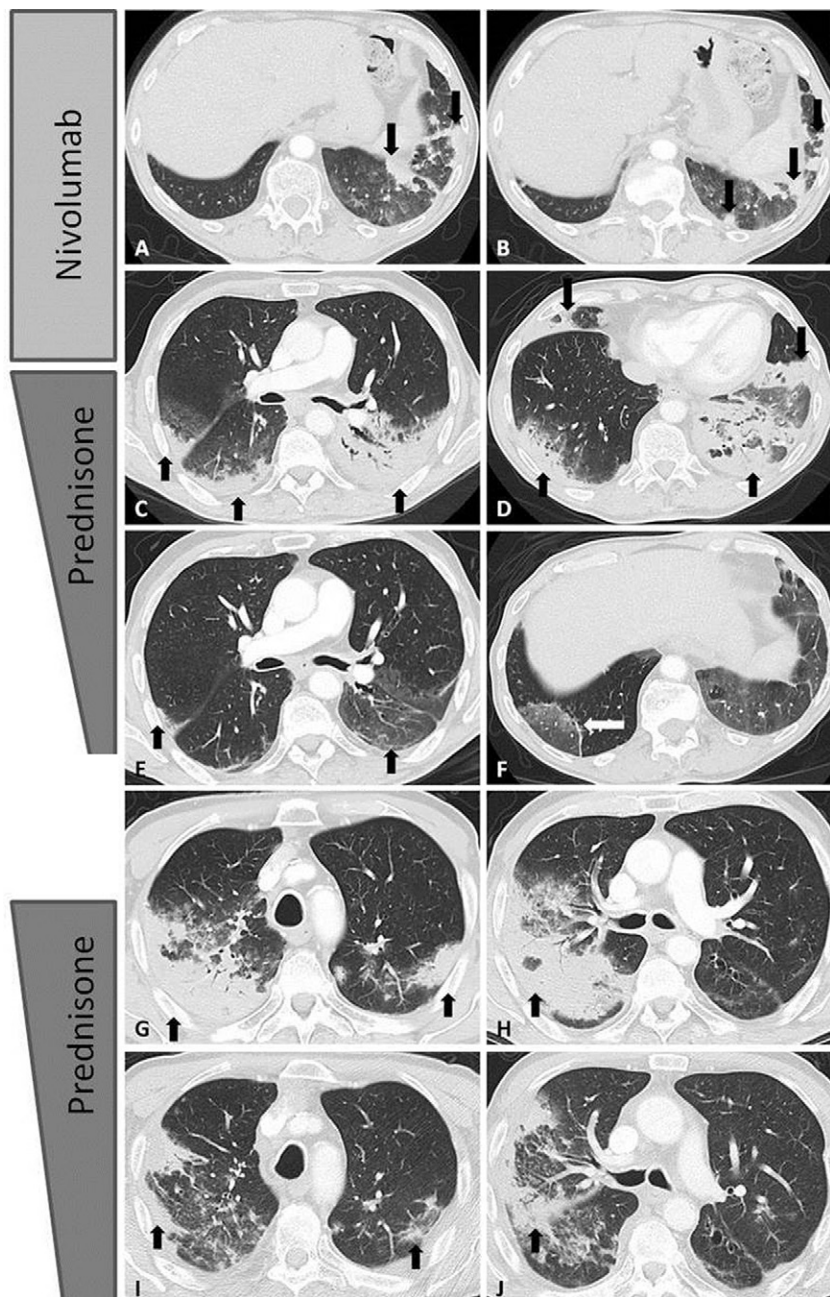


Figure 7: Axial chest CT scans show programmed cell death protein 1 (PD-1) inhibitor-related pneumonitis in a patient with advanced non-small cell lung cancer treated with nivolumab. A, B, CT scans at 8 weeks of nivolumab therapy show new ground-glass opacities (GGOs), reticular opacities, and consolidation in the lower lobes predominantly on the left, with a peripheral and lower distribution, radiographically representing a cryptogenic organizing pneumonia (COP) pattern (arrows). C, D, On CT scans obtained at 15 weeks of therapy, the findings have substantially increased and involve all lobes, with multifocal areas of GGO, reticular opacities, and consolidation (arrows), as well as centrilobular nodularity and traction bronchiectasis in a predominantly peripheral distribution, demonstrating the overall features of a COP pattern. E, F, Further follow-up CT scans obtained after 4 weeks of prednisone treatment show a marked decrease in the CT findings with residual GGOs, demonstrating a “reversed halo” sign with central GGO surrounded by dense air-space consolidation of a crescentic shape (arrows in F). G, H, CT scans obtained 4 weeks after the completion of prednisone treatment show development of dense consolidations with GGOs and reticular opacities (arrows) in peripheral and multifocal distributions, involving both upper and lower lobes, again demonstrating the COP pattern noted during the first episode of PD-1 pneumonitis. Given the similarity of the radiographic and clinical manifestations to those of the first episode, the patient restarted prednisone for treatment of a “pneumonitis flare.” I, J, Follow-up CT scans obtained 2 weeks after starting the second course of prednisone therapy show decrease of consolidation and GGOs (arrows), indicating improving pneumonitis in response to corticosteroid therapy. (Reprinted, with permission, from reference 55.)

(63). The median time from treatment initiation to the development of pneumonitis was 2.6 months (range, 0.5–11.5 months). A wide spectrum of radiographic patterns was noted, including an acute interstitial pneumonia (AIP)/acute respiratory distress syndrome (ARDS) pattern, a cryptogenic organizing pneumonia (COP) pattern, a nonspecific interstitial pneumonia (NSIP) pattern, and a hypersensitivity pneumonitis (HP) pattern. Among these patterns, a radiographic COP pattern was the most common pattern seen across all tumors and treatment regimens (Fig 7) (63). The radiographic patterns were associated with toxicity grades of pneumonitis, and the AIP/ARDS pattern had the highest grade, followed by the COP pattern, whereas the NSIP and HP patterns were associated with lower grades (median grade: 3, 2, 1, and 1, respectively) (63). The results

indicated the utility of a radiographic pattern-based approach as a guide for patient treatment and monitoring for immunotherapy-related pneumonitis.

Treatment of pneumonitis consists of corticosteroids along with withholding the responsible immunotherapeutic agents for most cases. A subset of cases can be unresponsive to corticosteroids and may require additional treatment with infliximab (an anti-tumor necrosis factor- α immunosuppressant), mycophenolate mofetil, or cyclophosphamide (41,42,54,66,67). Re-treatment with immunotherapy after episodes of pneumonitis is another challenging issue. Although the data are limited, up to one-third of patients may be able to restart immune-checkpoint inhibitor therapy after successful treatment of pneumonitis. However, about one-fourth of these patients may experience recurrent pneumonitis due to retreatment (Fig 7) (42,63,66,67). Moreover, in a small subset of patients, pneumonitis may recur after the completion of a corticosteroid taper without restarting immune-checkpoint inhibitors or any other systemic agents, representing a phenomenon termed a “pneumonitis flare” (Fig 7) (27,63). These observations indicate a complex

immune-mediated nature for pneumonitis, which requires further investigations to optimize patient selection and monitoring.

Sarcoid-like Lymphadenopathy and Granulomatosis

Sarcoid-like lymphadenopathy and granulomatosis is also recognized as an irAE, most commonly noted in mediastinal and hilar lymph nodes, and noted in up to 5%–7% of patients treated with immune-checkpoint inhibitors (43,44,68). It is often clinically silent

without symptoms and can be self limited without specific treatment. Symptomatic patients can be treated with corticosteroids with good response (68). The median time from the initiation of therapy was 3.2 months (range, 0.2–9.1 months) in patients with melanoma treated with ipilimumab (43).

At imaging, mediastinal and hilar lymphadenopathy is seen in patients receiving immune-checkpoint blockade, with distributions and appearance that are similar to those of sarcoidosis. Lymph nodes can be FDG-avid at PET/CT. Lung parenchymal changes with nodular thickening of peribronchovascular bundles and the interlobular septum can also be noted (Fig 8). Histologic sampling of these cases revealed granulomatous inflammation in an interlobular, peribronchiolar, and subpleural distribution resembling sarcoidosis (43,44,68). A recent report (69) demonstrated that this entity can also occur as an isolated finding in the lung, with a focus of lung consolidation in the absence of lymphadenopathy or symptoms. These findings resolve after immune-checkpoint inhibitors are withheld.

Sarcoid-like lymphadenopathy and granulomatosis can create a diagnostic dilemma for radiologists, because most patients receiving immune-checkpoint blockade have advanced malignancy, and new or enlarging lymph nodes primarily raise a suspicion for recurrent or progressive cancer. Accompanying pulmonary changes resembling sarcoidosis can help distinguish this entity from tumor progression or recurrence; however, these are not always present. An elevated angiotensin-converting enzyme level has been reported in some cases but not in others (42–44,68). It is essential for radiologists to be familiar with the clinical and radiographic presentation of this entity, correlate the pattern and onset of imaging findings in relation to the detailed course of immunotherapy, and pay particular attention to the systemic tumor burden changes in other parts of the body. Discussion with clinical providers in terms of the symptoms and overall disease status of cancer also provides important clues for challenging cases (42).

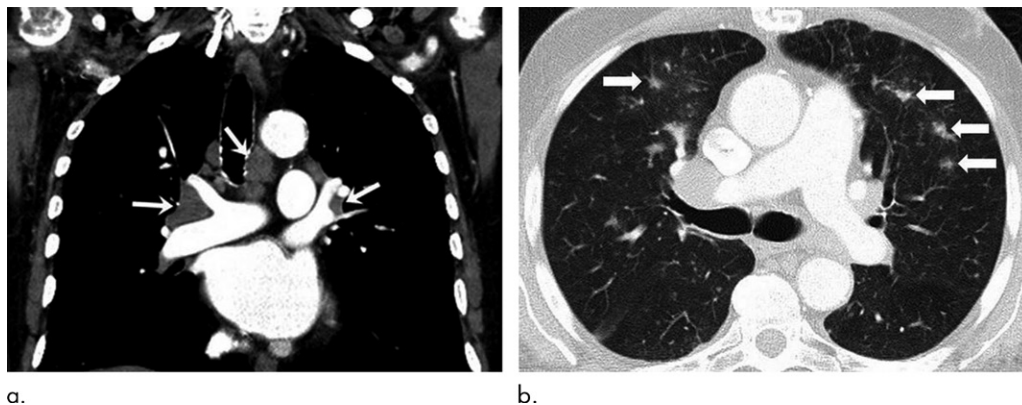


Figure 8: Sarcoid-like lymphadenopathy in an asymptomatic 81-year-old man with metastatic melanoma treated with ipilimumab. (Reprinted, with permission, from reference 43.) **(a)** Coronal reformatted contrast-enhanced chest CT scan obtained 4.9 months after the initiation of ipilimumab therapy shows new bilateral symmetric mediastinal and hilar lymphadenopathy (arrows) resembling sarcoidosis. **(b)** Axial CT image of the lungs shows bilateral irregular and nodular parenchymal opacities with upper- and middle-lung predominance (arrows) and peribronchovascular involvement, which falls in the spectrum of lung parenchymal manifestations of pulmonary sarcoidosis.

Colitis

Colitis during immune-checkpoint inhibitor therapy is one of the most common organ-specific irAEs, especially for those treated with ipilimumab. The incidence of colitis during immune-checkpoint inhibitor therapy ranges from 8% to 22% (43,70). In ipilimumab-treated patients, colitis usually develops 6–7 weeks after the initiation of treatment and resolves within 6–8 weeks (43,71). Two distinct patterns of clinical and radiographic manifestations of immune-related colitis have been reported. The first pattern is a diffuse colitis pattern, seen in about 75% of cases, which is characterized by mild diffuse bowel wall thickening or a fluid-filled distended colon with mesenteric vessel engorgement (Fig 9) (43,72,73). The second pattern is a segmental colitis associated with diverticulosis (SCAD) pattern, noted in approximately 25% of cases. SCAD is characterized by moderate wall thickening and associated pericolic fat stranding in a segment of preexisting diverticulosis (43,72,73). Although imaging findings of SCAD may be similar to those in infectious diverticulitis, patients with SCAD have relatively mild systemic symptoms and lack evidence of a fecal bacterial pathogen or fecal leukocytes (72).

Recognition of these two patterns is important because they are associated with clinical symptoms and management course. A diffuse colitis pattern manifests with profuse watery diarrhea, whereas a SCAD pattern manifests with mixed watery and bloody diarrhea with cramping pain (43,72,73). Diffuse colitis cases can often be managed with corticosteroids alone, while SCAD cases are treated with corticosteroids and antibiotics. A few cases may be corticosteroid refractory and may also require additional therapies (72). Early detection and diagnosis of colitis are critical, because serious complications, including bowel perforation and colitis-related deaths, although rare, can occur if patients are not promptly treated (43,71).

Hepatitis

Hepatitis during immune-checkpoint inhibitor therapy is a relatively rare event, seen in 1%–2% of patients (41,43,71).

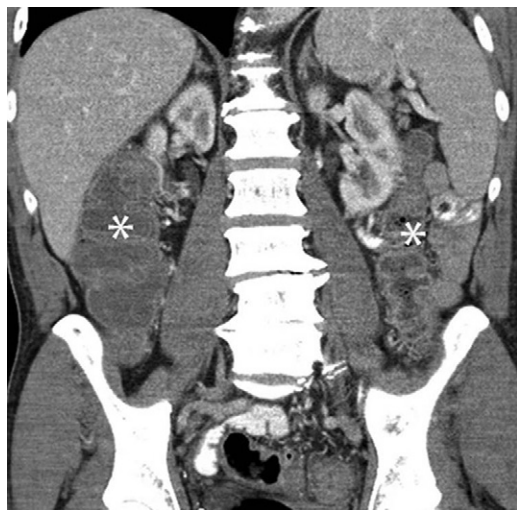


Figure 9: Colitis with a diffuse colitis pattern in a 64-year-old man with advanced melanoma treated with ipilimumab and with diarrhea at presentation. Coronal reformatted contrast-enhanced CT image of the abdomen obtained 2.6 months after the initiation of ipilimumab treatment shows a new finding of a fluid-filled dilated colon (*), with mucosal hyperemia indicating diffuse colitis. Colonoscopic biopsy confirmed colonic inflammation with mucosal injury consistent with ipilimumab-associated colitis. The patient was treated with oral steroids followed by intravenous infliximab, leading to resolution of the findings at the follow-up study performed 1.8 months after onset. (Reprinted, with permission, from reference 43.)

Time between therapy initiation and hepatitis is 5 weeks (range, 1–49 weeks) in patients treated with PD-1/PD-L1 or CTLA-4 inhibitor monotherapy (74). Hepatitis has a spectrum of manifestations, ranging from mild asymptomatic cases with mildly increased liver function without imaging abnormalities, to severe cases with systemic symptoms and highly elevated liver function test results. Severe cases are often accompanied by hepatomegaly, periportal edema, and periportal lymphadenopathy at imaging (Fig 10) (43,73,75). At histologic examination, two patterns of injury are noted—an acute hepatitis pattern with predominant injuries to hepatocytes, and a biliary pattern with predominant injuries to bile ducts (75). Most cases are treated with corticosteroids, while the addition of azathioprine or mycophenolate mofetil is considered in steroid-refractory cases according to the management guidelines of autoimmune hepatitis (41).

Other Organ-specific irAEs and Unmet Clinical Needs

A number of other organ-specific irAEs have been described in patients treated with immune-checkpoint inhibitors, including encephalitis, myelitis, arthritis, nephritis, pancreatitis, and myocarditis, to name a few. Among them, a few fatal cases of immune-related myocarditis have recently been reported (76,77). Myocarditis is a rare irAE, occurring in 0.27% of patients treated with PD-1 plus CTLA-4 inhibi-



Figure 10: Immune-checkpoint inhibitor-related hepatitis in a patient with metastatic melanoma treated with ipilimumab and with markedly elevated liver function test levels at presentation. Coronal CT scan obtained after 2.7 months of ipilimumab therapy shows new periportal edema (black arrows), new periportal lymphadenopathy (white arrows), and hepatomegaly with trace perihepatic free fluid, demonstrating ipilimumab-related hepatitis.

tors. MRI shows characteristic findings of acute myocarditis, including late gadolinium enhancement in a myocarditis-like pattern noted in the focal subepicardial lateral wall and myocardial edema, indicating another emerging need for radiologists' contributions (76,77). The concept and knowledge of irAEs are still evolving as we experience more cases in the clinical setting. Many of the irAEs require a multidisciplinary approach based on clinical, radiographic, and sometimes histologic findings for accurate diagnosis and management. The increased awareness of irAEs among health care providers, including radiologists, is essential to further understanding specific toxicities during immunotherapy. Furthermore, there are urgent and unmet clinical needs to further elucidate the mechanisms of irAEs, identify risk factors for improved safety profiles, develop accurate diagnostic methods, and establish optimal management and monitoring strategies for specific types of irAEs. Radiologists are at the front line for the detection, diagnosis, and monitoring of many of these novel irAEs and can make substantial contributions as key members of multidisciplinary cancer care in the era of immuno-oncology.

Emerging Approaches Using Molecular Imaging for Immunotherapy

Although conventional anatomy-based imaging can provide practical information on response and toxicity evaluations in patients treated with immunotherapy in the clinical setting, there are many important questions that remain to be addressed. To address the unmet needs in the field, molecular imaging techniques using novel radioactive tracers that target the key molecules of immune-checkpoint pathways and cellular immune responses have been explored (78–87).

Early efforts have focused on radiolabeling of antibodies against key molecules such as PD-1 and PD-L1 (78–85). Natarajan et al (78,79) developed an anti-PD-1 human antibody labeled with zirconium 89 or copper 64 (^{64}Cu) and demonstrated in

vivo imaging of PD-1–expressing tumor-infiltrating lymphocytes within the tumor and lymphoid tissues in mouse models. Heskamp et al (81) developed an indium 111–labeled anti–PD-L1 antibody and demonstrated specific uptake of the tracer in PD-L1–expressing tumors in mouse xenografts. Although these radiolabeled antibodies have advantages as imaging agents, including naturally high avidity, antigen specificity, and ease of production, several disadvantages have also been noted (80). These include long circulation times, high background signal, and nonspecific uptake, resulting in more than 24-hour intervals between the injection of tracers and visualization of target molecules (80).

As a measure to overcome these limitations of antibody-based imaging, Maute et al (88) developed a high-affinity competitive nonantibody antagonist of PD-L1, which demonstrated superior tumor penetration. The antagonist was conjugated with ⁶⁴Cu-DOTA (tetraazacyclododecane tetraacetic acid) and was tested as a PET tracer. High tumor uptake with favorable tumor-to-background ratios at 1 hour after injection in mouse xenografts was noted, with persistent strong uptake in PD-L1–positive tumors for 24 hours (88). Another approach by Larimer and colleagues (89) focused on in vivo visualization of granzyme B, a serine protease released by CD8+ T cells and natural killer cells during the cellular immune response. A PET imaging agent, gallium 68 (⁶⁸Ga)-NOTA-GZP, is a radiolabeled peptide developed to detect the release of granzyme B by activated immune cells (89). In tumor-bearing mice treated with PD-1 inhibitor therapies, ⁶⁸Ga-NOTA-GZP uptake was shown to reflect tumoral granzyme B expression. High ⁶⁸Ga-NOTA-GZP uptake at 12 days of therapy was predictive of subsequent tumor volume response in tumor-bearing mice treated with a PD-1 inhibitor plus a CTLA-1 inhibitor (89). These promising results in preclinical models support further investigations of these agents for clinical translation to human imaging, to supplement the current strategies to further optimize patient selection, response evaluations, and treatment decision making.

Conclusion

Cancer immunotherapy with immune-checkpoint blockade plays a major role in the treatment of advanced cancers, and clinical application of immune-checkpoint inhibitors continues to expand. Imaging is a key component for characterizing tumor response and progression and detecting and monitoring irAEs in patients treated with immunotherapy. Familiarity with the current strategies of immune-related response and toxicity evaluation and their limitations and pitfalls are essential for radiologists to provide useful information for clinical providers to guide their treatment decisions. Molecular-based imaging has shown promise in addressing unmet clinical needs in the field, and further studies are needed to translate the approach to the clinical setting for better selection and monitoring of patients to maximize the benefit of cancer immunotherapy.

Disclosures of Conflicts of Interest: M.N. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a consultant for WorldCare Clinical, Toshiba Medical Systems, and Daiichi Sankyo; institution has received research grants from Merck, Toshiba Medical Systems, and AstraZeneca; has received honoraria for lectures from Bayer and Roche. Other relationships: disclosed no relevant relationships. H.H. Activities related to the present

article: disclosed no relevant relationships. Activities not related to the present article: is a consultant for Mitsubishi Chemical Holding and Toshiba Medical Systems; institution has grants or grants pending with Toshiba Medical Systems, Konica-Minolta. Other relationships: disclosed no relevant relationships. E.S.H. Activities related to the present article: disclosed no relevant relationships. Activities not related to the present article: is a consultant for Merck, Bristol-Myers Squibb, Novartis, Genentech, and EMD Serono; institution has grants or grants pending from Bristol-Myers Squibb; institution has patents (planned, pending, or issued) and receives royalties for MICA-Related Disorders; has received payment for development of educational presentations from Harvard Medical School and George Washington Medical School. Other relationships: disclosed no relevant relationships.

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